UNIVERSITY OF PAVIA
DEPARTMENT OF BRAIN AND BEHAVIORAL SCIENCES
Doctoral Program in Psychology, Neuroscience and Data Science
Doctorate Cycle XXXII

SPATIAL ATTENTION ASYMMETRIES: BEHAVIORAL AND NEURAL EVIDENCE

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Academic year 2018/2019

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ABSTRACT

Spatial attention, the ability to process information selectively within a certain location in space, is not symmetrically distributed across the visual field. Accordingly, asymmetrical activations between hemispheres together with the dominant role played by the right hemisphere in visuospatial processing cause spatial attention to be biased towards the left side of the space, a phenomenon known as *pseudoneglect*. Interestingly, when asked to estimate the midpoint of a horizontal line, healthy participants place a mark slightly shifted toward the left of the veridical centre, due to the left portion of the line being perceived as longer than it actually is, as a result of an overestimation of the left side of the space. Interestingly, similar attentional biases have been demonstrated not only in the horizontal orientation but also in the vertical and radial planes, with healthy individuals showing an upward and distal bias, respectively. Nevertheless, vertical and radial spatial asymmetries seem to rely on asymmetrical activations between the ventral and dorsal streams, rather than between cerebral hemispheres. However, the relationship between spatial asymmetries across orientations, whether they depend on similar underlying mechanisms or tap to distinct cognitive/neural processes is still unclear. Hence, further investigations on this issue are valuable.

Furthermore, leftward attentional biases have been reported also in the absence of any visual input, for instance in the haptic modality, as demonstrated by haptic rods bisections. Interestingly, the consistent leftward bias shown by many studies on haptic bisections suggests that common attentional control mechanisms are at play across modalities. However, other investigations report only weak correlations between visual and haptic spatial asymmetries, thus suggesting that the two biases might be driven by distinct underlying processes. Additionally, normal individuals show a tendency to overestimate the left side of mental representations, the so-called representational pseudoneglect. Fascinatedly, in line with the assumption that numbers are represented as lying on an imaginary line oriented from left to right, healthy participants deviated towards lower numbers, when instructed to report the midpoint of a numerical interval without any calculation, thus showing a leftward bias comparable to that for physical lines. Similarly, if asked to memorize the elements of a visual

scene, subjects show a tendency to recall more items on the left than those on the right. However, the cognitive and neural underpinning of representational biases and their relationship with perceptual spatial asymmetries is still an issue that requires further investigations.

Therefore, it appears evident that in spite of the considerable amount of studies conducted on this topic in the last 30 years, several open questions remain to be investigated. In the present dissertation, I report part of the studies I carried out during my PhD in order to address some of the unsolved issues on spatial asymmetries.

The purpose of the first chapter is to provide a general overview of the main evidence on spatial asymmetries gathered through experimental investigations and clinical observations. In particular, psychophysical, neuropsychological, neuroimaging, electrophysiological and neurophysiological data are presented with the aim to describe how spatial attention is deployed in the general and clinical populations (e.g. with a particular interest in patients with brain lesions and blind individuals). Evidence reported here, describing the underlying cognitive and neural mechanisms of spatial asymmetries in different tasks, across different orientations and sensory modalities represent the theoretical and empirical basis on which the three studies, the core of the present dissertation, have been built upon.

To begin with, the experimental section of the thesis opens with a psychophysical investigation on the effect of cognitive load on horizontal and vertical spatial asymmetries. Indeed, previous researches have demonstrated that increasing cognitive load by introducing a secondary task, for instance in dual-task paradigm, reduced detection of targets presented in the left hemispace (e.g. information processed in the right hemisphere) compared to those in the right. Nevertheless, other investigations failed to report similar findings or suggested that load effects may depend on the overlap in content-specific processing between primary and secondary tasks. Interestingly, despite showing that cognitive load affects spatial asymmetries in the horizontal plane, previous research has not considered the effect of load on spatial asymmetries in the vertical dimension. Therefore, the aim of this first study was two-folded. Firstly, we were interested in investigating whether and how vertical attentional biases are modulated in dual-task conditions. The second goal was to study the relationship between horizontal and vertical attentional biases. To these aims, healthy participants were asked to carry out a line bisection (Experiment 1a) and a landmark task (Experiment 1b) in single and dual-task conditions (e.g. while concurrently performing an auditory working memory task), both in horizontal and vertical orientations. Our data demonstrated that increasing cognitive load reduced attentional biases in the line bisection task (Experiment 1a), whereas it increased spatial asymmetries in the landmark task (Experiment 1b). Interestingly, no differences between horizontal and vertical orientations were found. The similar effect of load on horizontal and vertical judgements challenged the idea that the two biases might be separated and suggested that they may depend on only partially functional independent mechanisms. Moreover, the disparate effects of load across the two experiments suggested that the effect of load might depend on the task at hand and confirmed prior evidence proposing that line bisection and landmark tasks might be engaging different mechanisms.

In the second study, we investigated the role of a normal binocular vision in driving pseudoneglect in the visual and haptic modalities. Indeed, evidence demonstrated that blind individuals show leftward biases in both haptic bisections and mental representations as control sighted participants, thus demonstrating that a normal visual experience is not necessary to the development of a right hemispheric dominance for visuospatial processing. However, the total lack of visual input may have different effects on lateralization patterns compared to distorted visual input, as suggested by studies in strabismic amblyopes that do not exhibit pseudoneglect in visual and number line bisections, suggesting a possible important role played by a normally developing binocular vision. In this study, we aimed to investigate whether an abnormal binocular childhood experience also affects spatial attention in the haptic modality, thus reflecting a supramodal effect. To this aim, we compared the performance of normally sighted, strabismic and early monocular blind participants in a visual and a haptic line bisection task. In visual line bisection, strabismic individuals tended to err to the right of the veridical midpoint, in contrast with normally sighted participants who showed pseudoneglect. Monocular blind participants exhibited high variability in their visual performance, with a tendency to bisect toward the direction of the functioning eye. In turn, in haptic bisection, all participants consistently erred towards the left of the veridical midpoint. Taken together, our findings demonstrated that a normal binocular visual experience shapes spatial asymmetries but only when visual feedback is available; moreover, our data support the view that pseudoneglect in the visual and haptic modality relies on different functional and neural mechanisms.

From a neural perspective, in Study 3 we explored the neural correlates of spatial asymmetries both on a perceptual and representational level. Although both perceptual and representational pseudoneglect are thought to depend on the activity of a right fronto-parietal network, recent evidence reported the existence of some differences in the contribution of brain regions both within and beyond this network. Accordingly, neuropsychological and neuroimaging studies suggested a possible role of cerebellar regions in mediating spatial attention mechanisms (in the physical and/or representational space). However, evidence is not consistent and the extent and significance of the cerebellar contribution are not clear. Here, we aimed to shed light on this issue by means of two online neuronavigated transcranial magnetic stimulation (TMS) experiments. In Experiment 3a participants completed a landmark task in two orientations (horizontal and vertical) while receiving single-pulse TMS over the cerebellar vermis, the visual cortex and the vertex (control sites). TMS over the vermis did not modulate participants' bias or response times, whereas TMS over the visual cortex delayed response latencies. In Experiment 3b, participants completed a landmark task and a number bisection task while TMS was delivered over the cerebellar vermis, the left cerebellar hemisphere, and the vertex. Neither cerebellar TMS affected participants' performance in the landmark task. Critically, TMS over the left cerebellar hemisphere slowed down participants' response latencies in the number bisection task. Our data suggest that the left cerebellar hemisphere (but not the vermis) is causally implied in spatial attentional mechanisms in numeric intervals, but not physical lines, bisection. Therefore, our findings shed light on the neural underpinning of spatial attentional orienting in the physical and representational space, by showing that the left cerebellar hemisphere (and not the vermis) should be considered, together with right parietal and frontal regions, as part of a cerebello–fronto-parietal network deputed to drive spatial attentional mechanisms at least in the representational space. Finally, our findings argue in favour of dissociation of mechanisms driving perceptual and representational biases, in line with studies showing a lack of correlation between biases in line and number bisection tasks.

Finally, the last chapter of the dissertation discusses and integrates the main findings of the studies illustrated in the experimental chapters.

Science tells us we are not angels, we are merely sophisticated apes.
Yet we feel like angels trapped inside the bodies of beasts,
Craving transcendence and all the time trying to spread our wings and fly off.

V.S. Ramachandran. The Tell-Tale Brain, 2012

CHAPTER 1

Spatial attention asymmetries

Spatial attention asymmetries: the *pseudoneglect* phenomenon

1.1 Perceptual pseudoneglect

Spatial attention, the ability to focus attentional resources on an event or object presented in a specific portion of the space, is asymmetrically distributed across the visual field, due to asymmetrical activations between the left and right cerebral hemispheres. Accordingly, each cerebral hemisphere controls the orienting of attention toward the opposite side of the space, with these opposing orientational tendencies being in reciprocally inhibitory interaction (Duecker & Sack, 2015; Kinsbourne, 1970, 1987; Reuter-Lorenz, Kinsbourne & Moscovitch, 1990). Moreover, the right hemisphere has been consistently demonstrated to play a dominant role in visuospatial processing (Corbetta & Shulman, 2011; De Schotten et al., 2011; Foxe, McCourt & Javitt, 2003; Shulman et al., 2010); indeed, neglect patients with right hemisphere lesions fail to attend or respond to contralesional stimuli more than left hemisphere damaged patients (Heilman, Bowers, Valenstein & Watson, 1987; Suchan, Rorden & Karnath, 2012). Accordingly, when asked to estimate the midpoint of a horizontal line, a classical task developed to assess spatial attention abilities, neglect patients tend to place a mark to the right of the veridical centre, seemingly ignoring part of or underestimating the length of the left side of the line (McIntosh, Ietswaart & Milner, 2017; Milner, Harvey, Roberts & Forster, 1993). Conversely, neurologically healthy individuals err systematically to the left of the true midpoint, likely due to a tendency to overestimate the left side of the space (Jewell & McCourt, 2000). Interestingly, such leftward attentional bias, known as *pseudoneglect* (Jewell & McCourt, 2000), has been demonstrated to be susceptible to individual variables such as hand dominance (Brodie & Dunn, 2005; Ochando & Zago, 2018; Sampaio & Chokron, 1992), age (Benwell, Thut, Grant & Harvey, 2014; Brooks, Darling, Malvaso & Della Sala, 2016; see Friedrich, Hunter & Elia, 2018 for a review) (but not gender – Hausmann, Ergun, Yazgan & Güntürkün, 2002), cultural factors as reading direction habits (Rinaldi, Di Luca, Henik & Girelli, 2014). Moreover, difference in experimental manipulations such as line length (Benwell, Harvey & Thut, 2014; Nicholls, Beckman & Churches, 2016), cueing (McCourt, Garlinghouse & Reuter-Lorenz, 2005; Nicholls, Roden, Thomas, Loetscher & Spence, 2014), hand used (Ochando & Zago, 2018) and location of space where the lines appear (Jewell & McCourt, 2000; McCourt & Jewell, 1999) affect pseudoneglect.

Nevertheless, the line bisection task requires the coordination of both visual perceptual and motor control skills. Interestingly, pseudoneglect may stem from either perceptual-attention or motor-intention sources or both (Dellatolas, Vanluchene & Coutin, 1996; Nicholls & Roberts, 2002). The perceptual-attentional bias relies either on an overestimation of the left side of the space or on a lack of awareness of or attention to the right. Conversely, a motor-intentional bias depends either on a preference to respond or initiate action toward the left side of the space or on a failure to respond to or initiate action toward the opposite direction. Therefore, by using line bisection tasks, it is not possible to dissociate perceptual from motor factors in driving attentional biases (Garza, Eslinger & Barrett, 2008; MacLeod & Turnbull, 1999; Nicholls & Roberts, 2002; Suavansri, Falchook, Williamson & Heilman, 2012). Therefore, Milner and colleagues (1993) developed a purely perceptual version of the line bisection task to study attentional biases regardless of any motor involvement: the *landmark task* (Bisiach, Ricci, Lualdi & Colombo, 1998; Milner et al., 1993). In this task, participants are instructed to make a two-alternative forced-choice decision regarding the length of two halves of a pre-bisected line that are typically briefly presented (e.g. from 250 to 500 ms). Healthy young adults demonstrate a systematic leftward bias of the subjective midpoint of the landmark lines, that is consistent with an overestimation of the size of left hemispace (Benwell, Thut, Learmonth, & Harvey, 2013; Rueckert, Deravanesian, Baboorian, Lacalamita & Repplinger, 2002). Given the similarity between line bisection and landmark tasks, it is perhaps unsurprising that a correlation in the direction and magnitude of pseudoneglect bias has been observed between the two tasks in healthy adults (Luh, 1995; Milner et al., 1993). However, other studies suggested that line bisection and landmark tasks are only weakly correlated (Milner et al., 1993; Rueckert et al., 2002), probably representing very distinct cognitive demands with different strategies used depending on the task (Cavézian, Valadao, Hurwitz, Saoud & Danckert, 2012). For instance, beside the aforementioned difference in the involvement of motor functions, whereas in line bisection tasks stimuli are processed globally as a single object with eye movements remaining close to the stimulus centre, in the landmark task, visual scanning extends to both hemifields with participants comparing the left and right side of the pre-bisected line to reach their decision (Cavezian et al., 2012), thus relying more on local attention processes (Falchook et al., 2013).

Nevertheless, this bias has been consistently described across studies using different paradigms such as luminance judgments (Mattingley et al., 2004), visual search (Gigliotta, Malkinson, Miglino & Bartolomeo, 2017; Nicholls, Hobson, Petty, Churches & Thomas, 2017), distance judgements (Brian Krupp, Robinson, & Elias, 2010) and memory tasks (Della Sala, Darling & Logie, 2010). Hence, attentional asymmetries have the potential to affect everyday interactions with the environment. Accordingly, several studies investigated the influence of spatial asymmetries on different ecological situations (Benedetto, Pedrotti, Bremond & Baccino, 2013; Nicholls, Loftus, Mayer & Mattingley, 2007; Nicholls, Loftus, Orr & Barre, 2008; Thomas, Stuckel, Gutwin & Elias, 2009). For instance, in an attempt to study attentional leftward bias in a driving context, Benedetto and collaborators (2013) asked participants to perform a driving simulator that requires to drive along a straight traffic-free three-lane road, change lanes according to the information provided by two identical road signs displayed concurrently on both left and right sides of the road. Participants directed most of their attention to the left-hand signs, as demonstrated by gaze behaviour, whereas the introduction of a secondary task – performed with the right hand, concurrently with the driving task – attenuated the leftward bias. These data not only demonstrated that the leftward attentional bias in line bisection might extend to real-life situations but shed light also on the effect of dual-task on spatial asymmetries (see Chapter 2 for further discussion). Similarly, with the aim to investigate spatial asymmetry in everyday situations, Nicholls and colleagues (2008), by asking participants to walk through a narrow doorway while entering text into the phone using their left, right or both hands, demonstrated that participants bumped to the right more often, with no effect of unimanual activation. However, other investigations, using the same paradigm, showed a significant effect of hand movement (Fujikake, Higuchi, Imanaka & Maloney, 2011; Nicholls et al., 2007), aperture width (Nicholls, Jones & Robertson, 2016) and covert visual attention to one side of the door (Fujikake et al., 2011). Accordingly, it has been demonstrated that directional biases (i.e., left vs. right) in collision behaviour might be modulated by both location in the visual field (central, upper, or lower) and handedness. Indeed, when participants completed a computer-based route-following task, they collided with the walls on the right side more often when the task was presented in the upper field, whereas more collisions on the left were found in the lower field condition. Interestingly, left-handed participants experienced more right-side collisions in the central condition (Thomas et al., 2009). It is likely that the movement of the hand and a visual stimulus serve as an attentional cue and are effective to avoid neglect of the ipsilateral side; as a result, the body midpoint is deviated to the contralateral side. Therefore, the directional bias in locomotor trajectories while passing through a doorway results from the combination of a motor factor, particularly the leading foot, and attentional/brain factors (Fujikake et al., 2011). Combined, these studies suggest that the rightward deviation seen for lines placed in far space (Nicholls et al., 2016; Varnava, McCarthy & Beaumont, 2002) extends to everyday activities such as walking through a doorway and kicking of a football.

In addition to the leftward attentional bias for horizontally aligned stimuli, consistent biases in line bisection have also been observed in the vertical and radial planes. With visually presented lines, neurologically healthy participants tend to err away from their body in the radial axis (e.g., Halligan & Marshall, 1993; Shelton, Bowers, & Heilman, 1990), and in the upward direction in the vertical axis (e.g., Drain & Reuter-Lorenz, 1996; Halligan & Marshall, 1993; Post, O'Malley, Yeh, & Bethel, 2006; Shelton et al., 1990). These biases have been interpreted as being either retinotopic, body-centred, or object-centred (Chewning, Adair, Heilman, & Heilman, 1998; Churches, Loetscher, Thomas & Nicholls, 2017; Geldmacher & Heilman, 1994; Previc, 1990). According to the retinotopic account (Previc, 1990), stimuli falling in the lower hemiretina (upper visual field) are processed preferentially because the lower hemiretina is specialized for visual search and recognition mechanisms directed toward far space (Geldmacher & Heilman, 1994; Previc, 1990). With vertical lines and radial lines presented below eye level, the upper and distal parts of the line are projected to the lower hemiretina, resulting in the upward and distal bias. Body-centred factors may also give rise to the observed bias: during visual exploration, attention is likely to be preferentially distributed away from the body because the visual system is tuned to detect distant stimuli (Shelton et al., 1990), leading to a distal bias in bisecting radial lines. In support of both the retinotopic and body-centred hypotheses, Geldmacher and Heilman (1994) found that when radial lines were presented above eye level, so that the proximal portion of the line appeared in the upper visual field/lower hemiretina, the bisection error did not significantly differ from zero, possibly because, in this condition, the head-centered and retinal factors were in conflict (Geldmacher & Heilman, 1994; see also Chewning et al., 1998). Finally, object-centred biases may also play a role. In particular, visual attention may preferentially be biased toward the upper part of objects (Jeerakathil & Kirk, 1994). However, whether hemispheric asymmetry in the control of spatial attention plays a role in determining the bisection biases in the vertical and radial planes is not fully clear (see Drain & Reuter-Lorenz, 1996). Behavioural studies have not always found a correlation between bisection performance in different spatial planes (e.g., McCourt & Olafson, 1997; Post et al., 2006; see also Nicholls, Mattingly, Berberovic, Smith, &

Bradshaw, 2004), as one may expect if the same cortical mechanisms lead to the observed biases in the three dimensions. From an evolutionary perspective, dating from at least the writing of William James (1890), vertical and radial biases have been explained with regard to their ecological significance. That is, we pay more attention to the upper part of objects because most of the time it is this part of the object that has the most useful information about what the object is and how we can interact with it (Previc, 1990). Similarly, we pay more attention to distal stimuli with the aim to foresee an eventual upcoming danger. However, there is no plausible ecological basis for the leftward bias because left and right are defined in terms of the observer, rather than the context of the observer (McManus, 2002).

1.2 Pseudoneglect in the haptic modality

Spatial asymmetries have been reported for the haptic modality as well. Accordingly, bisection tasks can be carried out also in the tactile modality in which blindfolded subjects estimate the midpoint of a rod after tactile exploration (Jewell & McCourt, 2000) (see Figure 1.1). In an early study by Bradshaw and colleagues (1986), participants had to adjust the extremities of a rod protruding from a copper tube. These investigators found a greater leftward bias under this condition than for visual line bisections. Indeed, as for the visual domain, participants' performance in haptic rod bisection tasks might be affected by several factors such as participants' handedness (e.g., Sampaio & Chokron, 1992) and the spatial position of the line with respect to the head– body axis (Bradshaw, Nettleton, Nathan, & Wilson, 1983). Additionally, it is worth noting that several studies consistently point to a right-hemispheric dominance in tactile shape discrimination, irrespective of the hand used (Harada et al., 2004; Loayza, Fernandez-seara, Aznarez-Sanado & Pastor, 2011). Therefore, it may be that the tactile exploration per se activates the right hemisphere, leading to a consistent leftward bias in bisection. Interestingly, whereas a right-hemisphere dominance in the control of visuospatial attention has been consistently observed in both neuroimaging (Corbetta & Shulman, 2002, 2011; Zago et al., 2017) and electrophysiological studies (Benwell et al., 2014; Foxe et al., 2003), similar neural evidence is lacking within the haptic domain. Nevertheless, the consistent leftward bias reported by many studies in haptic bisection suggests that common attentional control mechanisms are at play across modalities (Brooks, Della Sala & Logie, 2011; Cattaneo, Fantino, Tinti, Silvanto & Vecchi, 2010, Cattaneo et al., 2011a; Eardley, Darling, Dumper, Browne & Van Velzen, 2017). This is the case even if the magnitude of the bisection bias may be poorly correlated across vision and haptics (Eardley et al., 2017). Accordingly, the modality (visual vs. haptic) in which the bisection task is performed has been found to influence the extent of pseudoneglect. Accordingly, haptic bisection (in which both kinaesthetic and proprioceptive factors are involved) requires active manual motor exploration, whereas visual bisection does not. Moreover, although participants usually move their eyes to scan the visual line (typically making an initial leftward eye movement to the end of the line, followed by a rightward scan, after which they again move leftward to the centre of the line; see Kim, Anderson, & Heilman, 1997), the length estimation in visual bisection can also be obtained through parallel processing. Conversely, haptic exploration is inherently sequential, with participants having to maintain in memory both the start and end positions of the scan (whereas, in vision, the two extremities of the line are simultaneously available). It is important to note, that the extent of pseudoneglect in the haptic modality depends on numerous modality-specific factors, such as the way the rod is explored (one search vs. multiple searches; see Baek et al., 2002), whether the left or right hand is used for scanning (e.g., Brodie & Pettigrew, 1995), scanning direction (Cattaneo et al., 2011a) and whether tactile versus kinesthetic scanning is adopted (Sampaio & Philip, 1991).

As regards vertical and radial bisections, the bias reported in the haptic modality is the opposite of that observed with visually presented lines; that is, toward the body in the radial plane and in the downward direction in the vertical plane (Baek et al., 2002; Chewning et al., 1998; Shelton et al., 1990). This has been explained in terms of kinesthetic–motor mechanisms, which are inherent to haptic exploration and which are relatively body centred, thus inducing a toward-the-participant bias (Chewning et al., 1998; Shelton et al., 1990).

