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COMPUTATIONAL MODELING AND SIMULATION OF THE CEREBELLAR CIRCUITS INVOLVED IN EMOTIONAL CONTROL

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To God,

For placing me in the right place, with the right people, and giving me the necessary experiences — both opportunities and challenges. Every person and situation He has placed in my path, whether directly or indirectly, has contributed to my personal and professional growth.

Abstract

Understanding the neural basis of emotional processing has become a central theme in contemporary neuroscience. Fear conditioning, an evolutionarily conserved form of associative learning, is a widely used paradigm for investigating the neural basis of emotion. Its usefulness stems from its clear behavioral outputs, well-established experimental structure, and the cross-species conservation of key underlying neural mechanisms. This makes it a highly translational model for investigating how the brain detects, processes, and learns from emotionally salient or threatening stimuli, ultimately contributing to adaptive behavioral responses. While historically overlooked in emotion research, the cerebellum—and specifically lobule VI—has recently gained attention for its potential integrative role in both motor and affective processes.

In this thesis, we investigate the cerebellum's contribution to emotional learning by combining computational modeling and experimental datasets. We developed a detailed, data-driven reconstruction of the mouse cerebellar lobule VI (Declive) using the Blue Brain Cell Atlas, the Brain Scaffold Builder framework, and we simulated its dynamics as single-point neural networks by using NEST. This Declive-specific model was compared against a canonical cerebellar microcircuit to identify structural and functional region-specificities.

Building upon this, we challenged the model to explore Pavlovian conditioning in rodents, simulating neural responses to conditioned and unconditioned stimulation patterns. We therefore defined hypotheses for plasticity mechanisms and interactions between the olivocerebellar circuit and the periaqueductal gray region, involved in fear conditioning.

Moreover, at a large scale, we identified the human fear network within the Virtual Brain framework by tuning the whole-brain system parameters on subject-specific neuroimaging datasets. The focus was on the cerebellar nodes involved in the brain network. We then correlated the parameter sets with fear-related response outcomes.

Although these models operate at different scales and in different species, together they serve as complementary pioneer work aimed at investigating emotional processes and cerebellar involvement. This modeling strategy illustrates the potential of biologically grounded computational neuroscience to explore brain–behavior relationships across levels of organization.

Table of Contents

Abstract.....	3
General Introduction.....	9
Chapter 1: Theoretical and Conceptual Foundations.....	14
Section 1.1: Introduction.....	14
1.1.1 Emotions, evolution of the concept.....	14
1.1.2 Essential Distinctions: Emotions vs. Feelings.....	17
1.1.3 Emotional disorders.....	18
1.1.4 Computational and experimental models in the study of emotions.....	21
1.1.5 Fear conditioning, a core model for studying emotional behavior.....	23
Supplementary material.....	26
Section 1.2: The cerebellum as a new piece in understanding emotional processing.....	34
1.2.1 Comprehensive overview of Cerebellar structure, function, and connectivity.....	34
1.2.2 Role of the cerebellum in emotions, from rodents to humans.....	41
Section 1.3: Tracking the Cerebellum in Emotion Research.....	48
1.3.1 Methods.....	49
1.3.2 Analyses and Results.....	51
1.3.3 Discussion and Conclusions.....	69
Supplementary material.....	71
Section 1.4 State-of-the-Art on cerebellar lobule VI, from rodents to humans.....	83
1.4.1 Structural and functional organization.....	83
1.4.2 Lobule VI and Cerebellar pathology, from movement to emotion.....	86
1.4.3 Lobule VI, an integrative node?.....	88
Chapter 2: Data-driven reconstruction and simulation of the mouse lobule VI (Declive).....	89
Section 2.1 Introduction.....	89
2.1.1 Computational modeling of the brain.....	89
2.1.2 Modelling of the Cerebellum.....	91
2.1.3 Computational tools and Modeling frameworks: BBcAv2, BSB, and NEST.....	91
Section 2.2 Methods.....	94
2.2.1 Atlas-based mapping of the Declive model.....	94
2.2.2 The canonical microcircuit model.....	100
2.2.3 Modeling a subvolume of the Declive.....	100
2.2.4 Computational simulations of awake-state baseline activity.....	102
Section 2.3: Analysis and Results.....	103
2.3.1 Comparative analysis between the canonical and Declive model reconstructions ..	103
2.3.2 Simulation-based analysis of canonical and Declive circuits.....	109
Section 2.4 Discussions and Conclusions.....	115
Supplementary material.....	117
Chapter 3: Fear conditioning modeling in rodents.....	124
Section 3.1: Introduction.....	124
3.1.1 Fear conditioning paradigms in rodents.....	124

3.1.2 Fear network in rodents	127
3.1.3 Cerebellar fear circuit in rodents	132
Section 3.2 Methods	136
3.2.1 Modeling neural responses to conditioned and unconditioned stimuli	136
3.2.2 Pavlovian conditioning learning in the cerebellum	137
3.2.3 Extending the model for fear conditioning beyond the cerebellum	138
Section 3.3 Analysis and Results	142
3.3.1 Simulation-based analysis of CS-US induced activity	142
Section 3.4 Discussion and Conclusions.....	143
Supplementary material	145
Chapter 4: Fear Conditioning modeling in humans	148
Section 4.1: Introduction	148
4.1.1 Neuroimaging and modeling in the study of human fear conditioning	148
4.1.2 Fear conditioning paradigms in humans	150
4.1.3 Fear network in humans	154
4.1.4 Whole brain modelling using The Virtual Brain (TVB)	159
Section 4.2: Methods	159
4.2.1 Acquisition, preprocessing, and connectivity mapping	159
4.2.2 Virtual Brain modeling for fear network	162
Section 4.3: Analysis and Results	165
4.3.1 Outcome of TVB model optimization	165
4.3.2 Evaluation of TVB model performance, from SC construction to FC and FCD validation.....	168
4.3.3 Fear-related skin conductance response in relation to the optimized TVB model ...	174
Section 4.4: Discussion and Conclusions.....	183
Supplementary material	189
General Conclusions	203
References.....	205

List of Tables

Table S1.1.1.1 Evolution of the concept of emotions and theories over time*	26
Table 1.1 3WH* framework applied to the research question	49
Table 1.2 Funding Organizations***	64
Table S1.3.1 Type of publications*	71
Table S1.3.2 Leading Journals	76
Table S1.3.3 Leading cited publications	76
Table S1.3.4 Network Metrics** Evolutionary and Comparative Analysis	81
Table 2.1 Declive cell type distributions across layers	103
Table 2.2 Placement	105
Table 2.3 Connectivity	107
Table 2.4 Neural activity summary: Firing rate and ISI	111
Table S2.1 Cerebellar microcircuit connectome	117
Table S2.2 Placement strategies.....	118

Table S2.3 Connectivity strategies	118
Table S2.4 Cellular composition*	121
Table S2.5 LIF neuron parameters	121
Table S2.6 EGLIF neuron parameters	122
Table S2.7 Neuron Postsynaptic receptor parameters	122
Table S2.8 Presynaptic parameters	122
Table 3.1 Key elements in Fear Conditioning paradigms in rodents	125
Table 3.2 Brain Regions Involved in Fear Conditioning in Rodents	130
Table S3.1.1 Comparison of fear conditioning paradigms across species	145
Table S3.1.2 Comparison of the function and interconnectivity of brain regions in fear conditioning across species	146
Table 4.1 Key elements in Fear Conditioning paradigm in humans	152
Table 4.2 Brain Regions Involved in Fear Conditioning in Humans	154
Table 4.3 Independent Sample Test	178
Table S4.1 Cortical and subcortical regions considered in the TVB model	189
Table S4.2* TVB model parameters	191
Table S4.3* TVB Optimization parameters	191
Table S4.4* SCR Data and Metrics in Acquisition and Extinction	198

List of Figures

Figure 1.1 Chronological Overview of the Concept of Emotions.	17
Figure 1.2 Emotions and feelings.	19
Figure 1.3 Emotional tasks in rodents	24
Figure 1.4 Macroarchitecture of the Rodent Cerebellum.	35
Figure 1.5 Cerebellar microcircuit variants.	37
Figure 1.6 Cerebellar cortex.	39
Figure 1.7 Neuron density and thickness in the mouse cerebellum based on the Blue Brain Cell Atlas.	40
Figure 1.8 Efferent pathways from the rodent cerebellum	42
Figure 1.9 Contribution of the human cerebellum to motor, cognitive, emotional, social, and complex tasks	44
Figure 1.10 Venn's diagram based on the consulted bibliography of three functional domains (motor, cognitive, emotional/social).	46
Figure 1.11 Database identification according to the PRISMA method.	51
Figure 1.12 Publication Trends Over Time.	52
Figure 1.13 Annual Publications by Type.	53
Figure 1.14 Leading Journals.	54
Figure 1.15 Leading cited publications	55
Figure 1.16 keyword co-occurrence network.	56
Figure 1.17 Distribution of species	57
Figure 1.18 Thematic evolution by topic by species	58
Figure 1.19 Leading topics.	59
Figure 1.20 Techniques of research.	60
Figure 1.21 Leading authors	62
Figure 1.22 Distribution of Publications by Author Count	63
Figure 1.23 Collaboration Patterns by Number of Authors.	63
Figure 1.24 Geographic Distribution of Authors' Affiliations.	67
Figure 1.25 Evolution of the Collaboration Network in Different Periods of Time.	68
Figure S1.3.1a Role of the authors	79
Figure S1.3.1b Extended version of Figure S1.3.1a, highlighting authors outside the mean. ...	80

Figure 1.26 Anatomical comparison of the Simple Lobule and the Declive in humans and rodents.	83
Figure 1.27 Functional and anatomical organization of the Cerebellum and its Deep Nuclei. ...	85
Figure 1.28 Structural connectivity from cerebellar Lobule VI to major input and output hubs ..	86
Figure 1.29 Structural Connectivity Matrix in Mice.	87
Figure 2.1 Multiscale brain organization and modeling approaches.	90
Figure 2.2 BSB framework.	93
Figure 2.3 The E-GLIF point neuron model.	94
Figure 2.4 Declive Annotations corrections.	95
Figure 2.5 Declive orientation and depth field.	96
Figure 2.6 Blue Brain Cell atlas results.	97
Figure 2.7 Declive placement intermediate results	98
Figure 2.8 Morphology scaling and bending according to the shape of Declive..	99
Figure 2.9 Cerebellar microcircuit connectome	101
Figure 2.10 Subvolume of the Declive.	102
Figure 2.11 Neuron type distribution in Declive.	104
Figure 2.12 Volume, neuron counts, and composition in the Declive region..	105
Figure 2.13 Granule cell bending in Declive subvolume.	106
Figure 2.14 3D Placement.	106
Figure 2.15 3D morphological reconstruction of the canonical cerebellar microcircuit.	107
Figure 2.16 Raster plot	111
Figure 2.17 Firing rates.	112
Figure 2.18 Inter-spike interval (ISI)	113
Figure 2.19 Frequency.	114
Figure 3.1 Fear conditioning paradigms in rodents.	125
Figure 3.2 Proposed Neural Circuits of Fear Processing in rodents.....	132
Figure 3.3 Hypothesized fear circuitry in rodents based on literature review.	135
Figure 3.4 Hypothesized cerebellar fear microcircuit in rodents based on literature review. ...	136
Figure 3.5 Cerebellar-PAG Connectivity Model hypothesis.	139
Figure 3.6 Structural connectivity heatmap based on data from the Allen Mouse Brain Connectivity Atlas	139
Figure 3.7 Hypothetical model of the vIPAG and Olivocerebellar circuit for fear conditioning experiments.	141
Figure 3.8 Raster plot	142
Figure 3.9 Firing rates.	143
Figure 4.1 Fear conditioning paradigm in humans.	151
Figure 4.2 Neural Network of Fear in Humans.	157
Figure 4.3 Reduced Wong-Wang Model.	161
Figure 4.4 The virtual brain.	161
Figure 4.5 Fear Network considered in the model	163
Figure 4.6 Schematic representation of the modeling workflow.	164
Figure 4.7 TVB model parameters.	165
Figure 4.8 TVB optimization values - Box plot..	166
Figure 4.9 TVB optimization values – Line plot representation.	167
Figure 4.10 Correlation matrix of TVB model parameters.	168
Figure 4.11 Mean Structural Connectivity and Conduction Delay Matrices.....	170
Figure 4.12 Comparison between the mean experimental and simulated functional connectivity matrices	171
Figure 4.13 Mean Structural-Functional connectivity matrices comparison	172
Figure 4.14 Mean Experimental-Simulated Functional connectivity matrices comparison	173
Figure 4.15 Distribution of fear conditioning response measures and TVB model parameters.	175

Figure 4.16 Correlation matrix between fear conditioning response measures and TVB model parameters.....	176
Figure 4.17 Distribution of fear conditioning response measures and TVB model parameters by sex.	179
Figure 4.18 Correlation matrices between fear conditioning response measures and TVB model parameters for women and men.	181
Figure 4.19 Relationship between fear extinction responses and TVB model parameters in women.	183
Figure 4.20 Relationship between fear acquisition measures and TVB model parameters in men.	183
Figure S4.1a Relationships between TVB model parameters.	192
Figure S4.1b Relationships between TVB model parameters and optimization metrics.	193
Figure S4.2 Structural Connectivity and Conduction Delay Matrices (single subject).....	194
Figure S4.3 Comparison between the experimental and simulated functional connectivity matrices (single subject).....	195
Figure S4.4 Structural-Functional connectivity matrices comparison (single subject).	195
Figure S4.5 Experimental-Simulated Functional connectivity matrices comparison (single subject)	196
Figure S4.6 Experimental and Simulated Functional Connectivity Dynamics matrix (single subject)	196
Figure S4.7 Experimental-Simulated Functional Connectivity Dynamics matrices comparison (single subject)	197
Figure S4.8 Correlation between fear-related behavioral measures and TVB model parameters.	199
Figure S4.9 Correlation between fear-related behavioral measure and TVB model parameters by sex.....	202

General Introduction

The emerging view of the cerebellum's role in emotional processing challenges classical functional boundaries and opens novel avenues for understanding the neurobiological basis of emotions.

This thesis was developed within the framework of the *Cerebellum and Emotional Network* (CEN), a multidisciplinary European research consortium (<https://www.cen-itn.net>) focused on the cerebellum's role in emotional behavior. Specifically, CEN investigates how the cerebellum interacts with brain systems involved in fear, anxiety, and neurodevelopmental disorders such as autism.

The consortium brought together early-stage researchers (ESRs) from diverse scientific backgrounds, who contributed complementary expertise across behavioral assays, neuroimaging, electrophysiology, and neuroanatomical studies in both rodent and human models. Within this collaborative context, my primary role was to provide the computational modeling foundation of the project.

My contribution centered on the development of biologically grounded simulations of cerebellar function across multiple scales—from rodent microcircuits to human macroscale networks.

Rather than claiming to provide a conclusive model, this thesis introduces a proof-of-concept framework intended to support future integration, empirical validation, iterative refinement, generate hypotheses, guide experimental design, and encourage interdisciplinary integration.

In this regard, the work serves a pioneering function: presenting one of the first biologically grounded attempts to model the cerebellum's role in emotion.

This modeling strategy ultimately advances the consortium's broader aim: constructing biologically plausible, multiscale models that clarify the cerebellum's role in emotional behavior.

The motivation behind this work emerged organically, from both scientific challenges and community feedback.

This was not a linear process; it evolved through growing curiosity, conceptual refinement, technical obstacles, data limitations, early feedback that revealed conceptual uncertainty, and the inherent uncertainty of working at the edge of an emerging scientific field.

This foundational challenge directly shaped the structure of the thesis, highlighting the importance of establishing a clear conceptual framework before attempting to model emotions. As a result, the work begins with conceptual analysis and gradually progresses toward applied computational modeling.

Chapter 1 establishes the conceptual and theoretical foundation of this thesis. It begins with a critical review of the concept of emotion and its historical development—an intentional choice shaped by recurring questions I encountered during conference presentations.

These repeated inquiries—about the distinction between emotions and feelings, and the feasibility of modeling them in non-human species—highlighted a widespread conceptual ambiguity, both within academia and broader discourse.

In response, this chapter emphasizes the need to establish a clear and rigorous conceptual foundation as a prerequisite for modeling the emotional brain.

This reflects a core principle of the thesis: any meaningful model must be grounded in a solid theoretical understanding of the phenomenon it represents.

In the case of emotion, attempting to model its neural substrates without first defining what emotions are—and how they differ from feelings—risks generating models that oversimplify the complexity of the subject. Additionally, scepticism regarding the validity of emotional paradigms in animal models—especially the idea that genuine emotions are uniquely human—often surfaced in academic discussions.

These critiques reinforced the need for precise conceptual definitions and for justifying how emotion can be meaningfully studied across species. To address this, a coherent and well-justified modeling framework became essential for maintaining the scientific relevance and credibility of the thesis.

Establishing a rigorous foundation required clarifying both the conceptual landscape and the current state of the scientific field regarding the cerebellum's role in emotion. In this context, two

original publications —presented in Sections 1.2 and 1.3— were developed and subsequently integrated into Chapter 1. These works were not auxiliary contributions, but essential pillars in constructing the theoretical and contextual scaffolding of the thesis. The first offers a comprehensive review of cerebellar involvement in emotional processing from rodents to humans, while the second maps the evolution and structure of this emerging research domain through quantitative bibliometric methods.

Section 1.2 is based on the peer-reviewed publication: Ciapponi, C., Li, Y., Osorio-Becerra, Dianela A., Rodarie, D., Casellato, C., Mapelli, L., & D'Angelo, E. (2023). *Variations on the theme: focus on cerebellum and emotional processing*. *Frontiers in Systems Neuroscience*, 17:35. <https://doi.org/10.3389/fnsys.2023.1185752>

My contribution to this article was substantial and multifaceted. I was responsible for: Contributing to design of the structure of the thematic content, leading all human-related sections—including the literature review, drafting of text, and figure preparation, contributing to the introduction, conclusions and the formulation of core hypotheses, creating the figure depicting atlas data on cerebellar microcircuits and structural variations, conducting the full reference search for the manuscript, participating in the overall editing process and contributing extensively to the revisions.

The motivation behind this work was to organize and integrate the scattered findings on the cerebellum's role in emotion into a structured review. In doing so, it not only clarified the current state of the field but also led to the formulation of a new hypothesis regarding the involvement of lobule VI, further strengthening the foundation for our ongoing research.

Section 1.3 is based on the peer-reviewed publication: Osorio-Becerra, Dianela A., D'Angelo, E., & Casellato, C. (2025). *The Cerebellar Role in Emotions at a Turning Point: Bibliometric Analysis and Collaboration Networks*. *Cerebellum*, 24, 47. <https://doi.org/10.1007/s12311-025-01800-7>

I was solely responsible for: The conceptualization of the study, methodological design, data curation and formal analysis, conducting the investigation and visualization, writing the original draft, and leading the review and editing process. Co-authorship reflects their supervisory roles and their involvement in reviewing the manuscript before submission

The motivation for this work arose from the observation that, despite increasing interest in the cerebellum's role in emotion, no prior study had systematically applied a combined bibliometric and collaboration network analysis to this research domain. As a student immersed in this emerging field, I identified a need to explore its structure and evolution using quantitative tools capable of revealing underlying research dynamics.

This approach not only addressed a personal scientific curiosity but also aimed to provide a strategic reference framework for researchers entering the field. The analysis fills a gap in the literature by offering a comprehensive, data-driven overview of the field's development, highlighting key topics, methods, authors, and collaboration patterns. It also identifies emerging themes and underexplored areas, helping to guide future directions and hypotheses.

Finally, Section 1.4 presents a state-of-the-art review of cerebellar lobule VI—the target region modeled in this thesis. Lobule VI (Declive) was selected due to its consistent implication in emotional processing and its anatomical prominence across species. Despite frequent mentions in the literature, no comprehensive synthesis of its functional and structural characteristics had been conducted before this work. Chapter 1 closes with a review that fills this gap by integrating findings on its anatomy, connectivity, and proposed role in emotion. This provides both scientific justification and contextual support for the modeling and simulations presented in subsequent chapters.

Methodologically, the thesis follows a two-tiered approach: bottom-up reconstruction of rodent cerebellar microcircuits and top-down simulation of human brain dynamics. This strategy does not replace traditional anatomical methods but complements them by integrating diverse anatomical datasets into a unified, testable framework. While anatomical studies offer essential structural insights, they often lack the resolution or completeness needed to reconstruct entire microcircuits, particularly at the mesoscale level.

Computational modeling enables the synthesis of heterogeneous data, such as cell densities, spatial distributions, and connectivity patterns, and supports the generation of biologically

constrained network architectures. Crucially, it also permits dynamic simulations to explore circuit behavior, offering functional insights that go beyond what anatomical data alone can reveal.

Building on the conceptual and anatomical review of cerebellar lobule VI presented in sections 1.2 and 1.4, Chapter 2 focuses on its computational reconstruction and simulation. The Declive, a subregion of lobule VI, was selected as the first modeling target due to its strong anatomical features and implication in emotional processing.

This bottom-up modeling approach employed high-resolution anatomical data from the Blue Brain Cell Atlas (BBCAv2) and simulation platforms such as the Brain Scaffold Builder (BSB) framework and the NEST simulator to build a biologically plausible representation of this region. The work described in the section 2.2 was conducted at the Neurocomputational Laboratory as part of a collaborative project within the Department of Brain and Behavioral Sciences at the University of Pavia, and it leveraged tools developed through the EBRAINS research infrastructure.

The development of code and algorithms was a collaborative and iterative process, involving shared codebases that were continuously reviewed and refined. While these tools support multiple projects, in this case, they were specifically adapted to investigate cerebellar network dynamics in relation to emotional function.

My contributions included collaborating in the adaptation of the modeling pipeline, configuring and executing simulations, and validating the model outputs—all of which were essential for tailoring the model to address the functional questions related to emotional processing.

After completing the circuit reconstruction, the next objective was to evaluate its functional viability in this domain. To this end, we employed fear conditioning—a robust and extensively validated paradigm for studying emotional learning across species—as the conceptual and experimental foundation for our simulations. Its relevance in emotion research and its applicability across scales, from synaptic mechanisms to whole-brain dynamics, made it an ideal starting point for developing biologically grounded emotional behavioral models. This functional extension of the anatomical model forms a direct bridge to the simulation work presented in Chapters 3 and 4.

In keeping with the thesis's commitment to a solid theoretical foundation, Chapters 3 and 4 provide a detailed account of the fear conditioning paradigm and its neurobiological underpinnings, with a particular emphasis on cerebellar involvement in both rodent and human models. These chapters not only implement computational simulations but also contextualize them within current neuroscientific knowledge, describing the relevant brain structures and their functional roles in emotional learning. Together with Chapter 2, this lays the groundwork for future research. Once the necessary experimental data become available, the work presented in these chapters can be readily adapted to test hypotheses and validate the proposed mechanisms.

Chapter 3 builds upon the reconstructed circuit by simulating cerebellar involvement in fear conditioning paradigms in rodents. While a fully validated model could not yet be realized—due to current technical and data-related limitations—this chapter lays the conceptual and computational groundwork for such simulations, including the formulation of biologically grounded hypotheses. The model was adapted and tested as a proof of concept for implementing Pavlovian learning mechanisms, providing preliminary support for the proposed hypotheses.

While we do not claim direct equivalence between species or scales, we recognize the value of selecting modeling strategies according to the nature of the data and the resolution required to address specific scientific questions.

Within this framework, Chapter 4 presents a parallel line of work focused on human fear conditioning. The modeling workflow described in section 4.2 was conducted at the Neuroimaging and Brain Modelling Laboratory, Department of Brain and Behavioral Sciences, University of Pavia. It was developed using simulation tools from the Virtual Brain (TVB) framework, which enables large-scale brain modeling based on empirical neuroimaging data.

The model was constructed using pre-processed neuroimaging and behavioral data from a fear conditioning experiment, provided by the Experimental Cognitive and Affective Neuroscience (ECAN) group at Uppsala University. These data were obtained through a short research secondment I carried out within their group.

I proposed the integration of this dataset into the project, identifying it as a key opportunity to bridge human behavioral data and computational simulations. To ensure methodological coherence, I compiled the necessary conceptual and technical background supporting its compatibility with our modeling framework. I contributed to adapting the modeling pipeline, configuring and executing simulations, and validating the model outputs.

The success of this collaborative modeling effort laid the groundwork for future joint research. It directly inspired a follow-up project designed to build upon and extend the work presented in this chapter.

Due to space constraints in the main text, several key theoretical points, methodological details, and complementary analyses are provided as supplementary material within the relevant chapters or sections. These additions are essential for a comprehensive understanding and should be considered integral to the corresponding content. This chapter-specific structure enhances accessibility and keeps supplementary information closely connected to the main discussion, eliminating the need to consult a distant appendix.

Scientific dissemination and community engagement were integral throughout the development of this thesis. The project and its methodologies were presented in various international conferences, meetings, and workshops, both as oral communications and posters. These opportunities not only facilitated knowledge exchange and constructive feedback but also helped shape the direction of the research.

Selected presentations include: CEN Lab Meetings (2023–2025), CEN Annual Meetings (2022–2025), Federation of European Neuroscience Societies (FENS) Forum 2024, European Neuroscience Conference by Doctoral Students (ENCODS) 2024, 1st Dutch Cerebellum Meeting 2024, CERFA Brain Awareness Week 2024, 1st International Social and Affective Cerebellum Symposium 2023, ESI Systems Neuroscience Conference (SyNC) 2023, Human Brain Project (HBP) Summit 2023, Unconference on Neuroinformatics in Psychiatric Disorders 2023, International School of Brain Cells and Circuits 'Camillo Golgi' 2022.

In addition to these presentations, several components of the thesis have been accepted for publication or are currently in preparation.

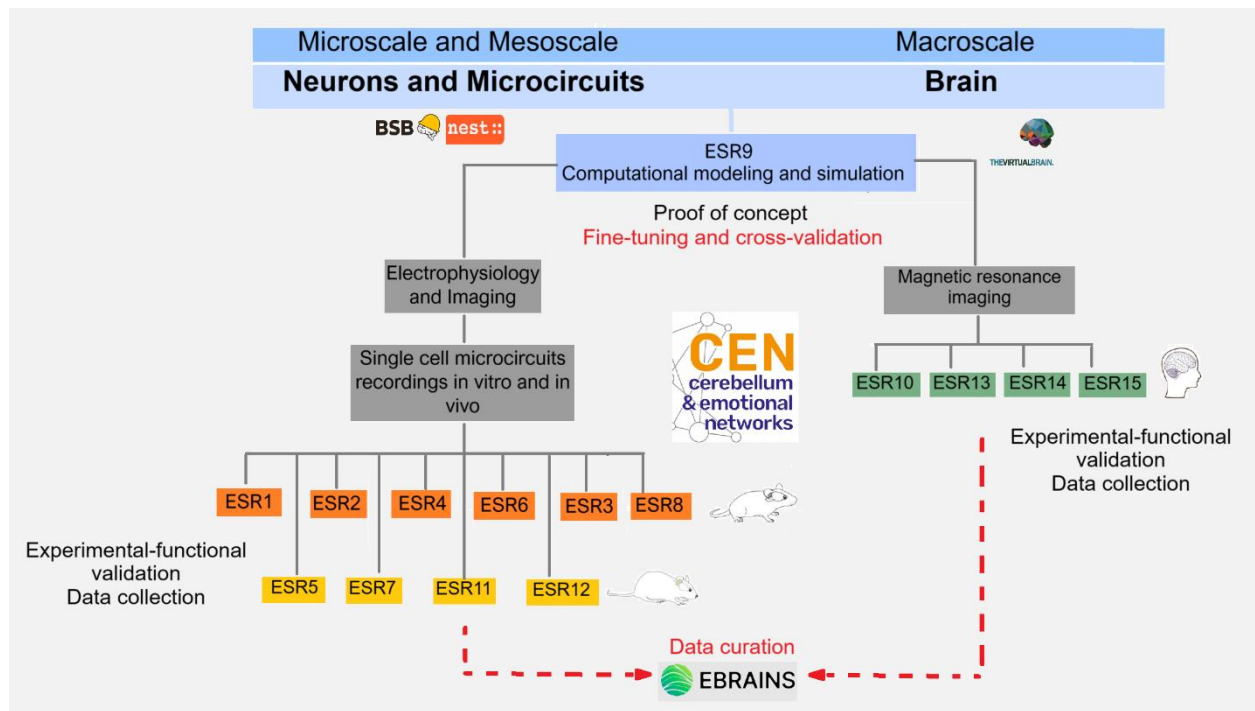
- The Methods section from Chapter 2 includes material from a manuscript currently in preparation for publication: *Rodarie D., Osorio-Becerra Dianela A., Casellato C., D'Angelo E. – An atlas-based approach to reconstruct the mouse cerebellar cortex*

- The work from Chapters 2 and 3 has been accepted as an extended abstract for presentation at the *Computational Neuroscience Conference (CNS2025)* under the title: *Reconstruction and Simulation of the Mouse Cerebellar Declive: An Atlas-Based Approach: Rodarie D., Osorio-Becerra Dianela A., Casellato C., D'Angelo E.*

- The work from Chapter 4 has been accepted as a poster presentation at *CNS2025* under the title: *Emotional Network Modelling: Whole-Brain Simulations of Fear Conditioning in Humans* – Osorio-Becerra, Dianela. A., Fusari, A.; Roy, A; B, Danilo; Frick, A;Palessi, F.; D'Angelo, E., & Casellato, C.

- In addition, material from Chapters 2–4 is part of a manuscript intended for submission to a peer-reviewed journal Osorio-Becerra, Dianela. A., Rodarie, D., Fusari, A.; Palessi, F.; D'Angelo, E., & Casellato, C. – *Rethinking Fear Conditioning Circuits: Computational Perspectives and Future Directions.*

These outputs reflect the collaborative, interdisciplinary nature of the project and underline its contribution to the emerging field of cerebellar emotion research.



Within CEN, each early-stage researcher (ESR) contributed from a different perspective. As ESR9 (in blue), my role centered on providing the computational modeling backbone of the project. Using tools such as BBCAv2, BSB, NEST, and TVB, I developed proof-of-concept models at different scales to simulate fear-related processes and cerebellar interactions. The long-term objective is to curate all experimental and simulation data within the EBRAINS platform, laying the foundation for the development of robust, complete, and biologically grounded multiscale models of cerebellar function in emotion.

Chapter 1: Theoretical and Conceptual Foundations

Section 1.1: Introduction

Understanding the role of the cerebellum in emotional behavior first requires a critical reflection on what is meant by "emotion." Despite its widespread use in both everyday language and scientific discourse, the concept of emotion has been subject to multiple interpretations throughout history, significantly influencing the design of experimental studies and theoretical models. For this reason, this chapter begins with a historical review of the concept of emotion, spanning from ancient philosophy to contemporary neuroscience. Given the extensive material collected, the table summarizing this conceptual evolution is presented in the supplementary material; however, its consultation is strongly recommended, as it offers a crucial conceptual foundation for a deeper understanding of emotions.

Subsequently, the essential distinction between emotions and feelings is addressed, a critical differentiation necessary to avoid terminological confusion that could affect the interpretation of experimental data and the development of computational models. Following this, emotional disorders are analyzed not only as clinical manifestations but also as valuable windows into the understanding of the fundamental mechanisms underlying emotional processing.

Finally, the use of computational and experimental models in the study of emotions, both in animals and humans, is introduced, highlighting their methodological importance in addressing complex questions within the field of affective neuroscience. Additionally, the fear conditioning paradigm is briefly presented, as it constitutes the experimental framework for the development and validation of the computational models proposed in this work. A detailed analysis of this paradigm, in both rodent and human studies, will be provided in Chapters 3 and 4, respectively. This thematic progression provides the necessary conceptual and methodological foundation for the development of the computational model and simulation that will be presented in later chapters.

Expanding on this, we examine the cerebellum as a critical but often overlooked piece in emotional processing. We provide an overview of its structure and function, followed by evidence from both human and rodent studies supporting its involvement in emotions. The section also analyzes the growing interest in this field, highlighting key trends, research gaps, and future opportunities.

Finally, we focus on lobule VI, which, based on literature evidence, plays a significant role in emotional processing, making it a key target for the computational model developed later in the chapter. Indeed, lobule VI emerges as a natural focus for our computational modeling efforts. To build a solid foundation for this, we dedicate a specific part to reviewing the state of the art on lobule VI, exploring its anatomy, connectivity, and functional contributions to emotional processing. This targeted approach allows us to refine our understanding of how lobule VI integrates different types of information and to develop a more accurate computational model that reflects its complex functional architecture.

1.1.1 Emotions, evolution of the concept

Emotions, recognized as central to human thought and behavior, have long been considered an intellectual challenge due to their complexity and multifaceted nature. Over time, their study has been approached by various disciplines, providing valuable insights into their fundamental role in human life. Despite these advances, a complete understanding of the nature and structure of emotions remains elusive, as reflected in the wide diversity of theories and perspectives on the subject. In this section, the historical evolution of emotion theories is traced through an exploratory, literature-based approach, with findings organized chronologically to offer a clearer view of how different thinkers and disciplines have shaped the current understanding of emotions.

➤ Ancient times (Greece and Rome)

Since ancient times, emotions have been the subject of reflection, marking debates on human nature and behavior throughout history. Greek and Roman philosophers (Campeggiani & Konstan, 2024) were the first to offer descriptions of their influence on action and morality, stressing that although natural, they must be educated and regulated to achieve a balanced, virtuous, and peaceful life.

Thinkers such as Pythagoras and the Pythagoreans believed that harmony in the soul was key to emotional health and well-being (Palmer, 2014; Prier, 2011). Heraclitus saw emotions as natural, arising from internal conflict and tension between opposites (Kahn, 1981). Sophists, such as Gorgias, believed that emotions could be manipulated through language (Spatharas, 2019). Democritus, on the other hand, argued that peace of mind and happiness are achieved through moderation and emotional control (Sorabji, 2000). In India, the Bhagavad-gītā taught that anger and desire are obstacles in the quest for peace and spiritual balance (Chauhan & Jain, 2024). Philosophers such as Socrates and Plato stressed the importance of aligning emotions with virtue and reason (De Sousa, 1990), while Aristotle defined them as rational reactions linked to perception and context (Leighton, 1982; R. C. Solomon, 2008). Epicureanism saw them as deriving from irrational beliefs, considering them negative (Annas, 1989), and Stoicism, led by Zeno and followers such as Seneca, Epictetus, and Marcus Aurelius, held that disturbing emotions should be eliminated to achieve tranquillity and well-being, controlling them through reason (Becker, 2004; Hourani, 2023).

➤ Middle Ages (5th-15th centuries)

A legacy that started with Greek and Roman philosophy was later reinterpreted and consolidated during the Middle Ages by Christian thought (Dixon, 2003).

Philosophical theologians like St. Augustine and his disciples considered emotions as passions that should be controlled by reason to prevent alienation from God (Hallman, 1984). On the other hand, St. Thomas Aquinas understood emotions as natural, automatic reactions that, while they are normal, should be moderated to align with the divine will (Lombardo, 2011; Roberts, 1992). Movements like Calvinism contributed to a negative perception of emotions, associating them with human corruption stemming from original sin (Fedler, 2002). However, some viewpoints reconciled emotions with the divine, as St. Teresa of Avila and St. John of the Cross believed that emotions are expressions of God's love (Swope, 2023).

➤ Modern age (15th- late 18th or early 19th century)

While their views on nature and function may differ, thinkers in this era commonly agree that emotions are fundamentally linked to human experience, regardless of whether they arise from physical, rational, or social origins (Schmitter, 2006).

For Hobbes, emotions guide behavior toward pleasure and away from pain (Barnouw, 1980). Descartes introduced the concept of basic emotions, considering them physical reactions that affect the soul and emerge from the interaction between body and mind (Hatfield, 2017). For his part, Hume recognized an integration between the physical and the cognitive, describing emotions as intense impressions influenced by beliefs and perceptions (Lyons, 1999).

On the other hand, Spinoza and Locke emphasized the role of reason and learning in the management of emotions (Bennett, 2001). Similarly, Kant considered emotions as organic and subjective reactions, which had to be controlled to maintain morality (Sorensen, 2002). In a more critical approach, Mandeville argued that emotions, even those seen as vices, are essential for social, economic, and political progress (Chiasson, 1970). Thomas Brown marked a turning point in the study of emotions by categorizing terms like passion and affection under the broader concept of emotion (Dixon, 2011). He aimed to study these feelings more systematically by observing their physical manifestations, signaling the beginning of a more scientific approach to understanding emotions.

➤ Contemporary Age (late 18th or early 19th century CE -present)

In this period, the study of emotions integrated evolutionary, physiological, and cognitive perspectives. Darwin and Spencer highlighted the evolutionary role of emotions in adaptation and survival (C. Darwin, 2003; K. Darwin, 1872; Hess & Thibault, 2009). Wundt introduced a multidimensional analysis of emotions based on three basic dimensions (Reisenzein, 2000), while Brentano and Meinong linked emotions to intentional judgments and values (Chrudzimski, 2009; Iocco, 2019; Montague, 2017). Bain emphasized that emotions involve both mind and body, influencing motivation and behavior (Bain, 1859).

In the late 19th and early 20th centuries, theories emerged that explored the relationship between emotions, body, and mind (Scarantino, 2024). For example, James and Lange described them as physiological responses (Coleman & Snarey, 2011; James, 1884), while Freud and Dewey

highlighted their links with unconscious processes and adaptive behaviors (Stein, 2004). Later, Cannon and Bard argued that emotional and physiological responses occur simultaneously and independently, with the thalamus playing a key role (Cannon, 1927, 1931). Around the same time, Scheler saw emotions as intentional experiences reflecting values, while Watson linked emotions to conditioned responses (Guthrie, 1939; J. B. Watson, 1919). Similarly, Hildebrand connected emotions to moral and aesthetic values (J. M. Müller, 2020).

Building on these early ideas, the discovery of the Papez circuit (Bhattacharyya, 2017) and MacLean's work on emotional systems emphasized the role of brain structures in emotional regulation (Gerald A. Cory & Russell Gardner, 2002). In parallel, Lorenz and Tinbergen linked emotions to instinctive behaviors (Burkhardt, 2005). Tomkins proposed the facial feedback hypothesis (Tomkins, 1995), and Schachter and Singer developed the two-factor theory (Schachter & Singer, 1962).

Subsequently, the cognitive approach gained strength with Arnold and Lazarus, who emphasized subjective appraisal and context in emotional responses (Reisenzein, 2000). Complementing this view, Ekman and Friesen identified universal facial expressions across cultures (Ekman & Friesen, 1971). However, Zajonc argued that emotions can arise without cognitive processing (Zajonc, 1998). Plutchik organized emotions into opposing pairs (Plutchik, 1982), Solomon proposed the opponent process theory, where extreme emotional responses trigger opposing reactions (R. L. Solomon & Corbit, 1974), Lyons stressed that emotions result from evaluative judgments (Dalgleish & Power, 2000).

Affective neuroscience then brought new insights. Panksepp identified seven core emotional systems that guide behavior (Panksepp, 2006). LeDoux demonstrated that emotional responses follow fast and slow brain pathways (LeDoux, 1995, 2000), and linked emotions and bodily changes to decision-making and behavior (Bechara et al., 2000; Damasio, 1998). Goleman highlighted emotional intelligence as a key to personal and social success (Goleman, 2000). Greene showed that emotions influence moral decisions (Greene, 2011), while Nussbaum suggested emotions reflect our core values (Nussbaum, 2004).

Later, Russell proposed the circumplex model, organizing emotions along two axes: arousal and valence (Posner et al., 2005). Thagard's semantic pointer theory integrates thoughts, physiological responses, and evaluations (Kajić et al., 2019). Scherer introduced the process model, where emotions arise from sequential appraisals of stimuli (Scherer, 2009). Izard supported the existence of basic emotions with distinct facial and physiological expressions (Izard, 2007).

In the 21st century, newer perspectives have continued to reshape the field. Barrett challenged the idea of basic emotions, proposing that emotions are culturally and individually constructed (Barrett, 2012, 2017). Fredrickson introduced the broaden-and-build theory of positive emotions (Fredrickson et al., 2000). Friston proposed the predictive coding model (Seth & Friston, 2016). Keltner emphasized the social function of emotions (Keltner & Kring, 1998), while Gross explored emotional regulation strategies (J. J. Gross, 2015). Davidson suggested that emotional styles are based on six dimensions of brain activity (Davidson, 2000).

Finally, Prinz proposed the perceptual theory, where emotions reflect bodily changes (Prinz, 2006), while Tappolet argued that emotions are perceptual experiences with representational content (Tappolet, 2023). Deonna and Teroni supported the attitudinal theory, seeing emotions as evaluative attitudes toward stimuli (Deonna & Teroni, 2015). Roelofs proposed the neurocognitive theory of flexible emotional control, emphasizing the adaptability of emotional responses (Roelofs et al., 2023).

In the digital era, Picard and Breazeal advanced emotional Artificial Intelligence, creating systems that recognize and respond emotionally (Breazeal & Picard, 2006). In a related line of work, Gratch and Pantic contributed to emotional agents, improving human-machine interaction (Breazeal & Picard, 2006).

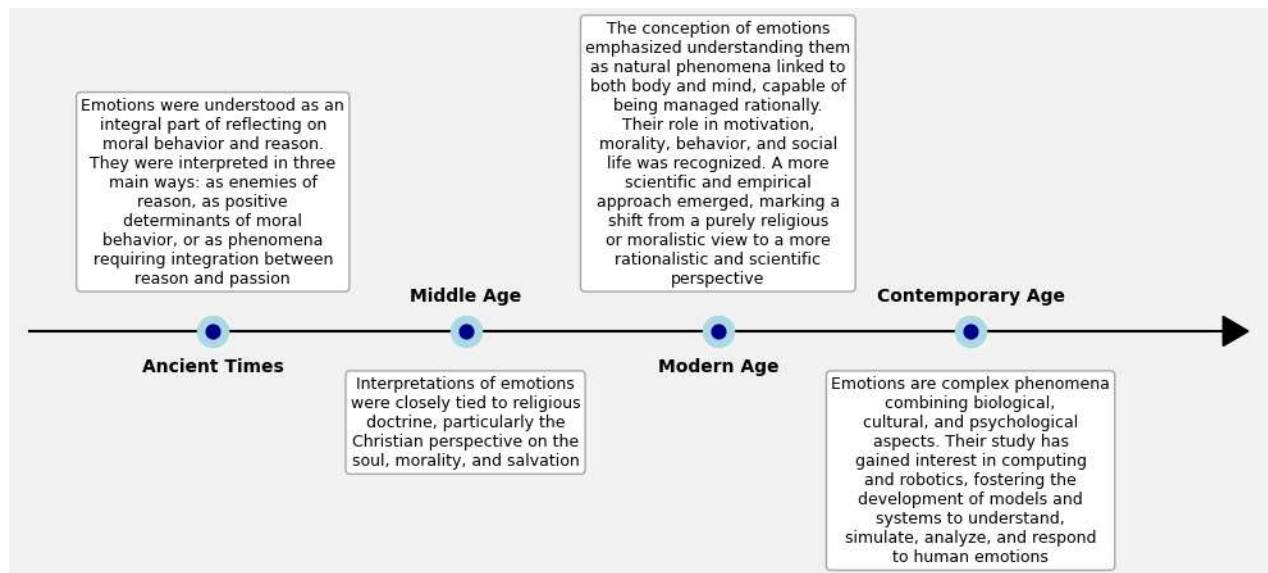


Figure 1.1 Chronological Overview of the Concept of Emotions. Historical perspectives on emotions, from antiquity to the contemporary age

1.1.2 Essential Distinctions: Emotions vs. Feelings

It is common to find the terms emotion and feeling used interchangeably as if they were synonymous. The confusion between these terminologies is due to a mixture of historical, cultural, philosophical, and scientific factors.

Historically, the distinctions between these terms were not clear in ancient and medieval philosophy. Physiologically, they share similar responses, making it difficult to differentiate between them in everyday life. Subjectively, experiences vary between individuals and cultures, creating different perceptions.

Everyday language and cultural conventions simplify these affective states, compounding the confusion. Psychology and neuroscience have not always provided uniform classifications, and the arts and literature often treat these terms metaphorically.

However, as we move forward in these areas, efforts have been made to differentiate them, see for example (Ben-Ze'ev, 2002; Damasio, 2004; M. Munezero et al., 2014). Still, the complex and multifaceted nature of human experience will continue to fuel the confusion.

Emotions are sudden, transient, and automatic reactions that represent a change in mood to an internal or external stimulus. These brief responses involve autonomic, physiological, and endocrine changes and serve an essential adaptive function by enabling the organism to respond quickly and effectively to situations that demand immediate attention and action (Scherer, 2005). Emotions have a universal and unique component. They are universal because basic emotions* (such as happiness, sadness, fear, anger, disgust, and surprise) are biological and shared by all cultures**, with similar expressions/patterns (facial and body). However, their interpretation is unique, as they integrate cognitive components.

*Although there is a consensus on the existence of basic emotions, the debate on their exact number and nature continues.

** Basic emotions are not exclusive to humans; they are also shared with many animals, especially those with complex nervous systems, such as mammals and birds.

Feelings are more stable and lasting affective states than emotions, with a lower intensity but a deeper impact on the person. They persist over time and engage the inner core of the individual, connecting with his or her values, ideals, and what he or she considers essential in life (R. C. Solomon, 2007).

Unlike emotions, which are usually quick and visible reactions, feelings are subjective and conscious experiences that arise from interpreting and evaluating emotions and are not usually manifested externally. Feelings are deeply influenced by personal experiences, thoughts, and cultural factors, making each individual's experience unique and non-transferable. For example,

love (toward family, friendship, homeland, or even ideals such as truth and beauty), gratitude, kindness, resentment, or hatred sustained over time.

Figure 1.2 provides practical examples to help us better understand the comparison between emotions and feelings. It demonstrates how a situation can trigger an emotion that, in turn, generates feelings.

1.1.3 Emotional disorders

Over the past few decades, emotional disorders have undergone ongoing revision, inclusion, and redefinition in diagnostic manuals such as (*Diagnostic and Statistical Manual of Mental Disorders*, 2013). These conditions are characterized by persistent disturbances in the experience, expression, or regulation of emotions, compromising not only subjective well-being but also biological, psychological, and social functioning (Cooper, 2014).

From a functional perspective, emotions such as fear, anger, and sadness serve essential adaptive roles by preparing the organism to respond to threats, cope with loss, or protect vital interests (Plutchik, 1966). However, when these emotions occur with disproportionate frequency or intensity, they lose their adaptive value and become risk factors for both mental and physical health.

The etiology of emotional disorders is complex and multifactorial, involving genetic and biochemical components, a history of stressful or traumatic life events, and personality traits (Schiele et al., 2020). These factors interact dynamically and do not operate in a strictly deterministic manner.

Diagnostically, emotional disorders are primarily classified into three major categories: anxiety disorders, mood disorders, and emotional dysregulation disorders (*Diagnostic and Statistical Manual of Mental Disorders*, 2013).

- Anxiety disorders encompass generalized anxiety disorder (GAD), characterized by persistent worry across multiple areas of daily life; panic disorder, marked by sudden episodes of intense fear; specific phobias; and social anxiety disorder, all involving excessive fear in response to particular objects or situations (Barlow, 2002). A pathological activation of fear is considered central to these conditions, including post-traumatic stress disorder (PTSD), highlighting how its dysregulation can become a key vulnerability factor in psychopathology.

- Mood disorders include major depression, marked by profound sadness, anhedonia, and hopelessness; dysthymia, with a more chronic and less severe course; bipolar disorder, featuring alternating episodes of mania or hypomania and depression; and cyclothymic disorder, involving mild but persistent emotional fluctuations (Akiskal & van Valkenburg, 1994). In these disorders, prolonged and intense sadness functions as a central maladaptive emotion, losing its adaptive value and assuming a pathological form.

- Disorders of emotional dysregulation include borderline personality disorder (BPD) and intermittent explosive disorder, both characterized by intense, uncontrolled emotional outbursts, particularly of anger, that significantly impair interpersonal and emotional functioning (Chapman, n.d.; Coccaro, 2003). In such cases, dysregulated anger forms the emotional core of clinical distress, contributing to impulsivity, relational instability, and functional impairment.

Additional relevant clinical conditions include disruptive mood dysregulation disorder (Baweja et al., 2016), seasonal affective disorder (Magnusson & Boivin, 2003), and complicated grief (Shear, 2015). Although not always formally categorized as emotional disorders, these conditions involve marked disruptions in emotional regulation and expression, underscoring the complexity of emotional functioning and the need for integrative models that address both their adaptive roles and pathological breakdowns.

➤ Influence and challenges of emotion theories in understanding emotional disorders

As outlined in Subsection 1.1.1, various fundamental theories regarding the nature and function of emotions have been proposed over time. These are summarized in Table S1.1.1 for reference. In this subsection, some of these perspectives will be reconsidered in light of emotional disorders to analyze how current clinical conditions illustrate and extend many of the earlier theoretical propositions and pose significant challenges to their most fundamental assumptions.

In Classical antiquity, philosophers such as Socrates, Plato, and Aristotle emphasized the need to align emotions with reason and virtue to achieve well-being.

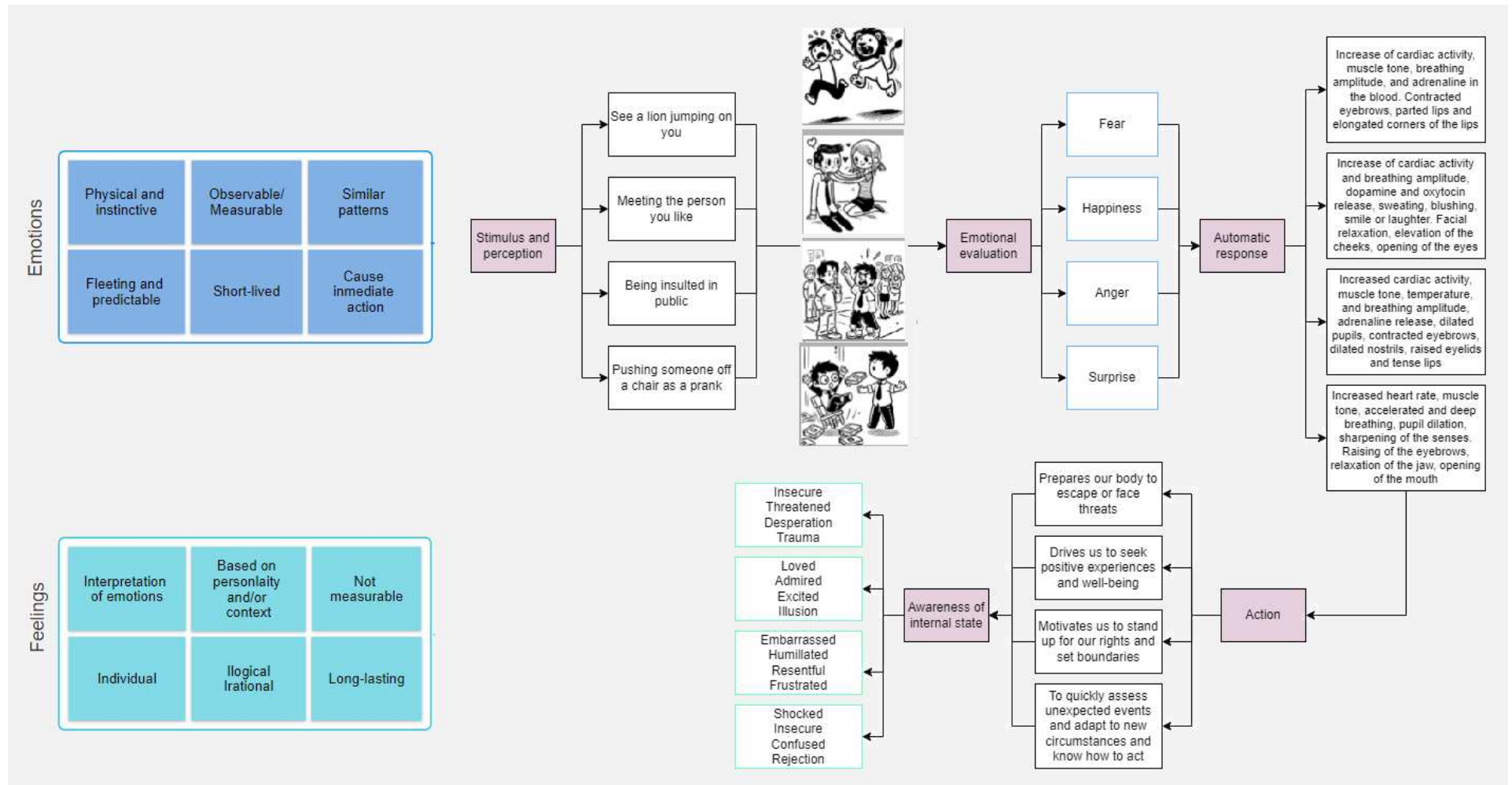


Figure 1.2 Emotions and feelings. Illustration of the distinction between emotions and feelings. Emotions are instinctive, short-lived, and measurable responses that trigger immediate action, while feelings are subjective, long-lasting interpretations shaped by personality and experience. When a stimulus is perceived, the brain generates an emotion, activating physiological responses such as increased heart rate and hormone release. These reactions prepare the body for action, but as the brain processes the experience through past memories, personality, and context, the emotion transforms into a feeling with deeper personal meaning.

Aristotle, in particular, defined emotions as rational reactions suited to context, foreshadowing current cognitive appraisal theories. Similarly, the Stoics advocated the elimination of disturbing emotions through reason, a perspective that resonates with modern models of emotional regulation implicated in disorders such as generalized anxiety disorder and borderline personality disorder. Philosophical and spiritual traditions, such as Pythagorean thought and the teachings of the Bhagavad-gītā, also emphasized emotional self-control, suggesting that its failure could lead to psychological imbalance. However, these frameworks should be understood as cultural and interpretative antecedents rather than direct theoretical equivalents of current concepts of emotional dysregulation.

During the Middle Ages, emotions were reinterpreted through a Christian lens, encouraging emotional repression, an attitude now seen as a potential vulnerability factor for depressive and anxiety disorders. Nonetheless, mystical currents such as those of Saint Teresa of Ávila offered a more positive view of emotions, anticipating contemporary approaches that recognize their adaptive function. While the emotional language of mysticism is not directly equivalent to psychological terminology, it serves as a cultural precursor to the acceptance of emotional experience.

With the advent of Modernity, philosophers such as Hobbes and Descartes introduced more secular frameworks, ideas that laid the foundational ground for current conceptions of automatic emotional responses. However, as previously discussed, emotional disorders illustrate how emotions can become dysfunctional, indicating that mechanistic models must be expanded to include cognitive and contextual dimensions.

The relationship between emotion and cognition was further developed by many authors, such as Hume and Spinoza, who argued that emotions depend on beliefs and perception, an idea that anticipates the role of cognitive distortions in disorders such as social anxiety and major depression. Likewise, Kant and Mandeville stressed the regulatory function of reason over emotions, highlighting the importance of emotional control for individual and societal well-being. However, emotional dysregulation disorders reveal that reason does not always succeed in modulating intense emotions, thereby partially challenging this rationalist perspective.

The evolutionary approach introduced by Charles Darwin framed emotions as adaptive mechanisms for survival, paving the way for physiological theories such as those of James and Lange, who proposed that emotions result from bodily changes. Later studies by Cannon and Bard nuanced this view, suggesting that emotional activation and physiological response occur simultaneously but independently. Although foundational, these theories encounter limitations in explaining clinical phenomena such as panic disorder or post-traumatic stress disorder, where dysfunctional emotions arise without clear environmental stimuli. Such clinical evidence suggests that purely physiological explanations are insufficient to capture the complexity of pathological emotional responses.

Later cognitive models, such as those of Schachter-Singer and Lazarus, posited that subjective interpretation of context determines emotional experience, a key insight for understanding how cognitive distortions sustain disorders like post-traumatic stress disorder and generalized anxiety. From affective neuroscience, Joseph LeDoux demonstrated that fear can be processed rapidly and unconsciously via subcortical pathways, while Karl Friston, through the predictive coding model, argued that emotions arise from errors in the prediction of internal states. Although still under development in clinical contexts, this model offers an innovative lens for interpreting maladaptive emotional responses like anxiety disorders and phobias. Together, these approaches emphasize that emotions can emerge from automatic or predictive processes beyond conscious control, challenging exclusively rational or deliberative accounts. These studies also helped identify key brain regions involved in emotional processing and have driven further research into the neural circuits and mechanisms underlying emotional experience.

Contemporary perspectives on emotion have also been enriched by Lisa Feldman Barrett's theory of constructed emotion, which proposes that emotions are individual and cultural constructions based on learned interpretations of bodily and contextual signals. This approach opens new therapeutic possibilities for anxiety disorders by focusing on reshaping dysfunctional interpretations. Similarly, Richard Davidson's model of emotional styles helps to explain individual vulnerability to disorders such as anxiety and depression through dimensions like resilience, optimism, and self-awareness.

In the field of emotional regulation, James Gross proposed the process model of emotion regulation, distinguishing between antecedent-focused and response-focused strategies. Deficits in these strategies, such as excessive suppression or difficulty in cognitive reappraisal of threatening situations, are implicated in the maintenance of disorders such as general anxiety disorder, panic disorder, and post-traumatic stress disorder.

Dacher Keltner has further argued that basic emotions serve essential social functions, a concept particularly relevant to social anxiety disorder, where emotions like fear of rejection or shame, though adaptive in moderation, can become pathological and inhibit healthy social interaction.

Karin Roelofs' neurocognitive theory of flexible emotional control underscores the importance of adaptability in selecting coping strategies when facing threats or challenges. This framework is particularly relevant for understanding how rigidity or dysfunction in emotional control contributes to the persistence of anxiety disorders.

Finally, the development of affective computing, pioneered by Rosalind Picard, has expanded emotional research into technological applications, enabling the automated recognition of emotional states in clinical settings. Recent advances by Maja Pantic in facial expression analysis and physiological signal detection using deep learning have refined the identification of emotional patterns characteristic of anxiety disorders, potentially enhancing early diagnosis and therapeutic monitoring. However, current technologies still face limitations in interpreting complex and culturally nuanced emotions, posing important challenges for their widespread clinical use.

1.1.4 Computational and experimental models in the study of emotions

Building on the historical theories and clinical foundations outlined thus far, the current subsection introduces three methodological approaches—computational modeling, experimental studies in humans and rodents. These approaches are now seen not merely as complements to traditional frameworks, but as fundamental tools to achieve an integrative understanding of emotional processing and regulation

In recent years, there has been a significant evolution in the understanding of emotions, recognizing them as adaptive mechanisms that influence cognition, behavior, and social interaction. Although neuroscience temporarily abandoned the study of emotions due to the rise of cognitive science and the apparent resolution of the issue through the limbic system theory (LeDoux, 2000), interest has resurged with more sophisticated approaches. The advancement of computational systems has opened new opportunities to simulate complex emotional processes, complementing and, in some cases, replacing traditional experimental methods (Ford, 2016; Rudroff, 2024; Sorguven et al., 2021). Furthermore, the study of emotions in animals has provided valuable insights into their neurobiological basis (Homberg et al., 2021), despite ongoing challenges in terminology and methodology when comparing across species (Anderson & Adolphs, 2014; Zych & Gogolla, 2021).

For emotion research to thrive, it is essential to adopt an integrative approach that enables the study of how the brain processes emotional information without relying solely on subjective experience. The integration of emotion and cognition within a unified framework will not only enrich cognitive science but also provide a more comprehensive understanding of the human mind, acknowledging that emotional and cognitive processes are not opposing forces but rather interdependent and fundamental to understanding brain function (LeDoux, 2000).

➤ Theoretical foundations for building Computational Models of emotions

Computational emotion modeling seeks to address fundamental questions regarding the biological, psychological, and social foundations of affective responses. Its main objectives include (Marsella et al., 2010):

- Biological foundations: Identifying the neural circuits involved in the generation and regulation of emotions (focus of the present study)
- Processing and response: Analyzing how emotional stimuli are perceived, processed, and translated into cognitive, behavioral, and physiological changes.
- Regulation and adaptive function: Exploring strategies that control the intensity and duration of emotions and how they have evolved to enhance survival.
- Influence on mental health and plasticity: Examining the relationship between emotional states and disorders such as anxiety and depression, as well as assessing the capacity for adaptation based on experience.

Computational models are based on the integration of various theoretical approaches (Marsella et al., 2010), including:

- Appraisal Theory: Emotions arise from individual evaluations of events based on personal beliefs and goals. This perspective emphasizes the subjective nature of emotional experiences, highlighting the role of cognitive appraisal in shaping affective responses.
- Dimensional Models: Emotions are represented within a continuous space defined by key dimensions such as valence (positive or negative affect), arousal (intensity of activation), and dominance (perceived control over the situation). This framework provides a quantitative approach to understanding emotional variability.
- Anatomical Approaches: These models focus on the neural circuits underlying emotional processing, such as the cerebellum's role in fear responses (focus of the present study). By mapping specific brain structures to emotional states, they offer insights into the biological mechanisms of emotional regulation.
- Rational Approaches: Emotions are analyzed in terms of their adaptive function in decision-making. This perspective considers emotions as evolved mechanisms that influence judgment, risk assessment, and behavioral strategies to optimize survival and well-being.
- Communicative Theories: Emotions are viewed as essential tools for social interaction, facilitating coordination, communication, and influence among individuals. This approach explores how emotions regulate interpersonal dynamics and contribute to group cohesion.

The decomposition of these complex processes into sub-models facilitates the identification of structural and functional similarities, allowing for the development of simulations. Despite certain challenges in parameter manipulation and the integration of multiple processes, these models serve as a bridge between classical theories and exploratory approaches.

➤ Experimental Studies and Human Models

Research in this field utilizes diverse methods, ranging from objective physiological assessments to subjective self-report instruments, to comprehensively grasp the complexity of human emotional experiences. As outlined by (Mauss & Robinson, 2009; Rogers & Robinson, 2014).

- The objective measurement of emotions focuses on quantifying bodily responses to emotional stimuli, providing direct data on nervous system activity and physiology. Among the most commonly used techniques are: 1) Electroencephalography (EEG) measures electrical brain activity, revealing the speed and patterns of responses associated with different emotional states. 2) Functional magnetic resonance imaging (fMRI) facilitates the identification of brain regions activated during emotional experiences, mapping the neural circuits involved. 3) Electrocardiography (ECG) and skin conductance record changes in heart rate and galvanic response, both considered direct indicators of emotional arousal. 4) Hormone measurement quantifies emotional responses through saliva, blood, or urine samples.

- Subjective emotion measurement addresses the internal and personal nature of emotional experiences through methods such as 1) Surveys and questionnaires, which collect data on the intensity and variation of emotions over time. 2) Pictorial tools are also employed to assess emotional responses in terms of pleasure, arousal, and dominance, facilitating their application across diverse populations. 3) Experience Sampling Method, which involves prompting participants to record their emotions at random intervals throughout the day, thereby capturing the real-time dynamics of emotional experiences in everyday contexts.

On the other hand, facial expression analysis (Wolf, 2015), grounded in the premise that emotions are universally expressed through distinct muscle movements, has evolved with advancements in machine learning and computer vision. These technologies have enabled the development of automated emotion detection systems that objectively quantify facial expressions. However, while the measurement itself is based on observable physiological markers, the interpretation of emotional states remains complex due to cultural variations, contextual influences, and potential biases in algorithmic training.

➤ Experimental Studies and Animal Models

The study of emotions in animals faces challenges in defining key concepts such as emotion, affect, and feeling, given the lack of consensus across disciplines (Anderson & Adolphs, 2014; de Vere & Kuczaj II, 2016). Emotions manifest through behaviors and neural activity, though debate remains on whether they drive behavior or emerge from it. Advances in genetics and

neuroscience provide insight into the evolution of affective states. Studying animal models helps uncover neural mechanisms of emotions, contributing to the understanding of human emotional disorders.

Two main theoretical approaches have been identified: (1) the discrete approach, which posits the existence of basic, innate emotions, each associated with specific neural circuits, and (2) the dimensional approach, which considers emotions as states emerging from a continuous affective spectrum, defined by valence and arousal (de Vere & Kuczaj II, 2016; Mendl et al., 2022). This debate is crucial to avoiding anthropomorphic interpretations and establishing operational criteria that enable the comparison of emotional states between humans and animals.

The study of animal emotions relies on a combination of physiological, behavioral tests (see Figure 1.3 as an example), and cognitive approaches (de Vere & Kuczaj II, 2016; Paul et al., 2005). However, finding valid and objective measures of animal emotions can be challenging. These approaches provide complementary insights. To refine emotion measurement, researchers explore the neurobiological mechanisms underlying affective states by studying key brain structures such as the amygdala, thalamus, ventral tegmental area, prefrontal cortex, etc.

- Techniques like electrophysiological recordings, neuroimaging (e.g., fMRI in select species), lesioning, and electrical stimulation help map the neural circuits involved in emotional processing. Additionally, physiological markers—including hormonal fluctuations (e.g., cortisol and oxytocin levels) and autonomic responses (e.g., heart rate variability)—provide measurable insights into emotional states. Genetic tools further enable targeted manipulation of pathways linked to affective experiences. However, distinguishing between different emotions remains complex, as physiological responses often overlap—heightened arousal, for instance, may signal excitement, fear, or anticipation, complicating the interpretation of an animal's precise emotional experience.

- Behavioral measures provide additional insights, as spontaneous actions like approach-avoidance responses, vocalizations, and facial expressions often indicate affective states. Certain primates display facial expressions homologous to human emotions, while vocal cues in species such as rats and pigs reflect variations in emotional intensity. Controlled behavioral tests, including the open field test and elevated plus maze, are widely used to assess emotional reactivity, though many focus on negative states, limiting their applicability for studying positive emotions.

- Cognitive approaches offer a promising alternative for understanding affective states beyond traditional physiological and behavioral markers. Judgment bias tests reveal that animals experiencing different emotional states interpret ambiguous stimuli differently, while memory biases indicate that mood influences recall patterns. These cognitive markers parallel findings in human psychology, where emotions shape decision-making and perception (Paul et al., 2005).

1.1.5 Fear conditioning, a core model for studying emotional behavior

Behavioral studies have been extensively used to investigate neurobiological aspects of emotions, as illustrated in Figure 1.3. Among these, fear conditioning is one of the most widely used paradigms to investigate emotional learning across species, including both rodents and humans. It elicits clear and measurable behavioral (and physiological) responses, such as freezing in rodents or skin conductance changes in humans, that make it particularly suitable for experimental research. Although the degree of reproducibility may vary depending on methodological factors and species-specific responses, its well-established protocol and translational potential have made it a cornerstone in the study of fear and emotion.

This subsection provides a general introduction to the historical origins of the paradigm, its theoretical foundations, and its relevance for understanding fear as an emotional construct. Detailed experimental applications, including species-specific protocols and the underlying neural circuits, are addressed in Chapters 3 and 4, focusing respectively on rodent and human studies.

Fear is a primary and universal emotion that serves as an adaptive response to real or perceived threats, promoting survival by activating physiological and behavioral mechanisms for fight-or-flight reactions (K. Darwin, 1872). Neurobiologically, it engages specific brain circuits (see subsections 3.1 and 4.1) and induces cardiovascular, hormonal, and cognitive changes. Additionally, fear can be learned through conditioning, enabling organisms to associate neutral stimuli with aversive experiences and anticipate potential threats.

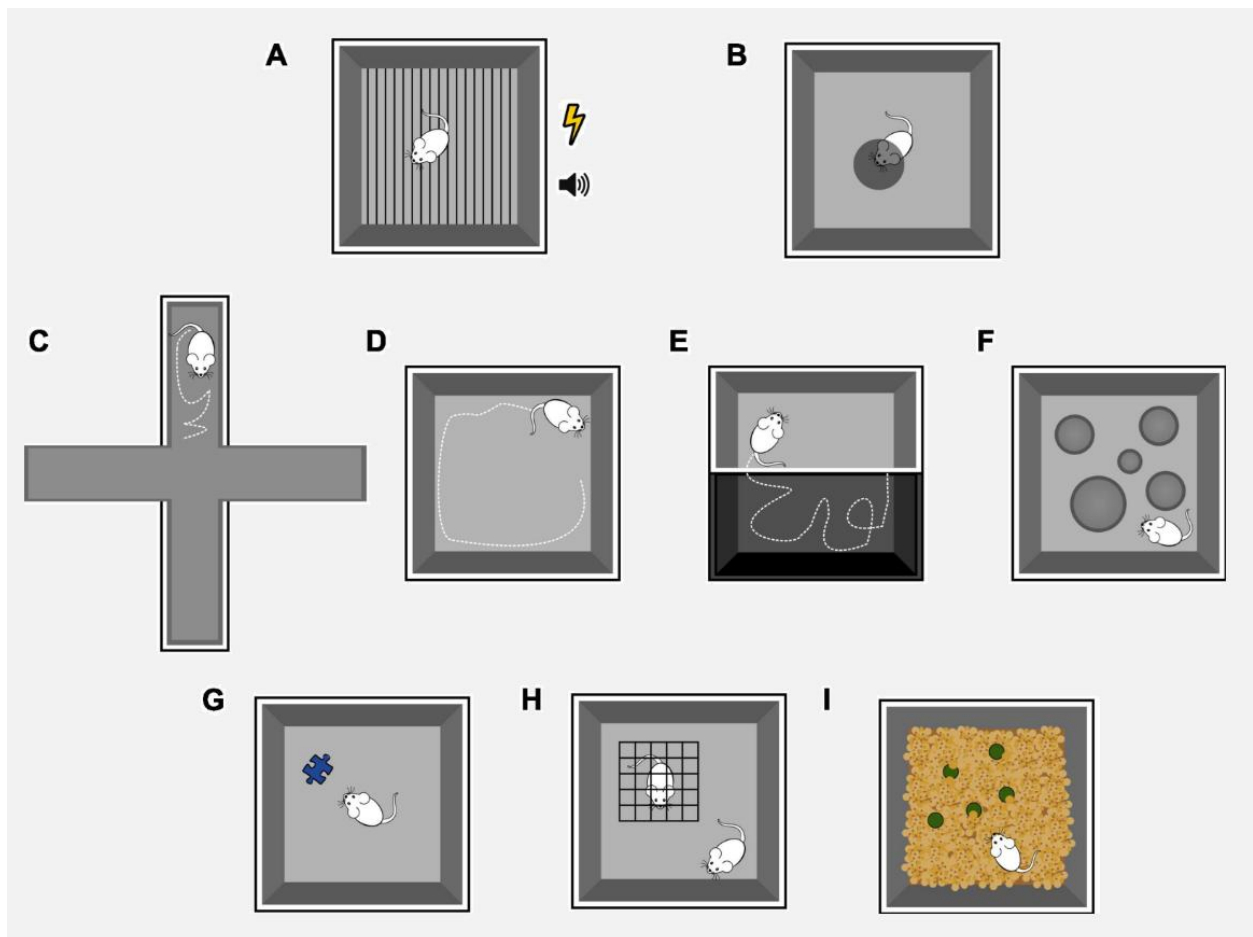


Figure 1.3 Emotional tasks in rodents A) Fear Conditioning: An associative learning task where rodents learn to associate a neutral stimulus with an aversive stimulus, leading to a conditioned freezing response. B) Looming Test: A non-associative fear test using a visual stimulus that mimics an approaching predator (an expanding black disc). It triggers innate defensive responses (escape or freezing). Unlike fear conditioning, it does not generate associative learning. C) Elevated Plus Maze: An anxiety test where rodents explore two open and two closed arms. Avoidance of the open arms reflects increased anxiety, assessing the conflict between exploration and safety. D) Open Field Test: An anxiety test measuring exploration of a bright, open area. Reduced time spent in the center and preference for the edges reflect higher anxiety levels. It assesses exploratory behavior and open-space fear. E) Dark-Light Box Test: Evaluates the conflict between exploration and safety. Rodents are placed in a box with a dark and a lit chamber; hesitation to enter the lit chamber reflects increased anxiety. F) Hole Board Test: Measures exploratory behavior and anxiety by recording the frequency of head dips into holes on a platform. Reduced exploration reflects increased anxiety. G) Novel Object Test: Assesses curiosity and response to novelty. Reduced interaction with a new object reflects increased anxiety or reduced motivation for exploration. H) Social Novelty Test: Measures social behavior by introducing a new rodent. Reduced interaction or avoidance indicates social anxiety or social deficits. I) Marble Burying Test: Measures stress-induced compulsive behavior by counting the number of marbles buried. Increased burying behavior reflects heightened anxiety or compulsive tendencies. Adapted from (Ciapponi C et al., 2023).

The fear conditioning paradigm, a variation of classical Pavlovian conditioning, is employed to investigate the mechanisms of fear and its generalization, given that the underlying neural circuitry is conserved across humans and rodents (J. J. Kim & Jung, 2006). While its development is rooted primarily in experimental and behavioral psychology, it has been progressively refined through the contributions of numerous researchers. Its origins can be traced back to the seminal work of Ivan Pavlov, John B. Watson and Rosalie Rayner, Burrhus F. Skinner, Orval H. Mowrer, as well as Robert Rescorla and Allan Wagner.

Classical conditioning, a phenomenon discovered independently in the United States and Russia in the early 19th century (Clark, 2004), has had a lasting influence on psychology and behavioral neuroscience. In the United States, Edwin B. Twitmyer, through his dissertation work on the conditioned patellar tendon reflex, identified a form of classical conditioning applied to somatic

muscle responses (Twitmyer, 1974). Although his findings did not receive the attention they deserved at the time, their consistency with the modern understanding of classical conditioning and related neurobiology, particularly in the conditioned blink paradigm, is recognized today.

On the other hand, in Russia, Ivan Petrovich Pavlov developed the fundamental principles of this phenomenon, with his conditional reflex experiment with dogs (Pavlov (1927), 2010), known today as the stimulus-response theory, the Pavlovian conditioning model, or the associationist theory of learning. This approach has been adapted in various contexts within the study of learning and behavior (Moore, 2012), and continues to be a key element in the understanding of how organisms acquire and modify their responses to environmental stimuli.

John B. Watson, excited by the discoveries of Ivan Pavlov, proposed that classical conditioning not only explained learning in animals but also in humans. Together with Rosalie Rayner, he argued that emotions could be learned through conditioned associations (J. B. Watson & Rayner, 1920) and suggested that differences in human behavior derive from the lived experiences of each individual. His famous Little Albert experiment empirically demonstrated that emotions such as fear could be conditioned in humans, marking a milestone in behavioral psychology by proving that emotions are not exclusively innate.

Although he faced criticism for his reductionist approach, ignoring internal mental processes such as cognition, memory, and intrinsic motivation, and his experiments were questioned for their ethical implications, his work laid the foundation for the study of fear conditioning, a paradigm that remains crucial in psychological and neuroscientific research, highlighting the importance of associative learning in understanding the human mind.

B.F. Skinner, influenced by Watson and a scientific and experimental view of psychology, developed the concept of operant or instrumental conditioning (Skinner, 1965), arguing that behavior is shaped by the consequences that follow: if an action has pleasant results, it is more likely to be repeated, while unpleasant consequences reduce its recurrence. This theory emphasizes the role of reinforcement and punishment in the acquisition and maintenance of behaviors.

Orval Hobart Mowrer extended the ideas of Pavlov and Skinner by integrating negative reinforcement to explain how avoidance behaviors reinforce fear and anxiety over time, with his bifactor theory (Mowrer, 1939) explaining that fear and phobias begin through classical conditioning, when a neutral stimulus is associated with a feared stimulus, and is perpetuated by operant conditioning, through avoidance and negative reinforcement. This theory became key to understanding not only the acquisition of fear, but also its maintenance and generalization.

Later, Robert A. Rescorla and Allan R. Wagner (Wagner & Rescorla, 1972), revolutionized the study of associative learning by providing a theoretical and quantitative explanation of how associations between stimuli and responses are formed and modified. This model introduced concepts such as surprise and the predictive ability of the conditioned stimulus (CS), and highlighted the influence of contextual cues on learning, extending not only Pavlov's original ideas, but also helping to understand and contextualize Watson's ideas, advancing the mechanistic understanding of fear learning at both the behavioral and neural levels (Paskewitz et al., n.d.; Yau & McNally, 2023)

Despite the mixed reception, the mathematical model had a significant impact, being considered a landmark in learning research and applicable in diverse contexts beyond animal conditioning. Its influence (Siegel & Allan, 1996; Soto et al., 2023) lies in its generalist approach, which highlights the dynamic interaction between stimuli and context, providing fundamental tools to advance the understanding of human and animal learning.

Its evolution has facilitated the development of computational approaches to analyze complex relationships and multiple phenomena in fear conditioning and responses (Gershman, 2015; Mattera et al., 2020), as well as the integration of biologically realistic computational models. When combined with experimental data, these models have advanced the understanding of neural circuits underlying fear and their dysfunction in mental disorders (Nair et al., 2016).

Today, the fear conditioning paradigm has evolved to become a crucial tool in psychology and neuroscience. Its great translational value allows its application in both animal and human studies (Delgado et al., 2006), as well as in clinical populations (Eelen & Vervliet, 2006; Fullana et al., 2020), contributing significantly to the advancement in the study and treatment of mental disorders.

Supplementary material

Table S1.1.1.1 Evolution of the concept of emotions and theories over time*	
Influential Thinker / Author	Key concepts / Theories
Ancient Age (Classical Antiquity 8th century B.C. to 5th century A.D.)	
6th century B.C. Pythagoras (Greece)	Harmony and balance in the soul are key to health and emotional well-being.
5th century B.C. Heraclitus (Greece)	Reality is a flux of constant opposites in tension; inner conflict and emotion are natural to human experience.
5th century B.C. Gorgias and the Sophists (Greece)	Emotions can be influenced and manipulated through language and rhetoric.
5th century B.C. Democritus (Greece)	Peace of mind, and happiness is achieved through moderation and emotional control.
5th century B.C. Bhagavad-gītā (Indian)	Anger and desire are obstacles in the search for peace and spiritual balance.
5th-4th century B.C. Socrates (Greece)	Emotions must be aligned with virtue and reason to live ethically.
4th century B.C. Plato (Greece)	The emotions in the “irascible” part of the soul (thymos) must be balanced by reason.
4th century B.C. Aristotle (Greece)	Defines and analyzes emotions as rational reactions, linked to perception and context.
1st century A.D. Epicureanism Epicurus (Greece)	Emotions are states of the soul derived from beliefs about external goods and desires, considered to be negative.
1st century A.D. Epicureanism Lucretius (Rome)	Negative emotions are the product of irrational beliefs that through knowledge, control of fear and desire, and moderate pleasure, inner peace and a happy life can be achieved.
3rd-2nd century B.C. Stoicism Zeno of Citium (Greece)	Disturbing emotions must be eliminated to achieve tranquillity and reason.
1st century B.C.-1st century A.D. Stoicism Seneca, Epictetus, Marcus Aurelius (Rome)	Emotions must be controlled by reason; well-being is achieved by accepting fate and avoiding irrational emotional reactions.
Middle Ages (~5th-15th centuries A.D.)	
4th-5th centuries A.D. Late Antiquity-Early Middle Ages St. Augustine	Emotions arise from the passions of the soul, triggered by external stimuli, and can divert people from the love of God. They must be understood in their causes and mastered by the will and reason to live in harmony with God.
1225-1274 Middle Ages St. Thomas Aquinas	Emotions are considered automatic reactions of the body to what is perceived as good or bad, and not free choices. These emotions, although natural, must be moderated by reason to align with the divine will.
1509-1564 Protestant Reformation Calvinism	Emotions are seen as signs of human corruption, associated with weakness due to original sin.
1515-1591 Counter-Reformation St. Teresa of Avila, and St. John of the Cross	Emotions are spiritual experiences, which are lived as expressions of divine love and are tools to reach union with God.
Modern age (15th- late 18th or early 19th century)	
1588-1679 Thomas Hobbes	Emotions are guided by hedonistic principles; that is, our behavior is oriented towards the pursuit of pleasure and the avoidance of pain.

1596-1650 René Descartes	Descartes introduced the concept of “basic emotions” and classified the emotions into six primary ones: admiration, love, hate, joy, sadness and desire. He saw them as passions of the soul provoked by movements in the body, and described them as physical reactions affecting the soul, resulting from the interaction between the body and the mind.
1632-1677 Baruch Spinoza	Emotions are affects linked to our perception and ability to act rationally. Understanding their causes allows us to manage them better, since they reflect immutable natural laws. Although mind and body are connected, they do not directly control each other.
1632-1704 John Locke	Emotions are responses that arise from our sensory experiences and the ideas we construct from them. They can be shaped through education and learning, allowing them to be studied as phenomena influenced by environment and training.
1670-1733 Bernard Mandeville	Emotions, often seen as vices, are fundamental to social and economic progress as they foster sociability and the building of society, and must be understood through their outward expressions. He criticizes the traditional idea of virtue as sacrifice, arguing that true virtue is masked by rational egoism.
1711-1776 David Hume	Emotions are intense physical impressions that can arise directly from pleasure or pain or indirectly, influenced by beliefs about the object that causes them, thus integrating both a physical and cognitive dimension.
1724–1804 Immanuel Kant	Emotion is an organic reaction without direct cognitive content, but related to mental representations. It is part of “feeling”, which encompasses the subjective dimension of experience. Emotions, generally considered weak, require control to maintain morality and well-being.
1778-1820 Beginning of the Contemporary Age Thomas Brown	The term emotion is popularized, replacing and/or grouping the ideas of affection, passion and appetites. His approach marked the beginning of the creation of a specific semantic field for emotions, proposing a study of feelings through experiments and anatomical observations, focusing on visible phenomena such as clenched teeth, tears or shivering.
Contemporary Age (late 18th or early 19th century CE -present)	
1809-1882 Charles Darwin	Emotions have an evolutionary origin and are universal, influenced by adaptation and survival. He emphasized that emotional expressions have a biological basis and are similar in diverse cultures and species.
1818–1903 Alexander Bain	Emotions are reactions that involve both the mind and the body, are interconnected with thoughts and physical movements, and play a crucial role in human motivation and behavior.
1820–1903 Herbert Spencer	Emotions, with an evolutionary basis, are crucial for human adaptation. He did not distinguish emotions from cognition; he believed that the two differ only in their emphasis and cannot exist entirely independently of each other.
1832–1920 Wilhelm Wundt	Emotions are explained by the conjunction of three bipolar dimensions: pleasure-pleasure, arousal-calmness and tension-relaxation. These basic dimensions merge six elementary forms of feelings: pleasure, displeasure, arousal, inhibition (tranquillization), tension and relaxation. Complex emotions result from the combination of these sensations

	directed at the different aspects of a complex situation or object.
1838-1917 Franz Brentano	Emotions, being based on intentional judgments, are key to recognizing value and motivating action. Their evaluative nature underpins an objective understanding of values, guiding our responses to them.
1842-1910 William James 1834-1900 Carl Lange	Emotions are the result of physiological responses to external stimuli. A physical reaction is first produced in the body and, as a consequence of this response, the emotion arises.
1853-1920 Alexius Meinong	Emotions are linked to the values and judgments we ascribe to objects, even though these values may exist independently. They are not isolated states but reflect our valuation of objects in terms of our desires and goals.
1856-1939 Sigmund Freud	Emotions consist of discharges of physical energy and feelings of pleasure or displeasure, originating from repressed desires or internal childhood traumas. These emotions, related to unconscious processes, arise to release accumulated instinctive energy and significantly affect our decisions and behaviors.
1859-1952 John Dewey	Emotions arise from conflicts in behavior, reflecting psychological and bodily adjustments, placing emotion at the center of rational behavior. Emotions prepare the organism to act, and are linked to both body and mind, playing an active role in adapting to the environment.
1871-1945 Walter Cannon 1898-1977 Philip Bard	Emotions and physiological responses occur simultaneously and autonomously, not one as a consequence of the other. The brain, especially the thalamus, plays a crucial role in this process.
1874-1928 Max Scheler	Emotions are intentional experiences, arising as reactions to the perception of values (Reactive theory of emotions). Emotions range from endogenous unmotivated to reactive motivated, and range from somatic to psychological and spiritual roots. These are categorized as: sensory feelings, localized in the body and manifested as physical discomforts. Vital feelings are more general and without specific localization, such as moods. Psychic feelings are detached from the body and present themselves as worries. Finally, spiritual feelings are transcendent and reflect a person's way of being.
1878-1958 John B. Watson	Emotions and behaviors are learned through experiences and stimulus-response associations, and are not innate or internal phenomena. Humans are born with basic emotional responses such as fear, anger and love, which are triggered by specific stimuli. All other complex emotions are learned through conditioning.
1883-1958 James Papez	Emotions have a specific brain circuit, known as the "Papez circuit". Emotional experiences occur when the cingulate cortex integrates signals received from the evolutionarily new part of the lateral cortex and from the hypothalamus. The information leaving the cingulate cortex to the hippocampus and from there to the hypothalamus allows the thoughts that take place in the cerebral cortex to control emotional responses.
	Emotions are not mere physiological reactions, but affective responses deeply linked to what we consider valuable,

1889-1977 Dietrich von Hildebrand	whether positive or negative (Reactive theory of emotions). These emotions, which can be directed toward aesthetic, ethical or spiritual values, have a significant moral dimension, as they reflect our moral evaluations of the world.
1903-1989 Konrad Lorenz 1907-1988 Nikolaas Tinbergen	Emotions have evolutionary roots and are closely linked to instinctive and adaptive behaviors. Lorenz highlighted aggression and attachment as essential instincts for survival and social cohesion, while Tinbergen provided a framework for analyzing how these behaviors evolve, develop, and function.
1903-2002 Magda Arnold	Emotions arise from a subjective evaluation of stimuli, intuitively considered as good or bad. Before a stimulus elicits an emotional response, the brain evaluates its meaning, influenced by previous experiences and beliefs, and this motivates behaviors to move towards desirable stimuli or away from undesirable ones.
1911-1991 Silvan Tomkins	The activation of certain facial muscles can induce the corresponding emotion (Facial feedback hypothesis). Each of the basic emotions (fear, anger, happiness, happiness, disgust, interest, surprise, contempt and shame) has a characteristic expression based on a neurological program, which amplifies behavior and affects our motivations.
1913-2007 Paul MacLean	There are three brain components: the reptilian brain, the limbic brain, and the neocortex. The limbic system in the brain is responsible for regulating and processing emotions. Structures such as the amygdala are responsible for the detection of emotional stimuli.
1922-2002 Richard Lazarus	Emotions arise from a cognitive appraisal of events, followed by an emotional response and a physiological response (Cognitive Appraisal Theory). It consists of four stages: stimulus, cognitive appraisal, emotional response and physiological response. This order is constant in all situations, highlighting that emotions and physiological responses depend on the interpretation of the event.
1922-1997 Stanley Schachter 1934-2010 Jerome Singer	Emotions are the result of physiological activation followed by cognitive interpretation (Two factor theory of emotions). First, the body experiences a physical response, then, this activation is interpreted according to the context, determining the specific emotion experienced.
1923-2008 Robert Zajonc	Emotions can arise without prior cognitive processing. Emotional responses such as liking or disliking can be automatic and do not require rational evaluation. Emotions can develop simply through familiarity with stimuli, known as the “mere exposure effect.”
1923-2017 Carroll Izard	There are basic and discrete emotions (fear, anger, shame, contempt, disgust, guilt, suffering, interest, surprise and joy), each with its own facial expression and physiological activation pattern (Differential Emotion Theory). These basic emotions are innate and essential, whereas “emotional schemas” are patterns of reasoning and behavior that develop over time and are influenced by culture and experience.
1927-2006 Robert Plutchik	Organizes the basic emotions into opposing pairs (Wheel of emotions): joy versus sadness, anger versus fear, trust versus disgust, and surprise versus anticipation. This taxonomic model illustrates how emotions can vary in intensity and combine to form more complex emotional states, similar to the mixing of primary colors.

1927-2016 Marvin Minsky	Human intelligence and emotions are the result of the interaction of multiple agents in the brain. Machines could simulate or respond to emotional processes.
1933- Wallace Friesen	Emotions are universal responses, together with Paul Ekman explained how to identify them and how to detect when people try to mask, simulate or neutralize them. He also emphasized that gestures and facial expressions not only communicate emotions, but also regulate social interaction and enrich spoken language.
1934- Paul Ekman	There are both positive and negative universal emotions (happiness, sadness, anger, surprise, fear, disgust and contempt), shared by all cultures and races, each associated with specific facial expressions that can be classified and measured with a Facial Action Coding System (FACS). Emotions influence our perception, thoughts, and actions, and, although brief, when expressed continuously, they become states of mind.
1941- William Lyons	Emotions arise from cognitive and evaluative assessments of the stimuli we perceive, comparing the situation with our expectations, values and beliefs (causal-valuational theory). They are complex processes that integrate internal and external factors, and can be regulated by cognitive reinterpretation and subjective appraisal, aligning with our goals and desires.
1942-2007 Robert Solomon	Emotions are actions we take, not simply conditions that occur to us, and therefore we are responsible for them. He suggests that the brain counters extreme emotional stimulation with opposite reactions, thus avoiding emotional extremes (opponent process theory). He also argues that emotions are judgments about our situation and our relationships with the world, where the judgment itself is the emotion, challenging the idea that emotions are passive events (Judgment theory of emotions).
1943- Klaus Scherer	Emotions result from a series of sequential evaluations of stimuli, which organizes different organ systems and synchronizes cognitive and physiological factors. Each phase of evaluation (novelty, relevance, consequence, and control or coping) contributes to the final emotional experience, affecting facial expression, tone of voice, physiological state, and readiness for action. Emotions are considered adaptive, helping the organism to respond effectively to changes in the environment.
1943-2017 Jaak Panksepp	There are seven fundamental motivational systems (Curiosity/seeking, Fear/anxiety (mistrust), Anger/anger (empowerment), Sexual desire/passion, Nurturing/fundamental care of the other, panic/suffering (sadness), and play (social joy)) which, depending on the situation, will activate one, several or others. These motivational systems, which encompass hormonal, neurological, and muscular aspects, drive our actions to satisfy needs, are located in subcortical regions of the brain and are similar in all mammals. They activate hormones that set the neurological system in motion and lead to actions to seek balance and adaptation.
	Emotions are physical-chemical processes that regulate life and seek the balance of the organism. Feelings, as mental

1944- Antonio Damasio	correspondences of emotions, help to preserve life. Emotions and bodily changes (somatic markers) guide decision making, influence behavior and allow rapid reactions, interacting in a complex brain network.
1946- Daniel Goleman	Emotions are powerful and mastering them is key to developing practical skills that strengthen our relationships and foster success in different areas of life. Emotional intelligence involves recognizing, understanding and managing both our emotions and those of others. It is based on two key skill sets: intrapersonal competencies, such as self-awareness, motivation and self-control, which help us navigate our inner world, and interpersonal competencies, such as empathy and relational skills, which enhance our interactions with others.
1947- Joshua Greene	Emotions strongly influence quick and instinctive moral decisions, whereas more deliberate and thoughtful decisions may be more influenced by logic and reasoning (Dual process theory).
1947- Martha Nussbaum	Emotions, fundamental to ethical reasoning and with deep cognitive value, are cognitive evaluations that reflect judgments about what matters deeply to us. These are not automatic reactions, but responses based on how we interpret and value events or situations based on their relevance to our goals, desires, or values (Judgment theory of emotions). Emotions such as compassion and indignation promote social justice and empathy, influencing both ethics and politics.
1947- James A. Russell	Organizes emotions in a circular space along two axes: arousal, which describes the intensity of the emotion, and valence, which indicates whether it is perceived as positive or negative, with opposite emotions on opposite sides. This model helps to understand and manage emotions by showing how they vary in intensity and combine in response to significant events (Circumplex Model of Emotions). Emotions are constructed from basic affects, helping to understand how emotions are perceived and experienced in different cultural and psychological contexts (Theory of the psychological construction of emotions).
1949- Joseph LeDoux	Emotions, especially fear, are fundamental to survival and that the brain circuits involved in this process are adaptive. People experience fear and anxiety before recognizing a threat, and then must use rational thinking skills to determine whether the threat is legitimate. Emotions can be processed through two routes in the brain: a fast, automatic route, involving the amygdala, and a slower, more deliberate route, involving the cortex. The fast route allows immediate emotional responses without conscious intervention, while the slow route involves a more detailed evaluation.
1950- 21st Century Paul Thagard	Emotions are like packages of emotional programming unique to each person (Semantic pointers Theory). A semantic pointer includes: a real situation that triggers a reaction, the evaluation of that situation, a physiological reaction (such as nervousness or calmness), and our experience and personality. These pointers evoke emotions that allow us to react quickly, as they integrate thoughts and physiological triggers. They can also explain emotional ambivalence, such as feeling love and hate simultaneously, due to the activation of two opposing semantic pointers.

1951- 21st Century Richard Davidson	Each person has a unique emotional style based on six dimensions (Emotional Style Theory): resilience, general outlook, social intuition, self-awareness, context sensitivity, and attentional style. These dimensions are reflected in the activity of specific neural circuits in the brain, which can be trained to improve emotional adaptation, with applications in psychological therapies and mindfulness practices.
1959- Karl Friston	The brain uses internal models to predict and interpret bodily states, which contributes to the generation of emotions (Theory of predictive coding of emotions). These are not pre-programmed or fixed, but are constructed from predictions and sensory feedback. Emotions not only respond to the environment, but are also modeled by the brain's anticipations and surprises.
1961- Christine Tappolet	Emotions depend on a cognitive basis that provides the objects and their natural properties. Emotions are perceptual experiences; they have a representational content and can be correct or incorrect depending on whether their objects exemplify the evaluated value (Perceptual theory of emotions). Emphasizes that emotions are non-conceptual representations of evaluative facts, but not perceptions in a strict sense (Receptive Theory of emotions). Emotions do not depend on specific stimuli nor are they tied to a specific sensory modality, instead, they analogously represent their intentional objects with properties such as being fearful or admirable.
1961- 21st Century Julien Deonna 1974- 21st Century Fabrice Teroni	Emotions are irreducible evaluative attitudes that are not reducible to other mental states such as beliefs or perceptions (Attitudinal theory of emotions). Emotions are correct if their object exemplifies the relevant value, but their correctness does not depend on the truthfulness of their content.
1962- 21st Century Dacher Keltner	Fundamental human emotions, such as happiness, fear, sadness, disgust, surprise, and anger, are universal and are manifested by specific facial expressions and physiological responses. Suggests that emotions can be organized in a semantic space (Semantic Space Theory) based on their characteristics and contexts. All emotions have an adaptive purpose in social life, even envy can lead to positive aspects if properly managed. Emotions such as sadness, anger, and fear connect us deeply with others, foster empathy, and act as crucial alerts in our lives.
1962- Rosalind Picard	Emotions are a form of intrinsic intelligence that can be used to humanize technology and have a positive impact on society. Digital systems can recognize and respond to human emotions, using data such as physiological signals, facial expressions, and tone of voice (Affective AI).
1963- 21st Century Lisa Feldman Barrett	Emotions are not automatic or universal responses but are active constructions of the brain, influenced by cognitive, social and physiological processes (Theory of emotion constructed). Emotions are formed from the interaction between past experiences, social and cultural context, and subjective perceptions. The brain categorizes ambiguous bodily sensations into emotions based on learning and context, in the absence of biologically determined basic emotions. This

	implies that emotions are the result of human consensus and vary according to culture and individual experience.
1964- 21st Century James Gross	People employ different strategies (situation selection, situation modification, attentional deployment, cognitive change and response modulation) to modify the intensity and duration of their emotions (Theory of emotional regulation). These emotional regulation strategies occur at different times in the emotional process, antecedent-focused regulation (before the emotion is fully developed) and response-focused regulation (after the emotion has been fully experienced).
1964- 21st Century Barbara Fredrickson	Positive emotions, such as joy, gratitude, serenity, interest, hope, pride, fun, inspiration, amazement, and love, not only generate immediate well-being, but also contribute to the development of long-term resources (The broaden-and-build theory of positive emotions). These emotions broaden our perspective and mental flexibility, strengthening psychological, social, cognitive, and physical capacities.
1965- 21st Century Jesse Prinz	Emotions are perceptions of bodily changes that inform us about relevant situations in our environment (Perceptual Theory of Emotion). These perceptions are evaluative, informing us whether something is good or bad for us based on its relevance. Influenced by biological and cultural factors, emotions develop with experience, generating situation-specific responses, and explaining emotional valence, distinguishing why some emotions are positive and others negative.
1965- 21st Century- Digital Age Jonathan Gratch	Emotions are complex processes that reflect evaluations and responses to specific situations. Advances in technologies such as artificial intelligence and machine learning make it possible to explore and model them more accurately and deeply. Emotional agents (human-like software agents) not only recognize and simulate human emotions but also social and decision-making behaviors.
1967- 21st Century- Digital Age Cynthia Breazeal	Emotions are key to humanizing technology, making it more accessible and enjoyable. Robots have the potential to understand, express, and respond to human emotions. They can interpret emotional cues, such as facial expressions, tone of voice, and behavior. As a result, robots can communicate emotionally with people through gestures and facial expressions, enabling them to interact meaningfully in social settings (Emotional and social robotics).
1970- 21st Century- Digital Age Maja Pantic	Emotions are a window to our inner self; with deep learning, they can be analyzed and recognized through facial expressions and physiological signals (Emotional AI). Improve the efficiency of machines in interpreting human signals, optimize human-machine interaction, and create more natural and adaptive systems.
1972- 21st Century Karin Roelofs	Emotions are adaptive brain responses to threatening or challenging situations (freezing responses), designed to guide behavior toward the most appropriate action, such as approach, avoidance, or coping. Regulating emotions involves a dynamic process that depends on the evaluation of the context and the interaction between brain structures, such as the lateral frontal pole, cortical and subcortical systems (Neurocognitive Theory of Flexible Emotional Control).