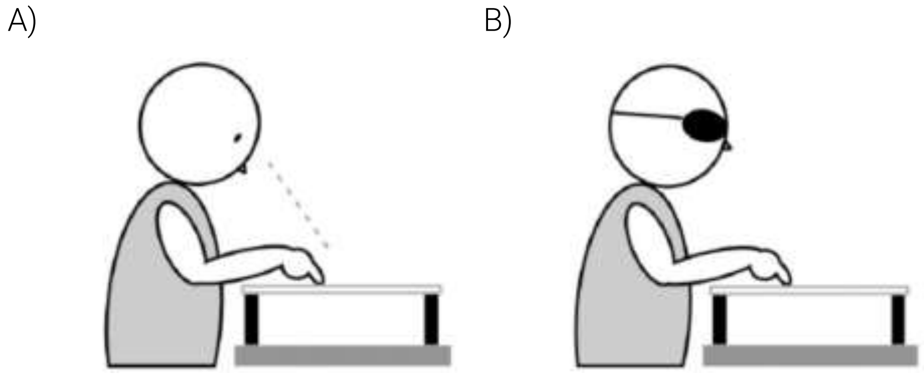


Figure 1.1 Visual (A) and haptic (B) line bisection task (Figure is taken from Mancini et al., 2011).

1.3 Representational pseudoneglect

Pseudoneglect has also been demonstrated in the absence of direct visual processing, that is when a person is required to mentally represent a stimulus, the so-called *representational pseudoneglect* (Brooks, Della Sala & Darling, 2014), which mirrored the representational form of neglect observed in brain-damaged patients (Bisiach & Luzzatti 1978; Beschin, Cocchini, Della Sala & Logie, 1997; Guariglia, Padovani, PAntano & PIzzamiglio, 1993). Accordingly, McGeorge et al. (2007) adopted a famous task developed for neglect patients (Bisiach & Luzzatti, 1978) by asking healthy participants, living in Milan (Italy), to imagine the highly familiar scene of the Piazza del Duomo (Cathedral Square) in Milan and to describe the landmarks on each side from two opposite viewing perspectives. Interestingly, a leftward bias was displayed regardless of the viewpoint, with more landmarks reported from the left side of the image than from the right. Other studies further replicated this finding in non-Italian participants (Bourlon et al., 2010; Friedman et al. 2012). Moreover, representational pseudoneglect has been shown for completely novel material. Indeed, some investigations demonstrated a leftward bias in the recalling of elements from real-world photographs (Dickinson & Intraub, 2009) and artificial arrays (Della Sala et al., 2010).

Nevertheless, it has been suggested that mentally representing spatial layouts from highly familiar scenes may activate a visuospatial representation (McGeorge et al. 2007), which causes the mental representation to ‘behave' in the same way as a visuospatial stimulus. One way to avoid this difficulty is to reduce any form of visual presentation by using verbal auditory descriptions. Brooks and Brandimonte (2013) by asking participants to mentally represent real-world scenes consisting of streets with landmarks (i.e., shop, school, church, park) from audio-verbal descriptions showed that the left side of the imagined street was reported as containing more landmarks than the right; however no lateralization in memory recall was found. It could, therefore, be argued that the left side of a mentally represented stimulus may indeed be more perceptually salient than the right side, but there may not be the capacity for retrieving greater detail from the more salient half (Brooks, Logie, McIntosh & Della Sala, 2011b). Recently, Darling et al (2012) presented horizontal lines for bisection in two conditions, a visuospatial condition (participants bisected a visible line) and a memory condition (participants identified where the midpoint of a line had been from memory only after the line to be bisected disappeared). The lines were presented in extrapersonal space, at a distance where there is evidence that typical patterns of left bias in visuospatial pseudoneglect either disappear or reverse to become right-bias (e.g. Longo & Lourenco 2006; Nicholls et al., 2016). No significant bias was observed in the perception condition, but a significant leftward bias was observed in the memory condition.

Furthermore, many studies have indicated that a form of representational pseudoneglect occurs for tasks involving the mental representation of numbers. Indeed, empirical observations indicated that numbers are typically represented as lying on an imaginary line (e.g. the so-called mental number line) with smaller numbers represented on the left side of space and larger numbers on the right (for a review see Hubbard, Piazza, Pinel & Dehaene, et al. 2005; see also Dehaene, Piazza, Pinel & Cohen, 2003; Gevers et al. 2010). A task usually adopted to measure representational biases is the number bisection task, derived from the physical line bisection task. In this task, subjects hear two numbers (for example, "1, 5”) that define a numerical interval, and then orally report the midpoint of this interval without any calculation (Zorzi, Priftis & Umiltà, 2002). In a seminal study, Zorzi et al. (2002) found that right brain-damaged patients show deviations in the number line bisection task, similar to what is typically observed in physical line bisection. In particular, subjects deviated the midpoint of numerical intervals towards larger numbers (Zorzi et al., 2002). This has been interpreted as a sign of spatial neglect for numbers on the left side of the mental number line and more generally as a strong argument for number-space interactions (Rossetti et al., 2004; Zorzi et al., 2002). As regards healthy individuals, Loftus et al. (2009) asked participants to decide which flanker number was further away from the middle number in a triplet (i.e., 15-22-47) and found a consistent bias in the direction of the lower numerical flanker. Moreover, Loetscher et al. (2010) demonstrated a comparative bias when participants were asked to choose a number between 1000 and 10,000; healthy participants were biased towards choosing a smaller compared to a relatively larger number. Additionally, there is evidence of a small number bias (i.e., leftward bias) in random number generation tasks (Loetscher & Brugger, 2007). Interestingly, leftward biases in physical line bisections might be influenced by the processing of large numbers (Loftus, Nicholls, Mattingley & Bradshaw, 2008; Longo & Lourenco 2007; Nicholls and Loftus 2007, for alphabet bisection). Accordingly, Longo & Lourenco (2007) found that healthy subjects present similar and correlated pseudoneglect in the two tasks, thus suggesting a close link between cognitive and neural mechanisms of number and physical line bisection. Consistently, Calabria and Rossetti (2005) showed that when healthy participants were asked to bisect lines of words that represented smaller numbers (i.e., ‘four’) there was a tendency to bisect towards the left but for lines of words that represented larger numbers (i.e., ‘nine’) the bias was significantly reduced. Relatedly, Di Luca et al. (2013) have shown that numeric laterality effects occur when participants carry out two-dimensional cancellation tasks, with participants’ attention being shifted to the left-hand side of the array if the star array also contained low numbers, and towards the right if it contained higher numbers. Furthermore, studies employing prismatic adaptation in neurologically normal participants that cause neglect-like distortions of visual perception also produce similar distortions of representation in the number line (Nicholls et al. 2008a). Moreover, mental number line bisection, like physical line bisection, shifted from a leftward bias at near distances (60 cm) towards a rightward bias at far distances (240 cm: Longo & Lourenco 2010)—furthermore, there was a correlation between individual participants' bias on physical and mental number line bisection.

As for the haptic bisection, recent evidence also suggests that touch-driven bisection biases can be influenced by the presentation of numbers. Cattaneo et al. (2012) showed that the presentation of repetitive task-irrelevant verbal stimuli modulated pseudoneglect on tactile bisection —when a high digit was presented, bisections deviated rightwards compared to a control condition (‘blah'), whilst low digits were associated with leftward deviations, a pattern consistent with some degree of commonality between spatial and numeric representations. Numeric biases can be manipulated by cognitive functions that selectively affect the activation of the hemispheres—tapping on the right of space increases rightward bias whilst tapping on the left-hand side of space increases leftward bias (Cattaneo, Fantino, Silvanto, Vallar, & Vecchi, 2011). The most powerful evidence for a purely representational pseudoneglect on the mental number line, however, comes from the finding that blind participants display the same leftward biases when bisecting mental number line; in the case of congenitally blind participants it is impossible that early visuospatial processing contributed to the bias (Cattaneo, Fantino, Silvanto, Tinti & Vecchi, 2011).

Taken together, these results provide evidence of a lateral bias within a number space that clearly has spatial characteristics. The commonality between the mental number line and the line bisection results here is striking, provoking the suggestion that similar attentional orienting mechanisms underlie both visuospatial and representational bisection tasks.

However, several studies reported that deviation in number line bisection is dissociable from that in physical line bisection, thus suggesting that the neural mechanisms involved in number line bisection are not identical to those recruited for physical lines (Aiello et al., 2012; Ashkenazi & Henik, 2010; Doricchi, Guariglia, Gasparini Tomaiuolo, 2005; Loetscher & Brugger, 2009; Loetscher et al., 2010; Pia et al., 2012; Rossetti et al., 2004; Rotondaro, Merola, Aiello, Pinto & Doricchi, 2015; Storer & Demeyere, 2014; van Dijck, Gevers, Lafosse, Doricchi & Fias, 2011).

1.4 Neural correlates of spatial attention asymmetries

Leftward attentional biases have been explained by the activation-orientation hypothesis (Reuter Lorenz et al. 1990). The contralateral attentional orienting by the right hemisphere leads to leftward bias because the leftward orientation of attention results in the left portion of the line being perceived as longer than the right portion of the line (see also Heilman & Van Den Abell, 1979; Kinsbourne, 1970). Hence, the perceived midpoint of the entire line is shifted towards the left-hand side. The central role played by the right hemisphere in such phenomenon is supported by evidence on neglect patients that confirms the right cerebral hemisphere involvement in orienting attention towards the left side of space: when damaged it loses this capacity and a strong rightward bias is shown.

Although critical lesion sites within the right hemisphere can be difficult to define (Karnath & Rorden, 2012), neglect is thought to most commonly follow lesions to the right parietal lobe (Bartolomeo & Chokron 2002; Danckert & Ferber 2006; Halligan, Fink, Marshall & Vallar, 2003; see also Gottlieb & Snyder 2010; Mort et al. 2003). Neuroimaging and electrophysiological studies also demonstrated that the right hemisphere itself is preferentially activated during visuospatial processing and line bisection in healthy participants (Fink et al. 2000; Fink, Marshall, Weiss & Zilles, 2001; see also Benwell et al., 2014; Çiçek, Deouell & Knight, 2009; Foxe et al. 2003; Zago et al., 2017). In particular, activations in a right fronto-parietal network have been reported during line bisection and landmark tasks characterized by the contribution of right superior posterior and inferior parietal cortices (or intra-parietal sulcus; IPS), temporo-parietal junction, anterior cingulate, premotor and dorsolateral prefrontal cortices (Cicek et al., 2009; Zago et al., 2017) (see Figure 1.2). However, although line bisection and landmark tasks share some brain activations (Cicek et al., 2009), landmark tasks show a more pronounced right lateralization (Seydell-Greenwald et al., 2019) whereas line bisection tasks involve more bilateral activations (Cavezian et al., 2012) with greater frontal areas contribution, such as in the frontal eye fields, likely due to the increased contribution of eye movements (see section 1.1.1) (Cicek et al., 2009) (see Figure 1.3).

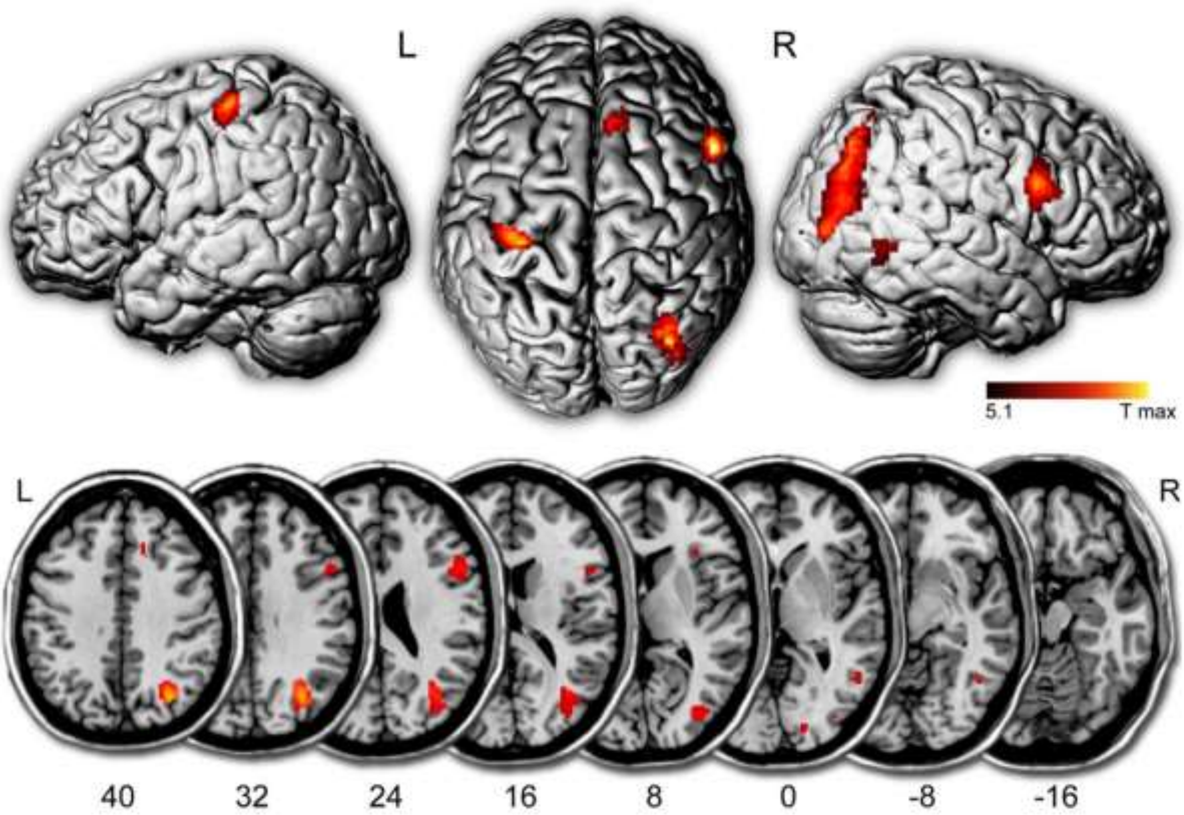


Figure 1.2. Asymmetrical map of the line bisection task compared to Control task (saccadic eye movements towards a visually presented dot and simultaneously pressing the response pad with the right index finger at each dot movement). (R: right; L: left, N=51). The numbers (in mm) refer to the Z coordinates of the axial slices. (Figure is taken from Zago et al., 2017).

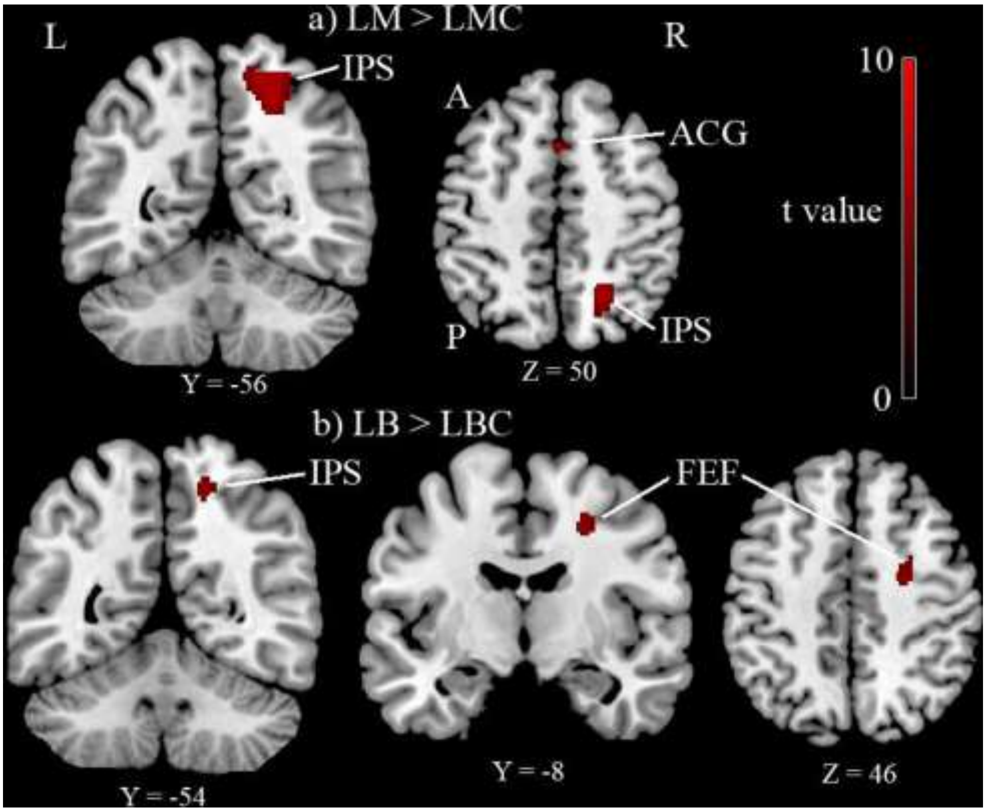


Figure 1.3 (A) Landmark task (LM) versus Landmark control (LMC) activated intra-parietal sulcus (IPS), anterior cingulate gyrus (ACG) and lateral peristriate cortex (not shown in this picture). (B) Line bisection task (LB) compared to its control (LBC) activated again IPS, FEF also lateral peristriate cortex not shown in this picture. A, anterior; P, posterior; L, left; R, right. (Figure taken from Cicek et al., 2009).

The fronto-parietal connections involved in visuospatial attention are separated into three dorsal superior longitudinal fasciculus (SLF) tracts: SLF I, SLF II, and SLF III. In their seminal study, de Schotten et al. (2011) reported that of the three tracts, the SLF II (middle) and SLF III (ventral) are right lateralized (see Figure 1.4) and the degree of hemispheric lateralization was found to predict the degree of specialization of the right hemisphere for visuospatial processing. Correlational analysis revealed that larger SLF II volume in the right hemisphere corresponded to larger deviations to the left on the line bisection task (De Schotten et al., 2011). The SLF II has been proposed to facilitate direct communication between the dorsal and ventral attention networks, as the track overlaps with the parietal component of the ventral network and the prefrontal component of the dorsal network (De Schotten et al., 2011).

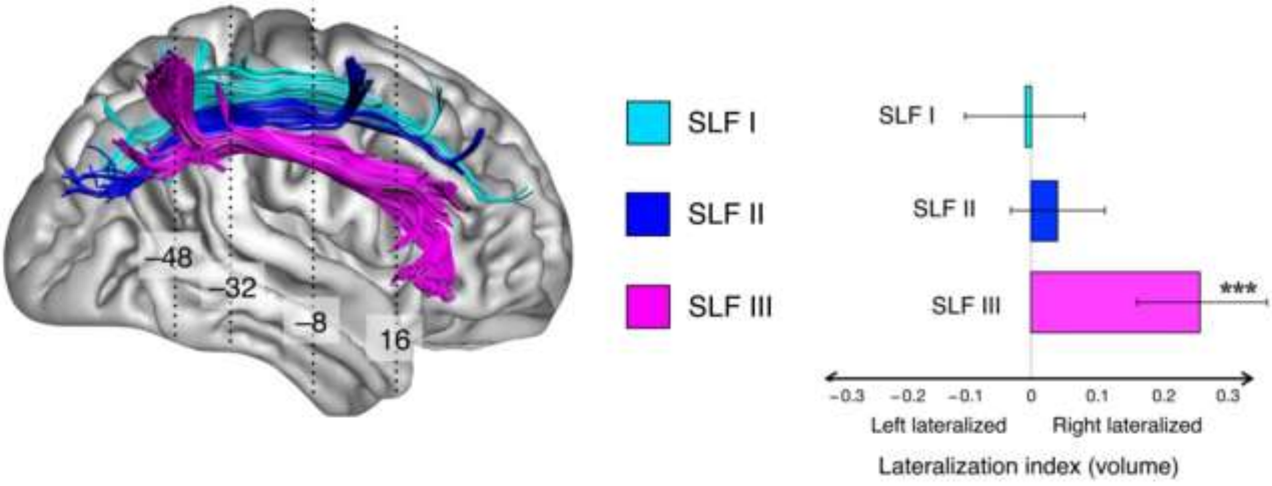


Figure 1.4. *In vivo* SD tractography in humans (left panel). Hemispheric lateralization of the three SLF branches with 95% confidence intervals (right panel). (Figure is taken from De Schotten et al., 2011).

As regards spatial asymmetries in the vertical and radial orientations, differential activation between the ventral and dorsal visual streams (Drain & Reuter-Lorenz, 1996; Duecker & Sack, 2015; see Milner & Goodale, 2008 and Goodale & Milner, 1992 for a description of ventral and dorsal visual streams) are thought to underpin asymmetries in the vertical plane (Drain & Reuter-Lorenz, 1996; Post et al., 2006). More specifically, the upward shift of attention is typically associated with greater activation of the ventral stream network, specialized for object–based processing (Duecker & Sack, 2015; Milner & Goodale, 2008) and directing attention to the upper hemispace (Previc, 1990; Weiss et al., 2000), relative to the dorsal stream that directs attention toward the opposite direction (Chieffi et al., 2019; Churches et al., 2017; Falchook et al., 2013). This relationship between the dorsal streams and the lower visual hemispace and the ventral streams and the upper visual hemispace has been linked to attentional biases in the radial dimension, as well. Specifically, the dorsal stream is also associated with attention to space near the body, and the ventral stream is associated with attention further away from the body (Bjoertomt, Cowey, & Walsh, 2002; Chieffi et al., 2019). This suggests that while attentional biases in the vertical dimension are not correlated with attentional biases in the horizontal dimension, they may be correlated with attentional biases in the radial dimension.

Further evidence comes from brain stimulation studies using Transcranial Magnetic Stimulation (TMS). Accordingly, interfering with the activity of the right (but not left) posterior parietal cortex (PPC) (Ellison, Schindler, Pattison & Milner, 2004; Fierro et al., 2000; Fierro, Brighina, Piazza, Oliveri & Bisiach, 2001, Mahayana, Tcheang, Chen, Juan & Muggleton, 2014; Pourtois, Vandermeeren, Olivier & De Gelder, 2001; Ricci et al., 2012; Salatino, Poncini, George & Ricci, 2014) and the right frontal premotor areas (Brighina et al., 2002) results in a reduction or an inversion of the typical spatial attention asymmetry. In an interesting study by Salatino and collaborators (2014) the authors propose a new site-finding TMS protocol to easily identify the optimum parietal location, or "hot spot," where TMS modulates visuospatial perception on a landmark task. Interestingly, the stimulation of right PPC induced a significant left neglect-like bias, when the coil was applied over the most posterior and dorso-posterior sites. Unexpectedly, TMS over left PPC also produced left neglect-like bias when targeting the most anterior and dorso-anterior portions of the grid. Furthermore, some investigations combining TMS with neuroimaging data (fMRI) showed that the rightward bias observed when TMS is delivered over the right posterior parietal cortex is associated with decreased neural activity in fronto-parietal areas, often lesioned or dysfunctional in patients with left neglect (Ricci et al., 2012).