* This table represents a careful synthesis of key elements and is not intended to be exhaustive or definitive.

Section 1.2: The cerebellum as a new piece in understanding emotional processing

This section is adapted from Ciapponi, C., Li, Y., Osorio-Becerra, Dianela A., Rodarie, D., Casellato, C., & Mapelli, L. (2023). *Variations on the theme: focus on cerebellum and emotional processing*. *Frontiers in Systems Neuroscience*, 17:35. <https://doi.org/10.3389/fnsys.2023.1185752>.

1.2.1 Comprehensive overview of Cerebellar structure, function, and connectivity

The cerebellum contains a well-defined set of cells and fibers and is organized in *parasagittal modules* and *transverse zones*, which are further subdivided based on biochemical mapping (Figure 1.4). The intersection of these sagittal and transverse maps generates smaller units called *cortical microzones*, which, once connected to the deep cerebellar nuclei (DCN) and inferior olive (IO) neurons (see abbreviation list), form the *olivo-cortico-nuclear microcomplexes* (Apps et al., 2018; Apps & Hawkes, 2009).

The concept of microcomplex now roots in the specific organization of the climbing fibers (CFs) emitted by the IO and in their projections to Purkinje cells (PCs) and DCN cells (Apps & Hawkes, 2009) (Figure 1.5). Indeed, CFs first contact DCN cells and then branch on the sagittal plane, contacting several PCs (about 7 in rodents). These PCs in turn project back to the same DCN cells receiving a common IO input, and then these DCN cells, through inhibitory interneurons, project to the same IO neurons that generated the CF, forming a closed loop circuit. Mossy fibers (MFs) are the other major inputs to these circuits. Opposite to CFs, MFs spread on the transverse plane (some branches can cross the midline, reaching the contralateral cerebellum) and do not respect the borders of microcomplexes. And parallel fibers (PFs), the axons of granule cells (GrCs), bifurcate in the molecular layer, traveling transversally and connecting regions several millimetres away. In addition, intrinsic biochemical properties of PCs generate maps, often referred to as stripes (Apps & Hawkes, 2009) oriented along the longitudinal axis, increasing the possibility for MFs to intercept regions with different PC properties. Recently, *Zebrin II* (Aldolase C) positive and negative stripes have been identified (Figure 1.4). The zebrin stripes largely overlap with longitudinal cerebellar modules to generate microzones (Apps & Hawkes, 2009) and PCs within a microzone show synchronous firing when activated by the IO loops through the CFs (Witter & De Zeeuw, 2015).

Functionally, zebrin stripes show *upbound* and *downbound* properties depending on CF connectivity, PC discharge regulation, and PF-PC long-term depression. Thus, we have an intricate mesoscopic organization that overlaps with a broad mapping of anatomical subdivisions to bodily and mental functions. This brings about two main consequences. First, specific behavioral functions impinge on complex anatomic-functional maps made of many microcomplexes and patches rather than on simple maps residing in uniform cerebellar regions and differentiated by their input-output connectivity. Secondly, mapping of bodily and mental functions involves multiple cerebellar regions, mostly due to the distribution of MF terminal branches and PFs. These considerations challenge the historical view that the cerebellum is made of multiple parallel non-communicating processing units, leaving space to what we may call “multimodal fusion”. As a consequence, the focus moves from the definition of cerebellar functions on a pure anatomical basis to that of the cerebellar algorithm that operates with different inputs and outputs (D’Angelo & Casali, 2013). This algorithm, in turn, might be tuned depending on the local properties of the microcomplexes that are involved.

➤ Function

Independent of the nature of the inputs, be they motor, sensory, cognitive, or emotional, the cerebellum is thought to implement a core algorithm that learns to predict the precise timing and sequence of correlated events (D’Angelo & Casali, 2013). This capacity allows the cerebellum to establish causal relationships between sequential afferent signals and generalize its predictive function across a variety of contexts: from coordinating motor primitives to associating sensory stimuli in classical conditioning, or even manipulating abstract elements during logical or emotional processing. In voluntary behavior, the cerebellum compares motor intention (via descending cortico-cerebellar pathways) with sensory feedback, enabling error prediction and real-time correction, which generates the hallmark precision of vertebrate motor control.

revealing a complex set of neuronal and synaptic properties that can generate the input-output transformation and plastic changes required to process the input signals, for review see (De Schepper et al., 2022). The circuit operates a complex spatio-temporal transformation of the MF input and uses the CF input to drive plasticity. On top of this, the circuit governs intrinsic oscillatory dynamics that allow the time correlation of the processes involved (D'Angelo, 2011; D'Angelo et al., 2011).

➤ Cellular and circuit variants in the rodent cerebellum

Since the cerebellar computational algorithm is likely to be tuned depending on the local properties of microcomplexes, it is important to consider how circuit properties vary across cerebellar regions. This section is based on rodent studies, in which accurate investigations have addressed the molecular and cellular mechanisms and the potential sources of heterogeneity underlying functional specialization.

Anatomical and physiological studies have shown that the midline cerebellar vermis is particularly involved in emotional processing and that lesions and other interventions on this cerebellar compartment affect emotion-related behaviors (reviewed in (Apps et al., 2018)). The cerebellar vermis receives olivo-cerebellar (CF) input from the caudal medial accessory olive and emits a cortico-nuclear output to the medial (fastigial) cerebellar nucleus, which, in turn, has widespread projections to the cingulate cortex, prefrontal cortex, parietal cortex, amygdala, hypothalamus, hippocampus, periaqueductal gray, and striatum (Blatt et al., 2013; Rolls, 2019; Voogd & Ruigrok, 2004) (see also chapter 3).

Different cerebellar vermal lobules are associated with different aspects of emotion (see Figure 1.3). From rostral to caudal: lobules IV–VI with fear learning/memory and affective state; lobule VI–VII with orientation of gaze; lobule VIII with fear-induced freezing behavior; and lobules IX and X with cardiorespiratory control (Apps et al., 2018). Different parts of the vermis could therefore regulate and integrate the cognitive, motor, and autonomic aspects of fear-related behavior (Clausi et al., 2017).

➤ The cerebellar microcircuit and its variants

The cerebellar circuit includes several cell types connected according to the general circuit scheme shown in (Figure 1.5A and 1.6). A recent modeling work summarized the general knowledge on the cerebellar microcircuit, generating a reference ground-truth that binds together structure, function, and dynamics (De Schepper et al., 2022). In the granular layer, each glomerulus hosts ~50 excitatory and ~50 inhibitory synapses on as many GrCs dendrites, plus ~2 excitatory synapses on basolateral dendrites of as many Golgi cells (GoCs). Each one of the 4 GrCs dendrites receives an excitatory and (in most cases) an inhibitory input from as many different MFs and GoCs, respectively. Each GoC receives ~320 ascending axon (AA) synapses on basolateral dendrites and ~910 PF synapses on apical dendrites, and there are ~7-8 electrical synapses plus 160 GABAergic (using the Gamma-aminobutyric acid neurotransmitter) synapses per GoC-GoC pair. In the molecular layer, ~25% of AAs contact the distal dendrites of the overlaying PCs (each AA forming 2.4 synapses on average), while PFs form 1 synapse per PC dendritic intersection. In summary, each PC receives 12% of the whole GrC inputs from AAs. Among the molecular layer interneurons (MLIs), we consider the Stellate cells (SCs) and basket cells (BCs) populations. There are ~25 SC-PC and BC-PC synapses altogether. Moreover, there are ~17'600~176'00 PF-MLI-PC synapses, ~2,600~26,00 PF-SC-PC, and ~15,000~150,00 PF-BC-PC synapses.

Beyond the canonical description of the cerebellar network (Figure 1.5A), there is growing evidence that the cerebellar cortex is not homogenous in structure, physiology, or gene expression (Chen et al., 2022; E. Fujita et al., 2012; Ito, 2006; Martinez et al., 2013; Nedelescu & Abdelhack, 2013; Nishiyama & Linden, 2004; Sillitoe et al., 2009) and these variations of regional features (Figure 1.5) may influence information processing. Several cell clusters have recently been reported based on transcriptomic profile: 9 PCs clusters are overlapping with zebrin stripes, 3 GrCs clusters showing antero-posterior segregation (anterior-central zone, central-posterior zone, nodular zone), 2 GoC clusters, and two clusters of MLIs, including both SCs and BCs (Kozareva et al., 2021).

- **Purkinje cells**

Two large groups of PCs were identified based on the expression of Aldoc (aldolase C, the enzyme responsible for the zebrin II pattern). The Aldoc positive and negative PCs define the “zebrin stripes”, consisting of longitudinal alternating bands of positive (Z+) and negative (Z-) PCs (see Figure 1.4). This distribution is typical of the anterior and posterior cerebellar zones (comprising lobules I – V, and VIII – dorsal IX, respectively), while the central and nodular zones (lobules VI – VII and ventral IX – X) are uniformly characterized by Z + PCs. From the functional point of view, Z- PCs are characterized by higher spontaneous firing compared to Z + PCs (Xiao et al., 2014; Zhou et al., 2014). More recently, Z- PCs were shown to undergo simple spike suppression (*downbound*) (B. Wu et al., 2019) and Z + PCs to undergo simple spike facilitation (*upbound*) (De Zeeuw, 2021).

In addition to heterogeneity between stripes, PCs also display functional variations along the transverse axis. PCs in the anterior lobes have a more pronounced adaptation of tonic firing compared to those in the nodular zone (C.-H. Kim et al., 2013), where PCs show lower firing rates and reduced excitability (Witter & De Zeeuw, 2015). These differences likely make PCs in the nodular lobe more suitable to integrate vestibular inputs, which are slower compared to the faster and stronger inputs arriving in the anterior zone. An anteroposterior gradient has also been reported for the regularity of firing (increasing toward the nodular zones) (Witter & De Zeeuw, 2015). The difference in PCs firing along the transverse axis may simply match the different distribution pattern of zebrin, with more zebrin-negative PCs in the anterior cerebellum, and more positive PCs in the posterior and nodular cerebellum.

PCs regional diversity also impacts the microcircuit connectivity. In addition to the general scheme, in which granule cells activate PCs and DCN cells in sequence, recent evidence showed that PCs axon collaterals in the granular layer form functionally active contacts onto GrCs (Guo et al., 2016) and Unipolar Brushed Cells (UBCs) (Guo et al., 2021) that are less represented in the anterior cerebellum (Figure 1.5B,1.5C). Moreover, these collaterals show more complex morphology and more numerous contacts in the granular layer starting from lobule VI toward lobule X (Guo et al., 2016). This connection is characterized by a low probability of GABA release, suggesting that a robust activation of PCs is needed to activate this additional source of feedback inhibition to GrCs. These results show that, in lobules VI-X, PCs contribute to both phasic and tonic inhibition in the granular layer, therefore affecting the spatiotemporal dynamics of GrCs firing (D’Angelo, Solinas, Mapelli, et al., 2013; Mapelli et al., 2014).

- **Unipolar brush cells**

The canonical cerebellar microcircuit also differs based on the regional distribution of UBCs (Figure 1.5C). UBCs are excitatory neurons involved in the MF-GrC pathway. These neurons are located in the granular layer, with highest density in the medial cerebellum, particularly lobules I, IX, X, and the lowest density in the lobules IV-VI in mammals (Mugnaini et al., 2011; Takács et al., 1999). UBCs receive a robust synaptic input from a single MF and contact several GrCs, and are therefore called “intrinsic mossy fibers.” (Nunzi & Mugnaini, 2000). Their response patterns amplify the vestibular inputs, significantly modifying the transmission pathway from MFs to PCs (Balmer & Trussell, 2019; Locatelli et al., 2013; Nunzi & Mugnaini, 2000).

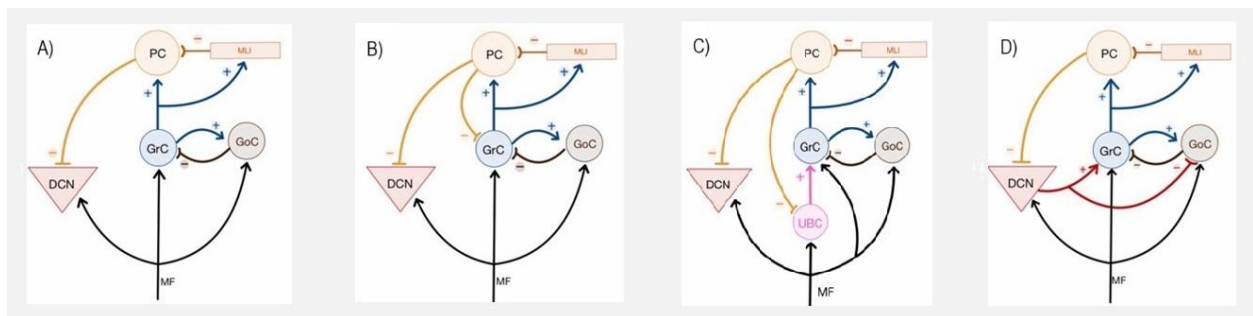


Figure 1.5 Cerebellar microcircuit variants. A) Canonical circuit of the cerebellum. The primary input of mossy fibers (MF) projects to deep cerebellar nuclei (DCN), granule cells (GrCs), and Golgi cells (GoC). GoC inhibits GrC in a feedforward and feedback loop. Besides GoC, GrC axons activate Purkinje cell (PC) and molecular layer interneurons (MLI). PCs provide the sole output of the cerebellar cortex and inhibit the

cerebellar nuclei. B) A first variant of the canonical circuit is represented by PCs axon collaterals projecting to GrC in the granular layer. C) A second variant is represented by unipolar brush cells (UBC), which are contacted by MF and excite GrC. UBC receives inhibition through PC axon collaterals. D) A third variant shows the nucleo-cortical projections: DCN axon collaterals contact GrCs with excitatory connections and inhibit GoCs, in the granular layer.

- **Granule cells**

GrCs' functions and connectivity are heterogeneously distributed in different subregions of the cerebellum. First, GrCs receive excitatory inputs from UBCs, where these neurons are enriched (mainly in the nodular zone). Second, PCs' axon collaterals contribute to GrC inhibition with a regional gradient increasing toward the posterior and nodular zones. It has also been reported an antero-posterior gradient for GrCs' efficiency in responding to burst vs. tonic inputs, based on the differential expression of the CaV3-Kv4 complex (N. C. Heath et al., 2014; Witter & De Zeeuw, 2015). This finding probably matches the differences in the inputs (with slower vestibular inputs arriving at the posterior and nodular zones). Moreover, GrCs receive excitation from nucleo-cortical projections in several lobules, with a sagittal arrangement (Houck & Person, 2014), which generates an internal amplification loop (Q. Gao et al., 2016).

- **Golgi cells (and molecular layer interneurons)**

Cerebellar inhibitory interneurons also show some specific spatial arrangement, in particular concerning GoCs. GoC dendrites are topographically organized within striped boundaries determined by the zebrin II expression patterns in PCs. There is no evidence in the literature that different GoC subtypes are present in positive and negative stripes, though two clusters have been identified based on the transcriptomic profile (Kozareva et al., 2021). Moreover, a recent study highlighted the functional heterogeneity of GoCs depending on the expression of the human glycine neuronal transporter type 2 (GlyT2), affecting the inhibitory control over GrCs (Dumontier et al., 2022). Additionally, GoCs receive inhibition from nucleo-cortical projections in several lobules (Ankri et al., 2015), decreasing GoC inhibition over GrCs. MLIs are involved in complex inhibitory loops that shape PC responses (Brown et al., 2019; Prestori et al., 2019). To the best of our knowledge, a differential spatial distribution of MLIs subtypes in different zones or lobules has not been reported yet.

- **Deep cerebellar nuclei cells**

The cellular heterogeneity in the DCN is less studied compared to the cerebellar cortex. Nevertheless, DCN can be subdivided based on the connectivity pattern in caudo-ventral and rostro-dorsal axes, based on innervation from zebrin II positive and negative PC, respectively [for a comprehensive review on this subject, see (Kebschull et al., 2024)]. Different functional nucleo-cortical projections have also been identified in several lobules, arranged in a sagittal organization mainly matching the territories of PCs sending inputs to those DCN regions (Houck & Person, 2014). Therefore, nucleo-cortical projections (Figure 1.5D) match the cortico-nuclear ones, originating closed loops, but the amount of reciprocal connections can differ in different regions (Houck & Person, 2014). Excitatory and inhibitory projections from DCN affect GrCs and GoCs activity, respectively (Ankri et al., 2015; Q. Gao et al., 2016). Anatomical tracing studies in rats reported that certain regions of the cerebellar cortex seem to lack nucleo-cortical projections, such as the lateral vermis (longitudinal zone B, see Figure 1.4), the lateral paravermis (C3 zone), and some patches of the paravermis C1 zone and the hemisphere (D zone) (Buisseret-Delmas & Angaut, 1988, 1989). As a result, each lobule shows different patterns of connectivity. For example, in cats, Lobule V has been reported to lack nucleo-cortical projections in the C1 zone (medial paravermis) (Trott et al., 1998a) and be enriched in them in the C2 zone (lateral paravermis) (Trott et al., 1998b). Inside zones, the distribution can be uneven, too. For example, the C2 zone of the paraflocculus lacks nucleo-cortical projections (Trott et al., 1998b). Further anatomical and functional characterization of these projections is needed to clarify the specific impact on regional processing.

- **Structural variants**

In addition to differences in local microcircuit connectivity, there are also differences in the density and distribution of the different cell types, as well as in the thickness of cerebellar regions.

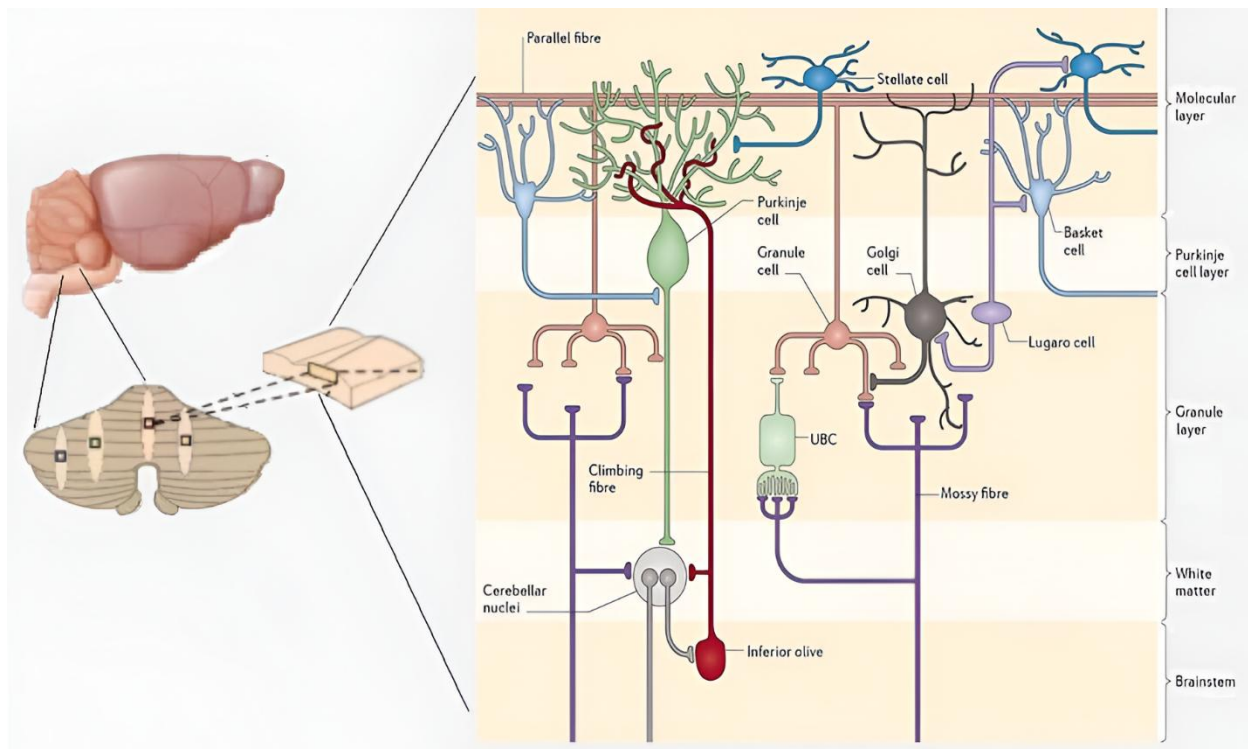


Figure 1.6 Cerebellar cortex. Three layers compose the cerebellar cortex: the molecular layer, Purkinje cell layer, and the granular layer. The principal inputs to the cerebellar cortex are conveyed by mossy fibers (MF) originating from different brain stem and spinal cord nuclei and climbing fibers (CF) originating from the inferior olive. MFs contact GrCs and GoCs in the granular layer. GrC axon ascends to the molecular layer and bifurcates, originating the parallel fibers (PF). GrC axons contact Purkinje cells (PCs) and molecular layer interneurons (MLIs). PCs provide the sole output of the cerebellar cortex and feature a wide, flat, highly branching dendritic tree and a single long axon projecting to the deep cerebellar nuclei (DCN), from where cerebellar efferent projections are sent to other brain areas. The MLI are Stellate and basket cells (SC, BC) located in the molecular layer. The candelabrum cells (CC) are present in the PC layer, while unipolar brush cells (UBC) and Lugaro cells (LC) are reported in the granular layer. Modified from (Cermignani et al., 2015).

- **Cell types and density**

Geographical differences in PC pertain to neuronal locations, packing density, and diameter, as well as axon and dendritic arbor morphology. In rats, there are fewer PCs at the base of each cerebellar folium than at the apex (Armstrong & Schild, 1970; Braitenberg & Atwood, 1958; Eccles, 1967) and the packing density of PCs in the anterior lobe is greater than that of the posterior lobe (Armstrong & Schild, 1970). For example, Lobule X is known to have a greater PCs density than other lobules, such as Lobules II and VI (Keller et al., 2018a). There are also significant regional differences in PC size, with larger PC diameter and organelle volume in phylogenetically older cerebellar regions (such as the vermis) (U. Müller & Heinsen, 1984; Parma, 1969). Consistent changes in PC axons' diameter between white matter compartments and dendritic arbor morphology at the base of a folium, compared to the apex, have been described (Nedelescu et al., 2018a; Nedelescu & Abdelhack, 2013; Voogd, 2011). The biophysical parameters and energy consumption of individual PC in various cortical regions could be drastically altered by these variations. Similarly, GrCs exhibit regional variations in packing density, higher in the apex than in the base of a folium, and a bigger cell size in the vermis than in the hemispheres (Cermignani et al., 2015; Friede, 1955). The packing density of GoCs in a variety of mammals, including humans, is lower in the hemispheres (except for the flocculus) than in the vermis, where the densities are highest in the flocculus and lobules IX (W. Lange, 1974; Palay & Chan-Palay, 1982). Moreover, GoCs in the hemisphere are smaller than those in the vermis (Geurts et al., 2001, 2003).

- **Cortical thickness**

On average, the granular layer is 73% thicker than the molecular layer (Zheng et al., 2023), whereas the Purkinje cell layer is single-cell thick. The difference in layer thickness constrains the area occupied by neurons on the parasagittal surface, e.g., size and width of PCs' dendritic trees. Synapse development and maturation, as well as plasticity, impact the branching and elongation of dendrites (Takeo et al., 2021). A difference in layer thickness will also impact the number of neurons, as in the granular layer.

Granular layer thickness changes from the anterior to posterior cerebellum, being much larger at lobules VI-VIII than at lobules I-V and smaller in lobules IX-X than in the flocculus (Zheng et al., 2023). In the depth of the sulci, all three layers are thicker than at the crowns of the gyri. Globally, the lateral-posterior-inferior area has a thicker granular layer than the medial-superior region.

Unique PCs' dendritic tree shapes in the sulcus result in more arbor field overlap between nearby PCs than at the apex (Nedelescu & Abdelhack, 2013) and cause quantitative variations in dendritic branching patterns between lobules V and IX. Two physically different PC subtypes have been identified. Type 1 PCs adhered to the conventional concept of a PC morphology, with a single primary dendrite and a rather uniform branching density across the molecular layer's thickness. On the other hand, Type 2 PCs have two major dendrites and little branching in the bottom portion. PCs in the anterior lobe (lobule V) of adult mice exhibited a preponderance of type 1 dendritic arbors, while the posterior lobe (lobule IX) contained a bigger proportion of type 2 isoforms. Overlapping in adjacent PC arbors varies across lobules, with more overlap in lobule V than in lobule IX, and arbors in lobule V use the surrounding space more efficiently than those in lobule IX. Those distinctions in neurons may raise the potential question concerning the afferent system differentiation. For example, lobules IV and V are the key areas receiving significant MF projections from the lateral reticular nucleus, while lobules VI-VIII and IX get a less dense distribution of this input (H. S. Wu et al., 1999).

- **Atlas data for microcircuit and structural variations**

The cerebellum holds remarkable variations in cell morphology, density, volume, and cellular properties. These variations are further enriched considering microcircuit connectivity of different cerebellar regions, which go by lobules, stripes, modules, and eventually identify specific microzones and microcomplexes. Using atlases introduces a new method to combine evidence collected through the different studies. For example, the extensive datasets from the Allen Brain Institute (*ISH Data: : Allen Brain Atlas: Mouse Brain.*, n.d.) and Blue Brain Cell Atlas (Rodarie et al., 2022) provides exhaustive information on cell types and densities that might be used for detailed model reconstructions (Figure 1.7a and 1.7b). This information must now be crossed with that on cerebellar regional connectivity and behavioral localization of functions, addressing those regions and pathways that are critical for emotional processing.

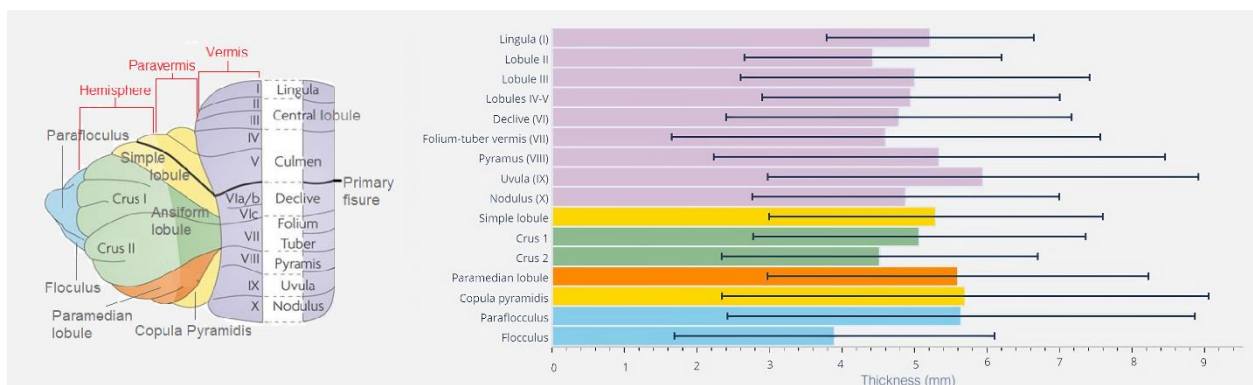
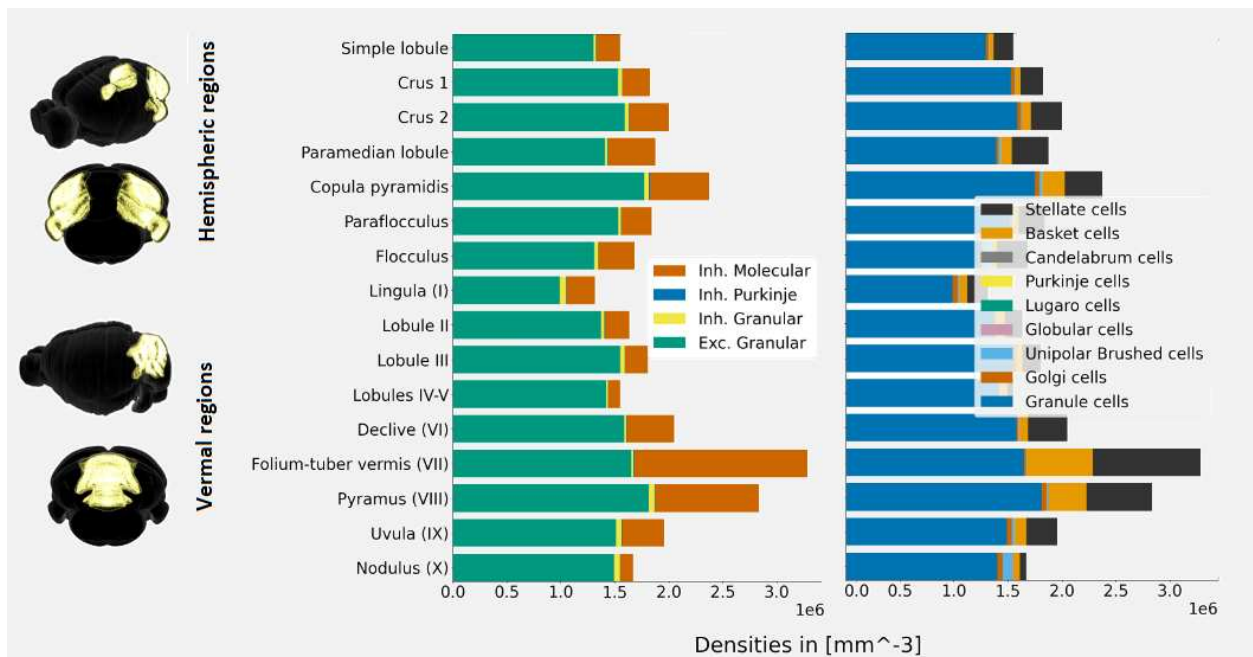


Figure 1.7 Neuron density and thickness in the mouse cerebellum based on the Blue Brain Cell Atlas. A) Estimations of the thickness of the molecular layer in mm for each subregion of the cerebellar cortex, using the algorithm proposed by (Rodarie et al., 2022)



b) (Left) Estimations of the density of excitatory and inhibitory neurons in the molecular, granular, and purkinje layers for each region of the cerebellar cortex. (Right) Densities of each cell type in each layer. The data are based on the publicly available (*Blue Brain Cell Atlas*, 2023) website, and neuron densities were estimated using the (Rodarie et al., 2022) algorithm.

1.2.2 Role of the cerebellum in emotions, from rodents to humans

➤ A unified framework for motor, cognitive, and emotional processing?

The intricate neuronal circuitry of the cerebellum is thought to encode internal models that reproduce the dynamic properties of body parts, allowing the brain to precisely control movement without the need for sensory feedback. It is thought that the cerebellum might also encode internal models that reproduce the essential properties of mental representations elaborated in the cerebral cortex. This hypothesis suggests a possible mechanism by which intuition and implicit thought might function and explains aspects of cognitive and emotional reasoning, as well as symptoms exhibited by psychiatric patients (Ito, 2008).

Recently, it was argued that a similar circuit structure in all cerebellar areas may carry out various operations using a common computational scheme (D'Angelo & Casali, 2013). The authors attributed different roles of the cerebellum to the specific connectivity of the cerebellar modules with motor, cognitive, and emotional functions at least partially segregated into different Cerebro-cerebellar loops. This led to the formulation of a meta-level hypothesis: from cellular/molecular to network mechanisms leading to the generation of computational primitives, thence to high-level cognitive/emotional processing, and finally to the sphere of mental function and dysfunction. It has been proposed that the intimate interplay between timing and learning (reminiscent of the "timing and learning machine" capabilities long attributed to the cerebellum) reverberates from cellular to circuit mechanisms. Subsequently, integration within large-scale brain loops could generate the disparate cognitive/emotional and mental functions in which the cerebellum is implicated. The cerebellum should therefore operate as a general-purpose co-processor, whose effects depend on the specific brain centers to which individual modules are connected. Abnormal functioning in these loops could eventually contribute to the pathogenesis of major brain pathologies, including not just ataxia but also dyslexia, autism, schizophrenia, and depression. These functions and dysfunctions are deeply involved in cognitive and emotional processing.

➤ A system view

In engineering, the cerebellum has been assimilated to a double *forward and inverse controller*, capable of predicting system states based on contextual information and previous memory (Ito, 1993, 2008). The fact that our understanding of cellular phenomena is sufficient to explain the predictive capabilities of the system is demonstrated by the ability of neuro-robots, embedding a canonical cellular representation of the cerebellar circuit dynamics and mechanisms, to reproduce

a wide set of sensory-motor control tasks (Antonietti et al., 2017, 2018, 2022; Casellato et al., 2015). This same system approach may be applied to cognitive and emotional processing, provided the controller, to which the cerebellar circuit is connected, is appropriately designed and implemented. Eventually, a precise representation of the neuroanatomical principles based on cerebellar connectivity and subdivisions may help understand the computational principles and mechanisms underlying the cerebellar involvement in emotion (D'Angelo et al., 2016; D'Angelo & Jirsa, 2022).

➤ Studies in rodents

• Cerebellar circuits in rodent emotional behavior

While the cerebellum has canonically been implicated in motor control and motor learning, which it exerts through a set of well-studied circuits and pathways (Figure 1.8A), neuroimaging and clinical data recently identified the cerebellum as a key region among the emotion and cognition-relevant structures (Adamaszek et al., 2017; Apps & Strata, 2015; Strata, 2015°; Strick et al., 2009). Anatomical studies in rodents have highlighted indirect connections from the DCN, the sole output of the cerebellum, to various brain structures involved in cognitive (Figure 1.8B) and emotional processing (Figure 1.8C). This topic will be addressed in detail in Chapter 3.

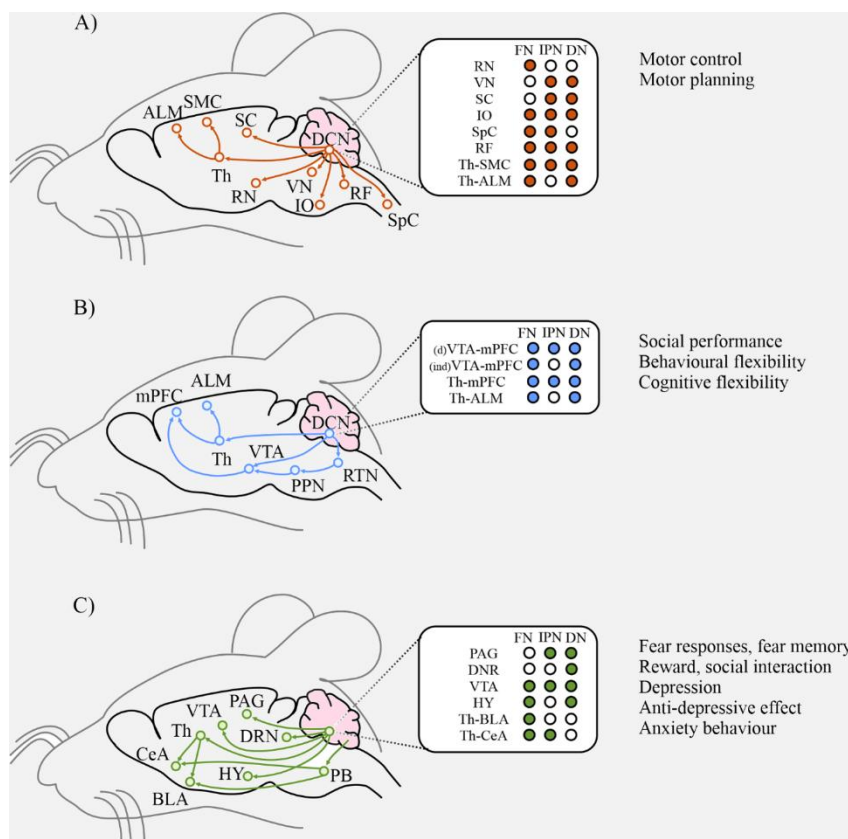


Figure 1.8 Efferent pathways from the rodent cerebellum (Left) Schematic diagrams of historically studied efferent pathways related to A) motor functions, and of direct or indirect efferent pathways that are considered to be associated with B) cognitive and C) emotional functions. Middle: target brain regions from each DCN. Right: summary of the broad functions of the pathways illustrated on the left. ALM, anterior lateral motor cortex; SMC, sensorimotor cortex; SC, superior colliculus; Th, thalamus; RN, red nucleus; VN, vestibula nucleus; IO, inferior olive; RF, reticular formation; SpC spinal cord; mPFC, medial prefrontal cortex; VTA, ventral tegmental area; PPN, 42ollaborate42tine tegmental nucleus; RTN, reticulotegmental nuclei; DRN, dorsal Raphe nucleus; HY, hypothalamus; PB, parabrachial nucleus; CeA, central amygdala; BLA, basolateral amygdala; PAG, periaqueductal gray. Modified from (Kang et al., 2021).

➤ Studies in humans

A growing literature on functional neuroimaging (Guell & Schmahmann, 2020; C. Stoodley & Schmahmann, 2009) evaluates structure-function relationships in motor and non-motor areas of the human cerebellum, together with clinical findings. These studies highlight the involvement of different circuits depending on the task being performed. The imaging studies in humans were used to reconstruct a functional topographic map of the cerebellum. The results of these studies can be interpreted according to Larsell's nomenclature (J. D. Schmahmann et al., 1999), that divides the cerebellum along the anterior-posterior axis in lobules denoted by roman numerals from I to X (optional labels, H and v, are used to denote the hemispheres and the vermal region). In addition, the two largest hemispheric lobules are separated into two parts, namely lobule VII (into VIIA comprising crus I and crus II, and VIIB), and lobule VIII (into VIIIA and VIIB), according

to the intraviventer fissures (Figure 1.9A). It should be noted that, in human studies, the gross subdivisions of the cerebellum are anterior and posterior; the latter includes superior and inferior parts and the flocculo-nodular lobe.

In general, in functional studies, the cerebellum is usually divided into two representations, motor and non-motor (Buckner et al., 2011; Guell et al., 2018b, 2019; Guell & Schmahmann, 2020; C. J. Stoodley et al., 2012; C. Stoodley & Schmahmann, 2009). Specifically, areas involved in motor representations are the anterior lobe and parts of lobule VI and VIII, while the areas involved in non-motor representations are lobules VI, crus I, crus II, VIIIB, and IX, with extensions to lobule X. Some authors, such (King et al., 2019) promotes a functional parcellation to re-define lobar boundaries as it better matches the experimental data. Also, (Boillat et al., 2020) highlighted that the activation patterns observed in functional studies do not strictly adhere to lobar boundaries, and suggested that the cerebellar cortex is a continuous sheet.

Although extensive fMRI studies have been performed, a composite unified picture of the cerebellar functional topography is still lacking. (Figure 1.9B) represents the activation of the different cerebellar lobules in motor, cognitive, emotional, and social tasks. The most significant observation coming from our analysis is that, besides a preference for specific modalities, there is a considerable overlap of functions in several cerebellar areas.

- **Motor cerebellum**

As commonly used in literature, we distinguish motor tasks into simple motor tasks, eye movement tasks, and complex motor tasks.

Studies on simple motor tasks (Boillat et al., 2020; Guell et al., 2018a; Riecker et al., 2005; C. Stoodley & Schmahmann, 2009) report activation of the anterior lobe and lobule VIII, confirming the electrophysiological studies of body maps (R. Snider & Eldred, 1951). More specifically:

- Right/left leg and foot movements activate ipsilateral lobules II, III, and IV, with extensions to lobule I,
- Orofacial movements activate medial regions of lobule VI,
- Right/left hand movements activate ipsilateral lobules V, VIII,
- Tongue movement activates ipsilateral lobule VI,
- Articulation activates medial hemispheric lobules IV to VI and VIII.

Studies on eye movements (Alvarez et al., 2010; Boillat et al., 2020; Dieterich & Brandt, 2000; Dimitrova et al., 2002; King et al., 2019) report activation of the anterior lobe and lobule VIII, including vermal areas and lobule VII. For example, optokinetic reflex, smooth pursuit, vergence, and saccades activate vermal lobules VI and VII and extend into vermis lobules IV-V and adjacent medial regions of crus I and crus II.

Studies on complex motor tasks (Ashida et al., 2019; Debas et al., 2010; Hardwick et al., 2013; King et al., 2019; Ma et al., 2010, 2010; Schlerf et al., 2010; C. J. Stoodley et al., 2012; Tzvi et al., 2020) report activation of the anterior lobe, lobule VIII as well as lobule VII. More specifically:

- Motor learning activates bilateral anterior/medial cerebellum extending into lobule VI,
- Motor planning activates lobules VI, crus I and crus II,
- Motor sequencing activates anterior regions extending into lobule VI, VIIIA/B and crus II,
- Motor adaptation activates anterior lobules IV-V, VIII bilaterally,
- Visuomotor adaptation activates lobules IV-V, VI, VIII, crus II,
- Finger tapping activates ipsilateral anterior lobe (lobules IV-V) and lobules VI, VIII,
- Left and right button press activates ipsilateral anterior lobe and lobule VIII,
- Skilled movement activates lobules VI, crus I,
- Execution (reported in both motor and cognitive studies) activates lobes V, VI, VIII

Clinical studies (Bultmann et al., 2014; Kumral et al., 2007; Maderwald et al., 2012; J. D. Schmahmann et al., 2009; C. Stoodley, 2016; C. Stoodley & Schmahmann, 2009; Urban et al., 2003) support the previously reported experimental findings on motor tasks. Affections of these lobules or regions have been additionally found to be related to neuromotor disorders. For example, patients with poor finger tapping have lesions in the ipsilateral anterior cerebellum, ataxia scores correlate with damage of the anterior lobe (lobules II to V extending into lobule VI), and lesions responsible for cerebellar dysarthria include lobules I, II, III.

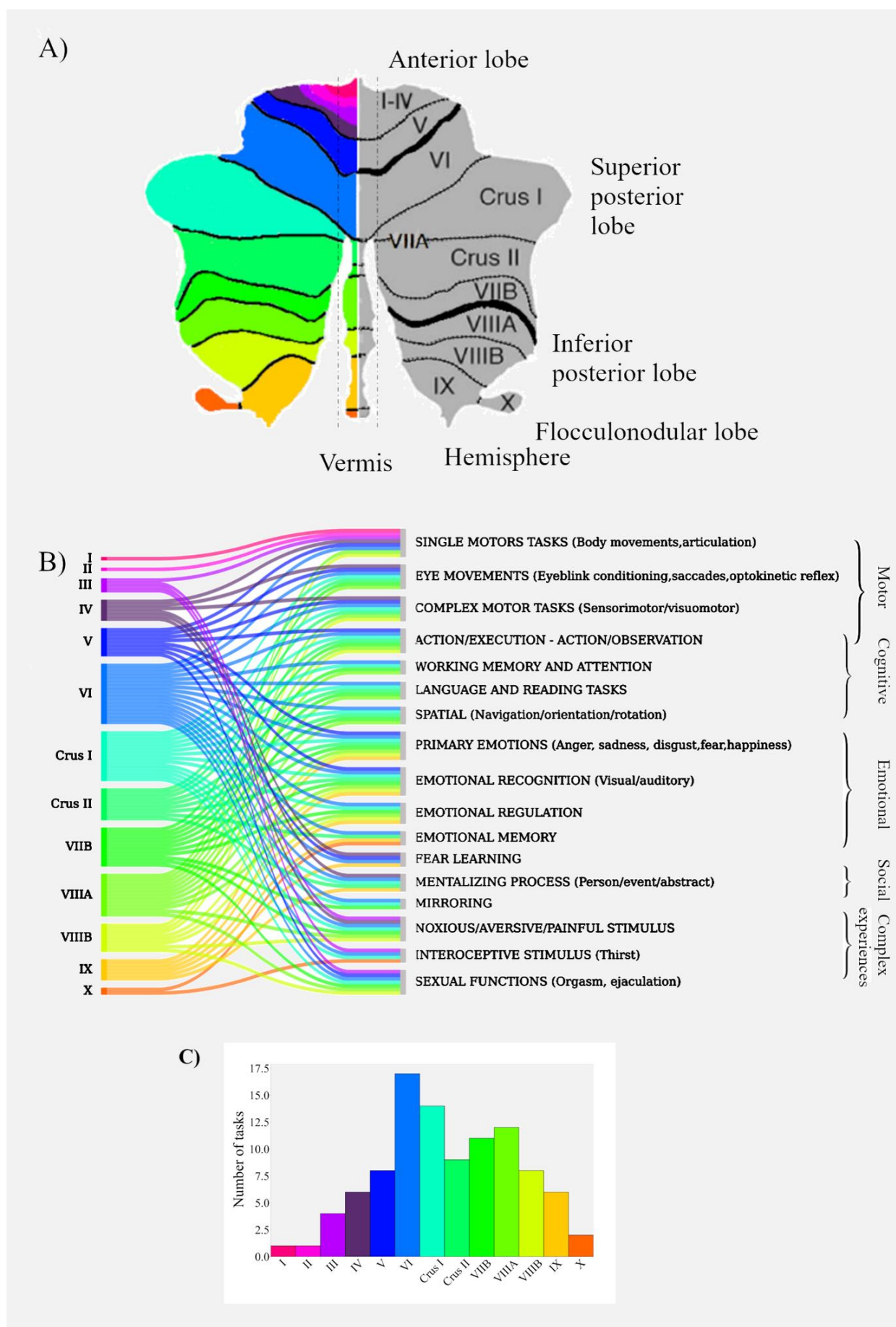


Figure 1.9 Contribution of the human cerebellum to motor, cognitive, emotional, social, and complex tasks. A) Classical nomenclature of the division of the human cerebellum, from anterior lobe (I to

V) to posterior lobe (Superior posterior: lobules VI to VII B and Inferior posterior: lobules VIIIA to IX) separated by intraviventer fissures (dark black line), and flocculo-nodular lobe. B) Association of the activation of the different cerebellar lobes (in colours) to different functional tasks, based on the consulted bibliography. The tasks were divided into motor, cognitive, emotional, and social. Complex experiences cannot be strictly classified into motor, cognitive, emotional, or social tasks. C) Lobules' involvement in functional tasks of panel B). The height of each bar corresponds to the number of tasks (out of the 17 listed) related to the activation of each lobule.

- **Cognitive cerebellum**

fMRI analyses in cognitive tasks (Ashida et al., 2019; Balsters et al., 2014; Casiraghi et al., 2019; E et al., 2014; Fink et al., 2000; Guell et al., 2018a; King et al., 2019; C. J. Stoodley et al., 2012; C. Stoodley & Schmahmann, 2009) report vermal activation of lobules VI and VII, as well as hemispheric activation of these lobules with lobule VIIIA and extensions to lobule V. More specifically:

- Action/execution tasks (reported in both motor and cognitive studies) activate lobules V, VI, VIII, and regions of crus I
- Action/observation tasks activate areas of lobule VI, crus I, and crus II,
- Working memory activates hemispheric lobules VI, crus I, and VII B to VIIIA,
- Visuospatial working memory and attention activate hemispheric lobules VI, crus I,
- Linguistic and reading tasks activate right lobules VI, VII, and VIIIA,
- Spatial (mental rotation) activates left-lateralized lobules VI, VII to VIIIA, crus I and midline VIIA,
- Spatial (navigation/orientation/mutual rotation) activate right crus I, bilateral lobules VI, and VII

Clinic evidence (Hoche et al., 2018; Mariën et al., 2010, 2015; J. D. Schmähmann & Sherman, 1997; C. Stoodley, 2016) proves that cognitive impairments correlate with posterior lobe lesions (lobules VI and VII, including crus I, crus II) in abstract reasoning, working memory, planning, executive functioning, spatial cognition, language, and cognitive regulation. Damage to the left hemisphere is more related to spatial difficulties, while the right cerebellar hemisphere to language problems.

- **Emotional cerebellum**

Most studies (Adamaszek et al., 2014, 2017; An et al., 2018; Baumann & Mattingley, 2022; T. Ernst et al., 2019; Kilts et al., 2003; King et al., 2019; I. Lange et al., 2015; Moulton et al., 2011; Nummenmaa et al., 2014; Schraa-Tam et al., 2012; C. J. Stoodley et al., 2010, 2012; C. Stoodley & Schmähmann, 2009; Thomasson et al., 2019; Wildgruber et al., 2005) agree that the regions involved in emotional processing are in the posterior lobes, including the vermal area.

Vermal and paravermal regions are involved in fundamental or primary emotions, namely:

- Anger: vermal lobule IX and paravermal lobules VI, crus I and crus II,
- Sadness: vermal lobules, crus I, crus II and paravermal lobule VI,
- Disgust: vermal lobules V, VIIIA to IX and paravermal lobule VI,
- Fear: vermal lobule VII B and paravermal lobes VI, crus I, and crus II,
- Happiness: paravermal lobe VII B

In the domain of Emotional recognition:

- Seeing emotional vs neutral images activates the posterior lobes, including lobules VI, VII
- Seeing pleasant images activates the right lobules VI and crus I
- Seeing unpleasant images activates bilateral lobules VI to VII B, vermis of lobule IX, and left crus I
- Processing an angry facial expression activates the right lobule V
- Identifying emotional intonations activates midline lobule VII and lateral lobules VI and crus I
- Listening to others' spoken emotional narratives induces activation in lobules VI and IX, right lobules VII B, VIII, and IX
- Processing of emotion-laden visual and auditory art activates crus I and crus II are reported.

Emotion regulation activates vermal and hemispheric lobules VI, crus I, VII B, VIIIA/B, and IX. Emotional memory activates crus II and lobules VI, IX, X.

Finally, Fear learning activates the culmen, right and left hemispheric lobule IV-V, and left lobule

VI, and right and left lobule hemispheric lobule IX (More detail about the role of the human cerebellum in fear will be addressed in Chapter 4).

- **Social cerebellum**

The study of the role of the cerebellum in social behaviors (Leggio & Olivito, 2018; Olivito et al., 2023; Van Overwalle et al., 2014, 2020) has recently gained attention. More precisely, on the mentalizing task, which evaluates the ability to understand the mental state of oneself or others, that underlies overt behavior:

- Social mentalizing activates crus I, crus II, and lobule IX,
- Person mentalizing activates crus I, lobules IV and VI,
- Event mentalizing activates Crus I,
- Abstract mentalizing activates crus I, lobules VI and IX

Mirroring is the behavior in which one person subconsciously imitates the gesture, speech pattern, or attitude of another. This task activates crus I, lobules VIIIB and VI.

Clinical data (Adamaszek et al., 2014; Levisohn et al., 2000; J. Schmahmann et al., 2007; Tavano et al., 2007) reports the relationship between damage to the posterior vermis with extensions in the medial cerebellar regions with social, behavioral, affective deficits and emotional disorders in patients with affect dulling, anxiety, depression, impulsivity, irritability, aggression, and autism spectrum disorder.

- **Complex experiences involving multiple cerebellar areas**

fMRI studies indicate that the cerebellum responds to other complex experiences, such as aversive and painful stimuli (Becerra et al., 1999; Borsook et al., 2018; Dimitrova et al., 2003; Jackson et al., 2005; Moulton et al., 2011; Ploghaus et al., 2003; Singer et al., 2004), interoceptive stimuli (Parsons et al., 2000) as well as sexual experiences (Holstege & Huynh, 2011; Wise et al., 2017).

Aversive stimuli (noxious heat, electricity, unpleasant images) activate lobule VI, crus I, and VIIIB, while painful stimulation evokes bilateral activation of lobules III, IV, and VIII as well as the vermal and hemispheric parts of lobule VI and crus I. Therefore, pain experiences activate multiple areas: the anterior regions in relation to the motor component as reflex, the posterior regions in relation to the anticipation of pain or unpleasant situation, and the posterior vermis for the painful experience itself, including fear or startle reactions. Pain empathy activates bilaterally lobule VI and crus I.

Interoceptive stimuli such as thirst activate vermal lobe III, whereas during maximal thirst lobes X, VI, and crus I are activated, and the left lobe VI is strongly activated after drinking to satiety.

Men's ejaculation evokes activation in lobule VIII, right vermal lobule V, left vermal lobule VII, left lobule VI, and bilateral crus I. Women's orgasm elicited activity in left lobule V and right lobule III, while during the post-orgasm recovery activates vermal and hemispheric lobule VI and lobule VII.

It would be wrong to limit an area of the cerebellum strictly to either motor, cognitive, emotional or social tasks. However, lobules task-dependent predominance can be delineated (Figure 1.9 and 1.10).

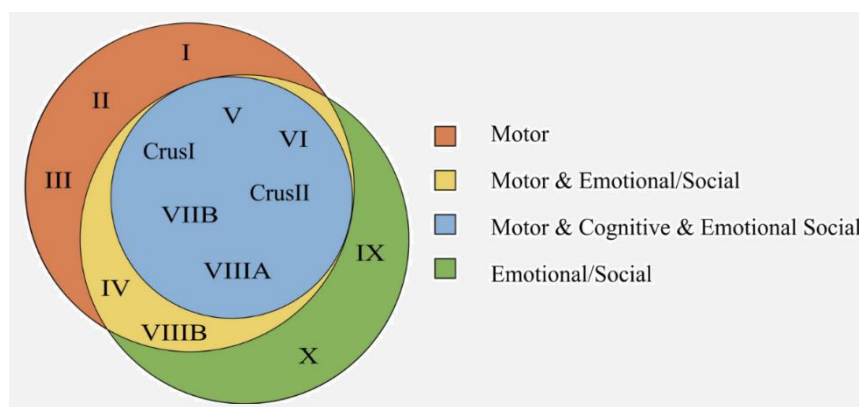


Figure 1.10 Venn's diagram based on the consulted bibliography of three functional domains (motor, cognitive, emotional/social). The emotional and social tasks are joined within the same functional domain, and complex experiences are excluded. The Venn diagram shows the lobules involved in motor, cognitive, and emotional/social tasks. Overlapping parts contain the

lobules that are common to two or all regions. Notice that lobules involved in the cognitive function are common to both the motor and emotional/social function.

- **Extra cerebellar connectivity**

Studies on resting-state functional connectivity showed that most of the cerebellar regions partake in 5 intrinsically connected circuits or networks (Brissenden et al., 2018; Habas et al., 2009):

- The sensorimotor network (lobule V-VI and VIII),
- The default-mode network (lobules VIIa and IX),
- The right and left central executive network (lobule VIIa),
- The dorsal attentional network (lobules VIIB and VIIIA)
- The salience network (lobules VI and VII)

Furthermore, at least 2 functional macroscale circuits involving the cerebellum have been identified (Leggio & Olivito, 2018): a sensorimotor zone (anterior cerebellum) functionally correlated with premotor, motor, somatosensory, visual, and auditory cortical regions, and a supramodal zone (posterior cerebellum) functionally correlated with dorsolateral prefrontal and inferior posterior-parietal regions.

Resting-state fMRI studies report connections of the cerebellum with the cerebral cortex (Krienen & Buckner, 2009; O'Reilly et al., 2010), striatum (C. Stoodley & Schmahmann, 2009), basal ganglia (Bostan et al., 2010, 2013, 2018), antero-medial and mediodorsal thalamus, and habenula (Habas & Manto, 2018; Milardi et al., 2016). Moreover, tracts have been identified between the medial part of the posterior lobule of the cerebellum and with insula (Baur et al., 2013; Cauda et al., 2011), frontal operculum, anterior cingulate cortex, medial prefrontal cortex, amygdala, and hippocampus, as well as between the lateral part of the cerebellum with the hypothalamus and anterior cingulate cortex (Bostan et al., 2013; Habas, 2018; Murty et al., 2014; Sang et al., 2012).

- **Segregation, distribution, and specialization**

The evidence reviewed here reveals, as a fundamental aspect of emotional processing in the cerebellum, the interplay of *segregation* and *distribution* of functions in multiple cerebellar regions. The corollary is the concept of *specialization*, which could adapt the general circuit mechanisms of the cerebellum to the specific needs of emotional control.

- Segregation. Numerous studies (Solstrand Dahlberg et al., 2020; C. J. Stoodley et al., 2010; C. J. Stoodley & Schmahmann, 2023) have shown that lobules of the central cerebellum, in particular lobules VI, VII, and VIII, show most of the fMRI-related activity during emotional tasks. Likewise, the data summarized in (Figure 1.9B) indicate that several cerebellar regions are engaged in multiple functions, as opposed to being specific for a single function. It is plausible to ask whether and to what extent the functional specialization of lobules VI, VII, and VIII entails molecular, cellular, or local network specializations as compared to other modules. The search for circuit specializations in the cerebellum may start from central lobules, especially lobule VI, which presents the most extensive implications for emotional processing (Figure 1.9C).

- Distribution. Since the emotional response entails sensorimotor, cognitive, and autonomic aspects, numerous cerebellar lobules that generically operate motor or autonomic control are indeed also contributing to emotion. As a corollary, some lobules should be convergence sites for emotional, cognitive, and motor responses, as we have pointed out for lobule VI.

- Specialization. The processing role of the cerebellum at the system level notwithstanding, the cerebellar network repeats itself in the general motive but not in the details, suggesting that some properties may differentiate microcircuit computation. Focusing on central lobules, the following pattern emerges:

1. Lobules VI and VII are almost entirely Z + (or upbound), PCs have a lower firing rate and show PF-PC long-term potentiation. Lobule VIII has alternating Z + /Z- stripes.
2. Lobules VI to X show an increasing amount of PC axonal collaterals contacting GrCs, UBCs, and GoCs.
3. Lobules VI to VIII have almost no UBCs.
4. Lobules VI to VIII have higher cortical thickness than the other lobules, and lobule VI has a higher PC density than most of the other lobules.
5. There is an anteroposterior gradient in GrC and PC firing adaptation.

It is possible that these different properties subtend the higher need for multimodal integration of lobules VI-VIII bringing about larger input-output fiber sets, different management of recurrent

loops and local processing of signals on specific frequency bands, differential processing of burst and tonic firing depending on the nature of the input, different needs for plasticity generation and memory storage. To what extent these properties impact microcircuit function and spatiotemporal dynamics is currently unknown, and their understanding will require accurate physiological recordings and model simulations.

- **Implications for behavioral processing**

Since the cerebellum is involved in learning the association of time-correlated events, and it is likely to do so in all its modules (D'Angelo & Casali, 2013). A core hypothesis is that *the cerebellum orchestrates the time domain for the suppression/initiation of fear responses* as much as it does in other conditioning tasks, e.g., in eye-blink classical conditioning. In other words, the cerebellum should perform in emotional control the same operation it performs in motor control and coordinate the many components of the emotional response, including motor and visceral reactions. Lobules VI to VIII are involved, and studies in rodents support their functional connection to the amygdala, hypothalamus, and periaqueductal gray. Regions IX and X play a major role in orchestrating the autonomic response. In humans, the pattern of explorable emotions is larger than in rodents, but evidence still supports a *specialization* of lobules VI to VIII. In humans, the high resolution of fMRI techniques during tasks has reinforced the concept of a remarkable *distribution and overlapping* of areas involved in emotional control with those controlling motor, cognitive, and social behaviors. In addition to coordinating the components of the emotional response, the cerebellum may likewise be involved in *comparing the cortical commands with their execution* to predict possible errors and correct them. Again, the cerebellum may play the same coordinating role in emotion as it plays in sensorimotor control.

Section 1.3: Tracking the Cerebellum in Emotion Research

This section is adapted from Osorio-Becerra, Dianela A., D'Angelo, E., & Casellato, C. (2025). *The Cerebellar Role in Emotions at a Turning Point: Bibliometric Analysis and Collaboration Networks*. *Cerebellum*, 24, 47. <https://doi.org/10.1007/s12311-025-01800-7A>.

This subsection critically evaluates the current state of knowledge, identifies gaps, and highlights emerging trends in the field.

We propose a method that combines bibliometric analysis with collaboration network analysis, following a systematic search based on a clear and detailed methodological framework. This approach ensures a comprehensive study while promoting the reproducibility of results, thereby advancing research rigor and transparency.

Bibliometric analysis (Öztürk et al., 2024) and collaboration network analysis (Ajiferuke et al., 2021) are key tools that offer a clear view of the field's trends and dynamics.

Bibliometrics uses mathematical and statistical methods to analyze the scientific literature, identifying trends and characteristics of a specific discipline. A comprehensive view of the research landscape is obtained by considering elements such as publications, topics, authors, citations, and affiliations.

Meanwhile, integrated through complex network analysis and graph theory, collaboration networks offer an in-depth understanding of scientific collaborations, highlighting key patterns and dynamics in these interactions.

We employ a systematic approach to enhance the clarity, organization, and rigor of our research by combining a search framework (3WH) with the PRISMA statement. The 3WH framework helps define research questions, organize the search process, and focus on relevant aspects, ensuring comprehensive data collection. PRISMA complements this by providing clear guidelines for reporting the review process, including inclusion and exclusion criteria.

Our purpose with this analysis is not only to trace the evolution of knowledge on the cerebellar role in emotions but also to serve as a reference resource for people interested in exploring the field and its existing connections.

1.3.1 Methods

- Search frame

None of the most common search frameworks (Harris et al., 2018) are fully suitable for our purposes, therefore we have adapted the existing framework 3WH to better structure and direct our research questions, by adding the Why factor (Table 1.1).

Table 1.1 3WH* framework applied to the research question				
What	Why	When	Who	How
What is the current state of research on the cerebellum's role in emotional processing? -This question is open-ended and allows for a broad exploration of the topic -Focuses the research specifically on the cerebellum's role in emotions	Why does this research matter? -Address a gap in understanding -Synthesize existing knowledge, creating a much-needed overview of this emerging field. -Provide a foundation for future research -Highlight clinical potential and therapeutic implications	Timeline -From the first available publication to the present	Who are the research subjects and studies to be considered? -Studies involving any species and approaches (experimental, clinical, computational), discipline, or field of study	How to conduct the investigation? -Identify the corpus of literature over time by conducting a systematic search -Identify how the focus of research has changed over the years, map out existing publications, reveal trends, influential authors, and potential research areas -Gain a deeper understanding of the social dynamics within the field, revealing the collaborative landscape -Graphic visualization

* 3WH: What (topical), Who (population), When(temporal), and How (methodological); Why (purpose) has been added.

- Database Identification

In our study, 4 highly known bibliographic reference databases have been considered, the most commonly used search engine in biomedicine: PubMed (*PubMed*, n.d.) and ScienceDirect (*ScienceDirect.Com / Science, Health and Medical Journals, Full Text Articles and Books.*, n.d.), and the multidisciplinary databases Scopus (*Scopus Preview - Scopus - Welcome to Scopus*, n.d.) and Web of Science (*Web of Science Platform*, n.d.).

In all databases, the same criteria were employed, using Boolean operators and keywords: emotion, emotions, emotional, feeling, feelings, affect, affective, cerebellum, cerebellar. Specifically, the search builder in each database was:

- In PubMed ("emotions"[All Fields] OR "emotions"[MeSH Terms] OR "emotions"[All Fields] OR "emotion"[All Fields] OR "emotional"[All Fields] OR "feeling"[All Fields] OR "feelings"[All Fields] OR "affect"[All Fields] OR "affective"[All Fields]) AND ("cerebellum"[MeSH Terms] OR "cerebellum"[All Fields] OR "cerebellums"[All Fields] OR "cerebellum s"[All Fields] OR "cerebellar"[All Fields]).
- In Scopus, TITLE-ABS-KEY(emotion OR emotions OR emotional OR feeling OR feelings OR affect OR affective) AND TITLE-ABS-KEY(cerebellum OR cerebellums OR cerebellar).
- In Web of Science (ALL=(emotions OR emotion OR emotional OR feeling feelings OR affect OR affective) AND ALL=(cerebellum OR cerebellums OR cerebellar)).

- In ScienceDirect (emotion OR emotional OR feeling OR affect OR affective) AND (cerebellum OR cerebellar).

As the complete evolution of this area is of interest, no restriction in the search or downloading of data in terms of time limit, language limit, or type of document (journals, case studies, meta-analyses, reviews, books, conference papers, etc.) was imposed.

At the time of the search (end of March 2024), a total of 38,316 publications were obtained, specifically: 7,282 in PubMed, 11,080 in Scopus, 17,117 in Web of Science, and 2,837 in ScienceDirect. The complete records were exported in .ris format and/or .csv format.

To facilitate the screening of articles, Rayyan (*Rayyan – Intelligent Systematic Review - Rayyan*, 2021) was used, a free tool specially dedicated to systematic reviews, which has an efficient interface for data management. In total, Rayyan recognized 38,312 publications.

- **Screening**

After importing all the references collected into Rayyan, potential duplicates were identified by considering main factors like title, authors, journal, and year. To speed up the process of elimination of duplicates, the Auto-Resolver was used for those who had a confidentiality percentage greater than or equal to 95%. Those detected as a possible duplicate, but with a smaller percentage, were evaluated one by one. A total of 17,423 publications were removed, which is not surprising since the same publication can be in several databases. Although Rayyan automatically creates a list of inclusion and exclusion keywords, our own standardized list was defined by adapting it to our research objectives. Then, inclusion/exclusion filtering was carried out by considering the keywords in the title and abstract.

The entire paper was read for those publications where the filtering process remained uncertain. Subsequently, the full-text articles deemed suitable for eligibility were assessed for final inclusion. To minimize the repetition of findings, special attention was also paid to original papers versus other types of publications such as reviews, book chapters, and conference proceedings, with the goal of avoiding redundant content. During the screening process, it was verified that the selected publications did not significantly overlap with material already covered in other sources. This approach ensured that original findings were represented without unnecessary duplication.

The remaining 1,164 publications were imported into the free reference manager Zotero (*Zotero / Your Personal Research Assistant*, n.d.) to identify and exclude retracted papers. Zotero offers this functionality in collaboration with Retraction Watch (Chawla, 2024), which maintains the largest available database of retracted articles. After this process, 1,162 articles were included in the final analysis (see Figure 1.11 for more details) and can be consulted in the supplementary material.

- **Data adjustments and management**

When using more than one database, it is normal to find disambiguation in the data, since each source has a different format, so it is essential to check the .csv files. Not all publications provided included the number of citations, so the Zotero citation count manager was used (Schnetter, 2020/2024), an add-on that auto-fetch citation counts for journal articles. On the other hand, the main metrics, such as the impact factor (JIF) and the quartile (Q) of scientific journals, did not appear in most of them, so the JCR (Journal Citation Reports) with Web of Science (*Clarivate*, n.d.) was integrated.

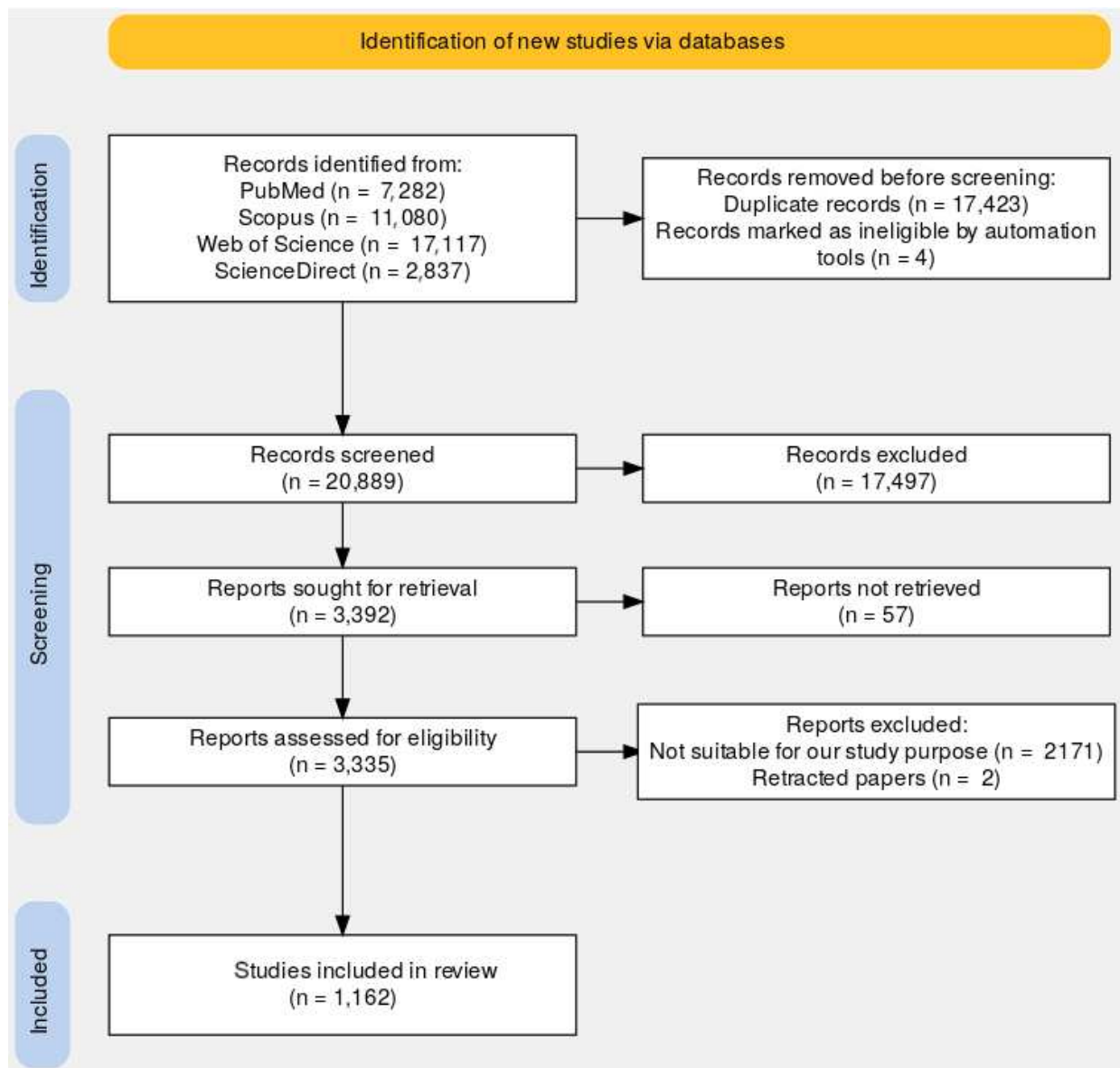


Figure 1.11 Database identification according to the PRISMA method. Flow chart for selecting publications, according to the PRISMA method

Disambiguating author names is still one of the biggest challenges in bibliometrics (Strotmann et al., 2009). Some discrepancies were easily resolved using the Python pandas library (*Pandas - Python Data Analysis Library*, n.d.). The more challenging problem involved identifying authors who published with different abbreviations that had similar names or shared common name structures, and it required manual intervention.

Due to the large number of publications, Python was applied because of its capability to manage extensive data and create clear visualizations. A total of 1,162 publications were exported in .csv format, due to their readability, scalability, and easy handling to integrate them with Python libraries necessary for our data analysis in bibliometrics and networks.

1.3.2 Analyses and Results

➤ Bibliometric analysis

Bibliometric research investigates authorship, publication patterns, citations, and content by applying quantitative measures to a selected body of literature (Haddow, Gaby, 2013).

To address this analysis, Python libraries such as Pandas (*Pandas - Python Data Analysis Library*, n.d.). For data manipulation and analysis, matplotlib (*Matplotlib — Visualization with Python*, n.d.) and seaborn (Waskom, 2021) for visualization, were employed.

- **Scientific productivity**

To evaluate the evolution and growth of literature in this field, a graph mapping the number of publications each year and the cumulative number of publications over time was generated (Figure 1.12).

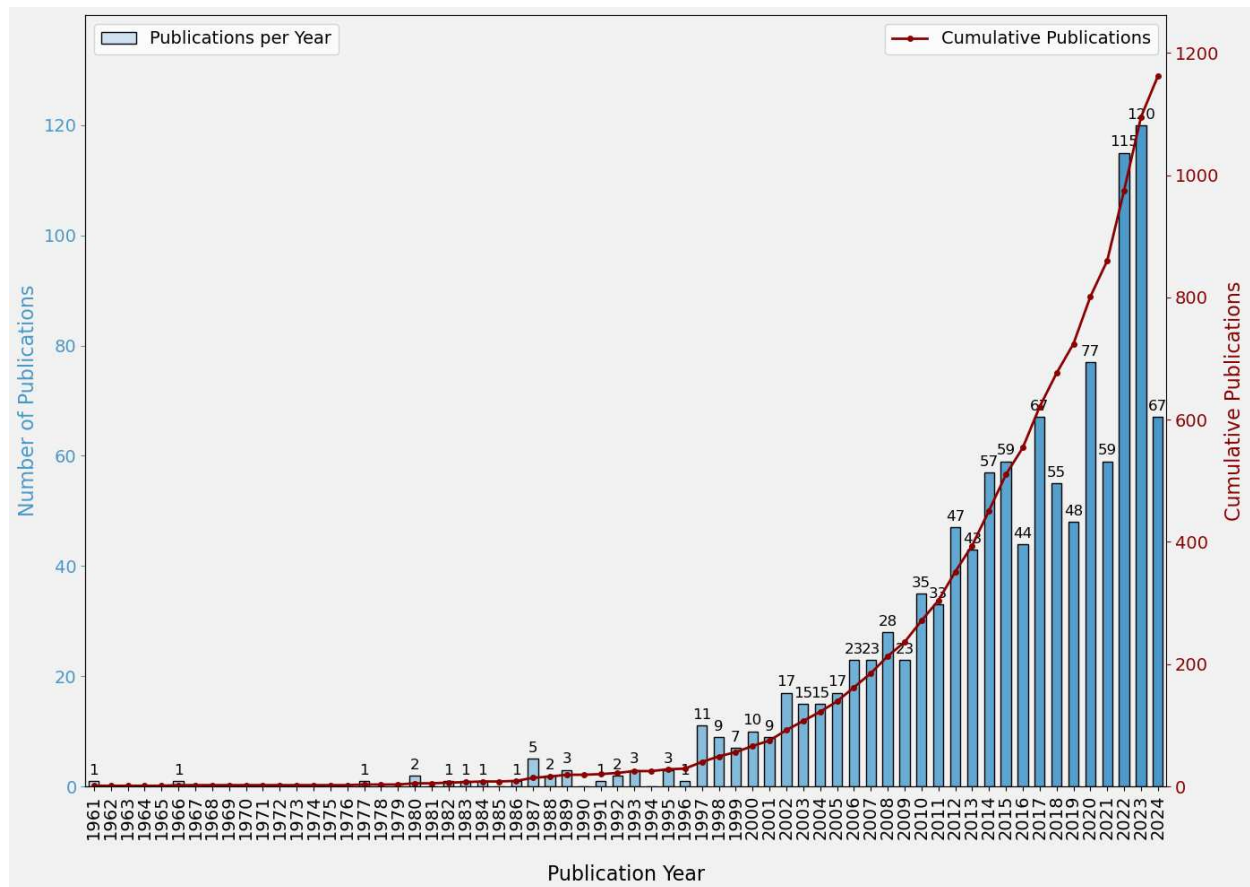


Figure 1.12 Publication Trends Over Time. Each bar in the graph represents the number of articles or studies published in each year. Each point in the graph represents the total number of publications that have been produced up to that year, adding up all the publications from previous years.

Research on the ‘cerebellum in emotions’ has grown significantly over time. Despite some minor fluctuations, interest in this field has consolidated and increased exponentially. Since 1997, publications have shown a steady increase, exceeding 100 per year as of 2022. This growth may be due to technological or methodological advances and new applications, with a marked acceleration phase coinciding with the formalization and broader recognition of the cerebellar cognitive affective syndrome (J. D. Schmahmann & Sherman, 1997), which synthesized and brought renewed attention to earlier findings suggesting non-motor functions of the cerebellum. As is often the case in science, certain figures or publications can help shape the direction of research. Sherrington’s early 20th-century work contributed to a predominant focus on the cerebellum’s motor functions, while Schmahmann’s work later helped bring cognitive and affective aspects into greater focus. This shift reflects a broader pattern in scientific development, where key contributions may guide emerging priorities.

Nevertheless, the notable increase in research outputs over the past decades is likely influenced not only by growing theoretical interest but also by the advent and accessibility of advanced technologies, particularly neuroimaging techniques such as fMRI. These tools have enabled more precise investigations into the cerebellum’s non-motor functions, fostering broader engagement with emotional and cognitive topics, as reflected in Figures 1.16 and 1.20.

To gain a deeper understanding of the evolution of research dissemination and to identify the dominant types of publications during specific periods, stacked charts were generated (Figure 1.13), depicting the number of publications per year by publication type (e.g., Journals,

Congresses, Books, etc.) and domain (e.g., Neuroscience, Pharmacology, etc.), as shown in Table S1.3.1

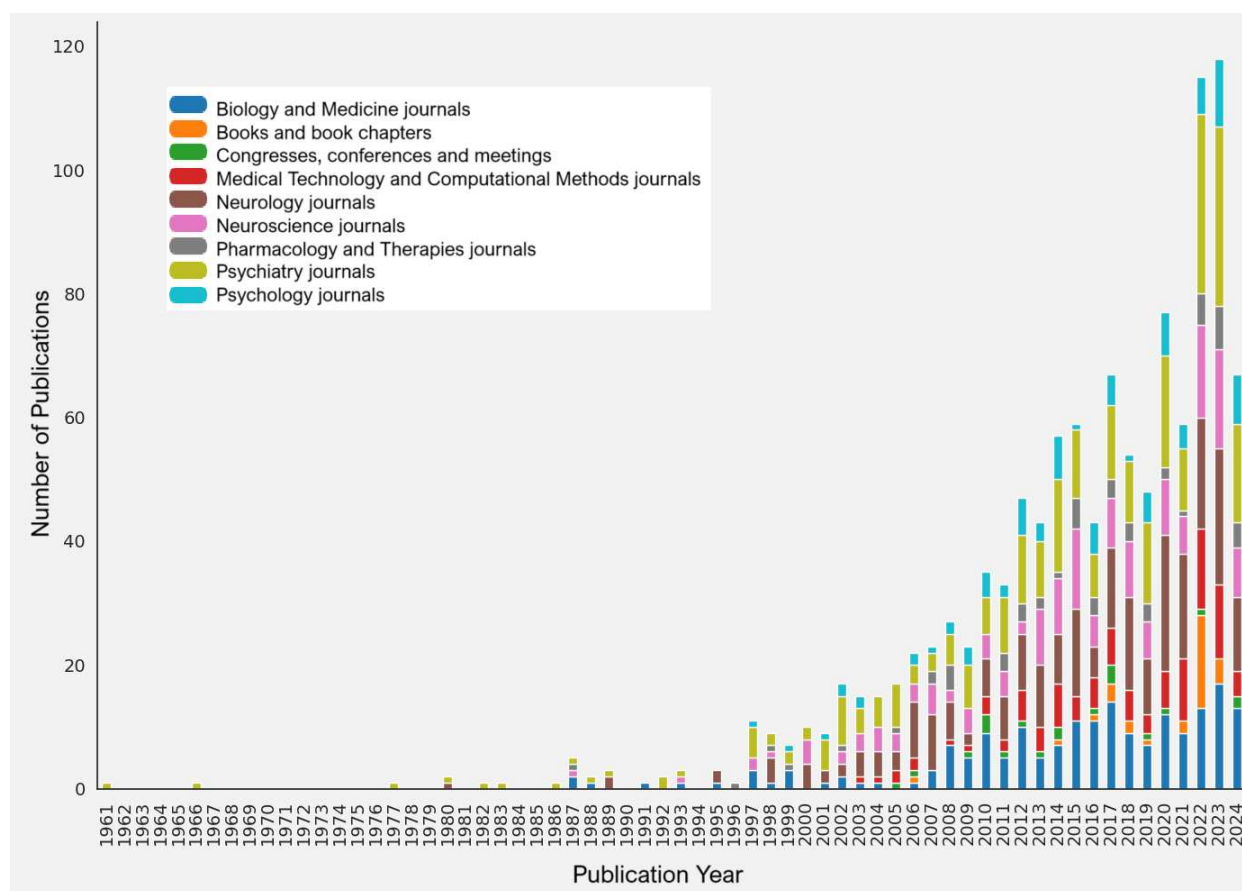


Figure 1.13 Annual Publications by Type. Each type/domain of publication is represented by a different colour.

Initial publications primarily focused on psychiatry, followed by neurology, biology, medicine, and neuroscience. These areas later expanded to include psychology, medical technologies, computational methods, pharmacology, and therapy, reflecting a progressive diversification. Scientific papers predominate over books and conference presentations, highlighted academic journals as the main means of dissemination.

As we mentioned in the previous figure and from a review of the titles and abstract, we note that the finding of the relationship between cerebellar damage and emotional and cognitive deficits, along with studies conducted in humans, prompted a successive wave of investigations that were consolidated by methodological refinements and technological advances.

- **Journals**

Identifying the journals with the largest number of publications helps us understand where the most significant advances in the area are being shared and where to look for information. A bar chart (Figure 1.14) represents the leading journals with their quantitative impact indicators and the type/domain of the publications on them. As an extension of this figure, a table (Table S1.3.1) presenting the impact factors and quartiles of each journal is included in the supplementary material.

Most publications are concentrated in journals focused on psychiatry, followed by neuroscience and neurology. The leading journals in this area are *The Cerebellum* (SpringerLink, n.d.), dedicated to cerebellar research and related disorders, and the *Journal of Affective Disorders* (Elsevier, n.d.), which covers affective disorders, including depression, mood spectrum, emotions, anxiety, and stress.

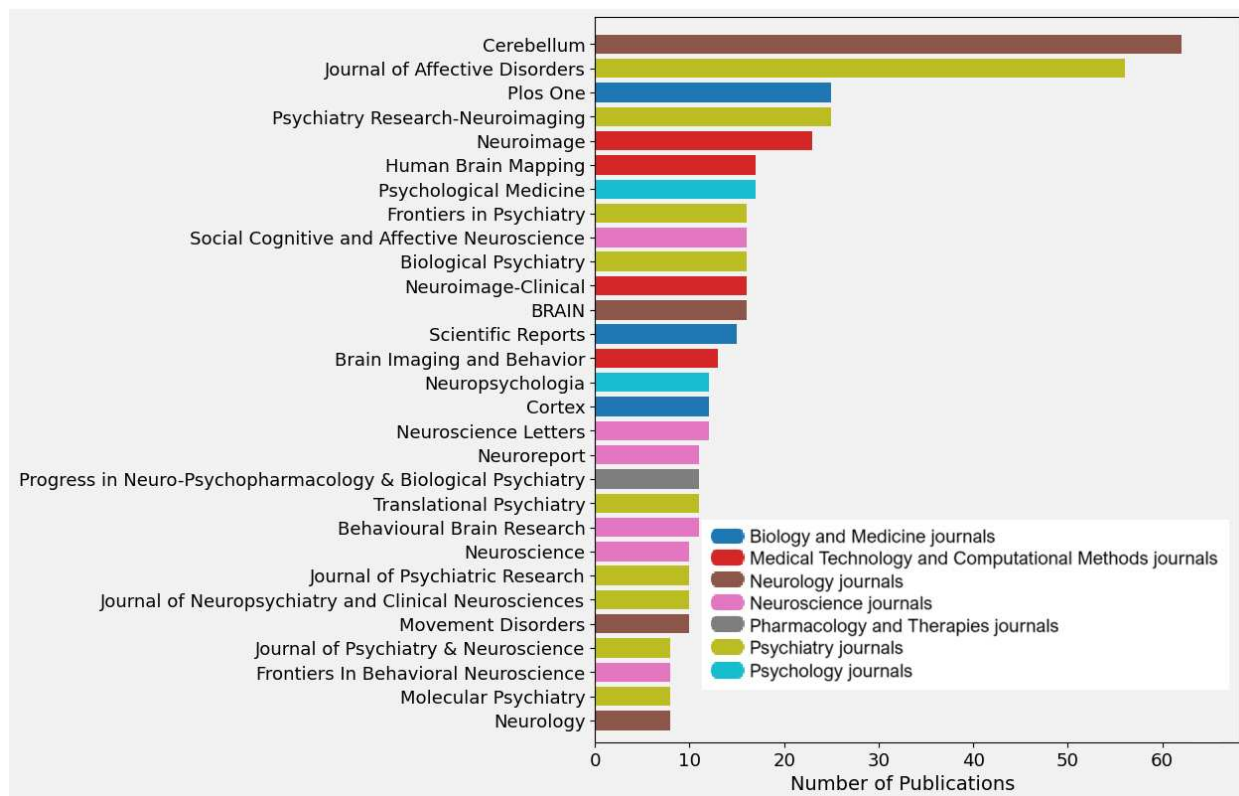


Figure 1.14 Leading Journals. The X-axis shows the number of publications and the Y-axis the name of the journal, the colour still codes the type/domain of papers.

- **Citations**

Citations are an important indicator of the influence and impact of research. The most cited publications were selected and represented through a simple bar plot (Figure 1.15). For more detailed information on the names of the journals in which each paper was published and the authors, see Table S1.3.1.

Two publications have a significantly greater impact with citations of 5,679 and 3,740, which is much higher than the others, starting to decrease from 1,873 citations onward. The first of them, published in 2004, although it is not the first to address the role of the cerebellum in the experience of pain, is one of those that provides the clearest evidence about its activation in the context of empathy towards the pain of others. The second, from 1998 on the cognitive-affective cerebellar syndrome was a key point in the recognition of the role of the cerebellum in emotions and marked a change in the traditional view of the cerebellum. Also, most of the highly cited publications are human imaging studies, with great relevance and impact, as they provide key information for the diagnosis, treatment, and understanding of diseases. This explains their high number of citations, given that findings in human imaging are often highly applicable both in research and clinical contexts.

Also, most of the highly cited publications are human imaging studies, which have great relevance and impact as they provide key information for the diagnosis, treatment, and understanding of diseases. These studies have become invaluable tools in translational neuroscience, allowing researchers and clinicians to study emotional brain function. They have significantly advanced the understanding of emotional processes, moving beyond traditional animal models and providing insights that are highly applicable in both research and clinical contexts (Whitten, 2012; Yen et al., 2023). Figures 1.18 and 1.19 support this observation, showing the thematic evolution and leading topics in the field.

It is important to acknowledge that the output numbers could be influenced by the larger and more interconnected ecosystem of imaging researchers and clinicians. As shown in Figure 1.17, the more extensive network in the imaging field could contribute to a higher volume of publications and citations, which may explain the higher concentration of research in neuroimaging and its corresponding citation rates.

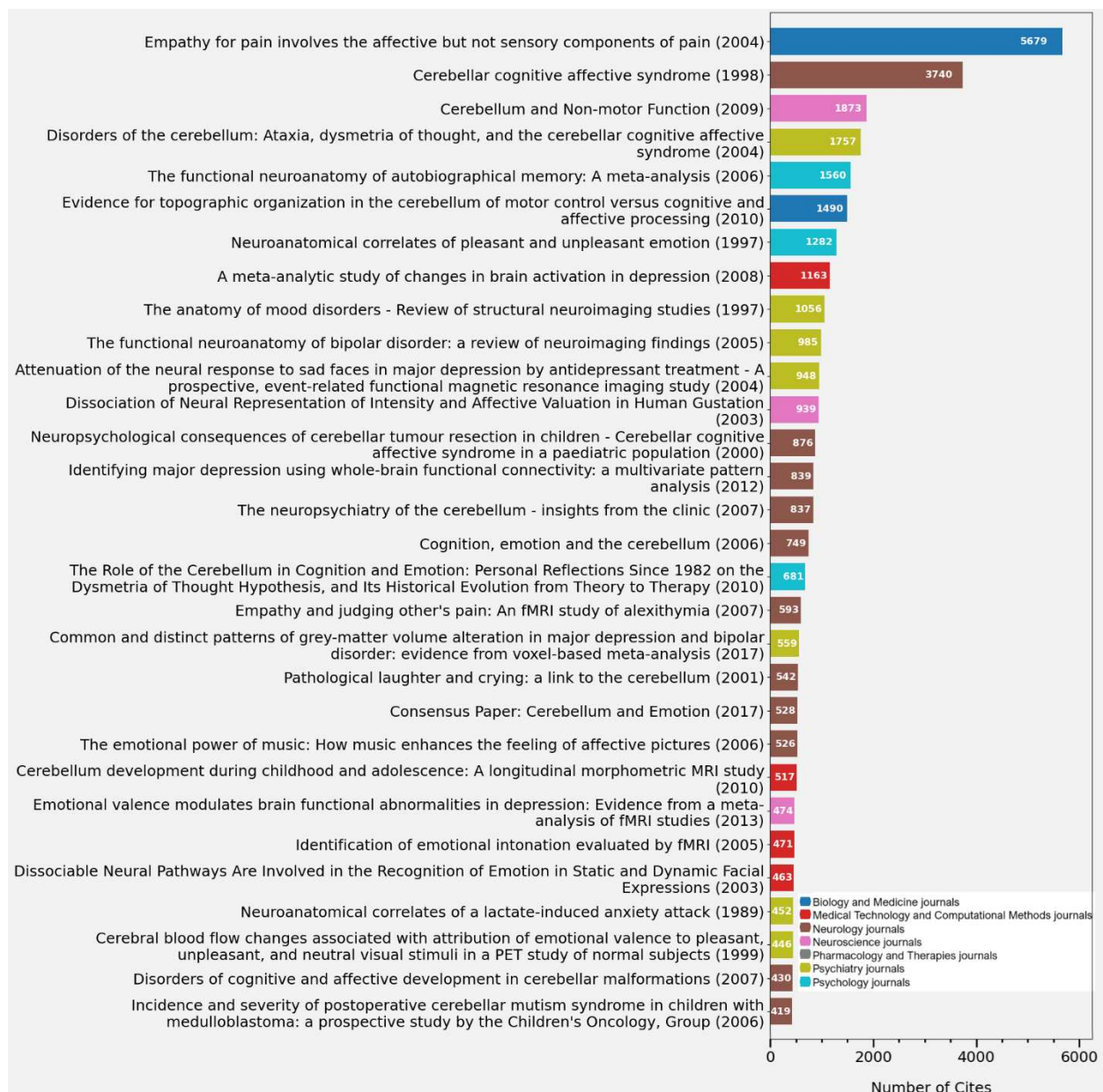


Figure 1.15 Leading cited publications. The Y-axis lists each research study along with its publication year, while the X-axis represents the number of citations received. Each bar is coloured according to the type of publications, making it easy to identify the most prolific and interesting areas.

- **Keyword co-occurrence**

Keyword co-occurrence analysis examines relationships and patterns between terms in a body of literature, visualizing their interconnectedness and revealing thematic structure. It allows identifying major themes, mapping knowledge networks, discovering promising or understudied areas, and focusing research on unexpected or less explored connections.

For the co-occurrence analysis, we considered the titles of scientific publications and used VOSviewer (*VOSviewer - Visualizing Scientific Landscapes*, n.d.), a software tool specifically designed for the construction and visualization of bibliometric networks.

The word “cerebellum” is the main core of the corpus, and “emotion” is one of the central nodes, which is not surprising given our search approach. Other relevant words (themes) are “functional connectivity”, “depression”, and “disorder”. Subthemes are connecting the cerebellum with specific conditions such as “major depression”, “schizophrenia”, and “anxiety disorders”. One particular cluster is related to “cerebellar cognitive affective syndrome”, which links to other nodes such as “patient”, “ataxia”, and “case study”. Other minor semantic clusters connect the cerebellum with cognitive and social functions, while another one links “behavior” with nodes such

as “rat” and “mouse”, highlighting the study of the cerebellum in motor and emotional functions through animal models.

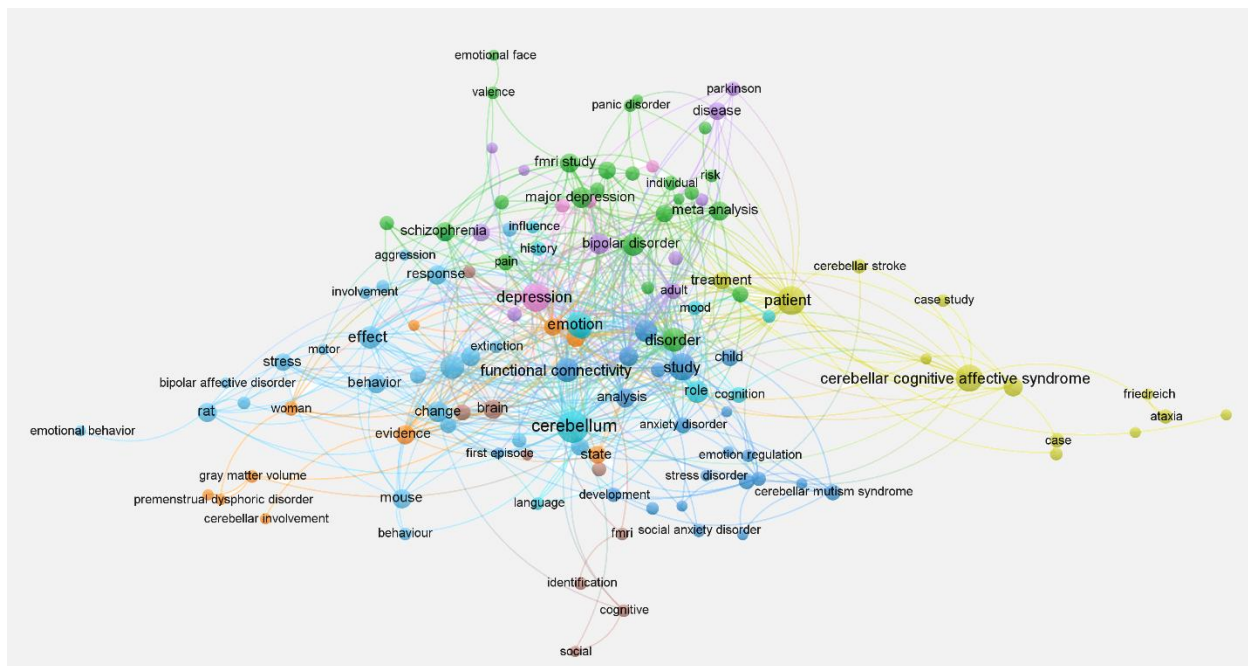


Figure 1.16 keyword co-occurrence network. Each node represents a keyword; its size indicates its importance or frequency, while the lines show co-occurrences in the same context. Colors group semantic clusters linked to specific topics. The most central words in the network are near the center, indicating greater relevance, while peripheral words have less significant connections or deal with more specific topics.