Furthermore, interoperative electrical stimulation of parietal regions and in particular the superior occipitofrontal fasciculus has been observed to mediate the severity of line bisection deviation (De Schotten et al. 2005), pointing to subcortical (right) fronto-parietal pathways that may form the basis of a network related to the emergence of neglect-like symptoms (see also De Schotten et al. 2012). Besides, a study using parietal theta burst stimulation has indicated that neglect and pseudoneglect share common neural mechanisms (Varnava, Dervinis & Chambers, 2013). Taken together these data provide a sound basis in brain structure to explain the right hemisphere dominance suggested by the action-orientation hypothesis.

As regard representational pseudoneglect, the presence of a leftward bias similar to visual line bisection tasks suggests that similar neural networks might drive both perceptual and representational pseudoneglect. Accordingly, Gobel et al. (2006) found that repetitive TMS applied over right parietal regions (but not the occipital region) during mental number line bisection induced performance consistent with 'neglect' – a bias towards larger numbers with the perceived numerical midpoint shifted rightward. Oliveri et al. (2004) observed that TMS over the right parietal region counteracted the typical leftward mental number line bias, while Cattaneo et al. (2009) found that TMS over the right angular gyrus, but not the left, disrupted the priming of attention towards smaller numbers on the left side of the mental number line for healthy participants. However, Oliver and colleagues (2011) demonstrated that TMS applied over the left (but not the right) cerebellar hemisphere affect attentional bias in a number bisection task but not in a landmark task, probably by means of crossed cerebro-cerebellar connections. Recently, a neuroimaging study, comparing physical and number bisection tasks activations, demonstrated that the two tasks shared bilateral parietal-frontal networks contributions. Nevertheless, bilateral parietal-frontal areas, right cerebellum, left insula and supplementary motor area (SMA) showed higher activity when contrasting the number line with a physical line bisection task. Importantly, left SMA and right cerebellum were connected to parietal-frontal areas for implementing the number line bisection task (Liu et al., 2019) (see Figure 1.5).

Taken together, evidence consistently demonstrated the involvement of a fronto-parietal network mainly lateralized in the right hemisphere in attentional bias; however, further studies are necessary to understand not only the specific role played by different brain regions in generating representational pseudoneglect but also the specific neural correlates of attentional biases in different orientations and across different sensory modalities.

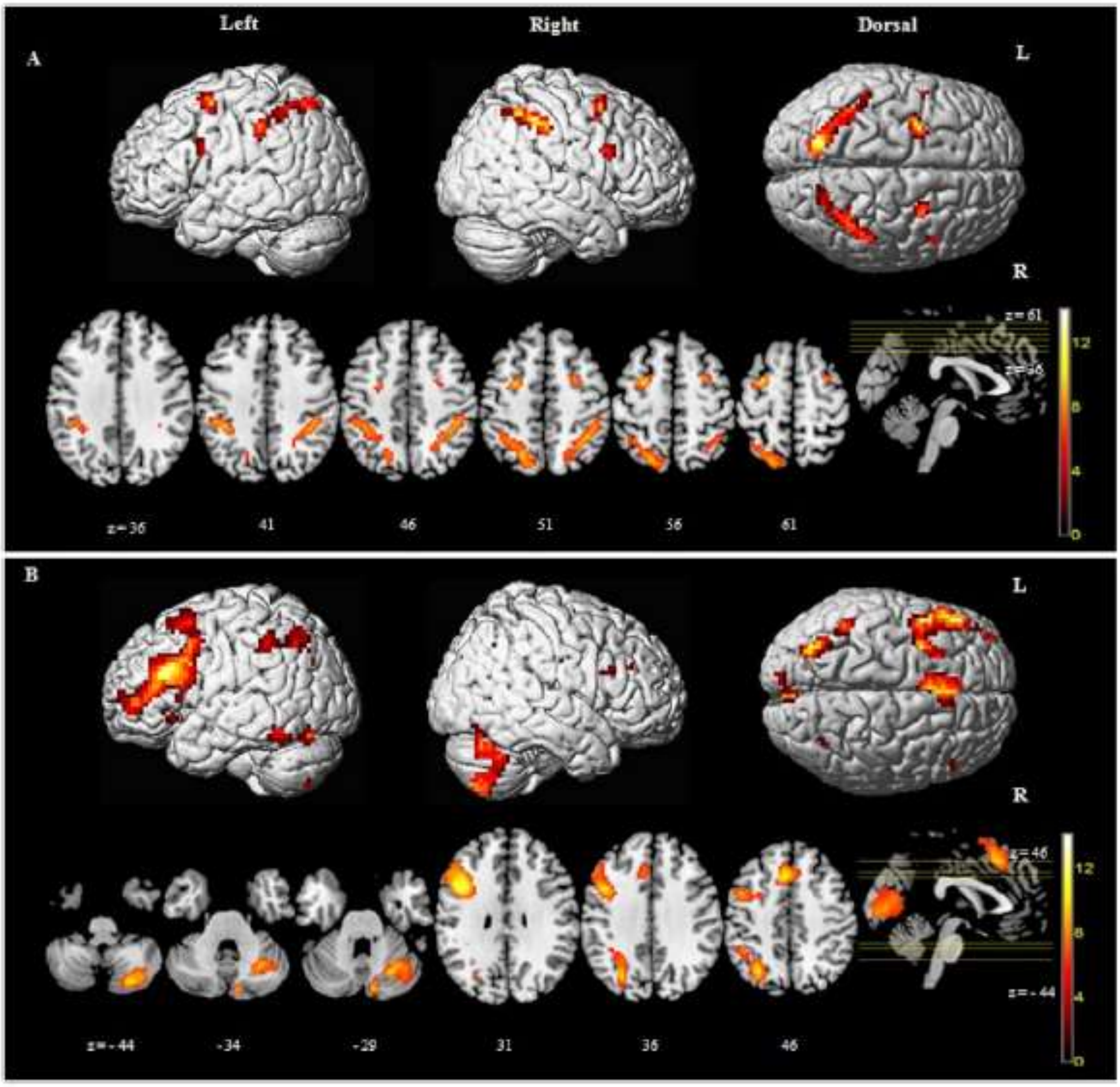


Figure 1.5. Neural correlates of shared activations between physical and number line bisection tasks (A) and contrast of number line bisection vs. physical line bisection (B) (Figure is taken from Liu et al., 2019).

1.5 Aim of dissertation

Despite the impressive amount of psychophysical, neuropsychological, neuroimaging and electrophysiological studies conducted on the pseudoneglect phenomenon over the past 30 years, several issues remain unsolved. In the present dissertation, I will describe part of the studies I conducted during my PhD with the aim to address some of the interesting open questions regarding pseudoneglect.

For instance, spatial asymmetries have been demonstrated to exist not only in the horizontal plane but also in the vertical and radial orientations. Although consistent evidence documented that attentional biases across orientations tap to separate mechanisms (Churches et al., 2017; Heber, Siebertz, Wolteer, Kuhlen & Fimm, 2010; Nicholls et al., 2004), other findings proposed common underlying processes acting on both of them (Fink et al., 2001). Moreover, recent studies investigated spatial attentional asymmetries under load (e.g. in dual-task condition), to further understand attentional biases in real-life situations, that is when we are asked to perform multiple tasks simultaneously (for instance when we are driving while talking with the person sitting next to us). Interestingly, as regards the horizontal plane, prior evidence reported either a reduction of the typical leftward bias (Benedetto et al., 2013) or the induction of a rightward bias (Peers, Cusack & Duncan, 2006; for a review see Chen & Spence, 2017) in dual-task conditions. However, other studies failed to report similar findings (Dodds et al., 2008; Santangelo & Spence, 2007). Nevertheless, whether the increased attentional load affects spatial asymmetries in the vertical plane has not been investigated before. In Chapter 2, I present data from a research we carried out to investigate vertical spatial asymmetries under load by asking participants to complete a line bisection task (Experiment 1a) and a landmark tasks (Experiment 1b) while concurrently performing a secondary auditory working memory task. The aim of Study 1 was twofold: firstly, to shed light on the mechanisms underlying spatial asymmetries under load; secondly, to further understand the relationship between horizontal and vertical attentional biases.

Another interesting topic in the pseudoneglect literature, on which a considerable amount of researches have been conducted, is the role of a normal visual experience in shaping spatial asymmetries. On this regard, numerous studies investigated the presence of attentional bias in early blind individuals (Cattaneo et al., 2011a, b; see Chapter 2 for more evidence). Interestingly, blind participants show a leftward bias, similar to the one reported by sighted individuals, both in haptic rods and number bisection task, thus proposing that a normal visual experience is not necessary to the development of the right-hemispheric dominance for visuospatial processing (Gougoux et al., 2005; Renier et al., 2014; Ricciardi & Pietrini, 2011). However, the total lack of visual input may have different effects on lateralization patterns compared to distorted visual input, as suggested by studies in amblyopes, which show a rightward bias in visual line and number bisection tasks (Mohr, Mues, Robol & Sireteanu, 2010; Thiel & Sireteanu, 2009). On these grounds, Study 2 investigated whether a distorted binocular vision that leads to alterations in typical visuospatial attention asymmetries (Mohr et al., 2010; Thiel & Sireteanu, 2009) also affects spatial attention in the haptic modality, thus shedding light on the difference between line bisection across modalities. Moreover, an extreme case of loss of binocularity is that of individuals with monocular blindness, which has been shown to impact on many visual functions (Cattaneo et al., 2014; Kelly et al., 2013; Moro, Hoover & Steeves, 2019; Steeves et al., 2002, 2004; Vecchi et al., 2006; for a review see Steeves, Gonzales & Steinbach, 2008). Therefore, in Study 2 we investigated whether and how early monocular blindness affects the typical pattern of hemispheric asymmetry in the control of spatial attention.

Finally, as already mentioned above, pseudoneglect has been demonstrated in the absence of any visual input, as with number bisection task, the so-called representational pseudoneglect. Although an attentional bias toward the same direction (e.g. leftward) might one think that both biases might be driven by a right hemispheric dominance, several evidence pointed out to the existence of separate mechanisms between perceptual and representational pseudoneglect (Ashkenazi & Henik, 2010; Loetscher & Brugger, 2009; Loetscher et al., 2010; Pia et al., 2012; Storer & Demeyere, 2014; van Dijck et al., 2011). On a neural level, the involvement of the right fronto-parietal network has been demonstrated for both biases, however, recent neuroimaging finding supports the presence of partially separated underlying neural processes (Liu et al., 2019). On this regard, in Study 3, we adopted a brain stimulation approach to examine the neural correlates of perceptual and representational biases. In particular, we explored the role of different regions within the cerebellum in the pseudoneglect phenomenon by asking healthy participants to complete a landmark task and a number bisection task while receiving single-pulse TMS.

CHAPTER 2

Spatial asymmetries under load

2.1 *Study 1*: The effect of cognitive load on horizontal and vertical spatial asymmetries

Despite horizontal and vertical spatial asymmetries are linked to relatively independent cognitive/neurological mechanisms, the relationship between attentional biases in the two dimensions requires further investigations. Indeed, little is known about spatial asymmetries in dual-task conditions, that is when cognitive processing resources cannot be dedicated to one task only. Accordingly, prior evidence reported that the addition of a secondary task affects the strength of horizontal spatial asymmetries. Specifically, a disadvantage (e.g. slower response latencies and lower accuracy rates) for left side targets (e.g. information processed in the right hemisphere) compared to those on the right has been shown in dual-task conditions both in right-hemisphere damaged patients (Andres et al., 2019; Bellgrove, Eramudugolla, Newman, Vance, & Mattingley 2013; Bonato & Cutini, 2016; Bonato, Prifitis, Marenzi, Umiltà, & Zorzi, 2010; van Kessel, van Nes, Geurts, Brouwer, & Fasotti, 2013) and healthy participants (Benedetto et al., 2013; Golob, Winston, & Mock, 2017; Lisi, Bonato, & Zorzi, 2015; Naert, Bonato, & Fias, 2018; Peers, Cusack, & Duncan, 2006), with the latter group showing either a reduction of the typical leftward attentional bias (Benedetto et al., 2013) or a rightward bias (Peers et al., 2006; for a review see Chen & Spence, 2017). However, other investigations failed to report similar effects (Dodds et al., 2008; Santangelo & Spence, 2007) or suggested that load effects may depend on the overlap in content-specific processing between primary and secondary tasks (Golob et al., 2017; Kim, Kim, & Chun, 2005). On a neural level, both electrophysiological and neuroimaging studies reported that the disadvantage for left-side stimuli is associated with a selective disruption of neural responses in the right (Bonato, Spinorelli, Lisi, Priftis, & Zorzi, 2015; O'Connell, Schneider, Hester, Mattingley, & Bellgrove, 2011), but not the left hemisphere (Vuilleumier et al., 2008), thus suggesting that increasing cognitive load might affect hemispheric asymmetry by weakening the dominance of the right hemisphere (O'Connell et al., 2011; Pérez et al., 2009).

Despite showing that cognitive load affects spatial asymmetries in the horizontal plane, previous research has not considered the effect of cognitive load on spatial asymmetries in the vertical dimension. By considering this issue we aimed to shed light on the underlying mechanisms driving spatial attention in dual-task conditions. To this aim, we compared horizontal and vertical spatial asymmetries under load, by asking healthy participants to perform a line bisection (Experiment 1a) and a landmark task (Experiment 1b) both in a single and a dual-task condition. Indeed, if cognitive load selectively affects left-side stimuli processing as a consequence of a weakening of the right hemispheric dominance for visuospatial processing as previously reported (Benedetto et al., 2013; Golob et al., 2017; Lisi et al., 2015; Naert et al., 2018; Peers et al., 2006), then the typical leftward attentional bias in the horizontal plane should be reduced. Conversely, if the effect of load depends on the overlap in content-specific processing between tasks (Golob et al., 2017; Kim et al., 2005), then line bisection and landmark task might be differently affected by the addition of a secondary task. Moreover, if cognitive load affects the orienting of spatial attention by modulating hemispheric asymmetries as suggested by neuroimaging and electrophysiological findings (Bonato et al., 2015; O'Connell et al., 2011; Pérez et al., 2009), then by adding a concurrent secondary task, we should be able to modulate attentional biases in the horizontal but not in the vertical dimension, since hemispheric asymmetries drive horizontal but not vertical attentional biases (Churches et al., 2017; Fink, Dolan, Halligan, Marshall, & Frith, 1997, Fink et al., 2000; Zago et al., 2017). However, if cognitive load has a similar effect on horizontal and vertical judgements, then some underlying mechanism other than hemispheric asymmetries might underpin the allocation of spatial attention resources under load.

2.1.1 *Experiment 1a*: Horizontal and vertical line bisection under load

In our first experiment, we compared horizontal and vertical attentional biases under load by asking healthy participants to perform a line bisection task in single and dual-task conditions. In particular, in the single-task condition participants performed the line bisection task, either in the horizontal or vertical orientation, with no additional secondary task; in turn, in the dual-task condition, the line bisection task was carried out together with a secondary auditory working memory task. If the increased cognitive load affects spatial asymmetries by modulating hemispheric asymmetries as previously reported (Bonato et al., 2015; O'Connell et al., 2011; Pérez et al., 2009), then horizontal and vertical bisection biases should be differently modulated in the dual-task condition. Conversely, if horizontal and vertical spatial asymmetries are driven by similar mechanisms under load, then we should find similar modulation of bisection biases across orientations.

Participants

Twenty-four participants from Flinders University (19 females, *M* = 24.58 years, *SD* = 9.74) received $15AUD for their participation. All participants had normal or corrected-to-normal vision and were right-handed as assessed by the Flinders Handedness Survey (FLANDERS) (Nicholls, Thomas, Loetscher, & Grimshaw, 2013). The procedures in the present research complied with the Declaration of Helsinki and were approved by, and carried out in accordance with, the guidelines of the Social and Behavioural Research Ethics Committee of Flinders University. Informed consent was obtained from all participants.

Apparatus and stimuli

Experiments were presented on a 559mm Dell monitor with a resolution of 1680 x 1050 pixels running at 60 Hz and programmed using MATLAB software (MathWorks) and the Psychophysics Toolbox extensions (Brainard & Vision, 1997; Kleiner et al., 2007; Pelli & Vision, 1997). In the line bisection task stimuli were white lines of three possible lengths (13°, 15° and 18° of visual angle) and 0.1° thick presented on a black background and viewed at an approximate distance of 570 mm, with viewing distance unconstrained. Participants completed a line bisection task with stimuli consisting of horizontal or vertical lines. To decrease the use of external cues in determining the midpoint of the line, horizontal stimuli were presented in the center of the screen, and shifted to either the left or the right of center by 2°; similarly, vertical lines were presented in the center of the screen, and shifted to either above or below it by 2°. The length of the line and its spatial position were manipulated to increase stimulus variability and avoid any visual adaptation effect. Half of the participants completed the task in the horizontal orientation and the other half in the vertical orientation. As regards the secondary working memory task stimuli were sequences of words representing four different basic geometrical shapes (circle, square, rectangle, triangle), chosen to ensure that all memory items were comparable in terms of aspects known to affect memory performance (e.g. frequency, imaginability, familiarity). Words were presented binaurally one at a time, through Sennheiser HD 201 circumaural headphones (Sennheiser, Germany). On each trial, the names of all four shapes were read aloud, with no repetition of a shape within a single trial.

Procedure

Participants completed the line bisection task in two different conditions: single- and dual-task. In the single-task condition, participants carried out the line bisection task with no additional secondary task. A blank screen appeared for 500ms, followed by the presentation of the line to be bisected, which remained on the screen until the participants' response. Participants were instructed to estimate the midpoint of the line by positioning the mouse cursor on it using their right hand. Although there was no time limit, a combination of speed and accuracy was emphasized in the task instructions. In the dual-task condition, a sequence of four words that had to be memorized was read aloud by the experimental program, before the to-be-bisected line appeared on the screen (see Naert et al., 2018 for a similar procedure). Participants were instructed to memorize the shape words in the same order that they were presented. Once all the words had been read aloud, a horizontal/vertical line appeared on the screen and participants made their bisection. After bisecting the line, participants were presented with a memory test, which asked participants to evaluate whether the statement about the order of presentation of two of the words was true or false (e.g. "The triangle was before the circle"). Figure 2.1 depicts the timeline of a dual-task condition experimental trial. Participants made their responses to the memory task using a response pedal (Olympus Foot Switch RS-28H, Olympus, Japan), which was positioned under the table. Specifically, they pressed the left pedal with their left foot if the sentence was true and the right pedal with the right foot if it was false, with this response mapping being counterbalanced across participants. Subsequently, participants received auditory feedback regarding the accuracy of their memory response. The order of conditions (e.g. single and dual-task) was counterbalanced across participants. Before the start of the experiment, participants completed 18 practice trials for each condition. The experiment consisted of two blocks (each corresponding to single and dual-task conditions, respectively) with 120 trials each. After the task, participants were administered with the FLANDERS survey and were debriefed and thanked for their time. The experiments took about 45 minutes.

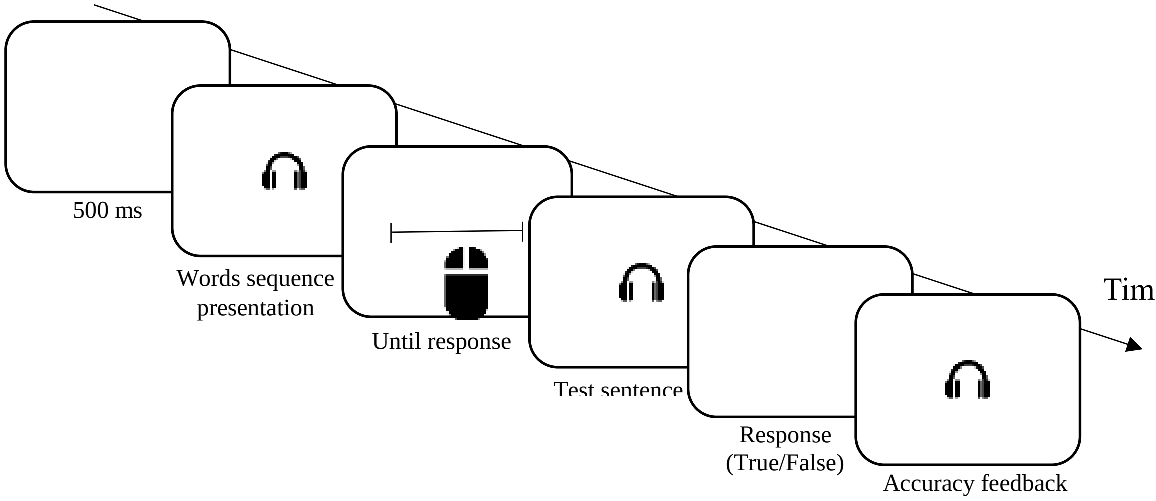


Figure 2.1. Schematic overview of a dual-task condition trial for Experiment 1a. Only an example trial with horizontally oriented lines is depicted; procedure and timing for the vertical condition were identical to the horizontal one.

Statistical analysis

For each participant, mean bisection bias for single and dual-task conditions were computed by subtracting the estimated midpoint from the true centre of the line, dividing the result for the line length and multiplying the quotient by 100, with a negative score indicating a leftward/upward bias. Mean accuracy scores for the secondary task were also computed, with participants with an average accuracy level below 70% in the secondary task excluded from the analysis as we could not be sure that they understood task instructions. One sample *t*-tests were conducted to compare mean bisection biases against zero (the true line midpoint) for each orientation (horizontal and vertical) and each condition (single and dual-task) separately. Then, repeated-measure analyses of variance (ANOVA) with load (single vs. dual) as within-subject variable and orientation (horizontal vs. vertical) as between-subjects factor were carried out to compare mean bisection biases across conditions.

Results

Mean accuracy score for the secondary task was 83.95% (*SD* = 8.95). Only one participant, with a mean accuracy score below 70%, was excluded from the analysis; therefore analysis were conducted on a sample of twenty-four participants. In the horizontal line bisection, participants did not show a significant pseudoneglect neither in the single, $t(11) < 1$, $p = 0.914$, $d = 0.03$, nor in the dual-task condition, $t(11) = 1.34$, $p = 0.207$, $d = 0.39$. When lines were vertically oriented, a significant upward bisection bias was found in the single-task, $t(11) = 3.00$, $p = 0.012$, $d = 0.87$, but not in the dual-task condition, $t(11) < 1$, $p = 0.719$, $d = 0.11$. The repeated-measure ANOVA revealed a significant main effect of load, $F(1,22) = 19.87$, $p < .001$, $\eta_p^2 = .475$, with bisection bias in the dual-task condition being reduced as compared to the single-task condition (Figure 2.2). In turn, the main effect of orientation was not significant, $F(1,22) = 2.94$, $p = .100$, $\eta_p^2 = 118$, nor was significant the interaction load by orientation, $F(1,22) = 3.30$, $p = .083$, $\eta_p^2 = .130$.

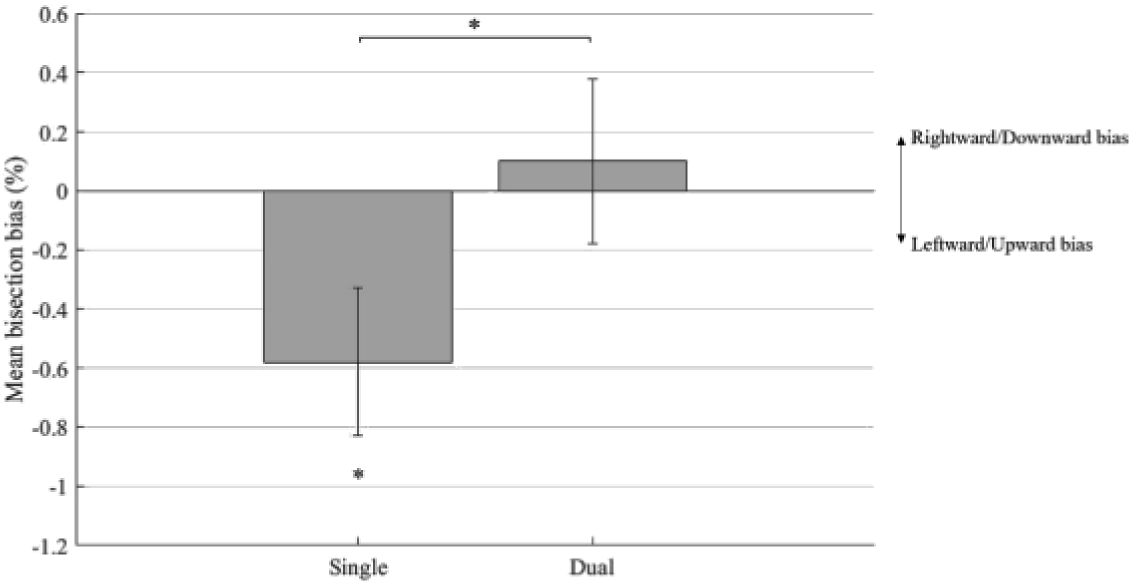


Figure 2.2. Mean bisection bias (%) for single and dual-task conditions in Experiment 1a. A negative score represents a leftward/upward bias and a positive score represents a rightward/downward bias. Error bars represent ± SEM. Asterisks denote a significant difference (p<.05).

Discussion

Taken together our data demonstrated for the first time that increasing cognitive load affects spatial attention asymmetries not only in the horizontal dimension, as previously reported (Bellgrove et al., 2013; Benedetto et al., 2013; Golob et al., 2017; Lisi et al., 2015; Naert et al., 2018), but also in the vertical orientation. In particular, in the single-task condition participants reported an upward bias, in line with the presence of an altitudinal pseudoneglect (Churches et al., 2017; Drain & Reuter Lorenz, 1996; Suavansri et al., 2012), whereas in the dual-task condition no significant attentional bias was found. Interestingly, although no directional bias was found for the horizontal orientation neither in the single nor the dual-task conditions, no difference emerged regarding the effect of the increased cognitive load when compared to the vertical orientation. Therefore, our data suggest that horizontal and vertical spatial asymmetries are driven by similar underlying mechanisms under load.

2.1.2 *Experiment 1b*: Horizontal and vertical landmark task under load

In Experiment 1a we demonstrated, through a manual line bisection task, that horizontal and vertical spatial asymmetries might be similarly modulated by the increased cognitive load. Nevertheless, prior evidence suggested that the effect of load on spatial attention might depend on the task at hand (Golob et al., 2017; Kim et al., 2005). Hence, in our second experiment attentional biases were measured by means of a landmark task, which is widely adopted to assess spatial asymmetries in both clinical and experimental settings, while keeping the secondary working memory task identical to Experiment 1a. The landmark task requires participants to indicate which half of a pre-bisect line is longer (left or right, upper or lower) by means of a two-alternative forced-choice discrimination, thus being considered a more perceptual measure of spatial asymmetries, since it reduced the involvement of motor functions as compared to the manual line bisection task (Bisiach, Ricci, Lualdi, & Colombo, 1998; Milner, Brechmann, & Pagliarini, 1992). Furthermore, unlike the previous experiment where participants were instructed to use only their right hand to respond, here they were asked to use both hands to respond, to further reduce the influence of any lateralized motor activation on the spatial biases produced.

Participants

Twenty-four participants from Flinders University (18 females, *M* = 20.75 years, *SD* = 5.15) received course credit for their participation. Inclusion criteria were the same as Experiment 1. None of these participants had taken part in Experiment 1. Ethical approval was granted by the Social and Behavioural Research Ethics Committee of the Flinders University.

Stimuli and materials

Stimuli were pre-bisected lines appearing in two orientations: horizontal and vertical. As in Experiment 1, the lines were of three different lengths (13°, 15° and 18° of visual angle) and were 0.1° thick. Lines were asymmetrically bisected to make either the left/upper or right/lower side longer by 0.5 mm (.047°), 1 mm (.095°) or 2 mm (.19°); the bisection was never located in the veridical centre, meaning one side of the line was always longer than the other. Each stimulus type, one of the six types of lines (three left/upper-side longer and three right/lower-side longer), was presented an equal number of times (i.e. 20 times per block). As in the previous experiment, to decrease the use of external cues in determining segment length, horizontal stimuli were presented in the center of the screen, or shifted to either the left or the right side by 2°; similarly, vertical lines were presented in the center of the screen, or shifted either above or below it by 2°. Half of the participants completed the task in the horizontal orientation and the other half in the vertical orientation. Participants made a two-alternative forced-choice discrimination, pressing the left/upper button if the line was longer on the left/upper side or the right/lower button if the right/lower one was longer. In the horizontal condition, participants pressed the left button with their left index finger and the right button with the right one with response key mapping being maintained across all participants, due to the intuitive nature of the response. In turn, in the vertical condition, response mapping was counterbalanced across participants, with half of the sample pressing the upper button with their left index finger and the lower one with the right index finger and the other half using the opposite mapping. Participants were asked to respond as quickly as they could, but not to sacrifice accuracy for speed. Responses were scored as leftward/upward when the left/upper side was chosen as longer and as rightward/downward when the right/lower was chosen as longer.

Procedure

Task procedure was identical to Experiment 1a, with the landmark task replacing the line bisection task. In the landmark task, a central fixation cross appeared for 500ms, followed by the presentation of the pre-bisected line for 500ms. Afterward, a blank screen appeared until the participants' response or for 2000ms, whichever happened first. Figure 2.3 shows the timeline of a dual-task condition experimental trial.

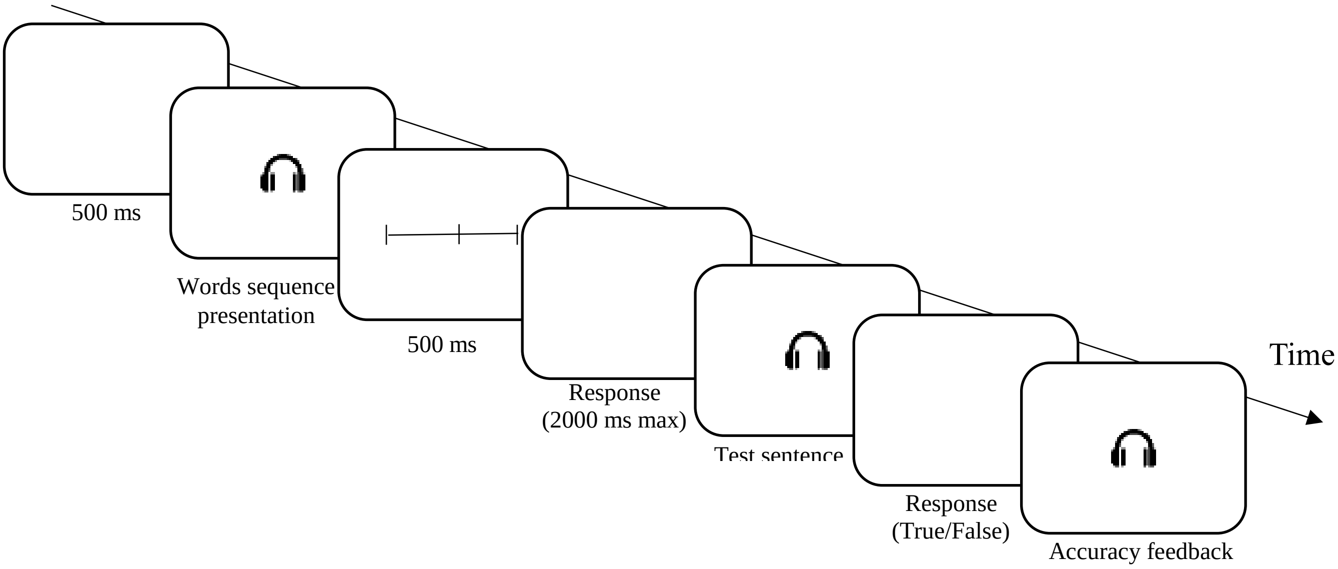


Figure 2.3. Schematic overview of a dual-task condition trial for Experiment 1b. Only an example trial with horizontally oriented lines is depicted; procedure and timing for the vertical condition were identical to the horizontal one, with the exception that participants made an up/down response.

Statistical analysis

As in Experiment 1a, dependent variables were mean bisection biases, which were calculated by subtracting the number of leftward/upward responses from the number of rightward/downward responses and dividing by the total number of trials and multiplying the results for 100, with a negative score indicating a leftward/upward bias. Additionally, mean accuracy scores for the landmark task were calculated. Accuracy data were used to determine whether the performance was above chance levels (50% given a two-response forced-choice format). As the bisection point was never located in the true center, each trial had a correct response. Two participants with accuracy scores below chance level were excluded from analyses. Two further participants with mean accuracy score below 70% in the secondary task were excluded. Therefore, data were analysed as in the previous experiment on a sample of twenty-four participants.

Results

Mean accuracy score for the secondary load task was 77.72 % (*SD* = 8.36). Mean accuracy scores for the landmark task were 69.40 % (*SD* = 6.17) and 69.16 % (*SD* = 7.03) for single and dual-task conditions, respectively. One-sample *t* test reported the presence of significant pseudoneglect for both single, *t*(11) = 4.09, *p* = .002, *d* = 1.18, and dual-task conditions, *t*(11) = 4.27, *p* = .001, *d* = 1.23, for horizontal landmark task. Conversely, no directional biases were found for vertically oriented lines in the single-task, *t*(11) < 1, *p* = .714, *d* = 0.11, nor in the dual-task condition, *t*(11) < 1, *p* = .499, *d* = 0.20. The repeated-measures ANOVA showed a significant main effect of load, *F*(1,22) = 4.98, *p* = .036, η_p^2 = .185, with bisection bias in the dual-task condition being shifted more to the left/upper side than the single-task condition (see Figure 2.4). Moreover, the main effect of orientation was also significant, *F*(1,22) = 10.26, *p* = .004, η_p^2 = .318, with participants showing greater bisection bias for horizontally oriented lines (*M* = -26.36, *SD* = 22.21) than when lines were presented in the vertical orientation (*M* = -1.42, *SD* =19.93). The interaction load by orientation, *F*(1,22) < 1, *p* = .631, η_p^2 = .011 was not significant.

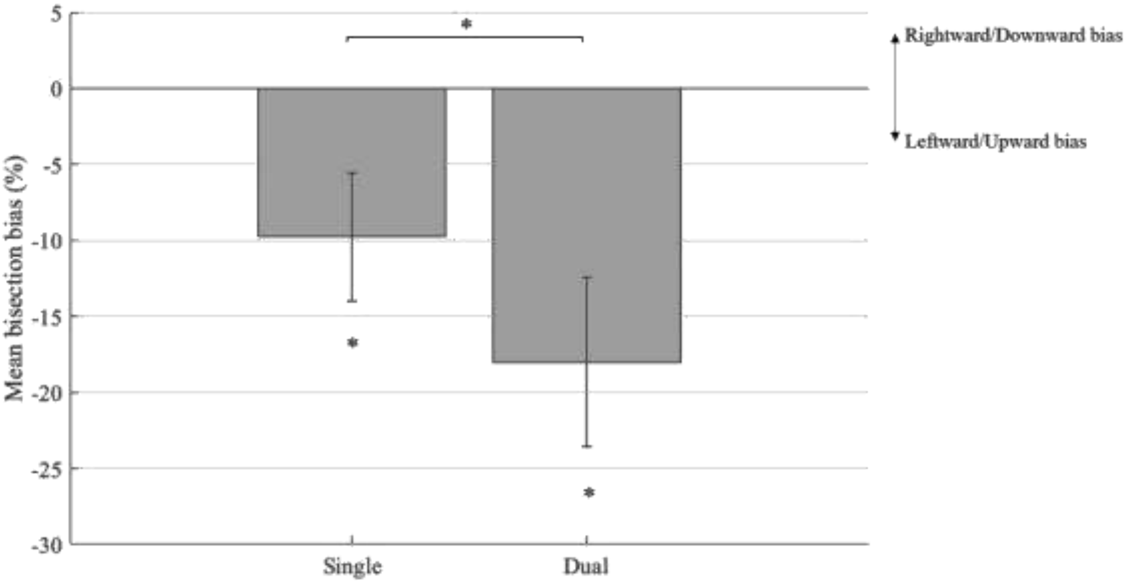


Figure 2.4. Mean bisection bias (%) for single and dual-task conditions in Experiment 1b. A negative score represents a leftward/upward bias and a positive score represents a rightward/downward bias. Error bars represent ± SEM. Asterisks denote a significant difference (p<.05).

2.1.3 General discussion

In two experiments we demonstrated that spatial asymmetries in the horizontal and vertical planes are similarly modulated under load. In particular, in the dual-task condition of both experiments bisection biases were similarly affected by the concurrent presentation of a secondary auditory working memory task independently from lines orientation. Hence, our data suggest the presence of common underlying mechanisms driving horizontal and vertical spatial asymmetries under load.

Prior evidence (Bonato et al., 2015; O'Connell et al., 2011; Perez et al., 2009; Vuilleumier et al., 2008) associated spatial asymmetries under load with a modulation of the relative hemispheric asymmetry, likely driven by a weakening of the right hemispheric dominance for visuospatial processing (O'Connell et al., 2011; Pérez et al., 2009). However, if that was the case, we should have found distinct effects between orientations since asymmetrical activations between hemispheres are considered to be the underlying mechanism of horizontal (but not vertical) attentional biases (Drain & Reuter-Lorenz, 1996; Fink et al., 2000; Zago et al., 2017).

Accordingly, our findings are consistent with the notion that spatial attention in the two planes rely on different mechanisms (Churches et al., 2017; Halligan & Marshall, 1993, 1995; Nicholls et al., 2004; Pitzalis et al., 2001; Post et al., 2006), with horizontal biases depending on space-based mechanisms and those in the vertical dimension on object-based mechanisms (Churches et al., 2017). In particular, horizontal attention asymmetries are driven by greater activation of the dorsal stream in the right hemisphere, which favours spaced-based attention, as compared to the left hemisphere (Churches et al., 2017; Fink, Dolan, Halligan, Marshall, & Frith, 1997, Fink et al., 2000; Zago et al., 2017). Conversely, vertical attentional biases originate from greater activation of the ventral stream, favouring object-based attention and directing attention to the upper hemispace, relative to the dorsal stream, which directs attention to the lower hemispace (Drain & Reuter-Lorenz, 1996).

Nevertheless, our data demonstrated that the reduction of attentional resources associated with the dual-task paradigm affected spatial asymmetries independently from stimuli orientation. Indeed, in the single-task condition, participants were free to focus all available attentional resources on the primary spatial task (e.g., line bisection and landmark task), whereas in the dual-task, processing resources needed to be divided (and alternately shifted) between the two tasks, likely through top-down monitoring processes. In line with this, attentional biases (at least in the horizontal plane) are affected by the decrease of processing resources as in case of low sustained attention abilities (Bellgrove, Dockree, Aimola, & Robertson, 2004; Dodds et al., 2008) as well as caused by drowsiness, fatigue or increased attentional demands (Benedetto et al., 2013; Benwell, Harvey, Gardner, & Thut, 2013; Dufour, Touzalin, & Candas, 2007; Fimm, Willmes, & Spijker, 2006; Manly, Cornish, Grant, Dobler, & Hollis, 2005; Newman, O'Connell, & Bellgrove, 2013). Interestingly, our findings add evidence to the previous literature by showing that the lessening in processing resources affects not only horizontal but also vertical spatial asymmetries. Furthermore, horizontal and vertical pseudoneglect are similarly modulated by top-down attentional processes, for instance when numerical cues are adopted to shift spatial attention, which are thought to involve endogenous volitional control mechanisms (Galfano, Rusconi, & Umiltà, 2006; Ranzini, Dehaene, Piazza, & Hubbard, 2009; Ristic, Wright, & Kingstone, 2006) or when participants are explicitly asked to focus their attention on a specific portion of the line (Lamb, Balavage, Williamson, Knight, & Heilman, 2019). Therefore, our data further confirm that attentional biases might be affected by top-down processes, regardless of stimuli orientation.

On a neural level, the underlying mechanism that might explain the similar effect of load on horizontal and vertical attentional biases might be found in the contribution of higher-level regions involved in top-down monitoring processes located in a bilateral fronto-parietal network (Corbetta & Shulman, 2002, Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Hopfinger, Buonocore, & Mangun, 2000; for a review see Katsuki & Constantinidis, 2013). Accordingly, the same network is affected by the increased attentional load (Culham et al., 2001; Seydell-Greenwald et al., 2017; Tomasi et al., 2007) and contributes to verbal, visual and auditory working memory processes (Attout, Fias, Salmon & Majerus, 2014; Cavanagh et al., 2015; Quentin et al., 2019; Samrani et al., 2019; van Dam et al., 2015), along with the maintenance and control of attention over time (Blankenburg et al., 2010; Lee et al., 2013; Thakral & Slotnik, 2009; for a review see Gottlieb & Snyder, 2010). Interestingly, dorsal and ventral pathways project to shared target regions within the right prefrontal cortex (Corbetta, Patel, & Shulman, 2008; Fox et al., 2006; Takahashi et al., 2013; for a review see Vossel, Geng, & Fink, 2014), but receive anatomically separated feedback projections with diverse top-down signals to specific areas depending on stimulus properties and task demands (Ninomiya et al., 2012). With regard to hemispheric asymmetry, larger activations in frontal and parietal regions in the left hemisphere, have been reported in visual attention tasks with increasing difficulty (Tomasi et al., 2007; Seydell-Greenwald et al., 2017), thus proposing that interactions between fronto-parietal networks are essential for cognitive control (Davis & Cabeza, 2015;

Gerlach et al., 2014; Meehan et al., 2017), possibly due to larger left hemisphere activations that may balance a right hemisphere dominant asymmetry (Szczepanski et al., 2010).

Therefore, spatial attentional asymmetries under load (e.g., independently from stimuli orientation) may indeed depend on the modulation of hemispheric asymmetry, as previously reported (Bonato et al., 2015; O'Connell et al., 2011; Perez et al., 2009; Vuilleumier et al., 2008) but driven by the contribution of higher-level areas of both hemispheres involved in top-down monitoring processes, rather than due to a weakening of the right-hemispheric dominance (O'Connell et al., 2011; Pérez et al., 2009). However, our data do not allow us to derive definitive conclusions regarding the neural underpinning of such effect and further neuroimaging and/or electrophysiological studies comparing horizontal and vertical spatial bias under load would be valuable.

Another interesting point raised by our study is the differential effect of load on spatial asymmetries between line bisection and landmark tasks, with the addition of a secondary task inducing opposite effects. Indeed, in the line bisection task cognitive load reduced attentional biases, whereas in the landmark task attentional asymmetries were increased under load. Even though such a finding may appear inconsistent at first, prior studies have revealed that line bisection and landmark tasks are only weakly correlated (Milner et al., 1993; Rueckert, Deravanesian, Baboorian, Lacalamita, & Repplinger, 2002), probably as a result of the very distinct cognitive demands with different strategies used depending on the task (Cavezian, Valadao, Hurwitz, Saoud, & Danckert, 2012). For instance, in line bisection tasks participants have to actively move the mouse cursor to indicate the estimated midpoint of the line, thus involving both visual perceptual and motor control skills (Garza, Eslinger, & Barrett, 2008; Luh, 1995). Conversely, in the landmark task participants are instructed to make a two-alternative forced-choice decision regarding the length of two halves of a pre-bisected line, thus being considered a purely perceptual measure of spatial attention, with reduced motor load (Bisiach et al., 1998; Milner et al., 1992). Moreover, whereas in line bisection tasks stimuli are processed globally as a single object with eye movements remaining close to the stimulus centre, in the landmark task, visual scanning extends to both hemifields with participants comparing the left and right side of the pre-bisected line to reach their decision (Cavezian et al., 2012), thus relying more on local attention processes (Falchook et al., 2013). Additionally, on a neural level, although both tasks activate the right superior parietal cortex and right temporo-parietal junction (Cicek, Deouell, & Knight, 2009), landmark tasks show a more pronounced right lateralization (Seydell-Greenwald et al., 2019) whereas line bisection tasks involve more bilateral activations (Cavezian et al., 2012) with greater frontal areas contribution (Cicek et al., 2009). Therefore, although initially surprising, our results are consistent with a large body of research that shows that line bisection and landmark tasks are functionally unrelated.