- **Species**

Knowing which species have been investigated the most in the field and which have been investigated the least not only identifies trends and applicability of the studies, but also measures the diversity of approaches and methodologies, identifies possible biases in the research, and reflects economic or political influencing factors. A pie chart (Figure 1.17) illustrates the distribution of species in the publications. Although computational modeling is not technically a species, it can be included in the analysis, since it represents a source of valuable in-silico data.

Human studies dominate research, reflecting a focus on medicine, psychiatry, and clinical applications. Rats and mice are the second and third most studied species, although rodents differ significantly from humans in terms of brain structure, particularly in cortical morphology, as their lissencephalic brains contrast with the gyrencephalic brains of primates; they remain essential models in neuroscience.

Their value lies not in overall anatomical similarity but in their well-characterized neurobiology, genetic manipulability, and the availability of standardized behavioral and physiological protocols. These features make rats and mice especially useful for studying specific neural circuits and functions, including those related to emotion. The emotional system is an ancient evolutionary structure and is well-preserved across species, although specific behavioral responses may vary. Therefore, the analysis of basic mechanisms can benefit from the extensive knowledge that has been gained in rodents.

The greater use of mice over rats in recent years is largely due to the earlier availability of advanced genetic tools, which positioned mice as a preferred model in biomedical research, as mentioned in (Ellenbroek & Youn, 2016).

Other species are minimally represented, emphasizing the translational focus on human applications. For example, monkeys are subject to stricter ethical regulations, while species such as fish, rabbits, and zebrafish may offer limited relevance for studying complex emotional processes. Dogs, while used in some behavioral studies, are less common due to ethical

concerns and practical limitations. These factors help explain the predominance of rodent models in the field.

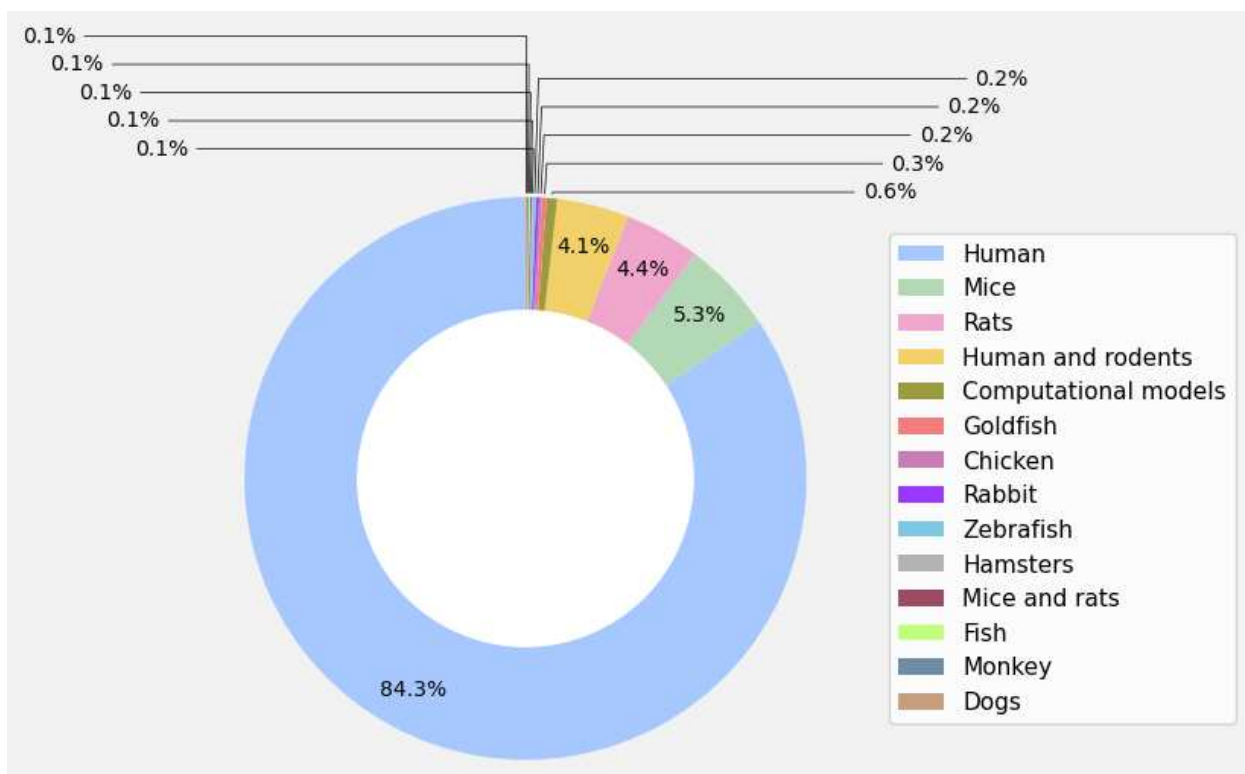


Figure 1.17 Distribution of species. Each segment of the pie chart represents the relative share of each species (including “modeling”) in the total.

Several factors may explain these patterns. Animal studies, especially in vivo experiments, often require longer time frames to complete, which may affect the overall volume of publications. Moreover, ethical and regulatory restrictions on animal research, particularly regarding the investigation of emotional processes, can constrain both the feasibility and frequency of such studies. In contrast, human neuroimaging studies are often faster to conduct and less encumbered by these limitations, potentially contributing to their greater prevalence. Computational modeling, though promising, remains underdeveloped, comprising only 0.6% of studies. Existing models, such as the Emotional Cerebellar Model Articulation Controller (CMAC) and its variants, simulate cerebellar functions for complex system control, but further advancements are needed to match the depth of biological research.

- **Topics**

A deeper understanding of how research has been oriented over time combines both what is being investigated (topics) and on which species it is conducted. First, the thematic category is identified; second, the thematic evolution by species is displayed by a heat map (Figure 1.18). Spikes in specific topics can indicate scientific breakthroughs, technological changes, or discoveries that have driven that topic forward.

To offer an even more detailed view, a bubble chart shows the 5 most dominant topics in each area (Figure 1.19). To construct it, an automated keyword frequency analysis was first conducted using bibliometric tools in Python to identify the most common terms in the dataset. Then, thematically related terms were grouped into broader categories based on semantic similarity and relevance (e.g., ‘depression’, ‘major depressive disorder’, and ‘affective disorder’ were grouped under ‘Affective and Mood Disorders’). This combined quantitative and qualitative method ensured both statistical representativeness and conceptual coherence in topic selection.

Predominant topics include “neurological disorders”, “affective and mood disorders”, and “emotional processing, arousal, and valence” in humans. The least explored areas so far are “neurodevelopmental disorders”, “substance use disorder”, and “neuromodulation and

neurostimulation”. In detail, in the area of “affective and mood disorders”, human studies predominate, with a significant increase starting in 2010 and a peak starting in 2022. To a lesser extent, there were publications on this topic in mice and rats, whose studies began in 2007, but without continuity.

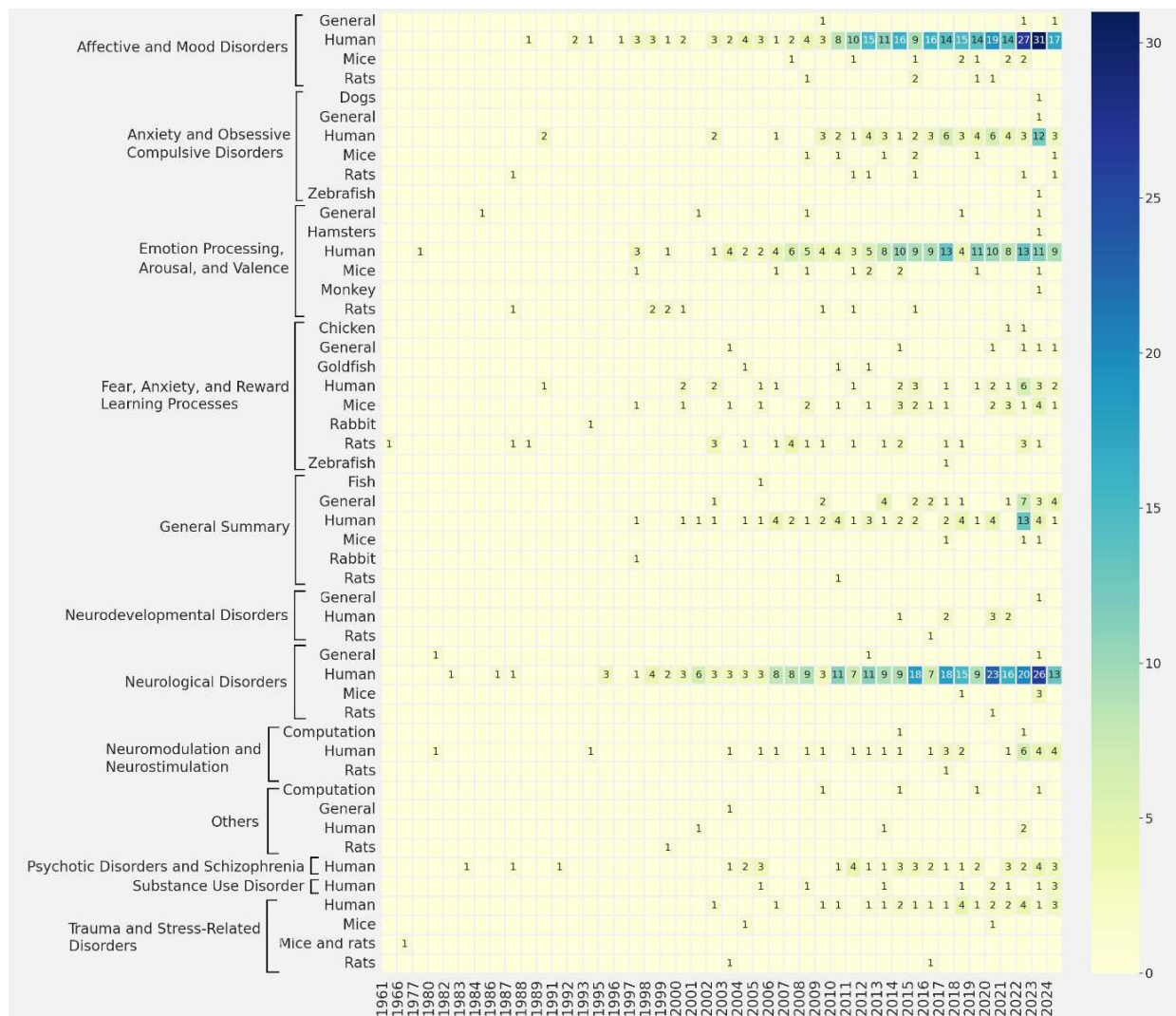


Figure 1.18 Thematic evolution by topic by species. Years on the horizontal axis, and topics and species on the vertical axis. Colours indicate the number of publications for each topic-species combination in a given year, and the colour gradient corresponds to the number of publications.

In the area of “anxiety and obsessive-compulsive disorders”, publications in humans also predominate, with interest emerging since 2009 and peaking in 2023. Regarding “emotional processing, arousal, and valence”, studies in humans have been constant since 2001, showing an increase since 2013. There are also publications in mice and rats, which are smaller and less frequent. In the area related to “fear, anxiety, and reward learning processes”, research is more evenly distributed between humans, mice, and rats, with a slight predominance in humans. In the area we call “general summary”, the focus on humans stands out, with a peak in 2022, followed by those writings where more than one species is mentioned (General). “Neurodevelopmental disorders” are a relatively under-researched topic, and focus especially on humans. Most studies focus on “neurological disorders”, which have seen steady growth since 2006, with a notable peak in 2020. Publications involving rodents in this area are quite limited. Additionally, fields such as “neuromodulation and neurostimulation”, as well as “trauma- and stress-related disorders”, also show a clear preference for human studies. Finally, research on “psychotic disorders and schizophrenia” and “substance use disorders” has been conducted exclusively on humans.

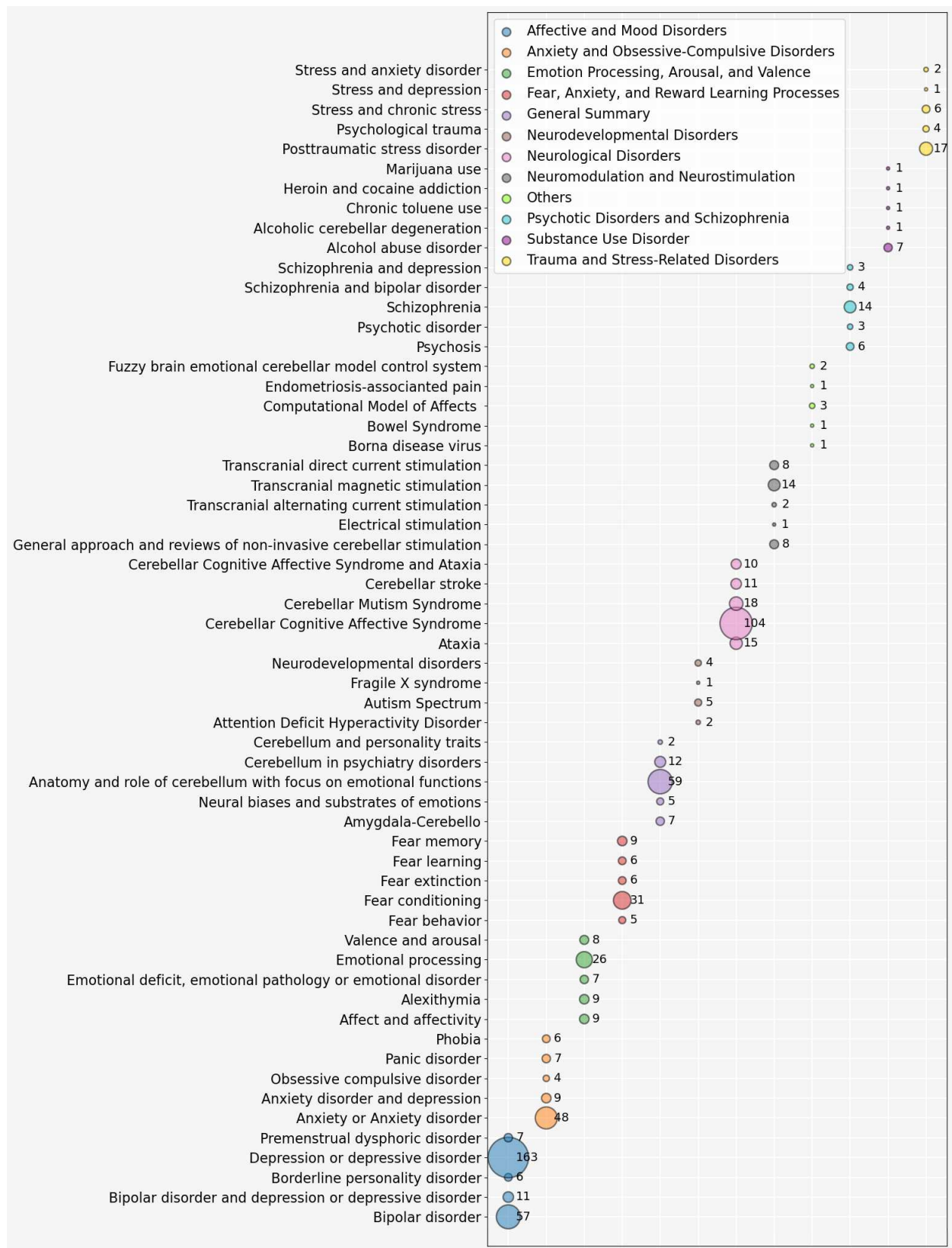


Figure 1.19 Leading topics. The X-axis displays the macro research areas, while the Y-axis represents specific topics within those areas. The size of each bubble indicates the number of publications related to that topic.

- **Main techniques used in the research**

The analysis of the techniques employed in the investigation of the cerebellum and its role in emotions provides a comprehensive and simplified view of a complex picture. This helps to

highlight trends, identify the most researched areas, and reveal possible gaps in the use of methodologies, which is essential to guide future research. For this analysis, we used a Sankey diagram (Figure 1.20), which effectively organizes and displays the connections between categories.

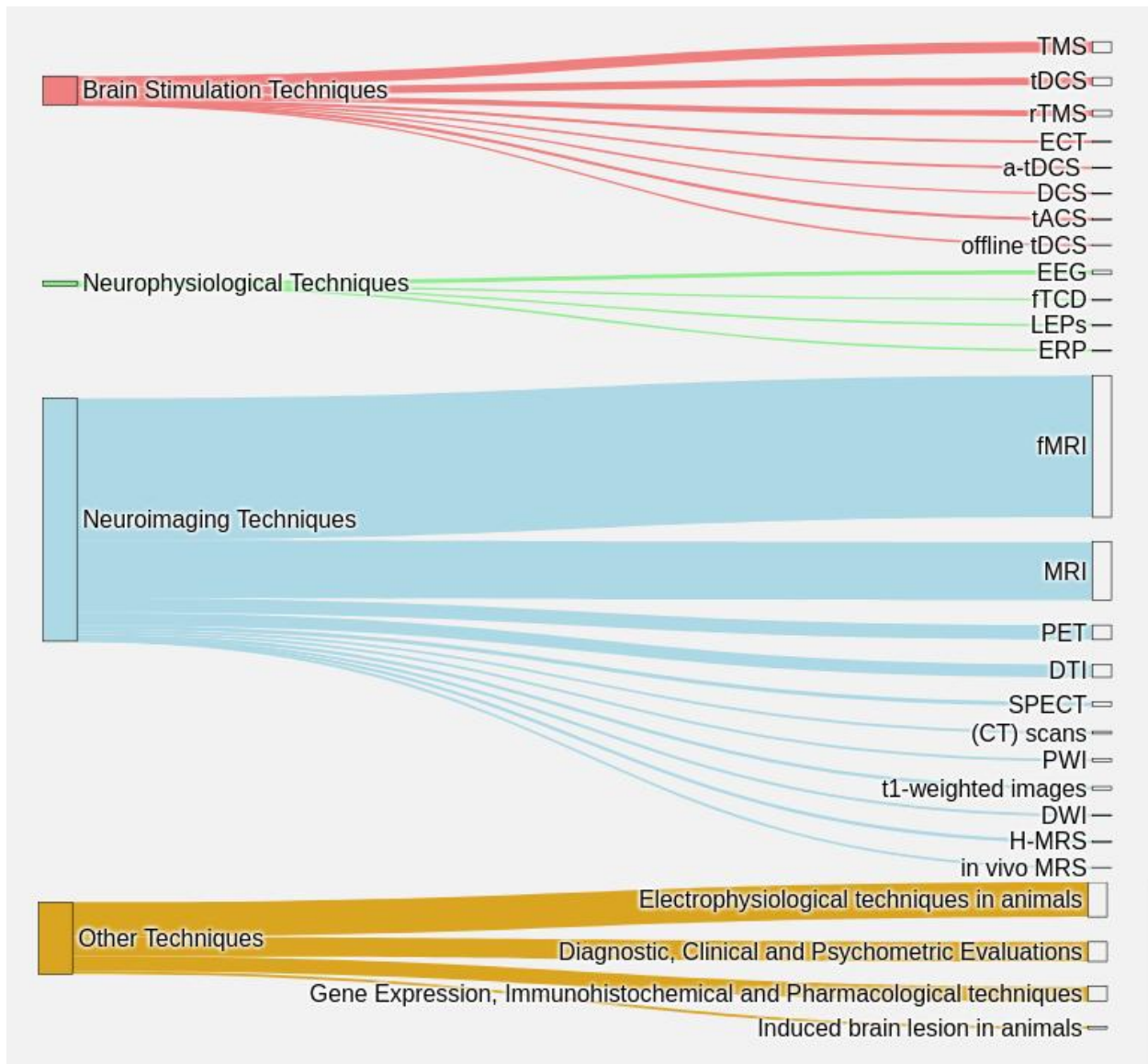


Figure 1.20 Techniques of research. The thickness of the lines indicates the frequency of use of each technique in the studies analyzed. Main Categories: Brain Stimulation Techniques: Includes methods such as rTMS (Repetitive Transcranial Magnetic Stimulation), ECT (Electroconvulsive Therapy), a-tDCS (Anodal Transcranial Direct Current Stimulation), DCS (Direct Current Stimulation), tACS (Transcranial Alternating Current Stimulation), Offline tDCS (Offline Transcranial Direct Current Stimulation), which are used to stimulate or modulate brain activity. Neurophysiological Techniques: include EEG (Electroencephalography), fTCD (Functional Transcranial Doppler), LEPs (Laser-Evoked Potentials), ERP (Event-Related Potentials) methods, which measure brain activity. Neuroimaging Techniques: Comprises advanced methods such as fMRI (Functional Magnetic Resonance Imaging), MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography), DTI (Diffusion Tensor Imaging), SPECT (Single Photon Emission Computed Tomography), (CT) Scans (Computed Tomography Scans), PWI (Perfusion-Weighted Imaging), T1-weighted Images, DWI (Diffusion-Weighted Imaging), H-MRS (Proton Magnetic Resonance Spectroscopy), In vivo MRS (In vivo Magnetic Resonance Spectroscopy), used to study structures, functions and biochemical processes in the brain. Other techniques include experimental and analytical tools in both animals and humans.

Neuroimaging techniques emerge as the predominant methodological approach in research on cerebellar involvement in emotion, primarily due to their non-invasive nature and their applicability to human populations. As illustrated, neuroimaging techniques, particularly fMRI, MRI, and PET, dominate the literature. Brain stimulation techniques such as TMS and tDCS are also represented, though to a lesser extent. Neurophysiological techniques (e.g., EEG, ERP) appear even less frequently.

Other Techniques, which include electrophysiological recordings in animals, diagnostic/psychometric evaluations, and invasive experimental approaches such as gene expression analysis, pharmacological interventions, and lesion studies in animals, form a non-negligible portion of the dataset. Their relative scarcity compared to neuroimaging methods highlights the human-centered focus of current research, as observed previously, rather than indicating a limitation in scientific value. Many key affective circuits are evolutionarily conserved across species, and animal models remain indispensable for investigating the causal and circuit-level mechanisms that cannot yet be directly explored in humans. Far from being of limited use, these approaches are essential complements to human studies and fundamental to advancing our understanding of the cerebellum's role in emotional processes.

- **Researchers**

In a bibliometric analysis, identifying the authors with the highest number of publications in a specific area of interest is essential. It helps pinpoint the most influential and active researchers, who often drive advancements and set trends within the field.

Additionally, these authors are frequently part of key collaboration networks, making it easier to recognize scientific communities and their working dynamics. It also reveals which areas or topics an author publishes in most, allowing for insights into their expertise and research focus.

A stacked bar chart (Figure 1.21) shows the ranking of authors, assigning equal weight to all to reflect collective contributions without specific hierarchies.

It is known that, at times, the position of authors in a publication may reflect the roles they played in the project (study leader, key support in analysis, experiments, or knowledge, supervisor, project manager, and funding). This aspect, detailed in Figures S1.3.1a and S1.3.1b, helps to clarify the contributions and leadership of each author, offering a perspective on their academic impact.

Figure 1.21 shows that the author with the highest publication frequency in the dataset is Schmahmann, with a greater number of publications in Neurology, which is not surprising since he is known for his pioneering work. (*Jeremy Schmahmann, MD - Department of Neurology, n.d.*) On the role of the cerebellum in cognition and emotion, and the description of the cerebellar cognitive-affective syndrome (also called Schmahmann syndrome). The five authors with the highest number of publications are Schmahmann, with more than 30 publications; Wang, with 25 publications; Schutter and Timmann, with more than 20 publications each; and Zhang, with 16 publications. This indicates a high level of research activity. In general, most authors have between 5 and 15 publications. It is observed that researchers publish in journals of different related topics, which suggests a trend toward interdisciplinarity.

It is important to consider that collaboration frequency may be influenced by subfield-specific dynamics, such as higher output rates in clinical domains, which may act as potential confounding factors in interpreting the data. For this reason, the bibliometric analysis presented incorporates a range of complementary approaches to provide a more balanced and multidimensional understanding of research activity in the field.

- **Patterns of Collaboration**

To understand how knowledge is produced in this field, patterns of collaborations and authorships can be described, specifically how researchers collaborate on publications, focusing on the number of authors involved and the frequency of their contributions across multiple works (Figures 1.22 and 1.23). Figure 1.22 shows how the total number of publications varies according to the number of authors involved in each publication. On the other hand, Figure 1.23 illustrates how many authors are involved in different numbers of collaborations, focusing on the frequency of their collaborative activity.

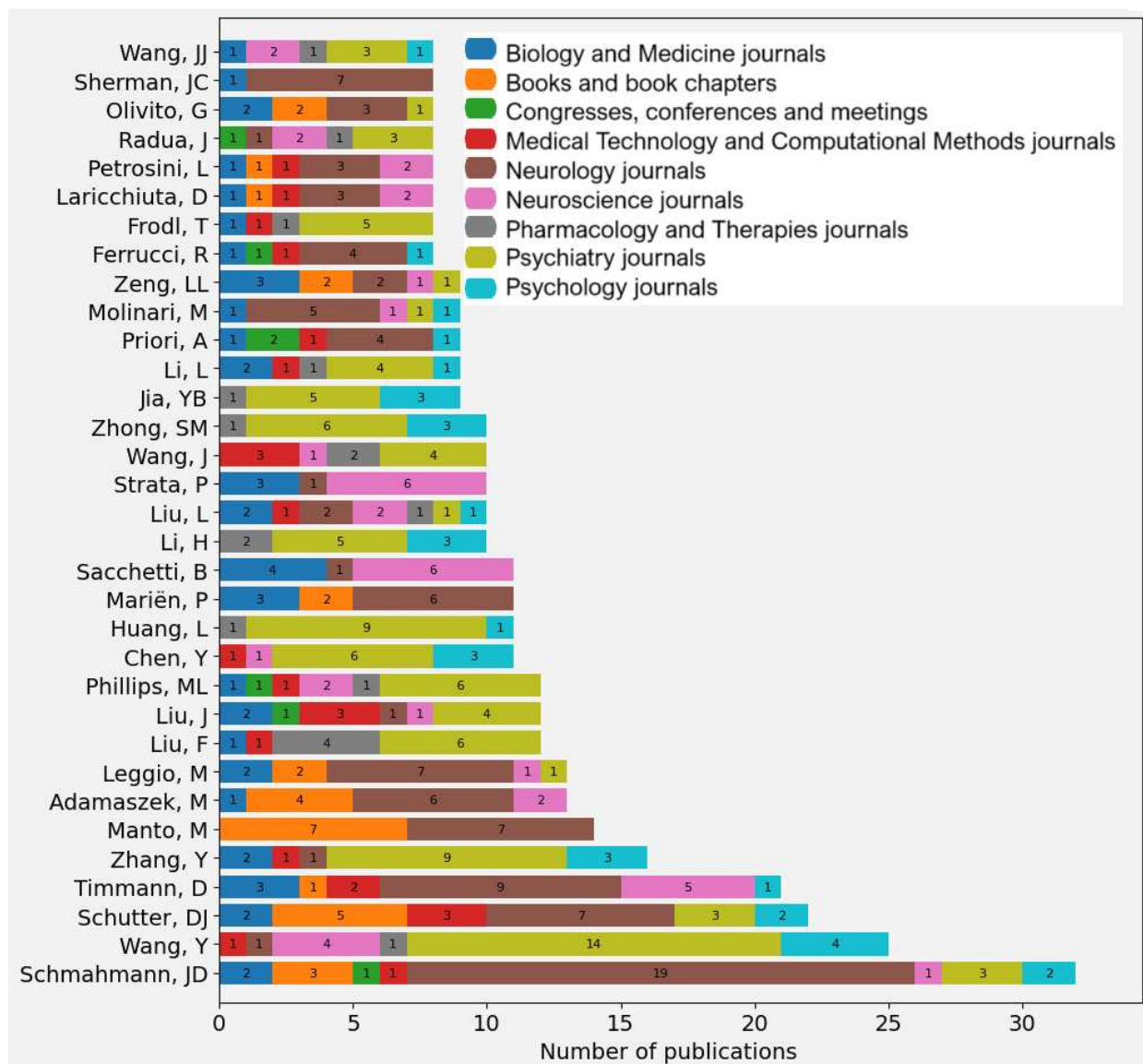


Figure 1.21 Leading authors. Each bar represents an author and is divided into colouring segments indicating the number of publications according to his/her type/domain of publication. The X-axis shows the number of publications, while the Y-axis shows the names of the authors.

Most of the publications have between two and eight authors, with a peak of four. Only two publications stand out for their high number of authors (50 and 110) in the field of clinical research. These high-author counts are attributed to multi-center studies, diversity of specializations, large clinical trials, and international collaborations. The prevalence of publications with fewer authors suggests that limited collaborations may enhance specialization in specific research topics (see Figure 1.22).

The majority of authors have few collaborations, 62 collaborations increase, the number of authors decreases exponentially, forming a “long tail”. This tail represents a small group of highly prolific authors, some with over 100 collaborations. This suggests a collaborative structure where a core group of authors frequently contributes to multiple projects, while most participate occasionally. Additionally, these collaborations involve various combinations of authors rather than fixed teams, as illustrated in Figure 1.23.

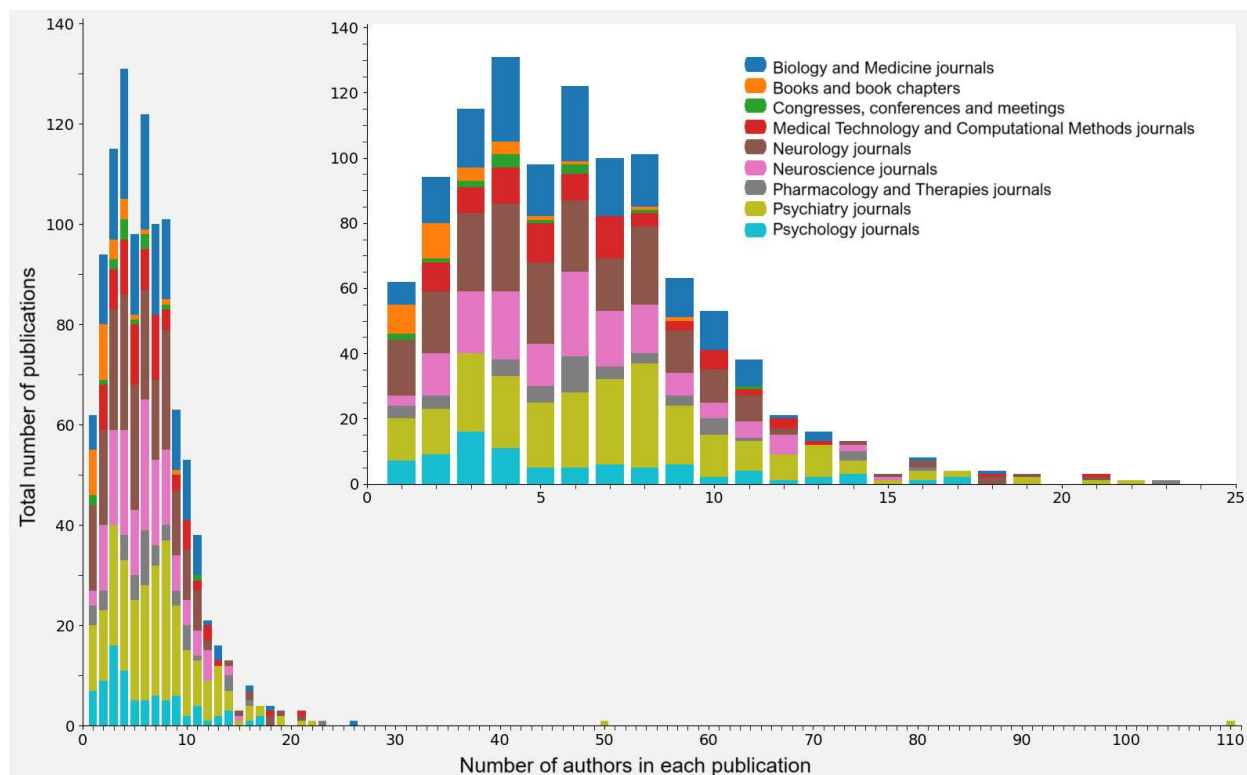


Figure 1.22 Distribution of Publications by Author Count. Distribution of publications based on the number of authors, with stacked bars differentiating between the type/domain of publications.

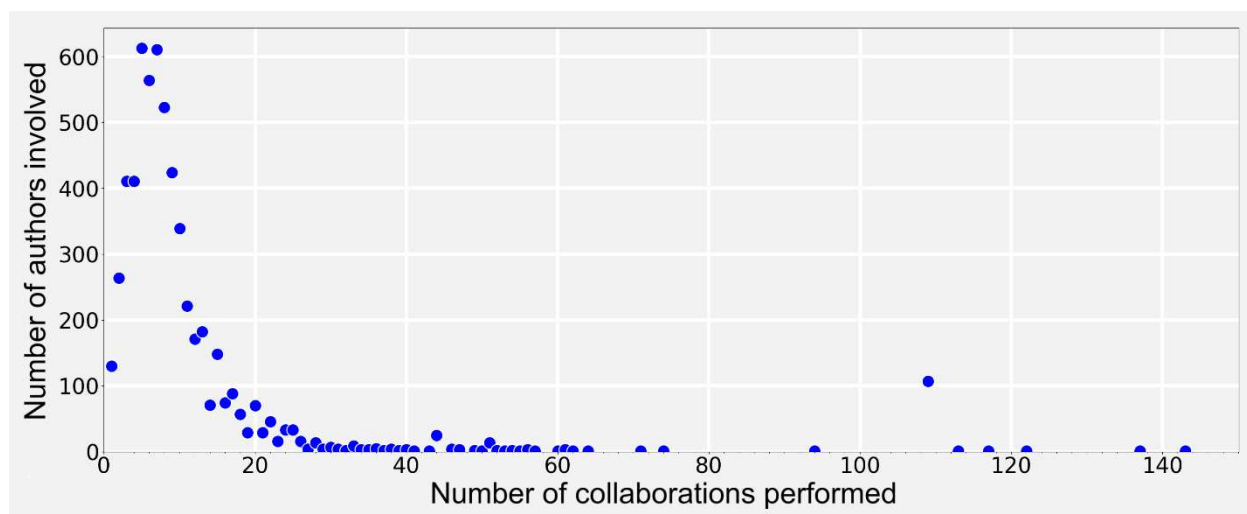


Figure 1.23 Collaboration Patterns by Number of Authors. Scatter plot of the number of collaborations per author. It displays individual collaboration levels.

• Funding

Analyzing the sources of funding sheds light on the resources available to researchers and the priorities of funding agencies, evaluates the relationship between investment and scientific impact, facilitates strategic collaborations, and helps in planning for future investments in research and development. However, it is important to note that not all research articles report funding due to various reasons, such as the use of their own resources, standard institutional infrastructure, or public data that do not require explicit funding. Also, not all journals have strict policies on funding disclosure, mainly in older papers. In other cases, funding may be indirect, coming from previous projects, institutional resources, or general grants not specifically assigned to the work in question.

Table 1.2 shows the public and private organizations that have funded research on the cerebellum and its role in emotions, based on the information reported in the scientific publications.

Table 1.2 Funding Organizations *****Private**

Alexander von Humboldt Foundation, DE
 Alzheimer's Association, US
 Baasch-Medicus Foundation, CH
 Baylor College of Medicine (BCM), US
 BCM-Intellectual and Developmental Disabilities Research Center (IDDRC), US
 Béatrice Ederer-Weber Stiftung, CH
 Birmingham Foundation, US
 Brain & Behavior Research Foundation (BBRF), US
 BBRF-Young Investigator Grant, US
 BBRF- National Association for Research on Schizophrenia and Depression (NARSAD), US
 Brain Research Foundation (BRF), US
 Davis Fellowships, US
 Deutsche Stiftung Neurologie (DSN), DE
 Erasmus MC Foundation, NL
 Else Kröner-Fresenius-Stiftung, DE
 Fondation Leenaards, CH
 Fondation pour la Recherche Medicale, FR
 Friedreich's Ataxia Research Alliance, US
 Fund for Medical Discovery (FMD) Clinical Research Fellowship Award, US
 Hamill Foundation, US
 Heidehof Stiftung, DE
 Hertie-Stiftung, DE
 Instrumentarium Science Foundation, FI
 James S. McDonnell Foundation, US
 James McKeen Cattell Fund, US
 La Caixa Foundation, ES
 Max Planck Society, DE
 MINDLink Foundation, US
 National Ataxia Foundation, US
 Physiological Society, UK
 Physiological Society- Undergraduate training in in vivo sciences grant, UK
 Physiological Society-Vacation Scholarship awarded, UK
 Sigrid Juselius Foundation, FI
 Swiss National Science Foundation (SNSF), CH
 Texas Children's Hospital, US
 The Ataxia Telangiectasia Children's Project, US
 The Berthold Leibinger Stiftung GmbH, DE
 The Paulo Foundation, FI
 The Phyllis & Jerome Lyle Rappaport Foundation, US
 The Reinhold Beitlich Foundation, DE
 The Synapsis Foundation, CH
 The Finnish Medical Foundation, FI
 Wellcome Trust, UK
 Wellcome Trus-Sir Henry Wellcome Postdoctoral Fellowships, Sir Henry Dale Fellowships, UK
 Whitehall Foundation, US
 Wyss Foundation, US

Public

Agence Nationale de la Recherche (ANR), FR
 ANR, CerebelliEMO, FR
 Australian Research Council (ARC), AU
 ARC-Australian Laureate Fellowship, Centre of Excellence for Integrative Brain Function, Centre of Excellence in Cognition and its Disorders, Discovery Early Career Researcher, Science of Learning Research Centre, AU

Australian Government, AU

Research Training Program (RTP) Scholarship, Primary health and medical research funding agency, AU

Austrian Science Fund (FWF), AU

Beijing Municipal Science & Technology Commission Grant, CN

Biotechnology and Biological Sciences Research Council (BBSRC), UK

Canadian Institutes of Health Research (CIHR), CA

Consejo Nacional de Investigaciones Científicas y Técnicas, AR

Consejo Nacional de Ciencia y Tecnología (CONACYT), MX

Consejo Superior de Investigaciones Científicas (CSIC), ES

Conselho Nacional de Desenvolvimento Científico e Tecnológico, BR

Deutsche Forschungsgemeinschaft (DFG), DE

Dutch Ministry of Health, NL

Department of Health and Human Services (HHS), US

European Molecular Biology Laboratory (EMBL)

European Molecular Biology Conference (EMBC)

EMBC- European Molecular Biology Organization (EMBO)

European Regional Development Fund (FEDER) grant

European Research Council (ERC)

ERC-Horizon 2020 (H2020), Seventh Framework Programme (FP7), Starting Grant

H2020- ActionContraThreat, NeuroTRACK, REALNET, LTFCOFUND2013, Human Brain Project (HBP), Cerebellum and Emotional Networks (CEN)

FP7, CEREBNET

Foundation for Dutch Scientific Research (NWO), NL

NOW-Veni grant, NL

Fondazione IRCCS, IT

Fundação de Amparo à Pesquisa do Estado de São Paulo, BR

Fundação para a Ciência e a Tecnologia, PT

Guangdong Basic and Applied Basic Research Foundation, CN

Grants-in-Aid for Scientific Research (KAKENHI), JP

Institut National de la Santé et de la Recherche Médicale, FR

Italian Ministry of Health, IT

Japan Agency for Medical Research and Development, JP

Japan Society for the Promotion of Science (JSPS), JP

Korea Science and Engineering Foundation (KOSEF), KR

Labex Memolife, FR

Ministry of Education, Universities and Research, IT

Ministry of Education, Universities and Research, MNESYS, IT

Ministry of Health, Welfare and Sport, NL

Ministry of Science and Technology (MOST), TW

Munich University Hospital of the Ludwig-Maximilians-Universität München (LMU), DE

National Basic Research Program of China, CN

National Institute of Health Carlos III (ISCIII), ES

ISCIII-Miguel Servet contract, ES

National Key Research and Development Program of China, CN

National Natural Science Foundation of China, CN

National Research Foundation of Korea (NRF), KR

NRF- KOSEF grant, KR

National Science Foundation CAREER award, US21

Natural Science Foundation of Hunan Province, CN

National Competence Center for Research SYNAPSY, CH

National Institute of Neurological Disorders and Stroke, US

National Institutes of Health (NIH), US

NIH-National Institutes of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), National Cancer Institute (NCI), National Institute on Aging (NIA), National Center for Advancing Translational Sciences (NCATS), National Center for

Complementary and Integrative Health (NCCIH), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute on Drug Abuse (NIDA), NIH, National Institute of Environmental Health Sciences (NIEHS), National Institute of Child Health and Human Development (NICHD), National Center for Research Resources (NCRR), National Institute of General Medical Sciences (NIGMS), National Institute of Mental Health (NIMH), US
 Natural Sciences and Engineering Research Council of Canada (NSERC), CA
 Nederlandse Organisatie voor Wetenschappelijk Onderzoek, NL
 Projekt DEAL, DE
 Russian Science Foundation, RU
 Rutherford Discovery Research Fellowship, NZ
 Shandong Provincial Natural Science Foundation, CN
 Strategic Basic Research funding programme (SBO), BE
 UK Research and Innovation (UKRI), UK
 UKRI- Medical Research Council (MRC), UKC
 Veterans Affairs (VA), US
 VA-Clinical Science Research and Development (CSR), US
 West China Medical School and West China Hospital, CN
 21st Century Frontier R&D Program, Korea
 Brain Korea 21 Program for Leading Universities & Students, Korea

***The classification is not strict. Although a careful categorization has been attempted, it is an approximation aimed at improving the understanding and analysis of information obtained from scientific articles.

Financial support from diverse funding bodies including government agencies, ministries, national research councils, associations, foundations, and independent public and private organizations, are supporting this research field. Particularly in the U.S., Europe, Australia, the U.K., and China. However, limited funding in Latin America, Africa, and parts of Asia highlights disparities in resources and infrastructure, restricting participation in this field.

- **Affiliations**

Author affiliation plays a key role in scientific production, reflecting the resources and infrastructure of institutions rather than the researchers' nationality. Understanding affiliations helps identify leading countries and institutions, reveals regional inequalities, guides global collaboration, and informs funding priorities. A world map (Figure 1.24) combines geographic and scientific data to illustrate these dynamics, created using GeoPandas (*GeoPandas 1.0.1 — GeoPandas 1.0.1+0.G747d66e.Dirty Documentation*, n.d.)

Author's affiliations show significant regional disparities. The U.S. and mainland China lead in publications, followed by some European countries, the U.K., and Canada, supported by strong infrastructure, technology, and funding (observed in Table 1.3). Countries like Australia, Japan, South Korea, Brazil, and Mexico rank at an intermediate-low level, while regions/economies such as Taiwan (China), Hong Kong (China), Israel, Singapore, India, Argentina, Chile, South Africa, Russia, Saudi Arabia, and Iran show very low output. Africa, more Latin American countries, and Central Asia are largely underrepresented due to limited infrastructure, funding (observed in Table 1.3), and prioritization of research, further exacerbated by the "brain drain" and difficulties in gaining global recognition.

- **Collaboration Networks**

The temporal analysis of academic collaboration networks and co-authorship dynamics is carried out using two Python libraries designed for creating, manipulating, and studying complex network structures, NetworkX (*NetworkX — NetworkX Documentation*, n.d.) for exploratory analysis and the calculation of metrics, and Graph-tool (*Graph-Tool*, n.d.) for large-scale network visualization.

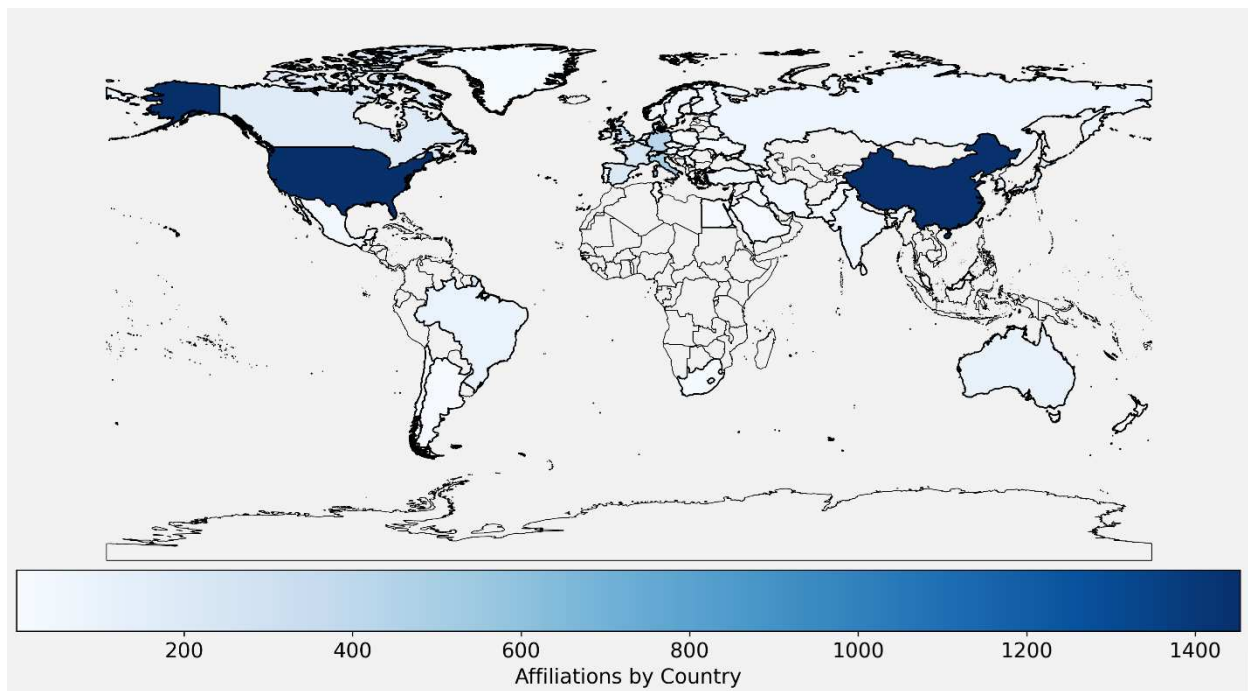
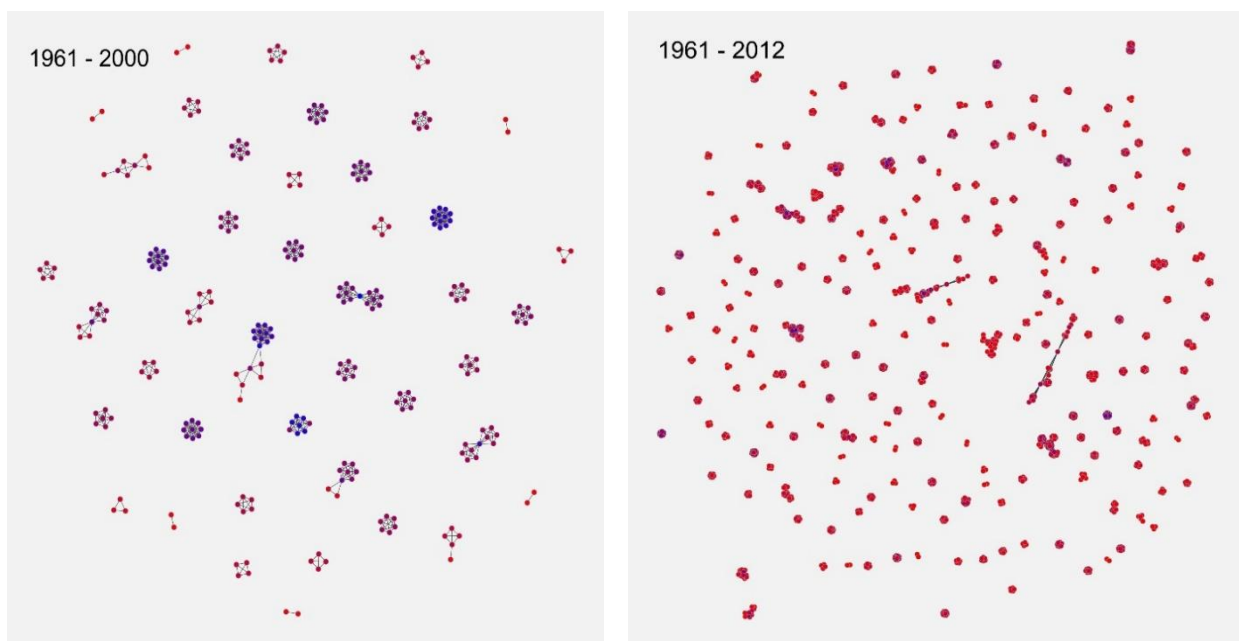


Figure 1.24 Geographic Distribution of Authors' Affiliations. A colour gradation identifies leading and less-developed regions in terms of involvement in this scientific research.

- **Visualization of the Collaboration Network**

A network graph is useful to understand a complex system and how its components interact with each other (Albert-László Barabási, n.d.). In a collaboration network, the nodes represent individual entities (authors), while the connections indicate collaborative relationships between them in scientific publications. The Scalable Force-Directed Placement algorithm, available in the NetworkX library (*NetworkX — NetworkX Documentation*, n.d.) provides a clear and scalable visualization of the graph structure over different periods. Figure 1.25 illustrates how the network has evolved, based on four selected periods, allowing us to assess how collaborations develop and change throughout these intervals.



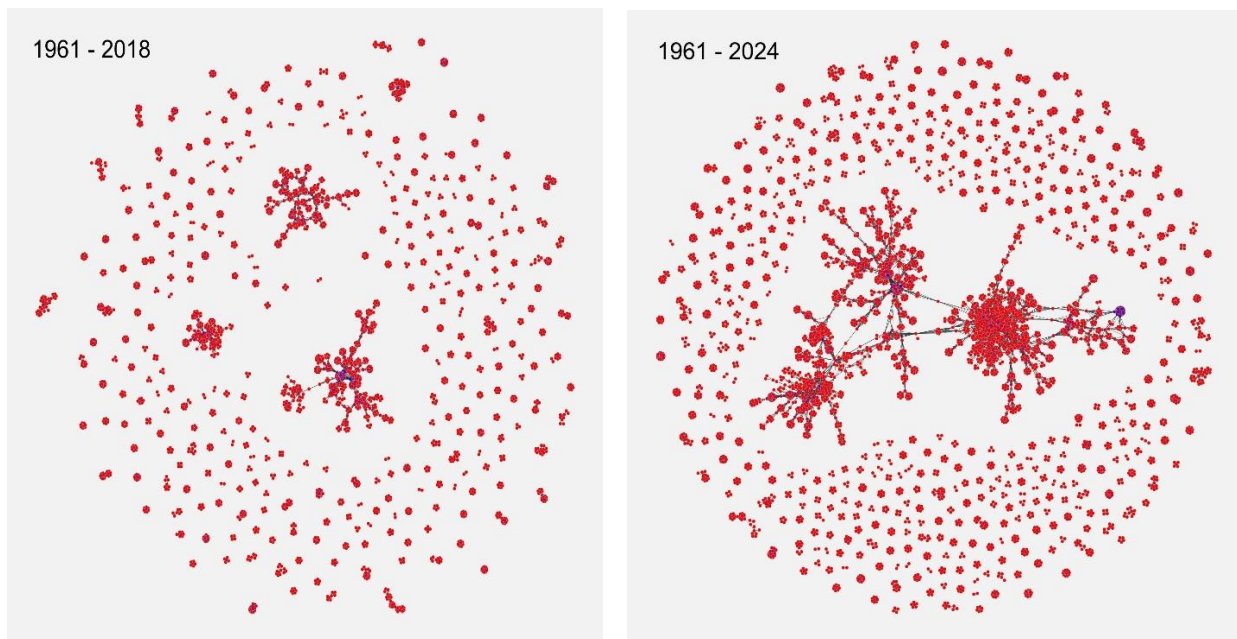


Figure 1.25 Evolution of the Collaboration Network in Different Periods of Time. Evolution of the network in four periods. Nodes are coloured and scaled based on their degree centrality, which reflects the number of connections each node has. Highly connected nodes are blue, peripheral ones with fewer connections are red, and intermediate nodes are purple. The layout minimizes overlap, clustering more connected nodes together. Duplicate edges are removed to avoid clutter, and “bunches of grapes” represent clusters or communities of closely connected nodes.

In the first period 1961-2000 (top left image) the network is small, consisting of compact, isolated groups with limited connections. Key nodes (in purple and blue) serve as links between groups, indicating preliminary alliances.

During the period 1961-2012 (top right image), a significant increase in nodes and connections is observed, leading to a dispersed network with no dominant nodes or groups. Clusters operate autonomously, with strong internal connections but limited interactions between clusters, except for a few bridging groups.

Between 1961-2018 (bottom left image), the network grows further, with higher connection density and reduced isolation of peripheral clusters. Emerging hubs act as central nodes, fostering inter-group collaboration and reflecting a growing number of collaborators.

The complete network, spanning from 1961-2024 (bottom right image) achieves high complexity, with numerous nodes and dense clusters. Subgroups are clearly visible, indicating frequent collaborations within areas of expertise or specialized teams. The absence of a dominating node highlights a balanced, distributed network structure

- **Metrics Analysis**

The metrics used in graph theory (Albert-László Barabási, n.d.; Arif, Tasleem, 2015; Newman, 2018; Reinhard Diestel, 2024) not only enhance visualizations by providing concrete data but are also essential for characterizing and analyzing the collaboration network, offering a deeper understanding of its structure, key nodes, and temporal dynamics.

We strongly encourage readers to review (Albert-László Barabási, n.d.; Arif, Tasleem, 2015; Newman, 2018; Reinhard Diestel, 2024) for theoretical foundation, as well as the Supplementary Table S1.2.3.4 which presents a detailed analysis and explanations of the network’s main metrics, assessing its structure and behavior over time. This will provide a better understanding of the analysis.

The metrics confirm quantitatively the previous observations in Figure 1.25. There is significant growth in the number of publications, researchers, and collaborations, reflecting increased scientific activity and interaction among participants. In addition, the network is becoming more cohesive, with larger groups of people working together and an increase in the formation of small, well-connected teams, which act as “hubs” for collaboration in specific areas.

When analyzing the most important connections within the network, it is observed that, although researchers are more distributed and less concentrated in one place, some of them become key intermediaries to connect different areas of knowledge. There is also a general improvement in connectivity among participants, which means that it is easier for anyone within the network to access information or collaborate with others.

Diversity in connections increases, indicating that researchers are collaborating with more people and on more varied topics. At the same time, small groups that used to be very isolated are becoming more integrated, forming a more interconnected network. However, while the network is more resilient to the loss of random connections, it is still vulnerable if certain key individuals or teams that act as important bridges are lost.

Overall, the network not only grows in size, but also becomes more complex, diverse and integrated. This reflects more efficient scientific collaboration, with broader interactions and a structure that fosters both specialization and connection between different areas of knowledge.

1.3.3 Discussion and Conclusions

- Advances in the field: Research on the cerebellum's role in emotions has expanded significantly, driven by the identification of cerebellar affective-cognitive syndrome, technological advancements and interdisciplinary approaches. Early research focused primarily on psychiatry and neurology, but the field has since expanded to incorporate disciplines such as psychology, medical technologies, computational methods, pharmacology, and therapeutic strategies. These developments have deepened our understanding of the cerebellum's impact on emotional processing particularly in the context of neurological and affective disorders.

- Methodological and thematic trends: Neuroimaging techniques have become indispensable due to their noninvasive capacity to analyze brain activity and structure, particularly in studying the interactions between the cerebellum and emotional regions. While stimulation and neurophysiological methods provide complementary insights, their application remains secondary. Research is predominantly focused on human studies, underscoring their clinical relevance and importance to medical practice. In contrast, animal models, such as mice and rats, are underrepresented, with limited exploration of other species. Similarly, computational models, although promising, are still in their early stages, emphasizing the need for further development of multiscale models (D'Angelo & Jirsa, 2022; Lytton et al., 2017; Ramaswamy, 2024) that integrate structural, functional, and dynamic aspects across multiple levels—from micro to macro scales—will be pivotal in advancing our understanding of its multidimensional functions. These models should leverage insights from experimental studies, computational modeling, and clinical research to construct a comprehensive framework for exploring the cerebellum's complexity and its interactions within broader neural networks.

- Evolution of collaboration scientific networks: The analysis of collaboration networks reveals a balance between specialization and interdisciplinarity. These networks are characterized by large nodes or "clusters," which represent influential authors or highly productive teams, alongside numerous peripheral nodes that reflect less integrated participants. While these decentralized structures foster innovation and resilience, challenges related to global connectivity and integration remain. Efforts should focus on strengthening global connectivity in collaborative networks by promoting international funding and open-access initiatives. Encouraging deeper interdisciplinarity, particularly with emerging fields like artificial intelligence and medical technologies, could drive innovation. Supporting less integrated participants and leveraging advanced computational tools for network analysis may further enhance collaboration and scientific impact.

- Comparison with other research areas: The evolution of research on the cerebellar role in emotions shares similarities with other fields in terms of exponential growth, although the driving factors vary. For example, although with a higher volume of publications, in areas such as resting-state fMRI research on schizophrenia (Fu et al., 2024) growth also started slowly but has increased considerably reflecting a growing interest. In contrast, fields like artificial intelligence applied to radiation therapy (Lv et al., 2024), virtual reality for addressing depression and anxiety (Jingili et al., 2023), and deep learning in cancer (Wang et al., 2024) present a growth starting much later and abruptly and explosively in a very short time. On the contrary in areas such as

emotional intelligence and social interaction (Ida Merlin & Prabakar, 2024) exhibit lower but steady production, with occasional fluctuations.

- Comparison with other Neuroscience fields using similar approaches: Although the use of bibliometric and collaboration network analysis is still emerging in neuroscience, several studies have successfully applied these methods to specific subfields, demonstrating their utility in identifying research gaps and guiding future directions. For example, (Xu et al., 2022) used these techniques to map the evolution of cultural neuroscience, revealing key contributors, emerging topics, and collaboration dynamics. (Emissah et al., 2023) conducted a bibliometric study on neural morphology, showing how data sharing through NeuroMorpho.Org enhances citation impact and promotes reuse, contributing to research efficiency and visibility. Similarly, (Tekin & Dener, 2025) examined artificial intelligence in neuroscience, uncovering publication trends and collaborative hubs in areas like brain–computer interfaces and neuroimaging. Other examples include collaboration network studies in translational neuroscience (Marchand et al., 2018), which focused on understanding research activity and team dynamics within a research center. These studies illustrate how this type of analysis can go beyond simply mapping literature to inform funding priorities, foster interdisciplinary connections, and guide hypothesis generation.

- Regional challenges and inequalities: Global research output tends to be concentrated in high-income areas with strong resources and infrastructure, while other regions face challenges such as limited funding, "brain drain," and lower visibility in the scientific community. These disparities highlight the importance of fostering international collaborations, increasing public and private investment in research, and enhancing access to resources in underrepresented areas. Encouraging the use of open-access journals and reducing or eliminating publication fees can also contribute to greater equity in knowledge dissemination and visibility.

- Philosophical perspective, the evolution of the paradigm: Traditionally, the cerebellum was considered a structure dedicated exclusively to motor control, and research for decades adhered to this paradigm. However, evidence of its involvement in emotional and cognitive functions has challenged this view, prompting a significant revision of the paradigm. Rather than discarding the previous framework, these discoveries have enriched and reconfigured scientific understanding, revealing a more complex and multidimensional role for the cerebellum. According to Thomas S. Kuhn (Kuhn, 1997), a scientific revolution involves the replacement of a dominant paradigm when anomalies accumulate and cannot be explained within the existing framework. In the case of the cerebellum, although anomalies have emerged, they have not led to a paradigm shift or scientific revolution. Instead, this represents a refinement of the existing paradigm. Other philosophical perspectives offer complementary insights. Imre Lakatos' theory of research programs (Lakatos, 1978) might interpret these advancements as a progressive transition within the current framework of cerebellar studies. Similarly, Willard Van Orman Quine's view of science as a continuous, interconnected system of beliefs (van Orman Quine, 1976) could frame this as an adjustment within the broader network of scientific knowledge, rather than a radical transformation.

In conclusion, this study provides a state-of-the-art overview of research on the cerebellum's role in emotions by systematically analyzing all available publications up to the study date, employing advanced bibliometric and collaboration network techniques. In contrast to other studies, this research introduces new elements in the search and analysis process, and the integration of multiple software tools. These innovations allow for a more comprehensive and robust analysis. To the best of our knowledge, this is the first published study to examine the evolution of research on this topic using these methodologies, making a unique and significant contribution to the field. Our findings reveal significant growth in scientific output and interdisciplinary collaboration, particularly in studies focused on neurological and affective disorders, while also highlighting persistent challenges such as knowledge fragmentation, unequal resource access, and underexplored research areas.

Table S1.3.1 Type of publications*	
Biology and Medicine Journals ■	Books ■
Acta Medica Portuguesa	Anatomy of Neuropsychiatry
Advances in Experimental Medicine and Biology	Anticipation and Medicine
African Journal of Medicine and Medical Sciences	Development of the Cerebellum from Molecular Aspects to Diseases
Aging-Us	Developmental Disorders of the Brain
American Journal of Medical Genetics	Disorders of Emotion in Neurologic Disease
Anales de Pediatría	Essentials of Cerebellum and Cerebellar Disorders
Archives de Pédiatrie	Emotions and the Psychodynamics of the cerebellum
Archives Italiennes de Biologie	Handbook of Clinical Neurology
Archives of Gerontology and Geriatrics	Progress in Brain Research Book series
Archives of Physical Medicine and Rehabilitation	Neural Mechanisms of Language
Archivos Argentinos de Pediatría	Pattern Analysis of the Human Connectome
Biology Letters	The Emotional Cerebellum
Biomed Research International	The Cerebellum Disorders and Treatment
Biomedical Sciences	The Linguistic Cerebellum
Biomedicines	Understanding Emotions
Biorxiv	
Brain, Behavior and Evolution	Congresses, Conferences and Meetings ■
Brain, Behavior, and Immunity	18th European Congress of Psychiatry
Brazilian Journal of Medical and Biological Research	2013 International Conference on Advanced Computer Science Applications and Technologies
British Journal of Anaesthesia	17th International Computer Conference on Wavelet Active Media Technology and Information Processing
British Journal of Hospital Medicine	Abstract of the 25th European Congress of Psychiatry
Bulletin of Experimental Biology and Medicine	Abstract Supplement
Cancer	Abstracts of the 14 European Congress of Clinical Neurophysiology and the 4 International Conference on Transcranial Magnetic and Direct Current Stimulation
Case Reports in Medicine	Neuroimage: Clinical
Cell Reports	Abstracts of the 20th European Congress of Psychiatry
Child Abuse & Neglect	Abstracts of the 21st European Congress of Psychiatry
Clinical Case Reports	Abstracts of the 22nd European Congress of Psychiatry
Clinical Neurophysiology	Abstracts of the 24th European Congress of Psychiatry
Cureus	Interspeech 2009: 10th Annual Conference of The International Speech Communication Association
Current Biology	Journées de Neurologie de Langue Française 2017
Developmental Disabilities Research Reviews	Annual International Conference of The IEEE Engineering in Medicine and Biology Society
Elife	
European Journal of Pediatrics	
Folia Morphologica	
Frontiers in Cell and Developmental Biology	
Frontiers in Neurology	
Frontiers in Public Health	
Hormones and Behavior	
Human Molecular Genetics	
Internal Medicine	
International Journal of Legal Medicine	
International Journal of Molecular Sciences	
International Journal of MS Care	
International Review of Neurobiology	
Journal of Cancer Survivorship	
Journal of Clinical and Diagnostic Research	

Journal of Medical Case Reports Journal of Neurochemistry Journal of Pediatric Hematology/ Oncology Journal of Pediatric Hematology/Oncology Nursing Journal of Pediatric Rehabilitation Medicine Journal of the American Geriatrics Society Journal of Trace Elements in Medicine and Biology JPMA The Journal of the Pakistan Medical Association Kaohsiung Journal of Medical Sciences Medical Hypotheses Medical Science Monitor Medicine Medrxiv Metabolic Brain Disease Metabolites Molecular Neurobiology Molecular Nutrition & Food Research Molecular Therapy Nucleic Acids Nan Fang Yi Ke Da Xue Xue Bao Nature Communications Neurobiology of Learning and Memory Neurobiology of Stress Neurogenetics Neuro-Oncology Advances Neuropsychobiology Oncotarget Orvosi Hetilap Pediatria de Atencion Primaria Pediatric Hematology and Oncology Physiological Genomics Physiological Research Physiology & Behavior Plastic and Reconstructive Surgery Plos One Proceedings of the National Academy of Sciences of the United States of America Psychosomatic Medicine Psychosomatics Reproductive Sciences Science Scientific Reports Trials Zhejiang Da Xue Xue Bao Yi Xue Ban Zhongguo Dang Dai Er Ke Za Zhi Zhongguo Ying Yong Sheng Li Xue Za Zhi Zhonghua Yi Xue Za Zhi Neuroscience Journals ■ Aims Neuroscience American Journal of Play Annual Review of Neuroscience Behavioral and Brain Functions	Proceedings of the 10th International Child Neurology Congress Evolution and Development of Nervous System The Abstracts from the 2024 Southern Regional Meeting IBRO World Congress Medical Technology and Neurocomputing Journals ■ Acta Polytechnica Hungarica Adaptive Behavior Applied Biochemistry and Biotechnology Applied Sciences-Basel BMC Medical Imaging Brain Imaging and Behavior Brain Stimulation Chinese Journal of Medical Imaging Technology Computational and Mathematical Methods in Medicine European Journal of Radiology European Radiology Experimental Hellenic Journal of Nuclear Medicine Human Brain Mapping IEEE Transactions on Neural Systems and Rehabilitation Engineering International Journal of Fuzzy Systems International Journal of Nanotechnology Journal of Hazardous Materials Journal of Neuroimaging Neurocomputing Neuroimage Clinical Neuroimage Neuroinformatics Plos Computational Biology Scientific Programming Statistics in Medicine Neurology Journals ■ Acta Neurochirurgica Acta Neurologica Belgica Acta Neurológica Latinoamericana Alzheimer's & Dementia Annals of Indian Academy of Neurology Annals of Neurology Archives of Neurology Archives of Pediatric Neurosurgery Archivos Argentinos de Pediatría Behavioral and Brain Functions Behavioural Brain Research Behavioural Neurology Biological Psychiatry-Cognitive Neuroscience and Neuroimaging BMC Neurology
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Behavioral Neuroscience	Brain & Development
Behavioural Brain Research	Brain: A Journal of Neurology
Brain Circulation	Brain and Behavior
Brain Connectivity	Brain and Cognition
Brain Research	Brain and Nerve = Shinkei Kenkyu no Shinpo
Brain Research Bulletin	Brain Injury
Brain Research Reviews	Brain Structure & Function
Brain Sciences	Brain
CNS Neuroscience & Therapeutics	British Journal of Neurosurgery
CNS Spectrums	Cerebellum & Ataxias
Cognitive Affective & Behavioral Neuroscience	Cerebellum
Cognitive Neurodynamics	Cerebral Cortex
Cognitive, Affective & Behavioral Neuroscience	Cerebral Cortex Communications
Developmental Cognitive Neuroscience	Cerebrovascular Diseases
eNeuro	Child's Nervous System
Experimental Brain Research	Clinical Neurology and Neurosurgery
Frontiers in Aging Neuroscience	Cognitive and Behavioral Neurology
Frontiers in Behavioral Neuroscience	Cortex
Frontiers in Cellular Neuroscience	Current Neurology and Neuroscience Reports
Frontiers in Human Neuroscience	Current Opinion in Behavioral Sciences
Frontiers in Neural Circuits	Current Opinion in Neurology
Frontiers in Neuroendocrinology	Dementia
Frontiers in Neuroscience	Der Nervenarzt
Frontiers in Synaptic Neuroscience	Developmental Medicine and Child Neurology
Frontiers in Systems Neuroscience	Epilepsia
IBRO Reports	Epilepsy & Behavior Reports
International Journal of Neuroscience	Epilepsy & Behavior
Journal of Clinical Neuroscience	European Journal of Neurology
Journal of Integrative Neuroscience	European Journal of Paediatric Neurology
Journal of Neurolinguistics	Frontiers in Neurology
Journal of Neuroscience	Frontiers in Physiology
Journal of Neuroscience Methods	Genes, Brain, and Behavior
Journal of Neuroscience Research	Journal of Alzheimer's Disease
Nature Neuroscience	Journal of Clinical Neurology (Seoul Korea)
Nature Reviews Neuroscience	Journal of Geriatric Psychiatry and Neurology
Neural Plasticity	Journal of Intellectual Disability Research
Neural Regeneration Research	Journal of Neural Transmission
Neurocase	Journal of Neurological Surgery Part B: Skull Base
Neuron	Journal of Neurology Neurosurgery and Psychiatry
Neuroreport	Journal of Neurology
Neuroscience and Biobehavioral Reviews	Journal of Neurology, Neurosurgery, and Psychiatry
Neuroscience Letters	Journal of Neurosurgery
Neuroscience Research	Journal of Neurosurgery: Pediatrics
Neuroscience	Journal of Stroke & Cerebrovascular Diseases
Nutritional Neuroscience	Journal of The Neurological Sciences
Reviews in the Neurosciences	L.O.G.O.S. Interdisziplinair
Social Cognitive and Affective Neuroscience	Movement Disorders
Social Neuroscience	Multiple Sclerosis
Synapse (New York, N.Y.)	Nature Reviews Neuroscience
The Neuroscientist	Nervenarzt
The European Journal of Neuroscience	Neurologia I Neurochirurgia Polska
The Journal of Neuroscience	Neurologic Clinics
Zhurnal Vysshei Nervnoi Deiatelnosti Imeni IP Pavlova	Neurological Research and Practice

Pharmacology and Therapies Journals ■ Archives of Physical Medicine and Rehabilitation Behaviour Research and Therapy Biochemical Pharmacology Brain Stimulation Cellular Physiology and Biochemistry Biochemistry, and Pharmacology Chemosphere Clinical Psychopharmacology and Neuroscience Cognitive Therapy and Research Complementary Therapies in Medicine Current Neuropharmacology Environmental Toxicology and Pharmacology European Journal of Pharmacology International Journal of Immunopathology and Pharmacology International Journal of Neuropsychopharmacology Journal of Child and Adolescent Psychopharmacology Journal of Clinical Psychopharmacology Journal of Psychopharmacology Molecular Therapy Nucleic Acids Neuropharmacology Nihon Shinkei Seishin Yakurigaku Zasshi Physical Medicine and Rehabilitation Progress in Neuropsychopharmacology & Biological Psychiatry Psychopharmacology Psychology Journals ■ Acta Psychologica Sinica Adicciones Alcohol and Alcoholism Annales Médico-Psychologiques, Revue Psychiatrique Applied Neuropsychology: Adult Applied Neuropsychology: Child Archives of Clinical Neuropsychology Australian Journal of Psychology Child Neuropsychology Cogent Psychology Cognition & Emotion Cognizance of Schizophrenia: A Profound Insight into the Psyche Current Addiction Reports Development and Psychopathology Developmental Neuropsychology Emotion	Neurological Research Neurological Sciences Neurology Asia Neurology India Neurology Perspectives Neurology Neurooncology Advances Neurooncology Parkinsonism & Related Disorders Pediatric Neurology Pediatric Neurosurgery Perceptual and Motor Skills Progress in Neurological Surgery Revista de Neurologia Revue Neurologique Surgical Neurology International The Primary Care Companion for CNS Disorders The Cerebellum World Neurosurgery Zhurnal Nevrologii I Psikhatrii Imeni S.S. Korsakova Psychiatry Journals ■ Acta Neuropsychiatrica Acta Psychiatrica Scandinavica Actas Españolas De Psiquiatría American Journal of Geriatric Psychiatry American Journal of Psychiatry Archives of General Psychiatry Arquivos de Neuropsiquiatria Asia-Pacific Psychiatry Australian and New Zealand Journal of Psychiatry Biological Psychiatry: Cognitive Neuroscience and Neuroimaging Biological Psychiatry Global Open Science Biological Psychiatry Bipolar Disorders BMC Psychiatry British Journal of Psychiatry Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie Case Reports in Psychiatry Ceskoslovenska Psychiatrie Chronic Stress Clinical Schizophrenia and Related Psychoses, Cognizance of Schizophrenia: A Profound Insight into the Psyche Current Psychiatry Reports Current Psychiatry Research and Reviews Dementia & Neuropsychologia Depression and Anxiety Epidemiologia e Psichiatria Sociale
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European Journal of Psychotraumatology	European Archives of Psychiatry and Clinical Neuroscience
European Journal of Trauma & Dissociation	European Psychiatry
Frontiers in Psychology	Frontiers In Psychiatry
Indian Journal of Psychological Medicine	General Psychiatry
International Journal of Clinical and Health Psychology	International Journal of Psychiatry in Clinical Practice
International Journal of Psychoanalysis	International Review of Psychiatry
International Journal of Psychology	JAMA Psychiatry
International Journal of Psychophysiology	Journal of Affective Disorders
Italian Journal of Psychopathology	Journal of Clinical Psychiatry
Journal of Addictive Diseases	Journal of Nervous and Mental Disease
Journal of Child Psychology and Psychiatry and Allied Disciplines	Journal of Neurodevelopmental Disorders
Journal of Physiology	Journal of Neuropsychiatry and Clinical Neurosciences
Journal of Psychophysiology	Journal of Psychiatric Research
Journal of the International Neuropsychological Society	Journal of Psychiatry & Neuroscience
Motivation Science	Journal of the American Academy of Child and Adolescent Psychiatry
Neuropsychologia	Molecular Psychiatry
Neuropsychology Review	Neurochemical Research
Personality and Individual Differences	Neurochemistry International
PhD Existence 2014	Neuropsychiatric Disease and Treatment
Psychological Bulletin	Noropsikiyatri Arsivi
Psychological Medicine	Praxis
Psychoneuroendocrinology	Psiquiatria Danubina
Psychopathology	Psiquiatria Polska
Psychophysiology	Psychiatric Annals
Psychotherapie Psychosomatik	Psychiatry And Clinical Neurosciences
Medizinische Psychologie	Psychiatry Investigation
Sante Mentale au Quebec	Psychiatry Research
The Clinical Neuropsychologist	Psychiatry Research: Neuroimaging
	Revista Brasileira de Psiquiatria
	Revista Colombiana de Psiquiatria
	Revista de Psiquiatria Clinica
	Rivista di Psichiatria
	Schizophrenia
	Schizophrenia Bulletin
	Schizophrenia Research
	Suicide & Life-Threatening Behavior
	The American Journal of Geriatric Psychiatry
	The Canadian Journal of Psychiatry
	The British Journal of Psychiatry
	The Journal of Neuropsychiatry and Clinical Neurosciences
	Tijdschrift Voor Psychiatrie
	Translational Psychiatry
	World Journal of Biological Psychiatry

* Owing to the complex nature of the brain and human behavior, it is common for journals in this field of study to cover a wide range of fields, as boundaries between fields are often fluid and research can be interdisciplinary. In other words, a journal may publish articles related to neuroscience, psychiatry, and medical technologies at the same time; in such cases, we opt for the thematic approach as a measure to classify them.

Table S1.3.2 Leading Journals		
Publication Title	JIF	Quartile
Cerebellum	2.7	Q3
Journal of Affective Disorders	4.9	Q1
Plos One	2.9	Q1
Psychiatry Research-Neuroimaging	2.1	Q3
Neuroimage	4.7	Q1
Human Brain Mapping	3.5	Q1
Psychological Medicine	5.9	Q1
Frontiers in Psychiatry	3.2	Q2
Social Cognitive and Affective Neuroscience	3.9	Q1
Biological Psychiatry	9.6	Q1
Neuroimage-Clinical	3.4	Q2
BRAIN	10.6	Q1
Scientific Reports	3.8	Q1
Brain Imaging and Behavior	2.4	Q2
Neuropsychologia	2.0	Q3
Cortex	3.2	Q1
Neuroscience Letters	2.5	Q3
Neuroreport	1.6	Q4
Progress in Neuro-Psychopharmacology & Biological Psychiatry	5.3	Q1
Translational Psychiatry	5.8	Q1
Behavioural Brain Research	2.6	Q2
Neuroscience	2.9	Q2
Journal of Psychiatric Research	3.7	Q1
Journal of Neuropsychiatry and Clinical Neurosciences	2.4	Q2
Movement Disorders	7.4	Q1
Journal of Psychiatry & Neuroscience	4.1	Q1
Frontiers In Behavioral Neuroscience	2.6	Q2
Molecular Psychiatry	9.6	Q1
Neurology	7.7	Q1

Citation, impact factor (IF) and quartile (Q) are widely used metrics in bibliometric analysis. The impact factor measures the average number of citations that a journal's articles receive in a given period, while the quartile positions the journal in a relative ranking within its area of expertise. Although these metrics are useful for evaluating the relevance, visibility, and influence of research and publications, they do not capture all aspects of scientific quality. Therefore, they are presented as complementary information for broader analysis.

A notable aspect of the table is that most of the leading journals are located in the first quartile (Q1), which indicates that they are above 75% of the journals in their category. This quartile groups the journals with the highest impact factor (JIF) in that category.

Table S1.3.3 Leading cited publications		
Title	Journal	Authors
Empathy for pain involves the affective but not sensory components of pain	Science Vol 303, Issue 5661 pp. 1157-1162	T Singer, B Seymour, J O'Doherty, H Kaube, RJ Dolan, and CD Frith
Cerebellar cognitive affective syndrome	Brain Apr;121 (Pt 4):561-79	JD Schmammann and JC Sherman
Cerebellum and Non-motor Function	Annual review of neuroscience	PL Strick, RP Dum, and JA Fiez

	Vol. 32:413-434	
Disorders of the cerebellum: Ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome	The Journal of Neuropsychiatry and Clinical Neurosciences Volume 16, Number 3	JD Schmahmann
The functional neuroanatomy of autobiographical memory: A meta-analysis	Neuropsychologia 44(12):2189-208	E Svoboda, MC McKinnon, and B Levine
Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing	Cortex 46(7):831-44	CJ Stoodley, and JD Schmahmann
Neuroanatomical correlates of pleasant and unpleasant emotion	Neuropsychologia 35(11):1437-44	RD Lane, EM Reiman, MM Bradley, PJ Lang, GL Ahern, RJ Davidson, and GE Schwartz
A meta-analytic study of changes in brain activation in depression	Human Brain Mapping 29(6):683-95	PB Fitzgerald, AR Laird, J Maller, and ZJ Daskalakis
The anatomy of mood disorders - Review of structural neuroimaging studies	Biological Psychiatry 1;41(1):86-106	JC Soares, and JJ Mann
The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings	Molecular Psychiatry 10(1):105-16	SM Strakowski, MP Delbello, and CM Adler
Attenuation of the neural response to sad faces in major depression by antidepressant treatment - A prospective, event-related fMRI study	Archives of General Psychiatry 61(9):877-89	CHY Fu, SCR Williams, AJ Cleare, MJ Brammer, ND Walsh, J Kim, CM Andrew, EM Pich, PM Williams, LJ Reed, MT Mitterschiffthaler, J Suckling, and ET Bullmore
Dissociation of Neural Representation of Intensity and Affective Valuation in Human Gustation	Neuron 14;39(4):701-11	DM Small, MD Gregory, YE Mak, D Gitelman, MM Mesulam, and T Parrish
Neuropsychological consequences of cerebellar tumour resection in children - Cerebellar cognitive affective syndrome in a paediatric	Brain 123(5), 1041-1050	L Levisohn, A Cronin-Golomb, and JD Schmahmann
Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis	Brain 135(Pt 5):1498-507	LL Zeng, H Shen, L Liu, L Wang, B Li, P Fang, Z Zhou, Y Li, and D Hu
The neuropsychiatry of the cerebellum - insights from the clinic	Cerebellum 6(3):254-67	JD Schmahmann, JB Weilburg and JC Sherman
The Role of the Cerebellum in Cognition and Emotion: Personal Reflections Since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy	Neuropsychology Review 20(3):236-60	JD Schmahmann

Empathy and judging other's pain: An fMRI study of alexithymia	Cerebral Cortex 17(9):2223-34	Y Moriguchi, J Decety, T Ohnishi, M Maeda, T Mori, K Nemoto, HMatsuda, and G Komaki
Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence	Molecular Psychiatry 22(10):1455-1463	T Wise, J Radua, E Via, N Cardoner, O Abe, TM Adams, F Amico, Y Cheng, JH Cole, C de Azevedo Marques Périco, DP Dickstein, TFD Farrow, T Frodl, G Wagner, IH Gotlib, O Gruber, BJ Ham, DE Job, MJ Kempton, MJ Kim, PCMP Koolschijn, GS Malhi, D Mataix-Cols, AM McIntosh, AC Nugent, JT O'Brien, S Pezzoli, ML Phillips, PS Sachdev, G Salvatore, S Selvaraj, AC Stanfield, AJ Thomas, MJ van Tol, NJ A van der Wee, DJ Veltman, AH Young, CH Fu, AJ Cleare, and D Arnone
Pathological laughter and crying: a link to the cerebellum	Brain 124(Pt 9):1708-19	J Parvizi, SW Anderson, CO Martin, H Damasio, and AR Damasio
Consensus Paper: Cerebellum and Emotion	Cerebellum 16(2):552-576	M Adamaszek, F D'Agata, R Ferrucci, C Habas, S Keulen, KC Kirkby, M Leggio, P Mariën, M Molinari, E Moulton, L Orsi, F Van Overwalle, C Papadelis, A Priori, B Sacchetti, DJ Schutter, C Styliadis, and J Verhoeven
The emotional power of music: How music enhances the feeling of affective pictures	Brain Research 23;1075(1):151-64	T Baumgartner, K Lutz, CF Schmidt, and L Jäncke
Cerebellum development during childhood and adolescence: A longitudinal morphometric MRI study	Neuroimage 1;49(1):63-70	H Tiemeier, RK Lenroot, DK Greenstein, LTran, R Pierson, and JN Giedd
Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies	Neuroscience & Biobehavioral Reviews 37(2), 152-163	NA Groenewold, EM Opmeer, PJA Aleman, and SG Costafreda
Identification of emotional intonation evaluated by fMRI	Neuroimage 15;24(4):1233-41	D Wildgruber, A Riecker, I Hertrich, M Erb, W Grodd, T Ethofer, and H Ackermann
Dissociable Neural Pathways Are Involved in the Recognition of Emotion in Static and Dynamic Facial Expressions	Neuroimage 18(1):156-68	CD Kilts, G Egan, DA Gideon, TD Ely, and JM Hoffman
Neuroanatomical correlates of a lactate-induced anxiety attack	Archives of General Psychiatry 46(6):493-500	EM Reiman, ME Raichle, E Robins, MA Mintun, MJ Fusselman, PT Fox, JL Price, and KA Hackman
Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects	The American Journal of Psychiatry 156(10):1618-29.	S Paradiso, DL Johnson, NC Andreasen, DS O'Leary, GL Watkins, LL Ponto, and RD Hichwa

Disorders of cognitive and affective development in cerebellar malformations	Brain 130(Pt 10):2646-60	A Tavano, R Grasso, C Gagliardi, F Triulzi, N Bresolin, F Fabbro, and R Borgatti
Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group	Journal of Neurosurgery 105(6 Suppl):444-51	PL Robertson, KM Muraszko, EJ Holmes, R Sposto, RJ Packer, A Gajjar, MS Dias, JC Allen; Children's Oncology Group

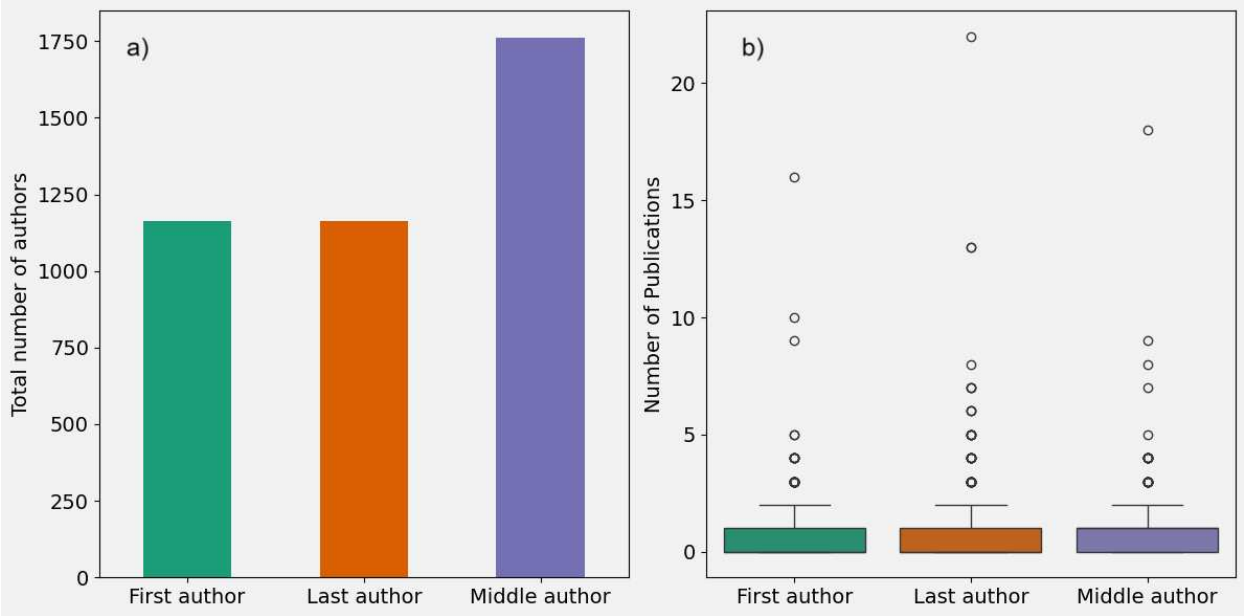


Figure S1.3.1a Role of the authors. a) Displays a bar chart showing the total number of authors by role, with bar length indicating the number of authors, allowing for quick visual comparison. b) Features of a box plot illustrating the distribution of authors by role in each publication. Each box shows the interquartile range, the line inside indicates the median, and the whiskers represent the data range, while points outside the whiskers are outliers.

The first author typically carries out the bulk of the research and writing, signaling their leadership in the study, whereas the last author often represents the principal investigator, responsible not only for supervision but also for the management of the project and its funding. On the other hand, intermediate researchers participate in key aspects such as data collection and analysis, experiments, or providing specific knowledge.

To better understand the roles of authors, we used two complementary graphs. Panel a) shows that the most predominant role is the middle author, suggesting that publications frequently include multiple middle authors, which is typical for collaborative papers involving larger teams. Importantly, an author can be the first author in one publication and the middle or last author in another. Therefore, when counting contributions in each position, more than one can be added for the same author.

In Panel b), we see that for each role, most authors have on average, two publications (the range represented by the box). The circles that are scattered above the whiskers represent authors who have a significantly greater number of publications than the majority.

The circles range from darkest to least dark according to the number of authors in that range. There are a greater number of authors who have published 3 or 4 papers, while there are significantly fewer authors with 5 or more publications, with some authors reaching more than 10 publications and one with more than 20 publications, as in the case of the last author.

To identify authors who belong to these outside-the-mean circles (the outliers, which are shown outside the box), we used a bubble chart, which allows for clear visualization of the authors who have a significantly greater number of publications than the majority do.

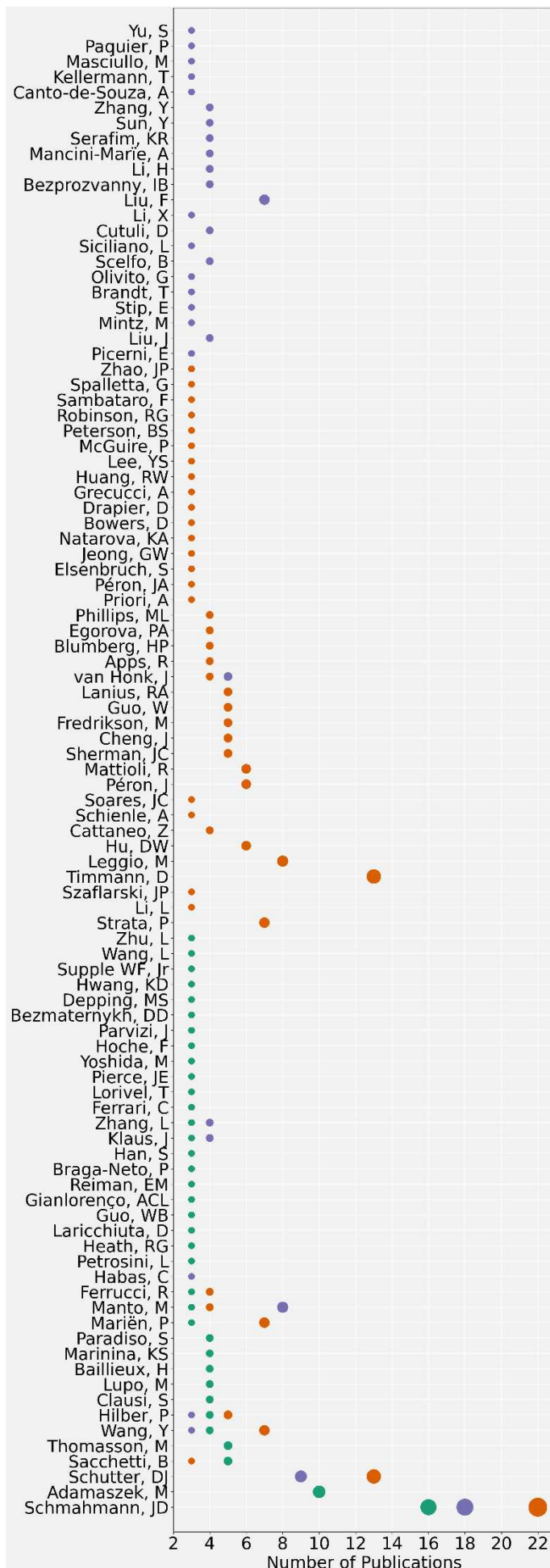


Figure S1.3.1b Extended version of Figure S1.3.1a, highlighting authors outside the mean. The Y-axis lists the authors' names, while the X-axis indicates the number of publications attributed to each author. Additionally, the size of the bubbles represents the number of publications; larger bubbles correspond to a greater number of publications. The colours of the bubbles match those in the previous figure, distinguishing between the first, last, and middle authors

Table S1.3.4 Network Metrics** Evolutionary and Comparative Analysis				
Period	1961-2000	1961-2012	1961-2018	1961-2024
Publications and Collaborations				
Number of publications	66.0	351	676	1.16E3
Total Collaborations	1.51E3	1.06E4	2.61E4	6.33E4
Average number of collaborations per author (Average degree of connectivity)	5.56	6.78	8.28	10.9
Network and Connectivity				
Number of nodes	271	1.57E3	3.15E3	5.82E3
Number of links	772	5.77E3	1.43E4	3.39E4
Connected graph	No	No	No	No
Most connected node	Reiman, EM	Wiesmann, M	Phillips, ML	Phillips, ML
Giant Cluster	17.0	52.0	536	2.71E3
Efficiency and Paths				
Characteristic Path Length	1.92	2.34	4.84	7.80
Global Efficiency	2.31E-2	6.06E-3	1.32E-2	3.50E-2
Average Distance	1.92	2.34	4.84	7.80
Network Diameter	4.00	3.00	12.0	18.0
Average Length of Shortest Path	1.92	2.34	4.84	7.80
Centrality				
Average Degree Centrality	2.06E-2	4.33E-3	2.63E-3	1.87E-3
Average Betweenness Centrality	2.56E-5	3.84E-6	5.06E-5	2.53E-4
Average Closeness Centrality	2.20E-2	5.55E-3	1.12E-2	2.91E-2
Average Eigenvector Centrality	1.28E-2	8.74E-2	2.48E-3	1.81E-3
Clusters and Communities				
Total Communities	43.0	203	328	502
Average Community Size	6.30	7.73	9.60	11.6
Total Cliques	56.0	314	618	1.10E3
Average Cliques Size	5.18	5.87	6.24	6.74
Average Clustering Coefficient	0.92	0.93	0.92	0.92
Diversity and Modulation				
Diversity and Degree Entropy	3.25	3.76	4.09	4.32
Modularity	0.96	0.99	0.95	0.91
Density and Resilience				
Network Density	2.06E-2	4.33E-3	2.63E-3	1.87E-3
Assortativity	0.84	0.58	0.64	0.92
Resilience (degree of nodes)	17.0	52.0	536	2.71E3
Vulnerability (degree of nodes)	43.0	203	318	474
Resilience (random)	0.36	0.35	0.34	0.40
Vulnerability (random)	0.64	0.65	0.66	0.60

****For more details on how each metric is calculated, refer to (*Networkx/Networkx*, 2010/2025; *Tiago Peixoto / Graph-Tool · GitLab*, 2025)**

The metrics quantitatively confirm the observations in Figure 1.25. The network has experienced significant growth in publications, authors, and collaborations, indicating increased interest and relevance in this field within the scientific community. Publications have risen exponentially from 66.0 to 1.16E3, accompanied by a substantial increase in the number of nodes from 271 to 5.82E3, indicating that more researchers are joining and diversifying the collaborative network. Links between authors have grown even faster, from 772 to 3.39E4, reflecting more frequent and diverse collaborations. The average number of collaborations per author nearly doubled from 5.56--10.9, demonstrating strengthened coauthorship and network cohesion. This complexity suggests interdisciplinary collaboration and enriched interactions among researchers.

The network's most connected nodes change over time, with "Reiman, MS" and "Wiesmann, M" initially leading and "Phillips, ML" becoming the dominant node in later periods, playing a critical role in knowledge dissemination. The giant cluster grows significantly, from 17.0 to 2.71E3 nodes, reflecting increased collaboration and cohesion in the network. Higher average connections and giant cluster expansion create a more robust, stable, and resilient network. The global efficiency improves, reaching 3.50E-2, enhancing internode communication. However, the characteristic path length increases from 1.92 to 7.80, and the network diameter expands from 4.00 to 18.0, indicating greater dispersion and complexity in collaborative paths as the network grows.

The network's growth shows diversification and increasing collaboration. Degree centrality decreases steadily, reflecting a less dense and more fragmented structure, whereas betweenness centrality slightly increases, indicating a greater influence of certain nodes as bridges. Closeness centrality initially decreases but later increases, showing improved cohesion and shorter paths for communication. Eigenvector centrality starts at 1.28E-2, peaks at 8.74E-2, and then decreases to 2.48E-3 and 1.81E-3, indicating a shift from concentrated influence to a more evenly distributed structure. The number of communities grows from 43.0--502, with the average community size increasing from 6.30--11.6. Similarly, the number of cliques increases from 56.0 to 1.10E3, with the average size increasing from 5.18 to 6.74. These trends reflect a network that, despite its expansion, fosters specialized, cohesive, and efficient scientific collaboration.

The degree entropy increases from 3.25 to 4.32, indicating greater diversity in connections, as new authors join or existing ones collaborate with a wider, more interdisciplinary group. Modularity decreases slightly from 0.96 to 0.91, suggesting that the network remains highly modular but becomes more integrated, with diminishing barriers between subgroups.

The network density decreases from 2.06E-2 to 1.87E-3, as not all new authors establish connections, reflecting a sparser structure. Rising assortativity suggests that more connected nodes collaborate, fostering impactful projects but concentrating collaboration among core researchers. The giant component remains central to communication and information flow. Over time, the network shows increased resilience but also greater vulnerability to the removal of key nodes, indicating a growing dependence on influential participants. Random node removal initially reduces resilience and increases vulnerability, but improves by 2024, highlighting a trend toward greater robustness to random failures while remaining reliant on critical nodes.

Section 1.4 State-of-the-Art on cerebellar lobule VI, from rodents to humans

1.4.1 Structural and functional organization

➤ Structure and anatomy

Cerebellar lobule VI comprises two main anatomical parts: the *declive*, which forms the central portion of the cerebellar vermis, and the *simple lobule*, which extends into the cerebellar hemispheres (Figure 1.26). This organization reflects the segmentation of the cerebellum into lobules and sub-lobules, where each vermian portion corresponds to structures in the cerebellar hemispheres (Jimshelishvili & Dididze, 2025; Luo et al., 2017).

Anatomically, lobule VI lies between the primary fissure and the horizontal fissure of the cerebellum. The primary fissure separates it from the anterior lobule, while the horizontal fissure distinguishes it from more posterior structures (See Figure 1.9 for humans and Figures 1.3 and 1.6a for rodents in Section 1.2: Comprehensive overview of Cerebellar structure, function, and connectivity). The *Declive* is positioned in the superior region of the posterior cerebellar lobule, just behind the primary fissure that separates the anterior (I–V) from the posterior lobules (VI–IX). In humans, lobule VI includes the medial portion (the *Declive* within the vermis) and the lateral portions (often referred to as the *Simple lobule*) within the cerebellar hemispheres (Jimshelishvili & Dididze, 2025) (see Figure 1.9). In rodents (see Figure 1.3), a homologous lobule VI is also present, as the lobulation pattern (I–X) is highly conserved across mammals. However, there are significant differences in scale and proportion: the human cerebellum is larger and more deeply fissured (with numerous folia) than the rodent cerebellum, especially in the lateral hemispheric regions (Luo et al., 2017; Schröder et al., 2020).

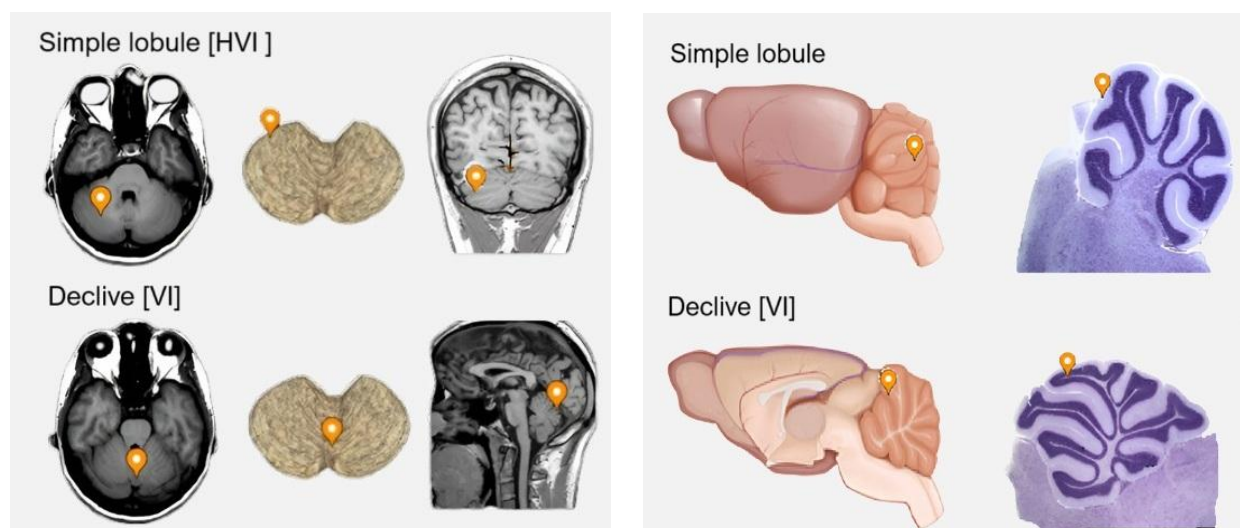


Figure 1.26 Anatomical comparison of the Simple Lobule and the Declive in humans and rodents. Comparison of the anatomical organization of the simple lobule (HVI) and the declive (VI) between humans (left panel) and rodents (right panel). The images display axial, coronal, and sagittal MRI scans in humans, alongside anatomical models and histological sections in rodents. Orange markers indicate the corresponding location of each structure in both species.

The vermian portion of lobule VI connects to both cerebellar hemispheres via underlying white matter and is separated from the hemispheric zones by paramedian fissures. In humans, the declive appears as a narrow elevation along the midline, while the hemispheric portions form part of the superior roof of the posterior cerebellum, contributing to its visible surface. In rodents, lobule VI is smaller and has fewer folial subdivisions but remains clearly identifiable in sagittal and dorsal sections (Jimshelishvili & Dididze, 2025; Schröder et al., 2020).

The posterior lateral lobules are more expanded in humans, whereas in rodents, the vermis and paravermian regions occupy a larger proportion of the total cerebellar volume. Despite these differences, the fundamental folding pattern of the cerebellum remains highly conserved between species. It is the only cortical structure with consistent folding present in both rodents and humans,

facilitating the extrapolation of anatomical and functional findings between species (Luo et al., 2017).

Microscopically, lobule VI shares the typical cerebellar cortical architecture described in detail in Section 1.2. A key distinguishing feature of lobule VI is the pattern of recurrent local circuits: axonal collaterals from Purkinje cells establish functional synapses within the granular layer, providing additional GABAergic inhibition. As discussed in Section 1.2, this pattern is less prominent in the anterior lobules but becomes more complex from lobule VI onward.

Lobule VI also exhibits a distinct molecular pattern of zebrin II expression. Lobule VI is predominantly composed of zebrin-positive Purkinje cells, although zebrin-negative zones are also present. These molecular compartments have been associated with distinct physiological profiles, including lower and more regular firing rates in zebrin-positive cells, as discussed in Section 1.2.

➤ Functional and anatomical connections

Functionally, the medial vermal portion of lobule VI is part of what has traditionally been referred to as the spinocerebellum, while the lateral portions are integrated into the cerebrocerebellum (Purves et al., 2001). Although these terms are commonly used to distinguish cerebellar regions based on their predominant inputs and outputs, it is important to acknowledge that both vermal and hemispheric areas maintain extensive bidirectional connections with subcortical as well as cortical structures. Thus, while this classification can serve as a general framework, it oversimplifies the complex and overlapping functional organization of cerebellar circuits.

This functional distinction is reflected in its projection patterns: The cerebellar lobule VI (especially its lateral parts) receives extensive input from the cerebral cortex via the pontine nuclei. Cortical axons (from frontal motor, premotor, and parietal areas) synapse in the pontine nuclei, which send mossy fibers across the midline through the middle cerebellar peduncle to the contralateral cerebellar hemisphere. This cortico-pontocerebellar pathway supplies lobule VI with information about planned movements and higher-order association signals (J. A. Bernard et al., 2012). The somatotopic organization of these cortico-cerebellar projections allows lobule VI to process cortical input essential for coordinating limb and trunk movements, as well as cognitive tasks in humans (Middleton & Strick, 2001).

Lobule VI also integrates proprioceptive and sensory information through spinocerebellar pathways and brainstem relays. As explain in detail (Batini et al., 1978): The dorsal spinocerebellar tract (from Clarke's column and external cuneate nucleus) and the cuneocerebellar tract carry ipsilateral body position signals via the inferior cerebellar peduncle, mainly targeting vermal and paravermal regions of lobule VI. The ventral spinocerebellar tract, which crosses twice, enters through the superior cerebellar peduncle, providing limb-feedback input. Mossy fiber projections from the medullary reticular formation (e.g., lateral and paramedian reticular nuclei) deliver somatosensory and motor feedback. Vestibular and perihypoglossal nuclei send input to the vermis of lobule VI, aiding in head and eye movement coordination. Additionally, minor inputs from visceral and trigeminal relay nuclei (e.g., nucleus tractus solitarius and external cuneate nucleus) further support the integration of sensory feedback with cortical commands.

A major input to Lobule VI is from the contralateral inferior olivary complex (see Figure 1.28), which sends climbing fibers through the inferior cerebellar peduncle to synapse on Purkinje cells. This topographically organized projection, especially from the dorsal accessory olive, transmits error signals and timing information essential for motor learning and error correction. Combined with mossy fiber input, this olivary input helps lobule VI compare intended motor commands with actual performance (Batini et al., 1978).

In addition to the classic afferents, Lobule VI's vermal portion (the declive) receives input from limbic and autonomic centers, including fibers from the hypothalamus (lateral, posterior, and dorsal regions) via the inferior peduncle. These hypothalamocerebellar fibers, which reach all cortical layers, may modulate cerebellar activity during autonomic and emotional states, linking the cerebellum to the limbic system states (Habas et al., 2009; Haines et al., 1997).

Lobule VI receives diffuse neuromodulatory inputs, including serotonergic fibers from the raphe nuclei and noradrenergic fibers from the locus coeruleus, which regulate its excitability during stress, arousal, and mood changes. It serves as a convergence zone for motor commands, sensory feedback, and visceral signals, integrating inputs through all three cerebellar peduncles:

middle (cortical), inferior (spinal, olivary, hypothalamic), and superior (ventral spinocerebellar) (Batini et al., 1978).

Lobule VI spans the midline vermis, intermediate (paravermal) zone, and parts of the lateral hemisphere; each of these mediolateral regions targets a different deep nucleus (see Figure 1.27). Purkinje cells in the vermal declive (lobule VI, vermis) primarily project to the fastigial nucleus (see Figure 1.28), the most medially located deep nucleus. In contrast, Purkinje cells in the intermediate zone of lobule VI project to the interposed nuclei (emboliform and globose), while those in the lateralmost parts of lobule VI project to the dentate nucleus (Corbetta & Fitzpatrick, 2011; Middleton & Strick, 2001). Through these deep nuclear connections, lobule VI influences a wide array of downstream targets. Notably, there is a minor direct projection from cerebellar cortex to the vestibular nuclei (Purkinje cells of the flocculonodular lobe send axons to vestibular nuclei), but lobule VI's Purkinje cells do *not* significantly project directly to vestibular nuclei; instead, they relay via the deep nuclei as described below.

The fastigial nucleus sends excitatory projections to the vestibular nuclei and the pontine and medullary reticular formation (Yu & Wang, 2025). It also projects to the contralateral ventrolateral thalamic nucleus via the superior cerebellar peduncle, which influences the primary motor cortex and premotor areas. Furthermore, the fastigial nucleus projects to the hypothalamus and the ventral tegmental area (VTA), providing a route for lobule VI to influence autonomic activity and reward circuits (H. Fujita et al., 2020a; Haines et al., 1997; Yu & Wang, 2025).

The interposed nuclei (globose and emboliform) receive input from the intermediate zone of lobule VI (see Figure 1.28) and project to the magnocellular division of the red nucleus, thereby influencing the rubrospinal tract. They also send fibers to the ventrolateral thalamus, which relays signals to the motor cortex. Additionally, collateral projections to the brainstem reticular formation assist in integrating cerebellar corrections (Judd et al., 2021).

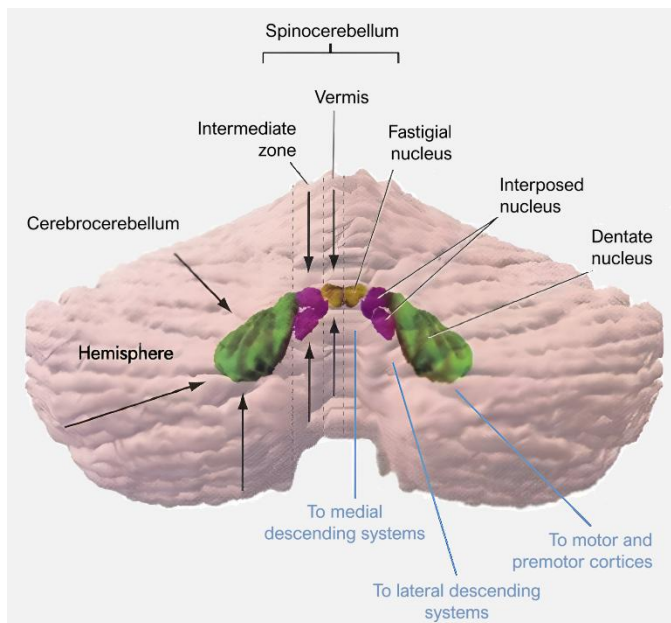


Figure 1.27 Functional and anatomical organization of the Cerebellum and its Deep Nuclei. The cerebellum is divided into the spinocerebellum (vermis and intermediate zone) and the cerebrocerebellum (hemispheres). The fastigial nucleus (yellow) is primarily linked to the vermis and projects to medial descending motor systems. The interposed nuclei (purple) are connected to the intermediate zone and influence lateral descending motor pathways. The dentate nuclei (green) are associated with the hemispheres and are involved in motor and premotor control through cortico-ponto-cerebellar circuits. Arrows indicate the direction of projections and functional pathways.

The dentate nucleus receives projections from the lateral hemisphere of lobule VI (see Figure 1.28) and sends outputs to the ventrolateral and ventral anterior thalamic nuclei. From there, thalamocortical fibers project to motor and premotor areas, as well as prefrontal areas involved in motor planning and cognitive functions. Dentate projections to the parvocellular red nucleus form the dentato-rubral tract, which relays signals to the inferior olive, providing feedback to the cerebellum (J. A. Bernard et al., 2014; Haines et al., 1997; Küper et al., 2013; Middleton & Strick, 2001).

The observed structural connectivity patterns (Figure 1.29) support and complement the described functional anatomy of cerebellar lobule VI. Specifically, the strong bidirectional cortical and thalamic connections visualized in the connectivity matrices align well with the established cortico-ponto-cerebellar pathways involved in coordinating complex sensorimotor and cognitive functions. Additionally, a clear structural connection between the hypothalamus and the Left

Simple lobule underscores the proposed involvement of lobule VI in autonomic and emotional integration. Interestingly, the connectivity data also suggests a potential lateralization, with notably stronger cortical and subcortical connections involving the left cerebellar hemisphere. Conversely, weaker structural connectivity to vestibular and brainstem regions further emphasizes lobule VI's specialization toward higher-order cortical networks rather than basic vestibular or brainstem-mediated functions

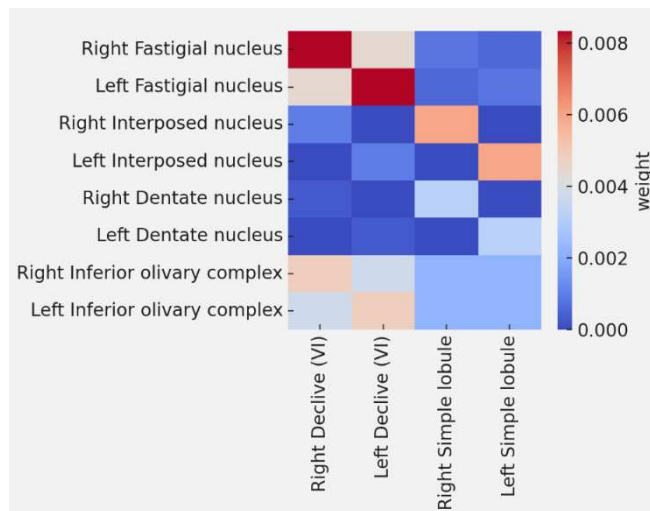


Figure 1.28 Structural connectivity from cerebellar Lobule VI to major input and output hubs. Values represent normalized anatomical connection weights derived from a mesoscale connectome of the mouse brain, based on tracer studies (Connectivity Data in Mice, n.d.). Weights reflect the relative projection strength between regions, and do not imply functional or physiological connectivity.

➤ Cross-Species Comparison: Humans and Rodents

Both human and rodent cerebellum share the fundamental circuitry outlined above for lobule VI, but there are important differences in connectivity and function across species:

In rodents, the fastigial nucleus is relatively larger and receives more substantial input from the vermis, while in humans, the lateral portions are more extensively integrated into the cortico-ponto-cerebellar circuits. In primates, particularly humans, the cerebellar hemispheres (especially the lateral parts of lobule VI) are significantly expanded and receive more diverse cortical inputs than in rodents. Humans have extensive pontine projections from both the sensorimotor cortex and higher-order association areas (e.g., prefrontal, posterior parietal), targeting lobules VI–VII, which support complex functions (J. A. Bernard et al., 2012). In rodents, the lateral cerebellum is smaller, and cortico-pontine input primarily originates from motor-sensory cortices, which limits cognitive contributions (Shipman & Green, 2019). The difference lies in degree: the human lobule VI supports abstract reasoning and complex planning, while rodent lobule VI handles simpler analogues of these behaviors.

In both humans and rodents, lobule VI has functional links to the limbic system that drive basic emotional behaviors (more details in Chapters 3 and 4). However, humans experience a wide range of nuanced emotions, and correspondingly, the cerebellar contribution to emotional processing may be more elaborate.

1.4.2 Lobule VI and Cerebellar pathology, from movement to emotion

Dysfunction in this region may present as a broad spectrum of motor, cognitive, and emotional symptoms, as demonstrated by conditions such as:

- Spinocerebellar ataxia (SCA), particularly SCA6, involves selective degeneration of Purkinje cells in lobule VI, resulting in impaired motor coordination and timing. Interestingly, patients with SCA6 often exhibit excessive timing precision but poor motor modulation, underscoring the critical role of lobule VI in fine-tuning motor calibration (Teaford, 2020).
- Cerebellar lesions located in the anterior lobe and parts of lobule VI interrupted cerebellar communication with cerebral and spinal motor systems, and caused cerebellar motor syndrome (Lin et al., 2020)

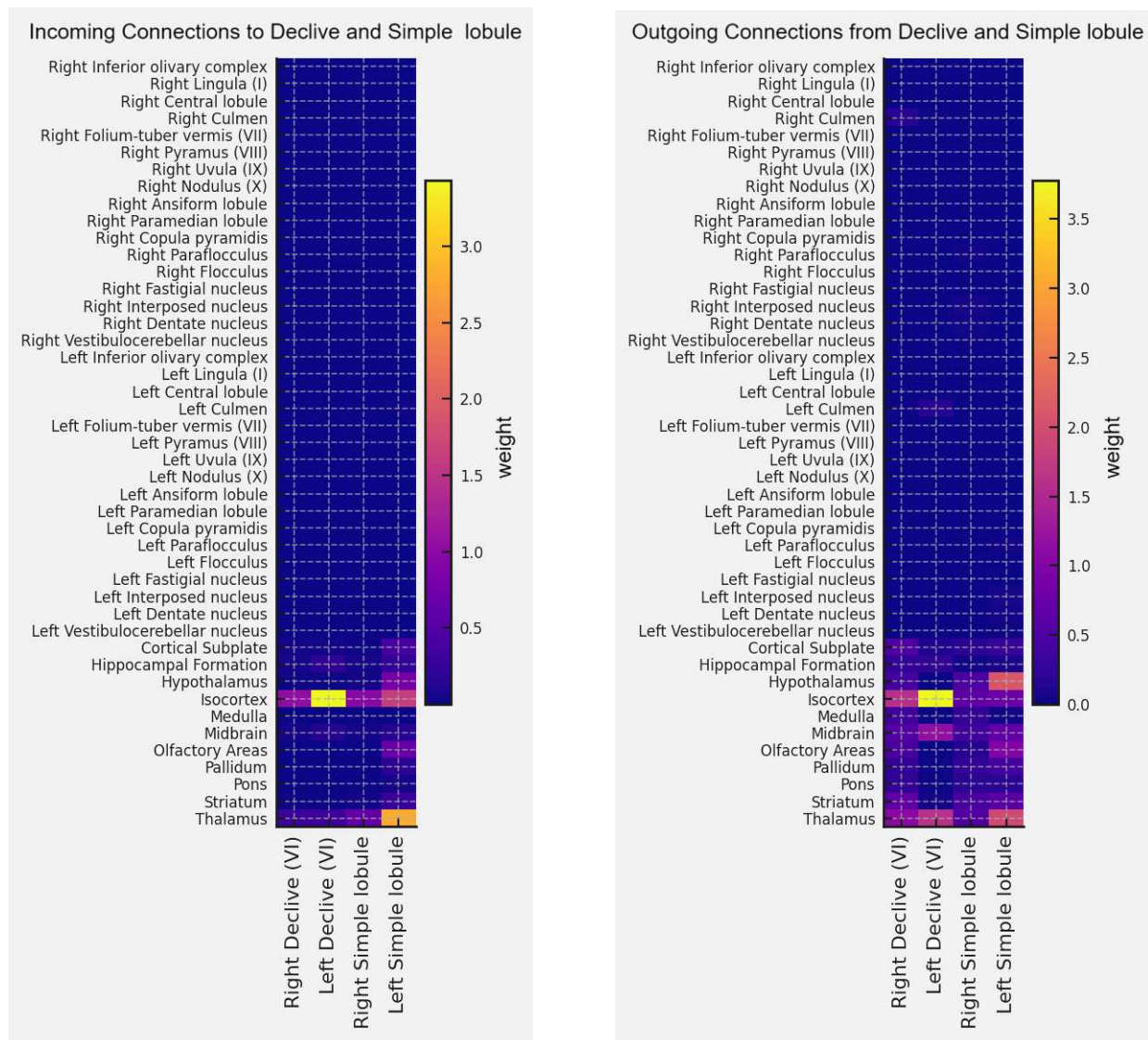


Figure 1.29 Structural Connectivity Matrix in Mice. Structural connectivity matrix showing directed anatomical projections related to cerebellar lobule VI (Declive) and the Simple Lobule in the mouse brain. Left panel: incoming projections to these lobules. Right panel: outgoing projections from them. Data represent normalized projection weights derived from mesoscale tract-tracing studies (Connectivity Data in Mice, n.d.). Connection strength reflects relative axonal projection density and does not indicate functional or synaptic efficacy.

- Congenital disorders such as Joubert syndrome and Dandy-Walker malformation are characterized by agenesis or hypoplasia of the vermis, including lobule VI. This developmental disruption leads to motor symptoms such as hypotonia, ataxia, and oculomotor deficits, while cognitive impairment can range from mild to severe, depending on the extent of the structural abnormalities (Zamora et al., 2025)
- Cerebellar cognitive affective syndrome (CCAS), results from lesions in lobule VI, which produce a combination of executive dysfunction, impaired language, and emotional dysregulation. This syndrome highlights the dual role of lobule VI in both motor coordination and higher-order cognitive and emotional processing (Lin et al., 2020; Toniolo et al., 2018; Xie et al., 2024)
- Structural studies have shown volumetric reductions in lobule VI and the vermis (declive) in patients with schizophrenia, both in first-episode psychosis and chronic schizophrenia. Reduced volume in lobule VI correlates with poorer performance in executive functions, supporting the "cognitive dysmetria" hypothesis, which posits that dysfunction of the fronto-thalamo-cerebellar circuit disrupts thought coordination (T. Kim et al., 2018; Phillips et al., 2015)
- Depression is associated with reduced cerebellar volume, particularly in the posterior vermis and lobule VI. Functional imaging studies have also reported decreased connectivity between

lobule VI and prefrontal and limbic regions, which may underlie deficits in emotional regulation and affective symptoms (Depping et al., 2018; Yucel et al., 2013)

- Patients with post-traumatic stress disorder and social anxiety disorder exhibit reduced volume in the vermis and lobule VI, along with hyperactivation of lobule VI in response to intense emotional stimuli. Abnormal connectivity between lobule VI and the amygdala may explain exaggerated or dysregulated emotional responses (Blithikioti et al., 2022; Gil-Paterna & Furmark, 2023)

- Neuroimaging studies have reported reduced volume in lobule VI and the vermis and altered connectivity between the vermis and limbic and motor areas. Dysfunction in cerebello-cortical communication correlates with the severity of mood symptoms, suggesting that lobule VI may play a role in mood stabilization (Baldaçara et al., 2012; Saleem et al., 2023)

- Hypoplasia of lobules VI and VII and Purkinje cell loss in the vermis (Declive) have been implicated in autism. These alterations may impair the inhibition of sensory and social signals, contributing to difficulties in social interaction and repetitive behaviors (Mapelli et al., 2022; Phillips et al., 2015). In Attention-Deficit/Hyperactivity Disorder, the vermis (including the declive) tends to be smaller, with its size correlating with greater inattention and impulsivity. In Obsessive Compulsive Disorder and borderline personality disorder, hyperactivation or abnormal connectivity of the vermis and lobule VI may contribute to emotional regulation and impulse control difficulties (Phillips et al., 2015).

1.4.3 Lobule VI, an integrative node?

Lobule VI of the cerebellum has been implicated in a wide range of motor, cognitive, emotional, social, and complex processing functions, as reported in previous studies (Figure 1.9, Section 1.2). This broad functional involvement suggests that lobule VI may serve as an integrative or modulatory node within the cerebellum, facilitating the coordination of motor, cognitive, and emotional signals through its extensive connections with cortical and brainstem areas.

Lobule VI appears to act as a motor and cognitive adjuster, refining voluntary motor coordination and executive functions. Additionally, its involvement in emotional regulation suggests that it also modulates the intensity and appropriateness of emotional responses. This modulatory capacity could explain why disruptions in lobule VI due to developmental anomalies (e.g., Joubert syndrome, Dandy-Walker malformation), neurodegeneration (e.g., spinocerebellar ataxia type 6), or acquired damage (e.g., cerebellar cognitive affective syndrome), result in combined motor (e.g., ataxia), cognitive (e.g., poor planning, memory deficits), and emotional (e.g., mood instability, emotional blunting) symptoms.

Clinical evidence from neuropsychiatric disorders supports this hypothesis. Dysfunction of lobule VI has been linked to exaggerated emotional responses (e.g., anxiety, mania), insufficient responses (e.g., depression, apathy), and disorganized responses (e.g., schizophrenia, autism). This ability to fine-tune emotional responses, alongside its role in motor and cognitive regulation, positions lobule VI as a key integrative node for complex behavioral and emotional homeostasis. Recent functional imaging studies support the hypothesis that lobule VI serves as an integrative hub, with overlapping cognitive and sensorimotor clusters and connectivity with motivational and emotional networks. This aligns with the proposed view that lobule VI plays a central role in coordinating motor, cognitive, emotional, and potentially social functions (Lin et al., 2020).

The predominance of zebrin-positive (Z+) stripes in lobule VI may further reflect its involvement in this functional integration. Evidence from neuroimaging, physiological, and anatomical studies suggests that zebrin compartmentalization may correspond, at least in part, to the organization of cerebellar circuits involved in distinct behavioral domains (Lin et al., 2020). (Z+) zones are more often linked to non-motor functions such as cognition and emotion, while (Z-) zones are associated with sensorimotor control (Viet et al., 2022). Although the precise relationships among the anatomical cerebellum, molecular stripe patterns, and functional topography are unknown, further research is needed to clarify these potential connections.

Chapter 2: Data-driven reconstruction and simulation of the mouse lobule VI (Declive)

Section 2.1 Introduction

This chapter presents the data-driven methodology and computational strategies used to reconstruct and simulate the cerebellar microcircuit of the Declive, a subregion of lobule VI. This effort aligns with the broader goal of the thesis: to explore the cerebellum's role in emotional processing by developing biologically plausible models that can support functional investigations. As introduced in Chapter 1, lobule VI has been implicated in emotional behavior in both humans and rodents. Its central position within the cerebellar architecture, along with converging anatomical and functional evidence, makes it a compelling candidate for a first computational case study within this thesis.

To achieve this, we follow a bottom-up modeling strategy grounded in detailed anatomical data and state-of-the-art simulation tools. The chapter is structured to guide the reader through the rationale, tools, methods, and outcomes of this modeling effort. We begin by introducing the principles of computational modeling in neuroscience and the specific challenges and opportunities related to cerebellar modeling. Next, we present the core computational tools used in this project, including the Blue Brain Cell Atlas (BBCA), the Brain Scaffold Builder (BSB), and the NEST simulator combined with the EGLIF neuron model.

Following this, we describe the methods used to reconstruct the microcircuit of the Declive, including atlas-based mapping, correction of anatomical artifacts, neuron density estimation, cell placement, and connectivity. Due to computational limitations, the full Declive could not be simulated; instead, a representative subvolume was modeled to capture key circuit dynamics. A canonical cerebellar microcircuit model is also introduced as a reference for comparison.

The final sections of this chapter present the results derived from both the reconstruction and simulation of the Declive subvolume, followed by a comparative analysis between the canonical and Declive-specific networks. These findings are then discussed in terms of their relevance to cerebellar structure and function, highlighting current limitations and future directions. Supplementary materials provide extended parameter tables and technical details essential for full model replication and understanding.

2.1.1 Computational modeling of the brain

The field of modern neuroscience emerged as a formal discipline in the mid-20th century, rapidly evolving into an interdisciplinary domain that integrates expertise from physiology, physics, mathematics, engineering, computer science, medicine, psychology, and philosophy. This broad collaboration reflects the complexity of understanding brain function and behavior. Given the significant global impact of neurological and psychiatric disorders, computational models have become essential tools for advancing research, diagnosis, and treatment in neuroscience (Nayak et al., 2018).

Computational neuroscience has made significant advances in the development of realistic brain models, which aim to capture the complex dynamics of neuronal activity through multiscale approaches (D'Angelo, Solinas, Garrido, et al., 2013; D'Angelo & Jirsa, 2022). These models are built on solid biological principles, distinguishing them from theoretical models that anticipate a desired function and design the model structure accordingly. In realistic modeling, properties naturally emerge from the biological structure of the system, enabling the simulation of processes ranging from molecular mechanisms to large-scale neuronal networks (D'Angelo, Solinas, Garrido, et al., 2013).

Neuroscience faces a fundamental challenge distinct from physics and engineering. Whereas other sciences progress by testing well-defined theoretical frameworks, neuroscience has traditionally placed more emphasis on experimental methods and the empirical collection of data (Nayak et al., 2018). However, the increasing availability of mathematical models of complex systems and high-performance computing is shifting this paradigm (Breakspear et al., 2010), positioning computational models as a central tool for understanding neuronal activity across different spatial and temporal scales (D'Angelo & Wheeler-Kingshott, 2017).

One of the key challenges in brain modeling is understanding brain network organization across multiple spatial scales (see figure 2.1), both structurally and functionally (D'Angelo, Solinas,

Garrido, et al., 2013; D'Angelo & Jirsa, 2022; D'Angelo & Wheeler-Kingshott, 2017). Significant progress has been made in studying microscopic brain dynamics, particularly at the level of individual neurons and synapses, using techniques such as patch-clamp recordings, voltage-sensitive dye imaging, and calcium imaging. At the mesoscale, the organization and emergent dynamics of local circuits are investigated through multi-electrode arrays, tracing studies, and optogenetics. At the macroscale, functional neuroimaging methods such as functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) provide insights into large-scale network activity. However, a major challenge remains in integrating these different levels of organization and understanding how neural dynamics at different spatial scales interrelate.

Two complementary modeling strategies have emerged to address these multiscale complexities (D'Angelo, Solinas, Garrido, et al., 2013; D'Angelo & Jirsa, 2022): 1) Bottom-up approach: reconstructs models based on well-characterized biological elements such as ion channels, synapses, and neuronal connectivity patterns. This approach generates biophysically detailed models that replicate single-neuron behavior and local circuit dynamics. 2) Top-down approach: starts from macroscopic functional measurements (e.g., fMRI, EEG) and seeks to infer the underlying neuronal mechanisms that give rise to observed patterns of brain activity (see figure 2.1). Both strategies converge in hybrid models, where top-down approaches help interpret large-scale dynamics, while bottom-up approaches provide mechanistic detail. This integration is crucial, as large-scale neural phenomena cannot be understood without linking them to their underlying biophysical and cellular mechanisms.

The development of large-scale brain models has been driven by advances in supercomputing and neuromorphic hardware, enabling real-time simulations of neural circuits and supporting experimental validation (D'Angelo & Jirsa, 2022; Nayak et al., 2018). Given the complexity of neuronal networks and the vast volume of data generated, neuroinformatics has emerged as a crucial field dedicated to data storage, analysis, and sharing. This includes the creation of standardized databases, computational tools for data extraction, and simulation platforms for large-scale brain modeling. High-performance computing systems, such as supercomputer architectures and neuromorphic processors, facilitate efficient simulations by optimizing the representation of neuronal dynamics (Calimera et al., 2013; Li et al., 2024).

The convergence of bottom-up and top-down modeling approaches, combined with neuroinformatics and high-performance computing, is paving the way for innovations in Artificial Intelligence, neuroengineering, and clinical applications (D'Angelo & Jirsa, 2022).

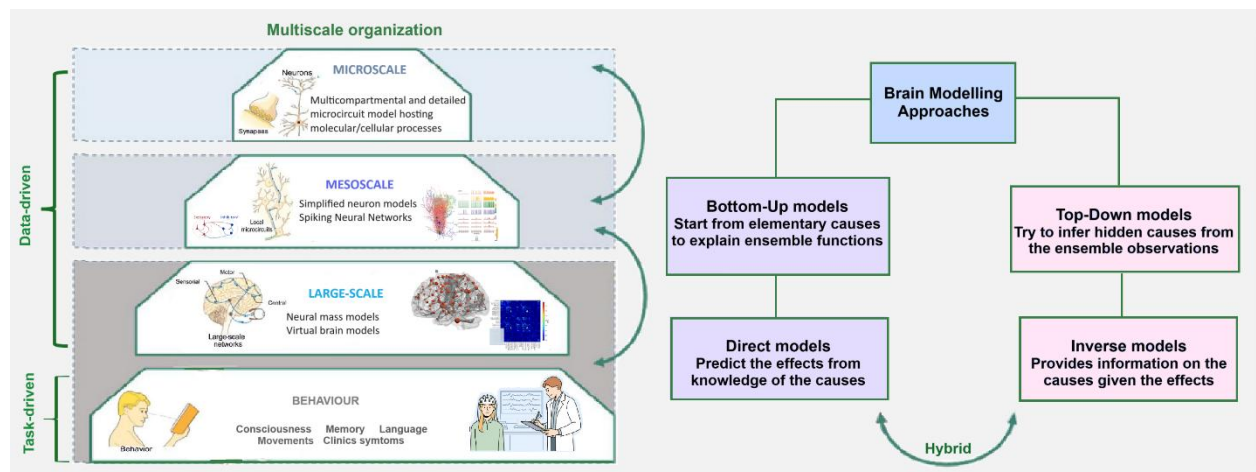


Figure 2.1 Multiscale brain organization and modeling approaches. The left section shows the multiscale organization of the brain, where data-driven models reconstruct information from microscale, to mesoscale, and large-scale; ultimately linking to behavior at the task-driven level. Double arrows indicate the hierarchical relationship between different scales. The right section shows brain modeling approaches, where bottom-up models follow a direct strategy, predicting effects from known causes, while top-down models use an inverse approach, inferring causes from observed effects. The curved double arrow represents the convergence of modeling strategies into hybrid models.

2.1.2 Modelling of the Cerebellum

The cerebellar microcircuit has been a reference in theoretical and computational modeling since the early days of neuroscience research. Its regular neuronal architecture has inspired multiple approaches to understanding motor learning and coordination. Initially, statistical-topological models were used, and later expanded to consider the geometric organization of local microcircuits (D'Angelo et al., 2016). However, anatomical and physiological advances have revealed greater complexity in connectivity, neuronal dynamics, and synaptic plasticity, necessitating more integrated and updatable computational models (Masoli et al., 2022).

Biologically precise, realistic models, based on bottom-up strategies, have enabled the representation of detailed connectivity and the nonlinear dynamics of neuronal membranes. This approach leverages the complexity of biological systems. For over 40 years, the cerebellum has served as a testing ground for developing detailed models that study neuronal dynamics and synaptic interactions at various organizational levels (D'Angelo et al., 2016).

Cerebellar modeling has evolved from the hypotheses of Marr and Albus (Albus, 1971; Marr, 1969) to advanced models incorporating detailed neurotransmission mechanisms and synaptic plasticity. Currently, these models integrate both the biological precision of neurons and closed-loop circuit simulations, allowing for the evaluation of how distributed plasticity influences motor learning and coordination. These advances have been crucial in understanding cerebellar computation and its applications in neurological disorders and neurorobotic systems.

Realistic models have enabled the reconstruction of neuronal functions through biophysical principles, explaining membrane potential generation, intracellular regulation, and synaptic integration within the cerebellar microcircuit. Additionally, they have served as a testing ground for developing simulation platforms, optimization strategies, and detailed representations of cells, such as Purkinje cells and complete microcircuits (Masoli et al., 2022).

Cerebellar modeling faces the challenge of integrating its essential structural and dynamic properties. Cerebellar neurons display complex behaviors, such as autorhythmicity, frequency band resonance, and burst encoding, while synapses exhibit both short- and long-term plasticity, enhancing the network's storage and processing capacity. These computational models have been crucial in understanding the cerebellum's role in motor control and cognition, as well as in facilitating the study of its interactions with other brain areas, including the brainstem, spinal cord, cerebral cortex, and basal ganglia, thereby evaluating how its architecture influences adaptation and learning in dynamic environments (D'Angelo et al., 2016; Masoli et al., 2022).

Realistic cerebellar modeling has advanced significantly, providing key tools for understanding its role in motor learning, coordination, and cognition. As more complex and precise models are developed, these simulations are expected to contribute to improved treatments for neurological disorders and the advancement of sophisticated neurorobotic control systems. The integration of experimental and computational techniques has enabled the reconstruction and simulation of complex models of neurons and synapses, facilitating a detailed understanding of neurotransmission and synaptic plasticity mechanisms within the cerebellar network. These advances continue to uncover how diverse synaptic mechanisms shape cerebellar circuit activity and computation, providing a foundation for developing biologically grounded models.

In particular, scaffold models (Casali et al., 2019; De Schepper et al., 2022) reconstruct cerebellar network architecture by simulating neuronal positioning, connectivity, and local microcircuit activation. Mean-field models (Lorenzi et al., 2023) capture population-level cerebellar dynamics using neuron-specific non-linear models. Cerebellar learning models (Geminiani A et al., 2024) provide insights into distributed synaptic plasticity in adaptive behaviors like eye-blink conditioning. Additionally, a cerebellar model with distributed plasticity enables adaptive motor learning in a neurorobot (Casellato et al., 2015), replicating human-like behaviors and optimizing memory across multiple time scales. These models exemplify how computational approaches, grounded in experimental data, contribute to understanding cerebellar function and its role in sensorimotor control.

2.1.3 Computational tools and Modeling frameworks: BBCAv2, BSB, and NEST

➤ Blue Brain Cell Atlas Pipeline

The Blue Brain Cell Atlas (BBCA) is a data-driven framework developed within the Blue Brain

Project to generate detailed estimates of neuronal and glial cell densities across the entire mouse brain. It integrates anatomical data from the Allen Mouse Brain Atlas (Dong, 2008) and computational methods to provide hierarchical cellular composition summaries for different brain regions. The BBICA (Blue Brain Cell Atlas, 2023) is based on two reference brain volumes derived from Allen Institute for Brain Science datasets: the Nissl-stained volume (Dong, 2008), containing coronal brain sections, and the Annotation Volume (AV), which maps voxels to defined brain regions within a hierarchical structure. These volumes are registered to the Common Coordinate Framework (CCF) to ensure spatial consistency.

Two versions of the BBICA have been released: BBICA v1 (Erö et al., 2018), which provided estimates of excitatory and inhibitory neurons, as well as glial cells, and BBICA v2 (Rodarie et al., 2022), which expanded the framework by incorporating additional inhibitory neuron subtypes. The BBICA v2 pipeline follows a structured four-step process: aligning *in situ* hybridization (ISH) images with the Nissl reference, computing neuron and glia densities for each brain region, estimating densities for specific inhibitory neuron subtypes (VIP+, SST+, PV+, GAD+), and ensuring consistency by applying constraints based on known anatomical and molecular properties. This systematic approach allows the BBICA to serve as a robust and extensible tool for modeling cellular distributions in the mouse brain.

➤ The Brain Scaffold Builder (BSB)

The Brain Scaffold Builder (BSB) is an evolving open-source framework for neural network modeling, under constant development and refinement by a research team at Neurocomputational Unit at the Department of Brain and Behavioral Sciences, University of Pavia (De Schepper Robin et al., 2023/2023). Its primary objective is to facilitate the construction of network topology by defining neuron placement and connectivity through custom algorithms. BSB enables various approaches, ranging from random neuron distribution to the integration of highly detailed cellular morphologies with connectivity rules based on probabilistic and geometric principles. Furthermore, it interfaces with simulators such as NEURON (Hines et al., 2019) and NEST (Graber et al., 2024), allowing the execution of models with varying levels of granularity. BSB is structured around the scaffold object, which bridges the model configuration with data storage. Through a parameterizable interface, users can define the network's architecture, spatial organization, and connectivity without requiring explicit programming. Its workflow encompasses the creation of the network volume, assignment and placement of cell types, connection of neurons based on predefined rules, and final circuit simulation (see figure 2.2). By integrating three-dimensional datasets, such as those from the Allen Brain Atlas, BSB enables the generation of large-scale, biologically realistic models, facilitating the detailed reconstruction of cortical microcircuits (De Schepper et al., 2022).

➤ Point Neuron modeling with NEST and E-GLIF

NEST is a simulator for spiking neural networks (SNNs), designed to model network dynamics, structure, and scalability rather than the detailed morphology of individual neurons (Graber et al., 2024). It is particularly suited for point neuron models, which simplify neuronal activity by representing dendrites, axons, and the soma as a single computational unit, focusing on functional behavior rather than spatial distribution (Yamazaki et al., 2022). This approach makes NEST an efficient tool for studying large-scale neural circuits while keeping computational costs low.

Widely used in computational neuroscience, NEST provides powerful tools for simulating spiking neural networks at various scales, making it a valuable resource for research in sensory processing, network activity dynamics, and synaptic plasticity. Additionally, its seamless integration with other neural modeling frameworks further enhances its applicability across different theoretical and experimental studies.

Supporting various levels of neuronal abstraction, NEST ranges from Hodgkin-Huxley (HH) models, which provide biophysically detailed membrane dynamics, to Leaky Integrate-and-Fire (LIF) and Extended-Generalized LIF (E-GLIF) models, which balance neurophysiological realism and computational efficiency. These features make NEST particularly effective for simulating complex mesoscale neural circuits, such as the cerebellar spiking network, where diverse neuronal populations can be efficiently represented using computationally optimized models.

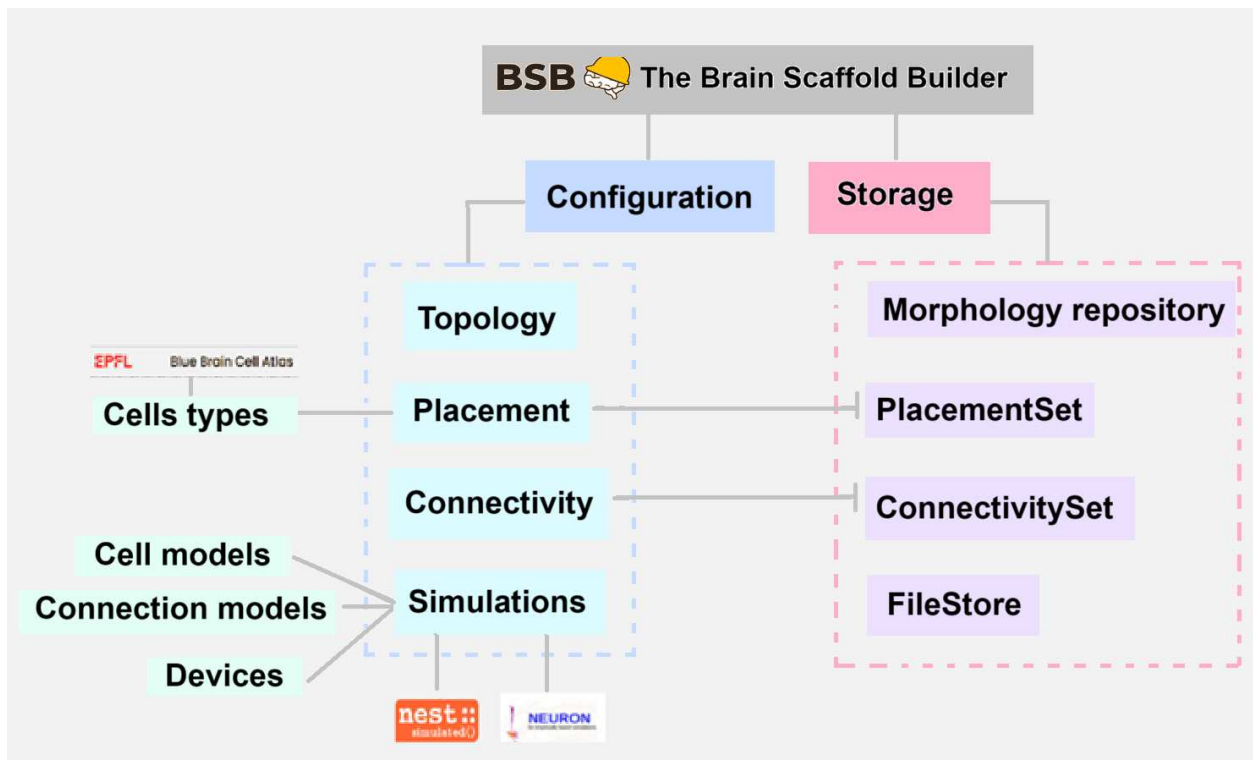


Figure 2.2 BSB framework. Concept map of the Scaffold model in BSB, illustrating its structured workflow. The process begins with the user's configuration, defining the network to be reconstructed and simulated. BSB interprets this configuration as a series of tasks, generating the topology, placing cells, and establishing connections based on connectivity rules. Finally, the simulation runs with an external simulator, with BSB acting as an intermediary. The Scaffold object ties together the configuration and storage, separating the model's description from its implementation and data. The relationship between Configuration and Storage is crucial, as Configuration generates the structural and connectivity data that Storage preserves for later access. This structured separation ensures that the model remains modular, efficient, and adaptable while enabling seamless interaction with the filesystem for optimized data retrieval and execution.

The Extended-Generalized Leaky Integrate-and-Fire (E-GLIF) model proposed by (Geminiani et al., 2018) extends the classical LIF model, adding two intrinsic currents, adaptive (*I_{adap}*) and depolarizing (*I_{dep}*), using a system of three ordinary differential equations. These state variables are continuously updated, and their values are adjusted at each spike event following predefined rules (see figure 2.3). The adaptive current regulates spike-frequency adaptation and slow hyperpolarization, mimicking potassium channel activity that influences firing patterns over time. This adaptation is crucial for post-inhibitory rebound bursting, intrinsic oscillations, and resonance, which are key to rhythmic neuronal activity. Meanwhile, the depolarizing current plays a role in fast excitatory dynamics, mimicking sodium channel activation and contributing to bursting activity and depolarization-induced excitation.

Unlike traditional integrate-and-fire models, where spikes occur upon crossing a fixed threshold, E-GLIF introduces a stochastic thresholding mechanism, making spike generation probabilistic and influenced by escape noise. This enhances the model's flexibility and adaptability, as the likelihood of firing increases as the membrane potential approaches the threshold, allowing it to capture diverse neuronal behaviors.

One of the key strengths of the E-GLIF model is its ability to predict neuronal behaviors by adjusting parameters, capturing temporal dynamics while maintaining computational efficiency, making it ideal for large-scale spiking neural network simulations. By balancing efficiency and neurophysiological realism, it ensures biologically plausible activity without compromising tractability. Additionally, its analytical solvability allows for larger simulation time steps, accurately reproducing cerebellar electroresponsive mechanisms with high precision (Geminiani et al., 2018; Geminiani, Pedrocchi, et al., 2019; Geminiani A et al., 2024).

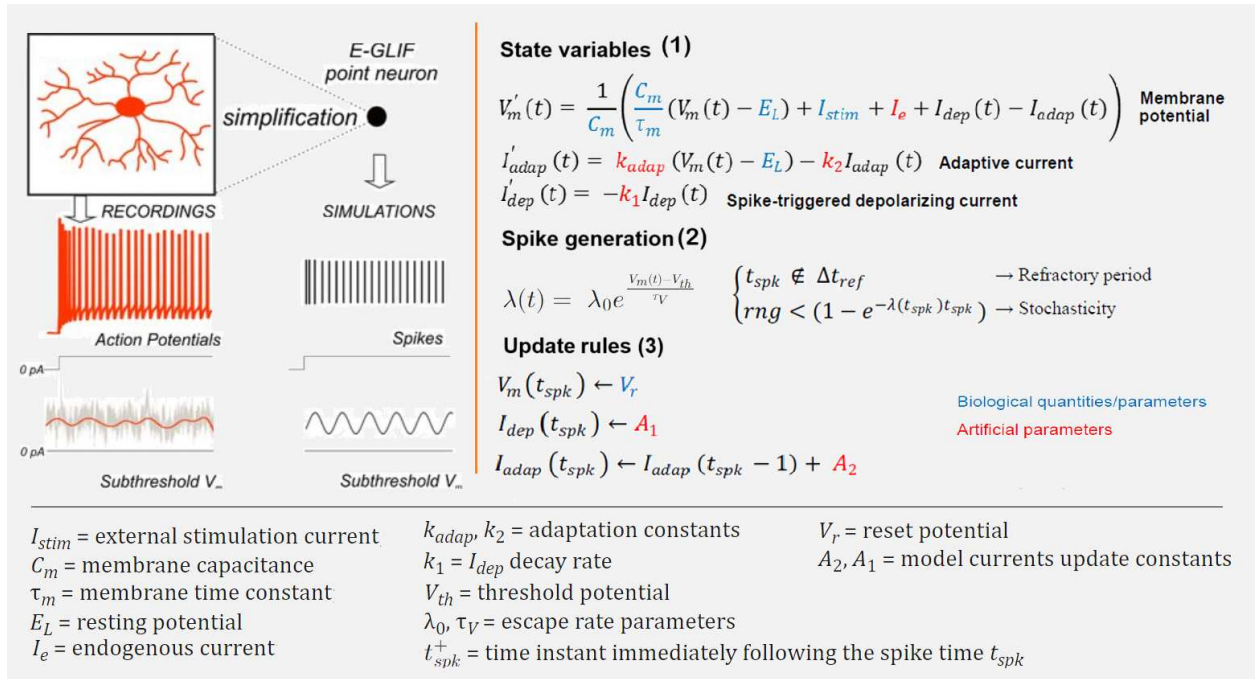


Figure 2.3 The E-GLIF point neuron model. The figure illustrates the simplification pipeline of Geminiani et al. 2019 to convert a biological neuron into an EGLIF model. The equations describe the time evolution of the membrane potential, adaptive current, and depolarizing current through a second-order three-dimensional ODE system (1) The figure also shows the stochastic spike generation mechanism (2) and update rules following a spike event (3) By analyzing its equations, it is possible to determine how specific changes in key parameters influence whether a neuron exhibits stable or oscillatory behavior. Some regions of the parameter space correspond to exponentially stable solutions, where the membrane potential gradually returns to equilibrium after a perturbation, while others allow for self-sustained oscillations, mimicking the rhythmic firing patterns observed in certain neuronal populations

Section 2.2 Methods

2.2.1 Atlas-based mapping of the Declive model

Building on the rationale presented in sections 1.2 and 1.4, where lobule VI was identified as a key region involved in emotional processing across species, we begin here with a computational model of this structure. The pipeline and workflow developed in this context provide a foundation that can later be adapted to other cerebellar regions. To optimize computational resources and work at a more manageable scale, we decided to focus on the vermal part of lobule VI, the Declive. The model follows an atlas-based reconstruction approach and is built upon the BBCAv2 pipeline (Rodarie et al., 2022). To implement this strategy, we outlined a step-by-step workflow:

➤ Corrections of the CCFv2 reference atlases' misalignment

We chose to use the CCFv2 annotation atlas and Nissl volume as reference volumes, as these can be more easily aligned to the datasets from the Allen Institute for Brain Science.

However, the alignment between the CCFv2 annotation atlas and its corresponding Nissl volume is not perfect. As highlighted by (Rodarie et al., 2022) this misalignment significantly affects cell density estimation when using the BBICA pipeline. To address this issue, we manually re-annotated the granular and molecular layers of the Declive region in the CCFv2 atlas to better correspond with its Nissl dataset.

For this purpose, we developed a graphical interface that presents a slice of the Nissl volume alongside its corresponding annotations, displayed with colour overlays (Rodarie, 2023). The intensity gradient in Nissl staining is particularly pronounced at the boundary between the molecular and granular layers, making it visibly distinguishable. Using this tool, we generated a refined version of the annotation atlas, as illustrated in Figure 2.4, improving the voxel labeling for the Declive region.

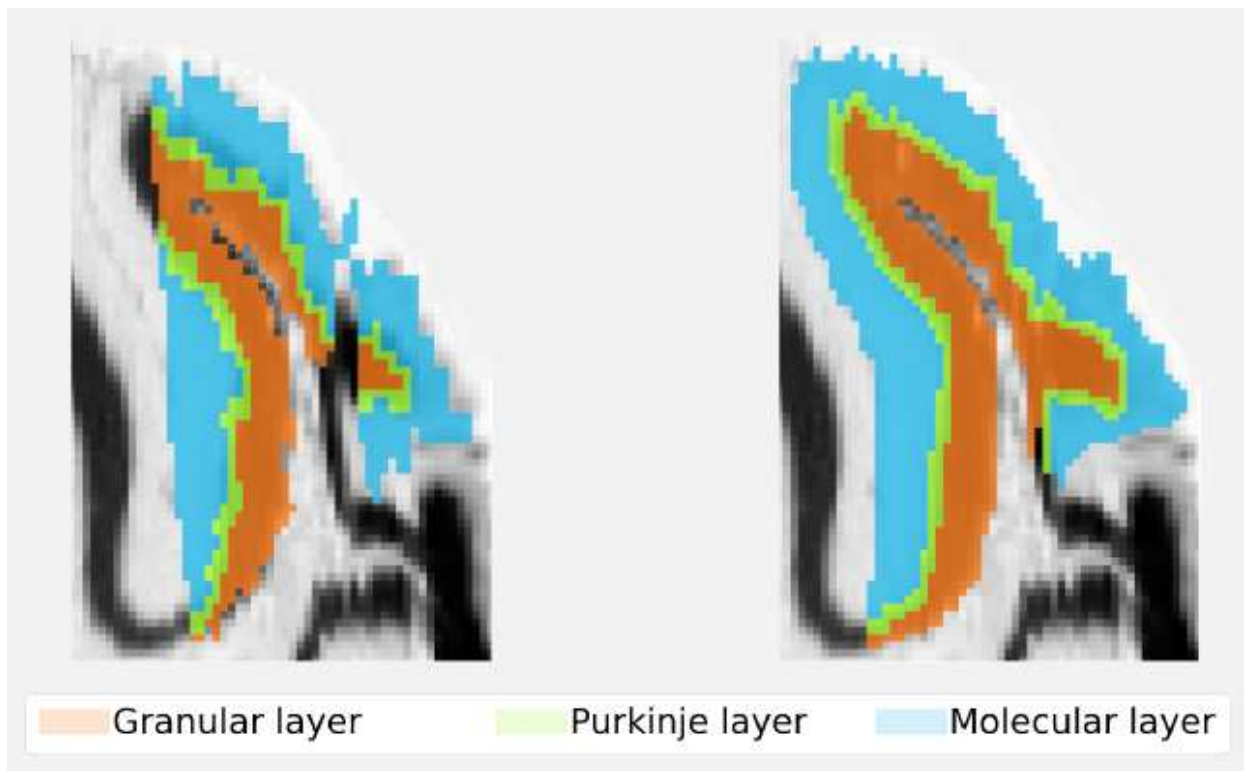


Figure 2.4 Declive Annotations corrections. (Left) CCFv2 Annotation atlas of Declive, shown in colours over the Nissl volume in levels of gray. The granular layer appears in orange, the molecular layer in blue, and the Purkinje layer in green. (Right) Corrected version of the annotation atlas.

➤ Labelling of the Purkinje layer

Beyond the realignment corrections discussed previously, we also expanded the Annotation Atlas to incorporate the Purkinje layer. This layer consists of a single-cell-thick band positioned between the granular and molecular layers and is well known for containing Purkinje cells. These inhibitory neurons, with a soma measuring approximately 15 μm in diameter, are among the most structurally complex neurons in the mouse brain (Hendelman & Aggerwal, 1980).

Since our annotation atlas dataset is structured as a voxel-based volume with a voxel size of 25 μm , the Purkinje layer is thinner than a single voxel in this framework. A manual review of the original Nissl-stained images from (Dong, 2008) reveals that Purkinje cells are frequently labeled within voxels corresponding to the granular layer. Based on this observation, we integrated the Purkinje layer into the granular layer. To ensure accurate estimations of neuron type densities within the Purkinje layer, including Purkinje cells (PC), globular cells (GIC), and candelabrum cells (CC), neurons, we extracted a one-voxel-thick section of the granular layer at its boundary with the molecular layer (see Figure 2.4).

➤ Orientations and depth field

The canonical model proposed by (De Schepper et al., 2022) assumes fixed layer thicknesses and orientations, which simplifies the positioning, orientation, and scaling of neuronal morphologies, as they are designed to fit within this predefined volume. However, the mouse cerebellar cortex is highly convoluted and curved. Consequently, accurately placing neuronal morphologies requires computing the local thickness and orientation fields to adapt neurite structures to the actual cortical shape.

To model orientation, we aimed to generate a vector field that extends outward from the arbor vitae fibers toward the molecular layer's external boundary, aligning with the trajectory of granule cell ascending axons. To address this, we implemented the algorithm described by (Rodarie et al., 2022) to construct a vector field within each sub-region of the cerebellar cortex.

In summary, this algorithm first generates a scalar field by assigning predefined weights to each voxel based on its proximity to specific cerebellar regions: Molecular layer: 1, Purkinje layer: 0, Granular layer: -1, Arbor vitae: -5, external brain regions: 3, other brain areas: 0

To minimize boundary artifacts, this scalar field is then extended to adjacent voxels of the region of interest. Additionally, a shading effect is introduced based on the distance to a designated fiber's target region, ensuring that the outermost voxels target the outward area. Hence, voxels near the molecular layer and outside the region of interest are assigned a value of 1 plus their distance to the molecular layer. Given that some cerebellar sub-regions face each other (as illustrated in Figure 2.5), each sub-region was processed independently to prevent interference between their respective shading effects.

The final scalar field for each region is then smoothed using a Gaussian filter, and the gradient of the normalized blurred scalar field is computed. The resulting gradient provides the direction vectors for each voxel across the different sub-regions of the cerebellar cortex (see Figure 2.5).

To properly position neuronal morphologies within our circuit, it is essential to determine the local thickness of the layer in which they reside. This information is also crucial for distinguishing between Basket and Stellate cells in the molecular layer based on their relative distance from the Purkinje layer (see Estimation of Declive neuron densities). To achieve this, we computed the local layer thickness for each voxel in the cerebellar cortex by measuring its distance to the nearest layer boundary. This process leveraged both the previously calculated orientation field and the depth estimation algorithm introduced by (Rodarie et al., 2022).

The algorithm initiates from the center of a given voxel and iteratively moves in the direction defined by the local orientation field vector, checking the region ID at each new position. This iterative process continues until the voxel reaches the target region. At each step, the movement vector is updated based on the orientation field at the current position. The resulting depth values provide insights into the distance to the outer boundary of the molecular layer in the Declive, as illustrated in Figure 2.5

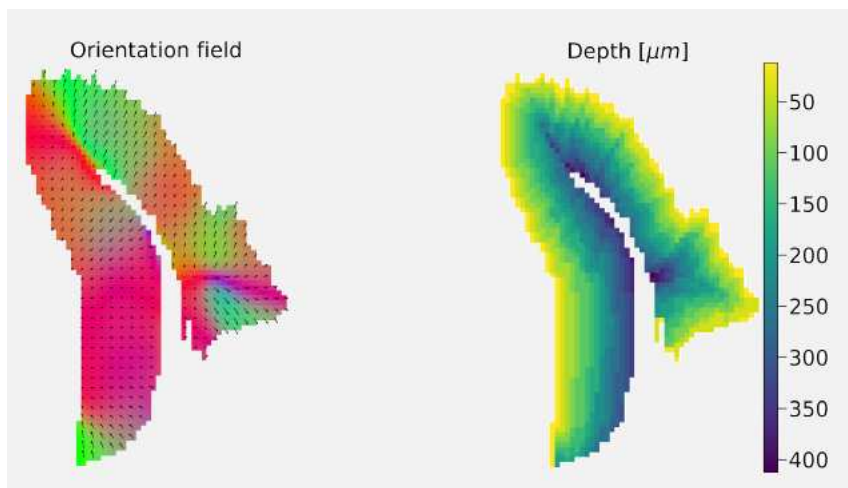


Figure 2.5 Declive orientation and depth field. (Left) Orientation field of each voxel of the Declive. The colours represent the orientation vectors' norm on their respective plane, the black arrows their projected vector. (Right) Distance of each voxel of the Declive to the outside border of the molecular layer, following the orientation field, expressed in μm .

➤ Nissl volume artifacts on neuron density estimation

The final density estimates produced by the BBCCA pipeline are inherently linked to the Nissl volume it processes. This volume originates from a series of coronal image stacks (Dong, 2008) that have been aligned with each other. However, certain images within this dataset contain artifacts, such as tissue damage (e.g., holes or tearing), as well as variations in exposure levels during image acquisition. These inconsistencies and their impact on both inhibitory and excitatory neuron densities are illustrated in Figure 2.6

In the Declive region, these artifacts have a particularly pronounced effect, resulting in a disproportionate accumulation of neurons in the most dorsal areas. To mitigate this issue and reduce the influence of such artifacts on the spatial distribution of cells, we applied a uniform redistribution of neurons across each layer of the cerebellar cortex.

➤ Estimation of Declive neuron densities

To estimate the densities of excitatory and inhibitory neurons in the Declive region, we implemented the BBCCA_{v2} pipeline (Rodarie et al., 2022). This computational framework integrates in situ hybridization (ISH) datasets with literature-derived density values to generate cell-type density estimates for the Declive region based on a given reference atlas pair.

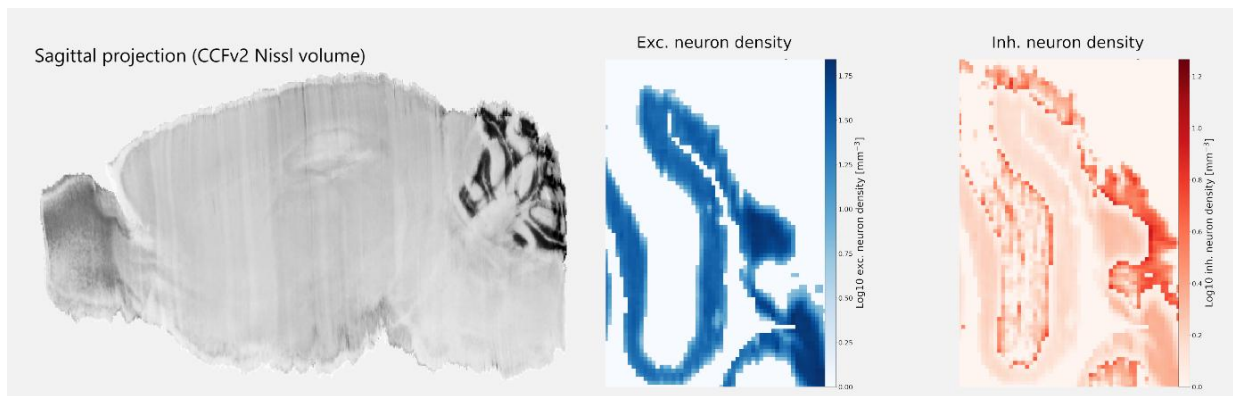


Figure 2.6 Blue Brain Cell atlas results. (Left) Sagittal projection of the median expression of the CCFv2 Nissl volume. Regions with high Nissl intensity appear in dark gray. This view highlights the rapid changes in Nissl expression coming from the original Nissl experiment from (Dong, 2008) (Right) Sagittal slice of respectively excitatory and inhibitory neuron densities in logarithmic scale in the Declive region. Darker regions contain more neurons. The most caudal regions show higher densities that are coherent with artifacts present in the Nissl volume

Since we modified the CCFv2 annotation atlas, an updated version of the cell atlas was required. To efficiently manage this workflow, we utilized the Snakemake pipeline developed by Rodarie, which allows for the automation of the BBCAv2 pipeline execution. Snakemake ensures that the necessary input datasets are retrieved when required, tracks the generated outputs, and determines which steps of the pipeline need to be re-executed whenever modifications occur in the input data or computational code.

The BBCAv2 pipeline itself consists of four main stages: 1) Alignment of ISH datasets – ISH images are registered to the reference atlas using a deformation algorithm, creating a continuous volumetric dataset. 2) Estimation of cell densities – Neuron and glial cell densities are computed based on ISH data. 3) Computation of neuronal subtypes – Densities of specific inhibitory neurons, such as parvalbumin (PV+), somatostatin (SST+), vasoactive intestinal peptide (VIP+), and other GABAergic neurons expressing GAD67, are estimated using literature data and transfer functions. 4) Integration into a cell atlas – A linear optimization process ensures consistency across estimates, producing a complete cell atlas.

Although the BBCAv2 pipeline estimates both excitatory and inhibitory neuron densities, it does not provide subtype-specific estimates for the cerebellar cortex. Our primary interest lies in the distribution of the nine major neuronal subtypes within this region: granule cells (GrCs), Golgi cells (GoC), unipolar brush cells (UBC), Lugaro cells (LC), Purkinje cells (PC), globular cells (GIC), candelabrum cells (CC), basket cells (BC), and stellate cells (SC).

- Purkinje Layer: To estimate neuronal densities in the Purkinje layer, we accounted for the region's thinness, which makes volume-based cell counts challenging. Since literature primarily provides linear or surface densities, we implemented an exploration algorithm that places neurons based on linear density values from (Osorno et al., 2022). This dataset offers para-sagittal density values for GIC and CC neurons across most cerebellar regions, with missing values approximated using the mean of available data. For Purkinje cells (PCs), we assumed a minimum spacing of 100 μm in the para-sagittal plane, considering dendritic tree amplitude (Nedelescu et al., 2018b). The algorithm estimates the mean intercellular distance, starting from the most lateral sagittal slice and sequentially placing PC, GIC, and CC neurons in the lowest available voxels. It explores the Purkinje layer, ensuring that newly placed neurons respect the computed mean spacing. Additionally, due to voxel size constraints (25 μm), we prevent GIC and CC from sharing the same voxel as a PC. Following the placement strategy of (De Schepper et al., 2022), we applied a one-voxel medial shift per parasagittal plane to prevent Purkinje cell dendritic overlap. The final output consists of the spatial positioning of PC, GIC, and CC neurons in the cerebellar cortex (see Figure 2.7), which can be converted into volumetric density.

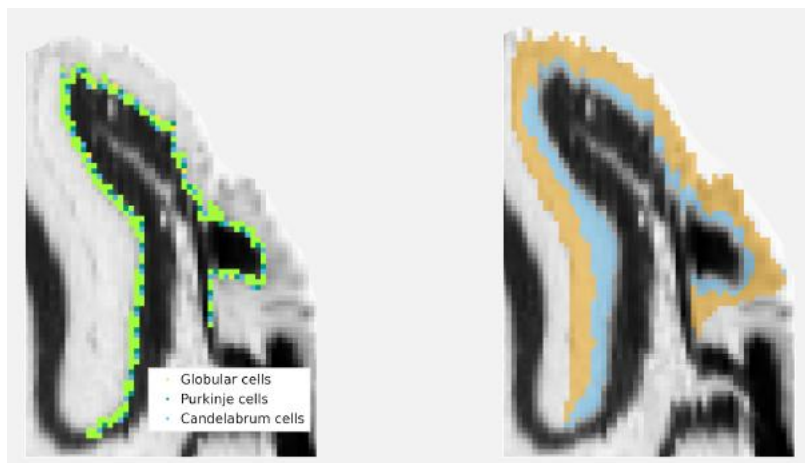


Figure 2.7 Declive placement intermediate results. (Left) Sagittal slice of the Declive showing the Purkinje layer in colours on top of the Nissl volume in levels of gray. The different voxel colours correspond to the location of a specific type of neuron. This slice shows that the spatial properties of the placement between consecutive cells are correctly implemented by my algorithm. (Right) Sagittal slice of the Declive showing the Molecular layer in colours on top of the Nissl volume in levels of gray. The different

colours show the respective space allocated to Basket (in light blue) and Stellate cells (in orange).

- Granular Layer: Since Purkinje layer neurons are exclusively inhibitory, their placement must align with inhibitory densities from the BBCAv2 pipeline. The remaining inhibitory neurons in the merged granular and Purkinje layers belong to either Lugaro cells (LCs) or Golgi cells (GoCs). LC counts were estimated as a ratio of PC counts, based on mouse data (Dieudonné & Dumoulin, 2000a). Once LC counts were subtracted from the total inhibitory neuron counts in each sub-region, GoC densities were derived.

The granular layer's excitatory neurons include granule cells (GrCs) and unipolar brush cells (UBCs). UBC densities were sourced from (Sekerková et al., 2014) and integrated into our model. The remaining excitatory neurons were classified as GrCs, calculated by subtracting UBC densities from the total BBCAv2-derived excitatory density.

Mossy fibers (mf) and UBC neurons form large axonal terminals known as glomeruli, which serve as distribution hubs for pre-cerebellar nuclei input within the granular layer (Berthié & Axelrad, 1994; Eccles et al., 1966). In our circuit, mf glomeruli were assumed to be uniformly distributed at a density of 300,000 per mm^3 (Korbo et al., 1993). Each UBC contributes 2-4 glomeruli (Diño et al., 2000; Rossi et al., 1995), though this is likely an underestimation due to the difficulty of tracking UBC axons throughout their full length (Mugnaini et al., 2011). We estimated UBC glomeruli density as four times the UBC density.

- Molecular Layer: All neurons in the molecular layer are inhibitory and belong to either basket cells (BCs) or stellate cells (SCs). BCs are located near the Purkinje layer, occupying the lower third of the molecular layer, while SCs are positioned in the upper two-thirds. Using previously computed layer boundary distances (see Orientations and depth field), we assigned neurons in the upper molecular layer as SCs and those in the lower molecular layer as BCs (see Figure 2.7). Through this method, we obtained volumetric density estimates for each major neuron type in the Declive region. These densities will serve as input for the next steps in constructing a point-neuron network of this region.

➤ Placement and connectivity with BSB

To position neurons in the Declive region, we used the Brain Scaffold Builder (BSB) framework (De Schepper Robin et al., 2023/2023). For more details on the placement process, please refer to the supplementary material Table S2.1. Since our goal is to develop a point-neuron network, precise soma placement is not the main priority. Instead, we applied a random uniform placement of neuron somas within each voxel. However, the connectome must be constrained by neurite locations within the complex shape of the Declive and by connectivity rules from (De Schepper et al., 2022). Therefore, we developed a method to position and adapt neuron morphologies to the available space in the cerebellar cortex. This approach assumes that neurons originating from the same voxel will yield similar results once scaled and bent. Starting from the soma, the method follows neurites as a tree, adjusting each segment individually based on spatial constraints.

Neurite bending is performed by rotating each morphology segment relative to its predecessor and the local orientation field (see Orientations and depth field). The root segment (soma) is

oriented toward the upper molecular layer, while subsequent segments are adjusted by computing the angle difference between the predecessor and the current orientation vectors. On the other hand, neurite scaling is applied according to the ratio between local layer thicknesses (calculated in Orientations and depth field) and the default thicknesses defined by (De Schepper et al., 2022). Since morphologies are initially fitted for these default values, each section is scaled proportionally to the local layer thickness. Before applying any bending or scaling, our algorithm verifies whether these transformations are valid. It ensures that neuronal arborizations remain within the cortical sheet boundaries and do not extend outside the cerebellar cortex (see Figure 2.8)

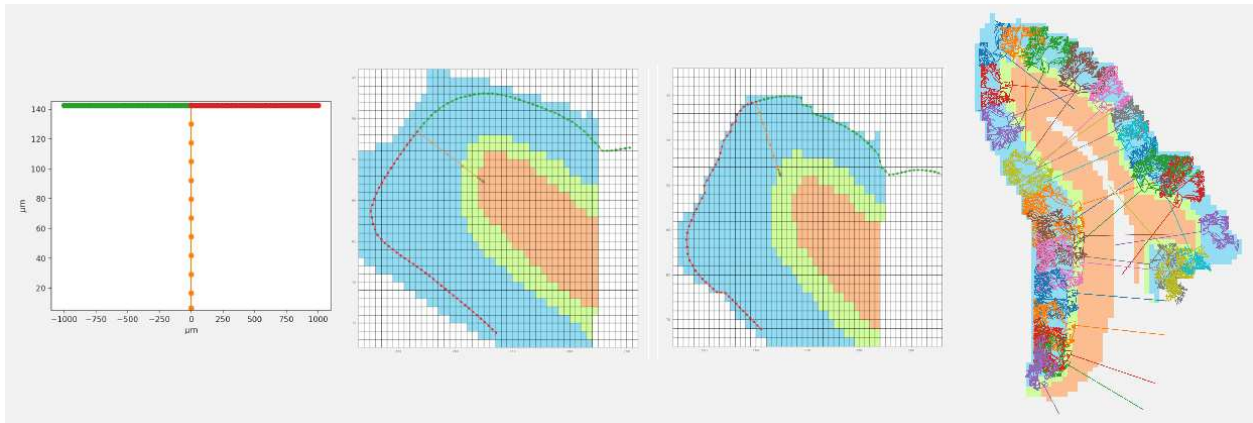


Figure 2.8 Morphology scaling and bending according to the shape of Declive. (Left) Original granule cell morphology represented on the coronal plane. Each branch of the morphology is painted with a different colour, with orange for the ascending axon, red and green for the two branches of the parallel fibers. (Middle) Coronal views of the Declive showing one granule cell morphology scaled and bent according to the depth and orientation field. In the first case, the morphology has enough space to grow without constraints, while in the other case, the ascending axon hits the border of the region, and the bending is adapted to not escape the region. (Right) Sagittal view of the Declive showing Purkinje cell morphologies scaled and bent according to the depth and orientation field. Each morphology is shown in different colours.

A segment is considered out of bounds if: 1) It extends beyond the cortical sheet. 2) The angle difference between the original and new orientation vectors exceeds 90° , preventing fibers from crossing into adjacent lobules. If a segment rotation results in boundary violations, the algorithm adjusts the rotation angle until the segment remains within valid limits. If no acceptable angle is found, the segment is removed from the morphology tree. Any angle adjustments are propagated to subsequent segments whenever space allows.

Different neuron types require specific transformations to preserve their structural and functional integrity. To ensure that each morphology adapts appropriately, we applied targeted modifications only where necessary. This was achieved using predefined morphology labels, allowing us to selectively adjust relevant sections while maintaining the overall consistency of neuronal structures.

Cerebellar connectivity is primarily governed by the intersection of two main fiber planes: 1) The parasagittal plane, which contains Purkinje cells (PC), stellate cells (SC), and basket cells (BC) with their dendritic and axonal trees. 2) The coronal plane, where the parallel fibers of granule cells extend (see Figure 2.8).

Since the current algorithm does not inherently preserve these planes, we introduced plane constraints: PC, BC, and SC are restricted to sagittal-plane rotations to ensure their dendritic trees remain properly oriented. Parallel fibers are limited to coronal-plane bending, preventing unwanted intersections. By applying these constraints, we ensure realistic morphology adaptations while maintaining the structural and functional integrity of cerebellar connectivity. Once the neurons are placed, we connect them using specific neuron type to neuron type connection strategies (see Table 2.1).

2.2.2 The canonical microcircuit model

➤ The Cerebellar circuit

A brief introduction to the canonical circuit is provided to give the reader context for comparison; however, a detailed explanation is beyond the scope of this thesis.

The canonical reconstruction of the cerebellar circuit, as presented in (De Schepper et al., 2022) models a cubic volume of the cerebellar cortex with fixed layer thicknesses. This approach simplifies the scaling and orientation of neuronal geometry while preserving structural integrity; in consequence, the canonical microcircuit is represented as a regular parallelepiped, without curvature or the need for local bending.

The microcircuit is vertically organized, with the granular layer at the bottom and the molecular layer at the top, following a right-hand coordinate system (x, y, z). The (y - z) plane aligns with Purkinje cell dendritic trees and is perpendicular to granule cell parallel fibers.

The reconstructed circuit consists of three main layers, each defined by its neuronal composition and morphological constraints. The Purkinje layer is a single-cell-thick sheet, with a thickness of 15 μm , determined by the average soma diameter of Purkinje cells. Above this, the molecular layer, measuring 150 μm in total, is subdivided into two distinct regions: the basket cell layer (50 μm), which lies directly above the Purkinje layer, and the stellate cell layer (100 μm), where stellate cells are primarily located, consistent with anatomical data. The granular layer, at the base of the circuit, has a thickness of 130 μm , matching the size of Golgi cell basal dendritic trees and imposing constraints on the ascending axons of granule cells.

Each cell type (For more details, refer to Supplementary Material, Table S2.1-S2.4) is assigned to a specific one of these layers, ensuring proper spatial organization, and a corresponding morphology is defined based on known structural properties. Additionally, mossy fibers and glomeruli serve as input relay structures, integrating external signals into the network.

➤ The Olivocerebellar circuit

Integrating the cerebellar cortex, deep cerebellar nuclei (DCN), and inferior olivary complex (IO) within a single computational framework represents a critical step toward modeling cerebellar processing at the systems level. Accordingly, we extend the canonical cerebellar circuit by incorporating both the IO and DCN, following the approach of (Geminiani et al., 2018). Each region consists of a single layer (IO: 100 μm thick; DCN: 200 μm thick) and is spatially arranged beneath the cerebellar cortex to preserve anatomical organization. Due to the lack of available morphologies, all neurons in these regions were modeled as point neurons and placed using a uniform random distribution. The number of IO neurons was estimated using a known 5:1 ratio between Purkinje cells and IO neurons (Blatt & Eisenman, 1985). To model the olivocerebellar circuit as a functional unit involved in emotional behavior, the inclusion of both excitatory (DCNp) and inhibitory (DCNi) neuron populations is fundamental, as recent studies have shown that these subtypes differ in neurotransmitter expression, projection targets, and functional roles (Bagnall et al., 2009; Cohen, 2024; Uusisaari & Knöpfel, 2011). The numbers of DCNp and DCNi were estimated based on reported proportions (57% and 32%, respectively) (Batini et al., 1992; Baumel et al., 2009; Erö et al., 2018) and scaled according to the number of granule cells and the DCN layer volume (see Table S2.1-S2.4)

This architecture allowed us to simulate the microcomplex organization of the cerebellum and reproduce dynamic interactions across regions. Figure 2.9 illustrates the full olivocerebellar microcircuit connectome modeled in this work, encompassing the cerebellar cortex, deep cerebellar nuclei (DCN), and inferior olive (IO).

2.2.3 Modeling a subvolume of the Declive

To contextualize our atlas-based reconstruction of the Declive, we compare it with the canonical olivocerebellar circuit. Due to computational limitations, it is not feasible to reconstruct the entire mouse Declive circuit, which comprises approximately three million neurons. Instead, we selected a representative subvolume for reconstruction and simulation, preserving the structural and functional characteristics of the region (see Figure 2.10).

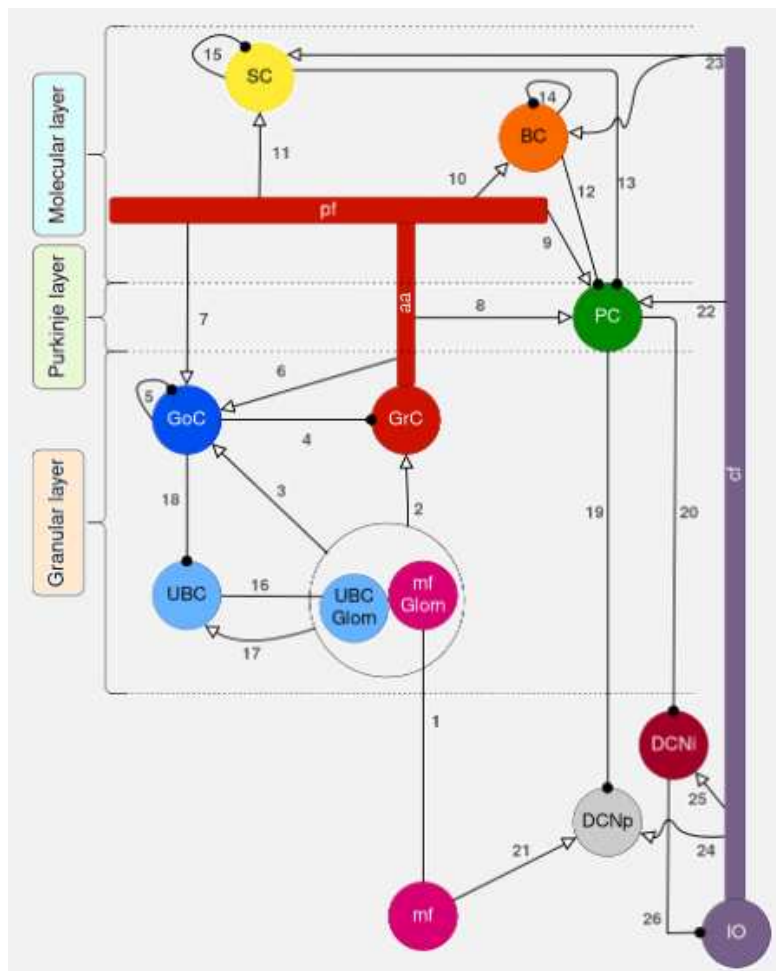


Figure 2.9 Cerebellar microcircuit connectome. The numbers and arrows represent the excitatory and inhibitory synapses between the neurons in the cerebellar circuit. The numbers correspond to the order assigned to the connections during the construction of the connectome, as shown in Table S2.1. Arrows ending in a pointed tip represent excitatory synapses, while those ending in a dot represent inhibitory synapses. Mossy fibers (mf) provide excitatory input to the granular layer, where they synapse onto glomeruli (mf Glom). Within these glomeruli, granule cells (GrCs) receive excitatory input from mossy fibers and extend their axons in two forms: ascending axons (aa), which travel vertically through the Purkinje layer, and parallel fibers (pf), which extend horizontally in the molecular layer. Granule cells (GrCs) excite multiple neuron types as their axons bifurcate in the molecular layer. Parallel fibers (pf) synapse onto Purkinje cells (PC), basket cells (BC), and stellate cells (SC), facilitating widespread excitatory transmission. Golgi cells (GoC) play an important role in regulating the activity of granule cells.

They receive excitatory input from granule cells and provide inhibitory feedback to both granule cells and mossy fiber glomeruli. This feedback mechanism controls the flow of excitatory input into the cerebellar cortex. Unipolar brush cells (UBC) are also involved in modulating mossy fiber input. They receive excitatory input from mossy fiber glomeruli and, in turn, provide excitatory feedback within the granular layer by connecting back to the glomeruli (UBC Glom), thereby influencing the transmission of mossy fiber signals. Purkinje cells (PC), located in the Purkinje layer, integrate excitatory input from both parallel fibers (pf) and climbing fibers (cf) originating from the inferior olive (IO). Climbing fibers provide a strong excitatory drive to Purkinje cells, playing a key role in motor learning and synaptic plasticity. In contrast, parallel fibers contribute to modulating and refining Purkinje cell output. Basket cells (BC) and stellate cells (SC) function as inhibitory interneurons in the molecular layer. They receive excitatory input from parallel fibers and, in turn, provide inhibitory feedback to Purkinje cells. Basket cells form axo-axonic inhibitory synapses on Purkinje cells, strongly regulating their output, while stellate cells target Purkinje cell dendrites, providing lateral inhibition within the molecular layer. Purkinje cells (PC) are the primary output neurons of the cerebellar cortex. They send inhibitory projections to deep cerebellar nuclei inhibitory neurons (DCNi), thereby controlling the activity of deep cerebellar projection neurons (DCNp). DCNp neurons represent the final output of the cerebellum, transmitting signals to motor and cognitive centers in the brain. Deep cerebellar nuclei (DCNi and DCNp) serve as the cerebellum's gateway for motor control and learning. DCNi receives inhibitory input from Purkinje cells and, in turn, modulates the activity of DCNp neurons, which project excitatory signals to other brain regions. A key feedback loop exists between the cerebellum and the inferior olive (IO). DCNp neurons send excitatory output to the IO, which, in turn, generates climbing fibers (cf) that project back to Purkinje cells. Additionally, DCNi neurons provide inhibitory modulation of IO activity, shaping its rhythmic output.

To ensure comparability with the canonical circuit, the extracted subvolume was constrained so that the area of the Purkinje layer matched that of De Schepper's model. Using the orientation field derived from the Purkinje layer voxels, we then extended the volume in both directions to include the associated granular and molecular layer voxels. The center of the final circuit was selected to maximize local uniformity in the orientation field, ensuring anatomical consistency within the reconstructed region.

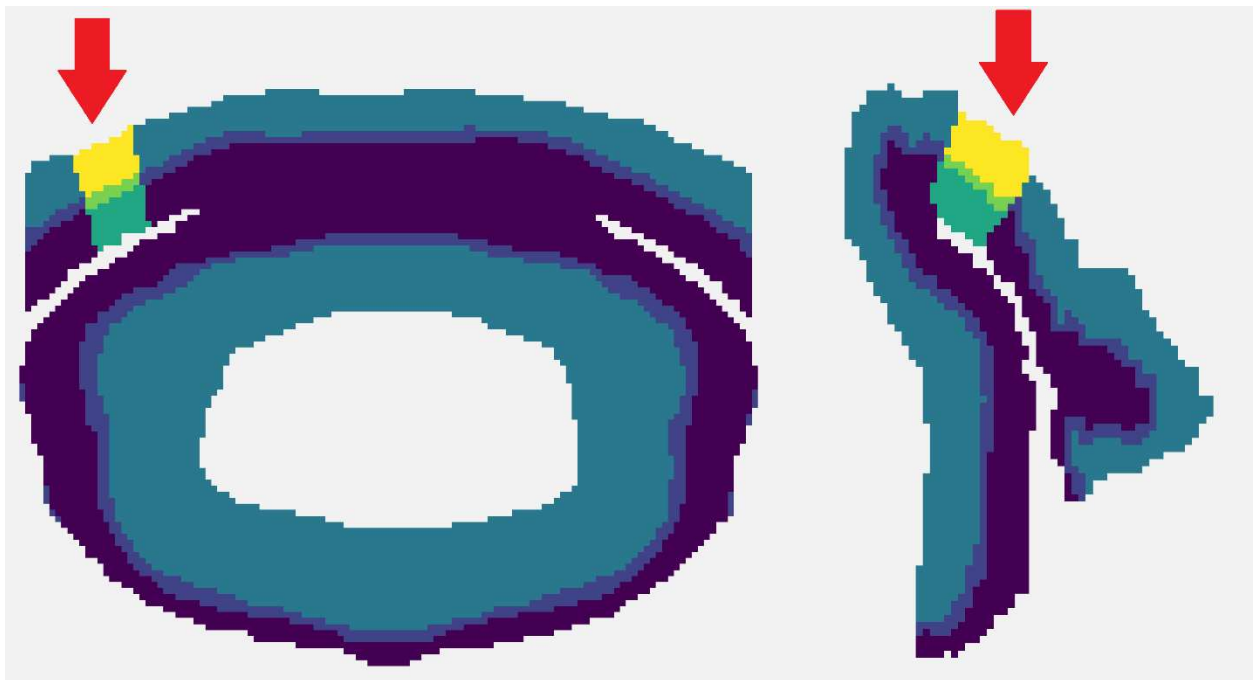


Figure 2.10 Subvolume of the Declive. (Left) Coronal plane, (right) Sagittal plane

To add IO and DCN (DCNp+DCNi) populations, in order to create the entire olivocerebellar circuit associated with the subvolume of the Declive, we made some adjustments to ensure the final density values were accurate. First, we recalculated the ratio of GrC/DCN with our updated cell atlas, which resulted in a value of approximately 162 for the Declive. Based on this, the density of DCN neurons in the subvolume of the declive was calculated by dividing the local density of GrC by 162. Then, following Tables S2.3 and S2.4, we adjusted the values for specific DCN populations: the density of DCNp was set to 57% of the DCN density, while the density of DCNi was set to 32% of the same value.

2.2.4 Computational simulations of awake-state baseline activity

For the simulations, we adopted the EGLIF-based olivocerebellar model developed by Geminiani et al, which served as the primary source for neuron and synaptic parameters. This model already incorporates distinct excitatory (DCNp) and inhibitory (DCNi) populations, each with specific firing properties and connectivity profiles, which we preserved in our implementation.

We used parrot neurons to represent mossy fibers and the glomerulus population, as these fibers merely transmit spikes originating from other brain regions. The parrot neuron is used with the point neuron models to provide identical input to multiple neurons. By connecting a Poisson generator to a parrot neuron and then linking the parrot neuron to a group of EGLIF neurons, we ensure that all EGLIF neurons receive the same spike train. This allows for controlled and synchronized input patterns, which are particularly useful for studying network dynamics and plasticity. The parrot neuron is a basic neuron model in NEST (*Parrot_neuron_NEST*, n.d.) that emits one spike for each incoming spike it receives.

A Poisson generator is a type of input source that produces spikes according to a Poisson process, which is a mathematical model used to describe random spike events over time (Heeger, 2000); in other words, it generates spikes at random intervals, with a certain average rate, simulating the natural variability observed in biological neural activity.

The connection weights to the parrot neuron are ignored, whereas the weights on the connections from the parrot neuron to the target neurons are processed as usual. Delays on both incoming and outgoing connections are respected.

➤ Neuron and synaptic parameters

To simulate the awake state, which reflects the natural physiological conditions of behaving rodents, we relied on the data reported and used in the studies by Geminiani and colleagues for the canonical cerebellar circuits. Accurately modeling the awake state is essential for

understanding the dynamics of neural activity under realistic conditions and ensuring that the model's behaviour closely resembles biological responses (Fina et al., 2013)

The parameters for the EGLIF model were extracted from Tables 2 and 3 in (Geminiani, Casellato, et al., 2019) and subsequently optimized using the method described in (Geminiani et al., 2018). For clarity and further reference, these values are also presented in Tables S2.5 and S2.6.

Postsynaptic currents act at the soma level, using alpha-exponential conductance functions, which are defined by a reversal potential parameter E_{rev} and a synaptic time constant τ_{syn} . These parameters depend on the type of connection and, in our model, are defined directly within the neuron equations in NEST. Furthermore, the postsynaptic receptor parameters used in our model are based on those reported in Table 2 of (Geminiani, Pedrocchi, et al., 2019). For clarity and further reference, these values are also presented in Table S2.7.

Regarding presynaptic parameters, to reproduce the values reported in Table 1 (Geminiani A et al., 2024), we targeted a tonic firing rate of ~80 Hz in the Purkinje cells population to match the range described. For further references see Table S2.8.

To implement synaptic transmission, we used static synaptic (Static_synapse_NEST, n.d.) to connect different neurons. This model transmits spikes as weighted signals to postsynaptic neurons after a defined delay. The synaptic parameters used correspond to those listed in Table B of the supplementary material in (Geminiani A et al., 2024) (see Table S2.8). The receptor id corresponds to the postsynaptic receptor involved in the connection, as detailed in Table S2.7.

➤ Basal activity simulation

To evaluate the basal activity of our model, we simulated the default activity of the cerebellar cortex circuit. The simulation was configured to run for 5000 ms with a time step of 0.1 ms.

To mimic the low-level, sparse synaptic input, we applied background noise represented as a 4 Hz Poisson spike generator to the mossy fiber population. The spiking activity of each neuron was recorded throughout the simulation. This simulation was designed to reflect the steady state activity of the network, providing a baseline for comparison with further simulation imposing ad-hoc stimuli patterns.

Section 2.3: Analysis and Results

2.3.1 Comparative analysis between the canonical and Declive model reconstructions

We obtained density estimates for the nine major neuron types in Declive (Figure 2.11, 2.12, and Table 2.1)

From Figure 2.12, we can see that the layers' thickness is significantly greater than the canonical counterpart (see Section 2.2: The canonical microcircuit), with large standard deviations. This implies, at least if the internal circuit remains the same across cerebellar regions as hypothesised in subsection 1.2, that we will observe a variability in structure and function just based on brain geometry.

We note that the counts of BC concerning SC are almost the same. Remember that the BC occupies the lower one-third part of the molecular layer and the SC the rest. An inspection of their respective volume shows that this proportion is roughly maintained in the atlas: 0.56mm³ for BC, and 1.17mm³ for SC.

Table 2.1 Declive cell type distributions across layers			
	Granular layer	Purkinje layer	Molecular layer
ID region	10723	10724	10725
Volumes (mm ³)	1,357421875	0,4715625	1,7380625
Neurons counts	1900114,75	732205,2526	105329,1315
Exc. Neurons counts	1870213,226	689477,7896	0
Inh. Neurons counts	29901,52389	42727,46302	105329,1315
Granule cells	1864213,226	683477,7896	0
Golgi cells	29901,52389	6571,350803	0
Unipolar Brushed cells	6000	6000	0
Globular cells	0	9735,719019	0

Lugaro cells	0	852,2023415	0
Purkinje cells	0	12783,03512	0
Candelabrum cells	0	12785,15573	0
Basket cells	0	0	151473,1093
Stellate cells	0	0	83177,7873

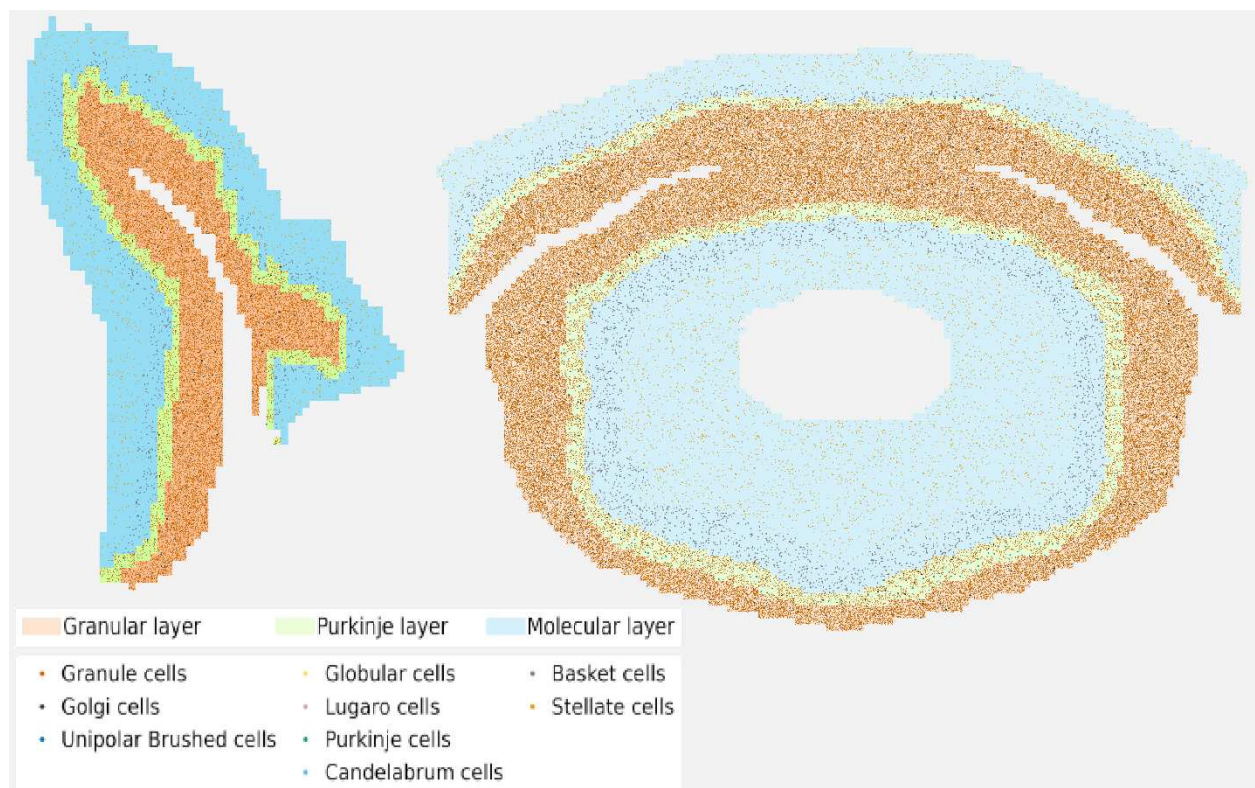


Figure 2.11 Neuron type distribution in Declive. Cell Type Mapping in Sagittal (Left) and Coronal (Right) views of the Declive

Looking at the right panel of Figure 2.13, we see that the bending algorithm was capable of orienting the ascending axon of granule cells properly towards the molecular layer. Each parallel fiber was individually inspected (detailed visual verification) to ensure that it remained confined to the molecular layer, confirming the anatomical accuracy of the reconstructions, and that they remain on their original sagittal plane (hence parallel to one another), as can be seen on the left panel. We can see the evolution of the parallel fibers bending within Declive, creating convex and concave curve lines depending on local surface curvatures (clearly visible on the right part of the right panel).