Nonetheless, differences in methodological choices between the two tasks in our study might have contributed to such discrepant results. For instance, in the line bisection task (Experiment 1a) only single hand responses were allowed since participants had to move the mouse cursor with their right hand to indicate the estimated line midpoint, whereas in the landmark task (Experiment 1b) participants were asked to make a two-alternative-forced-choice discrimination using both hands. Furthermore, in the line bisection task participants had an unlimited viewing time to inspect the line and indicate the midpoint, possibly influencing the performance in the secondary task, since the bisection trial occurred in the retention period of the working memory task. Indeed, it is possible that a longer maintenance period might have allowed subvocal rehearsal processes, thus increasing left hemisphere activations and consequently reducing pseudoneglect. Conversely, the increased attentional bias under load in the landmark task may depend on a more pronounced right hemisphere activation due to participants relying on visuospatial strategies (e.g. visual imagery) to retain working memory information, possibly driven by the high imaginability rate of the words (e.g. basic geometrical shapes) used in the secondary working memory task. Nevertheless, we cannot make any inference on the possible impact of the different mnemonic strategies, since we did not ask participants to use a particular strategy to memorize information, nor did they report the strategy they adopted. Future studies might investigate the effect of non-verbal rehearsal strategies on spatial biases.

Taken together, our findings indicate that the intrinsic differences between the two tasks may have led to the opposite effects of load seen in our study, suggesting that the influence of cognitive load might strictly depend on the task at hand. Moreover, our data further suggested that attentional biases as measured by line bisection and landmark tasks engage distinct mechanisms that are differently modulated by non-spatial factors.

It is worth mentioning that our study might present a few limitations. For instance, in contrast to the previous literature (Drain & Reuter Lorenz, 1996; Jewell & McCourt, 2000), we did not find significant leftward and upward attentional biases in the single-task conditions of

Experiment 1a and 1b, respectively, which could be explained by the small sample size (e.g. 12 participants for each orientation in each experiment) or the tasks not being sensitive enough to observe a significant directional bias. However, it is unlikely that this limitation affected our main finding since the absence in both experiments of a significant interaction between load and orientation ensures us that cognitive load had a similar effect on horizontal and vertical attentional biases. Furthermore, we adopted a between-subjects design, which might have complicated the comparison between horizontal and vertical attentional biases. Indeed, a within-subjects design would have allowed a direct comparison of the effect of load across orientations within the same participants. However, the choice of a between-subject design was justified by the necessity not to prolong the duration of experimental sessions, since prior studies (Benedetto et al., 2013; Benwell et al., 2013; Dufour et al., 2007; Newman et al., 2013) showed that attentional biases are affected by increased fatigue and time-on-task.

In conclusion, our study demonstrated that spatial biases in the two dimensions are similarly modulated by the reduction of attentional resources under load, thus suggesting the possibility that spatial asymmetries in horizontal and vertical dimensions relate to only partially independent mechanisms. However, the modulation of spatial asymmetries under load depends on the specific task adopted, with line bisection and landmark tasks possibly engaging distinct processes.

CHAPTER 3

How a normal binocular visual experience shapes spatial asymmetries

3.1 Study 2

The role of binocular vision in driving pseudoneglect in visual and haptic bisection: evidence from strabismic and monocular blind individuals

Citation

The entirety of this chapter has been published: Ciricugno, A., Rinaldi, L., Vecchi, T., Merabet, L. B., & Cattaneo, Z. (2019). The Role of Binocular Vision in Driving Pseudoneglect in Visual and Haptic Bisection: Evidence From Strabismic and Monocular Blind Individuals. *Multisensory Research,* 1(aop), 1-19, doi: 10.1163/22134808-20191347.

The article has been reproduced here in full. Authors CZ contributed to the conceptualisation of the current project and RL, VT, MLB, and CZ edited the manuscript.

Abstract

Prior studies have shown that strabismic amblyopes do not exhibit pseudoneglect in visual line bisection, suggesting that the right-hemisphere dominance in the control of spatial attention may depend on a normally developing binocular vision. In this study, we aimed to investigate whether an abnormal binocular childhood experience also affects spatial attention in the haptic modality, thus reflecting a supramodal effect. To this aim, we compared the performance of normally sighted, strabismic and early monocular blind participants in a visual and a haptic line bisection task. In visual line bisection, strabismic individuals tended to err to the right of the veridical midpoint, in contrast with normally sighted participants who showed pseudoneglect. Monocular blind participants exhibited high variability in their visual performance, with a tendency to bisect toward the direction of the functioning eye. In turn, in haptic bisection, all participants consistently erred towards the left of the veridical midpoint. Taken together, our findings support the view that pseudoneglect in the visual and haptic modality relies on different functional and neural mechanisms.

Introduction

When asked to estimate the midpoint of a line, neurologically normal individuals tend to bisect it slightly to the left of the veridical center, a phenomenon known as pseudoneglect (Bowers & Heilman, 1980; Brooks et al., 2014, 2016; Darling et al., 2012; Jewell & McCourt, 2000). Pseudoneglect is typically interpreted as reflecting a right hemispheric dominance in the allocation of spatial attention resources (Jewell & McCourt, 2000), which makes the segment of a line in the contralateral left hemispace appear longer than it physically is. Indeed, evidence for an attentional bias toward the left side of physical and mental space has been consistently reported with different experimental paradigms, such as line and number bisection, visual search, visual short-term memory, and spatial working memory tasks (e.g., Brooks et al., 2011a; Darling et al., 2012; Della Sala et al., 2010; Gigliotta et al., 2017; Nicholls & McIlroy, 2010; Nicholls et al., 2017), as well as across different modalities (e.g., vision, touch and audition) (Brooks et al., 2016; Cattaneo et al., 2012a, b; Eardley et al., 2017; Hach & Schütz-Bosbach, 2012; Sosa, Teder-Salejarvi & McCourt, 2010).

A critical issue when investigating the mechanisms underlying pseudoneglect in line bisection is whether right hemispheric dominance in the control of spatial attention is driven by a normal visual experience. Valuable insights on this topic may come from studies involving individuals with amblyopia. In amblyopia, ocular developmental disturbances occurring in early childhood, such as a misalignment (strabismus) or uncorrected refractive imbalance between the two eyes (anisometropia), lead to a loss of binocular functions, which in turn can be followed by either suppression of visual input from one eye, or by the alternating suppression of each eye (for a recent review, see Asper, Watt & Khuu, 2018). Functional losses in the suppressed eye include a wide range of changes within the visual system, starting from deficits in contrast sensitivity and spatial distortion (e.g., Farivar et al., 2017) up to changes of higher functions along the visual pathways (e.g., Bankó, Körtvélyes, Németh, Weiss & Vidnyánszky, 2013; Cattaneo et al., 2013; Constantinescu, Schmidt, Watson & Hess, 2005; Simmers, Ledgeway, Mansouri & Hutchinson, 2006; Tsirlin, Colpa, Goltz & Wong, 2018). Interestingly, the altered binocular input characterizing certain forms of amblyopia has been shown to affect spatial attention asymmetries. Indeed, when asked to estimate the midpoint of physical lines in the visual modality, participants with amblyopia showed a consistent rightward bias (Thiel & Sireteanu, 2009). Similarly, amblyopic participants (mainly with strabismus) demonstrated a weaker leftward bias in mean number estimation compared to control participants (Mohr et al., 2010). This pattern of findings in people affected by amblyopia has been interpreted as reflecting changes in the processing of visual information in the dorsal stream and in the system controlling visuospatial attention (Mohr et al., 2010; Thiel & Sireteanu, 2009). However, whether distorted binocular visual development also affects spatial attention allocation (and, hence, the relative pattern of hemispheric asymmetry) in other sensory modalities, such as touch, has never been investigated.

An extreme case of loss of binocularity is that of individuals with monocular blindness (for a review, see Steeves et al., 2008). Early monocular blindness is usually associated with ocular and/or prechiasmal damage or pathology such as optic atrophy, trauma, or retinal developmental disorders. Although monocular blind individuals may have typically normal visual acuity in one eye, this condition has nonetheless been found to impact on many visual functions such as motion perception (Kelly et al., 2013; Steeves et al., 2002), pattern and shape discrimination (Cattaneo et al., 2014a; Steeves et al., 2004), face processing (Moro et al., 2019), and visuospatial working memory (Vecchi et al., 2006). Interestingly, prior studies in early blind individuals have shown that the total lack of visual input does not prevent the development of a right hemispheric dominance in the control of spatial attention (Gougoux et al., 2005; Renier et al., 2014; Ricciardi & Pietrini, 2011). Indeed, blind individuals tend to show a leftward bias both in physical haptic line bisection (Cattaneo et al., 2011a; Cattaneo, Rinaldi, Geraci, Cecchetto, & Papagno, 2018; Coudereau, Gueguen, Pratte & Sampaio, 2006; Sampaio, Gouarir & Mvondo, 1995), and in numerical bisection tasks (Cattaneo et al., 2010; 2011c; Rinaldi, Vecchi, Fantino, Merabet & Cattaneo, 2015; for a review, see Rinaldi Merabet, Vecchi & Cattaneo, 2018), suggesting a tendency towards an overestimation not only of the left portion of physical space, but also of spatial mental representations, similar to what has been observed in sighted individuals. However, the total lack of visual input may have different effects on lateralization patterns compared to distorted visual input, as suggested by studies in amblyopes (Mohr et al., 2010; Thiel & Sireteanu, 2009).

On these grounds, here we aimed to investigate whether distorted binocular vision that leads to alterations in typical visuospatial attention asymmetries (Mohr et al., 2010; Thiel & Sireteanu, 2009) also affects spatial attention in the haptic modality. Consistent evidence suggests that the right hemisphere preferentially orients attention towards the left side of space in the haptic modality (Bowers & Heilman, 1980; Brooks et al., 2011a, 2016; Cattaneo et al., 2011b). That is, similar to the visual modality, a leftward bias has been repeatedly observed in haptic bisection tasks, although the magnitude of this bias across studies is affected by modality-specific factors like the hand used for exploration, the scanning direction and the starting point of exploration (Brooks et al., 2011a, 2016; Eardley et al., 2017). Despite the lack of neuroimaging evidence regarding the neural correlates of haptic bisection, the leftward haptic bias is generally interpreted as reflecting a right-hemisphere dominance in the control of spatial attention, much like the visual leftward bias (Brooks et al., 2011a, 2016; Eardley et al., 2017). Indeed, touch and vision may share a common attentional control mechanism (e.g., Chen & Spence, 2017; Spence, 2010, 2014; Spence & Driver, 2004). However, whether this common mechanism develops independently for each sensory modality remains unclear. The finding that early blindness does not prevent the development of a right-hemisphere dominance in spatial attention orienting (Cattaneo et al., 2010, 2011a, 2018) suggests that there may be a common mechanism. Yet, whereas deaf-blind individuals show a leftward bias in haptic bisection like in sighted and early blind individuals (Cattaneo et al., 2018), it is interesting that early deaf individuals show a rightward bisection bias both in the dominant visual and in the haptic modality (Cattaneo et al., 2018), suggesting that visuospatial attention mechanisms may also affect the deployment of attention in other sensory modalities. Accordingly, when the dominant visual input is distorted rather than absent (as in the case of strabismus), it may be that altered visuo-spatial attention neural mechanisms (Thiel & Sireteanu, 2009) are responsible for shaping attentional mechanisms in other sensory modalities.

Moreover, we were interested in understanding whether and how early monocular blindness affects the typical pattern of hemispheric asymmetry in the control of spatial attention. Monocular blindness is defined by the disconnection of one eye from the visual system, leaving only one stream of input to the brain from the functioning eye, with intact low–level spatial vision (Reed, Steeves, Steinbach, Kraft, & Gallie, 1996; Steeves et al., 2008). In contrast, the strabismic brain receives two streams of input, with one stream providing altered information. Hence, although both conditions lead to anomalies in binocular vision, they affect the visual system differently. This may influence the allocation of visuospatial attention resources for visual tasks.

Towards investigating these aims, we tested strabismic individuals with strong fixation preference (leading to amblyopia in certain participants), early monocular blind, and normally sighted participants in a line bisection task performed in the visual and in the haptic modality (i.e., with no visual feedback available). If impaired binocular vision affects the development of a right-hemispheric dominance in the control of spatial attention, strabismic and monocular blind individuals should show atypical spatial biases in the visual modality (Thiel

& Sireteanu, 2009), with these differences possibly extending to the haptic modality as well (Brooks et al., 2016; Eardley et al., 2017).

Participants

Eighteen individuals with strabismus or strabismic amblyopia (nine males, *M* age = 30.72 years, SD = 7.95, see Table 1 for details) and twenty-four normally age-matched controls with normal binocular vision (8 males, *M* age = 33.83 years, SD = 9.82) participated in the study. Among the strabismic participants, nine were diagnosed as having amblyopia and the remaining nine had strong fixation preference but no evidence of amblyopia (as clinically defined by reduced visual acuity in the affected eye). An additional group of twelve monocular blind individuals was recruited (three males, mean age = 37.5 years, SD = 11.33): eight left-eye blind (with functioning right eye), and four right-eye blind (with functioning left eye) (see Table 2 for details). All participants were right-handed (Oldfield, 1971). None of the participants reported neurological problems. Written informed consent was obtained from all participants before the experiment. The protocol was approved by the local ethical committee and participants were treated in accordance with the Declaration of Helsinki.

Material and Procedure

Stimuli consisted of wooden rods of five different lengths (300, 350, 400, 450 and 500 mm), with a diameter of 14 mm. Rods were positioned with Velcro strips (attached on the bottom of each rod) horizontally onto a wooden panel. They were placed centrally with respect to the body midline of each participant, guaranteeing a constant alignment between the participants' mid-sternum and the midpoint of the rod. The distance between the subject's mid-sternum and the midpoint of the rod was kept about 380 mm. Participants executed the task in two modalities: visual and haptic modalities. The same rods were used in the two conditions. At the beginning of the task, a vertical line (approximately 1 mm wide) was drawn with a pen in the middle of the tip of the participants' right index finger. At the end of each trial, the experimenter used this line to measure the difference between the participants' perceived midpoint and the actual midpoint, within the nearest mm. In particular, the experimenter measured the bias by means of a measuring tape whose left extremity was aligned with the left end of the rod; the measuring tape was positioned in such a way that numbers were visible to the experimenter only, thus preventing participants to possibly estimate their own level of performance in the visual condition. The order of the presentation of the visual and haptic conditions was counterbalanced across participants.

Visual Bisection

In the visual condition, participants were instructed to look at the rods and to indicate the estimated midpoint with their right index finger. A maximum of 5 s was given to respond. Strabismic and control participants were tested monocularly, once with the left eye blindfolded and once with the right eye blindfolded (monocular blind individuals were tested only once with their functioning eye), with the order of left/right eye testing counterbalanced. Each participant performed a total of 30 bisection trials (i.e., three for each rod length, 15 for each eye). Monocular blind individuals performed 15 bisection trials. Before the visual task, participants performed five practice trials to familiarize themselves with the task.

Haptic Bisection

All participants were blindfolded throughout the entire haptic task. They were instructed to explore the length of the rod in their preferred direction (left-to-right or right-to-left), using their right index finger only. At the beginning of each trial, the experimenter placed the palm of the participant's right hand on the rod, covering approximately the midpoint of the rod. Because of its approximate nature, this palm-based starting position could not be used as an accurate estimate of the rod's midpoint; moreover, at the start of each trial, participants were asked to lift their palm off the rod and to begin to explore it with their right index finger. This starting point for haptic exploration was used to control for systematic biases in scanning direction, which may influence bisection performance (see Cattaneo et al., 2010, 2011a, for a similar procedure). The exploration could last for a maximum of 10 s; within this time, participants could scan the rod as many times as they wished. At the end of the exploration, they were asked to indicate the midpoint of the rod, using their right index finger. No instruction was given to subjects as to the speed of movement of the index finger during the exploration. As for the visual task, each participant performed a total of 15 bisection trials (i.e., three for each rod length) in the haptic condition.

Statistical Analyses

Deviations from the objective midpoint were recorded to the nearest mm. As in previous studies (e.g., Cattaneo et al., 2012a, b; Nicholls et al., 2016), deviations from the veridical centre were converted to signed percentage scores (positive if bisections were to the right, negative if to the left) by subtracting the true half-length of the rod from the measured distance of each participant's estimate from the left extremity of it, and then dividing this value by the true half-length and multiplying the quotient by 100. Mean signed scores were computed.

Results

Visual Bisection Bias

Figure 3.1 depicts mean percentage bisection biases for each group (collapsed across rod length).

A one-sample *t*-test was first conducted by comparing the mean bisection error of strabismic and control participants with the null set (zero – that is, the true midpoint). The five different rod lengths were collapsed together in this analysis. Control sighted participants showed a consistent leftward bisection bias, reflecting pseudoneglect, regardless of the eye tested: left eye, $t(23) = 3.34$, $p = .003$, Cohen's $d = 0.68$; right eye, $t(23) = 3.16$, $p = .004$, $d = 0.65$. Strabismic participants did not show a significant bisection bias with the dominant eye (the right eye in six participants, the left eye in twelve participants), $t(17) = 1.18$, $p = .26$, while there was a tendency toward a rightward bias when bisecting lines with the non-dominant eye, $t(17) = 2.03$, $p = .06$, $d = 0.48$. Paired-sample *t*-tests were conducted to compare bisection bias between the left and right eye, separately for strabismic and control participants. In both groups the bias did not differ between the two eyes (control, $t(23) < 1$, $p = .98$; strabismic, $t(17) = 1.21$, $p = .24$). For strabismic participants, bisection biases did not differ even when considering the eyes as dominant and non-dominant, $t(17) < 1$, $p = .38$. A one-way ANOVA carried out on mean bisection error (collapsed for the two eyes) revealed a significant group difference, $F(1,40) = 12.24$, $p = .001$, $\eta_p^2 = 0.23$, with control participants erring more leftward than strabismic participants (see Fig. 3.1a). The same pattern emerged from a two-way ANOVA analysis, with eye (dominant vs non-dominant in strabismic individuals, and corresponding eye in control participants) as the within-subjects factor and group as the between-subjects factor, showing only a main effect of group, $F(1,40) = 12.24$, $p = .001$, $\eta_p^2 = 0.23$. The main effect of eye, $F(1,40) < 1$, $p = .37$, and the interaction eye by group, $F(1,40) < 1$, $p = .36$, were both not statistically significant.

Performance of monocular blind participants was analysed by means of non-parametric tests given the small sample size. Although visual inspection of Fig. 3.1c suggests that left-eye and right-eye blindness led to opposite bisection directional biases, a Mann–Whitney test conducted to compare bisection bias between left-eye blind and right-eye blind participants did not reveal any significant difference, $U = 10.0$, $z= -1.02$, $p = 031$. Moreover, the bisection bias was not significantly different from zero in either left-eye blind, $Z = -0.98$, $p = .33$, or right-eye blind participants, $Z = -0.73$, $p = 0.47$.

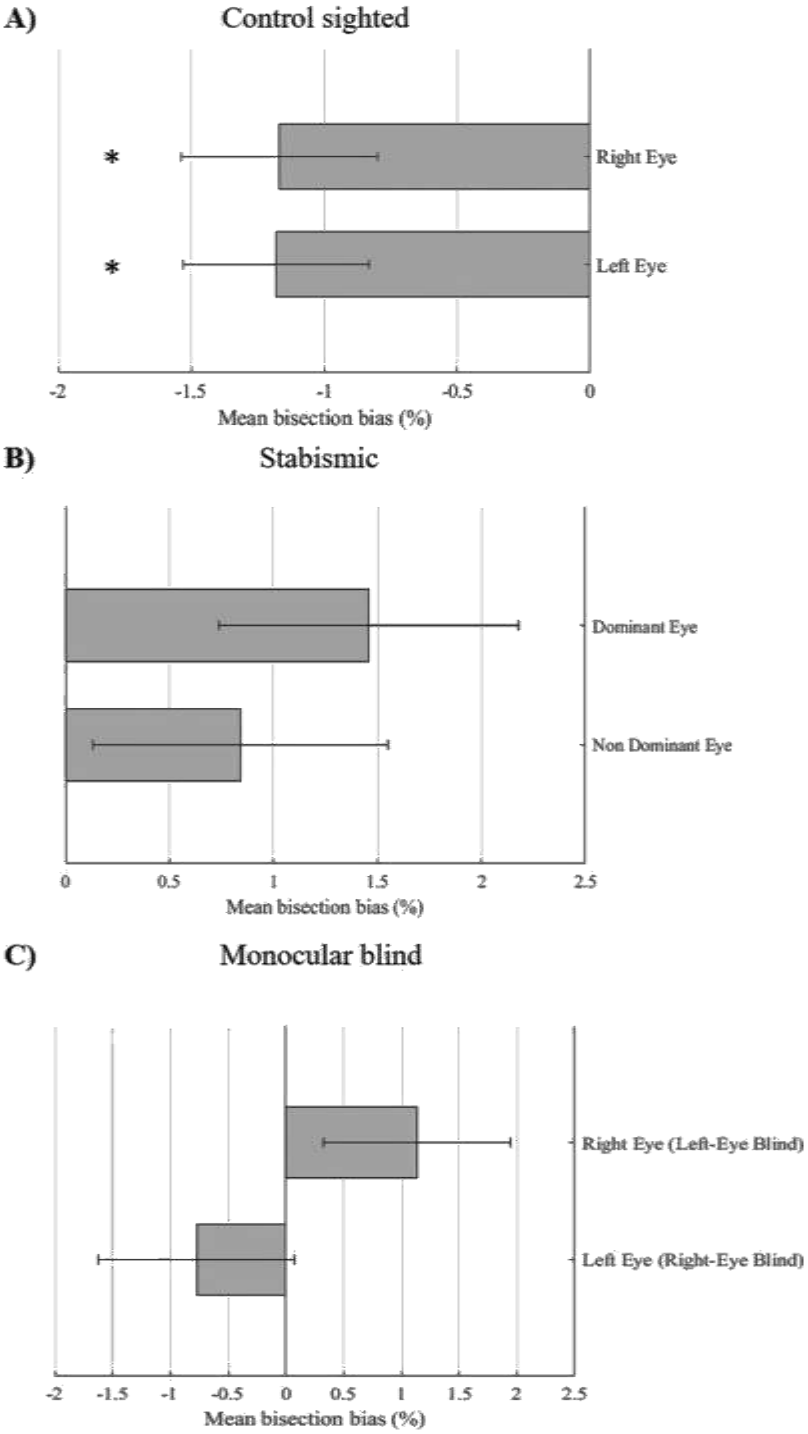


Figure 3.1. Mean percentage visual bisection bias of A) control sighted, B) strabismic, and C) monocular blind participants, as a function of the eye tested. Normally sighted participants showed a significant leftward bias, regardless of the eye-patched. Strabismic individuals tended to err toward the right (p = .06) when performing the task with the non-dominant eye (the right eye in 12 participants), whereas they did not show any significant directional bias when tested with the dominant eye (the right eye in six participants). Although a qualitative inspection of panel C suggests that right-eye blind participants erred leftward, and left-eye blind ones rightward, in neither case was the bias significant. Error bars represent ± SEM. Asterisks indicate a significant bisection bias (p < .05).