Figures 2.14 and 2.15 provide a point and detailed visual representation of the constructed cerebellar microcircuit in both the Declive subvolume and canonical volume, reflecting the realistic position and morphology of each cell type. They illustrate the spatial organization and connectivity, capturing the structural complexity and anatomical hierarchy of the cerebellar cortex. Table 2.2 shows the number and densities of placed cells in the two final circuits (Figure 2.14). The comparison between the canonical cerebellar circuit and the sub volume of Declive circuit reveals significant differences in cell counts and densities. In general, the Declive circuit exhibits a higher overall number of cells but lower cell densities across most cell types.

First, the densities of mf, glom, UBC, and UBC_glom are roughly the same between both reconstructions. This is because these densities were used as constraints to build the circuits. It has to be noted that the density of glom has been calculated in (Solinas et al., 2010) based on the “glomerulus to granule” convergence and divergence ratios (derived from values in (Korbo et al., 1993) and (Jakab & Hámori, 1988)). Yet in the Declive subvolume, the density of GrC is lower than in the canonical circuit. The input that receives the GrCs of the Declive circuit will be distributed over more mfs, resulting in less synchronized activity.

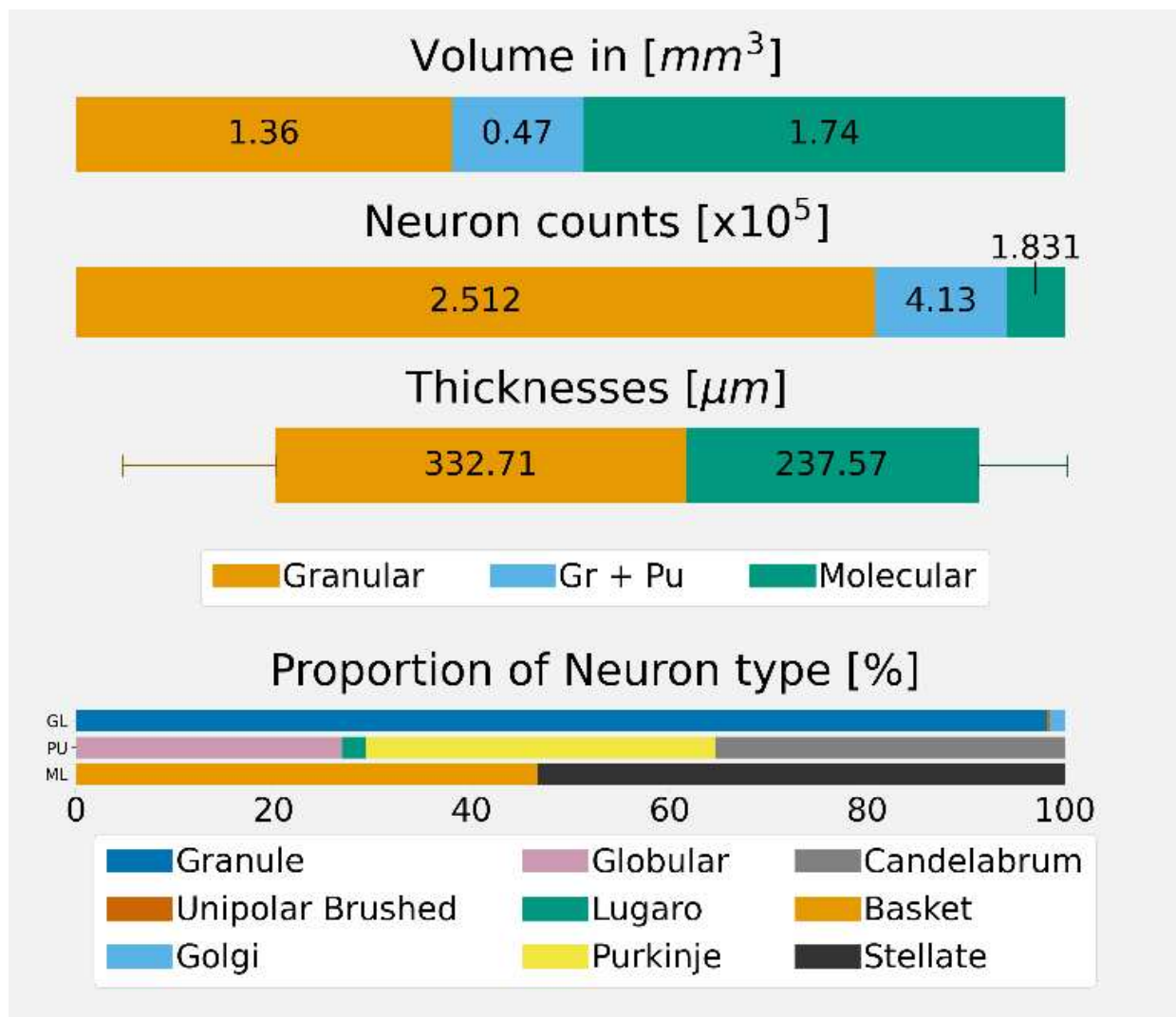


Figure 2.12 Volume, neuron counts, and composition in the Declive region. Summary of the Declive region results, showing volume, neuron counts, and layer thicknesses for the granular, Purkinje, and molecular layers. For the layer thicknesses Purkinje layer was considered as part of the granular layer since its thickness is thinner than on a voxel. The bar plot at the bottom indicates the proportion of different neuron types within each layer.

Table 2.2 Placement				
	Declive sub volume		Canonical	
	Cell counts	Cell densities [μm^{-3}]	Cell counts	Cell densities [μm^{-3}]
mf	223	1.53E-05	117	1.50E-05
glom	4362	3.00E-04	2340	3.00E-04
GrC	30607	1.56E-03	30400	3.90E-03
GoC	464	2.36E-05	71	9.10E-06
ubc_glom	489	2.49E-05	188	2.41E-05
UBC	127	6.47E-06	47	6.03E-06
PC	62	2.03E-06	69	7.67E-05
BC	1015	1.52E-04	150	5.00E-05
SC	1098	8.20E-05	298	4.97E-05
DCN_P	69	5.75E-06	120	1.00E-05
DCN_I	39	3.25E-06	69	5.75E-06
IO	12	2.00E-06	14	2.33E-06

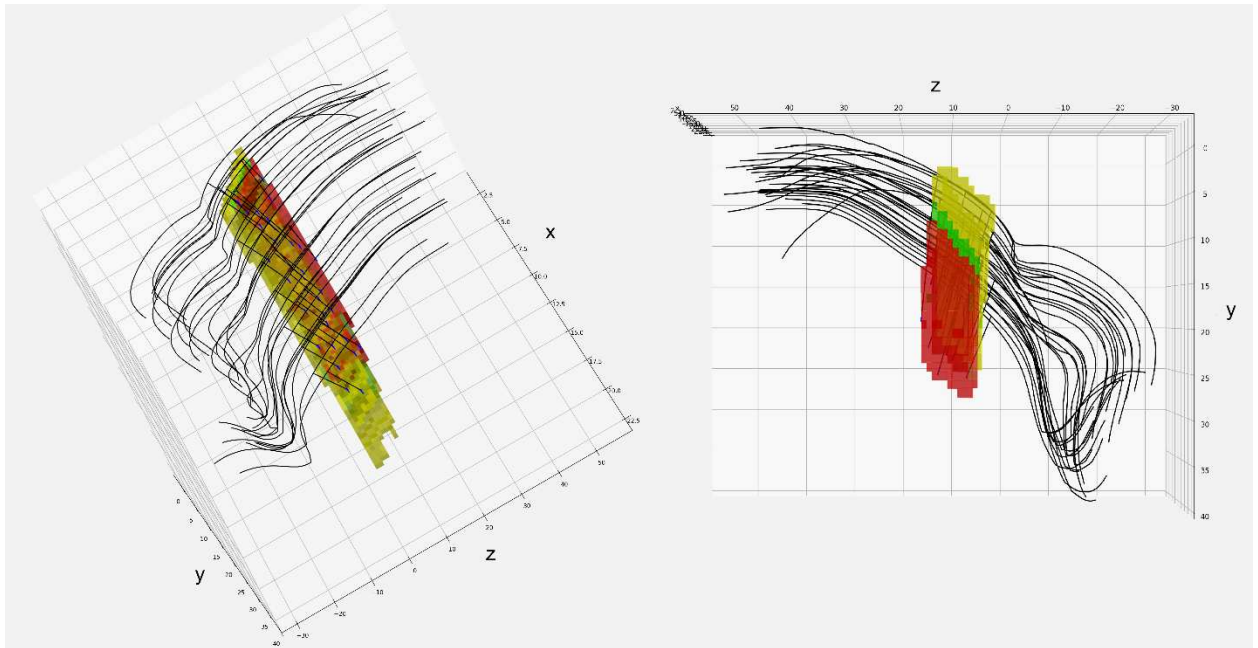


Figure 2.13 Granule cell bending in Declive subvolume. 3D representation of granule cell axons. Granule cells' axons (black lines) originate from the granular layer (red) and project vertically into the molecular layer (yellow), where they bifurcate into parallel fibers that extend horizontally across the molecular layer and spread outside the local region. The Purkinje cell layer (green) lies between the granular and molecular layers, where Purkinje cell dendrites receive synaptic input from the granule cells.

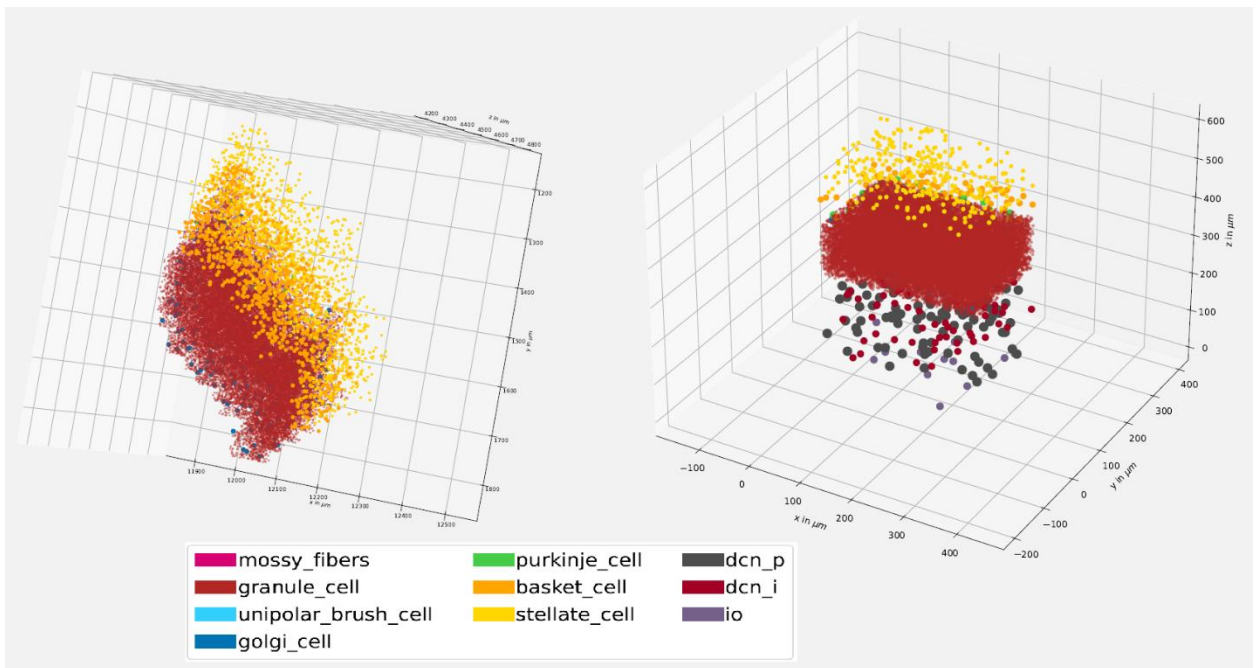


Figure 2.14 3D Placement. Position of each cell in the scaffold in 3D space. Each soma diameter and colour are based on its cell type radius as defined in Table S2.3. Left side: Declive subvolume, right side: canonical cerebellar cortex. In the canonical circuit, we can also see the DCN and IO layers since they are placed right below the cerebellar cortex region, while in the atlas reconstruction, these regions are out of the view of the subvolume of declive displayed.

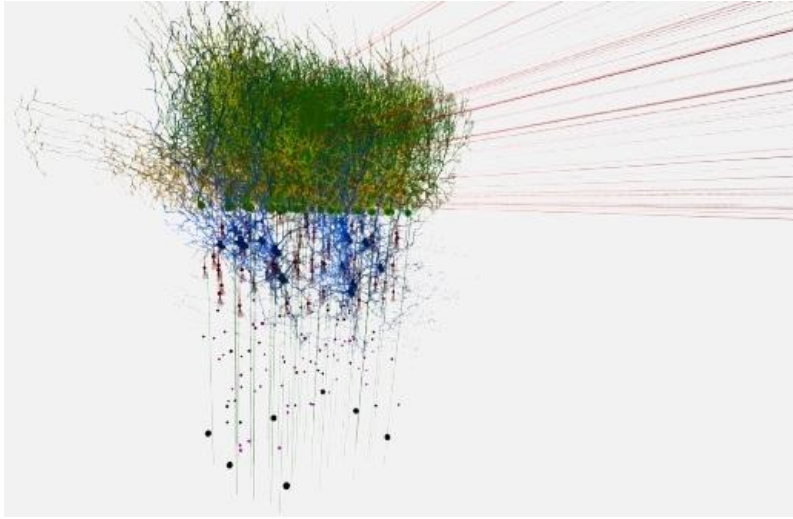


Figure 2.15 3D morphological reconstruction of the canonical cerebellar microcircuit. Detailed representation showing the morphology of each cell type: GrC (red), GoC (blue), PC (green), BC (orange), SC (yellow), DCNp (gray), DCNi (hot pink) and IO (dark purple); mf are represented by the red lines projecting toward the GrC layer, while cf originate from the IO neurons and ascend to make direct contact with PC. The representation of the Declive subvolume was not included due to its intricate shape, which made it difficult to visualize and interpret clearly.

In the Declive granular layer, the excitatory/inhibitory neuron ratio obtained from the BBCCA is lower than the canonical circuit. Specifically, GoC density is an order of magnitude greater. We would need to refine the cell atlas model to correct to overestimation of the inhibitory neuron density, for instance, by changing the level of overlapping of inhibitory neuron subtypes (as discussed in Rodarie et al. 2022).

The GrC densities are also lower in the atlas with respect to the canonical circuit. Yet GrC accounts for more than 80% of the neurons in the Declive (see Figures 2.12 and 1.6). This indicates either that the BBCCA predicts less neurons in general in the Declive than anticipated or that the assumption from the canonical circuit is too high. However, both values are in the ranges defined in literature sources, which estimate GrC densities in cerebellum spanning from 1.0×10^6 in (Förster, 2008) to 5.23×10^6 according to (Wetts & Herrup, 1983).

PC counts in the atlas are based on our specific placement strategy (see Table S2.2). Yet this strategy results in a lower density of PC with respect to the canonical circuit. This means that we would need to refine the atlas-based placement algorithm on the PC layer voxels and the assumptions regarding the space between consecutive PCs in a future version of the model.

As we anticipated previously, the counts of BC and SC are approximately the same, which results in a larger volume of BC with respect to SC, just based on their occupied volume. While the densities of SC are relatively similar across circuits, it seems the density of BC is an order of magnitude greater in the atlas with respect to the canonical. This result indicates either that the refinements of the annotations were not sufficient to correct for the cell density artifacts in the atlas or that the assumption of a unique density value for both MLI cells is inaccurate.

DCN and IO densities are derived in both circuits, respectively, from the GrC densities and the PC (see section 2.2.2), which explains the difference observed between reconstructions.

Table 2.3 shows the results of the connectivity for both circuits. This includes, for each pair of connected populations: the number of synapses per unique pair of connected cells, the convergence ratio defined as the mean number of afferent neurons converging on a single postsynaptic cell, and the divergence ratio defined as the mean number of neurons reached by a single presynaptic cell.

Table 2.3 Connectivity						
	Declive sub volume			Canonical		
	Synapses per pair	Convergence	Divergence	Synapses per pair	Convergence	Divergence
aa to GoC	1 ± 0	750 ± 180	11 ± 4.9	1 ± 0	310 ± 110	1.3 ± 0.52
aa to PC	1 ± 0	260 ± 92	1.3 ± 0.5	1 ± 0	93 ± 27	1.1 ± 0.25
BC to BC	99 ± 4	72 ± 31	72 ± 35	100 ± 4	17 ± 7.3	17 ± 7.2
BC to PC	1 ± 0	70 ± 25	4.5 ± 2.4	1 ± 0	11 ± 4.6	5.2 ± 2.6
DCN_I to IO	1 ± 0	33 ± 0.0	11 ± 1.3	1 ± 0	33 ± 0.0	6.7 ± 2.1

gap goc	3 ± 1	96 ± 21	96 ± 21	2.5 ± 0.95	11 ± 3.8	11 ± 3.2
glom to GoC	1 ± 0	110 ± 40	12 ± 4	1 ± 0	110 ± 32	3.5 ± 1.7
ubc_glom to GoC	1 ± 0	10 ± 4	9.8 ± 4.7	1 ± 0	9.0 ± 3.8	3.5 ± 1.6
glom to GrC	1 ± 0	3.1 ± 0.87	22 ± 12	1 ± 0	3.1 ± 0.8	41 ± 24
ubc_glom to GrC	1 ± 0	1.5 ± 0.74	59 ± 18	1 ± 0	1.4 ± 0.6	140 ± 34
glom to UBC	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
ubc_glom to UBC	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1.1 ± 0.34
GoC to GrC	1.1 ± 0.32	14 ± 4	94 ± 38	1.1 ± 0.24	4.4 ± 1.9	1900 ± 660
GoC to UBC	1 ± 0	4.2 ± 1.8	1.8 ± 1.3	1 ± 0	1.7 ± 0.93	1.6 ± 1.0
GoC to GoC	160 ± 5	190 ± 34	190 ± 34	160 ± 5.1	19 ± 6.6	19 ± 5.7
IO to DCN_I	1 ± 0	11 ± 1	33 ± 0	1 ± 0	6.7 ± 1.9	33 ± 0
IO to DCN_P	1 ± 0	11 ± 1	60 ± 0	1 ± 0	7.0 ± 1.9	60 ± 0
IO to BC	1.3 ± 0.5	3.6 ± 1.7	270 ± 140	1.2 ± 0.45	4.3 ± 2.0	45 ± 16
IO to SC	1.0 ± 0.093	1.0 ± 0.19	35 ± 19	1.0 ± 0.12	1.2 ± 0.42	21 ± 8.6
IO to PC	500 ± 0	1.0 ± 0.0	4.8 ± 2.5	500 ± 0	1 ± 0	4.9 ± 1.8
mf to DCN_P	1 ± 0	48 ± 0.0	15 ± 3.3	1 ± 0	48 ± 0	49 ± 5.1
mf to glom	1 ± 0	1 ± 0	19 ± 7.3	1 ± 0	1 ± 0	20 ± 9.2
pf to BC	1 ± 0	1000 ± 220	34 ± 15	1 ± 0	840 ± 150	4.2 ± 1.5
pf to GoC	1 ± 0	1200 ± 290	18 ± 6.7	1 ± 0	1100 ± 330	2.7 ± 1.2
pf to PC	1 ± 0	1600 ± 300	3.4 ± 1.4	1 ± 0	1500 ± 300	3.5 ± 1.0
pf to SC	1 ± 0	860 ± 210	32 ± 13	1 ± 0	510 ± 160	5.2 ± 2.6
PC to DCN_I	1 ± 0	19 ± 4	12 ± 0	1 ± 0	12 ± 2.7	12 ± 0
PC to DCN_P	1 ± 0	40 ± 4	45 ± 0	1 ± 0	26 ± 3.8	45 ± 0
SC to PC	9.5 ± 0.5	8 ± 4	1.0 ± 0.21	9.4 ± 0.5	4.5 ± 2.1	1.2 ± 0.43
SC to SC	100 ± 4	19 ± 7.4	19 ± 9.4	100 ± 4	13 ± 5.3	13 ± 4.5
ubc to ubc_glom	1 ± 0	1 ± 0	3.9 ± 1.8	1 ± 0	1 ± 0	4.1 ± 1.8

In relation to the comparison of connectivity, the subvolume of Declive reveals a substantial increase in inhibitory connectivity, particularly within basket cell (BC) and Golgi cell (GoC) networks. BC-to-BC and GoC-to-GoC connectivity increased significantly, with both convergence and divergence expanding several-fold. This is due to the increase of densities that we discussed previously; i.e., ~10 times more GoC can now connect to ~10 times more GoC, which results in ~100 more GoC-GoC connections. In fact, most of the changes in the counts of connections can be explained by the changes in densities observed, which would suggest that even in a curved circuit, our bending algorithm was capable of maintaining the connectivity of the canonical circuit.

However, we can predict from the changes of densities (and therefore connectivity) that the activity of inhibitory neurons in the simulation will be more synchronized as they create more auto-connections, and that the overall excitation of the circuit will be dropped.

2.3.2 Simulation-based analysis of canonical and Declive circuits

To analyze the results of the simulations, we computed the mean firing rate for each neuron population as the average number of spikes per second (in Hz) across all neurons that spiked at least once. This value was obtained by calculating the firing rate of each neuron (total number of spikes divided by simulation time) and then averaging across the population. Similarly, we computed the mean inter-spike interval (ISI) as the average time (in ms) between consecutive spikes, considering only neurons that spiked at least twice. The results for each neuron population are reported as mean $\pm$ standard deviation, providing a reference for evaluating the model's performance.

To generate the firing rate plot, we computed the instantaneous firing rate of a single neuron m , $\lambda_m(t)$ following the definition in (Nawrot et al., 1999) : $\lambda_m(t) = \sum_{i=1}^n K(t - t_i)$ where $t_i = \{t_0, t_1, \dots, t_n\}$ are the spike times of neuron m , and $K(t)$ is a kernel function with the

following properties:
$$\begin{cases} K(t) \geq 0 \\ \int_{-\infty}^{+\infty} K(t) dt = 1 \\ \int_{-\infty}^{+\infty} t \cdot K(t) dt = 1 \end{cases}$$

In our case, the kernel width σ is defined as: $\sigma = \sqrt{\int_{-\infty}^{+\infty} t^2 \cdot K(t) dt}$

Different kernel functions provide different smoothening properties. Here we used a normalized version of the triangle function from Scipy Python library (*Triang*, n.d.). To avoid edge effects in the kernel convolution with the spike train (i.e. where the kernel cannot fully overlap the spike train due to its width), we extract the computed $\lambda_m(t)$ values on the interval $[time_from + \sigma; time_to - \sigma]$. The final firing rate signal $\lambda(t)$ shown in the plot corresponds to the mean of all neurons' $\lambda_m(t)$ surrounded by its standard deviation (to ensure non-negativity, any values falling below zero were set to zero). In addition, we display the mean and standard deviation of $\lambda(t)$ as text on the plot to provide a clear representation of the overall activity pattern in our model.

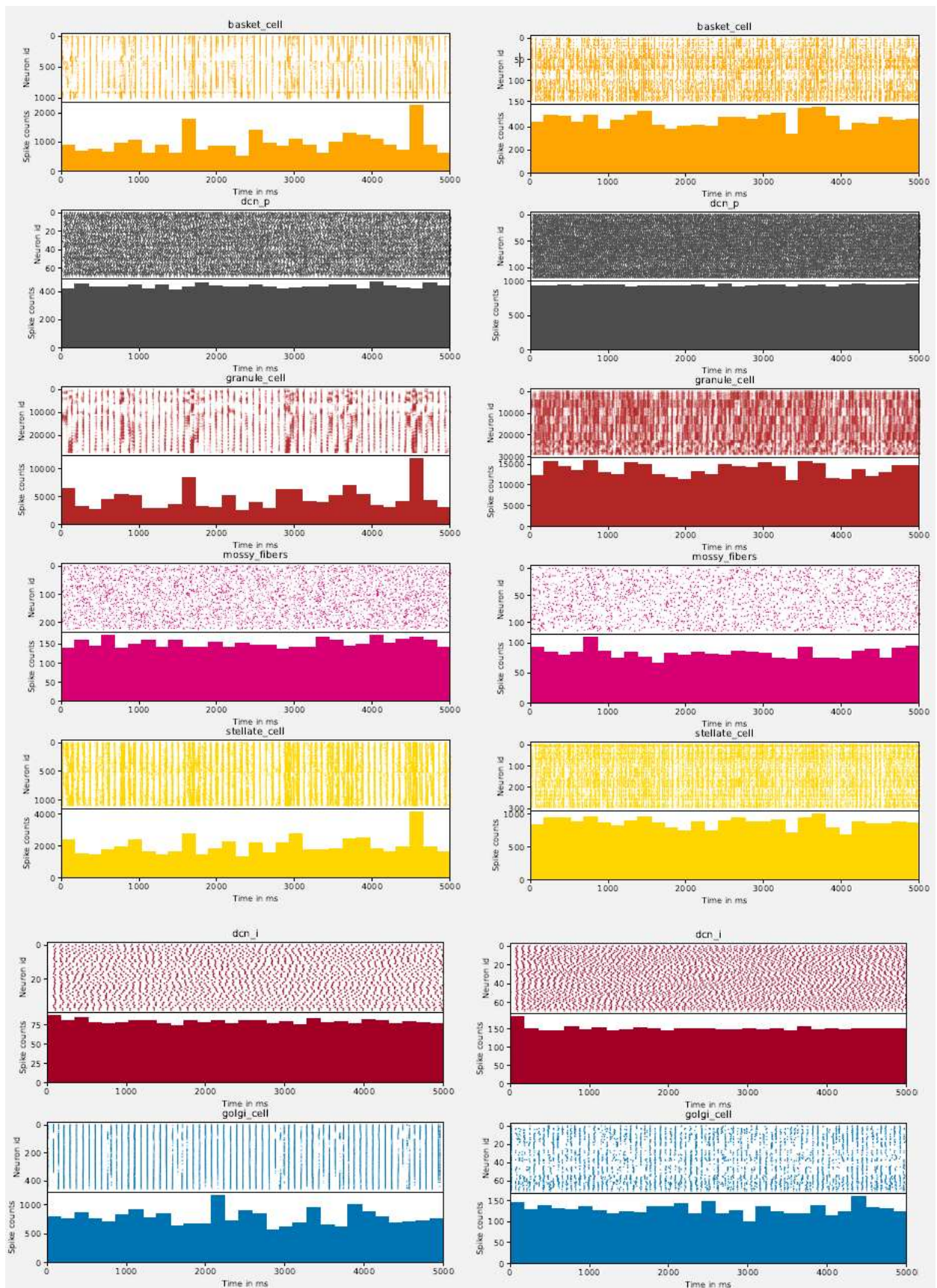
mf-glom was set according to the Poisson generator. UBCs are not very active during the basal simulation, there is no point in comparing them between the canonical and Declive subvolume. As we predicted previously, the GoC activity is quite synchronized in the Declive subvolume in comparison with canonical, due to recurrent connections. Their firing rate is therefore oscillating with a frequency of ~ 11 Hz (see figure 2.19). The oscillation of the firing rate of GoCs is also present in the GrC and MLI firing rates. As anticipated, GrCs receive more inhibition from GoCs, which results in a lower firing rate, which in turn means less excitation for the rest of the circuit. Similar to GoC, BC activity is more synchronized, due to its recurrent connectivity.

Apart from a slight drop in firing rate due to less excitation from GrCs, the PC activity seems to be similar between the two circuits.

The general activity in DCN (DCNp and DCNi) is lower in the Declive subvolume in comparison to the canonical circuit. This can be explained by the changes in cell density in DCN. Indeed, the density of this region is constrained by the number of GrC, which dropped significantly in Declive with respect to the canonical. The connection rule linking PC to DCN cells is a fixed outdegree that imposes a certain number of DCN targeted by a single PC (see Table S2.1 and S2.3). With the density changes in Declive, the DCN populations receive therefore more afferent connections from PC, especially for DCNp, resulting in overall more inhibition.

Table 2.6 shows each cell type's mean firing rate and Inter-Spike Interval (ISI) during the simulation time.

Then, we calculated the inter-spike interval (ISI) as the time (in ms) between two consecutive spikes to generate the ISI plot (Figure 2.18). For each neuron type, the values shown in the histogram represent the mean ISI value of each neuron, considering only neurons that spiked at least twice during the simulation. This approach allows us to assess the network's variability and regularity of spiking activity.



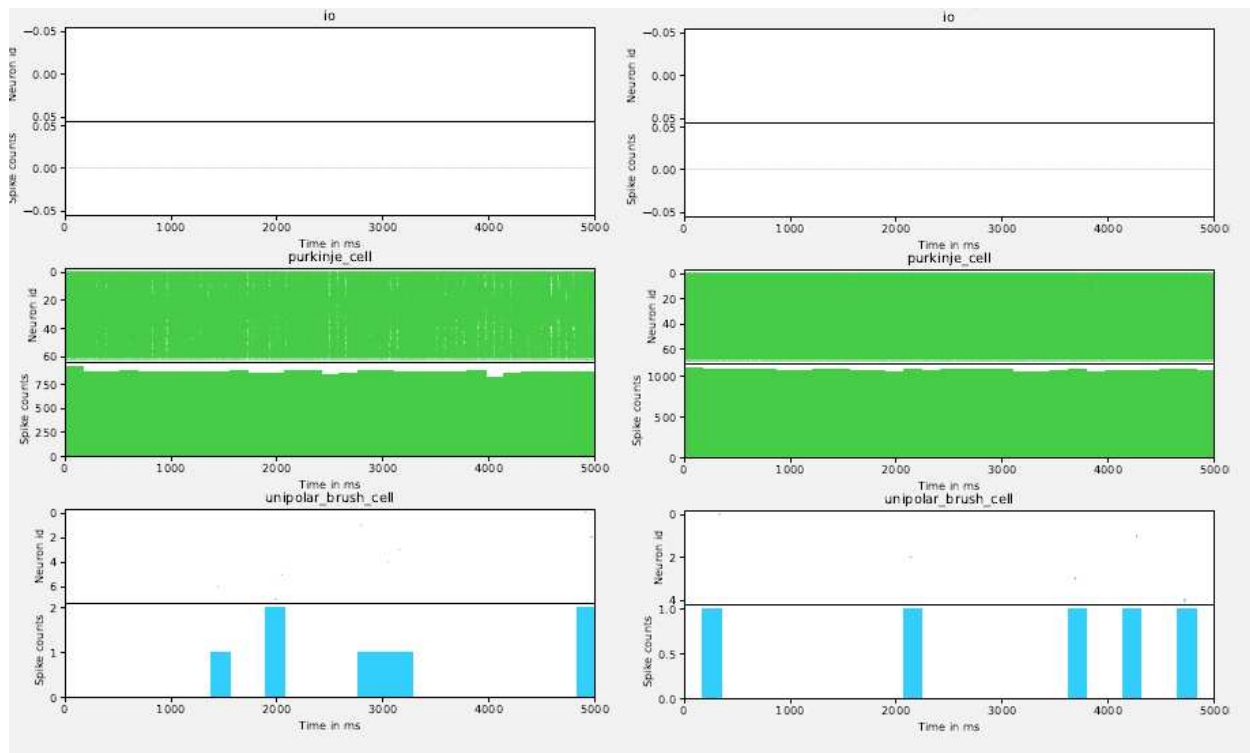


Figure 2.16 Raster plot. Spike times along the 2-s of the simulation, as well as the equivalent Peri-Stimulus Time Histogram (PSTH) for each of the cell types (spike counts) (Left side: Declive subvolume, right side: Canonical)

Table 2.4 Neural activity summary: Firing rate and ISI

	Declive sub volume		Canonical	
	Firing rate [Hz]	Inter Spike Intervals [ms]	Firing rate [Hz]	Inter Spike Intervals [ms]
BC	5.5 ± 2.7	210 ± 110	18 ± 7.3	72 ± 58
DCNi	12 ± 0.58	86 ± 4.3	13 ± 0.44	80 ± 2.8
DCNp	37 ± 2.9	27 ± 2.0	45 ± 3.2	22 ± 1.6
GoC	9.7 ± 1.9	110 ± 50	11 ± 4.5	130 ± 94
GrC	0.98 ± 0.75	960 ± 710	2.7 ± 2.6	560 ± 550
IO	/	/	/	/
mf	3.9 ± 0.89	250 ± 60	4.1 ± 0.92	250 ± 61
PC	82 ± 2.0	12 ± 0.3	90 ± 2.0	11 ± 0.25
SC	11 ± 4.0	110 ± 56	17 ± 11	150 ± 330
UBC	0.2 ± 0.0	/	0.2 ± 0.0	/

To analyze the frequency components (Figure 2.9) of our model's firing activity, we performed a Fast Fourier Transform (FFT) on the previously computed instantaneous firing rate. The FFT allows us to decompose the firing rate signal into its frequency components, providing insight into the oscillatory dynamics of the network. In the plot, we overlaid major frequency bands relevant to neural activity in rodents using dotted lines: Delta band (0.5–4 Hz), Theta band (4–8 Hz), Alpha band (8–12 Hz), and Beta band (12–30 Hz). This visualization helps us assess how well our model captures the expected neural activity patterns across different frequency ranges.

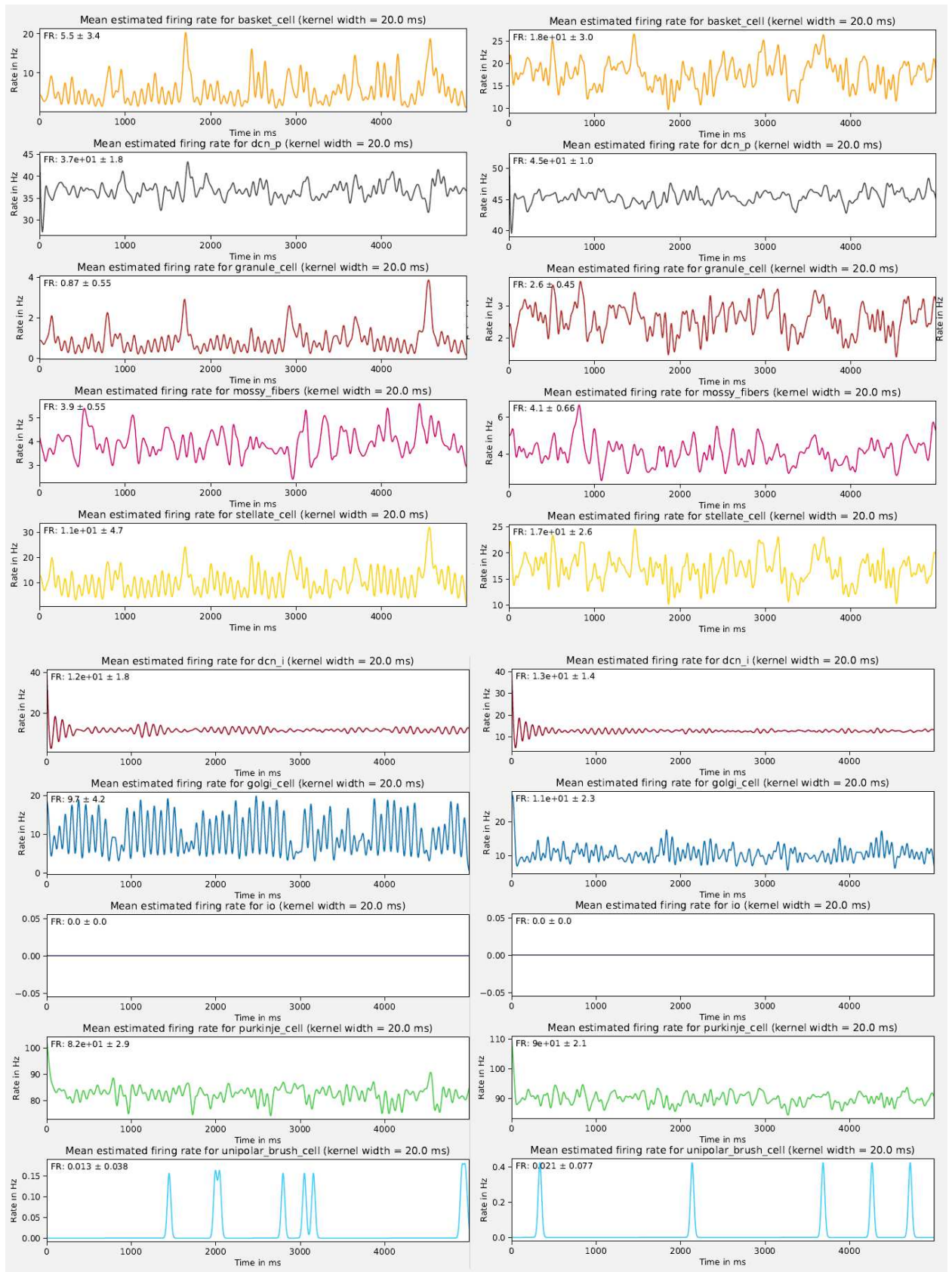


Figure 2.17 Firing rates. Mean instantaneous (time bin 20 ms) firing rate $\lambda(t)$ of each population. (Left side: Declive sub volume, right side: Canonical)

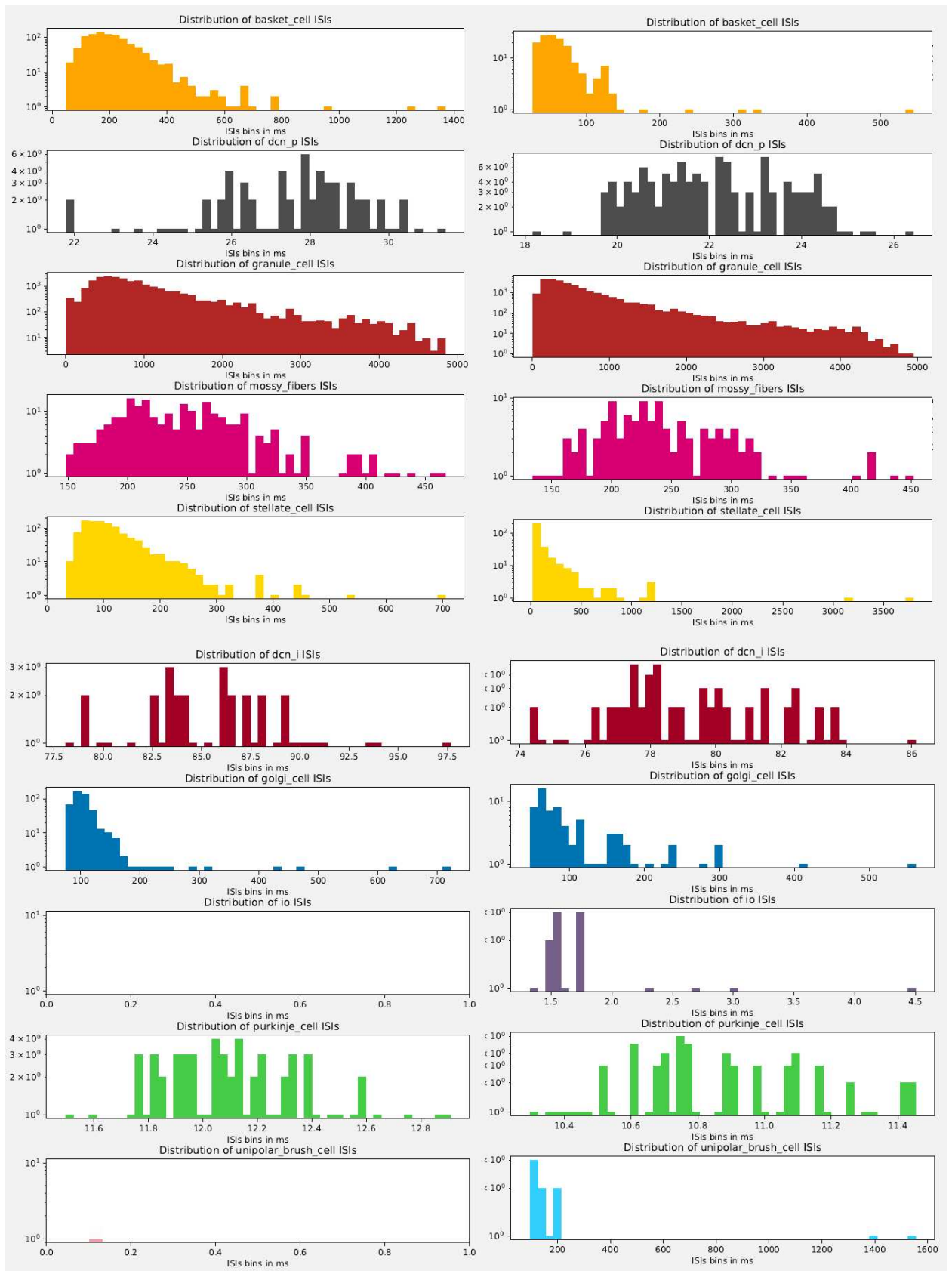


Figure 2.18 Inter-spike interval (ISI) histogram plot for each cell population. (Left side: Declive subvolume, right side: Canonical)

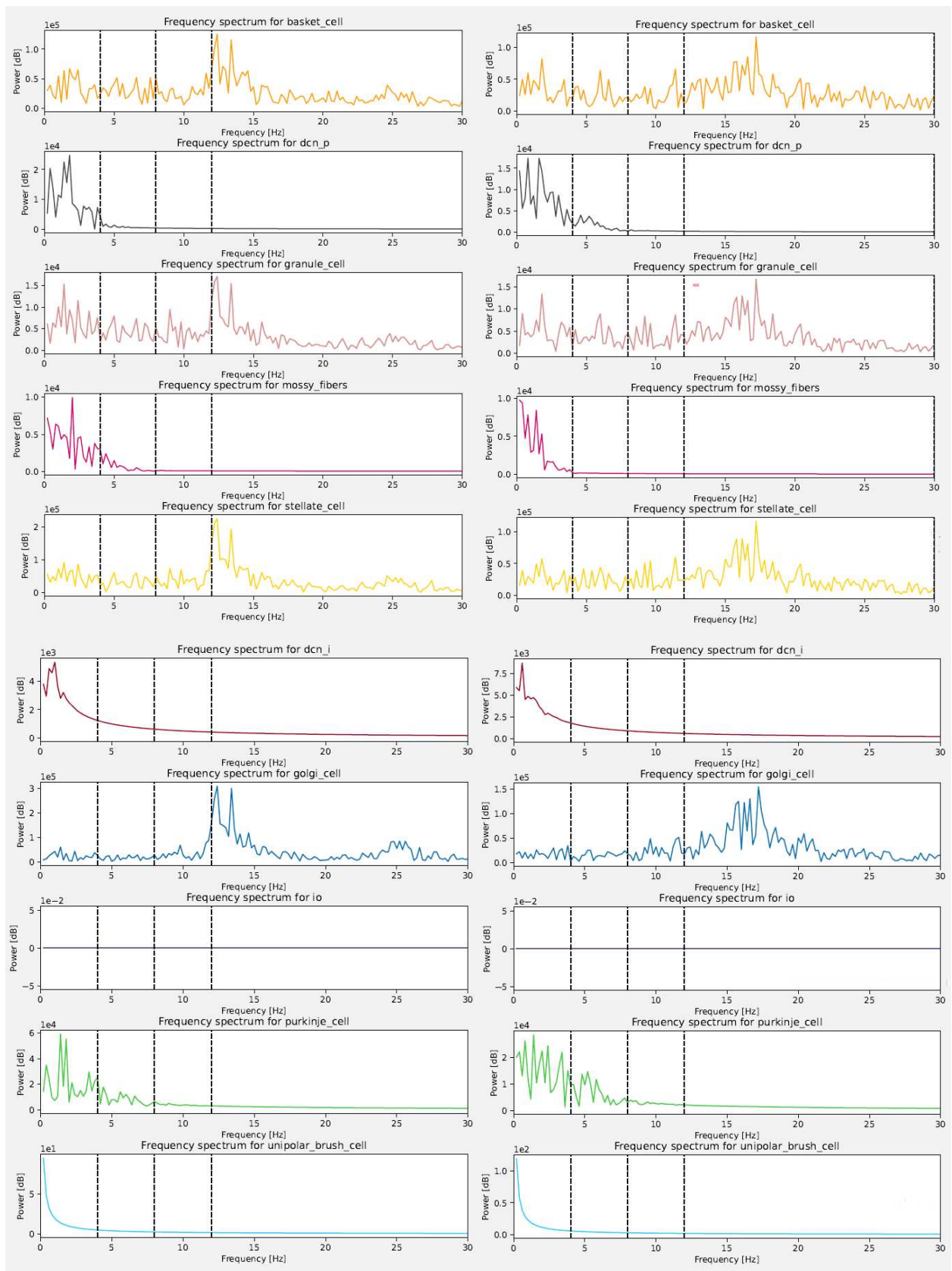


Figure 2.19 Frequency. Distribution plot of the instantaneous firing rate signal for each cell population. (Left side: Declive subvolume, right side: Canonical)

Mossy fiber (mf) activity remains stable between both models, indicating that functional differences arise from internal circuit processing rather than input variability. Broader ISI distributions in Declive suggest increased input variability, potentially compensating for reduced granule cell activity. Unipolar brush cell (UBC) activity remains minimal and infrequent in both

models (~1 Hz), reinforcing their specialized roles in synaptic modulation and error signaling rather than baseline activity. Inferior olive (IO) cells remain inactive under baseline conditions in both circuits.

GrC activity in Declive shows a reduction in firing rate and an increase in ISI, indicating more selective mossy fiber input and stronger inhibitory modulation from Golgi cells. Despite similar peak frequencies, the overall power is reduced, reflecting less frequent but more selective firing. Golgi cells (GoC) in Declive fire at a slightly lower rate with reduced ISI variability, reflecting more stable and consistent inhibitory control over granule cells. This aligns with enhanced Golgi-to-Golgi connectivity and increased regularity in the 10–15 Hz range, indicating more refined feedback inhibition.

Basket cell (BC) activity in Declive shows a reduction in firing rate and an increase in ISI in comparison with canonical, suggesting more auto-inhibition. Despite similar peak frequencies as in Canonical, the overall power is lower, indicating weaker but more targeted lateral inhibition. Stellate cells (SC) in Declive fire at a reduced rate with more consistent ISIs, indicating more refined and selective lateral inhibition of Purkinje cell activity. The lower overall power in the 5–15 Hz range reflects weaker but more targeted modulation.

Purkinje cells (PC) in Declive show a reduction in firing rate and a slightly longer ISI, reflecting more consistent but less frequent output due to enhanced inhibitory regulation from basket and stellate cells. The broader ISI distribution and lower overall power in the dominant low-frequency range indicate more precise and controlled firing. DCNp in Declive shows a reduction in firing rate and an increase in ISI, suggesting more precise but less frequent output. DCNi cells maintain similar firing rates but exhibit broader ISI distributions, reflecting more stable inhibitory modulation. Both DCNp and DCNi cells retain similar peak frequencies but with reduced overall power, indicating weaker but more temporally precise output.

The Declive circuit exhibits reduced excitatory output and increased inhibitory control, reflected in lower firing rates, broader ISI distributions, and greater temporal stability compared to the Canonical circuit.

Section 2.4 Discussions and Conclusions

We developed a data-driven pipeline to construct cerebellar circuit models based on the mouse brain atlas. Using this pipeline, we successfully reconstructed a model of the Declive and ran simulations using NEST. To adapt anatomical data into a functional circuit, we implemented novel algorithms to scale, place, and bend neural cells in alignment with the atlas-defined geometry.

On the positive side, the model exhibits a solid structural framework: it maintains consistent cell densities for major neuronal types and preserves key connectivity patterns even under altered density conditions. This highlights the robustness of the underlying algorithm. However, several refinements are still necessary to improve the model's biological accuracy.

A major limitation lies in the current imbalance between excitatory and inhibitory neuron densities, which stems from assumptions about spatial overlap and distribution in the atlas-based cell model—particularly for inhibitory neuron subtypes. Additionally, the lower-than-expected density of Purkinje cells likely reflects constraints in the placement algorithm and spacing assumptions, which in turn affect the densities of dependent cell types such as Lugaro and inferior olive neurons. The elevated density of basket and Golgi cells may also be contributing to excessive inhibitory synchronization, reducing overall circuit excitability and altering network dynamics. Addressing these issues will require adjustments not only in neuronal densities but also in connectivity rules to restore a more physiologically realistic balance between excitation and inhibition.

Simulation results reinforce these structural observations. The increased density of inhibitory interneurons enhances inhibitory synchronization, resulting in oscillatory firing patterns and reduced activity in granule cells. The decreased firing rates and increased inter-spike intervals (ISI) across multiple neuronal types underscore the need to recalibrate inhibitory strength and connectivity.

In this context, we also acknowledge that the tonic firing rates of Purkinje cells in our Declive circuit model are higher than what has been reported in the literature. This is particularly relevant given that the Declive is a predominantly zebrin-positive region, and Purkinje cells in zebrin-positive zones are known to exhibit lower tonic firing rates than those in zebrin-negative zones

(Xiao et al., 2014; Zhou et al., 2014). The point-neuron network used here was constructed based on the best available data, specifically the model developed by (Geminiani A et al., 2024). Although this model is based on recordings from a different cerebellar region, it provides the only complete dataset currently available for both point-neuron and synaptic parameters under in vivo conditions. We prioritized reproducing the overall dynamic behavior of cerebellar cortex–DCN–IO interactions over matching absolute firing rate values in a region-specific manner. Future work on the Declive circuit will involve retuning the neuronal and synaptic parameters to better reflect experimental data from this region as it becomes available.

➤ Study limitations

- The full reconstruction of the Declive circuit was not achieved due to its size and complexity (~3 million neurons), which limited the scope of the model. This limitation was further compounded by computational constraints.
- Due to the lack of region-specific electrophysiological data for the Declive, the model currently relies on parameters derived from other cerebellar regions. While this approach enables the reproduction of general cerebellar dynamics, it limits the model's ability to accurately reflect the unique electrophysiological properties of the Declive, particularly those associated with its predominantly zebrin-positive Purkinje cell population.
- Although the model includes nearly all cell types present in the Declive, the absence of reliable data on the connectivity and electrophysiological properties of Lugaro cells (LC), globular cells (GIC), and candelabrum cells (CC) prevented their incorporation into the current version of the circuit.

➤ Future directions

- Model Refinement and Optimization: Refining the spatial distribution and density of inhibitory and excitatory neurons to restore a balanced excitatory-inhibitory dynamic. Improving the connectivity rules, particularly for Golgi and basket cells, will help reduce excessive synchronization and enhance physiological accuracy. Additionally, adjusting the placement algorithm for Purkinje could further optimize circuit function and improve alignment with canonical cerebellar activity patterns.
- Physiological and Functional Retuning of the Declive Circuit: We plan to refine the model by incorporating region-specific electrophysiological data from the Declive, particularly targeting zebrin-positive Purkinje cell firing characteristics. This will involve retuning both neuronal excitability and synaptic dynamics to reflect the experimentally observed lower tonic firing rates and regular firing patterns typical of zebrin-positive zones. Furthermore, we aim to integrate molecular identity into the cell mapping pipeline, enabling selective placement and parameterization of zebrin-positive and zebrin-negative stripes. Finally, to validate the functional role of the Declive in cerebellar processing, we intend to simulate specific behavioral or sensory paradigms and assess how microcircuit tuning affects cerebellar output through the DCN and IO.
- Complete Declive reconstruction and simulation: Addressing the computational and technical challenges that currently limit the reconstruction and simulation of the entire Declive region will allow for the development of a more detailed and accurate model, enhancing our understanding of its structural and functional properties.
- Extension to hemispheric parts of lobule VI and Zebrin-based mapping of Purkinje cells: Extending the model to include the hemispheric parts of Lobule VI and zebrin patterns will provide a more complete understanding. While this study focused primarily on the Z+ zones within the Declive, extending the model to the hemispheric regions will allow for the inclusion of Z- zones, which are functionally distinct. This will also enable the mapping of different Purkinje cell subtypes according to their zebrin stripe identity (Section 1.2), enhancing the accuracy and biological relevance of the model.
- Extension to other cerebellar regions: A major future goal will be to extend the reconstruction to other cerebellar regions in order to build a large-scale cerebellar network. Priority should be given to lobules that have been identified as critical for emotional behavior, such as Lobule VII and Crus I in humans and Lobule VIII in rodents (see Section 1.2). This will enable the exploration of cerebellar contributions to emotional and cognitive processes at a network-wide level.

Supplementary material

Table S2.1 Cerebellar microcircuit connectome						
#	Source name	Source branch	Target name	Target branch	Strategy*	Reference
1	mf	---	glom	---	ConnectomeMossyGlomerulus	(Sultan, 2001)
2	glom&UBC Glom	---	GrC	dendrites	ConnectomeGlomerulusGranule	(Houston et al., 2017)
3	glom&UBC Glom	---	GoC	basal dendrites	ConnectomeGlomerulusGolgi	(Kanichay & Silver, 2008)
4	GoC	axon	GrC	same as through glom	ConnectomeGolgiGlomerulus	(Barmack & Yakhnitsa, 2008)
5	GoC	axon	GoC	basal dendrites	VoxelIntersection	(Hull & Regehr, 2012)
6	GrC	ascending axon	GoC	basal dendrites	VoxelIntersection	(Cesana et al., 2013)
7	GrC	parallel fiber	GoC	apical dendrites	VoxelIntersection	(Kanichay & Silver, 2008)
8	GrC	ascending axon	PC	ascending axon targets	VoxelIntersection	(Huang et al., 2006)
9	GrC	parallel fiber	PC	parallel fiber targets	VoxelIntersection	(Huang et al., 2006)
10	GrC	parallel fiber	BC	dendrites	VoxelIntersection	(Jörntell et al., 2010)
11	GrC	parallel fiber	SC	dendrites	VoxelIntersection	(Jörntell et al., 2010)
12	BC	axon	PC	soma	VoxelIntersection	(Jörntell et al., 2010)
13	SC	axon	PC	stellate cell targets	VoxelIntersection	(Jörntell et al., 2010)
14	BC	axon	BC	dendrites	VoxelIntersection	(Ito, 2014)
15	SC	axon	SC	dendrites	VoxelIntersection	(Ito, 2014)
16	UBC	---	UBC Glom	---	ConnectomeUBCGlomerulus	(Mugnaini et al., 2011)
17	glom & UBC Glom	---	UBC	---	ConnectomeGlomerulusUBC	(Mugnaini et al., 2011)
18	GoC	axon	UBC	---	ConnectomeGolgiGlomerulus	(Mugnaini et al., 2011)
19	PC	axon	DCNp	---	FixedIndegree	(Geminiani A et al., 2024)
20	PC	axon	DCNi	---	FixedIndegree	(Geminiani A et al., 2024)
21	mf	---	DCNp	---	FixedIndegree	(Geminiani A et al., 2024)
22	IO	---	PC	---	FixedIndegree	(Geminiani A et al., 2024)
23	IO	---	SC – BC	---	ConnectomeIO_MLI	(Geminiani A et al., 2024)
24	IO	---	DCNp	---	FixedOutdegree	(Geminiani A et al., 2024)
25	IO	---	DCNi	---	FixedOutdegree	(Geminiani A et al., 2024)
26	DCNi	---	IO	---	FixedIndegree	(Geminiani A et al., 2024)

Table S2.2 Placement strategies	
Strategy	Description
RandomPlacement	Except for Purkinje cells, all entities are assumed to be uniformly distributed within their respective layers. Each entity is positioned within its designated sub-partition without enforcing specific spatial constraints, ensuring a homogeneous distribution across the layer.
ParalellarrayPlacement	Purkinje cells are positioned in parallel arrays, spaced 30 μm apart along the para-sagittal plane (xz) to prevent dendritic arborization overlap. Additionally, each row of PC somas is shifted relative to its predecessor, forming an 80-degree angle in the (xy) plane to ensure a biologically realistic spatial organization.

Table S2.3 Connectivity strategies	
Strategy	Description
ConnectomeMossyGlomerulus	The algorithm selects one mossy fiber from within a rectangular box of size $x_length \times y_length \mu\text{m}$, centered around each glomerulus. Here, x_length defines the width of the selection area along the x-axis, while y_length determines its height along the y-axis, specifying the region where a mossy fiber can be connected to the glomerulus. Since z_size represents the total height of the partition where the glomeruli are located, there is no upper limit along the z-axis. The mossy fiber selection is random and follows a truncated exponential distribution, ensuring a controlled spatial distribution within the defined area.
ConnectomeGlomerulusGranule	The algorithm selects n unique glomeruli within a sphere of radius <i>radius</i> surrounding each granule cell soma, where n is equal to the convergence, meaning each granule cell must connect to exactly convergence glomeruli. Each selected glomerulus must be linked to a different presynaptic cell type, chosen from the <i>pre_cell_types</i> list, ensuring that each granule cell receives input from multiple distinct sources. For each granule cell, the algorithm randomly assigns connections by: 1) Selecting n unique presynaptic sources from <i>pre_cell_types</i>. 2) Identifying the corresponding glomerulus they connect to, following the <i>pre_glom_strats</i> connection strategy. 3) Determining the granule cell dendrite that will receive input from the glomerulus. If the required number of glomeruli (convergence) is not available within the defined radius, the algorithm selects the nearest glomerulus connected to a mossy fiber that has not yet been chosen, ensuring that each granule cell reaches its required connectivity.
ConnectomeGlomerulusGolgi	The algorithm selects all glomeruli within a sphere of radius <i>radius</i> surrounding each Golgi cell soma, ensuring that only glomeruli within this defined range are considered for connections. For each unique Golgi cell, the algorithm randomly selects one of its basal dendrites to establish a connection. The specific dendrite tip is chosen based on a truncated exponential distribution, which prioritizes closer connections by considering the distance between the dendrite tip and the target glomerulus. This method ensures a biologically plausible spatial distribution of Golgi cell inputs.

ConnectomeGolgiGlomerulus	This connection strategy establishes links between a Golgi cell and all postsynaptic targets associated with a glomerulus. The connections between each glomerulus and its postsynaptic targets are determined by a predefined set of reference strategies from <code>glom_post_strats</code>. The algorithm first identifies the closest glomeruli within a sphere of radius <i>radius</i> surrounding each Golgi cell soma. The maximum number of glomeruli that a single Golgi cell can connect to is defined by divergence. For each selected glomerulus, the algorithm randomly chooses the tip of an axonal branch from the Golgi cell to establish the connection. Once the connection is made, all postsynaptic targets linked to that glomerulus—following the strategies in <code>glom_post_strats</code>—are also connected to the Golgi cell. The target points on the postsynaptic dendrites are directly copied from the reference strategies to ensure consistency in connectivity. Additionally, the glomeruli themselves are categorized using <code>glom_cell_types</code>, which serve as reference points for establishing valid connections.
VoxelIntersection	This strategy voxelizes neuronal morphologies by converting them into a collection of cubic voxels, effectively reducing the spatial specificity of the original traced morphologies. Instead of evaluating connections between individual compartments, the algorithm identifies intersections between voxels and then randomly selects compartments within matching voxels to establish connections. Since connections are formed at the voxel level rather than at the exact morphology level, this approach reduces anatomical precision. However, it is particularly useful in scenarios where only a limited number of morphologies are available to represent a given cell type, allowing for broader connectivity patterns. The extent to which cells preferentially connect with others whose voxels intersect is determined by affinity, a value between 0 and 1. A higher affinity increases the likelihood of forming connections with overlapping voxels, while a lower value reduces this tendency, effectively regulating the total number of connections formed. Once two cells have been selected as connection partners, the exact number of synaptic contacts they establish is determined by contacts, which can be either a fixed number or a probabilistic distribution, depending on the desired connectivity model.
ConnectomeUBCGlomerulus	The algorithm selects one unipolar brush cell (UBC) from within a sphere of radius <i>radius</i> centered around each UBC glomerulus. This selection is performed randomly using a truncated exponential distribution, which prioritizes closer UBCs while still allowing for the possibility of selecting more distant ones. By applying this method, the algorithm ensures a spatially controlled distribution of UBC-glomerulus connections, maintaining biological plausibility within the given radius constraint.
ConnectomeGlomerulusUBC	The algorithm establishes connections between a population of unipolar brush cells (UBCs) and a list of glomeruli populations (e.g., mossy fiber (mf) or UBC-based glomeruli), while ensuring that the relative indegree ratios between different glomeruli types are preserved. To achieve this, the algorithm first identifies glomeruli within a sphere of radius <i>radius</i> surrounding each UBC chunk. For each UBC, it then selects the closest available glomerulus that has not yet been connected. This process helps to distribute connections more evenly and limits the number of UBCs assigned to any single glomerulus, maintaining a balanced connectivity structure.

	The relative probability of a UBC connecting to different glomerulus types is determined by <code>ratios_ubic</code>, a set of positive values representing relative indegree ratios. These ratios are normalized so that their sum equals 1, ensuring proportional assignment of UBCs across the available glomeruli types
ConnectomeGolgiGlomerulus	This connection strategy establishes links between a Golgi cell and all postsynaptic targets associated with a glomerulus. The relationships between each glomerulus and its postsynaptic targets are defined using reference strategies from <code>glom_post_strats</code>, ensuring consistent connectivity patterns. The algorithm first identifies the nearest glomeruli within a sphere of radius <i>radius</i> surrounding each Golgi cell soma. The maximum number of glomeruli that a single Golgi cell can connect to is determined by divergence, which limits the number of potential connections per cell. Once a glomerulus is selected, the algorithm randomly chooses the tip of an axonal branch from the Golgi cell to establish the connection. After this, all postsynaptic targets linked to the same glomerulus, as defined by <code>glom_post_strats</code>, are also connected to the Golgi cell. To maintain consistency, the exact dendritic locations of these postsynaptic targets are copied from the reference strategies. Additionally, the glomeruli themselves are classified using <code>glom_cell_types</code>, which serve as reference points for establishing valid connections between Golgi cells and postsynaptic targets.
FixedIndegree	This connection strategy assigns each postsynaptic neuron a fixed number of presynaptic neurons, which are selected uniformly at random from the available presynaptic population. The exact number of presynaptic neurons that each postsynaptic neuron connects to is determined by <code>indegree</code>, which specifies a fixed connection count per postsynaptic neuron. This approach ensures a consistent and unbiased distribution of connections across the network.
ConnectomeIO_MLI	This connection strategy establishes links between inferior olive (IO) cells, Purkinje cells (PCs), and molecular layer interneurons (MLIs). Specifically, each IO cell that is connected to a PC will also form connections with a subset of MLIs, but only those that are already connected to the same PC. This ensures that the connectivity pattern follows the established IO-PC-MLI pathway, preserving biologically relevant interactions. The presynaptic and postsynaptic neuron populations involved in this process are defined by presynaptic and postsynaptic, respectively, where specific cell types can be explicitly specified. The subset of MLIs available for connection is determined by <code>mli_pc_connectivity</code>, which defines the connectivity pattern between MLIs and PCs. Similarly, the set of IO cells considered for connection is specified by <code>io_pc_connectivity</code>, ensuring that only IO cells already connected to a given PC are included in the selection. Finally, the PC population used as a reference for these connections is defined by <code>pre_cell_pc</code>, serving as the central relay point in the IO-PC-MLI network.
FixedOutdegree	This connection strategy assigns each presynaptic neuron a fixed number of postsynaptic neurons, which are selected uniformly at random from the available postsynaptic population. The exact number of postsynaptic neurons that each presynaptic neuron connects to is determined by <code>outdegree</code>, which specifies a fixed connection count per presynaptic neuron. This approach ensures a balanced and unbiased distribution of connections across the network.

Table S2.4 Cellular composition*					
Layer	Cell name	Type	Radius (μm)	Density (μm^{-3})	References
Granular layer	Glomerulus	Excitatory	1.5	0.0003	(Solinas et al., 2010)
	Mossy fibers	Excitatory	---	Count relative to glom 0.05	(Billings et al., 2014)
	Granule cell	Excitatory	2.5	0.0039	(Casali et al., 2019)
	Golgi cell	Inhibitory	4.0	0.000009	(Casali et al., 2019)
	UBC	Excitatory		0.000078	(Sekerková et al., 2014)
	MfGlom			0.0003	(Korbo et al., 1993)
	UBC Glom			0.00033	(Diño et al., 2000)
Purkinje layer	Purkinje cell	Inhibitory	7.5	Planar 0.001166 PCs/ μm^2	(Keller et al., 2018b)
	Globular cell			0.0000000056	(Osorno et al., 2022)
	Lugaro cell			0.00000018	(Dieudonné & Dumoulin, 2000b)
	Candelabrum			0.0000000085	(Osorno et al., 2022)
Molecular layer	Basket cell	Inhibitory	6.0	0.00005	(Casali et al., 2019)
	Stellate cell	Inhibitory	4.0	0.00005	(Casali et al., 2019)
Inferior Olive	IO				
Deep cerebellar nuclei	DCNp	Excitatory	9.5	9.92	(Baumel et al., 2009)
	DCNi	Inhibitory	7.0	5.58	(Baumel et al., 2009)

*Most literature data in this table comes from rat data

Table S2.5 LIF neuron parameters						
Cell name	$C_m(pF)$	$\tau_m(ms)$	$E_L(mV)$	$t_{ref}(ms)$	$V_{rest}(mV)$	$V_{th}(mV)$
Granule Cell	7 (5.5 $\pm$ 0.5)	24.15 (24.15 $\pm$ 2)	-62 (- 62 $\pm$ 11)	1.5 (1.5 $\pm$ 0.4)	-70 (-70)	-41 (- 41 $\pm$ 3)
Golgi Cell	145 (145 $\pm$ 73)	44 (44 $\pm$ 22)	-62 (-62)	2 (2 $\pm$ 0.4)	-75 (-75)	-55 (- 55 $\pm$ 1)
Purkinje Cell	334 (334 $\pm$ 106)	47 (47 $\pm$ 32)	-59 (- 59 $\pm$ 6)	0.5 (0.5 $\pm$ 0.1)	-69 (-69)	-43 (- 43 $\pm$ 2)
Basket and Stellate Cells	14.6 (14.6)	9.125 (9.125)	-68 (-68)	1.59 (1.59)	-78 (-78)	-53 (-53)
UBC	16.5	13.2	-66.7	1.67	-76,7	-55.8
DCNp	142 (142 $\pm$ 31)	33 (33 $\pm$ 18)	-45 (- 45 $\pm$ 13)	1.5 (1.5 $\pm$ 0.2)	-55 (-55)	-36 (- 36 $\pm$ 7)
DCNi	56 (56 $\pm$ 26)	56 (56 $\pm$ 30)	-40 (- 40 $\pm$ 13)	3.02 (3.02 $\pm$ 0.3)	-55 (-55)	-39 (- 39 $\pm$ 8)
IO	189 (189 $\pm$ 12)	11 (11 $\pm$ 4)	-45 (-45)	1 (1)	-45 (-45)	-35 (-35)

Table S2.6 EGLIF neuron parameters						
Cell name	$k_{adap}(nS \cdot ms^{-1})$	$k_1(ms^{-1})$	$k_2(ms^{-1})$	$A_1(pA)$	$A_2(pA)$	$I_e(pA)$
Granule Cell	0.022	0.311	0.041	0.01	-0.94	-0.888
Golgi Cell	0.217	0.031	0.023	259.988	178.01	16.214
Purkinje Cell	1.491	0.195	0.041	157.622	172.622	700
Basket and Stellate Cells	2.025	1.887	1.096	5.953	5.863	3.711
UBC	1.17	0.14	0.76	0.0001	0.0001	1.0
DCNp	0.408	0.697	0.047	13.857	3.477	75.385
DCNi	0.079	0.041	0.044	176.358	176.358	2.384
IO	1.928	0.191	0.091	1810.923	1358.197	-18.101

Table S2.7 Neuron Postsynaptic receptor parameters				
Cell name	Receptor id	$E_{rev,i}(mV)$	$\tau_{syn,i}(ms)$	Type
Granule Cell	1	0	5.8	excitatory
Granule Cell	2	-80	13.6	inhibitory
Golgi Cell	1	0	0.23	excitatory
Golgi Cell	2	-80	10	inhibitory
Golgi Cell	3	0	0.5	excitatory
Purkinje Cell	1	0	1.1	excitatory
Purkinje Cell	2	-80	2.8	inhibitory
Basket Cell	1	0	0.64	excitatory
Basket Cell	2	-80	2	inhibitory
UBC	1	0	0.2	excitatory
UBC	2	-80	2.0	inhibitory
UBC	3	0	1.2	excitatory
DCNp	1	0	1.0	excitatory
DCNp	2	-80	0.7	inhibitory
DCNi	1	0	3.64	excitatory
DCNi	2	-80	1.14	inhibitory
IO	1	0	1	excitatory
IO	2	-80	60	inhibitory

Table S2.8 Presynaptic parameters			
Source-Target	weight(nS)	delay (ms)	Receptor id
Mf-glom	1	1	1
glom-GrC	0.23	1	1
glom-GoC	0.24	1	1
GoC-GrC	0.24	2	2
GoC-GoC	0.007	4	2
GrC(aa)-GoC	0.82	2	3
GrC(aa)-PC	0.41	2	1
GrC(pf)-GoC	0.05	5	3
GrC(pf)-PC	0.14	5	1
GrC(pf)-SC	0.08	5	1
GrC(pf)-BC	0.06	5	1
BC-PC	0.8	4	2
SC-PC	0.17	5	2
BC-BC	0.006	4	2
SC-SC	0.005	4	2
UBC-ubc_glom	1	1	1

glom-GrC	0.23	1	1
glom-GoC	0.24	1	1
GoC-GrC	0.24	2	2
mf-DCNp	0.25	4.0	1
PC-DCNp	0.35	4.0	2
PC-DCNi	0.02	4.0	2
IO-PC	1.6	4	3
IO-BC	5.0	40	3
IO-SC	5.0	40	3
IO-DCNp	0.4	4	1
IO-DCNi	0.25	5	1
DCNi-IO	0.45	25	2

Chapter 3: Fear conditioning modeling in rodents

Section 3.1: Introduction

This chapter explores the potential contribution of the cerebellum to emotional learning, focusing specifically on the classical fear conditioning paradigm. As discussed in Chapter 1, fear conditioning is one of the most widely used behavioral frameworks to investigate emotion-related learning and its neural basis, making it a relevant starting point for modeling cerebellar involvement in emotional behavior.

The initial aim of this work was to construct and validate a biologically plausible model of cerebellar function during fear conditioning, using data-driven approaches. However, due to the current lack of high-resolution, cerebellum-specific recordings during fear learning, direct experimental validation remains out of reach. This challenge is well recognized in the field, and current efforts—including those led by the Cerebellum and Emotion Network (CEN)—are beginning to generate the necessary experimental data to address it.

Despite these current limitations, this chapter presents a substantial effort to bridge the gap by conducting an in-depth review of the literature and formulating biologically grounded hypotheses for how the cerebellum may participate in fear learning and extinction.

As a first modeling step, we tested these hypotheses using a canonical cerebellar microcircuit informed by existing simulations of Pavlovian learning. While the circuit was originally tuned for eye-blink conditioning, we carefully adapted the stimulation protocol and mechanisms to better approximate the characteristics of fear conditioning, while fully acknowledging the conceptual differences between the two paradigms.

The chapter begins with an overview of fear conditioning paradigms in animal models, followed by a synthesis of the broader neural network involved in fear processing. We then focus on the cerebellum, reviewing its known anatomical connections and summarizing the evidence for its role in fear memory acquisition, consolidation, and extinction. From this foundation, we develop a conceptual model of cerebellar involvement in fear conditioning and propose plausible extensions to include its interaction with downstream structures such as the ventrolateral periaqueductal gray (vIPAG), the ventral tegmental area (VTA), and the mediodorsal thalamus (MD).

Simulation results from the cerebellar model are then presented, showing the response to conditioned and unconditioned stimuli. These results offer a first look at how cerebellar microcircuits might support the timing and expression of fear-related responses, even in the absence of full empirical tuning.

The chapter concludes by discussing the main limitations of the current model and proposing specific strategies for its improvement. This work opens a promising path toward modeling cerebellar contributions to emotional learning. While some physiological parameters are still missing, the model already demonstrates conceptual and technical feasibility. With targeted experimental data and minor adjustments, it could serve as a powerful platform for building biologically realistic simulations of fear-related processes.

3.1.1 Fear conditioning paradigms in rodents

Fear conditioning, in laboratory models, involves pairing a neutral stimulus such as a tone, light, or environmental context with an aversive stimulus, typically an electric shock. This pairing induces a fear response, most notably freezing behavior, which persists even when the shock is later omitted. Extinction occurs when the conditioned stimulus is repeatedly presented without the aversive event, leading to a reduction in the fear response (Mohammed R. Milad et al., 2011; I. Müller & Fendt, 2023), this decrease reflects new learning that the cue no longer signals danger rather than the erasure of the original memory. However, extinguished fear can reappear under certain conditions, over time (spontaneous recovery), in a different context (renewal), or following an unsignaled aversive event (reinstatement), underscoring the context-specific nature of extinction (Chang et al., 2009). Variations in experimental parameters allow researchers to investigate a wide range of physiological and pathological learning phenomena (Chang et al., 2009; Detert et al., 2008; Lonsdorf et al., 2017; I. Müller & Fendt, 2023; Navarro-Sánchez et al., 2024).

The fear conditioning paradigms primarily differ in how stimuli and context influence the association with an aversive event (Curzon et al., 2009): *Contextual fear conditioning* is the most basic procedure, in which an animal is placed in a novel environment, receives an aversive stimulus, and is then removed. Upon re-exposure to the same context, the animal exhibits a freezing response, indicating that it has learned the association between the environment and the aversive stimulus. In contrast, *cued fear conditioning* introduces a conditioned stimulus (CS) within the context, allowing researchers to assess the animal's response to the CS rather than the general environment. To dissociate contextual learning from cue-based learning, some studies include a pre-exposure phase where the animal experiences the context without receiving the unconditioned stimulus (US), thereby reducing confusion between both types of learning. Finally, in *delay and trace conditioning*, the key difference lies in the interval between the CS and US: in delay conditioning, the CS and US are presented in succession without interruption, whereas in trace conditioning, there is a temporal gap between them. The latter requires the activation of additional brain regions and multiple training trials to consolidate the association between the CS and US, although contextual learning remains strong. Together, these paradigms allow for the investigation of different aspects of fear learning and the underlying neural mechanisms (For more details, see Figure 3.1 and Table 3.1).

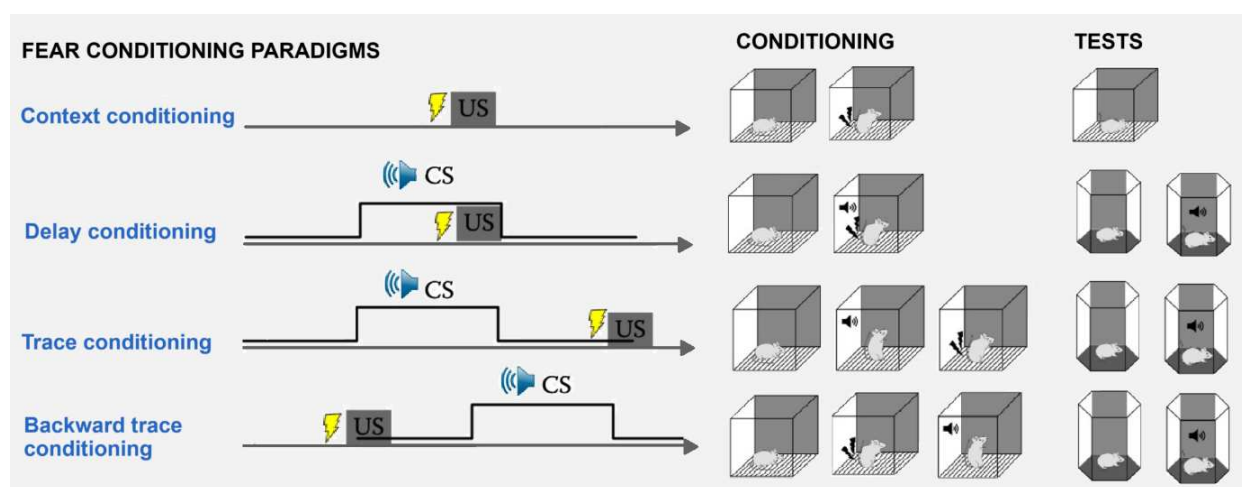


Figure 3.1 Fear conditioning paradigms in rodents. Schematic representation of the four basic fear conditioning paradigms, illustrating the timing of the conditioned stimulus (CS) and unconditioned stimulus (US) presentation. The arrow represents time elapsing, and the width of the rectangles represents stimulus duration. In context conditioning, the US (e.g., foot shock) is administered within a novel environment, leading to an association between the context and the fear response. Delay conditioning involves a CS (e.g., tone) that precedes and overlaps with the US, allowing for direct associative learning. Trace conditioning introduces a trace interval, a stimulus-free period between the CS and US, requiring additional neural processing for the association to form. Backward trace conditioning, used as a control, presents the CS after the US, preventing a predictive relationship and distinguishing associative learning from non-associative freezing behavior. The right panels illustrate the conditioning and testing phases for each paradigm.

Table 3.1 Key elements in Fear Conditioning paradigms in rodents	
Phases of a conditioning protocol Mostly single-cue, sometimes differential Multiple experiments allowing for consolidation	Habituation: Rodents are first habituated to the experimental environment to reduce stress and anxiety. This phase involves placing the rodents in the conditioning chamber without any stimuli. Conditioning: CS is paired with US Contextual Fear Conditioning: In this variation, the entire environment (context) in which the aversive stimulus is presented becomes associated with the fear response. When the rodents are placed back in the same environment, they exhibit a fear response even without the specific neutral stimulus. Cued Fear Conditioning: In this variation, a specific cue (e.g., a tone) is paired with the aversive stimulus. The rodents learn to associate the cue

between experimental phases Often based on a criterion	with the aversive stimulus, and they exhibit a fear response when the cue is presented, regardless of the environment. Extinction: CS is presented repeatedly without the US Spontaneous Recovery: After a rest period, the CS is presented again, and the fear response may re-emerge, although usually less intense. Controlled for (e.g. food) between session experiences
Population and samples	Mostly inbred strains or littermates
Stimulus type	Conditioned stimulus (CS) Auditory tones, olfactory, and visual cues (e.g. lights) Contextual stimuli In a novel context (as in single-cue studies, no control CS is available) Different cages (and odours) Unconditioned stimuli (US) -Typically, non-escapable -Intensity identical for all animals (non-calibrated and not experienced previously) -Typically foot shock
CS/US timing and duration	Can vary depending on the specific experimental design. - CS is typically presented for a duration of 10 to 30 seconds. - US is usually presented for a shorter duration, often around 0.5 to 2 seconds. -Interstimulus Interval (ISI) typically ranges from 200 ms to several seconds: 200 - 500 ms in delay conditioning 2 - 20 s in trace conditioning -Inter-trial interval (ITI) typically ranges from 3 s to 5 minutes: 30 -120 s in standard studies 2 - 5 min in contextual fear conditioning 30 - 60 s in auditory fear conditioning 1 - 5 min in extinction sessions
CS/US order	The order of presentation of stimuli is controlled to avoid non-associative effects such as latent inhibition. Can vary depending on the specific experimental design. - In delayed conditioning, the US is presented towards the end of the CS duration, with a slight overlap or co-termination - In trace conditioning, there is a gap (trace interval) between the end of the CS and the onset of the US, which can range from a few seconds to several minutes.
Reinforcement rate The probability of US occurrence in the presence of the CS	100% or partial (<100%)
Outcome measures	Fear behaviour (freezing and avoidance) - % time freezing (whole body) - Fear-potentiated startle (This includes a matching a procedure a couple of days before acquisition training to ensure similar baseline levels of sensitivity to the startle probe in animals)

	- Avoidance - Operant elements (bar presses for food) - Electrophysiology recordings
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This table was compiled in an effort to organize and summarize the available information. However, it should not be considered definitive, as there may be inaccuracies or variations depending on specific experimental conditions and interpretations.

3.1.2 Fear network in rodents

Fear is a fundamental survival mechanism governed by a complex and widely distributed neural network responsible for detecting, integrating, and executing defensive responses. This circuit comprises multiple interconnected brain regions, each playing a distinct role in processing and expressing fear-related behaviors. Over the past decades, significant progress has been made in mapping the core neural circuitry and elucidating the cellular and molecular mechanisms underlying fear conditioning. However, despite these advancements, a definitive fear network has yet to be fully established, as variations in the regions implicated continue to emerge in the literature.

Here, we synthesize findings from various studies (see Table 3.2 and Figure 3.3) to outline the anatomical and functional organization of the fear circuit. However, this framework should not be considered definitive, as ongoing research continues to refine our understanding, and variations in the reported neural components highlight the evolving nature of this field.

Sensory information regarding potential threats is initially processed by primary sensory cortices, including the auditory cortex for acoustic inputs, the primary visual cortex and superior colliculus for visual stimuli, and the olfactory systems for chemosensory cues. Importantly, sensory inputs follow parallel pathways toward the amygdala: Auditory signals reach the lateral amygdala through the medial geniculate nucleus of the thalamus. Fast-latency projections provide a rapid but coarse analysis of the stimulus, while slower thalamocortical projections enable more refined processing via the auditory cortex (LeDoux, 2000). Visual inputs are relayed via the lateral geniculate nucleus and the superior colliculus toward the amygdala, facilitating rapid threat detection through subcortical projections and detailed object recognition through cortical routes. Somatosensory signals (including pain) are conveyed via the parabrachial nucleus to the amygdala, providing an essential pathway for the detection of aversive stimuli (Tovote et al., 2015). Olfactory cues are processed through two parallel systems: the main olfactory system, which detects conspecific odors, and the accessory olfactory system, which is specialized for detecting predator odors, relaying signals to the cortical amygdala and medial amygdala.

The amygdala has been widely recognized as the key structure in fear processing (C. T. Gross & Canteras, 2012; Silva et al., 2016; Tovote et al., 2015). The basolateral amygdala complex, composed of the lateral amygdala (LA), basal amygdala (BA), and basomedial amygdala (BMA), plays a critical role in integrating sensory inputs from the thalamus, cortex, and hippocampus. The LA serves as a primary site for CS-US associations, auditory fear conditioning relies on direct projections from the medial geniculate nucleus to the LA, which encode aversive stimulus properties (LeDoux, 2000; Tovote et al., 2015). The BA and BMA further relay information to the central amygdala (CEA), which serves as the primary output hub for fear responses.

The CEA is subdivided into the lateral (CEl) and medial (CEm) components, which exert differential control over fear responses. The CEl consists of two opposing cell populations, the CElon and CEloff cells. CElon neurons are activated by threat cues and inhibit CEloff neurons; CEloff neurons exert tonic inhibition over the CEm. When CElon neurons inhibit CEloff neurons, the CEm is disinhibited, triggering defensive behaviors (Herry et al., 2008; Pellman & Kim, 2016; Tovote et al., 2015). The CEA is regulated by interneuron subtypes within the BLA: Parvalbumin-positive (PV+) interneurons provide fast somatic inhibition, and somatostatin-positive (SOM+) interneurons regulate dendritic excitability and are essential for plasticity underlying fear learning (Tovote et al., 2015). Projections from the CEA target multiple effector regions that orchestrate fear responses.

The ventrolateral periaqueductal gray (vIPAG) mediates freezing by inhibiting motor output, whereas the dorsal periaqueductal gray (dPAG) regulates escape and active defensive behaviors through direct glutamatergic projections to motor circuits (Frontera et al., 2020; E. J. Kim et al., 2013; Tovote et al., 2015; T. C. Watson et al., 2016). The dPAG also receives nociceptive inputs from the parabrachial nucleus (PB), which conveys unconditioned stimulus (US) information to

the amygdala. The PB also sends projections to the CEA, particularly to the CEI, where it modulates associative learning through calcitonin gene-related peptide (CGRP)-expressing neurons (Pellman & Kim, 2016; Tovote et al., 2015).

The hypothalamus serves as an essential hub for integrating innate fear signals, with distinct nuclei mediating responses to different threat categories. The anterior hypothalamic nucleus (AH), dorsomedial portion of the ventromedial hypothalamus (VMHdm), and dorsal premammillary nucleus (PMD) constitute the predator fear circuit, whereas the medial preoptic nucleus (MPN), ventrolateral VMH (VMHvl), ventral premammillary nucleus (PMV), and dorsomedial PMD (PMDdm) form the conspecific fear circuit (C. T. Gross & Canteras, 2012; Tovote et al., 2015). These hypothalamic nuclei project to the PAG to execute behavioural responses.

Fear conditioning and extinction involve additional structures, particularly the prefrontal cortex (PFC) and hippocampus. The emergence of 4-Hz oscillations in PFC–amygdala circuits predicts freezing onset and synchronizes activity, with optogenetic induction enhancing fear expression, underscoring the role of neural synchronization in fear regulation (Dejean et al., 2016; Karalis et al., 2016; Tovote et al., 2015). Specifically, within the PFC, the prelimbic cortex (PL) facilitates fear expression by modulating amygdalar activity (via projections to the BLA and CEA), whereas the infralimbic cortex (IL) plays a crucial role in fear extinction by inhibiting the CEm via projections to intercalated cell masses (ITC) (Kaplan et al., 2011; Tovote et al., 2015; Tronson et al., 2012). These ITC neurons, positioned between the BLA and CEA, act as inhibitory gates that suppress conditioned fear responses upon activation.

The hippocampus encodes contextual cues, specifically the dorsal hippocampus contributes to contextual fear learning by encoding spatial and contextual information, while the ventral hippocampus modulates fear generalization and regulates anxiety-related behaviors. Hippocampal projections to the BLA, CEA, and PFC integrate contextual information into fear memory processing (Herry et al., 2008; Tovote et al., 2015).

Further, the interconnections between the anterior cingulate cortex (ACC), retrosplenial cortex (RSP), and postrhinal cortex (POR) have been implicated in encoding and retrieving learned fear responses. These cortical regions, in conjunction with the hippocampus and amygdala, modulate contextual and associative fear processing (C. T. Gross & Canteras, 2012). The paraventricular nucleus of the thalamus (PVT) has also been found to regulate fear expression by projecting to the CEA, where it modulates the persistence and renewal of conditioned fear. PVT projections to the CEA influence long-term fear expression, and PVT neurons, sensitive to neuropeptides, regulate the incubation of fear (Tovote et al., 2015). In addition, the orbitofrontal cortex (OFC), particularly the medial orbitofrontal cortex (mOFC), interferes with fear extinction and impairs the discrimination between safe and dangerous contexts, facilitating the reappearance of fear (Hsieh & Chang, 2020). The lateral orbitofrontal cortex (lOFC) modulates threat discrimination and enhances fear responses under threat uncertainty, with lOFC hyperactivity leading to excessive fear responses (Shih & Chang, 2021).

➤ The role of the cerebellum and its pathways in fear conditioning in rodents

As early as 1976, reports suggested that the cerebellum plays a role in at least some functions of the circuit originally described by Papez as fundamental to emotional processing (R. S. Snider & Maiti, 1976). However, at the time, this idea received little attention. In recent years, accumulating evidence has revived interest in the cerebellum's involvement in emotion-related circuits. While emotional processing has traditionally been attributed to cortical and subcortical structures, increasing research indicates that the cerebellum and its connections also play a crucial role.

Evidence from lesion studies, neural recordings, and optogenetic manipulations suggests that different regions of the cerebellum contribute differentially to the acquisition, consolidation, and expression of fear responses, giving rise to several hypotheses about the specific cerebellar circuits involved in fear regulation (see Figure 3.2a-c).

Many authors agree that the deep cerebellar nuclei (DCN), particularly the interposed, dentate, and fastigial nuclei, play an essential role in the consolidation and retrieval of fear memories. While the interposed nucleus is particularly involved in the initial acquisition of conditioned stimulus–unconditioned stimulus associations, the dentate nucleus is primarily involved in the long-term consolidation of these memories. The fastigial nucleus, on the other hand, plays a distinct role in regulating the motor and autonomic components of defensive responses (Frontera

et al., 2020; Hwang et al., 2022; Jung et al., 2022; Strata, 2015b; Supple et al., 1987; Urrutia Desmaison et al., 2023; Vazdarjanova, 2002). Modulating these nuclei alters conditioned fear memory, suggesting that the cerebellum is not merely involved in the motor expression of fear responses but also in the encoding and storage of emotional memory (Kotajima et al., 2014)

Experimental evidence shows that the cerebellar vermis is crucial in regulating emotional expression and coordinating autonomic fear responses. Changes in its activity influence fear response intensity and impact the extinction of aversive memories. At the same time, studies have shown that lobules V and VI of the cerebellum are involved in the consolidation of conditioned fear memories through direct projections to the fastigial nucleus, which modulates freezing behavior via downstream connections to the ventrolateral periaqueductal gray (vIPAG). In contrast, lobule VIII is more directly involved in the execution of freezing behavior, likely through its direct connections with the PAG (Apps & Strata, 2015; Frontera et al., 2020; Koutsikou et al., 2014; Sacchetti, Scelfo, Strata, et al., 2009; Supple et al., 1987; Urrutia Desmaison et al., 2023; Sacchetti et al., 2004; Doublier et al., 2023; Hwang et al., 2022).

Beyond these findings, the cerebellum also regulates autonomic fear responses through its interaction with the inferior olive (IO). The IO transmits unconditioned stimulus information to the cerebellum via climbing fibers, which contribute to the acquisition and expression of conditioned autonomic responses. Lesions to the IO impair fear-conditioned bradycardia without affecting freezing, reinforcing the functional distinction between autonomic and motor responses in the cerebellum (Kotajima et al., 2014). The IO plays a key role in prediction error signaling during fear learning by encoding the discrepancy between expected and actual outcomes. Interestingly, the IO is also implicated in fear extinction, suggesting that it plays a role not only in the acquisition of conditioned fear but also in its suppression (Kalmbach & Mauk, 2012).

Recent evidence highlights a complex and functionally significant interaction between the cerebellum and the amygdala, suggesting a potential cerebellar role in emotional processing. Early physiological studies in cats and monkeys reported that electrical stimulation of the cerebellar vermis elicited short-latency responses in the amygdala, suggestive of a possible monosynaptic connection (R. G. Heath & Harper, 1974). In contrast, more recent anatomical studies in rodents support disynaptic pathways, particularly from the fastigial nucleus to the basolateral amygdala via the parafascicular nucleus of the thalamus (Jung et al., 2022). Complementing these anatomical findings, (Terburg D et al. , 2024) propose a theoretical framework emphasizing a functional cerebellum–amygdala pathway involved in social and affective behaviors, integrating action- and outcome-based processing. While direct monosynaptic projections remain to be conclusively demonstrated, these converging lines of evidence support the relevance of cerebellar–amygdalar interactions in emotional regulation.

These connections allow the cerebellum to influence emotional encoding and fear responses, contributing to both threat assessment and fear extinction. This cerebello-amygdala pathway forms part of a broader feedback loop involving the PAG, hypothalamus, and prefrontal cortex (Terburg D et al., 2024).

The cerebello-PAG pathway plays a pivotal role in fear learning and expression. The fastigial nucleus (FN) of the cerebellum projects to the ventrolateral periaqueductal gray (vIPAG), influencing glutamatergic, GABAergic, and dopaminergic activity. Glutamatergic projections from the FN excite Chx10-expressing neurons in the vIPAG, which in turn project to magnocellular reticular neurons that modulate freezing behavior. Activation of this pathway facilitates the extinction of fear responses, whereas inhibition impairs extinction learning and enhances freezing behavior (Frontera et al., 2020; Koutsikou et al., 2014; Lawrenson et al., 2022; Vaaga et al., 2020; T. C. Watson et al., 2016). This suggests that the cerebellum exerts a bidirectional influence over fear responses, dynamically adjusting defensive behavior according to environmental demands (Urrutia Desmaison et al., 2023).

Similarly, DCN projections to the ventral tegmental area (VTA) have been linked to the enhancement of fear extinction learning. The VTA is involved in reward-related learning and is modulated by cerebellar output, suggesting that the cerebellum influences extinction by engaging dopaminergic circuits involved in reinforcement learning (Carta et al., 2019; Couto-Ovejero et al., 2023; Urrutia Desmaison et al., 2023)

The cerebellum regulates fear memory and extinction through its interaction with the PFC and thalamus. The fastigial nucleus projects to the dorsomedial thalamus (MD), which in turn connects

with the dorsomedial prefrontal cortex (dmPFC), forming a cerebello-thalamo-cortical circuit. Disruption of this pathway increases 4-Hz oscillations in the dmPFC, which are associated with prolonged fear responses and impaired extinction. This suggests that the cerebellum contributes to the cognitive regulation of fear by modulating prefrontal cortical activity during both fear acquisition and extinction (Frontera et al., 2023; Urrutia Desmaison et al., 2023).

The zona incerta (ZI), a subthalamic structure, projects to both the pontine nuclei and the IO, influencing defensive responses. Its activation modulates the excitability of the cerebellum and other subcortical regions, integrating threat-related signals and influencing fear processing (Bhuvanasundaram et al., 2024).

The hippocampus, crucial for contextual fear encoding, also interacts with both the amygdala and cerebellum. Although the connection is indirect, cerebellar activity influences hippocampal function through thalamic and hypothalamic pathways, reinforcing the integration of spatial and emotional information during fear responses (Apps & Strata, 2015; Hwang et al., 2022; Urrutia Desmaison et al., 2023).