Haptic Bisection Bias

Deviations from the objective midpoint were recorded to the nearest mm and computed in the same way as in the visual bisection task. Figure 3.2 depicts mean percentage of bisection biases for each group. A one-sample *t*-test was first conducted by comparing the mean bisection error with the null set (zero, that is, the true midpoint). As for the visual bisection task, the five different rod lengths were collapsed together in this analysis. Both control participants, $t(23) = 5.28$, $p < 0.001$, $d = 1.08$, and strabismic individuals, $t(17) = 2.40$, $p = .028$, $d = 0.57$, showed a consistent leftward bisection bias. A one-way ANOVA was carried out to compare possible differences in mean bisection error between strabismic and control individuals. Results did not reveal any difference between the two groups, $F(1,40) < 1$, $p = .42$.

As shown in Fig. 3.2, monocular blind participants tended to bisect to the left of the veridical midpoint; however, this bias was not significant (left-eye blind, $Z= –1.40$, $p = .16$; right-eye blind, $Z = –0.73$, $p = .46$). Moreover, right-eye and left-eye blind participants performed similarly as assessed by a Mann–Whitney test, $U = 12.0$, $z = –0.679$, $p = .49$, (right-eye blind, $M = –2.17$, SE = 3.73; left-eye blind, $M = –5.13$, SE = 3.41).

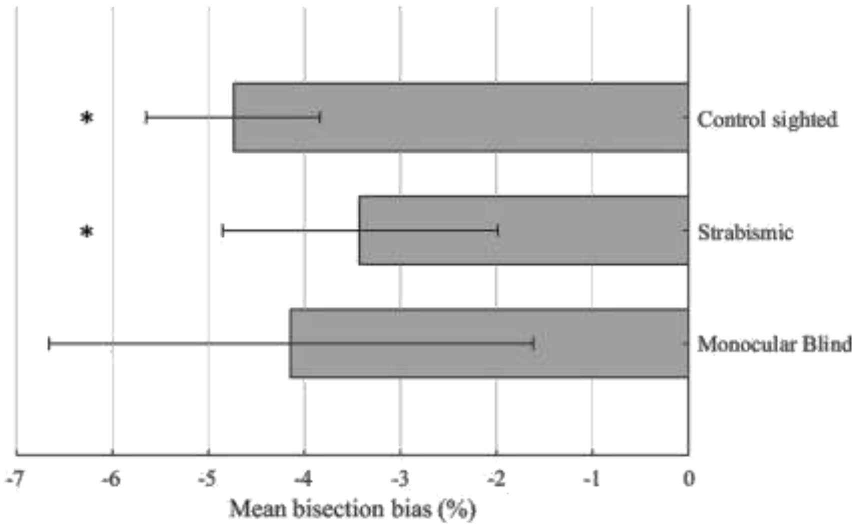


Figure 3.2. Mean percentage haptic bisection bias of control sighted, strabismic and monocular blind participants. Control sighted and strabismic participants showed a significant leftward bias. Although a qualitative inspection of monocular blind participants' performance suggests a leftward error, their bias was not significant. Error bars represent ± SEM. Asterisks indicate a significant bisection bias ($p < 0.05$).

3.1.2 Discussion

Previous research has pointed to the role of normal binocular vision development in driving pseudoneglect, as measured by means of the visual line bisection task (Thiel & Sireteanu, 2009). Here, we assessed whether strabismus (also leading to amblyopia in certain participants) and monocular blindness affect hemispheric asymmetry in the control of spatial attention beyond the visual domain since both these two ophthalmic conditions are known to impair the development of a normal binocular vision. Indeed, it is known that a distorted visual input can also affect attention in non-visual domains. Accordingly, individuals with visual impairments showed an altered pattern of haptic perception as compared to both sighted and blind participants (Heller, Brackett, Scroggs, Allen & Green, 2001; Heller, Wilson, Steffen, Yoneyama & Brackett, 2003). Moreover, altered binocular vision, like the case of strabismus (with or without amblyopia), is associated with anomalies in auditory spatial localization tasks (Richards, Goltz, & Wong, 2018), as well as in multisensory integration processes (Niechwiej-Szwedo, Chin, Wolfe, Popovich & Staines, 2016). We found that when participants were asked to visually bisect a series of lines, strabismic individuals tended to err to the right of the veridical midpoint, a tendency that was more pronounced when viewing with the affected eye. This was in contrast to the more typical leftward bias (i.e., pseudoneglect) observed in our normally sighted controls. In turn, monocular blind participants showed high variability in their visual performance. Overall, they tended to bisect toward the direction of the functioning eye, possibly reflecting a preferential activation of the contralateral hemisphere of the functioning eye (Posner & Rafal, 1987; Roth, Lora & Heilman, 2002). However, this pattern did not reach statistical significance (note that the sample size was quite small, thus limiting the statistical power of the study). Data from the strabismic participants were in line with prior evidence (Thiel & Sireteanu, 2009; see also Mohr et al., 2010). Thiel & Sireteanu (2009) suggested that the lack of pseudoneglect in strabismic amblyopes on the visual line bisection task may depend on impairment of the dorsal visual pathway that mediates the control of visuospatial attention (Corbetta & Shulman, 2002; Fierro et al., 2000). Interestingly, though, both strabismic and monocular blind participants performed similarly to sighted controls in the line bisection task in the haptic modality (i.e., with no visual input available). Indeed, in this condition, all participants showed a consistent leftward bisection bias, in line with prior studies with sighted participants (Cattaneo et al., 2011a).

The different pattern observed for visual and haptic bisection suggests that the effects on spatial attention related to ocular misalignment or monocular blindness may only pertain to the visual modality. This may appear surprising at first, as the same types of factors affect the bisection bias in both visual and tactile modalities (Bowers & Heilman, 1980; Brooks et al., 2011; Cattaneo et al., 2010). In interpreting these results, it is worth noting that several studies consistently point to a right-hemispheric dominance in tactile shape discrimination, irrespective of the hand used (Harada et al., 2004; Loayza et al., 2011). It may be that the tactile exploration *per se* activated the right-hemisphere more in all participants, leading to a consistent leftward bias in bisection. However, this interpretation would not account for prior findings reporting a rightward bias in tactile bisection in (neurologically healthy) deaf individuals or musicians (Cattaneo et al., 2018; Lega, Cattaneo, Merabet, Vecchi & Cucchi, 2014). Interestingly, whereas a right-hemisphere dominance in the control of visuospatial attention has been consistently observed in both neuroimaging (Corbetta & Shulman, 2002; Zago et al., 2017) and electrophysiological studies (Benwell et al., 2014), similar neural evidence is lacking within the haptic domain. Nevertheless, the consistent leftward bias reported by many studies in haptic bisection suggests that common attentional control mechanisms are at play across modalities (Brooks et al., 2011b; Cattaneo et al., 2010, 2011a; Eardley et al., 2017). This is the case even if the magnitude of the bisection bias may be poorly correlated across vision and haptics, existing discrepancies related to several factors affecting haptic bisection (like the hand used for exploration, the scanning direction, and the exploration starting point; Brooks et al., 2011b, 2016) and, more generally, the need to rely on a sequential acquisition (and updating) of the spatial information to be processed (e.g., line or rod) (Brooks et al., 2014; Eardley et al., 2017). Accordingly, tactile processing and tactile perception are consistently more sequential in nature than visual processing (Cattaneo & Vecchi, 2008; Gentaz, Baud-Bovy & Luyat, 2008). It has indeed been suggested that in tactile bisection, the individual creates a mental representation of the line length, which is updated by the tactile and proprioceptive information gathered as the finger sequentially moves on the bar (Brooks et al., 2014). For this very reason, it has been proposed that the tactile bias observed in sighted individuals can be classified into representational pseudoneglect, such as observed in numerical bisection (i.e., in which a mental continuum, the number line, needs to be activated and explored), thus being distinct from a purely perceptual one (Brooks et al., 2014; Eardley et al., 2017). Further insights on the opposite biases observed between visual and tactile bisection may come also from studies exploring the possible effects of visual interference on haptic spatial processing. In fact, a haptic bias has been demonstrated in a parallelity task (i.e., in which participants have to rotate a test bar until it is parallel to a reference bar) with respect to the simultaneous non-informative visual information (Volcic, van Rheede, Postma, & Kappers, 2008a). This is in line with studies showing that visual information may affect and, under certain circumstances, help haptic orientation processing (see Postma, Zuidhoek, Noordzij, & Kappers, 2008; Zuidhoek, Visser, Bredero & Postma, 2004; for a similar role of previous visual experience on blind individuals, see Postma, Zuidhoek, Noordzij & Kappers, 2008b). Accordingly, an altered binocular visual experience also affects spatial attentional mechanisms in non-visual domains other than the haptic modality, such as in a unimodal auditory condition (Richards et al., 2018). Thus, the observed dissociation between visual and tactile bisection observed here may not appear in line with previous evidence pointing to an influence of altered vision on haptic processing. We suggest that these different patterns of bias across visual and tactile modalities may strictly depend on the task at hand. Indeed, as compared to other tasks (i.e., such as the parallelity task described above), line bisection may rely to a lesser extent on multisensory processes and multisensory integration. In line with this possibility, no difference between unimodal haptic and cross-modal visuo-haptic presentations has been reported by a previous study employing a bisection paradigm in sighted individuals (Mancini et al., 2011).In our study, eye patching in sighted participants did not produce any relative lateralized bias as a function of the side of eye patched. Rather, sighted individuals showed a consistent leftward bias independently from the eye-patched. The impact of binocular vision in driving spatial attention asymmetries has been investigated in prior studies by asking normally sighted individuals to bisect lines while wearing an eye patch. This line of research has, however, produced mixed results with some findings suggesting a bias ipsilateral to the patched eye (Chen, Erdahl & Barrett, 2009), and others a more leftward bias when bisecting lines with the left eye (Graefe & Haase, 1997; McCourt, Garlinghouse & Butler, 2001). These divergent results may be explained by the fact that patching one eye for a short period produces a condition of weak binocular rivalry (Steeves et al., 2008). Alternatively, they may be related to differences in experimental paradigms (line bisection task vs landmark task) and procedures (i.e., variation in line lengths, timing of stimuli exposure, etc.) used.

Interestingly, improvements in visual functions (e.g., visual acuity and contrast sensitivity) have been reported after ocular realignment by means of surgical correction in strabismic individuals (Bucci, Brémond-Gignac & Kapoula, 2009; Klainguti, 2005; Legrand, Bui-Quoc & Bucci, 2012). Similar improvements have been documented in amblyopic individuals after visual training (Levi & Li, 2009; Polat, Ma-Naim & Spierer, 2009; Xi, Jia, Feng, Lu & Huang, 2014), non-invasive brain stimulation (Clavagnier, Thompson & Hess, 2013) or a combination of the two methods (Campana, Camilleri, Pavan, Veronese & Lo Giudice., 2014; Moret et al., 2018). Furthermore, video-game based training has also been shown to be effective in restoring higher-level functions in amblyopia such as visual attention (Li et al., 2008, Li, Ngo, Nguyen & Levi, 2011). In light of the evidence cited above and the preserved leftward attentional bias in the haptic modality in strabismic individuals (suggestive of a right hemispheric dominance, similar to sighted controls), it may be possible that reinstated binocular vision could lead to restored attentional control in the visual modality associated with a typical attentional bias within the visual modality as well. Future studies are needed to shed light on this interesting issue.

In conclusion, our study shows that an altered binocular vision affects the allocation of spatial attention resources in the visual modality, corroborating results from previous studies on strabismic individuals and extending this influence to early monocular blind participants. Critically, we also demonstrate that the effects of altered binocular visual development are restricted to the visual modality, as the typical spatial asymmetry is biased towards the left side of space in the haptic modality, in line with the notion of right hemispheric dominance in spatial tasks (Jewell & McCourt, 2000). Overall, our findings suggest that pseudoneglect in the visual and haptic modality rely on different functional and neural mechanisms (Eardley et al., 2017).

CHAPTER 4

Neural correlates of spatial attention asymmetries

4.1. *Study 3*: The role of the cerebellum in physical space perception and mental space representation: a TMS study

Neuroimaging evidence has recently suggested a possible involvement in spatial attention mechanisms of some regions outside the right fronto-parietal network, as the case of the cerebellum (Cavézian et al., 2012; Fink et al., 2000, 2001; Foxe et al., 2003; Hurwitz, Valadao & Danckert, 2011; Liu et al., 2019; Salmi, Rinne, Degerman, Salonen & Alho, 2007). Indeed, neuropsychological studies reported evidence of visuospatial anomalies after lesions to both medial (Aarsen, Dongen, Paquier, Van Mourik & Catsman-Berrevoets, 2004; Kim et al., 2008) and lateral sectors of the cerebellum (Botez-Marquard, Leveille & Botez, 1994; Daini, Arduino, Di Menza, Vallar & Silveri, 2008; Hildebrandt, Spang & Ebke, 2002; Milano & Heilman, 2014; Silveri, Misciagna & Terrezza, 2001). Nevertheless, neuroimaging investigations in healthy participants reported cerebellar contributions in spatial orienting tasks mainly lateralized in the left cerebellar hemisphere (Cavézian et al., 2012; Fink et al., 2000, 2001; Foxe et al., 2003; Hurwitz et al., 2011; Liu et al., 2019; Salmi et al., 2007), possibly by means of anatomical and functional connection with the right frontoparietal network (the core network engaged in line bisection tasks, Zago et al., 2017) (Habas et al., 2009; Stoodley, Valera & Schmahmann, 2012a). However, other investigations failed to report visuospatial deficits in cerebellar patients (Richter, 2005, 2007) or any cerebellar activations during line bisections tasks in healthy individuals (Cicek et al., 2009; Zago et al., 2017). Yet, disrupting the functioning of either the left or the right cerebellar hemisphere by means of TMS did not affect spatial biases in a landmark task (Oliver et al., 2011). Therefore, the extent and significance of the cerebellar contribution in spatial cognition is still a matter of debate.

However, evidence regarding the role of the cerebellum in the orienting of spatial attention along a mental number line is still unclear. Hence, a recent neuroimaging study (Liu et al., 2019) reported activations in the left lateral sector of the cerebellum in response to both line and number bisection task, whereas the right cerebellar hemisphere showed greater involvement in number bisection than in the landmark task. Nevertheless, another study reported that interfering by means of TMS with the activity of the left (but not the right) lateral cerebellum affected spatial biases in the number line bisection task (Oliver et al., 2011). Therefore, the issue regarding the involvement of different cerebellar regions in spatial attention mechanisms in the mental space needs further investigations.

The aim of the present study was twofold. Firstly, we aimed to investigate the causal involvement of different cerebellar regions, namely the vermis (lobule VII, Experiment 3a and 3b) and the left cerebellar hemisphere (Crus I, Experiment 3b), in the orienting of spatial attention in the physical space. Secondly, we aimed to shed light on the possible role played by the cerebellum in mediating spatial attention mechanisms in the representational space (as measured by a number bisection task, Experiment 3b). For these purposes, in Experiment 3a participants completed a landmark task while TMS was delivered over the vermis, the visual cortex and the vertex (as control sites). The landmark task was performed in two different orientations (horizontal, vertical) in light of previous evidence indicating that attentional biases can occur in both orientations (Churches et al., 2017; Fink et al., 2001; Heber et al., 2010; Mankowska, Heilman, Williamson & Harciarek, 2018; Suavansri et al., 2012). In Experiment 3b we interfered via TMS with the activity of the vermis, the left cerebellar hemisphere and the vertex (control site) while participants completed a landmark task (as in Experiment 3a) and a number bisection task. Based upon the available evidence we expected that disrupting the functioning of the cerebellar vermis should affect the orienting of spatial attention in the landmark task, while, in line with prior TMS evidence (Oliver et al., 2011), interfering with the activity of the left cerebellar hemisphere should alter participants' performance in the number bisection task.

4.1.1 *Experiment 3a*: TMS over the vermis did not affect the orienting of spatial attention in the landmark task

Participants

Thirty Italian students (6 males, *M* = 23.17 years, *SD* = 2.04) participated in the study. Before the experiment, each participant filled in a questionnaire to evaluate compatibility with TMS (translated from Rossi, 2011). All participants had normal or corrected to normal vision and were right-handed as assessed by a standard test (Oldfield, 1971) (*M* laterality quotient = 78.09%, *SD* = 14.75). The protocol was approved by the local ethical committee and participants were treated in accordance with the Declaration of Helsinki.

Materials and procedure

Participants sat in front of a 15.5'' PC (1280*800 pixels) screen at an approximate distance of 48 cm, in a normally lit and silent room and were asked to perform a computerized version of the landmark task. The landmark task consisted in the presentation of a series of black lines (on a white background) presented either vertically or horizontally. Lines (0.1° thick) were of three different lengths (20°, 21° and 22° of visual angle). All the lines were bisected by a (2.2° of visual angle) transection mark. Lines were asymmetrically bisected (half of which were bisected 1° to the left/above the true center and half 1° to the right/below the true center). Lines were presented such that the transection mark was always at the sagittal midline of the subject and at eye level. Figure 4.1 shows the timeline of an experimental trial. A central fixation cross appeared for 2500ms, followed by the presentation of a line for 250ms, which was immediately followed by a mask that remained on the screen until participants' response. The mask consisted of a thick horizontal or vertical line (thicker than the target line – 0.6° of visual angle), depending on the orientation of the to be judged line, with a transection mark in the same position of that of the target line, and it covered the entire area of the previously displayed stimulus extending to the edges of the projected screen (see Figure 4.1). Participants were instructed to indicate which side of the line was longer (half of the participants) or which side of the line was shorter (the other half of the participants). Participants had to respond by left and right key pressing using their right index and middle finger, respectively. Participants were asked to respond as fast as possible. Horizontal and vertical lines were displayed in different blocks, and each block was repeated three times (each corresponding to the TMS site, see below for details). The blocks were composed of 90 trials, 45 left/upper-side longer lines, and 45 right/lower-side longer lines). The software E-prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, USA) was used for stimuli presentation and data recording.

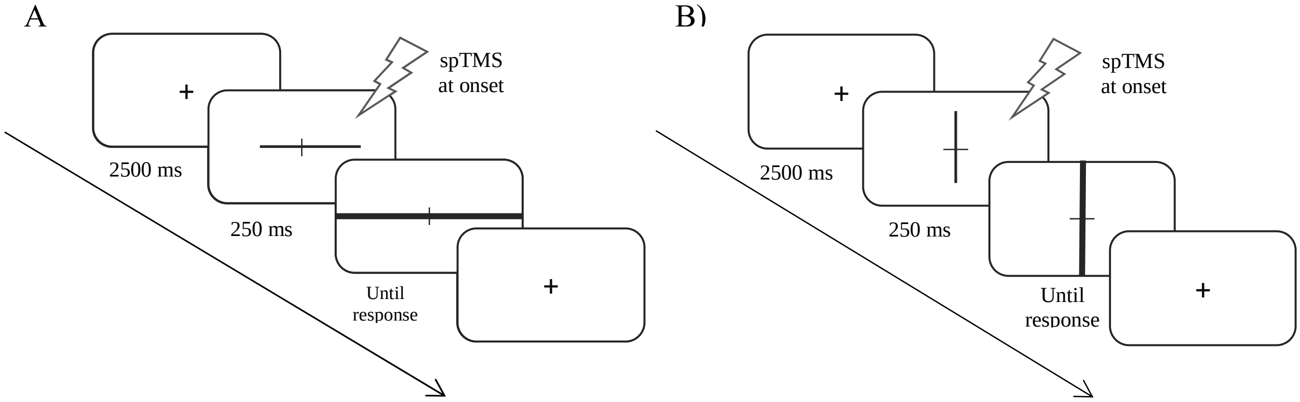


Figure 4.1. Schematic overview of an experimental trial of Experiment 3a: horizontal (A) and vertical (B) landmark task.