Additionally, the DCN projects to the lateral parabrachial nucleus (IPBN), establishing a crucial pathway for processing threat-related auditory signals. Activation of DCN/IPBN neurons is essential for auditory fear conditioning, highlighting the role of the IPBN in integrating aversive sensory stimuli and coordinating defensive responses. This connection suggests that the cerebellum, through its interaction with the IPBN, contributes to the encoding and execution of conditioned fear responses (Hwang KD et al., 2023).

Lastly, the superior colliculus, located in the midbrain, plays a key role in visual threat detection and defensive responses. The fastigial nucleus projects to the superior colliculus, facilitating rapid visual processing and adaptive motor responses to threats. Notably, the same fastigial nucleus neurons projecting to the vIPAG also target the superior colliculus, highlighting the integration of motor and emotional components of defensive behavior (Frontera et al., 2020; H. Fujita et al., 2020b; Urrutia Desmaison et al., 2023).

Table 3.2 Brain Regions Involved in Fear Conditioning in Rodents		
Brain Region	Function	
Auditory Cortex	Acquisition	Processes acoustic inputs for threat detection
Primary Visual Cortex	Acquisition	Processes visual stimuli for threat detection
Retinal Ganglion Cells	Acquisition	Initial processing of visual threats
Superior Colliculus	Acquisition	Facilitates rapid visual threat detection and motor responses, defensive behavior
Inferior Colliculus	Modulation	Processes auditory threat signals and relays to the amygdala
Olfactory System	Acquisition	Processes chemosensory cues, including predator odors
Anterior Cingulate Cortex	Expression	Fear anticipation and evaluation of conflict
Orbitofrontal Cortex	Expression	Threat discrimination and modulation of fear extinction
Retrosplenial Cortex	Processing	Contextual and associative fear processing
Postrhinal Cortex	Processing	Contextual fear processing
Entorhinal Cortex	Extinction	Contributes to contextual memory processing and fear consolidation
Prefrontal Cortex	Expression	Cognitive regulation of fear responses
Prelimbic Cortex	Expression	Facilitates fear expression via amygdalar activity
Infralimbic Cortex	Extinction	Inhibits fear expression during extinction
Lateral Amygdala	Acquisition	CS-US association, encoding aversive properties
Basolateral Amygdala	Consolidation	Storage and modulation of fear memory
Basomedial Amygdala	Modulation	Emotional modulation
Central Amygdala	Expression	Expression and processing of fear responses
Cortical Amygdala	Processing	Processes predator-associated cues and social threat signals

Intercalated Masses	Cell	Acquisition	Inhibits conditioned fear responses, regulates extinction
Hippocampus (Dorsal)		Acquisition	Encodes contextual information for fear learning
Hippocampus (Ventral)		Modulation	Modulates fear generalization and anxiety
Ventral Periaqueductal Gray		Modulation	Passive coping and freezing behavior
Ventrolateral Periaqueductal Gray		Expression	Mediates freezing by inhibiting motor output
Dorsal Periaqueductal Gray		Expression	Regulates active escape and defensive behaviors
Dorsolateral Periaqueductal Gray		Expression	Active coping and defensive behaviors
Dorsomedial Thalamus		Consolidation	Modulates fear expression and extinction
Parafascicular Nucleus (Thalamus)		Expression	Relays cerebellar input to the amygdala
Paraventricular Nucleus of the Thalamus		Expression	Persistence and renewal of conditioned fear
Intralaminar and Midline Thalamic Nuclei		Expression	Relay of sensory and associative signals to the amygdala
Anterior Hypothalamic Nucleus		Modulation	Regulates predator-related fear responses
Ventromedial Hypothalamus		Modulation	Regulates conspecific and predator-related fear
Dorsomedial Hypothalamus		Processing	Modulates stress responses and emotional arousal
Medial Preoptic Nucleus		Modulation	Regulates conspecific-related fear
Ventral Tegmental Area		Processing	Modulates emotional and motivational balance
Lateral Septum		Processing	Modulates emotional states and stress responses
Zona Incerta		Expression	Modulates defensive responses and fear integration
Parabrachial Nucleus		Acquisition	Conveys pain and aversive stimuli to the amygdala
Lateral Parabrachial Nucleus		Acquisition, consolidation, expression	Processes threat-related auditory signals
Inferior Olive		Acquisition	Prediction error signaling and bradycardia in fear conditioning
Cerebellum (Lobule V-VI, VIII)		Extinction, Expression	Modulates motor and autonomic fear responses, regulates emotional learning
Fastigial Nucleus (Deep cerebellar nucleus)		Expression	Regulates motor and autonomic components of fear
Dentate Nucleus (Deep cerebellar nucleus)		Consolidation	Long-term consolidation of fear memories
Interposed Nucleus (Deep cerebellar nucleus)		Acquisition	Initial acquisition of fear memories

Supplementary material includes a comparison between procedures used in rodent and human studies (Table S3.1.1), as well as a summary of differences in the function and interconnectivity

of brain regions across species (Table S3.1.2). These comparisons provide context regarding the limitations and scope of cross-species extrapolation.

3.1.3 Cerebellar fear circuit in rodents

As described in the previous chapter, the cerebellar microcircuit consists of complex excitatory and inhibitory interactions involving Purkinje cells (PC), parallel fibers (pf), climbing fibers (cf), molecular layer interneurons (MLI), and deep cerebellar nuclei (DCN). In this part, we will explore how this network contributes to fear learning and extinction through synaptic plasticity and downstream projections (Figure 3.4).

➤ Synaptic Plasticity and Cellular Mechanisms in Fear Learning

Fear memory acquisition is associated with Long-Term Potentiation (LTP) at PF-PC synapses. During fear learning, there is an upregulation of AMPA (*α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*) receptors at PF-PC synapses, leading to enhanced excitatory transmission and increased synaptic strength. Post-synaptic LTP at PF-PC synapses in cerebellar lobules V-VI is specifically observed after auditory fear conditioning, but not after unpaired auditory exposure. In hotfoot mice, which lack glutamate receptor delta2 at PF-PC synapses, deficits in both short- and long-term cued fear memory were reported.

Furthermore, genetic deletion of cerebellin1, which acts as a ligand for glutamate receptor delta2 at PF-PC synapses, impaired both contextual and auditory fear memory retrieval (Hwang et al., 2022; Sacchetti et al., 2004; Zhu et al., 2007).

Inputs from the basolateral amygdala (BLA) modulate PF-PC synaptic plasticity after auditory fear conditioning. BLA inactivation via muscimol or anisomycin administration blocked the synaptic potentiation at PF-PC synapses, supporting the role of amygdalar inputs in cerebellar fear memory formation (Hwang et al., 2022; Zhu et al., 2011). Interestingly, fear conditioning-induced LTP at PF-PC synapses was reduced in PC-specific STAT3 knockout mice, which also exhibited increased AMPA receptor expression and decreased GABAergic inhibition at MLI-PC synapses (Han et al., 2021; Hwang et al., 2022). This highlights the importance of the excitatory-inhibitory balance in cerebellar circuits during fear learning.

In addition to excitatory plasticity, fear conditioning induces presynaptic LTP at MLI-PC synapses, leading to increased GABAergic transmission onto PCs in lobules V-VI. Increased inhibitory input from MLIs to PCs enhances the precision and timing of PC firing, facilitating more effective signal processing during fear learning (Dubois et al., 2020; Hwang et al., 2022; Scelfo et al., 2008).

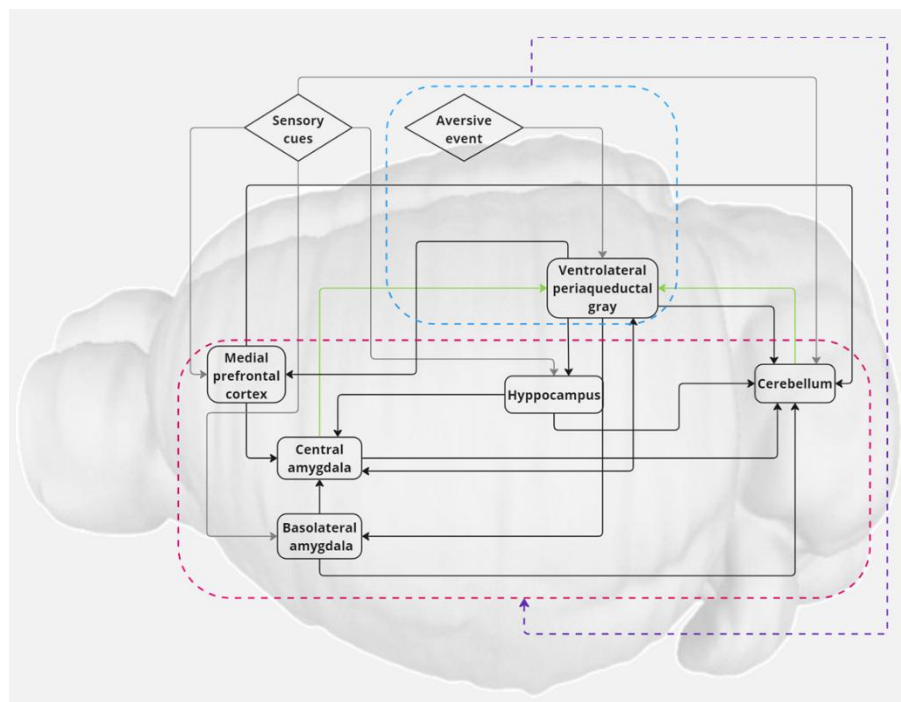
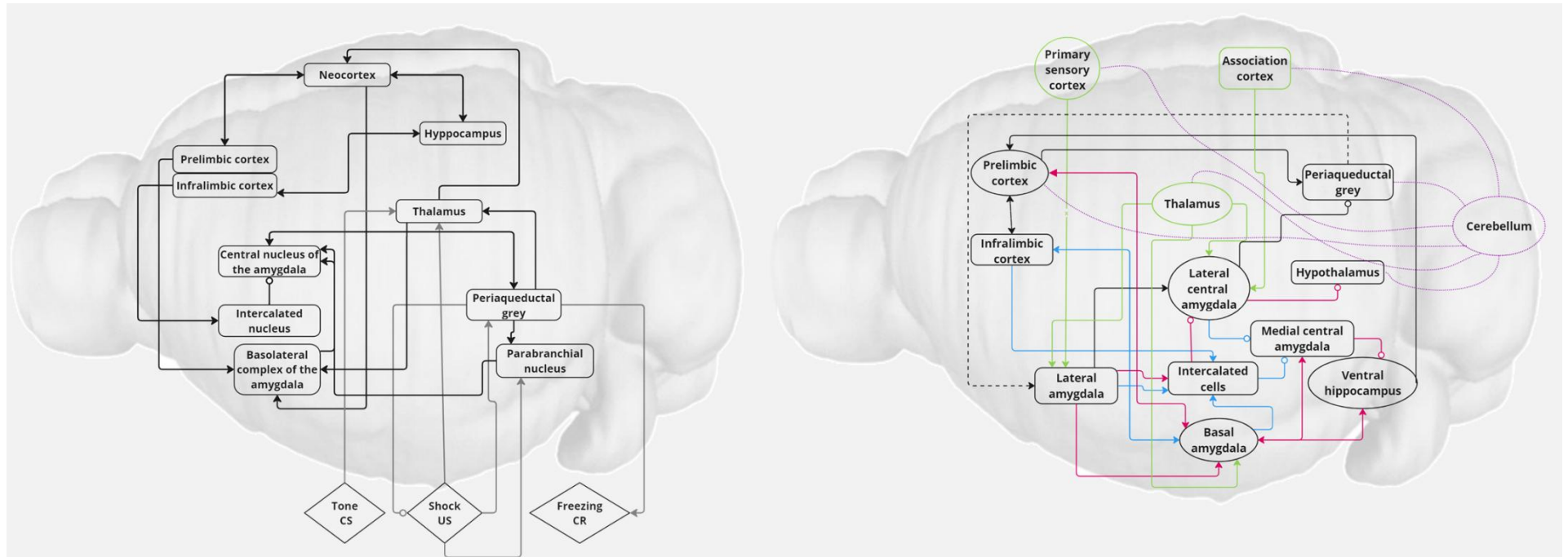
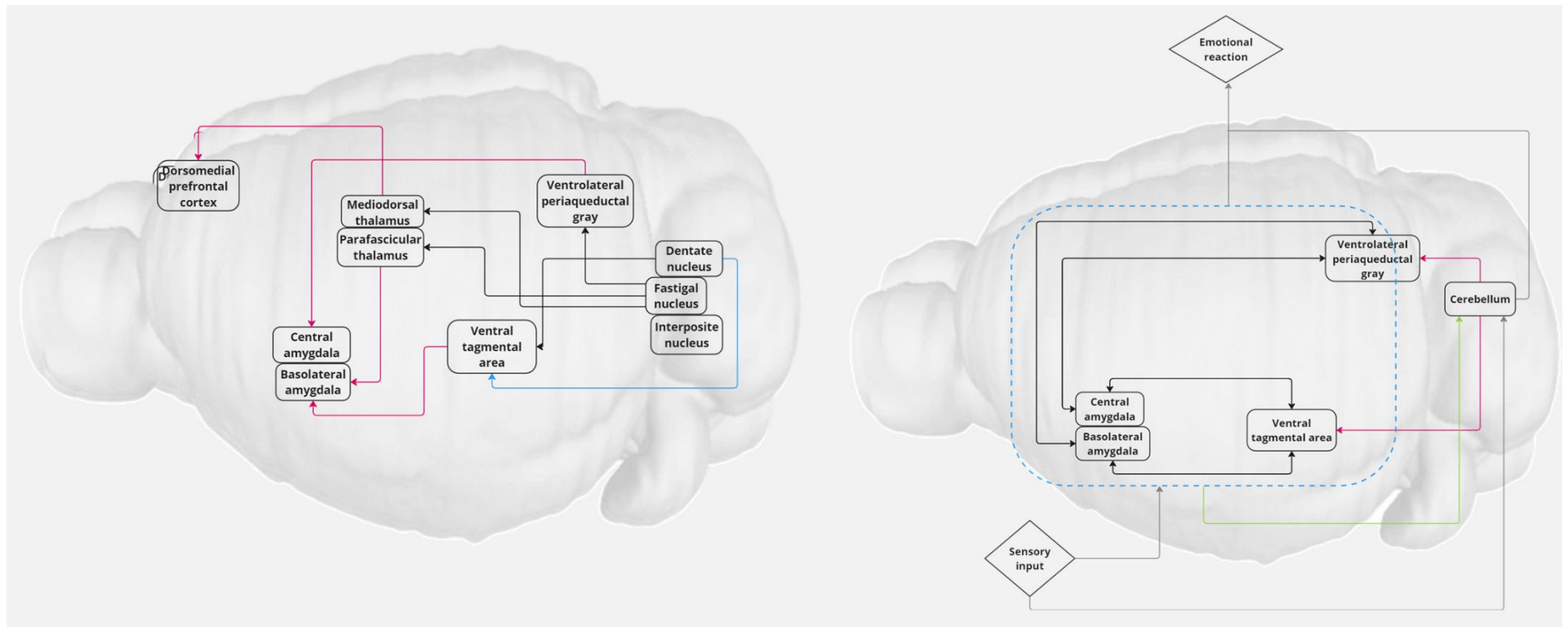


Figure 3.2 Proposed Neural Circuits of Fear Processing in rodents.

3.2a) Schematic representation of fear processing circuits based on (Frontera et al., 2020). The blue dotted rectangle represents the fear processing region. The red dotted rectangle indicates the fear memory system involved in memory updating. The purple dotted line represents fear prediction error, while the green line indicates fear prediction.



3.2b) (Left panel) Schematic representation of fear processing circuits based on (Pellman & Kim, 2016). Excitatory pathways are represented by arrows, and circles represent inhibitory pathways. (Right panel) Schematic representation of fear processing circuits based on (Apps & Strata, 2015; Tovote et al., 2015), blue lines indicate pathways that dampen fear, while red lines indicate pathways that promote fear. Black solid lines represent circuits where further studies are needed, and black dashed lines represent polysynaptic connections. Purple dashed lines represent cerebellar links proposed by Apps and Strata. Light green lines represent input areas. Ovals indicate identified local microcircuits. Excitatory pathways are represented by arrows, and inhibitory pathways are represented by circles.



3.2c) Schematic representation of fear processing circuits based (Urrutia Desmaison et al., 2023). (Left panel) Blue lines represent appetitive learning, black lines represent aversive learning, and red lines represent secondary pathways. (Right panel) The blue dotted rectangle highlights the regions involved in prediction error signaling. The red lines represent the pathways involved in updating prediction error generation, while the green lines indicate the pathways related to the prediction of emotional value.

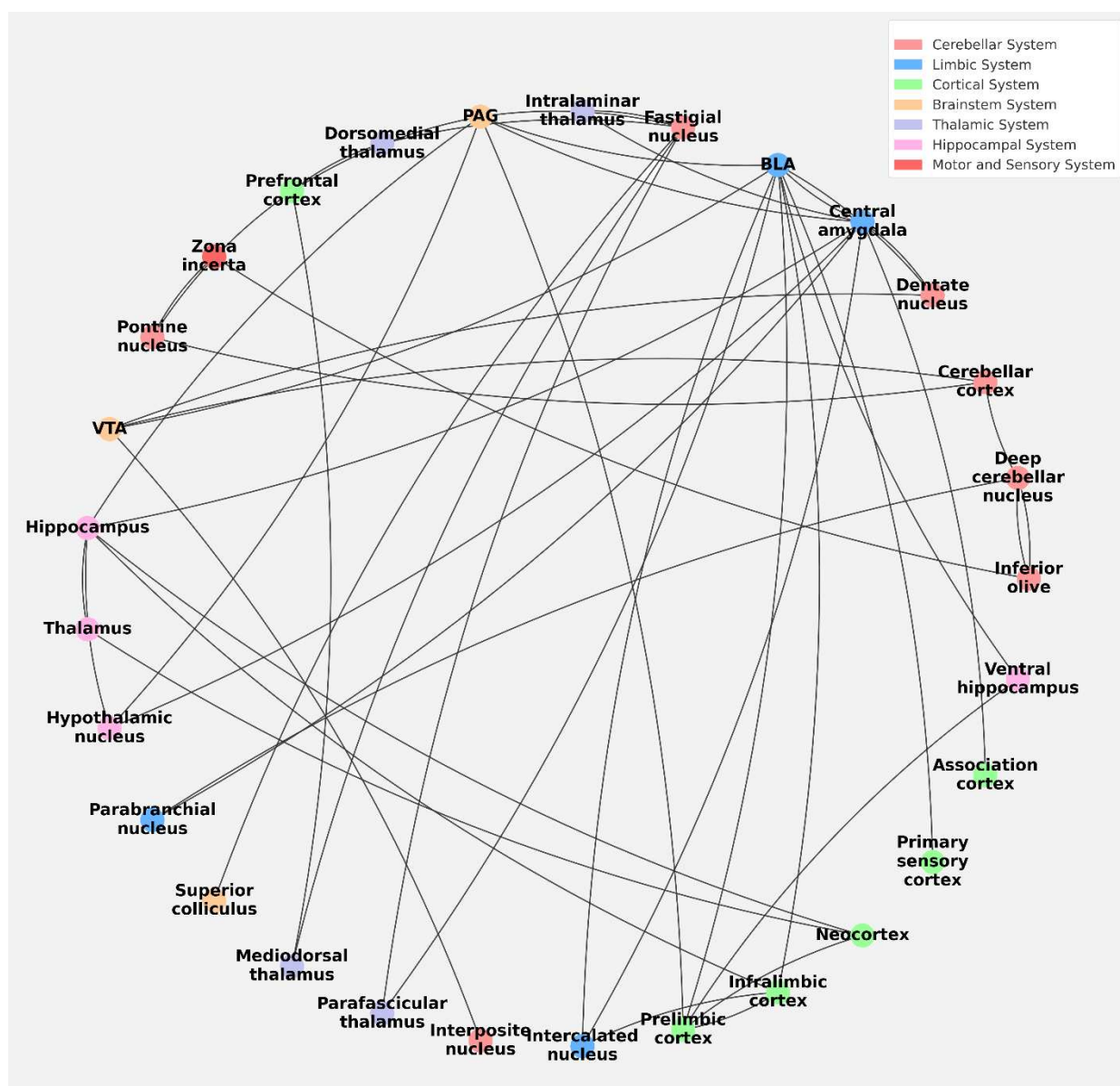


Figure 3.3 Hypothesized fear circuitry in rodents based on literature review. The diagram highlights key connections between major brain regions, including the cerebellar, limbic, cortical, hippocampal, thalamic, and brainstem systems. The circular layout was specifically designed to enhance visual clarity and facilitate a comprehensive map of the neural mechanisms underlying fear-related behavior

Endocannabinoid signaling regulates this form of inhibitory plasticity. Auditory fear conditioning accelerates endocannabinoid degradation by monoacylglycerol lipase (MAGL), reducing the inhibitory effect of endocannabinoids at MLI-PC synapses.

Chemogenetic activation of PCs reduced MAGL expression, impairing fear memory consolidation—a deficit that was rescued by pharmacological inhibition of endocannabinoid signaling (Dubois et al., 2020; Hwang et al., 2022).

While LTP at PF-PC synapses underlies fear acquisition, fear extinction is associated with LTD at SC-SC synapses. Auditory fear conditioning increases GABA release at SC-SC synapses in lobule V-VI, but fear extinction learning reduces this GABA release, suggesting that synaptic plasticity at SC-SC synapses is essential for the extinction of conditioned fear responses (Dubois & Liu, 2021; Hwang et al., 2022).

Functional removal of GABAergic signaling at SC-SC synapses impairs fear extinction learning, highlighting the role of local inhibitory circuits in regulating extinction. Mice lacking GluN2D receptors, which mediate SC-SC LTD, exhibited impaired fear extinction learning and reduced suppression of GABA release after repeated PF stimulation. This indicates that SC-SC synaptic

plasticity dynamically regulates fear extinction by modifying inhibitory tone within the cerebellar cortex (Dubois & Liu, 2021; Hwang et al., 2022).

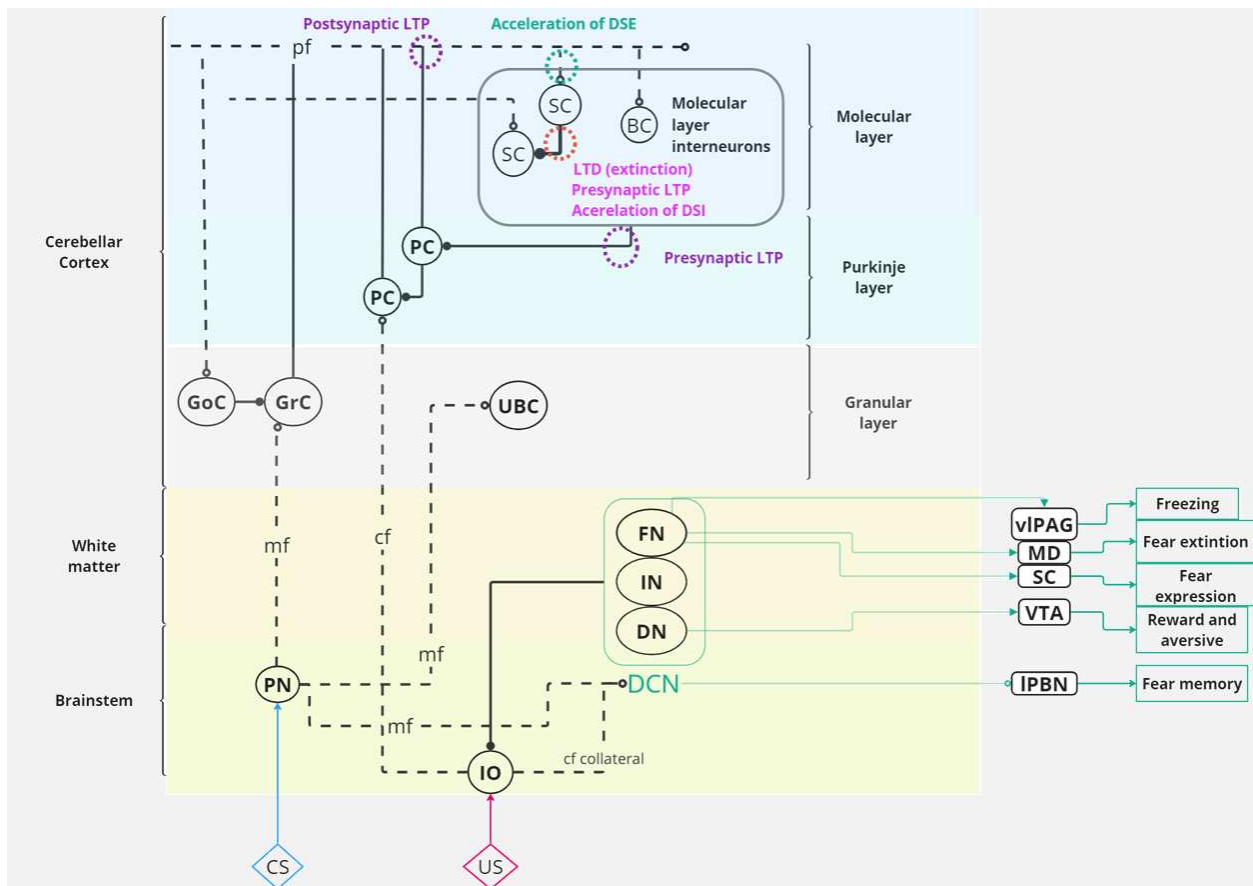


Figure 3.4 Hypothesized cerebellar fear microcircuit in rodents based on literature review. The inferior olive (IO) encodes the unconditioned stimulus (US), while the mossy fiber-parallel fiber (mf-pf) pathway encodes the conditioned stimulus (CS). During fear conditioning, postsynaptic long-term potentiation (LTP) occurs at parallel fiber (pf)-Purkinje cell (PC) synapses, while presynaptic LTP at molecular layer interneuron-PC synapses contributes to fear learning and memory. Fear conditioning also accelerates depolarization-induced suppression of excitation (DSE) at PF-stellate cell (SC) synapses and enhances presynaptic LTP and depolarization-induced suppression of inhibition (DSI) at SC-SC synapses. In contrast, fear extinction learning is associated with NMDAR-mediated presynaptic long-term depression (LTD) at SC-SC synapses. The deep cerebellar nuclei (DCN), particularly the fastigial nucleus (FN), have been implicated in the regulation of fear responses through projections to the ventrolateral periaqueductal gray (VIPAG), where they modulate freezing behavior via downstream motor circuits. Projections from the FN have also been identified toward the mediodorsal thalamus (MD) and the superior colliculus (SC), suggesting a role in fear extinction learning and fear expression, respectively. The dentate nucleus (DN) projects to the ventral tegmental area (VTA), where it has been linked to the processing of reward prediction error and aversive emotions learning. Furthermore, DCN projections to the lateral parabrachial nucleus (IPBN) have also been implicated in the formation and consolidation of fear memories. Dotted lines indicate excitatory connections; solid lines indicate inhibitory connections.

Section 3.2 Methods

3.2.1 Modeling neural responses to conditioned and unconditioned stimuli

To simulate the fear conditioning paradigm, we configured our model based on Pavlovian conditioning experiments for which we have available electrical parameters tailored to a point-neuron circuit (Geminiani A et al., 2024). These parameters were originally optimized for an eye-blink conditioning (EBC) experiment using the EGLIF model of the olivocerebellar circuit.

Eye blink conditioning is a well-established form of associative learning in which an animal learns to blink in response to a conditioned stimulus (CS), such as a tone, that predicts the delivery of an unconditioned stimulus (US), like a puff of air to the eye. This learning process requires precise temporal alignment between the CS and US, with an optimal interval of 250–500 ms. Deviations from this window, either too short or too long, result in reduced learning efficacy (Freeman, 2015; Takehara-Nishiuchi, 2018).

In contrast, as discussed earlier in this chapter and shown in Table 3.1, fear conditioning involves an emotional response, such as freezing or increased heart rate, and permits greater flexibility in timing. Effective CS–US intervals can range from 200 ms to several seconds, allowing associations to form even with longer delays between stimuli.

Despite differences in timing, duration, and behavioral output, EBC and fear conditioning share key features: both are classical conditioning paradigms that rely on the association between a CS and a US and involve cerebellar-dependent plasticity. This fundamental similarity allows us to adapt the eye-blink model to investigate the mechanisms underlying fear conditioning.

Moreover, our primary aim is to explore the cerebellum's role in emotional learning. Since our model—like the original EBC model—is based on the olivocerebellar system, it is particularly well-suited for examining how cerebellar mechanisms involved in motor learning may also contribute to the modulation of fear responses.

Importantly, both EBC and fear conditioning engage the olivocerebellar loop, in which climbing fiber input from the inferior olive (IO) plays a central role in error signaling and temporal processing. In EBC, this loop primarily modulates motor output. In fear conditioning, however, emerging evidence highlights the cerebellum's role in affective modulation, through projections from deep cerebellar nuclei (DCN) to limbic structures such as the VIPAG, VTA, SC, etc, as illustrated in Figure 3.4.

As discussed in Chapter 2, the Declive circuit we developed is not yet capable of reproducing the features required for Pavlovian conditioning simulations. Therefore, we focus on the canonical circuit for these simulations.

The general methodology for simulating E-GLIF point-neuron models in BSB-NEST was described in Chapter 2. In this section, we simulate neural responses to conditioned and unconditioned stimuli, following a classical Pavlovian conditioning paradigm (i.e., pairing a conditioned stimulus, CS, with an unconditioned stimulus, US), similar to previous studies in (Geminiani A et al., 2024). Specifically, the CS is applied to the mossy fibers (MF), and the US is delivered to the inferior olive (IO), as illustrated in Figure 3.4.

The mossy fiber input follows the same parameters used for basal awake-state activity described in Chapter 2, with an additional stimulus consisting of a 40 Hz Poisson spike train applied between 1000 and 1250 ms. The unconditioned stimulus is modeled as a 500 Hz burst delivered to the IO during the interval from 1250 to 1260 ms.

During this stimulation, the mean firing rates for each neuron population were recorded; the corresponding raster plots and firing rate curves are shown in the following sections.

3.2.2 Pavlovian conditioning learning in the cerebellum

Eye Blink Conditioning involves synaptic plasticity that relies on precise timing between the CS and the US, requiring multiple repetitions for learning through long-term potentiation (LTP) and long-term depression (LTD), which depend critically on temporal synchrony (Bao et al., 2002; Freeman, 2015). In contrast, fear conditioning involves faster learning driven primarily by the emotional salience of the stimulus rather than precise timing, with plasticity involving LTP and processes like reconsolidation and extinction, making the response more resistant to change (Luchkina & Bolshakov, 2019).

To simulate learning in eye-blink conditioning, the authors in (Geminiani A et al., 2024) incorporated long-term plasticity at parallel fiber to Purkinje cell (pf-PC) and parallel fiber to molecular layer interneuron (pf-MLI) synapses. In pf-PC synapses, stimulation of a parallel fiber (pf) together with a climbing fiber (cf) signal (acting as a teaching signal) triggered Long-Term Depression (LTD), while pf stimulation alone caused Long-Term Potentiation (LTP). The pf-MLI plasticity followed a similar mechanism but with reversed effects: cf activation caused LTP at pf-MLI synapses, depending on the timing of pf spikes relative to cf spikes, modeled using an alpha function with a 50 ms rise time. Without cf activation, pf-MLI synapses underwent LTD. The model

was tuned in two steps: first, synaptic strengths were adjusted to match baseline firing rates from experimental data, and then plasticity rates (LTP and LTD) were fine-tuned to match firing patterns after learning in control mice. The final parameters were scaled to reflect long-term learning patterns, ensuring that the model accurately reproduced experimental behavior.

In our case, to adapt this model for fear conditioning, we need to adjust the synaptic plasticity rules to reflect the distinct mechanisms involved in fear learning, as we explained previously shown in Figure 3.4. First, at the pf–PC synapse, long-term LTP should become the dominant mechanism, replacing LTD as the default response, while retaining a transient early phase of LTD during initial learning. Second, at the pf–MLI synapse, plasticity should switch from LTD to presynaptic LTP, which regulates inhibition following fear learning. Third, to capture the role of plasticity at the pf–SC synapse, we need to introduce depolarization-dependent plasticity (DSE) to modulate excitation based on the stellate cell's membrane potential. Fourth, we must include a dynamic balance of LTP (during acquisition) and LTD (during extinction) at SC–SC synapses. Finally, climbing fiber activity should remain a teaching signal but should primarily modulate the threshold for LTP and LTD at pf–PC and SC–SC synapses rather than directly inducing plasticity. These adjustments will allow the model to capture the specific learning dynamics underlying fear conditioning while preserving the core cerebellar circuit architecture.

Implementation of this model requires additional experimental data, which are currently unavailable, to properly tune and adjust the synaptic plasticity parameters.

3.2.3 Extending the model for fear conditioning beyond the cerebellum

The following describes how the prior simulation can be modified to simulate fear conditioning. Among the animal responses to the fear conditioning paradigm described previously, the freezing response was shown to involve the vIPAG region in the rodent brain. As we can see in Table 3.2 and Figures 3.1-3.4, this region is known to interact with the cerebellum during fear conditioning (Frontera et al., 2020; Vaaga et al., 2020). We will therefore try here to conceptualize the impact of vIPAG activity on the cerebellum during fear conditioning tasks.

We hypothesize a cerebellar connectivity model (see Figure 3.5) based on the findings from (Paci et al., 2023) that has been modified to better align with our case (see Fig. 3.5):

- First, we renamed the medial cerebellar nucleus to the fastigial nucleus (FN) to match the Allen Brain Atlas convention. Tracer injections in vermal regions of the cerebellum confirmed preferred projections toward these subregions (H. Fujita et al., 2020a). Fear conditioning experiments also show that FN plays a role in animal reactions (Koutsikou et al., 2014). We also changed the Purkinje cell (PC) of the original figure to cerebellar cortex (CBx) to integrate the rest of our canonical circuit.
- Second, we corrected the connection between the DCN and the IO, which was excitatory in both directions. However, this is not consistent with established physiology, as the projection from DCN to IO is inhibitory, while the projection from IO to DCN is excitatory, originating from the climbing fiber branches (Best & Regehr, 2009; De Zeeuw et al., 1998).
- Third, it must be noted that our canonical circuit currently does not have the excitatory connection between DCN and the CBx (see Figure 2.9). However, DCNp neurons' axons branch to generate recurrent mossy fibers, effectively exciting the CBx (Z. Gao et al., 2016).

The freezing signal is known to pass through the vIPAG, and the experiments from (Lawrenson et al., 2022) show that this signal takes the form of bursts of activity (see panel d in Figure 3.5). Moreover, the model of (Paci et al., 2023) suggests a direct transmission of the freezing signal from vIPAG to the IO nucleus. This is done via direct axonal projections that are present in the Allen Mouse Brain connectome (Oh et al., 2014) (Figure 3.6, to see an updated interactive online exploration with injection sites in the brain stem - cerebellar region, consult (*Reference Atlas :: Allen Brain Atlas: Mouse Brain*, 2011)). Thus, the vIPAG is most likely to be responsible for transmitting the US signal to the olivocerebellar circuit during fear conditioning. As for the Eye-blink simulation, this US signal is represented as a burst activity from IO, which would suggest an excitatory connection between vIPAG and IO (yellow line in Figure 3.5)

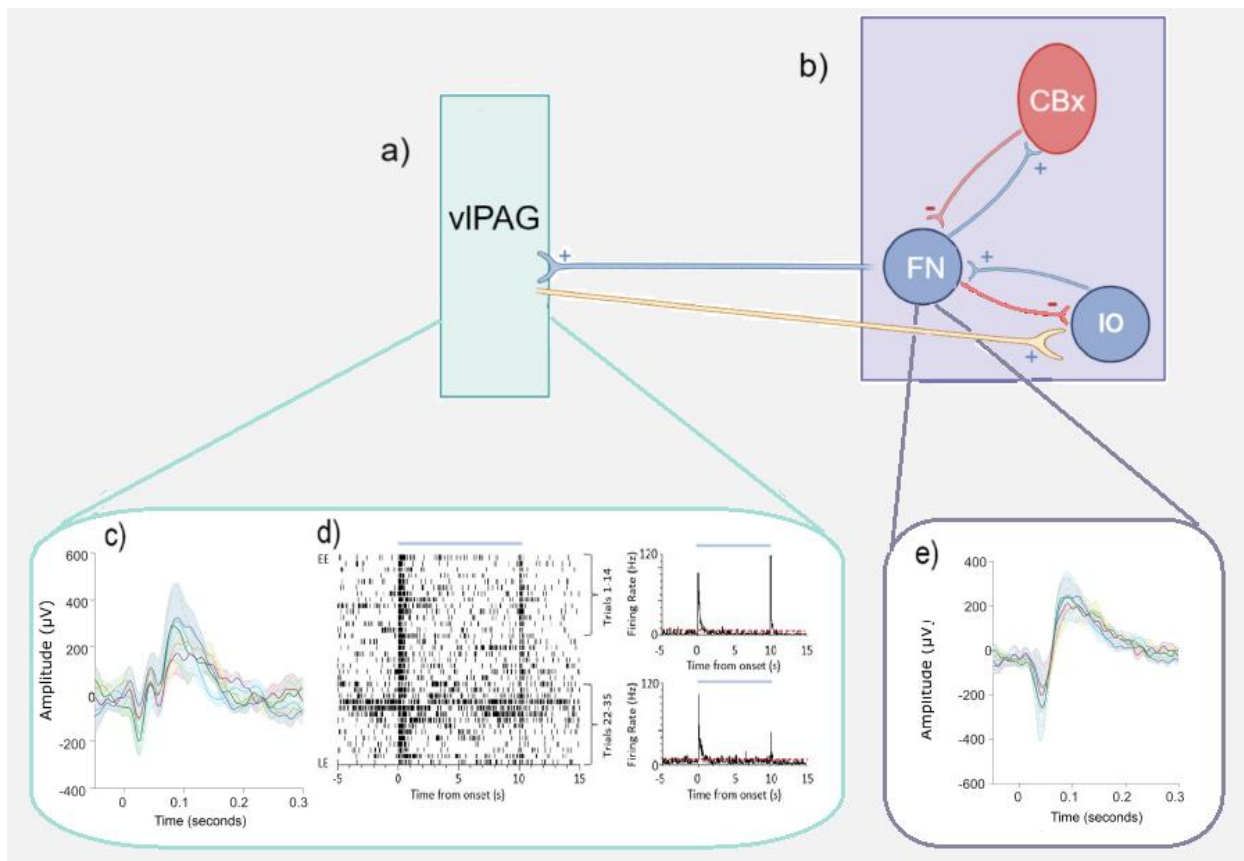


Figure 3.5 Cerebellar-PAG Connectivity Model hypothesis. We illustrate here our theoretical model of how the fastigial nucleus (FN) regulates freezing behavior through projections to the ventrolateral periaqueductal gray (vIPAG). FN receives excitatory input from the inferior olive (IO) (blue line) and inhibitory input from the cerebellar cortex (CBx) (red line). FN sends inhibitory feedback projections back to the IO (red line) and excitatory projections to CBx (panel b). Projections from the FN target vIPAG (excitatory connections). A connection from vIPAG to the cerebellum via IO (yellow). Neural dynamics from vIPAG recording (panels c and d) and FN recording (panel e). Modified from (Lawrenson et al., 2022; Paci et al., 2023)

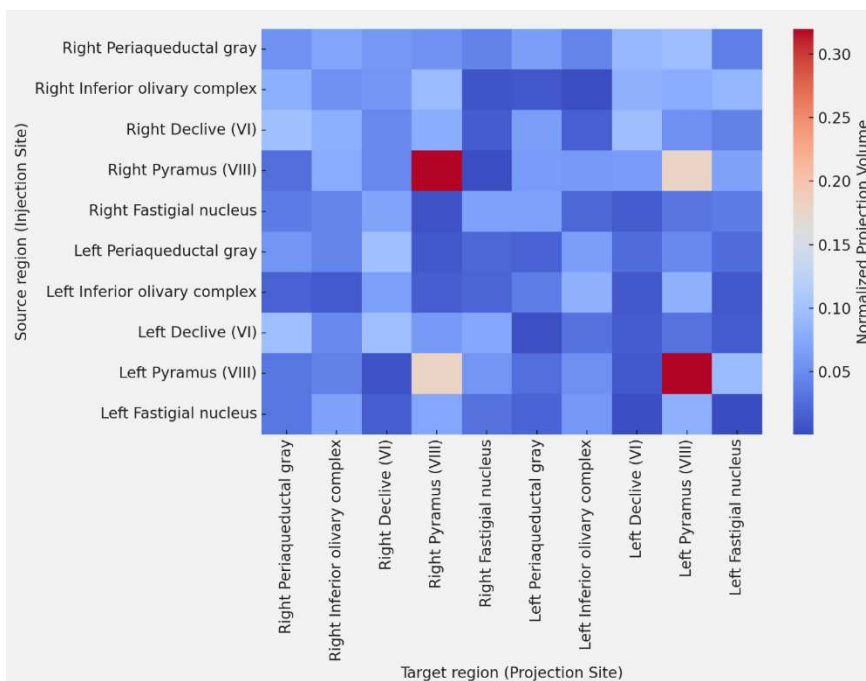


Figure 3.6 Structural connectivity heatmap based on data from the Allen Mouse Brain Connectivity Atlas (Connectivity Data in Mice, n.d.; Oh et al., 2014). The matrix displays the normalized projection volume between source (injection) and target (projection) brain regions, reflecting the density and spatial extent of anterogradely labeled axonal projections. These values represent mesoscale anatomical connectivity and do not imply physiological or functional connectivity.

We hypothesize that this signal is integrated by the cerebellum, as shown in experiments by (Sacchetti et al., 2009), which will learn the contextual fear paradigm of the experiment and effectively predict the delays between the CS and the US, as in Eye-blink conditioning (Geminiani A et al., 2024) (see our updated circuit in Figure 3.7). Fear conditioning experiments on rodents show that sound cues used as CS are most likely integrated by the vermal regions, including the Declive, coming here from mf (Doublier et al., 2023).

The output of the cerebellum integration is transmitted in turns to the FN, which will likely participate in motor control, or in this case, the freezing of the animal. This hypothesis is supported by the recording of the FN in (Paci et al., 2023) which is similar to the activity of our DCNp population in a similar situation: a pause followed by a burst (see Figure 3.9). Lesion experiments of the vermis, including Declive, show a deficit in evoked freezing to predators in rodents (Supple et al., 1987).

However, Declive might not be the only cerebellar region involved. For example, (Koutsikou et al., 2014) demonstrated that lobule VIII (Pyramus) receives input from the vIPAG via climbing fiber pathways, suggesting a potential role in modulating freezing behavior. While their recordings in anaesthetised rats showed responses primarily in lobule VIII, the absence of responses in other vermal regions does not exclude their involvement. It is possible that additional pathways exist, perhaps weaker or primarily mediated by mossy fibers, which are typically suppressed under anaesthesia. Further support for a functional link comes from anatomical data showing connections from lobule VIII to vIPAG via the inferior olive and fastigial nucleus (Vaaga et al., 2020).

This would indicate that the lobules VI and VIII are most likely both integrating the CS and US signals from fear conditioning experiments, but that their function differs.

While Koutsikou et al. suggest that stimulus of the vIPAG evokes response in Pyramus and different other vermal lobules of the cerebellum, it is not clearly stated that Declive is one of them. It is, however, most likely that the same US signal is transmitted from IO to both lobules. Some recordings in IO show that its neurons can even create gap junctions to synchronize input going to different lobules (Best & Regehr, 2009; De Zeeuw et al., 1998). Similarly, it is difficult to predict if these lobules receive the CS from the same origin. mf morphological reconstructions from Pons show that these cells' axons can indeed branch to reach distinct locations in the cerebellum (H. S. Wu et al., 1999).

In (Paci et al., 2023) the authors hypothesize that the excitatory neurons of the FN were also signaling back the result of their integration back to the vIPAG. This corresponds to direct synaptic connections, as was shown in experiments from (Frontera et al., 2020) and (Vaaga et al., 2020) projecting to most likely all populations of vIPAG. All these papers suggest that the cerebellum plays a role in fear learning by generating a "freeze prediction signal," which might be used by the animal to brace (freeze) before receiving the US. This would also mean that the cerebellum is capable of learning the coincidence of events that are separated by a couple of seconds (corresponding to the timing of fear conditioning protocol), which was not yet achieved by state-of-the-art cerebellar models. We would have to recalibrate the long-term plasticity rules using proper kernels with eligibility traces tuned on fear-stimuli temporal relationships, which we lack at the moment for both lobules involved.

Conversely, if the US signal is not received after the delay predicted by the cerebellum, then the signal will be used to stop the freezing behavior. This is why the cerebellum's function in fear conditioning was usually elicited in fear extinction and defensive behaviors.

However, little is known about the cerebellum's role in the control of movement during freezing. It is well known that DCN projects to regions (from the brain stem or spinal cord) that control muscles directly (Sathyamurthy et al., 2020). While the vIPAG stimulus (Koutsikou et al., 2014) seems to elicit alpha-motoneurons excitability, which are recruited during freezing; it is not clear how this signal is combined with DCN output. With the current circuit, the freezing signal originating from the vIPAG would have to pass through the IO and the cerebellum and be integrated and learned to produce a correct freezing signal in FN. Light stimulus experiments in glutamatergic neurons in vIPAG in mice induce strong freezing behavior (Tovote et al., 2016). This would indicate that the vIPAG signal is shutting down any ongoing movement, in turn any motor control induced by the cerebellum, and therefore shunting or forcing the activity of the output of the cerebellum, here FN.

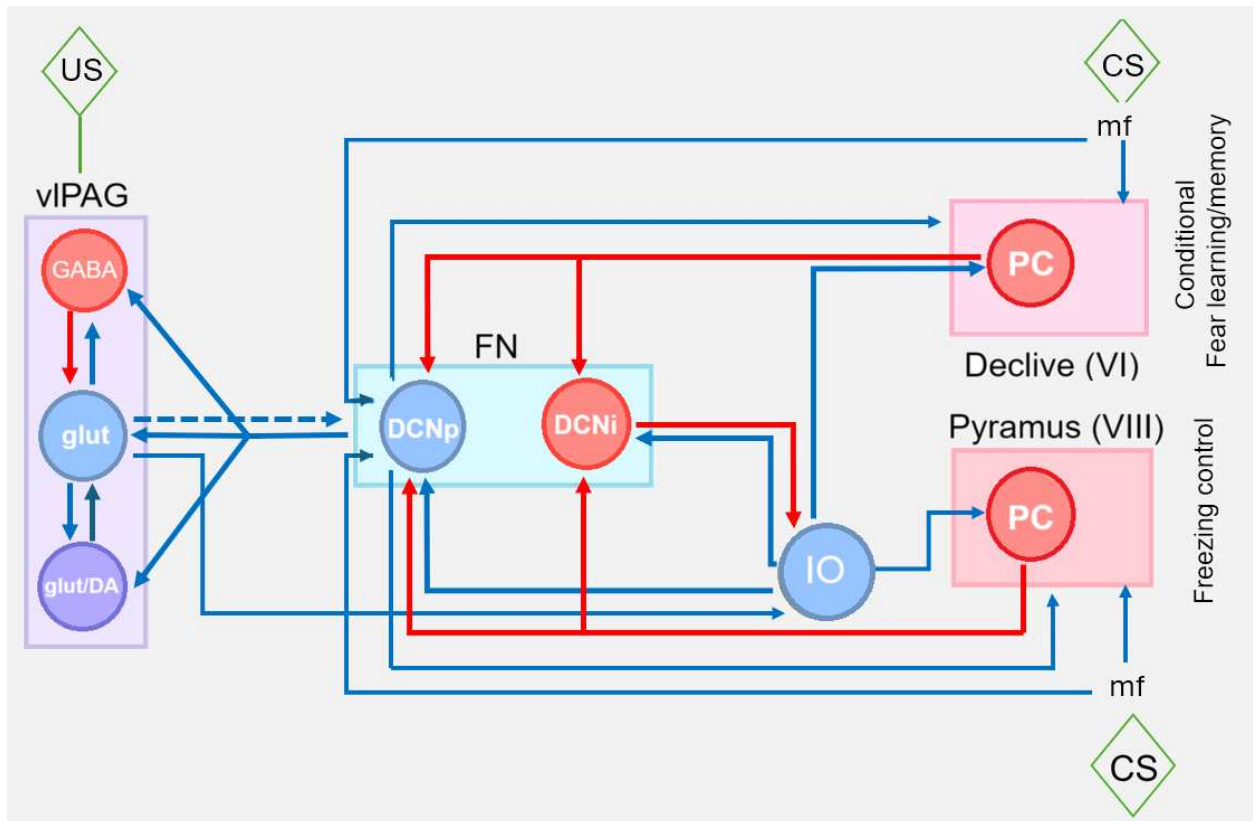


Figure 3.7 Hypothetical model of the vIPAG and Olivocerebellar circuit for fear conditioning experiments. Regions are represented as filled rectangles, and the neural populations as circles. Connections between neural populations or regions are represented as arrows. Colours depict the type of neurons and their efferent connections: blue for excitatory, red for inhibitory, and purple for modulatory. The stimuli of the circuits (CS and US) are represented as green diamonds. Our hypothesized connection between vIPAG and FN is shown as a dotted line.

If we assume that the vIPAG is directly connected to FN, then most likely the glutamatergic population of vIPAG sends its signal directly to the DCNp population (FN) as we show in Figure 3.6 (blue dotted line). While this hypothesis must be confirmed by experimental data that we are currently lacking, this would indicate that the freeze signal originates either from the vIPAG in unexpected situations or from the cerebellum during predicted situations. To test this hypothesis, we would need to simulate both the cerebellum circuit and the vIPAG under different fear conditions (CS + US or just US).

Unfortunately, it is difficult for us to produce a meaningful circuit of the vIPAG without the required data on its internal cellular composition, connectivity, and electrical parameters. We are also lacking experimental data on co-recording these regions during the whole protocol of fear conditioning to validate our model.

Section 3.3 Analysis and Results

3.3.1 Simulation-based analysis of CS-US induced activity

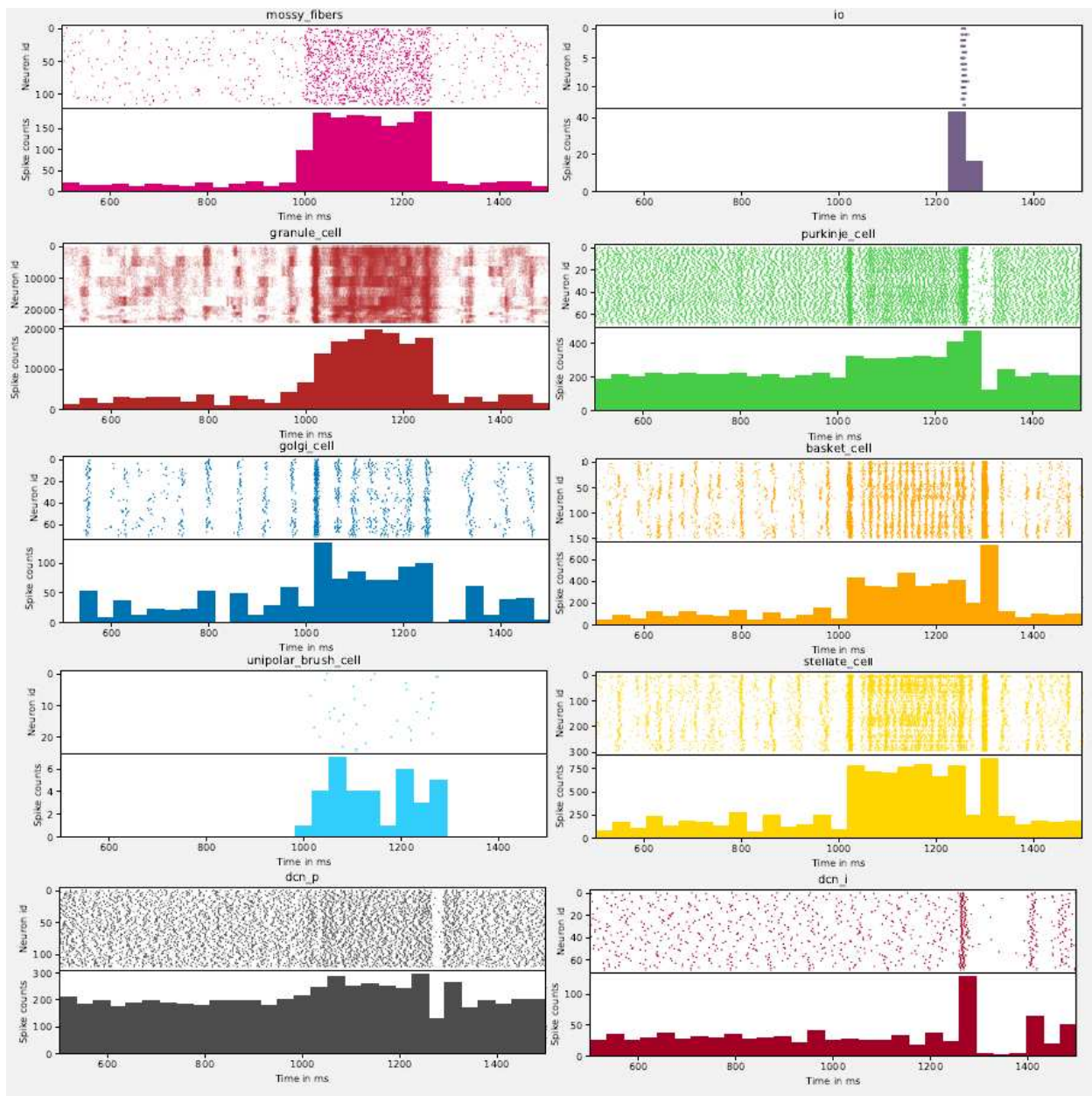


Figure 3.8 Raster plot. Spike times along the 2-s of the simulation, as well as the equivalent Peri-Stimulus Time Histogram (PSTH) for each of the cell types (spike counts)

From figures 3.7 and 3.8, we can see that GrC, GoC, and UBC activity are mostly driven by the mf stimulus, which results in an increase of their firing rate in the 1200-1250 windows. PC, BC, and SC activity are driven by mf and IO stimuli, showing an increase after each stimulus. IO has more impact on PCs and BCs. Finally, DCN shows interesting patterns: DCNp shows a pause and burst directly from the mf and IO stimulus. This is because PCs first inhibit the IO signal before they pause, leaving DCNp having a rebound burst. On the other hand, DCNi shows burst and pause as it is solely driven by the IO stimulus and partially inhibited by PC.

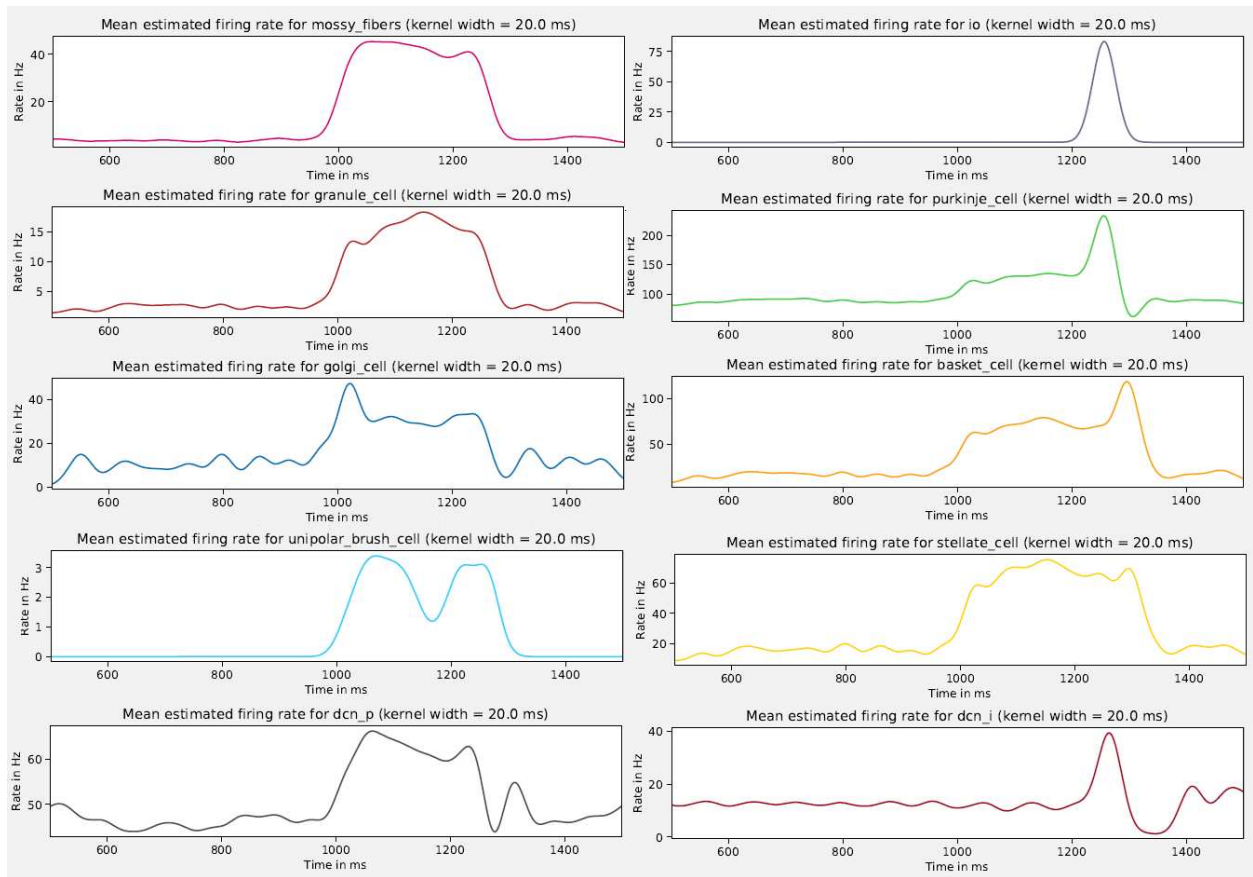


Figure 3.9 Firing rates. Mean instantaneous (time bin 20 ms) firing rate $\lambda(t)$ of each population

Section 3.4 Discussion and Conclusions

We successfully modeled neuronal responses to Pavlovian conditioning, validating the model's suitability for simulating associative learning processes. Although the model could not be directly extended to fear conditioning due to limited experimental data, clear hypotheses were outlined for adapting synaptic plasticity rules to reflect the specific dynamics of emotional learning. Given the shared underlying mechanisms between both forms of learning, such adaptations appear feasible through targeted modifications at the synaptic level.

Moreover, we grounded our hypothesis on the main cerebellar theories and available data. The theories on the background can be summarised in some major statements.

First, the cerebellum is needed, in a given behavioral context, to learn to predict the precise timing of correlated events (e.g., see (D'Angelo & Casali, 2013)). In our case, the CS precedes the US. Once learning has occurred, the behavioral response is released upon CS arrival, even before the US. This would prevent a fearful (and therefore potentially noxious stimulus) from causing harmful consequences.

Secondly, the cerebellum is always assisted by pre-cerebellar centers and circuits, in this case, the PAG. The general architecture is made of loops connecting the brain stem to DCN (short loop) and cerebellar cortex (long loop). When an action is going to be executed, the precerebellar loops set up an intense activity, and the cerebellar loop, by giving a precisely timed command, can eventually trigger the behavioral response. This is exactly the architecture that emerges from the PAG-DCM-CBx in Figures 3.5 and 3.7.

Unfortunately, it is difficult at the moment to elaborate a detailed PAG-DCM-CBx circuit because some data are incomplete. 1) PAG internal cellular composition, connectivity, and electrical parameters are not fully resolved. 2) We are also lacking experimental data co-recording of these regions during the whole protocol of fear conditioning. Nonetheless, a specific property of the model is just to help indicate the direction of the experimental exploration in the case of incomplete data. To this aim, the model can be used to explore the parameter space of missing data, generating mechanistic predictions. For example, some model branches may be needed, while others may be redundant to achieve an effective fear conditioning simulation. For instance, the

internal PAG circuit could be embedded with self-calibrating learning rules and be tested for different internal weight configurations. And validation could be done against different dataset, e.g., taken from high-field fMRI. Therefore, we foresee that the PAG-DCM-CBx model will soon be implemented and simulated interactively with data collection in companion laboratories to generate principled hypotheses on how the cerebellar circuit intervenes in fear conditioning.

➤ Study limitations

- One limitation of this work was the lack of parameters for Pavlovian conditioning simulations in NEST with synaptic plasticity (short and long-term). Developing and integrating the necessary plasticity mechanisms under this updated framework requires additional time for coding, testing, and optimization. This technical adjustment represents the main task to be addressed in future work.
- The lack of sufficient experimental data to validate and/or adjust the model prevented its complete implementation. Having specific empirical data will be key to improving and validating the model in the future. This highlights the importance of having more detailed experimental records to better understand the role of the cerebellar cortex in the fear circuit and to more effectively guide the next steps in research.

➤ Future directions

- Adjustment the parameters to replicate similar patterns in the Declive subvolume: We have obtained promising results with the canonical circuit, but our primary focus is on the lobule VI. Therefore, it is necessary to fine-tune all the parameters to ensure that the Declive exhibits the same behavior as observed in the canonical model.
- Implementation of plasticity rules in the cerebellar circuit: To better reflect the neurophysiological mechanisms underlying fear conditioning, exploring the role of the cerebellum in this process is a key direction. As we explained before, incorporating these dynamics will enable more precise modeling of fear adaptation and extinction, providing insights into how synaptic plasticity in the cerebellum regulates emotional responses under changing conditions.
- Expansion of the model to key fear processing regions: Extend the model beyond the cerebellar cortex to include cerebellar output to key regions, such as the vIPAG (to explore its role in freezing behavior) as we explained before, the VTA (to examine its involvement in reward prediction error) is valuable. Additionally, incorporating the mediodorsal thalamus (MD) and the lateral parabrachial nucleus will allow us to model their roles in fear extinction and memory consolidation, respectively.
- Development of a parallel multiscale co-simulation: To study the fear network, a promising approach would be to implement co-simulations (Kusch et al., 2024), combining detailed cellular-level modeling with large-scale network dynamics. This would involve simulating the cerebellar microcircuit using NEST to explore synaptic plasticity and modeling the broader fear network using The Virtual Mouse Brain (Meloizzi et al., 2017) to examine how cerebellar output influences key regions. This co-simulation framework could provide valuable insights into the cerebellum's role in emotional processing and corresponding brain dynamics.
- Experimental validation and refinement of the model: Improving the model's accuracy and predictive power will require validation with experimental data. Greater availability and sharing of data will be essential to ensure that the simulated dynamics accurately reflect biological processes.

Supplementary material

Table S3.1.1 Comparison of fear conditioning paradigms across species		
Aspect	Rodents	Humans
Conditioned Stimuli (CS)	Auditory tones, lights, olfactory cues, context (e.g., environment, cage)	Mostly visual (e.g., shapes, lights, faces), occasionally auditory; interoceptive stimuli (e.g., CO ₂ inhalation, breathing loads) used in specific paradigms (e.g., panic, dyspnea). Tactile stimuli are rarely used
Unconditioned Stimulus (US)	Foot shocks (fixed intensity, not calibrated, non-escapable)	Individually calibrated electric shocks, loud noises, and interoceptive stimuli (e.g., respiratory loads, balloon distension)
Contextual Conditioning	Strong, context often acts as the main CS	Present but more complex (includes spatial, temporal, interoceptive, cognitive, and social context; sometimes via Virtual Reality)
Acquisition Phase	CS–US pairing in delay or trace protocols; includes contextual and cued paradigms	Pre-acquisition calibration/familiarization; CS+ paired with US; CS– unpaired (differential)
Extinction Phase	Repeated CS presentation without US; assesses new learning (not memory erasure)	Similar, but often includes variations like immediate/delayed extinction, multi-context extinction, gradual extinction
Return of Fear	Spontaneous recovery, renewal, reinstatement observed across contexts	Same manipulations: spontaneous recovery, renewal, reinstatement, rapid reacquisition
Session Design	Multi-day experiments with clear phases, often allowing consolidation	Mostly single-day, but multi-day becoming more common, especially for extinction retention
Reinforcement Rate	100% or partial pairing of CS-US	Similar; Continuous (100%) or partial (<100%) pairings of CS+ and US
Trial Structure	ITI: 30–300s; ISI: 200ms to 20s depending on delay/trace	ISI/ITI vary by goal; CS: 4–8 s; 5–20 trials per CS type; CS+/CS– presented in pseudo-random order with matched frequencies
Population	Inbred or littermate rodents; controlled environments	Typically healthy volunteers (e.g., students), sometimes clinical samples; high variability
Outcome Measures	Freezing, avoidance, bar pressing, startle, electrophysiology	Skin conductance (SCR), fear-potentiated startle (FPS), fMRI, EEG, verbal and affective reports

Table S3.1.2 Comparison of the function and interconnectivity of brain regions in fear conditioning across species

Brain Region / System	Rodents	Humans
Amygdala	Central hub for fear learning; lateral amygdala (LA) forms CS–US associations; central amygdala (CEA) mediates output via CEI/CEm microcircuits; modulated by interneurons (PV+, SOM+).	Encodes CS and regulates fear expression; lateral and basal amygdala active during acquisition; central amygdala connected to brainstem/hypothalamus; differential lateralization in generalization; integrates fear and reward processes.
Hippocampus	Dorsal hippocampus encodes spatial/contextual cues; ventral hippocampus modulates fear generalization and anxiety; projects to amygdala and PFC.	Supports context-dependent acquisition and extinction; parahippocampal gyrus differentiates safety vs. threat; predicts fear renewal; interacts with vmPFC.
Prefrontal Cortex (PFC)	Prelimbic (PL) facilitates fear expression via amygdala; infralimbic (IL) critical for extinction via intercalated cells; PFC-amygdala 4 Hz synchrony correlates with freezing.	vmPFC stores safety memory and inhibits fear; dmPFC involved in renewal and generalization; dlPFC supports cognitive control; OFC resolves ambiguity and updates threat/reward expectations.
Cingulate Cortex (ACC, PCC)	ACC integrates contextual and emotional cues; interacts with hippocampus and retrosplenial cortex.	Rostral ACC regulates emotion; caudal ACC linked to autonomic responses; subgenual ACC engaged in extinction; PCC involved in extinction recall.
Insula	Less emphasized; contributes to interoceptive fear and emotional salience.	Anterior insula integrates interoception and emotion during acquisition/generalization; posterior insula linked to implicit generalization; strong activation during extinction recall.
Thalamus	Sensory relay to amygdala (MGN for auditory, LGN for visual); PVT modulates long-term fear expression via CEA.	Pulvinar and dorsomedial nuclei transmit sensory input; anterior and medial thalamus activate during extinction; pulvinar supports threat ambiguity processing.
Striatum & Ventral Pallidum	Not typically central in rodent fear conditioning paradigms.	Ventral striatum codes threat expectancy; putamen active in late extinction; nucleus accumbens supports reward processing and safety learning.
Periaqueductal Gray (PAG)	vlPAG mediates freezing; dPAG controls escape; receives input from CEA and cerebellum; key output of fear circuit.	Coordinates defensive motor responses; reactivated during fear renewal; connects with locus coeruleus and hypothalamus.

Brainstem and Locus Coeruleus	Parabrachial nucleus relays US to amygdala; inferior olive supports error signaling and bradycardia; ZI modulates cerebellar threat response.	Locus coeruleus regulates arousal; septal-hypothalamic area active in extinction recall; PAG and LC modulate autonomic fear responses.
Sensory Cortices	Auditory and visual cortices process threat-relevant sensory input; superior colliculus supports rapid detection.	Strong engagement of visual, auditory, and somatosensory cortices during acquisition and extinction; fusiform gyrus activated in visual paradigms.
Cerebellum	Deep cerebellar nuclei (interposed, dentate, fastigial) regulate acquisition, consolidation, extinction, and freezing; lobules V-VI and VIII modulate fear motor/autonomic output; interacts with amygdala, PAG, thalamus, VTA, and PFC.	Lobules VI, Crus I/II and vermis active during acquisition and extinction; tracks prediction errors and context changes; modulated by US type and reinforcement rate; supports fear generalization, extinction recall, and ambiguity resolution.
Orbitofrontal Cortex (OFC)	mOFC impairs fear extinction and discrimination under threat ambiguity; IOFC enhances fear under uncertainty.	mOFC codes reward value; IOFC updates threat/reward expectations and ambiguity processing during renewal.
Others (Retrosplenial, Entorhinal, Septum, etc.)	Retrosplenial and postrhinal cortices process contextual fear; entorhinal cortex aids in consolidation; lateral septum and zona incerta modulate threat.	Retrosplenial and PCC involved in extinction recall and contextual processing; septal-hypothalamic region regulates safety learning.

Table S3.1.1 compares fear conditioning paradigms in rodents and humans, based on the procedural elements summarized in Tables 3.1 and 4.1. The table highlights key methodological differences across species, such as stimulus types, outcome measures, trial structure, and the degree of experimental control. Rodent paradigms typically involve foot shocks and behavioral readouts (e.g., freezing), while human studies employ calibrated aversive stimuli and integrate physiological, verbal, and cognitive measures. These differences, along with variability in session design and participant characteristics, can limit direct comparability and must be accounted for when interpreting translational findings.

Table S3.1.2 was constructed by integrating and distilling the neural structures and functional roles described in Tables 3.2 (rodent fear network) and 4.2 (human fear network). It compares the function and interconnectivity of brain regions involved in fear learning and expression across species. Both rodents and humans share a core fear circuit—including the amygdala, hippocampus, prefrontal cortex, and periaqueductal gray—with analogous roles in acquisition, extinction, and fear generalization. However, the human circuit is further characterized by broader cortical integration, including regions like the dorsolateral prefrontal cortex, anterior insula, and striatum, as well as greater lateralization and modulation by social and cognitive factors. These comparisons illustrate both the translational strengths and the limitations of cross-species modeling in affective neuroscience, reinforcing the need for careful interpretation when extrapolating results across experimental systems.

Chapter 4: Fear Conditioning modeling in humans

Section 4.1: Introduction

This chapter presents a parallel approach focused on human data and large-scale modeling, aiming to explore the cerebellum's contribution to emotional learning through fear conditioning paradigms. Unlike the bottom-up strategy applied to rodents in the previous chapter, here we adopt a top-down perspective grounded in non-invasive neuroimaging and computational simulation. The primary objective remains the same: to investigate the cerebellum's role in affective processing, this time using human data and modeling at the macroscale level.

We begin by introducing the value of neuroimaging and biophysical modeling for the study of human fear conditioning, emphasizing how tools such as fMRI and The Virtual Brain (TVB) can bridge the gap between observed behavior and underlying network dynamics. A detailed overview of the fear conditioning paradigm in humans follows, including its behavioral, cognitive, and physiological components, with special attention to the skin conductance response (SCR) as a biomarker of autonomic arousal.

To ground our modeling strategy, we next describe the functional architecture of the human fear network, based on an extensive review of the literature. Within this network, we give special emphasis to recent findings that highlight the cerebellum's engagement in different phases of fear learning, acquisition, extinction, generalization, and renewal. With this background in place, we describe how TVB can be used to model large-scale human brain activity based on subject-specific resting-state fMRI and diffusion MRI data. Although no task-related fMRI is modeled here, due to current limitations in both TVB architecture and data availability, we use a network derived from fear-related regions to simulate resting-state dynamics. Furthermore, we incorporate SCR data acquired during an independent fear conditioning task in the same subjects, allowing us to explore correlations between behavioral responses and model parameters.

The methods section details the complete workflow—from data acquisition and preprocessing to connectivity mapping, model construction, and parameter optimization. In the results section, we evaluate model performance across structural, functional, and dynamic levels and explore how subject-specific connectivity relates to SCR-based indices of fear learning and extinction.

Finally, the chapter concludes by highlighting key limitations and outlining concrete future directions. Taken together, this work opens a promising new avenue for integrating empirical and computational research on fear processing in humans, providing a robust foundation for personalized models of cerebellar involvement in emotional behavior

4.1.1 Neuroimaging and modeling in the study of human fear conditioning

At the microscopic level, the fear conditioning data come mainly from rodent studies, where, in general, the activity of individual neurons and specific synapses is recorded using techniques that allow for the acquisition of highly detailed data (McGuire et al., 2012; Quilfeldt, 2016). In rodents, indeed, the use of invasive techniques allows the availability of multiscale data. Conversely, in humans, access to neuronal and microcircuits' direct data is limited by ethical and technical restrictions, making macroscopic approaches the primary means of gaining knowledge about the human brain (Poldrack & Farah, 2015)

The study of the human brain has advanced enormously thanks to the development of non-invasive neuroimaging and neurophysiology techniques (Nusslock et al., 2015), such as electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET).

These tools make it possible to analyze brain activity at the macroscopic level, providing a global view of the dynamics of large neuronal populations and their interaction within whole-brain networks. However, the integration of different neuroimaging modalities presents challenges (Botvinik-Nezer & Wager, 2023), as each technique offers measurements with distinct neurophysiological origins and signal characteristics.

In this era of integrative neuroscience, computational models have become an essential component of human neuroimaging research, providing both mechanistic insights and predictive tools for understanding cognition and behavior (Loosen et al., 2024). To simplify the brain's complexity, enhance data interpretation, and elucidate the relationships between anatomical structures and brain function, researchers use data-driven methods (grounded in biological data),

top-down techniques (inferring hidden causes from aggregate observations), and inverse strategies (deducing causes from observed effects). These models allow for the reconstruction of neural dynamics, with applications ranging from characterizing neurobiological and cognitive processes to developing artificial brains, brain-machine interfaces, and neuroprosthetics (D'Angelo & Jirsa, 2022).

Within biophysical modelling (Murray et al., 2018; Ramezani-Panahi et al., 2022), a key approach for realistically representing brain activity at various levels of detail, mean-field models play a crucial role at the neuronal population level, offering significant advancements in the field (Bojak et al., 2010). Rooted in statistical physics, the mean-field approximation reduces complexity by averaging over degrees of freedom, which, in the neural context, correspond to the activity of individual neurons.

Mean-field models of neuronal activity fall into two main categories: neural mass models and neural field models (Pinotsis et al., 2014). The key distinction lies in their treatment of temporal and spatial dynamics: neural mass models evolve only in time, assuming that all neurons in a population are located at the same point, whereas neural field models extend this framework by incorporating both time and space, allowing for the tuning of spatial parameters such as the distance between cortical columns. Neural mass models can distinguish contributions from different neuronal populations by adjusting physiological parameters, such as postsynaptic response modulation, making them useful for studying local network interactions. In contrast, more general mean-field models provide a statistical summary of large network activity without explicitly resolving distinct neuronal populations, often relying on parameters that are not necessarily tied to specific physiological properties (Byrne et al., 2020; Pinotsis et al., 2014).

These models are applicable across multiple scales, from neuronal subpopulations to the whole brain, making them fundamental tools for a wide range of research. Their flexibility and generalizability have led to their widespread use in large-scale *in silico* brain simulations, particularly in biologically realistic frameworks such as The Virtual Brain (TVB).

Incorporating these models into platforms like TVB represents a major advancement in large-scale brain simulations by leveraging biologically realistic structural connectivity. TVB integrates concepts from theoretical, computational, and clinical neuroscience to infer neurophysiological mechanisms across various brain scales, generating neuroimaging signals such as EEG, MEG, and MRI (Ritter et al., 2013; Sanz Leon et al., 2013; Sanz-Leon et al., 2015).

Unlike traditional simulations that focus on individual neurons or synapses, TVB captures the dynamics of the entire brain by considering both the spatiotemporal structure of brain connections and the intrinsic properties of brain regions. These regions, represented as network nodes governed by mesoscopic models, including neural mass models, neural field models, and mean-field models, simulate local neural activity. The connections between nodes, weighted and time-delayed based on anatomical data, add biological realism, enabling more accurate predictions of large-scale brain dynamics.

TVB's architecture also enables personalized simulations using individual patient data, facilitating the study of how anatomical variations, both normal and pathological, affect brain activity (see as examples Aerts et al., 2018; Angiolelli et al., 2024; Bernard & Jirsa, 2016; Falcon et al., 2016; Jirsa et al., 2023; Martí-Juan et al., 2023; Monteverdi et al., 2023). This modeling approach has improved understanding of brain dynamics and opened new avenues for clinical research and the development of innovative technologies in neuroscience. Its potential for understanding the functional organization of the brain and improving treatments continues to expand.

A novel application of biophysical modeling within the TVB framework is its use in studying fear conditioning in humans. Unlike traditional rodent-based models, human fear conditioning research relies on functional magnetic resonance imaging (fMRI) to capture the large-scale neural dynamics underlying these processes (Büchel & Dolan, 2000; Sehlmeier et al., 2009a). Recent neuroimaging findings have increasingly highlighted the cerebellum as a crucial node in fear learning and extinction (Batsikadze et al., 2022; Batsikadze G et al., 2024; Doubriez et al., 2023; T. M. Ernst et al., 2019; I. Lange et al., 2015), extending its role beyond motor control to higher-order cognitive and emotional functions.

Incorporating fMRI-derived connectivity data into TVB's mesoscopic neural models allows simulation of interactions between key structures involved in fear regulation and assessment of their contributions to the persistence or attenuation of conditioned fear responses. This approach

provides a biologically plausible bridge between experimental and clinical research, offering novel insights into the neural mechanisms of fear and its dysregulation in certain disorders.

In this chapter, we present a proof-of-concept study exploring the use of TVB to investigate emotional behavior through fear conditioning data, establishing a solid foundation for future research. We begin with a concise overview of the fear conditioning paradigm in humans and discuss the key regions including the cerebellum's role in modulating fear responses. Our computational approach simulates neural mass activity using the reduced Wong-Wang model (Deco et al., 2014), applied to each fear-network node. Local dynamics in each brain region are modeled using this dynamic mean-field method, one of TVB's most refined and biologically plausible techniques. These local dynamics are then integrated with each subject's experimentally derived structural connectome and resting-state fMRI-based functional connectivity to generate personalized virtual brain models.

Furthermore, we investigate the correlation between subject-specific fear response, measured via skin conductance response (SCR), and subject-specific TVB parameters optimized on fear-network nodes in resting-state. To achieve this, we integrate SCR data, a well-established measure of autonomic arousal (Christopoulos et al., 2019; Constantinou et al., 2021) and perform correlation and regression analyses with TVB parameters. We observed sex-related patterns in these correlations during our analyses, which led us to further explore this aspect. This observation aligns with previously reported differences in fear acquisition and extinction across sexes (Adkins et al., 2021; Bartholomew et al., 2022; Bauer, 2023; Fleischer & Frick, 2023; Velasco et al., 2019).

This multimodal approach enables a deeper understanding of how brain-wide dynamics interact with behavioral and physiological markers, shedding light on the neural mechanisms underlying fear regulation at both cognitive and autonomic levels.

4.1.2 Fear conditioning paradigms in humans

As mentioned in section 1.1, fear is a basic and universal emotion. However, when the fear response overflows or persists in the absence of real danger, it can lead to anxiety states. This manifests in disorders such as specific phobias, anxiety disorders, post-traumatic stress disorder, panic attacks, or even compulsive behaviors aimed at alleviating irrational thoughts (Chambless & Gracely, 1989; Graham & Milad, 2011). This demonstrates how a protective mechanism can become dysfunctional and significantly impact quality of life.

Fear arises in response to immediate or imminent threats and can be triggered by different stimuli, which are classified as innate or evolutionary, learned, and social or cognitive signals. Additionally, its perception varies depending on the sensory modality, including auditory, visual, olfactory, tactile, or interoceptive pathways (Coelho et al., 2023). The processing of these stimuli can occur explicitly or implicitly (Di et al., 2021; Manassero et al., 2019). Explicit processing involves the conscious recognition of fear-related stimuli, whereas implicit processing occurs without the individual's awareness of the presence or nature of the stimulus.

The adaptive function of fear is reflected in the motivation of defensive behaviors and the rapid formation of predictive associations, as seen in Pavlovian fear conditioning. This process has been a central focus of biological psychology for decades (Bitterman, 2006). Initially, most studies were conducted in animal models, allowing the identification of cellular, synaptic, and molecular mechanisms involved in learning and memory. However, with the development of neuroimaging techniques in the early 1990s (Abraham & Feng, 2011), researchers gained a deeper understanding of these processes, opening new opportunities for translational research (Scarpazza et al., 2020).

Numerous neuroimaging studies have demonstrated the importance of fear conditioning in emotional regulation (Brooke & Harrison, 2016; Diekhof et al., 2011; Etkin & Wager, 2007; Hartley & Phelps, 2010; Sehlmeier et al., 2009a). It not only allows us to anticipate danger but also contributes to a conditioned reduction of the emotional response when the threat materializes. This mechanism is essential for maintaining a balance between reacting to danger and regulating that reaction. Furthermore, it has reinforced the idea that fear conditioning is fundamental for studying and treating mental health disorders, as it focuses on neural function rather than merely on symptomatology.

Unlike animal models, where fear is primarily measured through basic motor and physiological responses, humans exhibit more complex cognitive and social mechanisms that influence fear acquisition and extinction, these mechanisms play a crucial role in clinical therapies aimed at treating pathological fear (Melchor-Eixea et al., 2023)

Fear conditioning in humans has been studied through controlled experimental paradigms. Thanks to these advancements, researchers now have a better understanding of how neutral stimuli become associated with aversive outcomes, allowing them to identify key neural networks involved in fear regulation and its potential applications in clinical interventions.

Although each laboratory employs its own protocol for studying fear conditioning in humans, with variations in stimulus selection, experimental design, response measurement, data analysis, and ethical considerations, a generally accepted standard framework exists (see Figure 4.1 and Table 4.1 for more detail). Despite specific adaptations introduced by individual research teams, this basic structure ensures sufficient comparability across studies, facilitates the drawing of robust conclusions, and supports the development of evidence-based clinical interventions (Bach et al., 2023; Haaker et al., 2019; Lonsdorf et al., 2017).

This general framework consists of an acquisition phase, during which associations between a neutral stimulus and an aversive event are established, followed by an extinction phase, in which the neutral stimulus is presented alone to observe a reduction in the learned response (see Figure 4.1). Within these key phases, the process begins with a pre-acquisition phase, where baseline measures are established, and neutral stimuli are introduced. Specifically:

During fear acquisition training, a conditioned stimulus (CS+) is repeatedly paired with an unconditioned stimulus (US), leading to the development of conditioned responses (CR), a phenomenon known as fear acquisition. Additionally, fear generalization is assessed by exposing participants to stimuli similar to the CS+ to determine the extent of the response. In the extinction phase, the CS+ is presented without the US, allowing the formation of an inhibitory memory through extinction learning, which reduces the CR. However, through the return of fear manipulations, such as contextual changes, re-exposure to the US, or the passage of time, the conditioned response may re-emerge, demonstrating the persistence of the original memory and the complex interaction between acquisition and extinction mechanisms.

Exploring the mechanisms of fear acquisition and extinction in greater depth, new possibilities arise for addressing disorders characterized by maladaptive emotional responses. This knowledge favors the application of these findings in both clinical practice and scientific research.

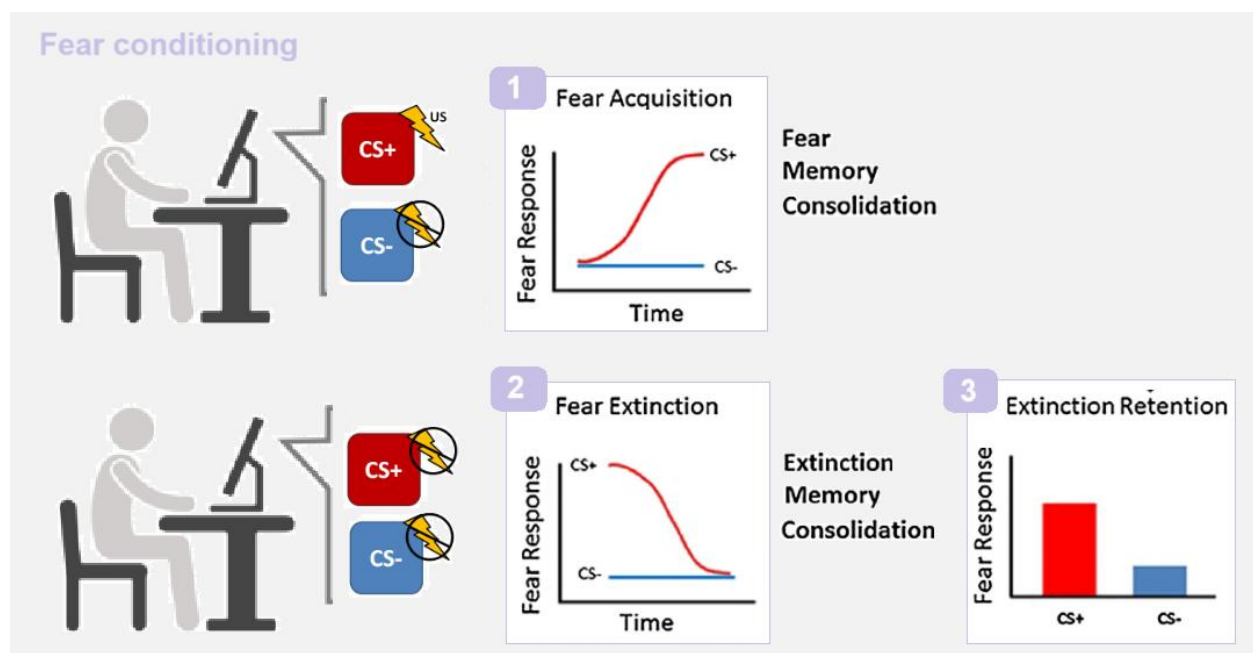


Figure 4.1 Fear conditioning paradigm in humans. Fear conditioning experiments involve participants undergoing three stages. In the first stage (Fear Acquisition), participants are repeatedly presented with a neutral stimulus (CS+), such as a shape or face, paired with an unconditioned stimulus (US) like an electric

shock or unpleasant noise. This pairing leads participants to associate the CS+ with the US, forming and consolidating a fear memory. Simultaneously, another neutral stimulus (CS-) is shown without ever being paired with the US, serving as a safety signal and controlling for non-associative responses. In the second stage (Fear Extinction), participants are exposed to repeated presentations of both CS+ and CS- without the US, allowing them to learn that these cues are safe and to consolidate new, non-fearful memories. Finally, during the Extinction Retention stage, when the CS+ is reintroduced, participants experience a competition between the original fear memory and the new safety memory, which may result in either the reappearance or suppression of the fear response depending on the circumstances.

Table 4.1 Key elements in Fear Conditioning paradigm in humans

Phases of a conditioning protocol Depend on the exact research question Mostly single day experiments with multiple day experiments becoming more popular	Pre-acquisition -US and/or CS calibration phase -A habituation/familiarization phase Fear acquisition training CS-US pairing Fear acquisition The theoretical process of CR development (<i>Mostly single session, rarely limited to a criterion, sometimes instructed about contingencies</i>) -Differential protocols (Mostly) -Single-cue protocols (Rarely) -Multiple cue protocols -Context conditioning protocols -Combined context-cue conditioning protocols Fear generalization Transfer of fear conditioned responding to a specific stimulus to stimuli resembling the original CS+ Extinction training The procedure of unreinforced CS presentation, after which the CS elicits reduced or no CRs anymore Extinction learning Takes place as soon as the first unreinforced CS+ trial is presented -Immediate extinction training -Delayed extinction training -Extinction training employing multiple contexts or cues -Gradual extinction training Return of fear manipulations -Spontaneous recovery and extinction recall protocols -Renewal protocols -Reinstatement protocols -Rapid reacquisition
Population and samples	-Usually non-related volunteers (possibly pre-selection), often student populations as healthy participants -In studies comparing clinical with healthy populations, the disorder-specific medication and the comorbidities requires special care
Stimulus type	Conditioned stimulus (CS) -Discrete exteroceptive cues: mostly visual (pictures of differently coloured lights, geometric shapes, human faces, or animals). Rarely auditory, tactile, olfactory, and taste -Proprioceptive: joystick arm movements -Interoceptive (mostly apply in pain-related and panic-related fear conditioning): respiratory loads, oesophageal balloon distension, and inhalation of CO2-enriched air Contextual stimuli Spatial, temporal, interoceptive, cognitive, and social aspects in experimental scenarios. Sometimes change between experimental phases -Computer background screens -Room illumination -Odours -Different physical rooms

	-Virtual reality paradigms Unconditioned stimuli (US) - Electrical stimulation to finger, wrist or shin, that is individually calibrated -Aversive tones: loud (white) noise, pure tones or human screams -Visual: pictures from the International APS* or socially relevant film-clips with critical comments -Interoceptive: dyspnea induced through respiratory loads, breathing occlusion, oesophageal balloon distension, CO₂ inhalation, painful rectal distension, and painful heat stimuli
CS/US timing and duration	-Delay conditioning procedure: the CS begins before the presentation of the US and continues at least until US onset -Trace conditioning procedure: the US occurs after a certain time interval after CS offset -CS duration encompasses several seconds (4, 6, or 8s), it depends on the modality -US duration depends on US modality (dependent on how long the stimulus needs to be presented to have sufficient unconditioned impact)
Interval, number, order	trial and Intertrial interval (ITI) The time elapsing between the end of one trial (indicated by stimulus offset, which might be CS or US offset) to the start of the next CS trial (CS onset) Inter-stimulus interval (ISI) Interval between CS onset and US onset -Depend critically on the outcome measure of interest -The ISI/ITI ratio should also be considered -ITI durations should not be shorter than the CS duration to avoid backward conditioning Number of trials -Between 5 and 20 CS trials (the number of presentations is set to be equal for conditioned stimulus (CS+) and control/non-conditioned stimulus (CS-)) -During extinction, the number of trials is a primary determinant of CR decrement -In retention tests, only a smaller number of trials are needed CS+ and CS- trial order - Pseudo-random series of CS presentations (no more than two consecutive trials of the same stimulus), and the CS+/CS- proportion is held constant within blocks of trials
Reinforcement rate The probability of US occurrence in the presence of the CS	-100% continuous pairing -In a smaller number of trials only (partial reinforcement <100%)
Outcome measures	Physiological -Electrodermal activity (Skin conductance responses (SCRs))** -Eye blink (Fear-potentiated startle (FPS) reflex) -Heart rate (less frequently) -Pupillary response (less frequently) Neurobiological Blood-oxygen-level-dependent (BOLD) -EEG -MEG -fMRI Verbal report -Cognitive (ratings of CS-US contingencies or 'risk')

	-Affective (ratings of valence, arousal, fear/anxiety, and liking associated with a CS) components General analysis -Multiple outcome measures -Multiple day paradigms -Statistical quantification -Performance-based exclusion of participants -Correcting for preceding within-session performance -Definition and treatment of zero-responses and missing values -Considering temporal dynamics
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*APS Affective Picture System (Bradley & Lang, 2017)

**Among the various physiological measures used in fear conditioning research, we will briefly describe the Skin Conductance Response (SCR), as this measure is used later in our study.

This table was compiled in an effort to organize and summarize the available information. However, it should not be considered definitive, as there may be inaccuracies or variations depending on specific experimental conditions and interpretations.

➤ Skin Conductance Response (SCR)

SCR is a phasic electrodermal response that reflects autonomic nervous system activation, primarily regulated by the sympathetic nervous system. It occurs due to sweat secretion from eccrine glands, predominantly found in the palms and soles, which increases skin conductance. SCR is widely used as a biomarker of emotional arousal, cognitive processing, and attentional engagement (Christopoulos et al., 2019; Constantinou et al., 2021)

In fear conditioning experiments, SCR follows a predictable pattern across different phases (Christopoulos et al., 2019):

- Acquisition Phase: A conditioned stimulus (CS+) is repeatedly paired with an unconditioned stimulus (US) (e.g., an aversive sound), leading to increased SCR as the subject learns to associate CS+ with the US. The response to the control stimulus (CS-), which is not paired with US, remains low.
- Habituation: Over time, repeated exposure to CS+ leads to a gradual reduction in SCR amplitude, reflecting reduced novelty and adaptation.
- Extinction: When CS+ is no longer followed by US, the SCR gradually decreases, indicating new learning that the stimulus is no longer threatening. However, impaired extinction, where SCR remains high despite the absence of US, is linked to anxiety disorders and PTSD.
- Extinction Recall: If tested after a delay, individuals with effective learning will show reduced SCR to CS+, while those with persistent fear responses may exhibit heightened SCR, indicating difficulty in suppressing fear memories.

4.1.3 Fear network in humans

➤ Neural network of fear

A wealth of neuroimaging studies has mapped a complex neural network that includes both subcortical and cortical regions. In this overview (Table 4.2 and Figure 4.4.2), we aim to summarize the *most consistently reported findings* across the literature. This synthesis is based on findings from (Di et al., 2021; Fullana et al., 2016, 2018, 2020; Huggins et al., 2021; Kirlic et al., 2022; Neumann N et al., 2023; Sehlmeier et al., 2009b; Webler et al., 2021), which collectively provide a broad perspective on the neural circuits involved. It is important to note that the body of work in this field is *extensive and heterogeneous*. Different research protocols, analytical approaches, and individual differences in the sample (such as age, sex, medication, and pathologies) can sometimes lead to the identification of additional brain areas or variations in the lateralization of regions. Therefore, these findings should not be taken as wholly generalizable, but rather as part of an evolving understanding of the neural circuits of fear.