Transcranial Magnetic Stimulation

Online neuronavigated-TMS was delivered using a Magstim Rapid2 stimulator (Magstim Co Ltd, Whitland, UK) connected to a 70 mm butterfly coil. Individual motor threshold (MT) was determined by applying single-pulse TMS over the left M1 at increasing intensities and measured from the first dorsal interosseous (FDI) muscle of the right hand, prior to the experiment. The MT was defined as the minimum stimulation intensity that produces motor evoked potentials (MEPs) 50 mV peak to peak in at least 5 out of 10 trials (Rossini et al., 2015). Single-pulse TMS was delivered at stimulus onset (simultaneously to the appearance of the to-be-judged line) at 100% of the MT (mean stimulation intensity=52.0% of the maximum stimulator output, SD=2.9). The intensity of stimulation was kept constant for the stimulation of all the three target sites. Targeted sites were the vermis, the visual cortex and the vertex (control site). The visual cortex was chosen as an additional control area to differentiate between cerebellar TMS effects and indirect stimulation of the visual cortex since previous evidence demonstrated that cerebellar vermis stimulation may spread to the adjacent primary visual cortex (Renzi et al., 2014). The vermis was localized by means of stereotaxic navigation on individual estimated magnetic resonance images (MRI) obtained through a 3D warping procedure fitting a high-resolution MRI template with the participant's scalp model and craniometric points (Softaxic, EMS, Bologna, Italy). This procedure has been proven to ensure a global localization accuracy of roughly 5 mm, a level of precision closer to that obtained using individual MRIs than to what can be achieved using other localization methods (Carducci & Brusco, 2012). Anatomical Talairach coordinates for the vermis (lobule

VII) were obtained from a previous neuroimaging study on landmark task (Fink et al., 2001) and were x=-6, y=−78, z=-30 (see Figure 4.2). The visual cortex was localized functionally in each participant by means of phosphenes search (see Walsh and Pascual-Leone, 2003, for a detailed description). In this method, the coil is initially positioned 2 cm above the inion and its location is subsequently adjusted until foveal phosphenes are induced. Phosphenes search was carried out for each participant, after dark adaptation, using a modified binary search algorithm that defines the phosphenes threshold (PT) (Tyrrell and Owens, 1998, Thilo et al., 2004). The mean PT was 61.7% (SD=20.7). For participants who could not perceive phosphenes (N=10), Talairach coordinates were obtained from a previous neuroimaging study (Fink et al., 2000) and were x=4 = y=−84, z=8; however, the coil was positioned medially on the sagittal plane (x=0) to prevent any lateralization effects. The vertex was localized as the point falling half the distance between the nasion and the inion on the same midline. For cerebellar and visual cortex stimulation, the coil was placed tangentially to the scalp and held parallel to the midsagittal line. The handle pointed backward in the vertex stimulation condition, and superiorly in the cerebellum and the visual cortex stimulation conditions (see Bijsterbosch et al., 2012; van Dun et al., 2017 for similar coil orientation). In order to minimize neck tension during the whole experiment, participants' head was stabilized using a chinrest and few minutes breaks were allowed after each block. None of the participants reported phosphenes perception, discomfort or adverse effects during TMS.

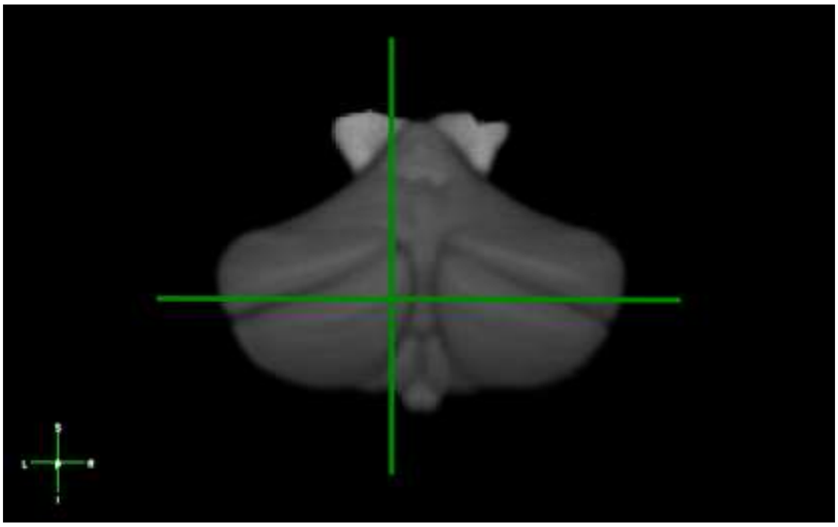


Figure 4.2. Localization of the anatomical coordinates used for the cerebellar vermis (lobule VII); image obtained using FLSeyes (Jenkinson, Beckman, Woolrich & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009) (x=-6, y=−78, z=-30, Fink et al., 2001).

Results

For each participant mean accuracy scores and mean reaction times (RTs) for correct responses were computed for each condition (see Figure 4.3). Trials with RTs exceeding +/-3 SD of the mean, for each participant in each TMS condition, were excluded from the analysis (following this criterion 1.39 % of trials were excluded). Repeated-measure ANOVAs with TMS (vertex, visual cortex and vermis) and side (i.e., which side of the line was longer) as within-subject factors were performed separately for each orientation. One participant with mean RTs above 2 standard deviations from the group mean was excluded from the analysis. Therefore, the final analyses were conducted on a sample of 29 participants.

Horizontal orientation

Mean accuracy scores were 77.21% (SD=19.02) for left and 71.90% (SD=18.31) for right-side longer lines. The ANOVA did not reveal any significant main effects or interactions: TMS, *F*(2,56)=1.23, *p*=.30; side, *F*(1,28)=1.70, *p*=.20; TMS by side, *F*(2,58)<1, *p*=.55.

The analysis on mean correct RTs revealed a significant main effect of TMS, *F*(2,56)=4.52, *p*=.015 η^2_p = .139, and a significant main effect of side, *F*(1,28)=4.93, *p*=.035, η^2_p = .150. The interaction TMS by side was not significant, *F*(2,56)<1, *p*=.71. The significant main effect of side was due to participants being faster with left-side longer lines (M=380ms, SD=195) that right-side longer lines (M=408ms, SD=234), this facilitation reflecting pseudoneglect. With regards to the main effect of TMS, post-hoc comparison (Bonferroni-Holm corrected) showed that when TMS was delivered over the visual cortex participants were significantly slower compared to both vertex, *t*(28)=2.96, *p*=.018, *d*=.55, and vermis TMS, *t*(28)=2.53, *p*=.034, *d*=.47. In turn, RTs were comparable between the vertex and the vermis conditions (*p*=.92).

Vertical orientation

The ANOVA on mean accuracy scores showed a significant main effect of side, *F*(1,28)=12.89, *p*=.001, η^2_p = .315, with participants being more accurate with upper-side longer lines (M=75.79, SD=21.64) than lower-side longer lines (M=59.07 SD=20.90). In turn, the main effect of TMS, *F*(2,56)<1, *p*=.38, and the interaction TMS by side, *F*(2,56)<1, *p*=.64, were not significant.

The analysis on mean correct RTs yielded a significant main effect of TMS, *F*(2,56)=7.89, *p*=.001 η^2_p = .220. Post-hoc comparisons (Bonferroni-Holm corrected) demonstrated that TMS over the visual cortex significantly delayed RTs as compared to both the vertex, *t*(28)=3.19, *p*=.009, *d*=.59, and the vermis conditions, *t*(28)=3.12, *p*=.008, *d*=.58; RTs between the vermis and the vertex condition were comparable (*p*=.94). The main effect of side, *F*(1,28)<1, *p*=.39, and the interaction TMS by side, *F*(2,56)<1, *p*=.86, were not significant.

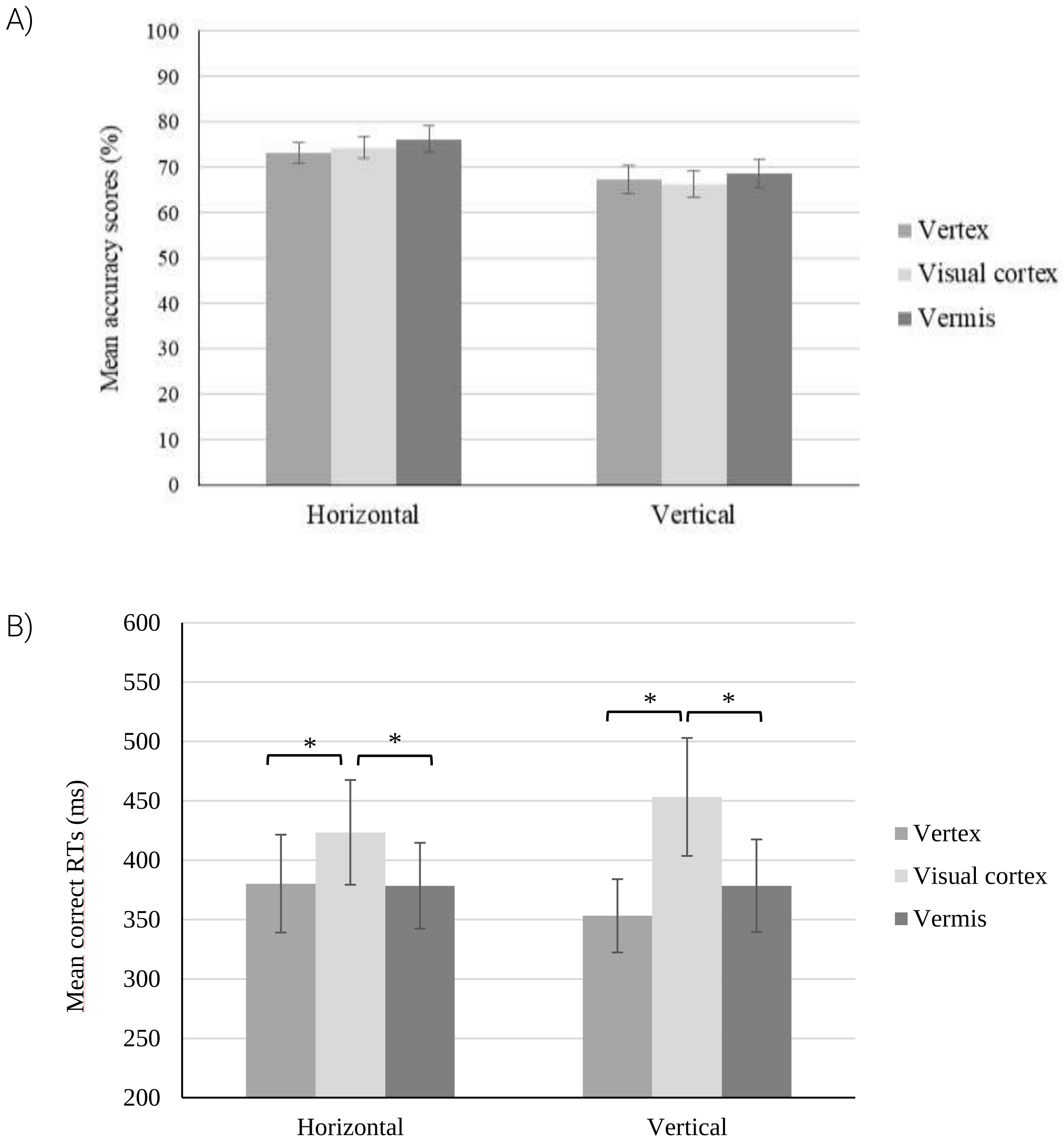


Figure 4.3. A) Mean accuracy scores (%) and B) mean correct RTs (ms) as a function of TMS sites (vertex, visual cortex, and vermis) and orientation in Experiment 3a. Error bars represent ± SEM. Asterisks denote a significant difference (p<.05).

4.1.2 *Experiment 3b*: TMS over the left cerebellum (but not over the vermis) affects asymmetries in space representation

In Experiment 3a, we found that delivering TMS over the vermis did not affect participants' ability to perform the landmark task, possibly indicating that the vermis might not be crucial in underpinning spatial judgments in the physical space. Nevertheless, neuropsychological and neuroimaging evidence suggested that the left lateral sector of the cerebellum might play an important role in spatial attention mechanisms (Botez-Marquard et al., 1994; Cavézian et al., 2012; Daini et al., 2008; Fink et al., 2000, 2001; Foxe et al., 2003; Hildebrandt et al., 2002; Hurwitz et al., 2011; Kim et al., 2008; Liu et al., 2019; Milano et al., 2014; Salmi et al., 2007). Accordingly, left cerebellar crus I is anatomically and functionally connected with the visuospatial right frontoparietal network (Habas et al., 2009; Stoodley et al., 2012a). In order to test this hypothesis, in Experiment 3b, we asked a new group of participants to perform a landmark task (the same used in Experiment 3a) while TMS was delivered over the vermis and the left cerebellar hemisphere (in addition to the vertex). The visual cortex was not included as a control area in Experiment 3b since findings of Experiment 3a showed differential effects of visual cortex TMS and cerebellar TMS upon participants' performance (RTs). Moreover, in Experiment 3b, we aimed to shed light on the involvement of both the vermis and left cerebellar hemisphere in driving attentional bias in the representational space by asking participants to perform a number bisection task during TMS stimulation of both regions.

Participants

Twenty-four Italian students (9 males, *M* = 22.54 years, *SD* = 1.91) participated in the study. Inclusion criteria were the same as Experiment 1 (*M* laterality quotient of participants of Experiment 2 was 71.23%, *SD* = 16.18). None of the participants of Experiment 3b participated in Experiment 3a. The protocol was approved by the local ethical committee and participants were treated in accordance with the Declaration of Helsinki.

Materials and procedure

Participants were asked to complete two computerized tasks: a landmark task (identical to the one used in Experiment 3a) and a number bisection task. The order of the presentation of the tasks was counterbalanced among participants who sat in front of a 15.5'' PC (1280*800 pixels) screen at an approximate distance of 48 cm sit in a normally lit and silent room. The software E-prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA, USA) was used for stimuli presentation and data recording.

Landmark task

Stimuli and procedure of the landmark task were the same of those used in Experiment 3a, with the exception that only lines oriented horizontally were included.

Number bisection task

Stimuli were black two-digit numbers triplets (2° x 1° degree of visual angle), ranging from 11 to 99 displayed against a white background, constituted by a target inner number and two outer numbers defining a number interval for each side. Figure 3 shows the timeline of an experimental trial. Each trial began with a central fixation cross (1000ms), immediately followed by the presentation of the two outer numbers for 2000ms (one on the left and one on the right of the centre of the screen, 10° degree of visual angle from the centre of the screen). Subsequently, the target number appeared on the screen (1000ms) followed by a blank screen until participants' response. Participants had to indicate whether the target number was farther (or closer, the answer was counterbalanced across participants) to the left- or to the right-sided outer number by left/right key pressing using their right index and middle fingers. Accuracy was stressed, but participants were instructed not to explicitly calculate the answer, but to respond intuitively as quickly as they could. Participants were allowed 2 seconds to respond, after which a new trial started. The two outer numbers had a numerical difference (largest minus smallest) of either 32, 34 or 36 units. The target number was shifted from the true arithmetic centre of five or six units either towards the smallest number of the pair (45 trials) or over the largest number of the pair (45 trials). In half of the trials, outer numbers were presented in ascending order (e.g. the left side number being the smallest of the interval), and in the other half in descending order. Each block consisted of 90 trials: in 45 trials the target number was farther from the smallest outer number and in 45 trials it was farther from the largest outer number. Participants completed 3 blocks (once for each TMS site, see below for details), for a total of 270 trials. The experiment took on average 1 hour and 30 minutes (including instructions, fill-in of TMS questionnaire and informed consent, neuronavigation, and debriefing).

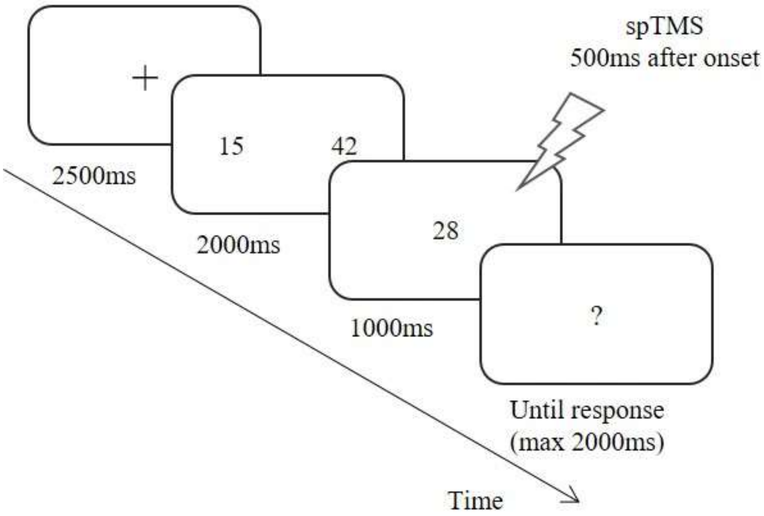


Figure 4.4. Schematic overview of an experimental trial of the number bisection task of Experiment 3b.

Transcranial Magnetic Stimulation

TMS protocol and parameters were similar to those used in Experiment 3a. Single-pulse was delivered at 100% of the MT (*M* stimulation intensity = 51.29% of the maximum stimulator output, *SD* = 4.54) over the vermis (as in Experiment 3a), the left cerebellar hemisphere and the vertex (control site). The vermis and the left cerebellum were localized by means of stereotaxic navigation on individual estimated MRI (as for the vermis in the previous experiment) using the same anatomical coordinates of the vermis used in Experiment 1 (x=-6, y=−78, z=-30, TAL) and for the left cerebellar hemisphere x=-28, y=-66, z=-36, (TAL) corresponding to Crus I (obtained from a previous fMRI study on landmark task, Fink et al., 2001) (see Figure 4.5). Single-pulse TMS was delivered at stimulus onset in the landmark task (as in Experiment 3a) and 500ms after the presentation of the inner number in the number bisection task. The latter TMS timing was chosen in light previous ERP evidence indicating that during mathematical problem-solving with complex two-digit arithmetic operations, similar to those used in the present study, frontal and parietal areas are engaged in a time-window ranging from 350 to 800ms after numbers presentation (Jost et al., 2004a, b; Ku, Hong, Gao & Gao, 2010; Núñez-Peña, Cortinas & Escera, 2006). Since the cerebellum is functionally and anatomically connected to frontal and parietal areas (Habas et al., 2009, Stoodley et al., 2012a), we assumed that cerebellar contribution might occur in a similar time-window. Moreover, previous TMS studies showed that applying TMS over the left (Andres, Seron & Olivier, 2005; Rusconi, Walsh & Butterworth, 2005; Sandrini, Rossini & Miniussi, 2004) and right parietal lobes (Andres, Pelgrims, MIchaux, Olivier & Pesenti, 2011; Dormal, Andres & Pesenti, 2012; Rusconi et al., 2005) during the first 600ms after stimulus presentation affected number magnitude processing.

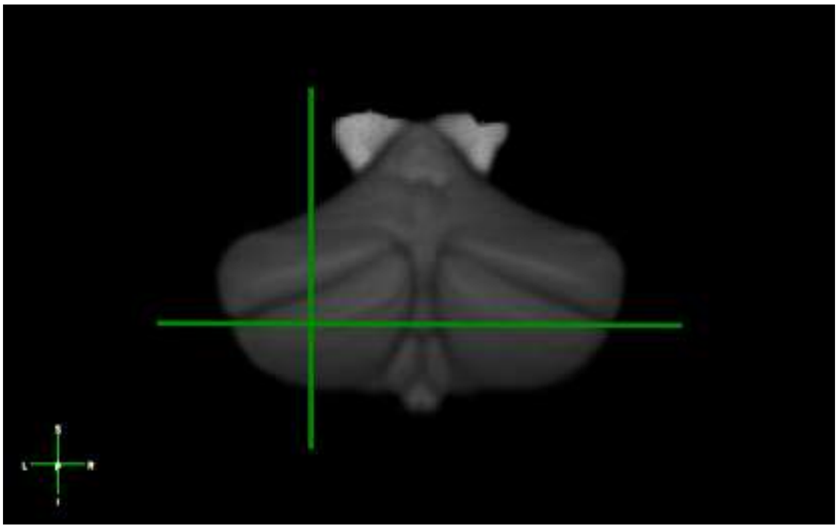


Figure 4.5. Localization of the anatomical coordinates used for the left cerebellum (crus I); image obtained using FLSeyes (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009) (x=-28, y=-66, z=-36, Fink et al., 2001).

Results

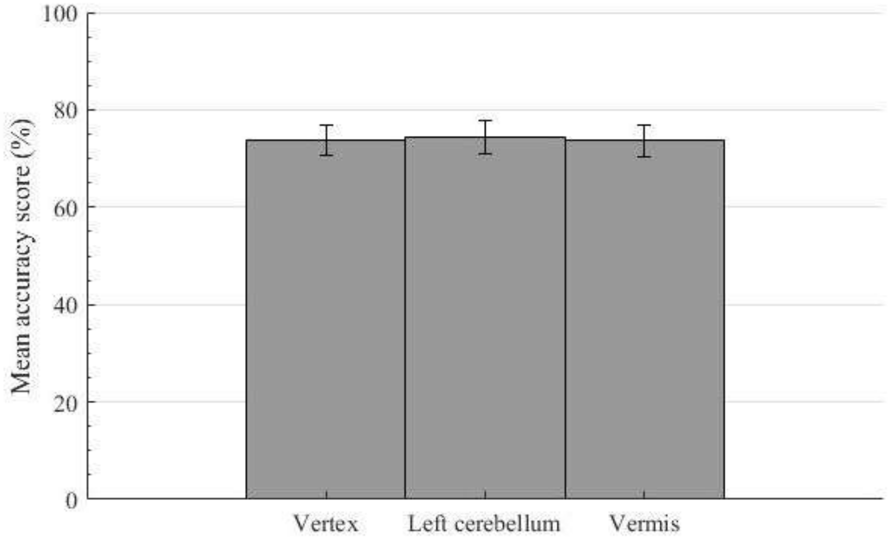
Mean accuracy scores and mean reaction times (RTs) for correct responses were computed for each condition for the two tasks for each participant, (see Figure 4.6). Trials with RTs above or below 3 SD of the mean, for each participant in each experimental condition, were excluded from the analysis (1.19% and 0.23% of the total amount of trials for the landmark task and number bisection task, respectively).

For the landmark task repeated-measure ANOVAs were carried out with TMS (vertex, left cerebellum and vermis) and side (i.e., which side of the line was longer) as within-subject factors; for the number bisection task repeated-measure ANOVAs with TMS, side (i.e. which side of the interval was larger) and order (ascending and descending) as within-subject variables were performed. Trials in which symmetrical lines/intervals were presented were not included in this analysis since there was no correct response.

Landmark task

Mean accuracy scores were 76.98% (SD=14.53) for left-side longer and 70.85% (SD=20.43) for right-side longer lines. The ANOVA did not show a significant main effect of TMS, *F*(2,46)<1, *p*=.93, side, *F*(1,24)=2.55, *p*=.12, or a significant interaction TMS by side, *F*(2,46)<1, *p*=.40 (see Figure 4.6a). The ANOVA on mean correct RTs showed no significant main effects or interactions; TMS, *F*(2,46)<1, *p*=.70, side, *F*(2,46)<1, *p*=.74, TMS by side, *F*(2,46)=1.65, *p*=.20 (see Figure 4.6b).