Table 4.2 Brain Regions Involved in Fear Conditioning in Humans		
Brain Region	Function	
	Acquisition	The lateral and basal amygdala encode the CS, while the central amygdala regulates

Amygdala		fear expression through connections with the brainstem and hypothalamus
	Generalization	The left amygdala is more active in implicit generalization, while the right amygdala responds more to explicit generalization. Its connectivity with the pulvinar facilitates threat detection, even for ambiguous cues
	Extinction	Amygdala activation progressively decreases, but renewal paradigms show that activation patterns depend on context manipulations
	Reward	The amygdala modulates stimulus-reward associations. The basolateral amygdala is active when a neutral stimulus acquires reward value, while the central amygdala regulates reward-driven motivated responses
Hippocampus and parahippocampal gyrus	Acquisition	It facilitates context-dependent fear associations, distinguishing between acquisition and extinction environments
	Generalization	The parahippocampal gyrus, in conjunction with the hippocampus, helps differentiate safety from threat signals. Connectivity with the vmPFC reduces generalization
	Extinction	The hippocampus' role in extinction is context-dependent and interacts with the prefrontal cortex
	Fear Reemergence	Increased hippocampal connectivity with fear-related structures predicts renewal and spontaneous recovery of fear
Prefrontal Cortex (vmPFC: Ventromedial Prefrontal Cortex, dmPFC: Dorsomedial Prefrontal Cortex, dlPFC: Dorsolateral Prefrontal Cortex, OFC: Orbitofrontal Cortex)	Acquisition	dlPFC activation increases with conditioning trials, facilitating cognitive control over learned fear
	Generalization	The dmPFC and dlPFC are more active as stimuli become increasingly similar to the CS+, indicating their role in threat evaluation
	Extinction	The vmPFC stores safety memories and inhibits fear responses, while the dmPFC is crucial in fear renewal
	Renewal	Context-change groups show reduced dlPFC activation and increased OFC activity, indicating a role in ambiguity resolution
	Reward	The medial OFC represents reward value, while the lateral OFC updates threat and reward expectations
Anterior Cingulate Cortex (ACC) and Posterior Cingulate Cortex (PCC)	Acquisition	The ACC is involved in differential fear conditioning and implicit/explicit fear processing. The rostral ACC is linked to emotional regulation, while the caudal ACC is associated with autonomic fear responses
	Generalization	The ACC evaluates conflicts between ambiguous stimuli and regulates responses to uncertainty

	Extinction	The subgenual ACC is more active during late extinction, modulating safety memory retrieval
	Extinction Recall	The PCC is occasionally recruited in extinction recall, possibly reflecting memory retrieval processes
Insular Cortex	Acquisition	The anterior insula integrates interoceptive and emotional signals
	Generalization	The anterior insula processes fear ambiguity, while the posterior insula is linked to implicit generalization
	Extinction	Strong anterior insula activation is observed, especially in recall phases
	Reward	The insula anticipates rewards and evaluates effort-reward trade-offs
Thalamus	Acquisition	The pulvinar and dorsomedial nuclei transmit sensory information for fear processing
	Generalization	The pulvinar modulates amygdala activation in response to ambiguous stimuli
	Extinction:	The anterior and medial thalamus show increased activity during late extinction phases
Striatum (NAcc: Nucleus Accumbens, Putamen, Caudate) and Ventral Pallidum	Acquisition	The ventral striatum encodes threat expectancy and CS relevance
	Extinction	The ventral putamen shows greater activation during late extinction, suggesting safety learning
	Reward	The NAcc facilitates reinforcement-based learning, and dopamine release reinforces goal-directed behavior
Periaqueductal Gray (PAG), Locus Coeruleus, Brainstem and Septal-Hypothalamic region	Acquisition	The PAG coordinates defensive responses, while the locus coeruleus regulates autonomic arousal
	Generalization	
	Extinction	The locus coeruleus shows decreased activity, possibly linked to reduced excitability
	Extinction Recall	The right septal-hypothalamic region is activated, possibly reflecting safety learning processes
	Fear Reemergence	The PAG shows increased activation in fear renewal, particularly to perceptually similar stimuli
Supplementary Motor Area (SMA) and Pre-Supplementary Motor Area (pre-SMA)	Acquisition	The pre-SMA and SMA, extending into the dACC, play a role in motor control of fear responses
	Extinction	
Sensory Cortices (Somatosensory, Visual, Auditory, Fusiform Gyrus)	Acquisition	Strong engagement of visual, auditory, and somatosensory cortices, with fusiform gyrus activation in visual paradigms
	Extinction	Strong engagement of visual, auditory, and somatosensory cortices, with fusiform gyrus activation in visual paradigms. Greater occipital cortex activation when extinction occurs in the same context as acquisition.

		The secondary somatosensory cortex (SII) is more active in early extinction
Cerebellum		It will be detailed in the next section, as it represents the central focus of our thesis.

This table is based on a summary of the literature and highlights the most frequently reported regions. However, it should not be interpreted as an exhaustive or definitive representation.

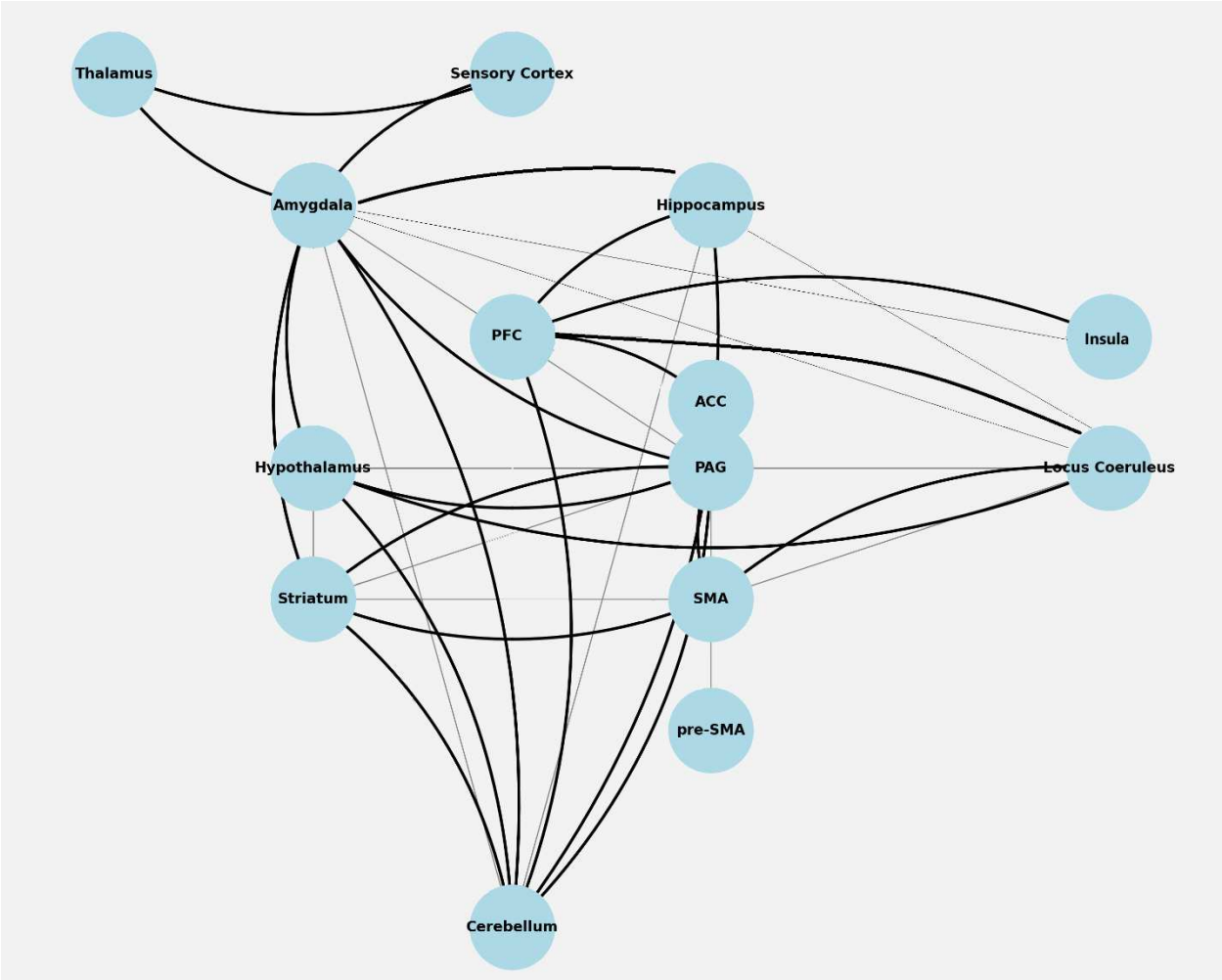


Figure 4.2 Neural Network of Fear in Humans. Network visualization of fear-related regions. The arrangement of lines (some curved and dark, others straight and light) is adjusted to avoid overlaps and keep the diagram readable, without indicating differences in the intensity or direction of connections. This visualization is based on a summary of the literature and highlights the most frequently reported regions. However, it should not be interpreted as an exhaustive or definitive representation.

- **Cerebellum's role in fear conditioning**
A growing body of literature reveals that distinct cerebellar regions contribute to various aspects of fear processing, including acquisition, prediction, and extinction, by handling predictive signals and temporal information. This *broad and concise review* shows that the cerebellum plays a multifaceted role in both forming and diminishing fear responses, with its functions in predictive control, temporal processing, and error signaling being essential for adapting fear responses and integrating contextual cues during learning.
- **Cerebellum in Fear Acquisition**
Multiple studies have highlighted cerebellar engagement in the acquisition phase of fear conditioning, indicating its role in predictive control and temporal processing of fear memories.
- Meta-analytic findings: (I. Lange et al., 2015) identified bilateral cerebellar activation during fear learning, with strongest peaks in left lobules V–VI and the culmen, though the consistency of

activation in lobule HIX remains uncertain across studies. Additional peaks were observed in the right lobules V–VI, left lobule HVI, and cerebellar tonsils.

- Early vs. Late Acquisition: (Batsikadze et al., 2022) observed early CS+-induced activation with initial left hemisphere dominance (lobules VI and Crus I), though bilateral involvement emerged as acquisition progressed. As acquisition progressed, both CS+ and CS– responses were detected bilaterally in lobules VI and Crus I, as well as in the vermis, suggesting dynamic processing of the conditioned stimulus and its unconditioned stimulus.

- Cerebellar Subregions and Stimulus Processing: (T. M. Ernst et al., 2019) examined cerebellar responses under three conditions, aligning with their reported activation patterns that include involvement of the dentate, interposed, and fastigial nuclei:

- US presentation: Widespread activation in the cerebellar vermis (lobules I–IV, V), left Crus I, and cerebellar nuclei (dentate, interposed, fastigial).

- CS+ prediction of unconditioned stimulus: Bilateral lobules VI and Crus I, plus right lobules VIIIa and VIIIb, were activated.

- US omission: Unexpected omission of the US activated the left Crus I and lobule VI, along with responses in right Crus I, vermis, and Crus II.

- **Cerebellum in Fear Extinction**

The cerebellum is strongly engaged in extinction learning, particularly in updating predictions and modulating fear responses.

- Extinction-related activations: (Doublier et al., 2023) reported fMRI activations in posterolateral cerebellar regions, including lobules VI, Crus I, Crus II, and the vermis; however, variability has been noted across studies, with some emphasizing context effects, US modality, and reinforcement rates as key modulators of cerebellar activation.

- Extinction Prediction Error: (T. M. Ernst et al., 2019) found that cerebellar activation linked to US prediction errors decreased during extinction, but under partial reinforcement, robust responses persisted in left Crus I, right Crus I, and bilaterally in lobules VI, Crus II, and the vermis.

- Context Dependency: (Batsikadze et al., 2022) demonstrated context-dependent cerebellar activation during extinction:

- Early extinction: CS+ and CS– presentations triggered robust bilateral activation in lobules VI and Crus I.

- Extinction recall: CS+ activation remained higher in the original acquisition context (vermis, lateral regions), while it was attenuated in the extinction context.

- **Cerebellum in Fear Generalization and Renewal**

- The cerebellum plays a role in modulating motor and autonomic responses to fear-generalized stimuli.

- Lobules VI, Crus I, and Crus II are activated when processing CS-like stimuli (Webler et al., 2021)

- The culmen, declive, and uvula also show activation, indicating a role in regulating conditioned responses to ambiguous threat signals.

- Persistent fear learning in renewal paradigms: The posterolateral cerebellum (lobules VI & Crus I) remains active even after extinction, supporting the idea that fear extinction does not fully erase conditioned fear memories (Batsikadze et al., 2022)

- **Modulatory Factors in Cerebellar Activation**

- Type of Unconditioned Stimulus (US): (Kattoor et al., 2014) found both vermal and posterolateral activation with visceral US, while Utz et al. (2015) (Utz et al., 2015)

- Reinforcement Frequency: High reinforcement rates do not necessarily lead to stronger cerebellar activation, suggesting that prediction errors, rather than reinforcement magnitude, are critical for engaging the cerebellum.

- Stimulus Modality & Context: Fear conditioning paradigms using visual, auditory, tactile, or olfactory CS–US pairings exhibit variable cerebellar engagement. Findings from (Kattoor et al., 2014; Utz et al., 2015) indicate that visceral US elicits both vermal and posterolateral activation, while electrical stimulation primarily engages the vermis, reflecting differences in sensory processing within the cerebellum. This highlights the flexibility of cerebellar involvement in fear learning.

4.1.4 Whole brain modelling using The Virtual Brain (TVB)

The Virtual Brain (TVB) is an advanced neuroinformatic platform designed to simulate large-scale brain networks based on biologically realistic structural connectivity (Sanz Leon et al., 2013). Integrating concepts from theoretical, computational, and clinical neuroscience approaches (Ritter et al., 2013), allows for the inference of neurophysiological mechanisms at different brain scales, helping to understand the generation of neuroimaging signals. TVB offers a unique approach to modeling whole-brain dynamics at the individual level, incorporating varying levels of complexity, from macroscale brain activity to mesoscale models, providing a comprehensive framework for exploring brain function.

Magnetic resonance imaging (MRI) allows non-invasive mapping of both the anatomical connectivity of the white matter and the dynamic patterns of neuronal activity. Structural connectivity (SC), obtained through techniques such as diffusion tensor imaging (DTI), describes the physical network of fibers that facilitates the exchange of signals between different brain regions. In contrast, functional connectivity (FC) is defined by temporal correlations in neurophysiological events, which are recorded by BOLD (blood oxygen level-dependent) signals from fMRI data, and reflect the synchronization of neuronal activity both in resting states and during task execution. These integrated approaches provide insight into how brain structure underlies functional interactions (Sporns, 2013).

One of the most widely used neural mass models in TVB is the reduced Wong-Wang model (Figure 4.3), a simplified version of the original model, extended by (Deco et al., 2014), which is used to simulate the regional dynamics of brain activity by integrating structural and hemodynamic connectivity. In this mean-field approach, each node represents a neuronal population composed of excitatory (E) and inhibitory (I) subpopulations, whose interaction is described by nonlinear stochastic differential equations modeling firing rate ($r_i^{E,I}$) the average synaptic gating variables ($S_i^{E,I}$), and the input current ($I_i^{E,I}$) to the populations in the local area i . Inter-area connections are weighted by a connectivity matrix and scaled by a global factor (G), while excitatory NMDA-mediated (J_{NMDA}), including local recurrent excitation represented by ($w+$) and inhibitory GABAergic (J_i) synaptic couplings allow to reproduce the attractor states of activity observed in models of point firing neurons.

Together, the cortical and subcortical regions, their local connectivity, the connectivity matrix, and the neural mass models at the network nodes define The Virtual Brain (Figure 4.4).

Section 4.2: Methods

In this section, we describe the *workflow* employed in this study, outlining its key steps. For improved clarity, a graphical representation is shown in Figure 4.6. The code employed in this study is available at (Schirner & Ritter, 2020/2024)

4.2.1 Acquisition, preprocessing, and connectivity mapping

This study utilizes Resting-State Functional Magnetic Resonance Imaging (rs-fMRI) and Diffusion Tensor Imaging (DTI) to analyze brain connectivity, combining functional and structural data. rs-fMRI captures spontaneous neural activity through Blood Oxygen Level Dependent (BOLD) signals, while DTI maps white matter pathways.

The DTI and rs-fMRI data used in this study were *acquired and pre-processed* by the Department of Medical Sciences, Experimental Cognitive and Affective Neuroscience (ECAN), Uppsala University, as part of a fear conditioning experiment published in (Frick et al., 2022). To ensure transparency in the methodology, we provide a brief overview of the MRI acquisitions and preprocessing of DTI and fMRI data conducted by them:

➤ MRI acquisitions

Resting-state BOLD fMRI data were acquired using a single-shot echo-planar imaging (EPI) sequence on a 3T Signa PET-MR scanner (GE Healthcare, Waukesha). The acquisition parameters were: TR = 3000 ms, TE = 30 ms, flip angle = 90°, matrix size = 64 × 64, voxel size = 3.0 × 3.0 mm, slice gap = 0.4 mm, and 45 slices. Anatomical 3D T1-weighted images were also acquired using an 8-channel head coil with the following parameters: TR = 8.6 ms, TE = 3.3 ms, inversion time = 450 ms, flip angle = 12°, matrix size = 256 × 256, and voxel size = 1.2 × 1.2 × 1.2 mm (Frick et al., 2022).

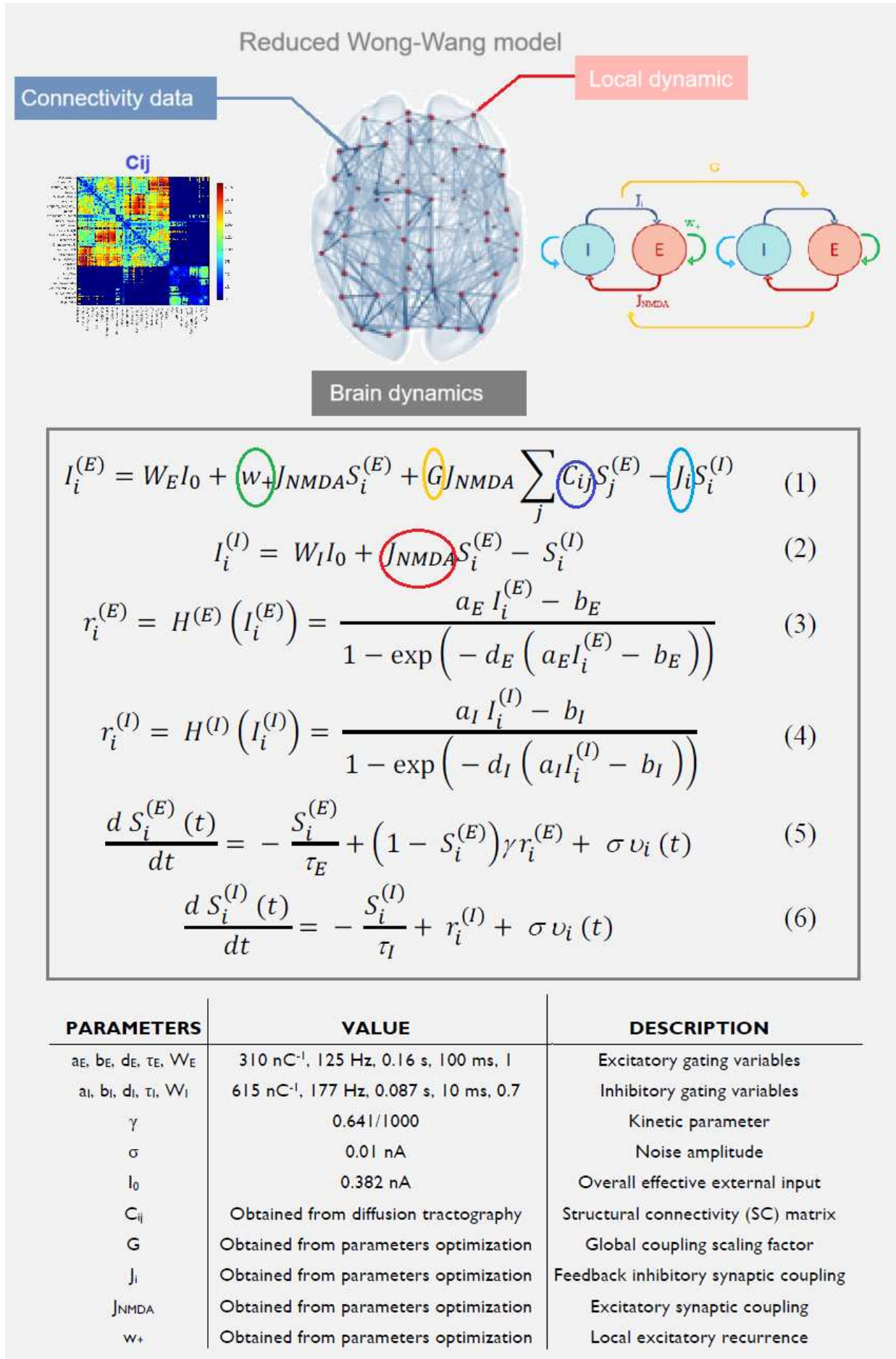


Figure 4.3 Reduced Wong-Wang Model. Brain dynamics is modeled as a network of nodes, each represented by the reduced Wong-Wang model (local dynamic), which includes excitatory (NMDA) and inhibitory (GABA) populations. Each node is described by a system of nonlinear differential equations governing the firing rates $r_i^{(E)}, r_i^{(I)}$, synaptic gating variables $S_i^{(E)}, S_i^{(I)}$, and input currents $I_i^{(E)}, I_i^{(I)}$ (For more details about the model and its mathematical formulation, consult (Deco et al., 2014)). In TVB, connectivity data, specifically the SC matrix C_{ij} encodes the interaction strength between each pair of regions ii and jj , while the parameter G acts as a global coupling factor that rescales these long-range connections. Additionally, three synaptic parameters: excitatory NMDA strength J_{NMDA} , inhibitory GABA strength J_i , and recurrent excitation $w +$ further shape the local balance between excitation and inhibition. These four parameters are estimated by fitting the simulation outputs to empirical fMRI data through systematic parameter space exploration and iterative optimization

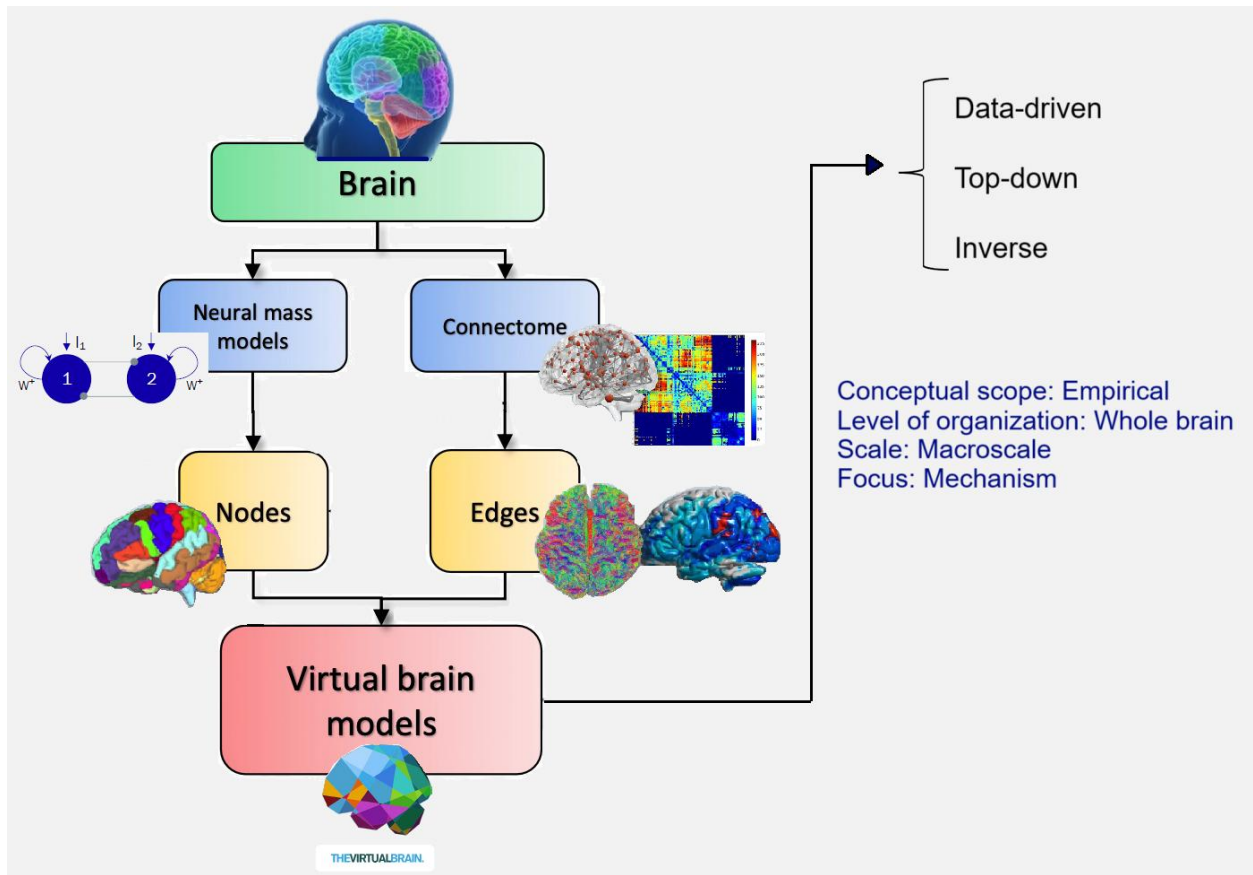


Figure 4.4 The virtual brain. Process of constructing a virtual brain model that integrates anatomical and functional information to simulate brain dynamics at the macroscopic scale. This approach follows an empirical framework, modeling whole-brain activity to understand the underlying mechanisms of connectivity and neuronal function. To achieve this, three simultaneous computational approaches are combined: (i) inverse modeling, starting from observable data (e.g., neuroimaging) to infer underlying causes; (ii) a top-down approach, which relies on global brain activity to explain functional connectivity patterns; and (iii) data-driven modeling, adjusting model parameters with empirical data to reproduce realistic brain dynamics. These components are supported by neural mass models (which describe the average activity of neuronal populations), the connectome (the structural and functional connectivity matrix), and the definition of nodes and connections (where each node represents a brain region, and each connection describes its interaction).

➤ Preprocessing of DTI and fMRI data

Data from 17 healthy adults (mean±SD age 26±4.6 years, 9 women) were processed using CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012) and SPM (Eickhoff et al., 2005) tools for fMRI analysis, including preprocessing steps such as alignment, distortion correction, normalization, segmentation, and smoothing, followed by denoising through confounding regression and

bandpass filtering. Functional connectivity was assessed using Fisher-transformed seed-based connectivity maps and Region of Interest (ROI)-to-ROI connectivity matrices

For DTI, artifact corrections for noise, distortion, and eddy currents were applied using MRtrix3 (Tournier et al., 2019) and FSL followed by probabilistic diffusion modeling and tractography with PROBTRACKX (Jenkinson et al., 2012) to estimate structural connectivity, with matrices normalized and symmetrized. Brain regions were segmented and analyzed using a combination of AAL and SUIT in order to account for the cerebellum (Diedrichsen et al., 2009; Palesi et al., 2020), and the Harvard-Oxford cortical and subcortical atlases (Desikan et al., 2006), all at a 2-mm resolution. As a result, both SC and FC matrices had a final dimensionality of 193×193 , ensuring a direct correspondence between structural and functional connectivity measures.

➤ Structural and functional connectivity

- Structural Connectivity (SC) represents the physical pathways linking different brain regions, primarily mapped using DTI-based tractography. It provides insights into the brain's anatomical organization, helping to understand how structural networks support functional interactions.

The provided dataset from Uppsala University was processed using PROBTRACKX for tractography, with SC matrices derived from this method. However, our workflow is specifically designed for MRtrix3's anatomically constrained tractography (ACT) with constrained spherical deconvolution (CSD) (Tournier et al., 2012). Adapting our pipeline to PROBTRACKX data would require substantial modifications, potentially introducing inconsistencies. To maintain methodological consistency, we instead used an existing MRtrix3-based tractography dataset. We carefully selected healthy subjects with an age range and sex distribution matching the original sample to minimize potential biases. By averaging tract length values across this group, we derived a standardized length matrix as a robust foundation for our analysis. While the whole-brain SC matrix was available, we focused exclusively on the fear network, extracting only the cortical, subcortical, and cerebellar regions identified in the literature as fundamental for fear processing. To achieve this, we generated a new ROI file containing only these anatomically relevant regions.

The resulting fear-network-specific SC matrices, including 88 cortical regions (Table S4.1, Figure 4.5), were then used as input for The Virtual Brain (TVB) to simulate network-specific neural dynamics.

- Functional Connectivity (FC) captures the temporal correlation of neural activity between brain regions, while Functional Connectivity Dynamics (FCD) examines how these patterns fluctuate over time. Together, they provide insight into both static and dynamic aspects of brain function.

Static and dynamic experimental functional connectivity (expFC and expFCD) were reconstructed from rs-fMRI data. The provided expFC matrix was computed by extracting the BOLD signal time courses for each node and calculating the Pearson's correlation coefficient (PCC) between atlas-defined brain regions. Fisher's z-transformation was applied to the matrix elements, and connections with z-values below 0.1206 were discarded to reduce weak or spurious correlations, following (Palesi et al., 2020). To ensure consistency with our MRtrix3-based SC matrices, we re-evaluated the FC estimation by computing PCC from the BOLD time series. This step ensured methodological alignment between SC and FC, maintaining coherence in our analyses.

The experimental functional connectivity dynamics (expFCD) matrix was constructed to capture time-dependent variations in functional connectivity. To achieve this, expFC was computed using a sliding window approach, where each window spanned 60 seconds (20 volumes) and was shifted by one repetition time (3 s TR), resulting in 119 overlapping windows across the total acquisition period. Each windowed expFC (expFCsw) was then vectorized by selecting the upper triangular entries of the connectivity matrix. The Pearson correlation coefficient (PCC) was computed between these vectorized expFCsw across all time points, producing a time-versus-time expFCD matrix that quantifies the time-evolving dynamics of functional connectivity. This methodology follows the approach described by (Battaglia et al., 2020; Monteverdi et al., 2023), adapted to our dataset specifications.

4.2.2 Virtual Brain modeling for fear network

The SC matrices served as input for The Virtual Brain (TVB) to simulate large-scale brain dynamics, modeling local activity within the 88 cortical regions that constitute the fear network.

Each node in the SC matrices corresponds to a reduced Wong-Wang dynamic model (Deco et al., 2014) optimized through C code (Schirner et al., 2022). This model integrates critical synaptic parameters, including excitatory NMDA-mediated synapses (J_{NMDA}), inhibitory GABAergic connections (J_i), and recurrent excitation ($w+$). Neural masses were coupled according to the subject-specific SC matrices, where inter-regional connection strengths were based on empirical structural data. Additionally, the excitatory activity across all regions was modulated by a global coupling factor G to facilitate inter-regional interactions and accurately propagate signals throughout the network.

Within the TVB framework, conduction delays between brain regions are computed by dividing the empirical tract lengths (obtained from tractography and included in the SC matrices) by a fixed conduction speed of 12.5 m/s. This constant value is based on estimates from neuroanatomical literature and allows for a consistent, computationally feasible simulation of large-scale dynamics. We acknowledge that this assumption simplifies the biological complexity of axonal transmission, as conduction time in the brain is influenced by multiple factors such as axon diameter, degree of myelination, and number of intercalating synapses. For example, long-range but heavily myelinated tracts (e.g., spinocerebellar) may conduct faster than some shorter unmyelinated pathways. Nonetheless, this simplified delay model remains a common practice in whole-brain simulations, and it enables robust comparison across subjects and conditions while maintaining tractable computational demands.

Simulated neural activity was then processed through the Balloon-Windkessel hemodynamic model (Friston et al., 2000) to reconstruct resting-state BOLD fMRI time courses over a 6.9-minute period. From these simulated time courses, functional connectivity (simFC) and functional connectivity dynamics (simFCD) were derived, allowing for comparison with experimental data.

To enhance the accuracy of functional connectivity predictions, a subject-specific parameter space exploration was performed, incorporating both global and local adjustments (see Table S4.2). The optimization (see Table S4.3) aimed to match simulated (simFC and simFCD) and experimental (expFC and expFCD) connectivity. Model inversion was used to maximize the Pearson correlation coefficient (PCC) for static FC and minimize the Kolmogorov–Smirnov (KS) distance for dynamic FC. This iterative process employed a global cost function, $(1 - \text{PCC}) + \text{KS}$, where lower values indicated a better model fit (Kong et al., 2021).

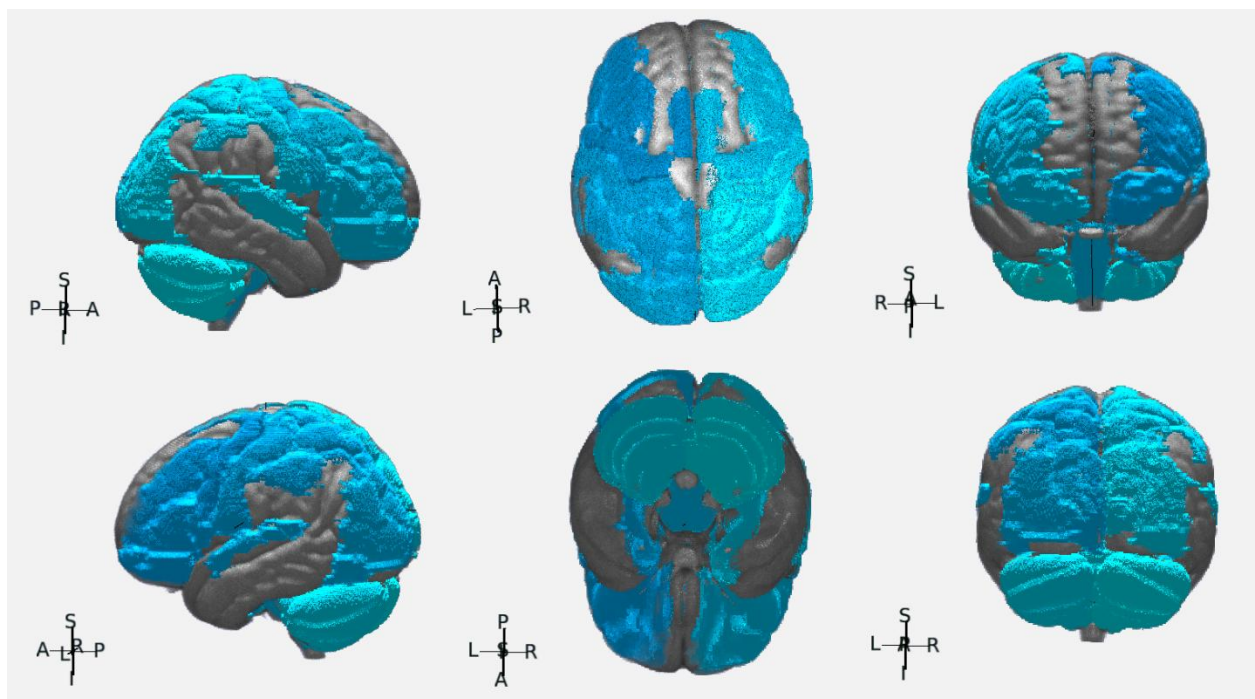


Figure 4.5 Fear Network considered in the model. 3D representation. The first row presents the right lateral (left), superior (middle), and anterior (right) views. The second row displays the left lateral (left), inferior (middle), and posterior (right) views. The 88 regions considered in the analysis (frontal, prefrontal, limbic, parietal, temporal, occipital, deep ganglia, brainstem, and cerebellum -including its deep nuclei and vermis-) are shown in cyan. Non-included areas appear in gray. See Table S4.1 for the full list.

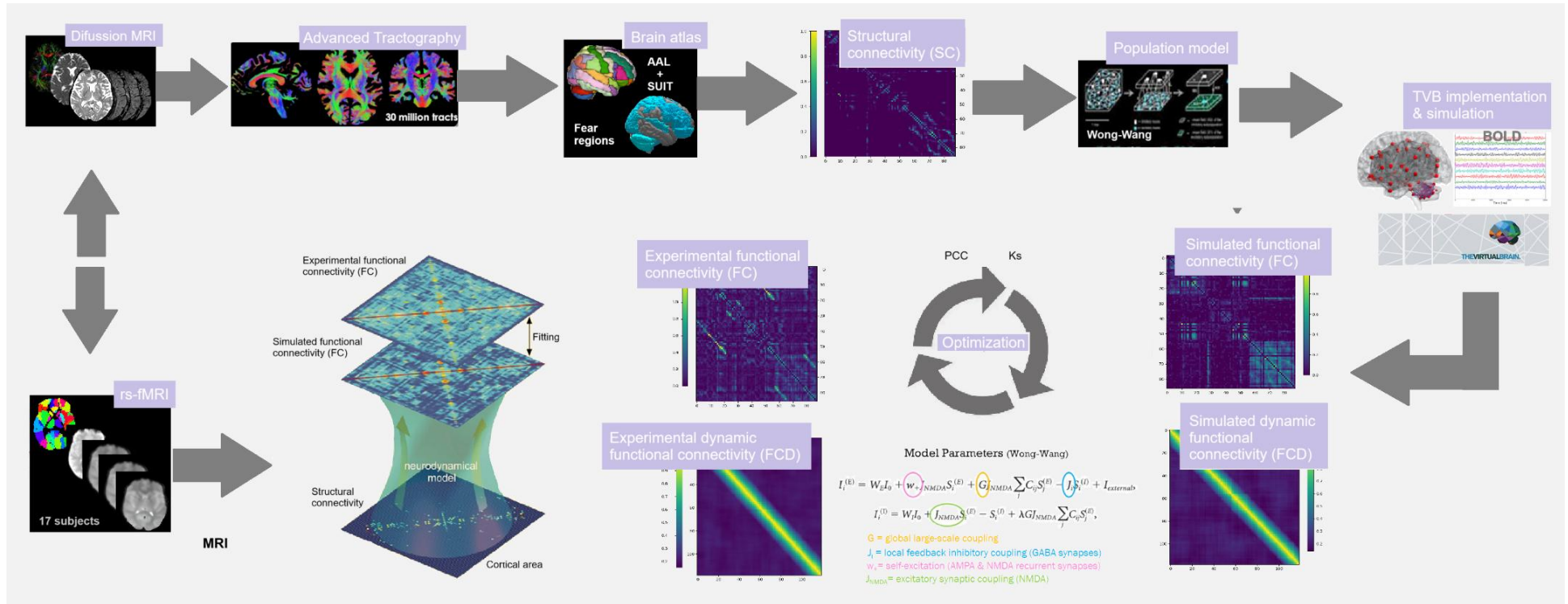


Figure 4.6 Schematic representation of the modeling workflow. From left down, clockwise: 1) MRI is used to obtain the structural (SC) and experimental static and dynamic functional connectivity (expFC and expFCD) matrices, which serve as inputs for TVB construction and optimization. 2) Diffusion-weighted images (DWI) are processed to estimate fiber orientation distribution and reconstruct whole-brain tractography. 3) Structural connectivity matrices are generated using a combined atlas (AAL and SUIT), considering regions associated with fear processing. 4) The SC matrix is used to build the TVB model, where nodes represent neural masses modeled using the Wong-Wang model, and edges define structural connections. Neural activity is simulated to extract BOLD signals and define simulated functional connectivity (simFC and simFCD). 5) The simulation is refined by comparing simFC and simFCD with experimental functional connectivity (expFC and expFCD) through model inversion, optimizing Pearson correlation (PCC), and Kolmogorov-Smirnov (KS) distance, and optimal node parameters are extracted.

Section 4.3: Analysis and Results

4.3.1 Outcome of TVB model optimization

Using a violin plot, the model parameters in TVB are displayed, offering a detailed visualization of their distribution and variability (Figure 4.7). This type of plot combines a box plot and a density plot, allowing the identification of value concentration and potential asymmetries in the data. For a more detailed analysis, a table with the specific values for each subject can be found in the supplementary material (Table S4.1).

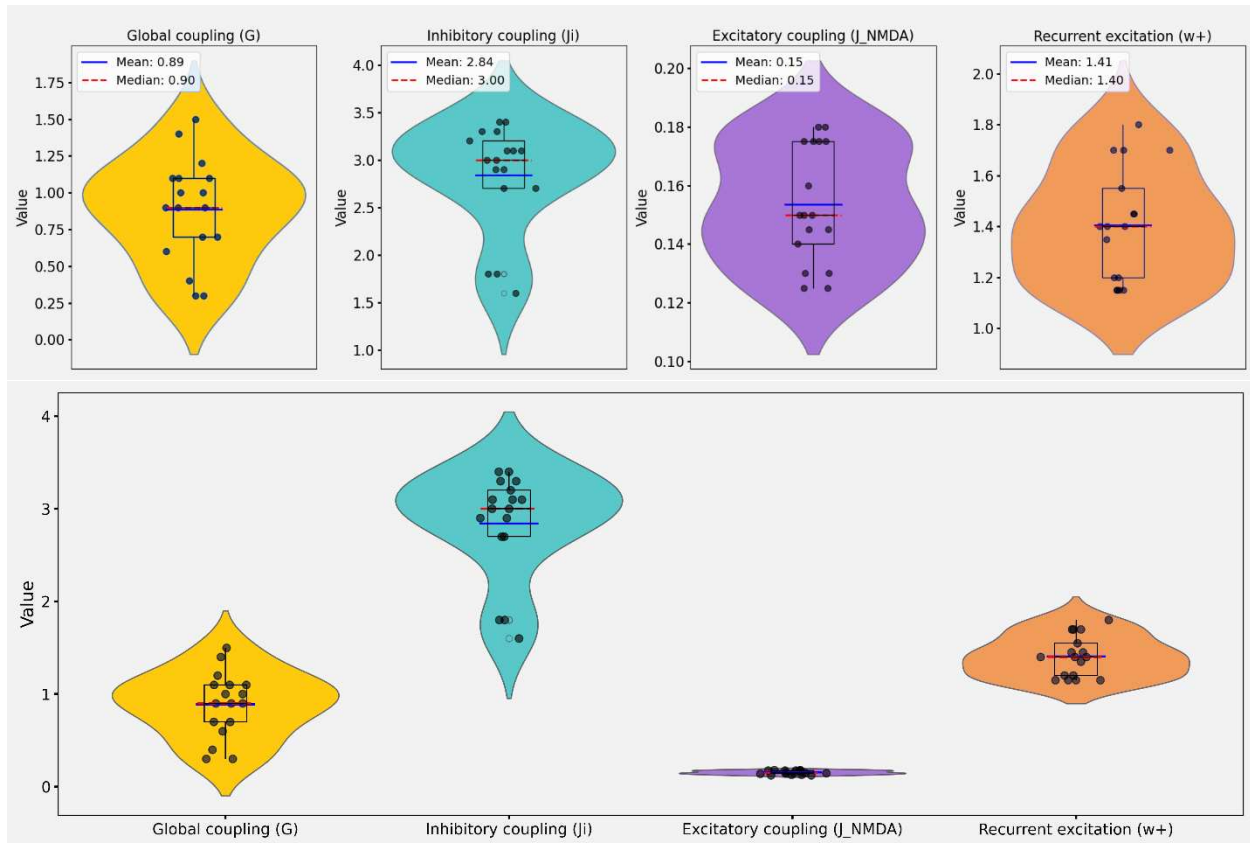


Figure 4.7 TVB model parameters. Violin plots showing the distribution of Global Coupling (G), Inhibitory Coupling (J_i), Excitatory Coupling (J_{NMDA}), and Recurrent Excitation ($w+$), with mean and median indicated. Individual distributions are shown above for clarity, as the combined plot below makes distinctions less visible due to the shared axis. Each point represents one of the 17 subjects. The values for each parameter fall within a constrained range determined by the parameter space exploration process, where optimal values were iteratively refined through a cost function. The distributions reflect the variability of these optimized values across subjects.

- The global coupling (G) is a key parameter in modulating the dynamics of the neural network, as it regulates the influence of structural connectivity (SC) on the system's global activity. In this analysis, it is observed that the mean G is 0.89 and the median is 0.90, indicating an approximately symmetric distribution centered around these values. This suggests that the parameter follows a normal distribution across subjects, with no significant deviations or skewness. The homogeneity of G values imply stability in network dynamics across individuals, without substantial variability in the propagation of activity

The violin plot shows that most values are concentrated around the mean and median, with slight dispersion. A wider region is observed around these values, indicating that the distribution of G has a higher density in this area, reinforcing the idea of a network with relatively homogeneous interactions. From a functional perspective, stability in G favors the uniform propagation of signals within the network, preventing both overexcitation and the isolation of certain regions. The shape

of the distribution suggests that the emerging functional connectivity remains within a controlled range, with no signs of hyperconnectivity or functional disconnection.

- The inhibitory coupling (J_i) modulates the influence of inhibition on the incoming current, adjusting the excitatory-inhibitory balance in the network. The mean J_i is 2.84, and the median is 3.00.

The violin plot indicates that the distribution of J_i is broader compared to other parameters, with values primarily ranging between 2.7 and 3.5. Although some points reach values close to 1.5, they do not appear to be outliers but rather part of the system's natural variability. This variability may be beneficial for regulating excitatory and inhibitory dynamics within the network, preventing overexcitation or activity collapse.

- The parameter J_{NMDA} represents the excitatory synaptic current mediated by NMDA receptors, which are essential for working memory and temporal integration. This analysis reveals that the mean and median of J_{NMDA} are 0.15, indicating a highly symmetric and homogeneous distribution. The violin plot shows that most values are concentrated between 0.14 and 0.16, and 0.176 and 0.18, with very low variability. Although the lower tail of the distribution is slightly longer, no significant outliers are identified. This low dispersion suggests that the contribution of NMDA receptors to network dynamics is uniform and well-regulated.

From a functional perspective, this stability in J_{NMDA} is beneficial for maintaining consistent temporal integration throughout the network. However, a low J_{NMDA} value may limit the persistence of functional activity in certain regions.

- The parameter $w +$ represents the strength of recurrent excitatory connections within the neural network. The mean $w +$ is 1.41, and the median is 1.40, indicating a symmetric and homogeneous distribution.

The distribution shows a concentration of values between 1.3 and 1.5, with moderate dispersion reaching values between 1.2 and 1.8. The absence of extreme values suggests a balanced network, allowing stable signal propagation without inducing overexcitation.

From a functional perspective, $w +$ regulates the persistence of neural activity within each node, facilitating sensory information integration and modulation of behavioral responses. A controlled variability in $w +$ enables the network to adjust its dynamics based on external stimuli, which is crucial in fear conditioning simulation.

J_i and $w +$ show greater variability compared to G and J_{NMDA} , indicating greater flexibility in modulating neural activity; in particular, J_{NMDA} exhibits the lowest variability across subjects, indicating a more consistent pattern of temporal integration within the network across individuals

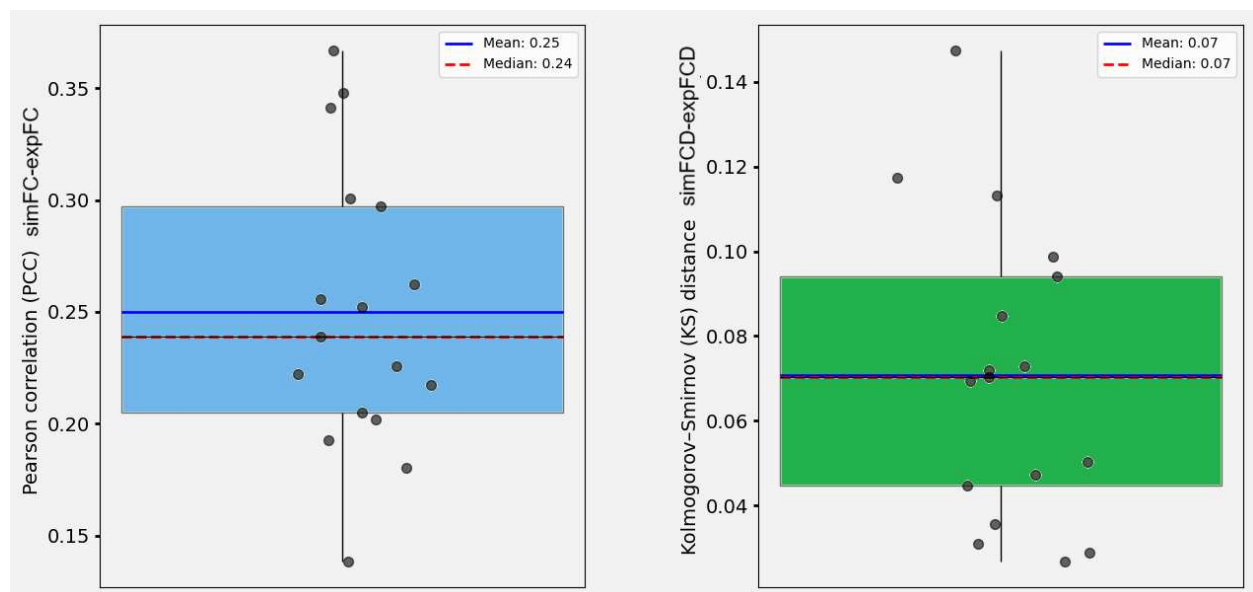


Figure 4.8 TVB optimization values - Box plot. illustrating the Pearson correlation coefficient (PCC) for static functional connectivity (FC). It represents the distribution of values across individual measurements, which are shown as dots that have been horizontally offset (jittered) for clarity. The shaded boxes represent the interquartile range (IQR), capturing the middle 50% of the data, while the horizontal lines within the boxes indicate the median (red dashed line) and mean (blue solid line). Whiskers extend to the most

extreme data points within 1.5 times the IQR, with individual dots representing data points beyond this range.

The model exhibits moderate consistency in reproducing functional connectivity (FC). Static FC fit, measured by the Pearson correlation coefficient (PCC), is relatively low (mean = 0.25, median = 0.24), with most values ranging between 0.20 and 0.30, indicating limited but consistent agreement across subjects.

Model performance was optimized by minimizing the cost function $(1 - \text{PCC}) + \text{KS}$ (Kong et al., 2021; Monteverdi et al., 2023), where an ideal fit would require PCC approaching 1 and KS approaching 0. While dynamic FC is better reproduced than static FC, neither measure reaches an optimal fit, reinforcing the model's relative accuracy in capturing FC dynamics over static connectivity.

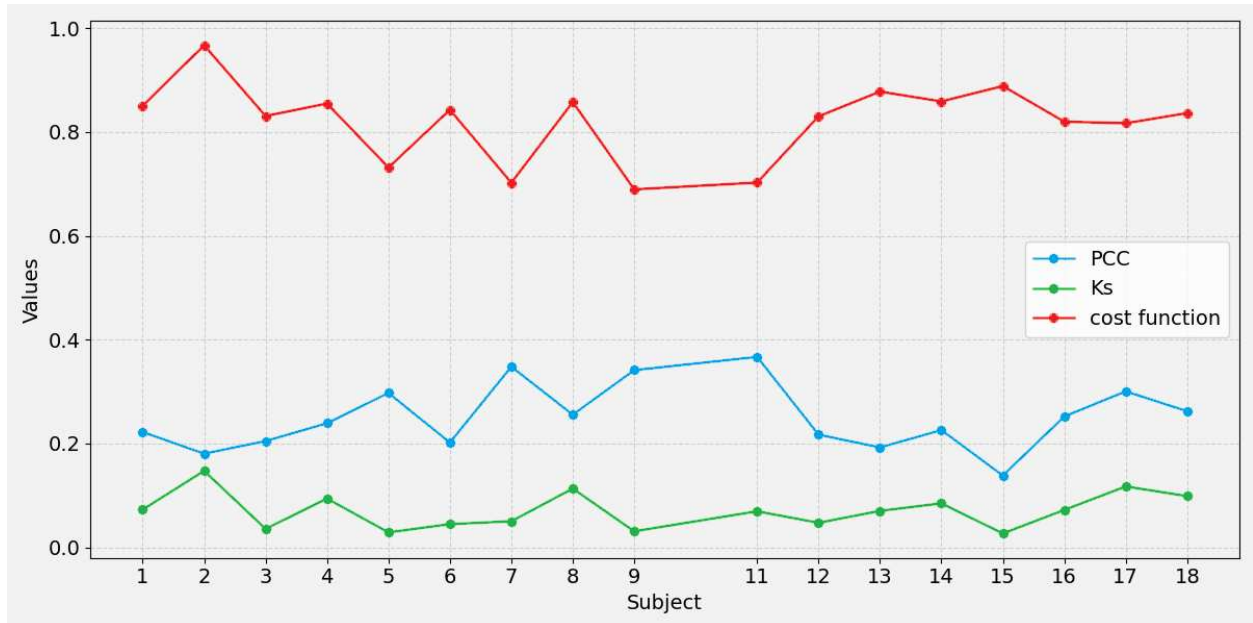


Figure 4.9 TVB optimization values – Line plot representation. Illustrating the subject-specific variation of Pearson correlation coefficient (PCC) (blue), Kolmogorov–Smirnov (KS) distance (green), and the cost function (red) across 17 subjects. (A gap is observed in the plot because subject 10 was excluded from the original dataset due to incidental findings.)

The cost function remains high (0.7–1.0), highlighting the need for further optimization, particularly for subjects with peaks (e.g., Subject 2). The highest observed cost function value is 0.97, suggesting that while optimization improved some parameters, further refinement is required to enhance static and dynamic FC agreement.

Static FC prediction remains weak, with PCC values below 0.4, though some subjects (e.g., 7, 9, 11) show good values of more than 0.3. In contrast, dynamic FC prediction is more robust, with KS values below 0.15. KS values are significantly lower than a null distribution obtained by circular shuffling each single node timeseries independently, i.e. by applying a random off-set to each node timeseries. While the model effectively captures the temporal evolution of FC, further refinements in structural connectivity parameters are needed to enhance static FC fit and reduce variability in dynamic FC replication.

In Figure 4.10, a strong correlation between G , J_i , and $w +$ is observed, implying that these parameters work together in regulating neuronal activity. This allows for model optimization by adjusting only one of them rather than modifying all simultaneously. In terms of optimization, if the goal is to maximize PCC and minimize KS, it may be beneficial to modify these parameters together rather than treating them as independent variables. For example, if increasing J_{NMDA} improves PCC but worsens KS, adjusting G or J_i in the opposite direction can compensate for this effect, achieving a better model fit without compromising stability.

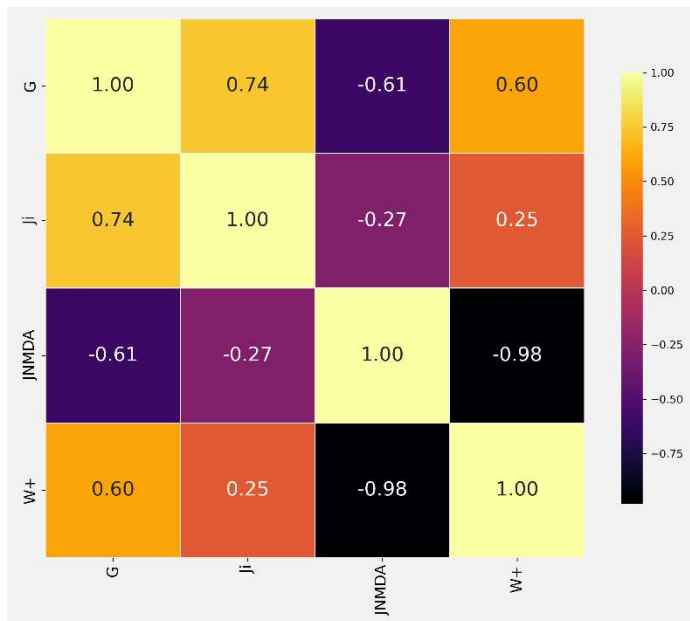


Figure 4.10 Correlation matrix of TVB model parameters. Correlation matrix illustrating the relationships between TVB model parameters. The colour scale ranges from -1 (black) to 1 (yellow), indicating the strength of correlations.

Additionally, to visually inspect these relationships, we include a pairplot (Supplementary Figure S4.1a) as part of the Spearman analysis, which allows for the identification of potential nonlinear patterns and variable distributions. Furthermore, to examine how TVB model parameters relate to the optimization parameters, we present scatter regression plots (Supplementary Figure S4.1b), which provide a more detailed view of their associations and trends. Together, these complementary visualizations offer a comprehensive understanding of the parameter space and its

underlying structure

The positive relationship between J_i and $w+$ suggests that an increase in recurrent excitation $w+$ requires a proportional increase in inhibitory drive J_i to maintain stability and prevent overexcitation. This aligns with the principle of excitation-inhibition balance in cortical circuits, where increased excitatory input typically recruits inhibitory mechanisms to stabilize neural dynamics. Consequently, if $w+$ must be increased without destabilizing the system, J_i should also be adjusted accordingly.

The negative correlation between J_{NMDA} and J_i suggests that an increase in excitatory NMDA mediated activity may be associated with a compensatory decrease in GABAergic inhibition, modulating the excitation-inhibition balance in brain dynamics. On the other hand, the negative correlation between $w+$ and J_{NMDA} suggests that an increase in recurrent excitation is associated with a lower contribution of NMDA receptors to synaptic transmission. This may reflect a regulatory mechanism in which excitatory activity modulates NMDA receptor engagement, possibly through synaptic plasticity or receptor desensitization, helping to maintain network stability and prevent excessive excitation.

The negative correlation between J_{NMDA} and G suggests a balance between local excitatory processing and large-scale network integration, a characteristic observed in neural models. Higher J_{NMDA} enhances local excitatory activity, promoting synaptic potentiation and short-range dynamics, while higher G facilitates large-scale connectivity and global signal propagation. This relationship aligns with known principles of cortical dynamics, where localized excitation supports detailed processing, while global coordination enables efficient communication across distant brain regions, maintaining a functional equilibrium between segregation and integration.

The observed relationships between model parameters align with theoretical expectations from the Wong-Wang model equations (Figure 4.3). Their empirical validation reinforces the robustness of the parameter optimization process.

4.3.2 Evaluation of TVB model performance, from SC construction to FC and FCD validation

➤ Mean Connectivity Matrices Across Subjects

To capture the global topology of the brain, we present the mean matrices, which reduce individual variability and highlight general trends.

The mean SC matrix (Figure 4.11) shows high values (yellow-light green) near the diagonal, indicating strong connectivity between anatomically close regions and revealing an efficient modular organization. Notably, the diagonal of the SC matrix is zero, as self-connections are not

considered in structural connectivity. This arrangement suggests high local interconnectivity, optimizing signal transmission within each cerebral module

Additionally, high and moderate values are observed in the cerebellum and deep cerebellar nuclei, as well as some isolated connections between the left amygdala and cerebellar lobes and deep cerebellar nuclei, between prefrontal and occipital regions, and between prefrontal and limbic regions.

The mean conduction delay matrix (Figure 4.11) exhibits variability in signal transmission times. Connections with prolonged delays (yellow-light green) are identified, while faster connections (blue-dark blue) are typically found within local modules or highly connected subcortical structures. Longer delays could affect functional integration between distant regions, impacting the temporal dynamics of neural activity.

Our SC matrix follows the approach described in (Palesi et al., 2020), incorporating cerebro-cerebellar tracts. The observed shorter conduction delays in cerebellar nodes may partially reflect tractography limitations, as spurious tracts can bias connectivity estimates. Nonetheless, modifying cerebro-cerebellar SC is unlikely to significantly impact whole-brain or cerebral subnetwork dynamics, given the relatively small proportion of these connections within the total SC. While additional filtering may enhance local precision, its overall effect on global network properties is expected to be minimal.

As illustrated in Figure 4.12 Compared to the simulated FC, the mean experimental FC exhibits more widespread functional correlations and stronger connectivity between distant regions. In contrast, the simulated FC shows a more modular structure, with well-defined clusters and reduced global integration. Notably, clearer segmented patterns emerge, particularly within the cerebellum and deep cerebellar nuclei, as well as among prefrontal, limbic, parietal, temporal, and occipital regions, suggesting distinct functional modules with strong intra-group connectivity. The simulation partially captures the functional structure of the network but shows lower “sparse” global connectivity compared to experimental data, with higher fragmentation.

The mean SC-FC difference matrix (Figure 4.13) reveals significant discrepancies, with areas of low correspondence where functional connectivity does not align with anatomical structure.

Given that both SC and FC matrices have a zero diagonal, the SC-FC difference matrix also has a zero diagonal, as expected, since self-connections are not defined in either connectivity measure. Regarding the interpretation of values, positive differences (warmer colours) indicate structural connections that are not reflected in functional connectivity ($SC > FC$), while negative differences (cooler colours) highlight regions where functional connectivity is stronger than structural connectivity ($FC > SC$), suggesting indirect or polysynaptic interactions. The correlation plot shows a moderate relationship ($r = 0.50$) between SC and FC, with a positive trend but high data dispersion. This is consistent with the neuroanatomy and neurophysiology knowledge: although structural connectivity affects functional connectivity, other factors such as conduction delays, neural dynamics, and synaptic modulation also contribute to the brain's functional activities.

On the other hand, the mean difference matrix between simulated and experimental FC (Figure 4.14) reveals some differences in pair-wise functional connections. The *correlation* between them is 0.45, indicating that the model does not fully replicate the functional patterns observed in fMRI data.

To ensure that the observed patterns in the mean matrices are not merely a result of averaging, we provide the same analysis at the individual subject level in the supplementary material. This allows for a direct comparison between individual and group-level dynamics. This additional analysis highlights inter-subject variability and ensures that the mean does not obscure important individual differences

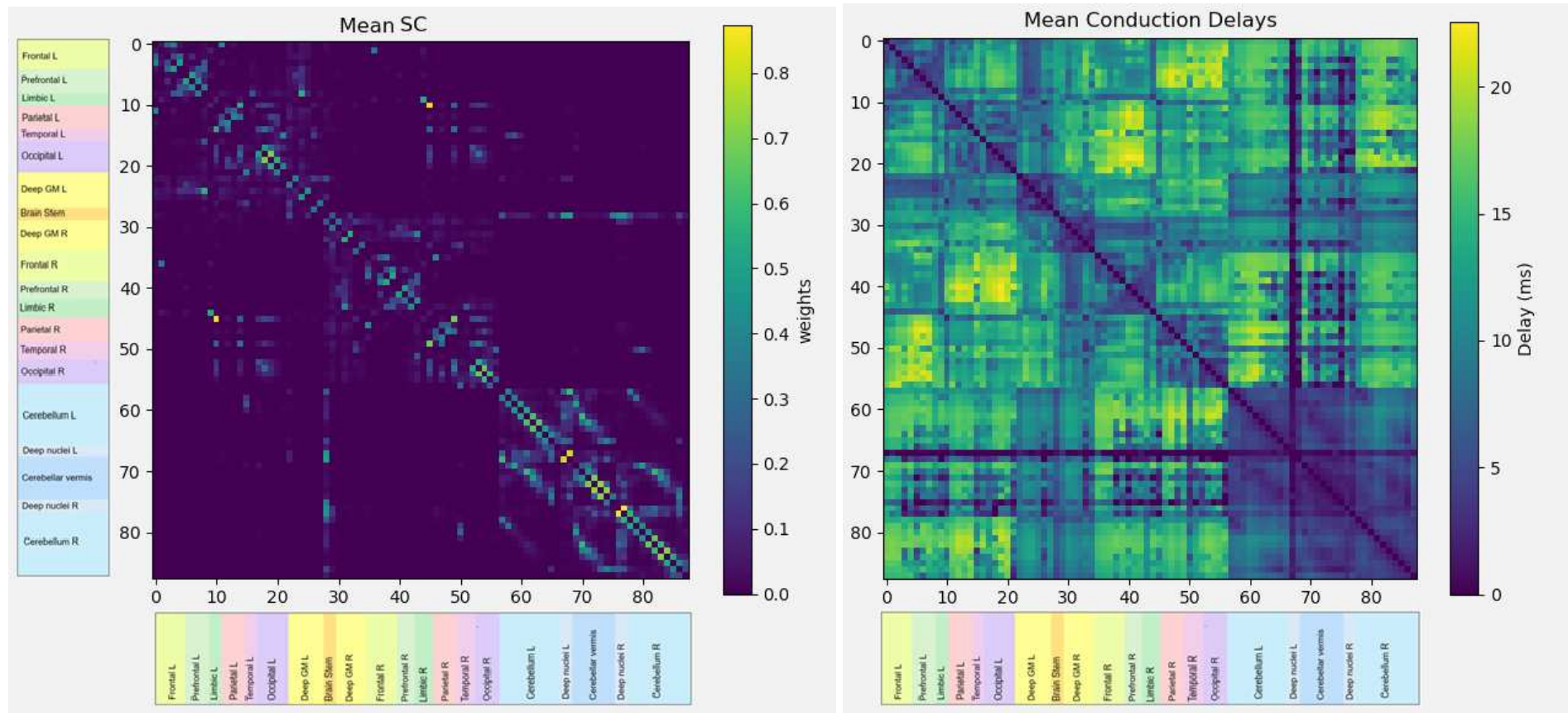


Figure 4.11 Mean Structural Connectivity and Conduction Delay Matrices. Each of the 88 nodes represents a brain region according to Table S4.1 (pastel colour bar), and each colour element in the matrix indicates the connectivity properties between two regions. The left matrix depicts SC, measuring anatomical connection strength (weights) via diffusion tractography. The right matrix illustrates conduction delays, representing the time (in milliseconds) for neural signals to propagate between connected regions.

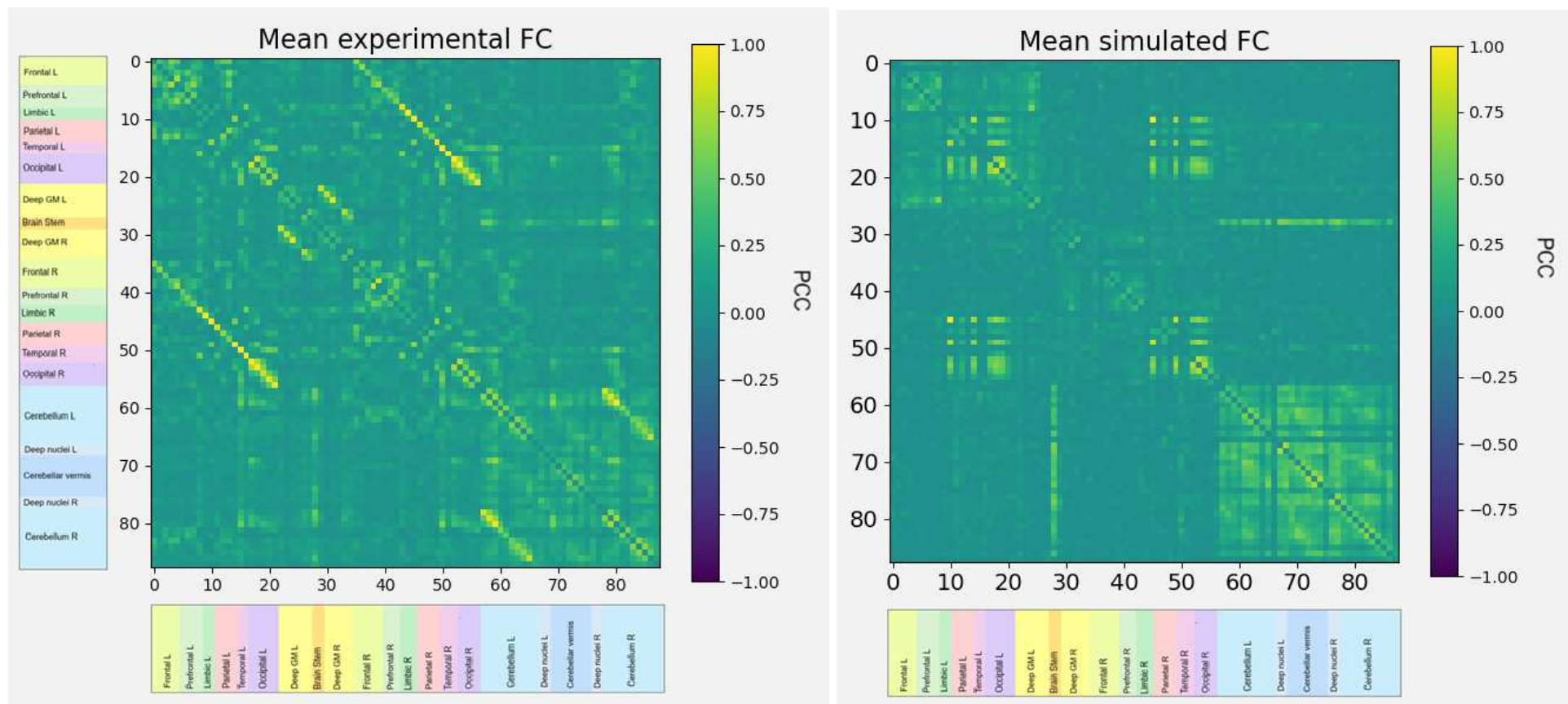


Figure 4.12 Comparison between the mean experimental and simulated functional connectivity matrices. Each of the 88 nodes represents a brain region according to Table S4.1 (pastel colour bar), and each colour element in the matrix corresponds to the Pearson correlation coefficient (PCC) between the time courses of each pair of regions. The left matrix displays the experimental FC, derived from empirical data, while the right matrix represents the simulated FC, generated by the computational model.

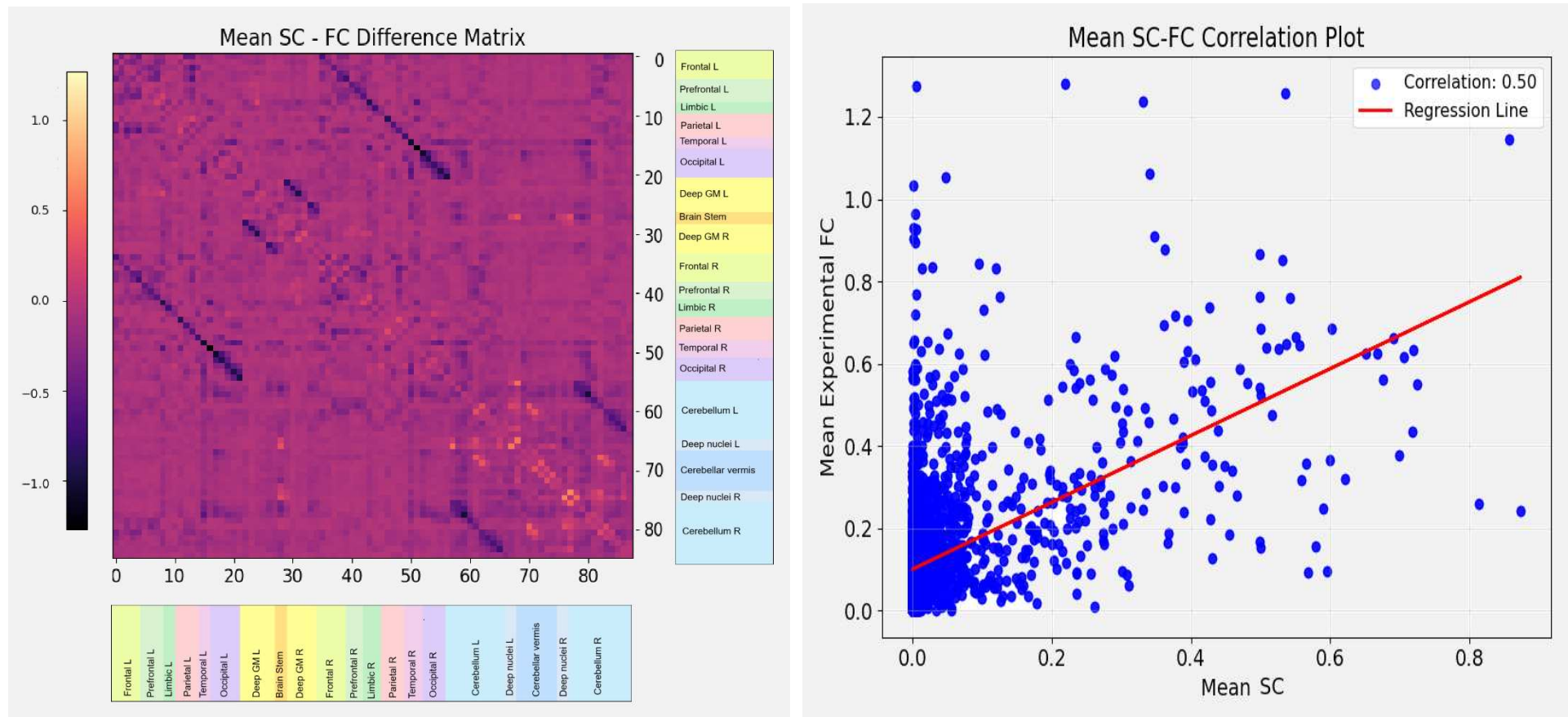


Figure 4.13 Mean Structural-Functional connectivity matrices comparison (Left) The difference matrix represents the element-wise subtraction of SC from FC (SC - FC), highlighting discrepancies between anatomical connections and functional correlations. Warmer colours or positive values (colour bar) indicate regions where SC exceeds FC, meaning structural connections exist with weak or absent functional correlations. Cooler colours or negative values (colour bar) denote regions where FC is stronger than SC, indicating functionally connected areas without direct structural pathways. Each of the 88 nodes represents a brain region, as detailed in Table S4.1, with values reflecting the difference between structural and functional connectivity for each connection. (Right) The correlation plot quantifies the relationship between SC and FC, with each point representing one connection between two brain regions. The red regression line illustrates the trend, and the reported correlation coefficient reflects a moderate match between SC and FC.

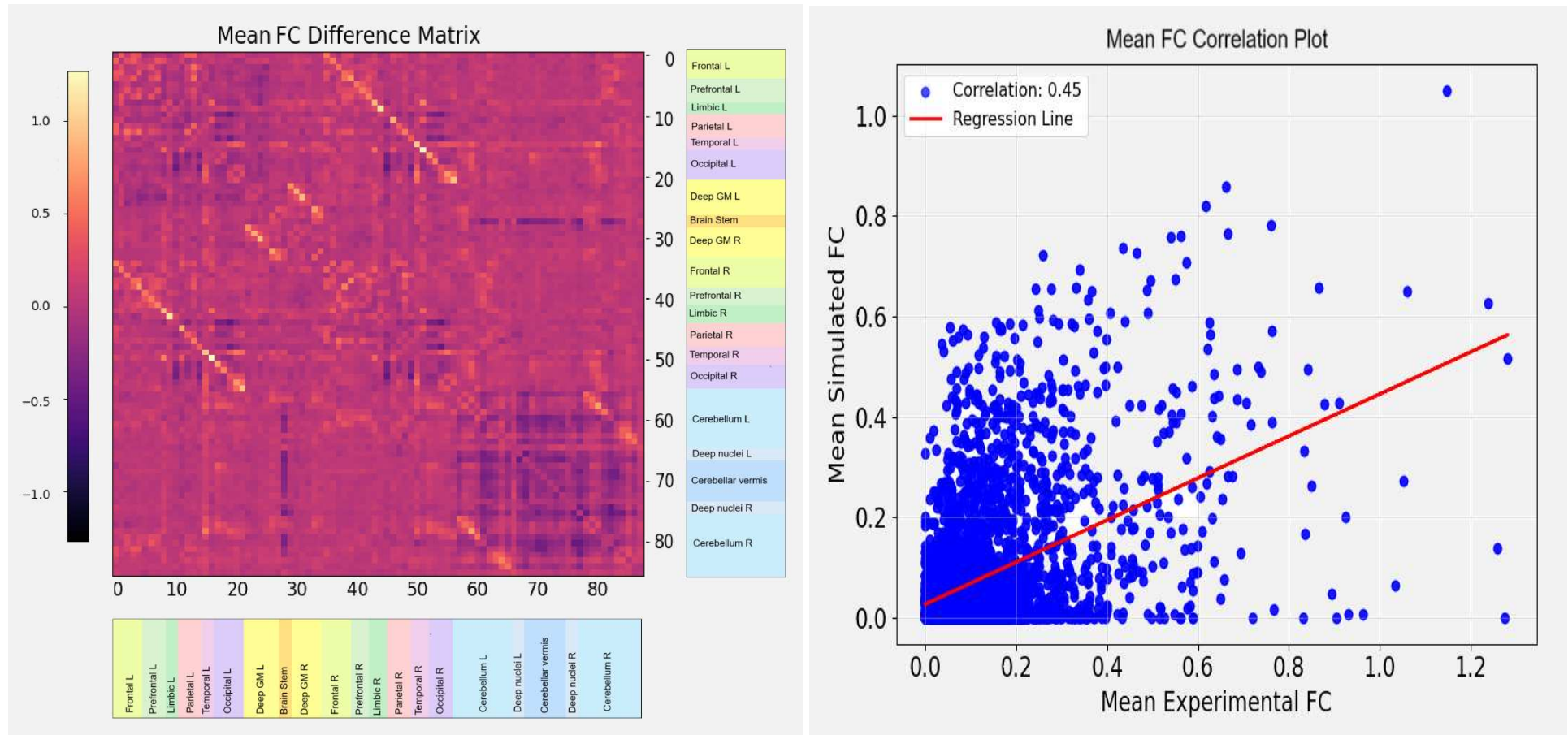


Figure 4.14 Mean Experimental-Simulated Functional connectivity matrices comparison (Left) The difference matrix represents the element-wise subtraction of the simulated FC from the experimental FC, which should be ideally zero. Warmer colours or positive values indicate regions where experimental FC exceeds simulated FC, while cooler colours or negative values denote the opposite. Each of the 88 nodes represents a brain region, as detailed in Table S4.1. (Right) The correlation plot quantifies the relationship between experimental and simulated FC, with each point representing a connection between two brain regions. The red regression line illustrates the trend, and the reported correlation coefficient reflects a moderate agreement between the experimental and simulated FC

4.3.3 Fear-related skin conductance response in relation to the optimized TVB model

The main objective of this study is to investigate the relationship between subject-specific fear responses, as measured by skin conductance response (SCR), and subject-specific TVB parameters optimized for fear-network nodes in the resting state. These TVB parameters were derived from the models developed in the previous section. To achieve this, statistical analyses were conducted to assess this correlation.

The SCR data analyzed in this study come from the same group of participants as the MRI data that was used to create the Virtual Brain models in the previous subsection.

The procedure developed and conducted by Uppsala University's, Department of Medical Sciences - Experimental Cognitive and Affective Neuroscience (ECAN) is briefly summarized here to provide context for the reader: SCRs were recorded using standard equipment and electrodes applied to the left hand during both the fear acquisition and fear extinction phases, but not during resting-state. Signals were processed by measuring the change in skin conductance from a local baseline (mean level 0–1 s after stimulus onset) to the peak response (1–5 s post-stimulus). To assess fear learning, mean SCRs were extracted for both CS+ (the conditioned stimulus paired with the unconditioned stimulus, US) and CS– (the neutral stimulus) during acquisition and extinction, as well as responses to the US (electric shock) during acquisition. Delta scores were calculated as the difference between SCR responses to CS+ and CS–, ensuring an unbiased measure of associative learning. For a detailed description of the fear conditioning experiment, please refer to (Frick et al., 2022).

The final dataset included the recorded measures for the 17 subjects, with mean responses to CS+ (acq_csp mean), CS– (acq_csm mean), and US (acq_us mean) during acquisition, and mean responses to CS+ (ext_csp mean) and CS– (ext_csm mean) in the extinction phase (see Table S4.3). These values reflect the expected learning patterns described in Subsection 4.1.1 on Skin Conductance Response (SCR).

To evaluate how responses varied across experimental conditions and phases, we computed the following ratios (see Table S4.3):

- US/CS+ Calculated by dividing the mean response to US (acq_us mean) by the mean response to CS+ (acq_csp mean). This ratio assesses the magnitude of the response to the unconditioned stimulus in relation to the response to the conditioned positive stimulus.
- US/CS– Obtained by dividing the mean response to US by the mean response to CS– (acq_csm mean), indicating the relationship between the unconditioned stimulus-response and the conditioned negative stimulus.
- CS+/CS– Calculated by dividing the mean response to CS+ by the mean response to CS– during acquisition. This index helps determine the difference in fear response between the positive and negative conditioned stimuli.
- CS+/CS+ext Obtained by dividing the mean response to CS+ during acquisition by the mean response to CS+ during extinction (ext_csp mean). This ratio evaluates the reduction in response to CS+ across the extinction phase.
- CS–/CS–ext Calculated by dividing the mean response to CS– during acquisition by the mean response to CS– during extinction (ext_csm mean), serving as a control for changes in response to the negative conditioned stimulus.

As illustrated in Figure 4.15, among the behavioral measures, acq_us_mean exhibits the widest spread and noticeable skewness, indicating greater inter-individual differences in responses to the unconditioned stimulus than other measures. In contrast, acq_csp_mean, acq_csm_mean, ext_csp_mean, and ext_csm_mean show more compact and symmetric distributions, suggesting that responses to conditioned stimuli during acquisition and extinction are more consistent across subjects. The mean and median of most behavioral measures are closely aligned, indicating minimal skewness, except for acq_us_mean, where the discrepancy suggests the presence of outliers or a non-uniform response pattern. When compared to TVB parameters (figure 4.7), the contrast suggests that while behavioral responses tend to be more constrained across subjects, their relationship with neural parameters may involve more complex, non-linear interactions.

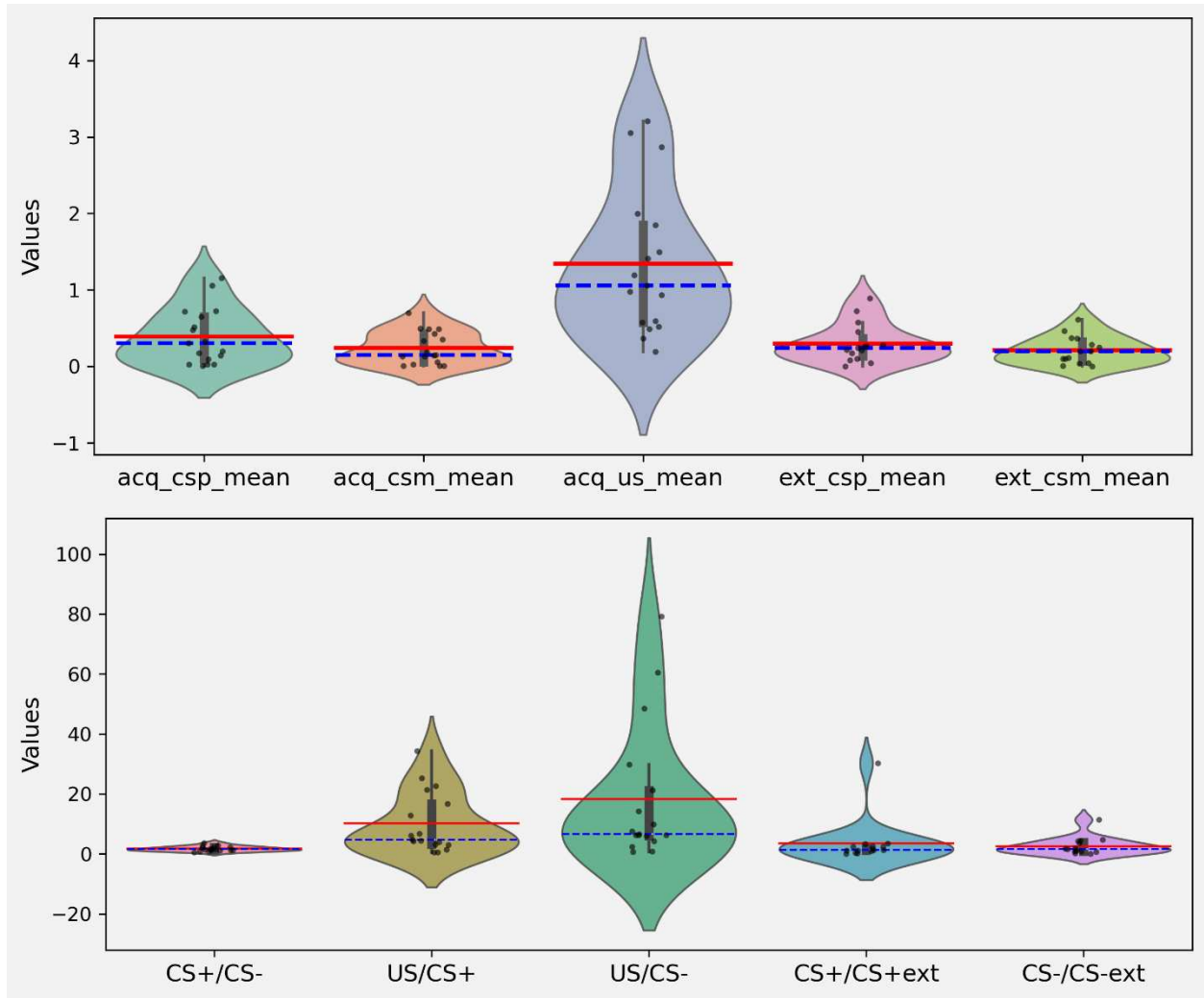


Figure 4.15 Distribution of fear conditioning response measures and TVB model parameters. Violin plot illustrating the distribution of fear-related behavioral measures `acq_csp_mean`, `acq_csm_mean`, `acq_us_mean`, `ext_csp_mean`, `ext_csm_mean` (Top) and fear-related behavioral ratios `CS+/CS-`, `US/CS+`, `US/CS-`, `CS+/CS+ext`, `CS-/CS-ext`, and TVB model parameters G , J_i , J_{NMDA} , and $w +$ (down). The blue dashed line represents the mean, and the red solid line represents the median.

Among the behavioral ratios, `US/CS-` exhibits the highest variability, with a broad distribution and extreme values, indicating considerable heterogeneity in responses to the unconditioned stimulus relative to the negative conditioned stimulus. `US/CS+` also shows notable spread, though to a lesser extent, while `CS+/CS-`, `CS+/CS+ext`, and `CS-/CS-ext` display more constrained distributions, suggesting greater consistency across subjects. This sharp contrast between the broad distributions of behavioral measures and the compact distributions of TVB parameters (Figure 4.7) suggests that resting-state TVB dynamics alone may not sufficiently account for inter-individual differences in fear-related responses.

In Figure 4.16, correlations between conditioned and unconditioned response measures, as well as their derived ratios, are not explicitly discussed, as these relationships are largely expected based on how these variables were computed. Similarly, the associations between `CS+` and `CS-` responses and between acquisition and extinction measures align with typical learning patterns in this paradigm and will not be further discussed. The correlations among the model parameters are discussed in Figure 4.10.

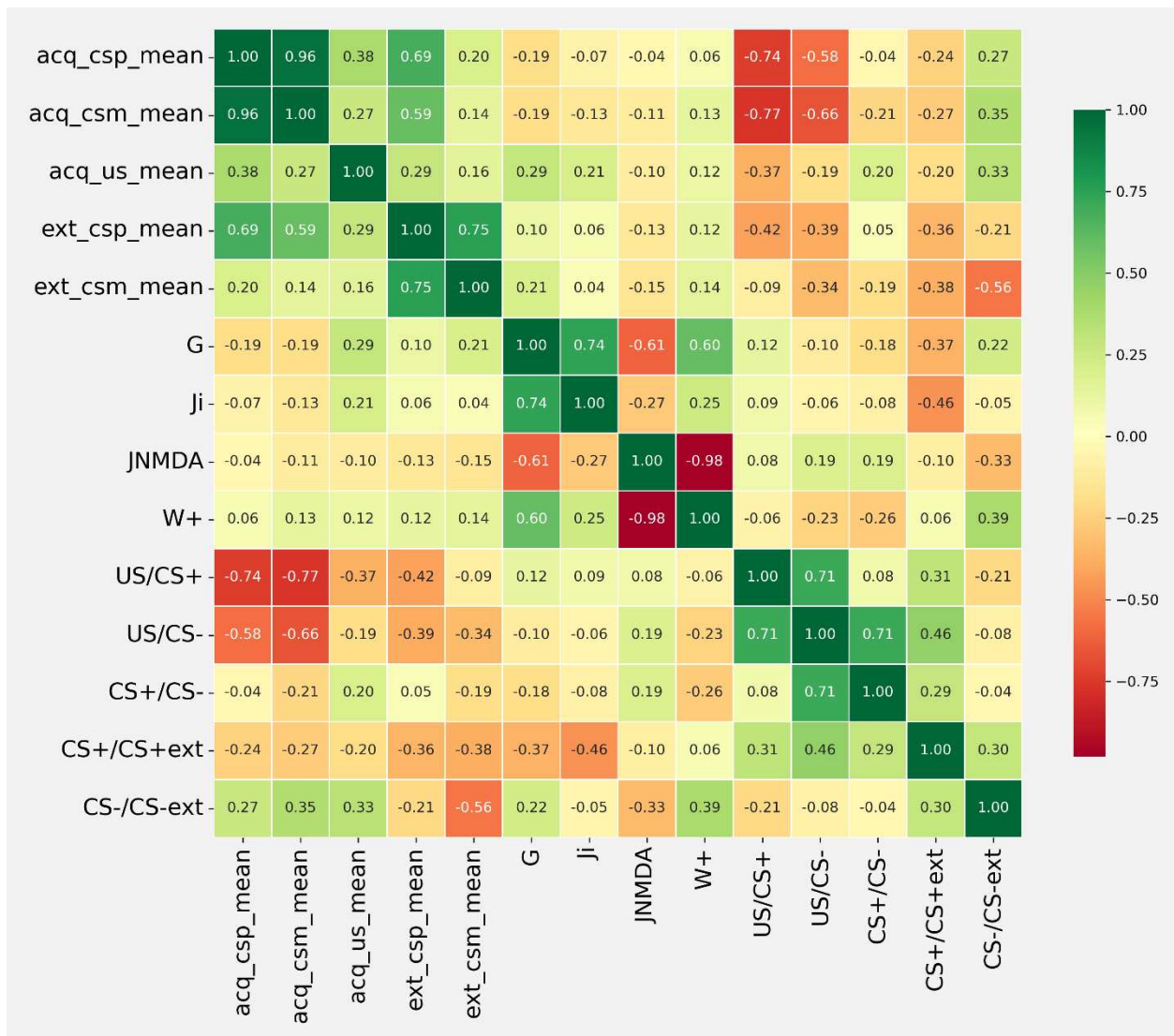


Figure 4.16 Correlation matrix between fear conditioning response measures and TVB model parameters. Correlation matrix illustrating the relationships between fear conditioning response metrics: acq_csp_mean, acq_csm_mean, acq_us_mean, ext_csp_mean, ext_csm_mean, CS+/CS- , US/CS+ , US/CS- , CS+/CS+ext , CS-/CS-ext, and TVB parameters G , J_i , J_{NMDA} , and $w+$

- Fear Learning (Acquisition phase): CS+ and CS- responses are largely independent of excitatory (J_{NMDA} , $w+$), and inhibitory (J_i) connectivity. Higher CS+ and CS- responses are weakly linked to lower global coupling (G), suggesting a shift from broad network integration to localized processing. The unconditioned stimulus (US) response shows a weak positive correlation with global and inhibitory connectivity (G, J_i), indicating a possible role of large-scale network engagement in unconditioned fear responses.

- Fear Extinction: The persistence of CS+ responses during extinction (CS+/CS+ext) is slightly positively associated with global coupling (G) and inhibitory connectivity (J_i), this indicates that, in this case, greater network-level coupling and higher inhibitory activity might be linked to the persistence of the conditioned response to CS+. Additionally, a negative correlation is observed with NMDA receptor-mediated connectivity (J_{NMDA}), and a slight positive correlation with recurrent excitation ($w+$), suggesting that local excitatory mechanisms also contribute to this persistence. On the other hand, the persistence of CS- responses during extinction (CS-/CS-ext) is positively related to global connectivity (G) and recurrent excitation ($w+$), indicating that network-wide integration and local excitatory mechanisms help maintain the CS-response. Correlations with inhibitory connectivity (J_i) are very weak, indicating that this measure has little impact on maintaining the response. On the other hand, the negative correlation with NMDA receptor-

mediated connectivity (J_{NMDA}) suggests that an increase in NMDA activity is associated with a reduction in the persistence of CS–, which could promote more effective extinction.

- Conditioned and unconditioned ratios: Most of these ratios show weak or expected correlations with connectivity parameters, suggesting that the observed relationships are largely a result of how these ratios were computed rather than revealing fundamentally new insights. Notably, the US/CS+ ratio has very modest positive associations with global connectivity (G), inhibitory connectivity (J_i), and NMDA receptor-mediated connectivity (J_{NMDA}), along with a slight negative correlation with recurrent excitation ($w+$). The US/CS– and CS+/CS– ratios exhibit weak positive correlations with NMDA receptor-mediated connectivity (J_{NMDA}), implying that NMDA-driven excitatory mechanisms may play only a minor role in distinguishing between CS+ and CS– responses. The extinction ratios (CS+/CS+ext and CS–/CS–ext) show somewhat stronger associations with the connectivity measures, but these patterns appear to be reflective of the computational approach rather than uncovering new mechanistic insights.

In general, although weak relationships are observed, TVB parameters do not strongly predict behavioral fear conditioning measures. For further exploration, Supplementary Figures S4.7a and S4.7b provide correlation and regression analyses, which illustrate individual data distributions and potential trends.

➤ Sex Differences in Fear Responses

Given the overall lack of strong statistical significance in these analyses and existing evidence of sex differences in fear-related behavior and physiological responses (Adkins et al., 2021; Bartholomew et al., 2022; Bauer, 2023; Fleischer & Frick, 2023; Velasco et al., 2019). We further investigated whether sex could be a contributing factor. To assess this, we conducted an independent samples t-test

The results of the independent samples t-test (Table 4.3) show significant differences between men and women in the acquisition phase for CS+ and CS– ($p = 0.008$), indicating a differential response to fear learning (marked with an asterisk). Although the average response to the unconditioned stimulus (US) during the acquisition phase showed unequal variances between groups ($p = 0.012$ in Levene's test), the mean difference was not statistically significant ($p = 0.216$).

No significant differences between sexes were found in the extinction phase or TVB model parameters (G , J_{NMDA}). J_i , and $w+$ were excluded from the t-test due to their low variability between sexes, making them irrelevant to the analysis.

The ability of these analyses to detect real differences depends largely on sample size and variance homogeneity between groups. In our case, the small sample size ($n = 8-9$ per group) may have reduced statistical power, making it harder to detect significant effects and potentially masking real differences. Additionally, the absence of extinction-related data (ext_csp_mean and ext_csm_mean) for two men subjects may have further affected the reliability of the comparisons, potentially influencing the variance estimates and group-level conclusions.

To further investigate potential sex differences and address the impact of missing data, we generated violin plots grouped by sex (Figure 4.17). Figure 4.17a reveals notable sex differences in fear acquisition, while differences in fear extinction appear less pronounced. During acquisition, men exhibit greater variability in their responses, with a broader spread and more extreme values compared to women.

In contrast, women show more uniform and stable responses, which suggests that men's responses to fear acquisition stimuli are more heterogeneous, whereas women's responses are more consistent across subjects.

In the extinction phase, the differences between sexes become less distinct, implying that the variability observed during acquisition does not strongly persist. However, men still exhibit a slightly greater spread, particularly in ext_csp_mean. The interpretation of extinction results should be approached with caution, as missing data from two men participants may influence the observed distributions.

Table 4.3 Independent Sample Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Conf. interval of the diff	
									Lower	Upper
acq_csp_mean	Equal variances assumed	3.923	0.066	3.070	15	0.008*	0.44194	0.14397	0.13507	0.74881
	Equal variances not assumed			2.941	9.324	0.016	0.44194	0.15028	0.10376	0.78012
acq-csm_mean	Equal variances assumed	3.815	0.070	3.045	15	0.008*	0.25878	0.08498	0.07765	0.4399
	Equal variances not assumed			2.923	9.599	0.016	0.25878	0.8852	0.06041	0.4572
acq_us_mean	Equal variances assumed	8.253	0.012*	1.293	15	0.216	0.58971	0.45610	-0.3824	1.5618
	Equal variances not assumed			1.246	10.150	0.241	0.58971	0.47322	-0.4625	1.6420
ext_csp_mean	Equal variances assumed	0.489	0.497	1.973	13	0.070	0.24132	0.12232	-0.0229	0.50559
	Equal variances not assumed			1.897	9.435	0.089	0.24132	0.12719	-0.0444	0.52704
ext_csm_mean	Equal variances assumed	0.001	0.987	0.340	13	0.739	0.3360	0.09877	-0.1797	0.24699
	Equal variances not assumed			0.352	12.004	0.731	0.3360	0.09560	-0.1746	0.24189
G	Equal variances assumed	1.283	0.275	0.957	15	0.354	0.16388	0.17128	-0.2011	0.52897
	Equal variances not assumed			0.936	12.370	0.367	0.16388	0.17501	-0.2161	0.54394
J_NMDA	Equal variances assumed	1.586	0.227	-1.613	15	0.128	-0.149	0.00925	-0.0346	0.00480
	Equal variances not assumed			-1.633	14.927	0.123	-0.1493056	0.00914	-0.0344	0.00457

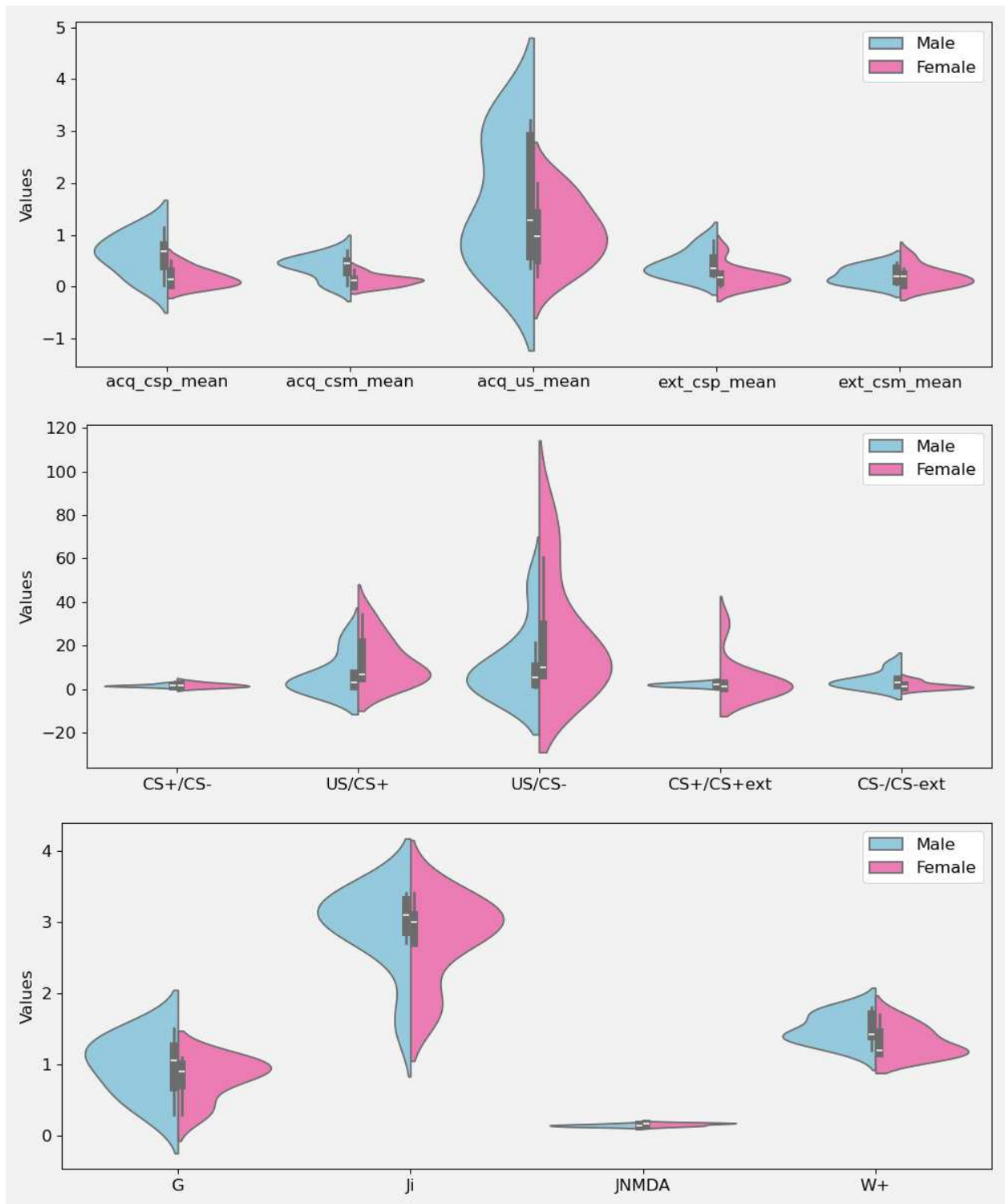


Figure 4.17 Distribution of fear conditioning response measures and TVB model parameters by sex. Violin plots comparing the distribution of fear conditioning response metrics: *acq_csp_mean*, *acq_csm_mean*, *acq_us_mean*, *ext_csp_mean*, *ext_csm_mean*, *CS+/CS-*, *US/CS+*, *US/CS-*, *CS+/CS+ext*, *CS-/CS-ext*, and TVB parameters *G*, *J_i*, *J_{NMDA}*, and *w₊*.

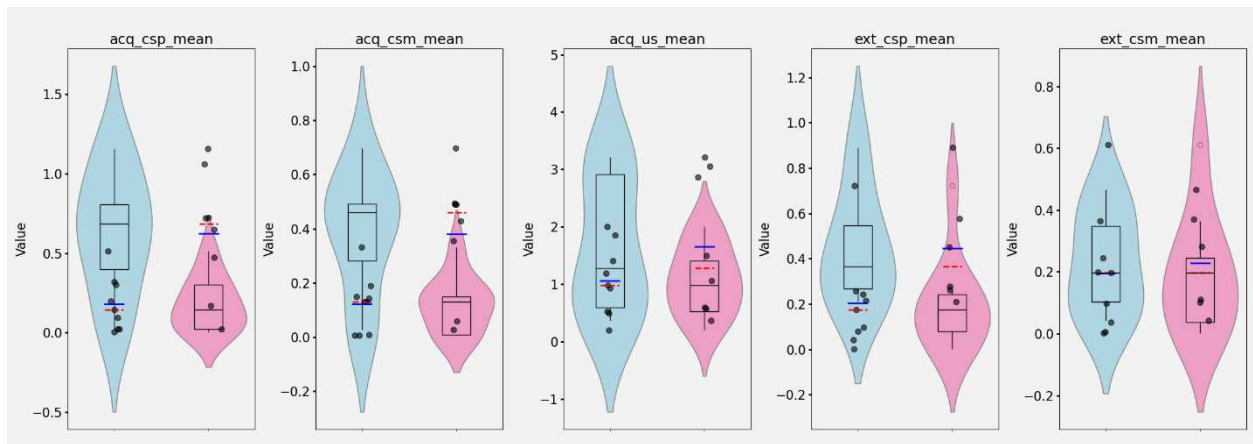


Figure 4.17a Violin plot comparing the distribution of fear-related behavioral measures

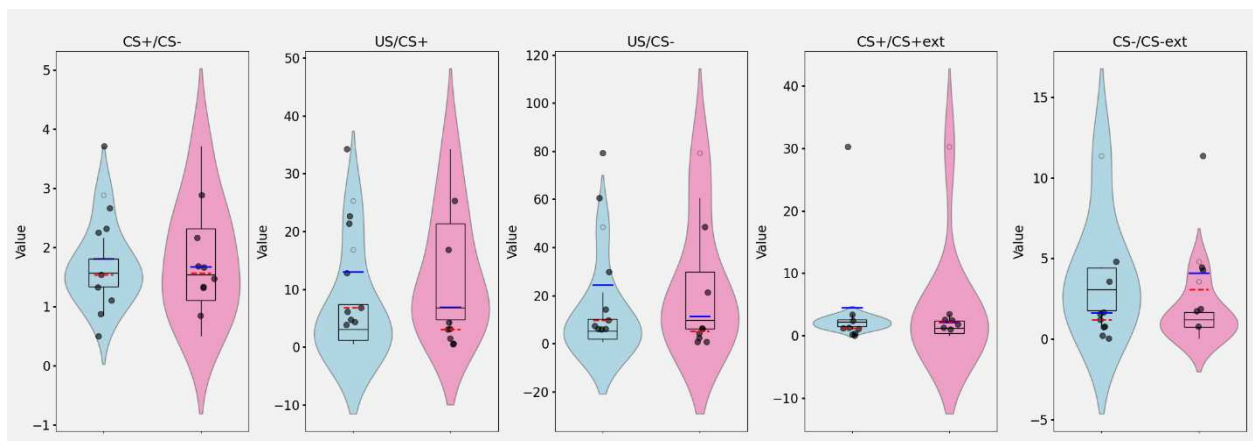


Figure 4.17b Violin plot comparing the distribution of fear-related behavioral ratios

An examination of fear discrimination and extinction ratios (Figure 4.17b) across sexes reveals notable variability in certain measures. CS+/CS- exhibits the most distinct sex difference, with women showing a broader distribution and higher median values, suggesting greater individual variability in conditioned fear discrimination. In contrast, US/CS+ and US/CS- appear more similar between sexes, indicating a consistent response pattern to the unconditioned stimulus (US) relative to both CS+ and CS-. US/CS- shows slightly more variability than US/CS+, but overall, both measures remain comparable across sexes.

During extinction, CS+/CS+ext is more variable in women, suggesting greater individual differences in how CS+ responses change across extinction trials, whereas in CS-/CS-ext men exhibit a broader and more variable distribution, while women have a more concentrated and lower-range distribution, suggesting that the extinction of CS- responses may follow a different trajectory in men compared to women. Given that these ratios were computed from extinction-related data, the missing values for two men participants may have influenced the observed distributions.

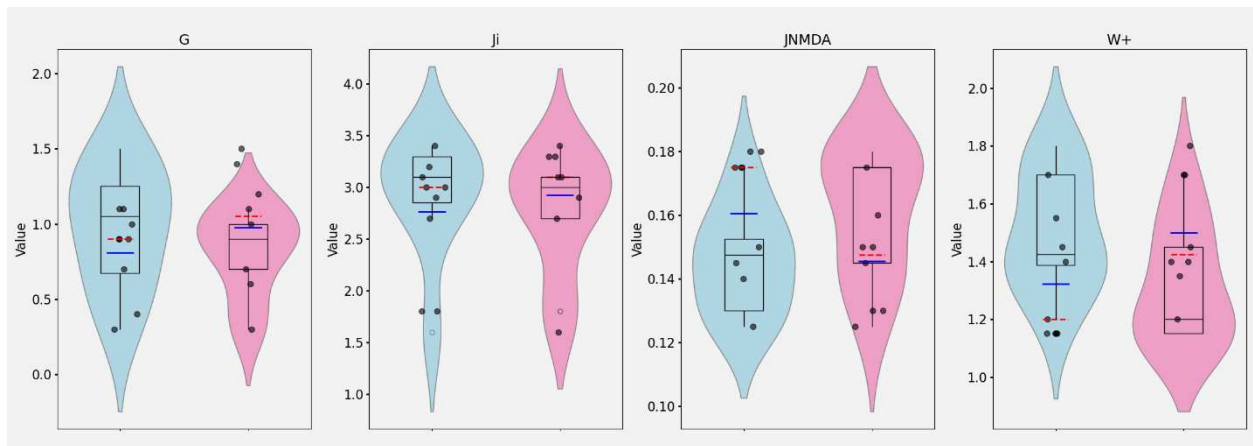


Figure 4.17c Violin plots showing the distribution of TVB model parameters

A comparison of TVB model parameters between men and women reveals some variability but no striking sex-based differences. Global coupling (G) shows broader distribution in men, with a few extreme values, whereas women's exhibit a more concentrated range, though both distributions overlap considerably. J_i (inhibitory synaptic coupling) appears to be slightly higher in women, with a more symmetric distribution, while men show greater spread and variability, suggesting inter-individual differences in inhibitory dynamics. J_{NMDA} remains highly constrained in both groups, with a nearly identical range, indicating minimal sex-based variation in this parameter. Local excitatory recurrence $w+$ shows more spread in men compared to women, though with overlapping distributions, suggesting that local excitation exhibits some individual variability but no clear sex-based differentiation.

Correlation analysis was conducted to examine the relationships between various fear measures and the model parameters separately for men and women, thereby allowing us to identify potential sex-specific differences.

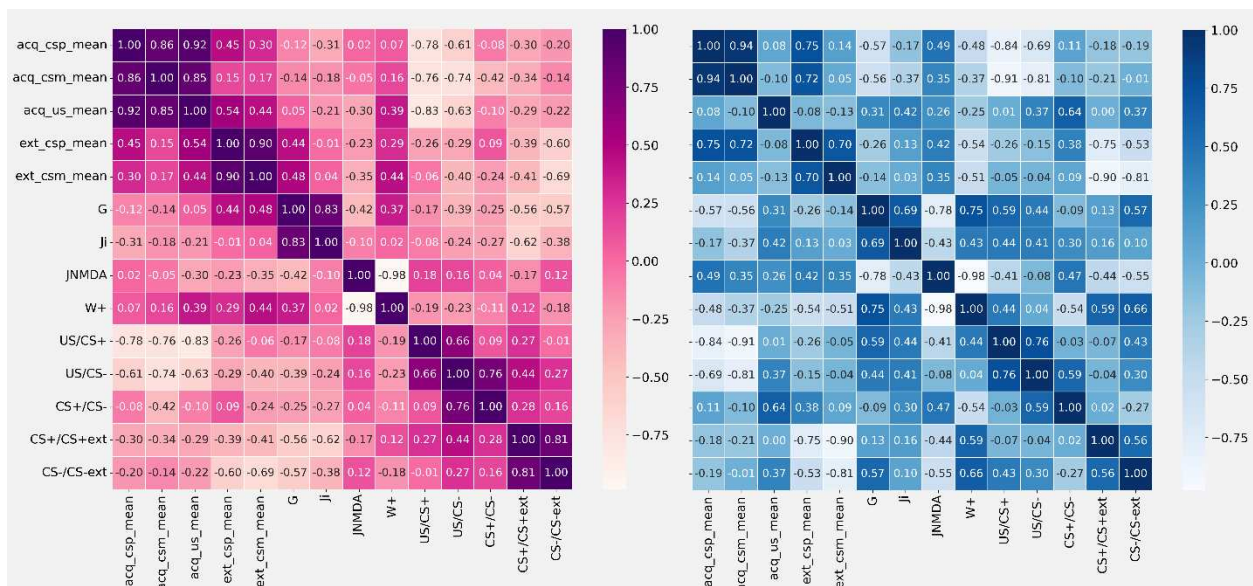


Figure 4.18 Correlation matrices between fear conditioning response measures and TVB model parameters for women and men. Correlation matrices of different parameters for women (left) and men (right). The colour and its intensity represent the strength of the association between variables, with deeper shades indicating stronger correlations. Notable differences in the pattern of associations are observed between the two groups, suggesting possible sex-specific responses in fear acquisition and extinction. For a more comprehensive understanding of these relationships, Figures S4.2 and S4.3 present a pairplot that complements the correlation matrix by visualizing data distribution, identifying potential outliers, and revealing nonlinear trends.

Women show moderate inverse correlations between G and conditioned responses during acquisition, but direct correlations in extinction, suggesting that greater global integration promotes the persistence of fear in the extinction phase. Moreover, in women, an increase in local excitation ($w +$) is associated with stronger fear responses, whereas NMDA activity (J_{NMDA}) tends to show inverse correlations. In men, G and conditioned responses display a more pronounced inverse association in both acquisition and extinction, accompanied by an opposite pattern for $w +$ and J_{NMDA} . Specifically, higher J_{NMDA} in men aligns with stronger fear responses, whereas higher $w +$ aligns with lower fear.

Inhibition (J_i) also exhibits distinct patterns: in women, it shows a stronger inverse relationship during acquisition and becomes nearly neutral in extinction, whereas in men, it can play a more facilitative role with the unconditioned stimulus and in extinction. Taken together, these findings suggest sex-specific network mechanisms, particularly regarding how global connectivity, local excitation, and NMDA activity influence fear acquisition and extinction.

In general, in women, higher ratio values (US/CS+, US/CS-, CS+/CS-, and their extinction counterparts) typically coincide with lower global connectivity (G), lower inhibition (J_i), and often lower local excitation ($w +$), while NMDA activity (J_{NMDA}) tends to show a slight direct association with these ratios. By contrast, in men, those same ratios rise alongside higher G , J_i , and $w +$, whereas an increase in J_{NMDA} typically reduces the ratio values. This contrasting pattern reinforces the idea that men and women rely on distinct network configurations to regulate fear responses and extinction.

In women, acquisition responses (CS+ and CS-) exhibit very strong correlations with each other and with the unconditioned stimulus (US), indicating a unified fear reactivity pattern that continues into extinction, where CS+ and CS- remain closely linked. In men, although CS+ and CS- also show a robust association during acquisition, their link to the US is much weaker. Moreover, in extinction, the CS+ response carries over more strongly from acquisition, while CS- becomes more detached, and the association between the two stimuli is lower than in women, suggesting somewhat greater stimulus discrimination during extinction in men.

Lastly, women demonstrate a more unified pattern in their fear measures: the various ratios involving CS+ and CS-, along with comparisons to the unconditioned stimulus (US), tend to be closely interrelated. In contrast, men show greater differentiation, such that while some relationships (e.g., US/CS+ with US/CS-) are strong, others (particularly those involving extinction ratios) are weaker or more variable. This implies that men's fear responses may be modulated more independently depending on the measure or ratio, whereas in women, changes in one measure often coincide with changes in the others.

For additional insights, Supplementary Figures S4.8a and S4.8b display correlation and regression analyses, showcasing individual data distributions and potential patterns in men and women.

Given the complexity of fear learning and extinction processes, it is unlikely that any single neural parameter fully explains individual variability in behavioral responses. Instead, multiple interacting factors may contribute to these differences. While pairwise correlations provide initial insights, they do not account for the combined effects of multiple neural parameters. Therefore, we applied a multiple backward regression analysis to assess whether a combination of TVB model parameters could better explain variations in fear discrimination and extinction measures.

The multiple regression analysis (Figures 4.19 and 4.20) revealed that a combination of TVB model parameters significantly predicts extinction responses for both CS+ and CS-. For CS+ extinction (ext_csp_mean), a model including global coupling G and inhibitory synaptic coupling J_i explained 64.7% of the variance ($R^2=0.647$, $p=0.044$), suggesting that these neural parameters influence individual differences in fear extinction. For CS- extinction (ext_csm_mean), the model incorporating G , J_i , $w +$, and J_{NMDA} explained 93.9% of the variance ($R^2=0.939$, $p=0.011$), indicating a stronger predictive relationship for safety learning. These results suggest that subject-specific resting-state neural dynamics contribute to fear extinction processes, with a greater influence observed for CS- CS-extinction, where excitatory and inhibitory mechanisms appear to play a key role.

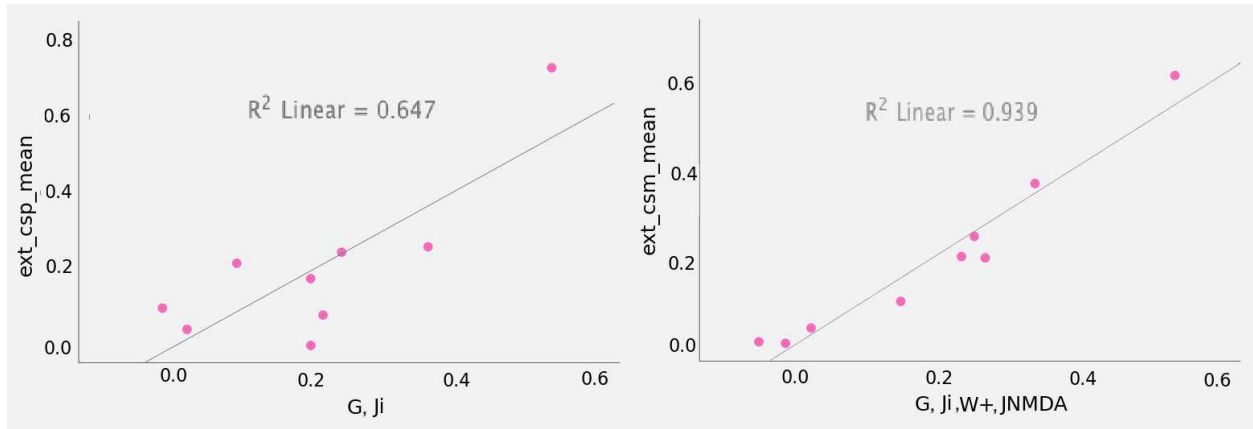


Figure 4.19 Relationship between fear extinction responses and TVB model parameters in women. Scatter plots illustrating the multiple regression models predicting extinction responses for CS+ (left) and CS- (right) in women. Data points represent individual subjects, and the fitted regression lines illustrate the predicted relationships. The CS+ extinction model includes G and J_i , while the CS- CS-extinction model incorporates G , J_i , $W+$, and J_{NMDA} .

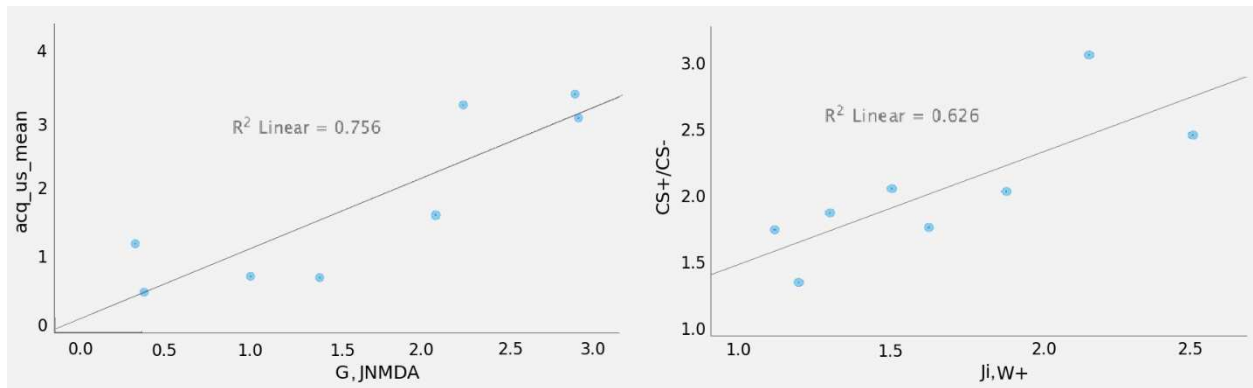


Figure 4.20 Relationship between fear acquisition measures and TVB model parameters in men. Scatter plots illustrating the multiple regression models predicting fear acquisition responses in men. The left panel shows the model predicting responses to the unconditioned stimulus (acq_us_mean) based on G and J_{NMDA} , the right panel shows the model predicting CS+/CS- discrimination based on J_i and $W+$. Data points represent individual subjects, and the fitted regression lines illustrate the predicted relationships.

G and J_{NMDA} predict 75.6% of the variance ($R^2 = 0.756$, $p = 0.029$) in responses to the unconditioned stimulus (US), suggesting that greater global connectivity and excitatory activity enhance the neural encoding of unconditioned stimuli. J_i and $W+$ predict 62.6% of the variance ($R^2 = 0.626$, $p = 0.085$) in CS+/CS- discrimination, indicating that the balance between inhibition and recurrent excitation plays a key role in distinguishing between threat (CS+) and safety (CS-). These findings suggest that individual differences in resting-state neural dynamics influence fear acquisition, with distinct mechanisms supporting US processing and conditioned fear discrimination.

Section 4.4: Discussion and Conclusions

The differences between the average SC, FC, and FCD matrices (Figures 4.11-4.14) and those of individual subjects (Figures S4.1- S4.6) highlight the impact of interindividual variability on functional connectivity. While average matrices smooth out these variations, individual data reveal stronger connections in specific regions and greater dispersion in the SC-FC relationship. Notably, individual functional connectivity exhibits a lower correlation with simulations, underscoring the need for specific calibrations to enhance model accuracy.

This observation aligns with prior findings highlighting the relevance of interindividual variability in functional brain organization. For example, results from (Ashida et al., 2019) emphasize that group-level fMRI analyses may not reliably capture individual patterns and that individual scans

are essential, especially when aiming for clinical and higher-order domains applicability. Regarding temporal dynamics, the model effectively captures functional connectivity dynamics (Figures S4.5-S4.6), showing a high correlation between simulations and experimental data. However, its ability to replicate static functional connectivity (FC) is limited (Figure 4.8, 4.12, 4.14, and S4.2, S4.4), as it exhibits lower global connectivity and excessive segmentation. From an optimization standpoint, the cost function (Figure 4.9) remains high (0.7–1.0), showing potential for enhancements in model adjustments.

Variations in the distribution and strength of structural connections may hinder global functional integration, affecting the model's accuracy. To mitigate this issue, it is advisable to use individual SC matrices derived from the tractography of experimental subjects whenever possible. These align with previous studies emphasizing the uniqueness of brain connectivity in each individual. For instance, (Kerepesi et al., 2018) demonstrated that while certain brain regions exhibit more conserved connectivity patterns, others show greater diversity. This underscores the need for personalized approaches in brain connectivity modeling to enhance the accuracy of functional simulations based on structural data.

Despite differences in tractography, the model accurately reflects functional connectivity dynamics (FCD). However, it struggles with SC-FC correspondence because static FC, while partially constrained by SC, is also influenced by neural dynamics, indirect connectivity, and global network states. In contrast, FCD captures temporal fluctuations and can adapt through dynamic compensatory mechanisms, making it less sensitive to tractography inaccuracies. While parameters like global coupling and conduction delays can help improve FCD by modulating network interactions, they do not always resolve SC-FC discrepancies, as static FC remains more structurally constrained despite contributions from indirect and dynamic neural interactions.

In conclusion, although the model successfully reproduces the temporal evolution of functional activity, it still requires minor adjustments in structural connectivity and specific synaptic parameters to optimize its correspondence with static functional connectivity and more accurately capture the neural mechanisms.

The correlation matrix of TVB model parameters (Figure 4.10) provides valuable insight into how these parameters interact, revealing expected mechanisms of synaptic regulation and excitation-inhibition balance observed in biological neural networks. This understanding not only improves model interpretation but also guides more effective parameter adjustments, enabling compensatory tuning that maintains system stability without compromising functionality.

Our findings indicate that conditioned fear responses (CS+ and CS-) during acquisition are largely independent of excitatory and inhibitory connectivity, although they show a slight negative relationship with global connectivity, suggesting a transition from network-wide integration to more localized processing. In contrast, the unconditioned stimulus (US) response exhibits a weak positive correlation with global and inhibitory connectivity, suggesting a possible role of large-scale network integration in unconditioned fear responses.

During extinction, the persistence of CS+ is slightly associated with higher global and inhibitory connectivity, indicating that greater network integration and inhibitory activity may contribute to resistance to extinction. Additionally, NMDA receptor-mediated connectivity shows a negative correlation with CS+ persistence, suggesting that increased NMDA activity could facilitate extinction. Similarly, CS- persistence is influenced by global connectivity and recurrent excitation but shows a negative correlation with J_{NMDA} , which could promote the extinction of non-reinforced fear.

Regarding the relationships between connectivity parameters and conditioned/unconditioned response ratios, most correlations are weak and appear to stem from the computational approach rather than providing new mechanistic insights. Likewise, correlation analysis between TVB model parameters and behavioral measures of fear acquisition and extinction reveals no statistically significant associations (Figures S4.7a-b). Low R^2 values and correlation coefficients suggest that resting-state network dynamics have limited predictive power for fear-related behavior.

On the other hand, sex-related differences in fear conditioning, extinction, and neural connectivity (Table 4.3, Figures 4.24-4.27, and S4.8a-b) were found, supporting the idea that fear conditioning is influenced by individual differences, as previously reported in (Lonsdorf & Merz, 2017; Tronson, 2018).

Men exhibited stronger CS+ responses during acquisition and a more pronounced reduction during extinction, suggesting more effective extinction learning. In contrast, women retained CS+ responses longer, indicating resistance to extinction or prolonged retention. These findings align with evidence that estradiol (E2) influences fear extinction and memory consolidation, where higher levels facilitate extinction, while progesterone (P4) may hinder it. (Bauer, 2023; Velasco et al., 2019). This is further supported by studies indicating that NMDA receptors (NMDAr) mediate fear extinction through their role in synaptic plasticity in both the amygdala and prefrontal cortex (Davis, 2011). Additionally, (Graham & Scott, 2018) provide evidence that estradiol-induced enhancement of extinction may be dependent on NMDAr activation, which could explain why some women show greater retention of CS+ responses when estradiol levels are low. Furthermore, hormonal contraceptives have been suggested to facilitate fear acquisition and extinction. (Bartholomew et al., 2022), which may indicate that the variability observed in women's extinction responses could partly depend on contraceptive use.

Regarding autonomic reactivity, men displayed higher and more variable responses to the unconditioned stimulus (US), reflecting greater physiological arousal, while women showed a more compact distribution, suggesting lower interindividual variability. Similarly, women exhibited greater dispersion in fear extinction and generalization, whereas men demonstrated more structured and homogeneous patterns. These findings align with studies indicating that hormonal fluctuations in estradiol (E2) and progesterone (P4) influence fear extinction and consolidation, where higher E2 levels facilitate extinction and P4 may hinder it. (Bauer, 2023; Velasco et al., 2019). Additionally, women and women rodents tend to be more hyperreactive to threats during low-E2 phases, which may contribute to the observed variability in extinction responses. (Bauer, 2023).

Furthermore, GABAergic neurotransmission plays a key role in memory stability, with reduced GABA transmission being essential for the reactivation of fear memory and extinction learning. (Makkar et al., 2010), this aligns with our findings that women show greater variability in extinction, as hormonal modulation may affect GABAergic activity. Moreover, experimental evidence suggests that blocking presynaptic GABA B receptors enhances fear extinction and reduces fear renewal in men rodents but not in women (Adkins et al., 2021), suggesting that sex-dependent GABAergic mechanisms may contribute to the observed extinction differences in our study.

At the neural connectivity level, men exhibited greater variability in global coupling (G) and recurrent excitation parameters ($w+$), while women showed more stable values but stronger correlations in J_{NMDA} and $w+$. This aligns with differences in fear regulation strategies, as women displayed negative correlations between G and fear responses during acquisition but positive correlations in extinction, indicating greater fear persistence. In contrast, men showed a consistently stronger inverse relationship between G and fear across both phases. These differences suggest sex-specific excitation-inhibition mechanisms influencing synaptic plasticity and fear regulation (Fleischer & Frick, 2023). Additionally, monoaminergic activity in the prefrontal cortex fluctuates across hormonal phases in women, which may contribute to their less structured connectivity patterns (Velasco et al., 2019). Given that NMDAr activation is necessary for both the plasticity induced by estradiol and the consolidation of fear extinction (Graham & Scott, 2018), our findings suggest that the sex differences in J_{NMDA} may reflect differential engagement of NMDAr-dependent mechanisms in fear extinction learning.

This funding supports the idea that the fear process is influenced by conditioning parameters and individual differences, including biological factors such as sex. Specifically, our findings suggest that men and women engage different neurobiological strategies for fear regulation, shaped by hormonal and neurotransmission differences. These results highlight the importance of incorporating these variables into fear conditioning studies, as they could be crucial for developing personalized treatments for fear-related disorders.

In conclusion, our study represents a significant step toward integrating rs-fMRI data into task-related models, providing a foundation for future research in The Virtual Brain (TVB). By characterizing the brain's resting-state manifold, this work opens new possibilities for constructing task-specific flows and manifolds, as proposed in (Fousek et al., 2024).

Additionally, this is the first study to explicitly incorporate the cerebellum into the fear network within a computational modeling framework, highlighting its potential role in fear-related processes. This novel approach paves the way for improved model adaptation, error

identification, and optimization for future applications. Ultimately, this work sets the stage for developing more dynamic, task-specific models that bridge the gap between resting-state and active brain function.

➤ Study limitations

- One limitation of this study was the establishment of a standardized network representation of nodes for modeling, which was hindered by a lack of consensus and variability in the literature. Different studies identify distinct brain regions, with some reporting discrepancies in the lateralization of activated areas. These inconsistencies are likely due to methodological differences.
- Another limitation of this study was the challenge of mapping fear-conditioning-related brain regions to the anatomical parcellation used in the TVB atlas. While we identified a set of regions implicated in fear conditioning based on the literature, some were represented as whole structures rather than being subdivided into their functional subregions. This lack of granularity in certain brain areas may have affected the precision of our network modeling, potentially limiting the accuracy of region-specific connectivity and functional dynamics.
- The use of structural tractography data from different individuals likely introduced variability and potential errors in reconstructing brain connectivity. Since this data may not fully correspond to the actual anatomical structures of our sample, it could impact spatial representation, neural simulations, and the reliability of conclusions regarding interindividual variability. As a result, these findings should be interpreted with caution.
- Finally, the lack of extinction phase data for two of the eight men participants may have impacted the statistical analysis and reduced the robustness of sex-based comparisons.

➤ Future directions

- Optimizing available data: Optimizing the dataset structure by acquiring raw DTI data will allow for reprocessing in FSL to generate individualized and precise connectomes. Using subject-specific information prevents model alterations that arise from employing tractography from other subjects, ensuring that structural connectivity accurately reflects each individual's unique anatomy and functional dynamics. This approach will enable a coherent integration of structural, functional, and simulated data within the TVB framework, ultimately enhancing the reliability and accuracy of the model.
- Incorporating available PET data: PET data available from the same group of subjects and study (Frick et al., 2022) would add dimension to the model, allowing the incorporation of metabolic and/or neurochemical information. These data can validate and calibrate functional dynamics simulations, integrating in a multimodal manner to explore the relationships between metabolic activity and brain connectivity. In addition, the inclusion of PET personalizes the model by differentiating regions according to their metabolic or receptor density profiles, improving the accuracy and predictive capacity of the simulations in TVB.
- Larger Sample Sizes: Increasing the sample size reduces variability, improves representativeness, and enhances statistical power. Additionally, a larger sample better captures the brain's complexity and ensures robust model validation, leading to more reliable and generalizable results.
- Expanding or replacing the current model: Neural Mass Models in TVB are useful for simulating large-scale brain dynamics, but they have limitations arising from the averaging of activity across extensive neuronal populations. This averaging can hinder the capture of heterogeneity, precise synchronization, and complex local phenomena. To overcome these constraints, one could consider using Neural Field Models, which incorporate spatial variability and more accurately depict the spread of activity within brain tissue.
- Enhancing Cerebellar and fear conditioning modeling: Future work should integrate specialized neural mass or mean-field models that reflect the cerebellum's unique microcircuitry and connectivity rules. Additionally, more adaptive and biologically realistic frameworks that better reflect the complexity of neural mechanisms involved in fear conditioning (Gershman, 2015; Mattera et al., 2020; Nair et al., 2016) will provide a more comprehensive understanding of its role in large-scale brain dynamics and its influence on affective learning processes.

- Using Dynamic Causal Modeling (DCM): Currently, TVB is mainly designed to simulate large-scale brain dynamics in the resting state (e.g., rs-fMRI) and capture pathological alterations, but it is limited in modeling task-dependent activity and explaining behavior. In contrast, DCM (Friston et al., 2003, 2019; Stephan et al., 2007) excels at inferring effective connectivity and causal relationships in task-related fMRI data. Combining rs-fMRI and task-related data, including diffusion and functional imaging from subjects involved in fear conditioning/extinction, presents a promising opportunity. Rather than relying solely on DCM for task-specific analyses, integrating it with TVB could leverage the strengths of both models. This combined approach would offer a more comprehensive understanding of brain function across various cognitive states.
- Generating an asymmetric connectome for integration into the TVB avatar: In this approach, the transmission between node pairs is not assumed to be symmetric, reflecting the biological reality that brain connections are indeed not homogeneous. This strategy not only provides a solid theoretical foundation for the inherent asymmetry in biology but also overcomes a fundamental limitation of TVB, which has traditionally relied on symmetric connections. This can be achieved by integrating directionality from advanced tractography methods, such as High Angular Resolution Diffusion Imaging (HARDI) or probabilistic tractography, or by incorporating computational models that introduce asymmetric synaptic delays and differential connection weights. These modifications allow for a more biologically realistic representation of connectivity and information flow within the brain.
- Task simulation in TVB: Expand the Virtual Brain to incorporate the dynamics of fear acquisition and extinction, validating the model with fMRI data and refining simulations by comparing them with empirical responses. Optimize the reconstruction of effective connectivity to enhance accuracy and explore different mean-field model configurations within the nodes to better capture the dynamics of fear response. Additionally, advancing the code to integrate task-related fMRI data into TVB, such as implementing critical node segmentation, is essential for defining precise stimulation patterns. By subdividing brain regions into functionally specific subareas, differentiated and customized stimulation protocols can be applied. This approach ensures that simulations accurately reflect distinct processing pathways and activation dynamics, which is crucial for faithfully reproducing brain activity in task-related contexts.
- Simulate learning: Incorporate independent weighting techniques based on machine learning to simulate learning processes. By dynamically adjusting the model parameters, this approach can replicate synaptic plasticity, specifically the strengthening or weakening of neural connections as a result of conditioned and unconditioned stimuli. This independent weighting system would enable the simulation to more accurately mirror the gradual reinforcement of fear responses and the adaptive changes in neural circuitry observed during fear conditioning experiments, ultimately bridging the gap between computational models and experimental data.
- Multi-scale integration: Developing a conceptual integration that spans all scales from micro to macro, to comprehensively capture brain structure, function, and dynamics. This hybrid approach would allow bottom-up and top-down processes to coexist by combining the modeling capabilities of TVB with simulators such as NEST and Neuron and frameworks like BSB. Such a co-simulation strategy would provide a unified and complete view of brain function.
- Integration of electrophysiological modalities: Another important direction is to expand the dataset by incorporating additional modalities, such as EEG and MEG, alongside MRI and PET. These techniques provide high temporal resolution and can capture dynamic neural activity patterns, yielding output time series that correspond to common neuroimaging recordings. This approach not only replicates the brain's intrinsic responses but also enables the simulation of how external stimuli modulate neural activity over time, thereby facilitating direct comparisons with experimental data. Ultimately, this integrated strategy promises a more comprehensive understanding of brain function across various cognitive and emotional states and experimental conditions.
- Enhancing fear response models through NMDA and GABAergic pathways and hormonal tracking: Future studies should consider incorporating direct measures of NMDA and GABAergic neurotransmission pathways, such as pharmacological manipulations or neuroimaging markers of receptor activity, as well as incorporating hormonal tracking (e.g., menstrual cycle phases, use of contraceptives) to refine the interpretation of sex-based variability.

- Interdisciplinary integrative approach: The integration of traditional models, probabilistic approaches, and latent cause models, along with clinical data, neuroimaging, and emotional assessments, is essential for advancing the understanding of fear learning and emotional regulation. This combined approach, developed in collaboration with clinicians, neuroscientists, and computational experts, will enable a more precise analysis.

Supplementary material

Table S4.1 Cortical and subcortical regions considered in the TVB model		
ID	Nodes	Modules
1	Precentral_L	Frontal L
2	Supp_Motor_Area_L	
3	Frontal_Mid_L	
4	Frontal_Inf_Oper_L	
5	Frontal_Inf_Tri_L	
6	Frontal_Sup_Orb_L	Prefrontal L
7	Frontal_Mid_Orb_L	
8	Frontal_Inf_Orb_L	
9	Insula_L	Limbic L
10	Cingulum_Ant_L	
11	Cingulum_Post_L	
12	Postcentral_L	Parietal L
13	Parietal_Sup_L	
14	Parietal_Inf_L	
15	Precuneus_L	
16	Fusiform_L	Temporal L
17	Temporal_Sup_L	
18	Calcarine_L	Occipital L
19	Cuneus_L	
20	Occipital_Sup_L	
21	Occipital_Mid_L	
22	Occipital_Inf_L	
23	Left-Thalamus-Proper	Deep GM L
24	Left-Caudate	
25	Left-Putamen	
26	Left-Pallidum	
27	Left-Hippocampus	
28	Left-Amygdala	
29	Brain-Stem	Brain Stem
30	Right-Thalamus-Proper	Deep GM R
31	Right-Caudate	
32	Right-Putamen	
33	Right-Pallidum	
34	Right-Hippocampus	
35	Right-Amygdala	
36	Precentral_R	Frontal R
37	Supp_Motor_Area_R	
38	Frontal_Mid_R	
39	Frontal_Inf_Oper_R	
40	Frontal_Inf_Tri_R	
41	Frontal_Sup_Orb_R	Prefrontal R
42	Frontal_Mid_Orb_R	
43	Frontal_Inf_Orb_R	
44	Insula_R	

45	Cingulum_Ant_R	Limbic R
46	Cingulum_Post_R	
47	Postcentral_R	Parietal R
48	Parietal_Sup_R	
49	Parietal_Inf_R	
50	Precuneus_R	
51	Fusiform_R	Temporal R
52	Temporal_Sup_R	
53	Calcarine_R	Occipital R
54	Cuneus_R	
55	Occipital_Sup_R	
56	Occipital_Mid_R	
57	Occipital_Inf_R	
58	Left_I_IV	Cerebellum L
59	Left_V	
60	Left_VI	
61	Left_CrusI	
62	Left_CrusII	
63	Left_VIIb	
64	Left_VIIIa	
65	Left_VIIIb	
66	Left_IX	
67	Left_X	
68	Left_Dentate	Deep cerebellar nuclei L
69	Left_Interposed	
70	Vermis_VI	Cerebellar vermis
71	Vermis_CrusII	
72	Vermis_VIIb	
73	Vermis_VIIIa	
74	Vermis_VIIIb	
75	Vermis_IX	
76	Vermis_X	
77	Right_Dentate	Deep cerebellar nuclei R
78	Right_Interposed	
79	Right_I_IV	Cerebellum R
80	Right_V	
81	Right_VI	
82	Right_CrusI	
83	Right_CrusII	
84	Right_VIIb	
85	Right_VIIIa	
86	Right_VIIIb	
87	Right_IX	
88	Right_X	

Table S4.2* TVB model parameters				
ID	G	Ji	J_NMDA	W+
Subject1	1.2	3.3	0.15	1.4
Subject2	1.4	3.3	0.125	1.8
Subject3	0.7	3	0.175	1.15
Subject4	0.4	1.8	0.15	1.4
Subject5	0.9	3	0.175	1.15
Subject6	1	3.4	0.13	1.7
Subject7	1	3.2	0.125	1.7
Subject8	0.9	3.4	0.175	1.15
Subject9	1.1	3.1	0.145	1.45
Subject11	0.3	1.6	0.16	1.35
Subject12	0.7	2.9	0.15	1.4
Subject13	1.5	3.1	0.13	1.7
Subject14	1.1	2.7	0.145	1.45
Subject15	1.1	2.7	0.14	1.55
Subject16	0.6	3.1	0.175	1.2
Subject17	0.9	2.9	0.18	1.15
Subject18	0.3	1.8	0.18	1.2
Mean	0.89	2.84	0.15	1.41
Median	0.90	3.00	0.15	1.40
Standard deviation	0.35157	0.56905	0.01998	0.22212
Variance	0.1236	0.32382	0.0004	0.04934

* To facilitate the analysis, blue and pink colours have been used to identify the recorded sex of the subjects. This coding is purely methodological and does not imply any further classification or interpretation.

Table S4.3* TVB Optimization parameters			
ID	PCC	Ks	cost function
Subject1	0.222248909	0.072781655	0.850532746
Subject2	0.180407147	0.147414898	0.967007751
Subject3	0.204815915	0.035607463	0.830791548
Subject4	0.239050856	0.094003703	0.854952847
Subject5	0.297318741	0.02891326	0.731594519
Subject6	0.201918425	0.044722974	0.842804549
Subject7	0.347998512	0.050277738	0.702279226
Subject8	0.255526633	0.113231733	0.8577051
Subject9	0.34137709	0.030907278	0.689530188
Subject11	0.366889218	0.069505768	0.70261655
Subject12	0.217135778	0.047286711	0.830150933
Subject13	0.192443752	0.070360348	0.877916596
Subject14	0.225878212	0.084745763	0.858867551
Subject15	0.138302071	0.026776812	0.888474741
Subject16	0.252103084	0.072069506	0.819966422
Subject17	0.300471727	0.117362199	0.816890472
Subject18	0.262248104	0.098703888	0.836455784

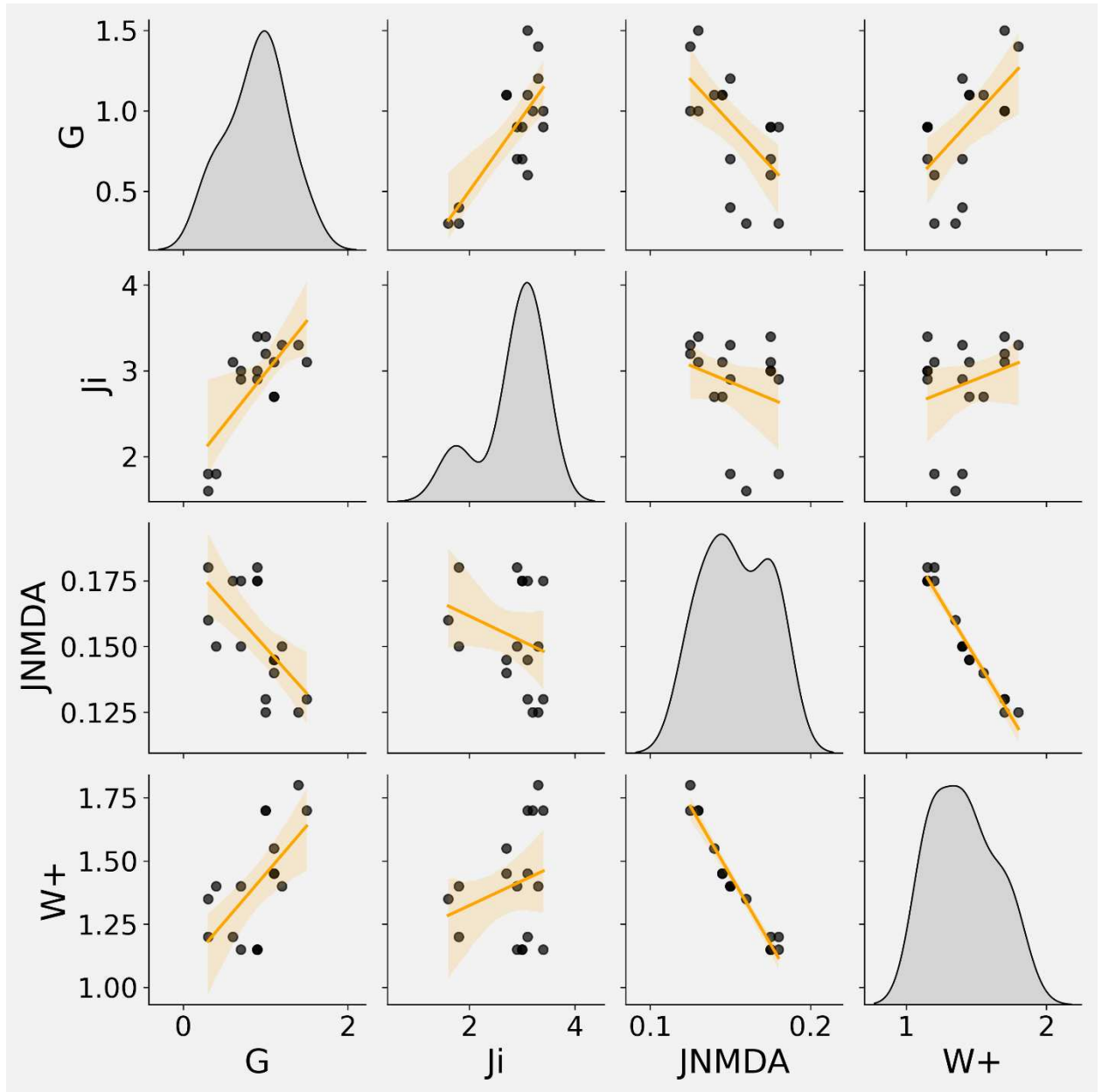


Figure S4.1a Relationships between TVB model parameters. Scatter matrix with regression fits (Spearman analysis) of the TVB model parameters. Each cell displays a scatter plot showing the data distribution and trends between two variables, complemented by an orange regression line with a corresponding confidence band. The diagonal presents the univariate distributions of each variable, allowing the viewer to appreciate their individual behavior.

A strong negative correlation is observed between J_{NMDA} and $w +$, indicating that as one of these parameters increases, the other consistently decreases. This pattern is the most evident in the plot, with a steep slope and a cluster of points aligned along the trend.

On the other hand, a positive correlation is identified between G , and J_i , suggesting that these two parameters increase together. Although the relationship is clear, it exhibits more dispersion compared to the negative correlation between J_{NMDA} and $w +$, implying that while they are related, other factors may influence their variability.

A negative relationship is also observed between G , and J_{NMDA} , suggesting that when the GG parameter takes higher values, J_{NMDA} tends to decrease. In contrast, the relationship between J_i and $w +$ is positive but more diffuse, indicating a possible dependency, although not as strong as in other variable pairs.

The individual distributions of each parameter, shown in the diagonal of the plot, reveal that some variables exhibit greater asymmetry or dispersion in their values. This is important because it

indicates that certain variables do not follow normal distributions, which could impact the type of statistical analysis to be used.

Finally, while the pairplot allows for the visualization of general trends, not all relationships appear strictly linear. Some point distributions suggest the possible presence of more complex relationships.

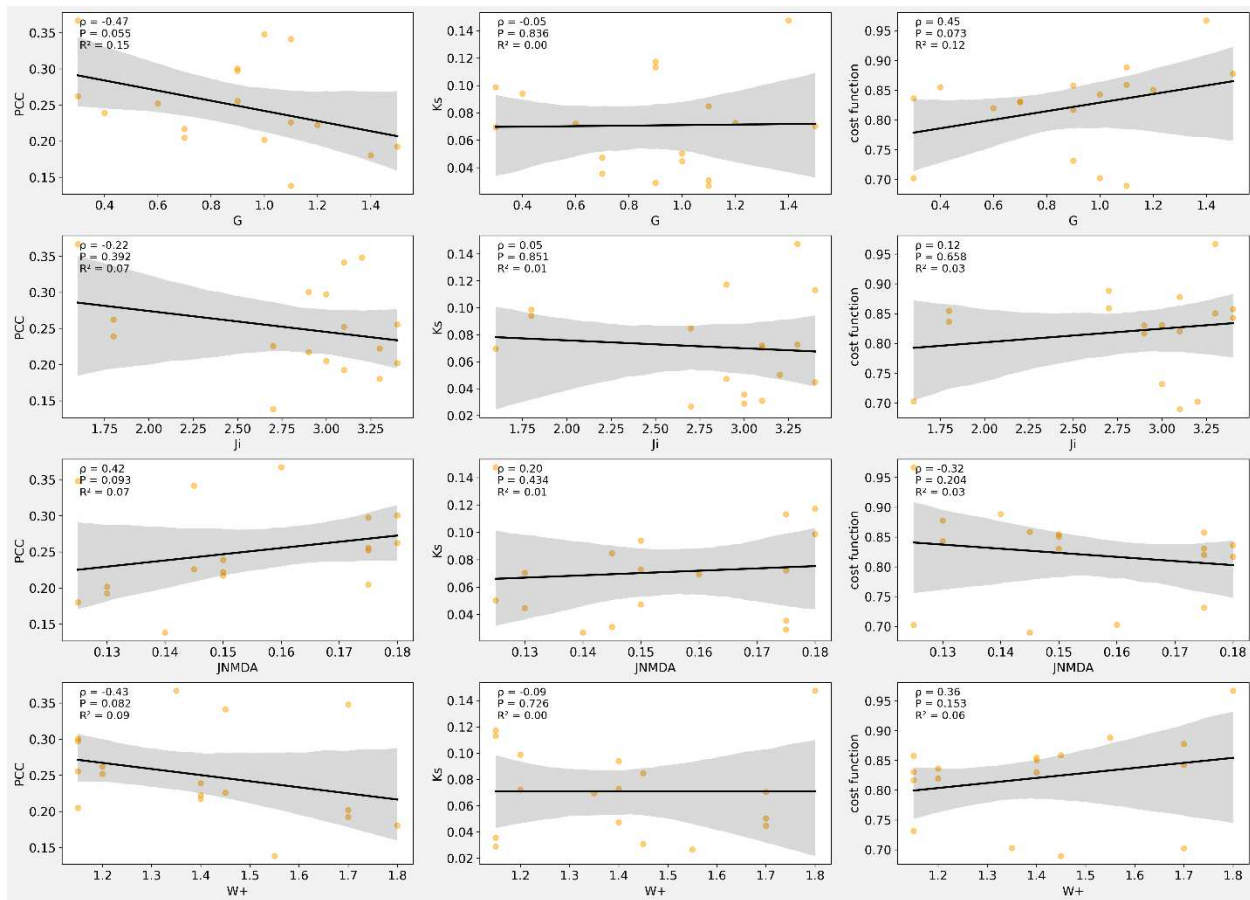


Figure S4.1b Relationships between TVB model parameters and optimization metrics. Scatter plots showing the relationships between TVB model parameters (G , J_i , J_{NMDA} , and $w+$), and optimization metrics (PCC, KS, and cost function). Spearman's rank correlation coefficient (ρ), p-values, and R^2 values from linear regression are reported in each panel. While some parameters exhibit moderate correlations, none reach statistical significance, suggesting potential underlying complexities in the optimization process. The shaded area represents the confidence interval of the regression fit.

The scatter plots illustrate the relationships between the TVB model parameters and the optimization parameters (PCC, KS, and cost function). One of the most notable findings is the moderate negative correlation between G and PCC, suggesting that higher values of G tend to be associated with lower PCC scores. However, the statistical significance is marginal. Similarly, $w+$ also shows a negative correlation with PCC, indicating a potential inverse relationship, though not reaching strong significance. In contrast, J_{NMDA} appears to have a moderate positive correlation with PCC, suggesting that as J_{NMDA} increases, PCC may also increase, though again without clear statistical confirmation.

Regarding KS, the correlation coefficients are close to zero across all parameters, with high p-values indicating no apparent relationship between the TVB model parameters and KS. This suggests that the KS metric remains largely unaffected by variations in G , J_i , J_{NMDA} , and $w+$. For the cost function, G shows a moderate positive correlation, implying that higher values of G might correspond to higher cost function values, though this relationship is not statistically significant. J_i exhibits a weak correlation with the cost function, suggesting no clear association. J_{NMDA} presents a weak negative correlation, hinting at a slight tendency for higher J_{NMDA} values to correspond to lower cost function values, though without statistical significance. Similarly, $w+$

demonstrates a moderate negative correlation with the cost function, indicating that larger values of $w + \text{might}$ be associated with lower cost function values, albeit with weak statistical support. Overall, while certain trends can be observed, none of the relationships reach statistical significance. This suggests that additional factors may be influencing the optimization parameters or that the relationships between the TVB model parameters and the optimization criteria are more complex than can be captured by simple linear or monotonic correlations. Subject-specific matrices provide deeper insights into interindividual variability and allow for a more precise assessment of model accuracy at the individual level. Here, we present the connectivity matrices of a randomly selected subject (Subject 9 in this case), chosen without any prior criteria or bias, solely for illustrative purposes.

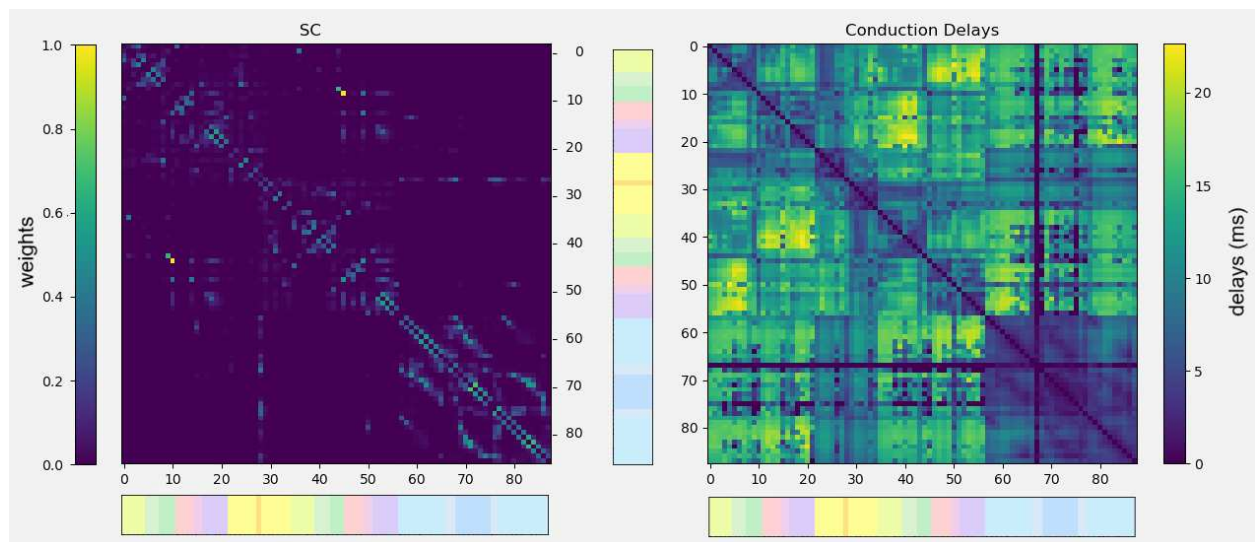


Figure S4.2 Structural Connectivity and Conduction Delay Matrices (single subject). Each node represents a brain region according to Table S1 (pastel colours), and each element in the matrix indicates the connectivity strength between two regions. The left matrix depicts SC, measuring anatomical connection strength via diffusion tractography. The right matrix illustrates conduction delays, representing the time (in milliseconds) for neural signals to propagate between connected regions. The colour bars indicate connection weights (left) and transmission delays (right), where higher values correspond to stronger structural connections and longer transmission times, respectively.

In line with the Mean SC and Delay matrices illustrated in Figure 4.11, the Subject SC and Delay matrices maintain a clear modular organization and a similar distribution of conduction delays. However, unlike the mean, the individual subject exhibits higher structural connectivity weights (up to 1.0 vs. 0.8 in the mean), indicating stronger connections in certain regions. Although delays have the same range in both cases (0-20 ms), individual variability in structural connectivity could influence the subject's functional synchronization.

Similar to Figure 4.12, the Subject FC exhibits a comparable modular structure, indicating consistent functional patterns. However, this comparison suggests that averaging smooths out individual variability, whereas the specific subject demonstrates greater functional synchronization in certain regions. Moreover, the simulation for the subject appears to produce stronger correlations than the mean, potentially indicating a better adaptation of the model at the individual level.

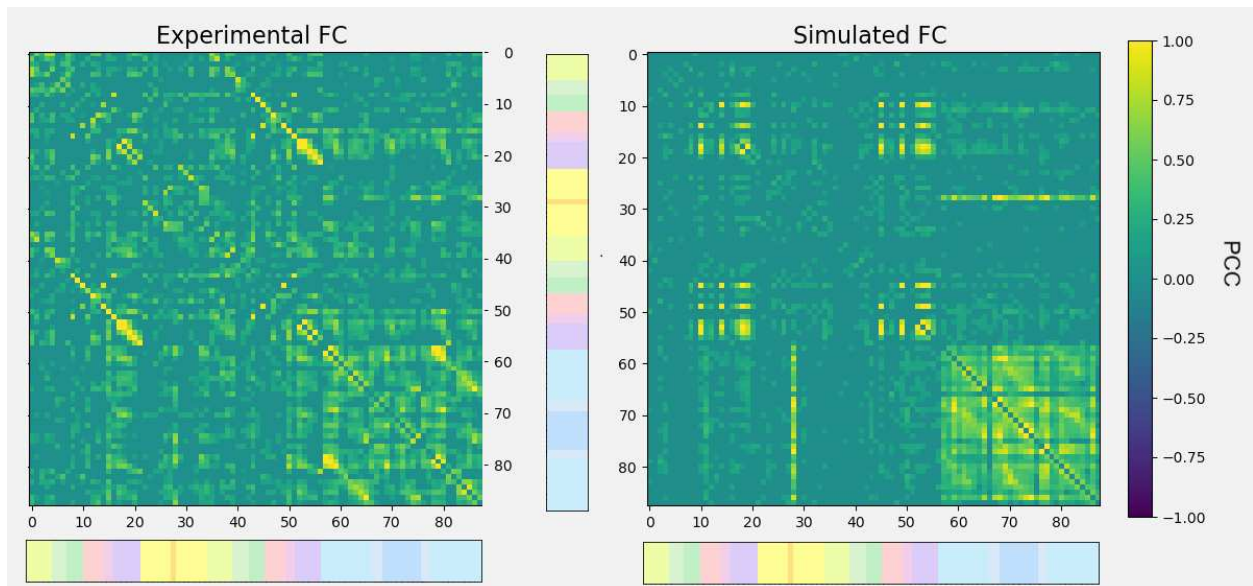


Figure S4.3 Comparison between the experimental and simulated functional connectivity matrices (single subject). Each node represents a brain region according to Table S1 (pastel colours), and each element in the matrix corresponds to the Pearson correlation coefficient (PCC) between the time courses of two distinct regions. The left matrix displays the experimental FC, derived from empirical data, while the right matrix represents the simulated FC, generated by the computational model. The colour bar indicates the strength of the correlation, with higher values reflecting greater functional synchronization between regions.

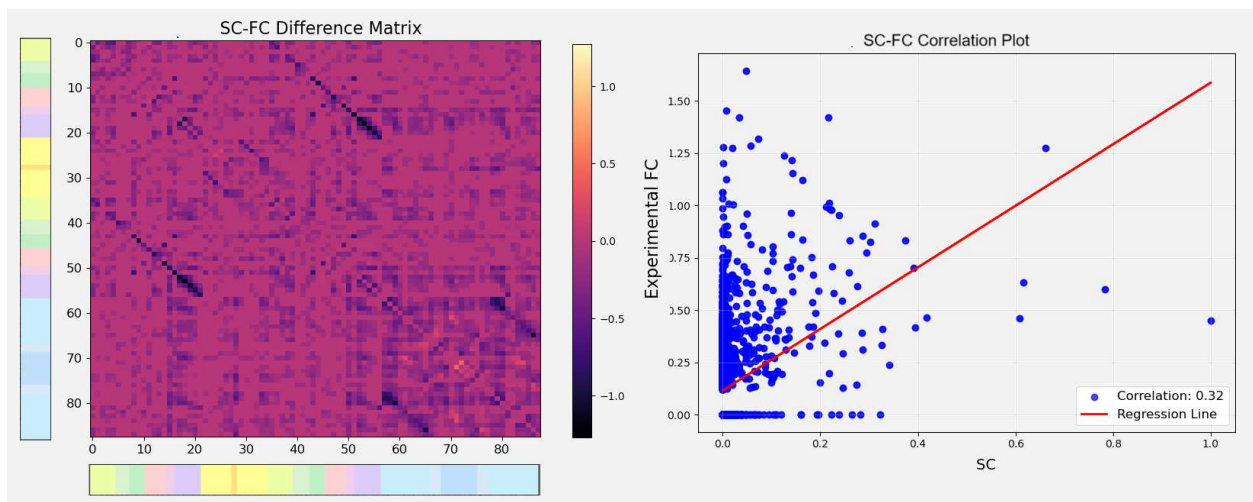


Figure S4.4 Structural-Functional connectivity matrices comparison (single subject). (Left) The difference matrix represents the element-wise subtraction of the SC from the FC, highlighting discrepancies between anatomical connections and functional correlations. Warmer colours indicate regions where FC exceeds SC, while cooler colours denote the opposite. (Right) The correlation plot quantifies the relationship between SC and FC, with each point representing a connection between two brain regions. The red regression line illustrates the trend, and the reported correlation coefficient reflects a moderate agreement between SC and FC.

Both Mean SC-FC (Figure 4.13) and Subject SC-FC exhibit a modular pattern with discrepancies between structural and functional connectivity in certain regions, and both show a positive relationship between SC and FC. Additionally, SC-FC correlation is lower in the subject (0.32 vs. 0.50 in the mean), reflecting greater individual variability. Increased data dispersion is also observed in the subject, suggesting that the SC-FC relationship is influenced by neural dynamics and conduction delays specific to the individual.

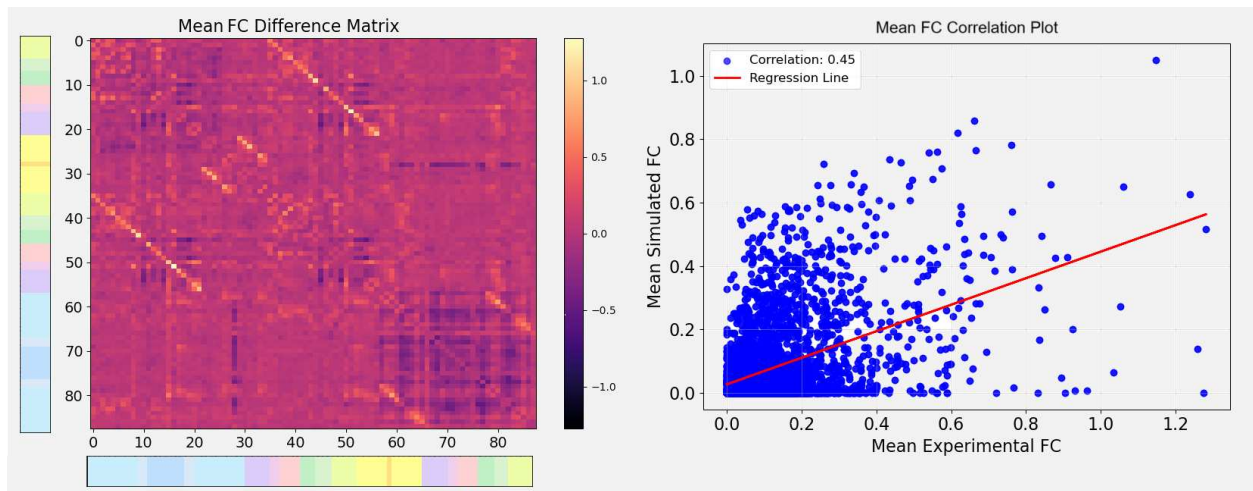


Figure S4.5 Experimental-Simulated Functional connectivity matrices comparison (single subject). (Left) The difference matrix represents the element-wise subtraction of the simulated FC from the experimental FC, highlighting discrepancies between simulated and real functional connectivity. Warmer colours indicate regions where experimental FC exceeds simulated FC, while cooler colours denote the opposite. (Right) The correlation plot quantifies the relationship between experimental and simulated FC, with each point representing a connection between two brain regions. The red regression line illustrates the trend, and the reported correlation coefficient reflects a moderate agreement between the experimental and simulated FC.

Comparable to Figure 4.14, Subject FC shows a positive but non-uniform relationship between experimental and simulated functional connectivity. In both cases, data points are highly concentrated at low values, with increasing dispersion as experimental FC increases. The subject-specific distribution suggests a greater proportion of moderate correlations, reflecting individual differences in functional synchronization. Additionally, the lower correlation in the subject (0.34 vs. 0.45 in the mean) indicates greater variability in how the model captures functional connectivity, emphasizing the need for personalized simulations.

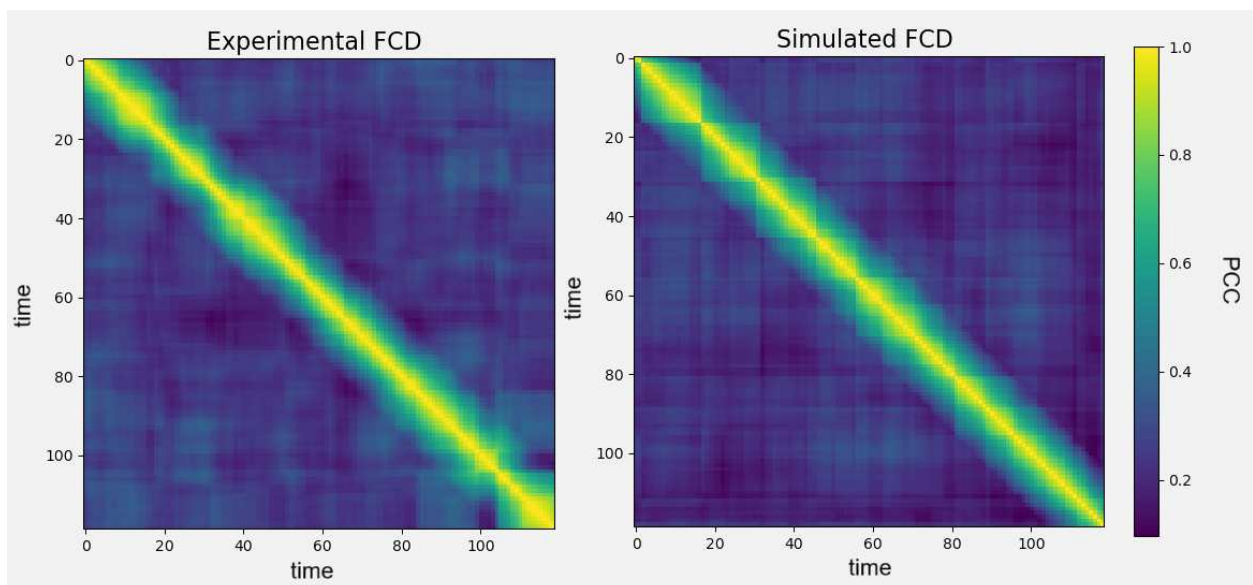


Figure S4.6 Experimental and Simulated Functional Connectivity Dynamics matrix (single subject). (Left) The experimental FCD matrix represents the temporal evolution of functional connectivity by computing the Pearson correlation between time-resolved functional connectivity windows. Higher values (yellow) indicate stable connectivity patterns over time, while lower values (dark blue) reflect transient or fluctuating connectivity states. (Right) The simulated FCD matrix shows the model's ability to replicate the temporal dynamics of functional connectivity.

Both FCD matrices display a highly similar functional connectivity pattern, with a pronounced diagonal that indicates the temporal coherence of correlations in each window. However, the experimental matrix exhibits slight irregularities off the diagonal, reflecting greater variability or “noise” inherent to real data, whereas the simulated matrix appears somewhat more uniform and stable. These differences suggest that, although the model satisfactorily reproduces the global dynamics of functional connectivity, the complexity and variability present in experimental data are captured by more pronounced fluctuations that are not as evident in the simulation.

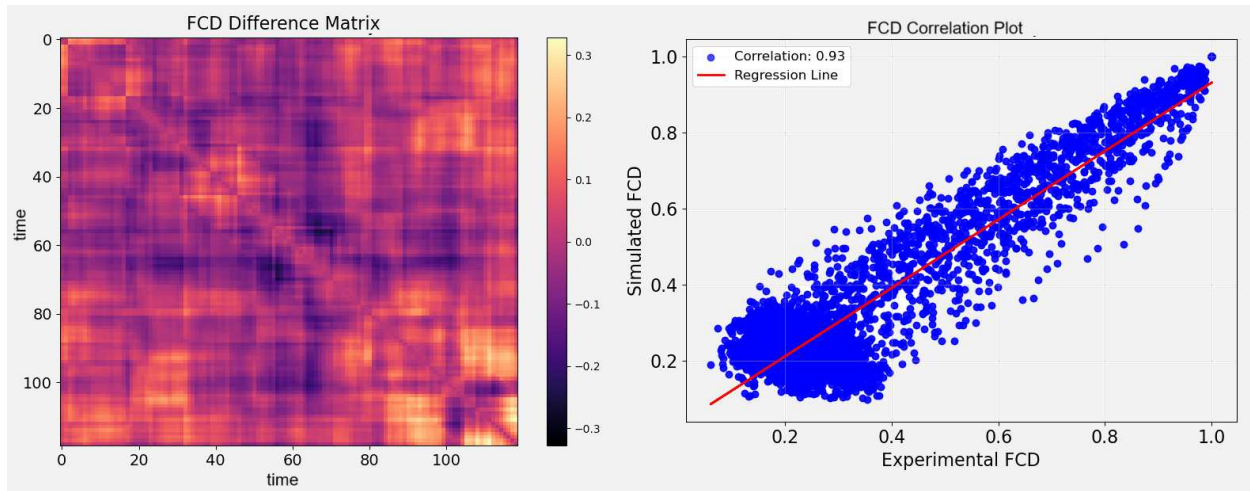


Figure S4.7 Experimental-Simulated Functional Connectivity Dynamics matrices comparison (single subject). (Left) The difference matrix represents the element-wise subtraction of the simulated FCD from the experimental FCD, highlighting discrepancies between simulated and real functional connectivity. Warmer colours indicate regions where experimental FC exceeds simulated FC, while cooler colours denote the opposite. (Right) The correlation plot quantifies the relationship between experimental and simulated FC, with each point representing a connection between two brain regions. The red regression line illustrates the trend, and the reported correlation coefficient reflects a high agreement between the experimental and simulated FCD

The FCD Difference Matrix (left) shows that, although there are some localized discrepancies, the overall differences between simulated and experimental FCD are relatively small. On the right, the FCD Correlation Plot reveals a strong linear relationship ($r = 0.93$) between simulated and experimental FCD values, with most points clustering tightly around the regression line. Taken together, these findings indicate that the model closely replicates the temporal dynamics of functional connectivity observed in the experimental data, despite minor regional variations.

Table S4.4* SCR Data and Metrics in Acquisition and Extinction											
ID	baseline_scl	acq_csp mean	acq_csm mean	acq_us mean	ext_csp mean	ext_csm mean	US/CS+	US/CS-	CS+/CS-	CS+/CS+ext	CS-/CS-ext
Subject1	0,057564	0,170505	0,059152	2,865998	---	---	16,8089	48,4516	2,8825	---	---
Subject2	0,075484	0,022626	0,02689	0,573473	---	---	25,3453	21,3269	0,84146	---	---
Subject3	0,037177	0,02292	0,006174	0,489101	0,09774	0,00512	21,3391	79,2219	3,71252	0,23449313	1,20571287
Subject4	0,032649	0,022842	0,00857	0,518474	0,00076	0,001783	22,6983	60,4959	2,66522	30,233668	4,80722065
Subject5	0,188614	0,198166	0,149672	0,93333	0,17451	0,097272	4,70984	6,23583	1,324	1,13554449	1,53869924
Subject6	0,052783	0,722984	0,429581	1,060061	0,20932	0,100871	1,46623	2,46766	1,683	3,454009	4,25873078
Subject7	0,157666	0,093096	0,188396	1,190889	0,07958	0,24501	12,792	6,32121	0,49415	1,16981581	0,76893012
Subject8	0,178504	0,144014	0,130386	0,978185	0,04232	0,036517	6,7923	7,50225	1,10452	3,40271512	3,57055052
Subject9	0,079667	0,321182	0,142668	1,409254	0,25711	0,196087	4,3877	9,87786	2,25126	1,24918265	0,72757436
Subject11	0,13787	0,64991	0,494105	0,365013	0,26362	0,110993	0,56164	0,73874	1,31533	2,46536281	4,45169093
Subject12	0,013386	1,156513	0,69784	0,592636	0,8902	0,370518	0,51243	0,84924	1,65728	1,29915672	1,88341536
Subject13	0,242398	0,719424	0,490529	3,053048	0,27825	0,04314	4,24374	6,22399	1,46663	2,58548495	11,3706612
Subject14	0,045538	0,47517	0,355764	1,497513	0,45116	0,466022	3,15153	4,20928	1,33563	1,05322877	0,76340712
Subject15	0,095883	0,300875	0,130064	1,851126	0,7226	0,611101	6,15248	14,2324	2,31327	0,41637602	0,21283636
Subject16	0,281753	1,059864	0,489891	3,20904	0,57665	0,281699	3,02779	6,55052	2,16347	1,8379523	1,73905777
Subject17	0,035422	0,00562	0,00646	0,192843	0,24292	0,365414	34,3126	29,8524	0,87001	0,02313551	0,01767828
Subject18	0,007852	0,512903	0,332769	1,998217	0,21434	0,199117	3,8959	6,00482	1,54132	2,39289391	1,67121856

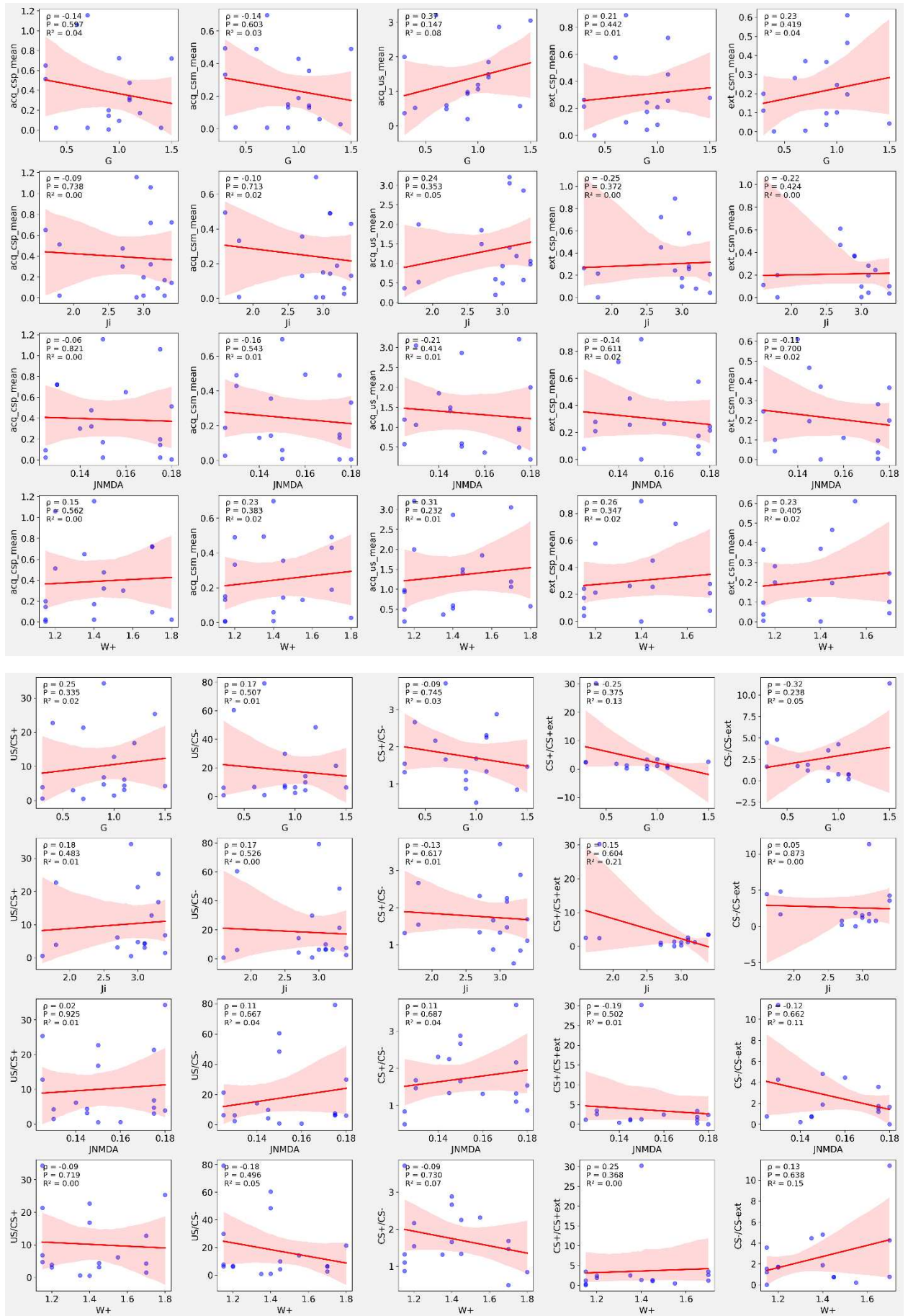


Figure S4.8 Correlation between fear-related behavioral measures and TVB model parameters.

The correlation analysis between TVB model parameters and behavioral measures of fear acquisition and extinction reveals no statistically significant relationships. The majority of Spearman correlation coefficients (ρ) are close to zero, and p-values remain well above the 0.05 threshold, indicating weak or no associations between neural dynamics at rest and fear-related behavioral performance. Furthermore, the low R^2 values ($\approx 0.00 - 0.08$) suggest that the TVB parameters explain minimal variance in the behavioral measures, implying limited predictive power of the resting-state network dynamics for fear discrimination or extinction processes. Although minor trends, such as a weak positive correlation between G and extinction-related measures, can be observed, none reach statistical significance.

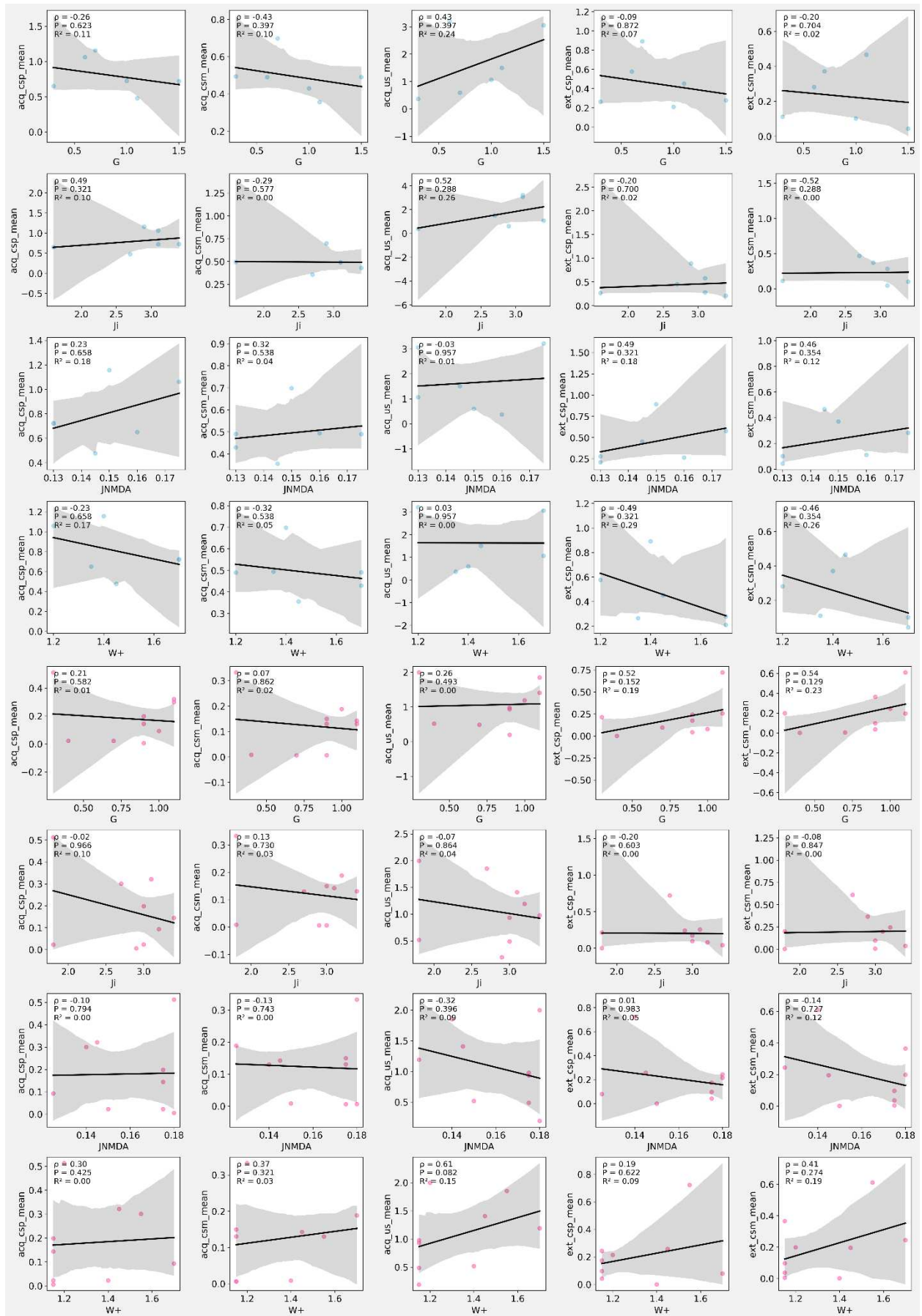
The correlation analysis between TVB model parameters and fear-related behavioral ratios reveals no statistically significant relationships. Most Spearman correlation coefficients (ρ) are close to zero, and p-values remain high, indicating weak or no associations between resting-state neural dynamics and behavioral performance. Additionally, R^2 values are low (mostly < 0.05), suggesting that the TVB parameters explain minimal variance in fear discrimination and extinction processes. However, a weak negative correlation between G and CS+/CS-ext suggests that higher global coupling may be slightly associated with reduced fear extinction discrimination. Similarly, J_{NMDA} shows a weak negative trend with CS+/CS-ext, though the effect size remains small and non-significant.

Figure S4.9 shows trends that do not reach conclusive statistical significance, but we highlight the most predominant ones: In men, a moderate positive correlation between inhibitory synaptic coupling J_i and CS+ responses during acquisition ($\rho=0.49$) suggest a possible link between increased inhibition and heightened conditioned responses. Similarly, J_{NMDA} shows weak positive correlations with CS+ and CS- responses during acquisition. In contrast, extinction measures (ext_csp_mean, ext_csm_mean) display no meaningful correlations with any TVB parameter, apart from a weak negative trend between J_i and ext_csm_mean ($\rho=-0.52$) should be interpreted cautiously given the small sample size and confidence interval. G and $w+$ do not show clear associations with either acquisition or extinction responses.

In women, a moderate positive correlation is observed between G and extinction measures (ext_csp_mean: $\rho=0.52$; ext_csm_mean: $\rho=0.54$), suggesting a possible trend where higher global coupling might be linked to greater persistence of conditioned responses during extinction. For acquisition measures, there are no meaningful correlations with any TVB parameter.

The correlation analysis in men participants reveals mostly weak to moderate correlations, with a few showing stronger trends. G shows a moderate positive correlation with US/CS+ ($\rho=0.71$, $p=0.111$, $R^2=0.55$), suggesting a potential relationship between global coupling strength and fear discrimination between the unconditioned stimulus (US) and CS+. However, this finding is not statistically robust given the p-value. Similarly, J_i exhibits moderate correlations with US/CS- ($\rho=0.52$, $p=0.288$, $R^2=0.25$) and CS+/CS- ($\rho=0.50$, $p=0.200$, $R^2=0.31$), suggesting a possible trend where increased inhibition could be linked to stronger differentiation between conditioned stimuli. J_{NMDA} and $w+$ exhibit generally weak correlations, with some moderate positive trends for CS+/CS+ext and CS-/CS-ext, particularly for $w+$ ($\rho=0.46$, $R^2=0.35$ for CS+/CS+ext and $R^2=0.43$ for CS-/CS-ext), indicating that local excitatory recurrence might play a role in extinction-related changes. In women participants, G exhibits weak negative correlations with most behavioral measures, including CS+/CS- ($\rho=-0.25$, $p=0.436$, $R^2=0.06$) and CS+/CS+ext ($\rho=-0.30$, $p=0.416$, $R^2=0.31$). A moderate negative correlation is observed between G and CS-/CS-ext ($\rho=-0.67$, $p=0.047$, $R^2=0.32$), suggesting a possible trend where higher global coupling is associated with reduced extinction-related changes in CS- CS-CS-responses.

Inhibitory coupling J_i shows weak to moderate negative correlations with CS+/CS- ($\rho=-0.47$, $p=0.201$, $R^2=0.07$) and CS+/CS+ext ($\rho=-0.52$, $p=0.166$, $R^2=0.39$), indicating that increased inhibition might be linked to weaker fear discrimination or extinction-related effects, though these findings do not reach strong significance. J_{NMDA} and $w+$ display weak or inconsistent trends, with most correlations near zero, except for a moderate negative trend between $w+$ and CS-/CS-ext ($\rho=-0.23$, $p=0.508$, $R^2=0.53$), suggesting a weak potential relationship between local excitatory recurrence and extinction-related changes in CS- CS-CS-responses. Given the limited sample size and confidence intervals, these results should be interpreted cautiously. Overall, while some trends emerge, none of the correlations reach strong statistical significance.



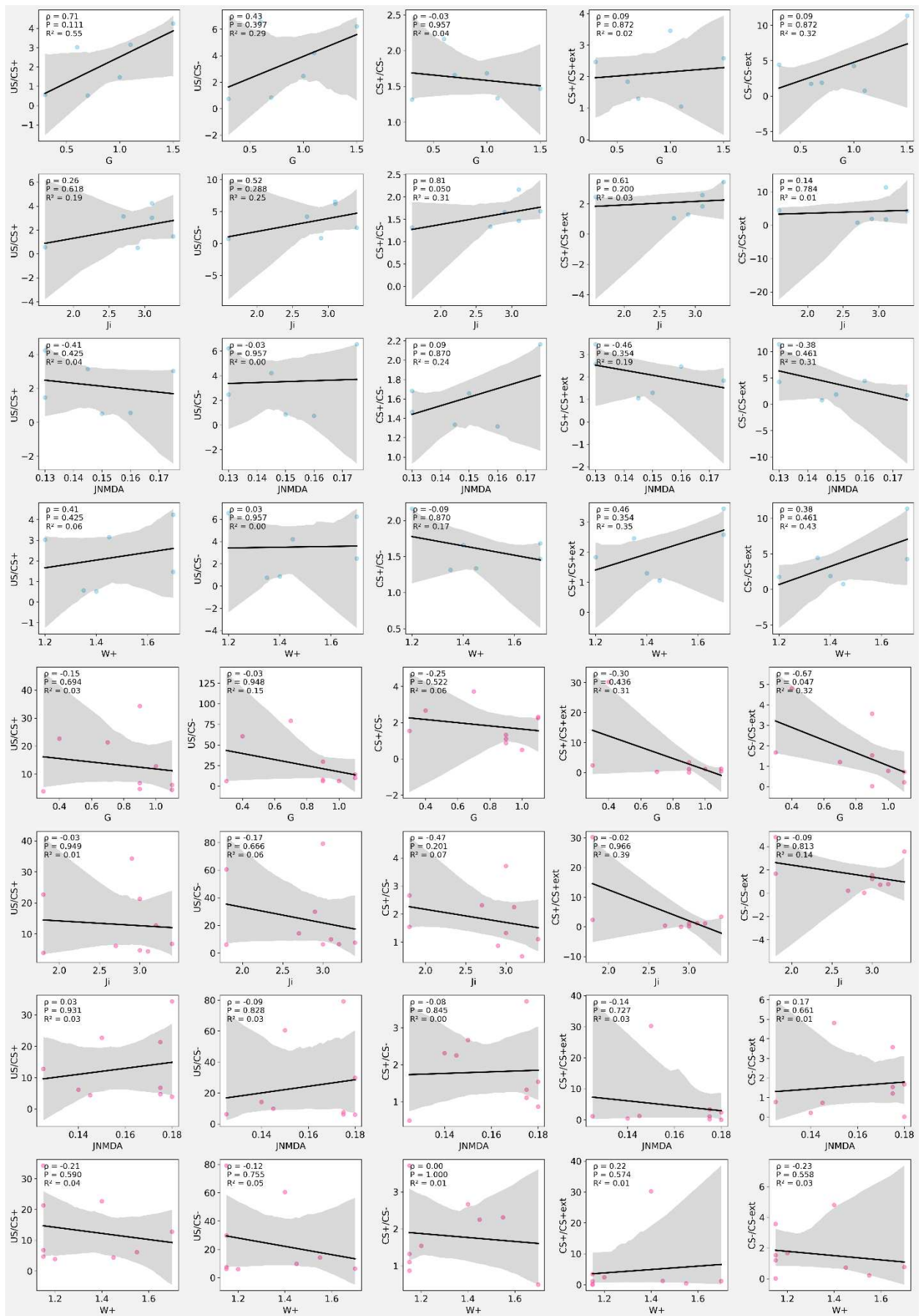


Figure S4.9 Correlation between fear-related behavioral measure and TVB model parameters by sex.

General Conclusions

This thesis set out to explore the cerebellum's role in emotional processing by employing a multiscale, cross-species computational modeling approach, centered on fear conditioning. Rather than constructing a single continuous model, the research developed complementary simulations at the microcircuit level in rodents and the macroscale network level in humans. These models were intended as proof-of-concept frameworks—not to offer definitive answers, but to support hypothesis generation, theoretical clarification, and experimental design.

The work spanned multiple levels of analysis, from foundational reflections on the concept of emotion to data-driven reconstruction of cerebellar microcircuits, and finally to large-scale simulations of fear learning in humans. In doing so, it contributes to the growing understanding of the cerebellum not only as a motor structure but also as a modulator of emotional and cognitive functions. Through integration of platforms such as the Brain Scaffold Builder, NEST, and The Virtual Brain, this research probed how structural and functional properties of cerebellar circuits—embedded in broader brain networks—may shape emotional behavior.

A central contribution of this thesis lies in its demonstration of how computational models can bridge data gaps, test mechanistic hypotheses, and guide experimental exploration, especially in emerging domains where empirical data are sparse or incomplete. This is particularly evident in the reconstruction of lobule VI (Declive), a region consistently implicated in emotional processing. The model maintained robust anatomical features but also revealed several biological limitations, including imbalances in inhibitory neuron densities and deviations in Purkinje cell firing properties. Addressing these challenges provided concrete directions for future refinements, including the incorporation of zebrin-related molecular identities, better connectivity rules, and region-specific electrophysiological data.

In parallel, rodent circuit simulations modeled learning dynamics relevant to Pavlovian and fear conditioning. While the model could not fully represent emotional learning due to missing synaptic plasticity parameters and circuit-level data, especially from the PAG, it proposed a realistic framework for future co-simulation strategies. These would incorporate plasticity mechanisms and explore bidirectional interactions between the cerebellum and key emotional hubs such as the vIPAG, VTA, and mediodorsal thalamus. This phase of the project underscored how even partially complete models can generate experimentally testable predictions and help prioritize future data collection.

Furthermore, the model offers specific predictions that can be empirically tested: temporally precise Purkinje and deep cerebellar nucleus activity during conditioned stimulus (CS) and unconditioned stimulus (US) intervals, learning-dependent modulation of firing synchrony, and target-specific influence on motor and autonomic fear responses via outputs such as the periaqueductal gray. These predictions are not merely theoretical but reflect plausible outcomes based on known cerebellar circuitry. At the same time, the model highlights areas where critical data are lacking—including electrophysiological recordings during emotional tasks, detailed input–output mappings of emotional circuits, and the timing of synaptic plasticity markers. By articulating these gaps, the model establishes a roadmap for targeted experimentation. Importantly, the modeling framework developed for lobule VI is anatomically grounded and computationally scalable, allowing future extensions to other cerebellar regions involved in emotional and cognitive processing with minimal methodological adjustment.

At the human macroscale level, large-scale simulations revealed the influence of structural and dynamic brain features on fear learning and extinction. Although the model successfully replicated dynamic functional connectivity (FCD), its ability to reproduce static functional connectivity (FC) was limited, primarily due to variability in individual tractography data and structural constraints of the atlas. Notably, sex-related differences in extinction learning and connectivity profiles were observed, suggesting that hormonal and neurotransmitter-related mechanisms may underlie individual variability in fear regulation. These findings argue for more personalized, multimodal modeling approaches that integrate neurochemical, hormonal, and structural data.

Limitations across all modeling scales were not only acknowledged but also used as constructive entry points for future research. From the need to refine Purkinje cell placement in mouse cerebellar circuits, to the integration of PET and DTI data for individualized connectomes, and the incorporation of NMDA- and GABA-dependent mechanisms in emotional learning, each challenge is mapped directly onto a future direction. This iterative relationship between model construction, validation, and refinement represents a methodological strength of the thesis.

The work also emphasizes the value—and necessity—of interdisciplinary collaboration. This thesis lays out both a methodological pathway and a set of computational tools for investigating the cerebellum's role in fear, anxiety, and neurodevelopmental disorders. Rather than providing definitive answers, it demonstrates how biologically grounded modeling can be integrated into interdisciplinary research to explore complex functions.

Achieving this kind of integration will require sustained coordination across diverse domains, including behavior, neuroimaging, neuroanatomy, and computational modeling. Future projects will need to actively contribute to and benefit from dynamic, interdisciplinary research environments, as addressing complex questions in affective neuroscience demands truly integrated science. Importantly, such efforts will also need to overcome the conceptual and methodological gaps that often arise when bridging traditionally separate fields.

In conclusion, this thesis contributes a foundational step toward biologically grounded modeling of the cerebellum's role in emotion. It advances the field conceptually by clarifying what it means to model emotion; methodologically, by offering scalable modeling pipelines across species and resolution levels; and scientifically, by highlighting concrete mechanisms that may underlie cerebellar involvement in emotional learning. Future work building on this foundation will benefit from increasingly integrative approaches—linking molecular, cellular, and systems neuroscience to a unified framework for emotional modeling. This vision is not only necessary for advancing basic science but may ultimately inform translational strategies for mental health conditions rooted in emotional dysregulation.

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