A)



B)

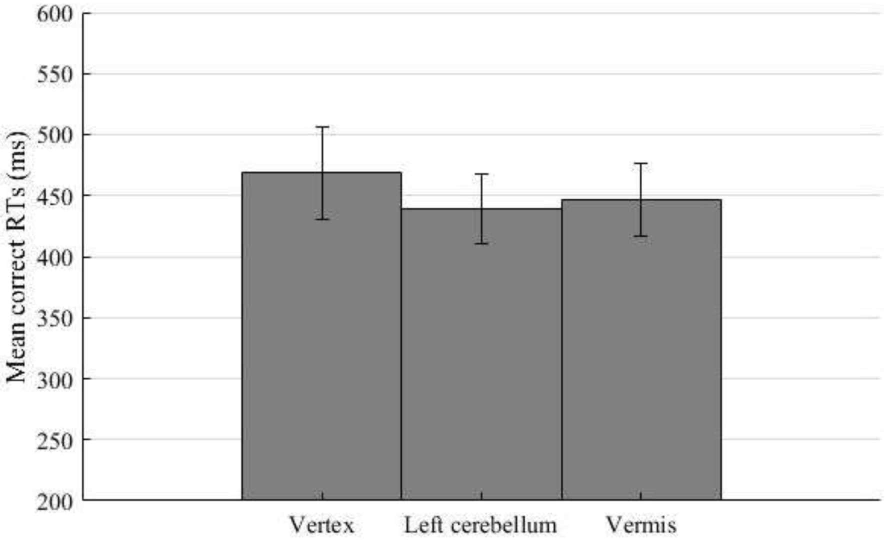


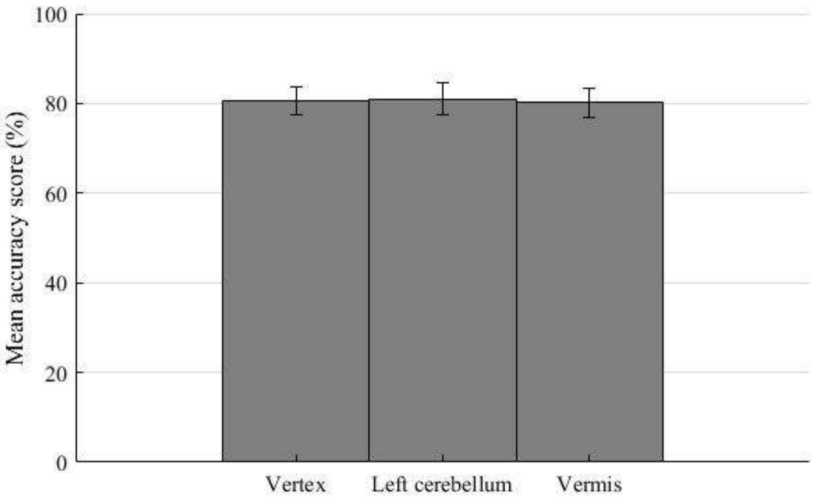
Figure 4.6. A) Mean accuracy scores (%) and B) mean correct RTs (ms) as a function of TMS sites (vertex, left cerebellum and vermis) for the landmark task in Experiment 3b. Error bars represent ± SEM.

Number bisection task

The ANOVA on mean accuracy scores showed a significant main effect of side, *F*(2,46)=4.82, *p*=.038, η^2_p = .173, with participants being more accurate when the target number was farther from the smallest number (M=83.51%, SD=14.11) as compared to intervals where the target number was farther from the largest number (M=77.69, SD=19.77), reflecting pseudoneglect. None of the other main effects or interactions reached significance: TMS, *F*(2,46)<1, *p*=.85, order, *F*(1,24)=2.59, *p*=.12, TMS by side, *F*(2,46)<1, *p*=.44, TMS by order, *F*(2,46)<1, *p*=.58, side by order, *F*(1,24)=2.54, *p*=.13, TMS by side by order, *F*(2,46)<1, *p*=.40. (see Figure 4.7a).

The analysis on mean correct RTs showed a significant main effect of TMS, *F*(2,46)=3.43, *p*=.041, η^2_p = .130, and a significant interaction TMS by side, *F*(2,46)=3.33, *p*=.044, η^2_p = .127. None of the other main effects or interactions reached significance: side, *F*(1,23)<1, *p*=.61, order, *F*(1,23)<1, *p*=.68, TMS by order, *F*(2,46)<1, *p*=.51, side by order, *F*(1,23)<1, *p*=.44, TMS by side by order, *F*(2,46)<1, *p*=.78. Post-hoc comparisons (Bonferroni-Holm correction applied) showed that TMS over the left cerebellum significantly delayed response latencies as compared to both the vermis, *t*(23)=2.87 *p*=.027, *d*=.59, and the vertex conditions, *t*(23)=2.56 *p*=.036, *d*=.52, only when the target number was farther from the smallest number. In turn, mean RTs were comparable between vermis and vertex conditions (*p*=.48). Conversely, mean RTs were comparable the three stimulation sites when the target number was farther from the largest number (all *p*s>.29) (see Figure 4.7b).

A)



B)

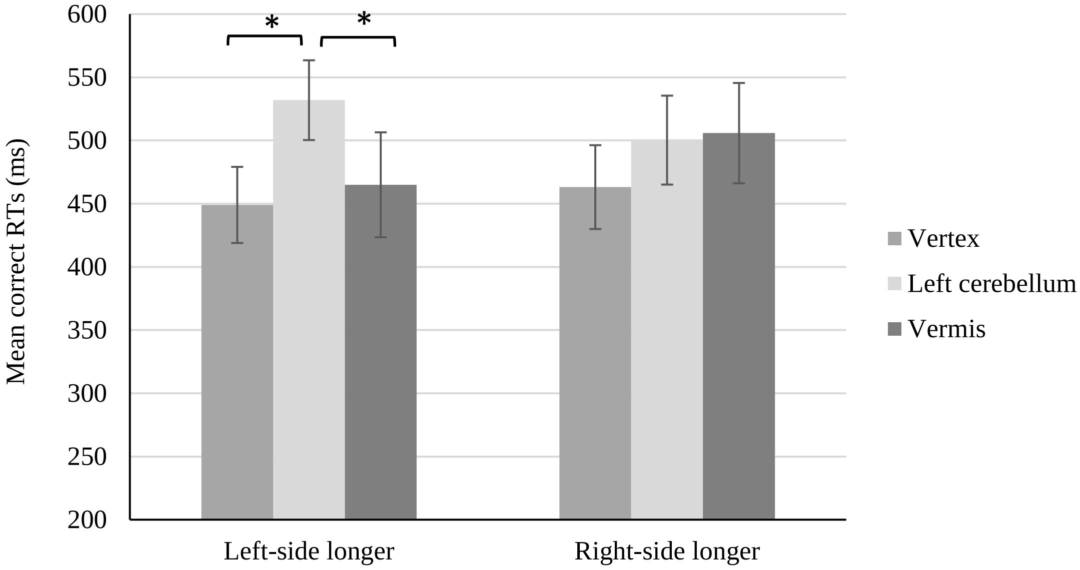


Figure 4.7. A) Mean accuracy scores and B) mean correct RTs (ms) as a function of TMS sites (vertex, left cerebellum and vermis) for the number bisection task in Experiment 3b. Left and right-side longer correspond to intervals where the target number was farther from the smallest one and from the largest one, respectively. Error bars represent ± SEM.

4.1.3 Discussion

In the present study, we aimed to shed light on the causal role played by different cerebellar structures, specifically the vermis (lobule VII) and the left hemisphere (Crus I), in mediating spatial attention mechanisms both in the physical (Experiment 3a and 3b) and in the representational space (Experiment 3b). We found that disrupting, via TMS, the functioning of the left cerebellar hemisphere, but not of the vermis, selectively affected spatial attentional asymmetries in the bisection of number intervals, leaving spatial attentional mechanisms in the landmark task spared.

Overall, our study suggests that neither the vermis nor the left lateral cerebellum is necessarily involved in the orienting of spatial attention in the physical space. Although previous neuroimaging and lesion studies reported that both the vermis and the left cerebellar hemisphere might be involved in spatial judgments (Aarsen et al., 2004; Botez-Marquard et al., 1994; Daini et al., 2008; Fink et al., 2000, 2001; Foxe et al., 2003; Liu et al., 2019; Kim et al., 2008; Milano et al., 2014; Salmi et al., 2007), our result is consistent with other evidence failing to demonstrate the recruitment of the cerebellum in the allocation of spatial attention resources in the physical space (Cicek et al., 2009; Oliver et al., 2011; Richter, 2005, 2007; Zago et al., 2017). In interpreting this null finding is important to note that we selectively targeted a specific region of the cerebellum, the posterior cerebellum (either in the vermis, lobule VII or in the left hemisphere, Crus I). Therefore, other regions in the cerebellum might be causally involved in orienting spatial attention. Moreover, neuropsychological studies reporting that cerebellar lesions resulted in impaired visuospatial abilities usually adopted a line bisection paradigm, in which individuals are asked to place a mark at the midpoint of a line, thus involving the co-ordination of both visuospatial and motor abilities (Learmonth, Gallagher, Gibson, Thut & Harvey, 2015). In turn, in the landmark task used in the present study participants are instructed to make a two-alternative forced-choice decision regarding the length of two halves of a briefly presented (e.g. 250ms) pre-bisected line, thus reducing motor load and requiring limited eye movements (Cicek et al., 2009; Learmonth e al., 2015). Since activity in the cerebellum has been traditionally linked to motor control and coordination (Manto et al., 2012), one might argue that performing the landmark task compared to the line bisection task requires less motor control thus relying to a lesser extent on the cerebellar contribution. If this might be the case of the vermal lobule VII which is functionally connected to the sensorimotor network in the cerebrum (Habas et al., 2009) and whose activity has been reported to be part of the oculomotor system deputed to control saccadic eye-movements (Striemer, Chouinard, Goodale & de Ribaupierre, 2015; Voogd, Schraa-Tam, van der Geest & De Zeeuw, 2012; for a review see Beh, Frohman, Frohman, Biousse & Galetta, 2017), it is not likely for the left cerebellum. However, although prior neuropsychological and neuroimaging evidence pointed out a critical role played by the left lateral sector of the cerebellum in spatial attentional mechanisms (Botez-Marquard et al., 1994; Daini et al., 2008; Fink et al., 2000, 2001; Foxe et al., 2003; Liu et al., 2019; Milano et al., 2014; Salmi et al., 2007), our results are in line with prior TMS evidence showing that neither the left nor the right cerebellar hemisphere is causally involved during a landmark task (Oliver et al., 2011).

Critically, our findings showed that disrupting the functioning of the left lateral sector of the cerebellum delayed RTs in the number bisection task as compared to both the vertex and the vermis conditions. Hence, our data suggest a crucial involvement of the left cerebellar hemisphere (Crus I), but not of the vermis, in the orienting of spatial attention in the representational space. Interestingly, our findings are in line with a previous TMS study (Oliver et al., 2011), demonstrating that the left cerebellar hemisphere is involved in spatial judgments in the representational space, but not in the physical one. In particular, in our study interfering with the functioning of the left cerebellar hemisphere resulted in a slowdown of response latencies only for low-elongated triplets, that is when the numerical distance was greater between the target digit and the smallest number of the triplet, whereas no effect was found for high-elongated triplets. Interestingly, in line with the idea of a mental number line with lower numbers being represented on the left and higher numbers on the right side of an imaginary line (Dehaene & Cohen, 1995), our data showed that our cerebellar TMS selectively affected the orienting of spatial attention towards the left side of such mental line (e.g. towards lower numbers), thus producing a pattern reminiscent of “neglect” in mental number space. Since it has been demonstrated that TMS over the lateral cerebellum can strongly affect the contralateral cerebral cortex (Oliveri, Koch, Torriero & Caltagirone, 2005) and that cerebellar TMS regulates the functional connectivity between Purkinje cells and deep cerebellar nuclei, modifying the excitability of interconnected cerebral areas (Koch et al., 2007), one possible underlying mechanisms of our results could be found in the inhibition of associative frontal and parietal areas caused by our cerebellar TMS. Accordingly, similar representational ‘neglect-like’ behaviours have been demonstrated when TMS is applied over the right parietal cortex (Oliveri et al., 2004; Göbel et al., 2006).

Interestingly, the difference in cerebellar contribution between space perception (e.g. landmark task) and representation (e.g. number bisection task) found in the present study is in line with evidence demonstrating distinct cerebellar involvement in spatial tasks requiring either direct manipulation or mental reconstruction of visual stimuli (Molinari et al., 2004; Molinari & Leggio, 2007). Indeed, in line with theories supporting the view of the cerebellum as a sensory data acquisition controller, that coordinates the brain's acquisition of sensory data (Bowers & Parson, 2003), it is possible that the contribution of the cerebellum might be more critical in tasks requiring the analyses of mental representations rather than in tasks that, although having similar spatial requests, allowed direct interactions with physical stimuli (Molinari & Leggio, 2007). Accordingly, when a stimulus is physically manipulated (e.g. as the case of lines in the landmark task) spatial properties are more easily extracted than when the same properties have to be extracted from a mental image (e.g. as a mental line in the number bisection task). Moreover, patients with lesions to the left cerebellar hemisphere performed similarly to controls when asked to judge the orientation of visually presented lines, thus showing preserved ability to process monodimensional spatial information, but clear visuospatial deficits were observed when asked to process complex figures mentally, such as in mental rotation tasks (Molinari et al., 2004, Stoodley et al., 2012a).

Our results also insight on the issue of whether shared neural network underpins both space perception and space representation. Although some evidence seems to suggest shared neural mechanisms underlying attentional biases in lines and number bisections (De Schotten et al., 2011; Göbel et al., 2006; Hubbard et al., 2005; Nicholls & McIlroy, 2010; Oliveri et al., 2004), our findings argue in favour of a dissociation of mechanisms driving perceptual and representational biases, in line with studies showing lack of correlation between biases in line and number bisection tasks both on a behavioural (Rotondaro et al., 2015) and a neural level (Aiello et al., 2012; Doricchi et al., 2005). Nevertheless, it is worth noting that the number bisection task includes judgments between two numerical quantities and has, therefore, a working memory component (Doricchi et al., 2005), that the typical line bisection does not have. Interestingly, cerebellar crus I activity has been linked to executive functions, such as working memory (Ding et al., 2012; Durisko & Fiez, 2010; Ferrari et al., 2018; Keren-Happuch et al., 2014) and approximate calculation (Kondo et al., 2004; Stanescu-Cosson et al., 2000; for a meta-analysis see Vandervert, 2017), with connections to the prefrontal and parietal areas in the right executive control network (Habas et al., 2009; O'Reilly et al., 2009; Stoodley, 2012a; Stoodley, 2012b). Hence, it is possible that our TMS effect could reflect a cerebellar contribution in executive functions rather than in spatial representations per se. Future studies should further address this issue.

Interestingly, it is important to note that, as demonstrated by data from Experiment 3a, our findings are unlikely to be caused by indirect stimulation of the visual cortex. Indeed, in the first experiment, consistently with ERP studies discussed above (Benwell et al., 2014; Foxe et al., 2003; Waberski et al., 2008), TMS applied over the visual cortex in the early stage of the visuospatial process (e.g. up to 100ms after stimulus onset) significantly delayed response latencies in the landmark task as compared to the vertex condition, while no effect was found when TMS was applied over the vermis. Hence, such a result ensured us that two distinct brain regions (e.g. cerebellar vermis and visual cortex) were targeted by our TMS. For this reason, the visual cortex was not included as an additional control area in Experiment 3b; nevertheless, in the number bisection task our single-pulse was delivered 500ms after numbers presentation, thus being too late to interfere with visual cortex activations that is believed to occur around 100ms after stimulus onset (Jost et al., 2004a, b; Ku et al., 2010; Núñez-Peña et al., 2006).

In conclusion, our study provides evidence in favour of a cerebellar contribution to high–order cognitive processes (for a detailed meta-analysis see Stoodley & Schmahmann, 2009, 2010) by demonstrating the causal role played by the left cerebellar hemisphere (Crus I) in spatial attentional mechanisms. Moreover, our findings shed light on the neural underpinning of spatial attentional orienting in the physical and representational space, by showing that the left cerebellar hemisphere (and not the vermis) should be considered, together with right parietal and frontal regions (Brighina et al., 2002; Cicek et al., 2009; Fink et al., 2000, 2001; Foxe et al., 2003; Göbel et al., 2006; Liu et al., 2019; Oliveri et al., 2004; Zago et al., 2017), as part of a cerebello – fronto - parietal network deputed to drive spatial attentional mechanisms at least in mental space.

CHAPTER 5

General discussion and Conclusions

When asked to estimate the midpoint of a line, healthy individuals place a mark slightly shifted toward the left of the veridical centre, due to a tendency to overestimate the left side of the space, a phenomenon known as *pseudoneglect* (Jewell & McCourt, 2000). Evidence demonstrated that this attentional bias depends on asymmetrical activations between the left and right hemisphere, with each hemisphere directing attention toward the contralateral side (Duecker & Sack, 2015; Kinsbourne, 1970, 1987; Reuter-Lorenz et al., 1990). Moreover, the right hemisphere plays a dominant role in visuospatial processing (Corbetta & Shulman, 2011; De Schotten et al., 2011; Foxe et al., 2003; Shulman et al., 2010), as demonstrated by patients with right hemispheric damages who fail to attend, orient or respond to events occurring on the contralesional side more than left-hemisphere lesioned patients do (Heilman et al., 1987; Suchan et al., 2012). Additionally, neuroimaging and brain stimulation evidence showed the involvement of a fronto-parietal network, mainly lateralized in the right hemisphere, in line bisection task in healthy individuals (Cavenzian et al., 2012; Cicek et al., 2009; Fink et al., 2000; Fox et al., 2003; Zago et al., 2017).

Interestingly, in addition to the leftward attentional bias for horizontal stimuli, pseudoneglect has been demonstrated also in the vertical plane (Drain & Reuter-Lorenz, 1996; Halligan & Marshall, 1993; Churches et al., 2017), with healthy participants showing an upward bias. Nevertheless, although horizontal and vertical attentional biases share right parietal activations (Fink et al., 2001) and stem from a common eye-scanning strategy (Durgin, Doyle, & Egan, 2008), the magnitude of the biases are not reliably correlated across dimensions (Churches et al., 2017; Nicholls et al., 2004). Indeed, whereas the leftward attentional bias depends on the difference in the relative activations between hemispheres, the upward bias relies on asymmetries in the activation between the ventral and dorsal visual streams (Drain & Reuter-Lorenz, 1996; Post et al., 2006). Hence, whether a common underlying mechanism is responsible for attentional biases across orientations is still unclear.

Furthermore, spatial asymmetries have been reported also in the absence of any visual input, as in the haptic and auditory modalities. As regards the haptic modality, blindfolded healthy participants, instructed to estimate the midpoint of a rod after haptic exploration, show a leftward bisection bias, similar to the one reported for visual line bisections, thus suggesting a right-hemispheric dominance also for the haptic modality. Indeed, the consistent leftward bias reported by many studies in haptic bisection suggests that common attentional control mechanisms are at play across modalities (Brooks et al., 2011; Cattaneo et al., 2010, 2011a; Eardley et al., 2017). Nonetheless, the modality (visual vs. haptic) in which the bisection task is performed has been found to influence the extent of pseudoneglect. Accordingly, despite being susceptible to several factors such as spatial position of the line (Bradshaw et al., 1983) and participants' handedness (Sampaio & Chokron, 1992) as attentional biases in the visual domain, the extent of pseudoneglect in the haptic modality depends on numerous modality-specific factors (Baek et al., 2002; Brodie & Pettigrew, 1995; Cattaneo et al., 2011a). Indeed, the magnitude of the bisection bias might be poorly correlated between vision and haptics (Eardley et al., 2017). Thus, further investigations are essential to disentangle whether spatial asymmetries across sensory modalities share the same underlying mechanisms or are driven by distinct cognitive/neural processes.

Furthermore, attentional biases have also been demonstrated for mental representations (*representational pseudoneglect*, Brooks et al., 2014). Typically, these attentional biases are measured with tasks involving the mental representation of numbers. Indeed, empirical observations indicated that numbers are represented as lying on an imaginary line (e.g. the so-called mental number line) with smaller numbers represented on the left side of space and larger numbers on the right (for a review see Hubbard et al. 2005; see also Dehaene et al., 2003; Gevers et al. 2010). On this basis, a task usually adopted to measure representational biases is the number bisection task, where subjects hear two numbers defining a numerical interval, and then orally report the midpoint of this interval without any calculation (Zorzi et al., 2002). Interestingly, healthy individuals reported a consistent bias in the direction of the lower number, thus showing a leftward representational bias similar to the one in physical line bisection. Indeed, studies reported correlations between individual participants' bias on physical and mental number line bisection, thus proposing that similar attentional orienting mechanisms underlie both visuospatial and representational bisection tasks. However, other evidence proposes that distinct neural mechanisms are involved in number and physical lines bisection (see sections 1.3, 1.4 and 4.1.3). Accordingly, neuropsychological evidence reported that deviation in number line bisection is dissociable from that in physical line bisection, whereas neuroimaging and brain stimulation evidence on healthy individuals showed distinct underlying neural correlates between the two biases, in regions both within and outside the right fronto-parietal network, as the case of the cerebellum (Liu et al., 2019; Oliver et al., 2011).

Clearly, despite the considerable amount of literature on this topic, several issues remain still unsolved requiring further investigations. In line with this, the present dissertation aimed to investigate distinct aspects of the pseudoneglect phenomenon in order to address some of the open questions.

In particular, prior evidence reported that increasing cognitive load, as in situations when a secondary task has to be performed simultaneously to a primary task (dual-task conditions), might affect spatial asymmetries in the horizontal plane. Specifically, previous studies demonstrated a selective disadvantage for left-side stimuli (e.g. slower reaction times and lower accuracy rates) in dual-task conditions, likely associated with a modulation of hemispheric asymmetries by means of a weakening of the right hemispheric dominance for visuospatial processing (O'Connell et al., 2010; Pérez et al., 2009; Vuilleumier et al., 2008). However, other evidence either failed to report similar findings (Dodds et al., 2008; Santangelo & Spence, 2007) or suggested that the effect of load on spatial asymmetries might depend on the overlap in content-specific processing between primary and secondary tasks (Golob et al., 2017; Kim et al., 2005). Nevertheless, despite showing that cognitive load affects spatial asymmetries in the horizontal plane, previous research has not considered the effect of cognitive load on spatial asymmetries in the vertical dimension. Therefore, in Study 1 we adopted a dual-task paradigm to investigate horizontal and vertical attentional biases under load. Our goal was twofold: first, we were interested in exploring how vertical attentional biases were modulated in dual-task conditions; secondly, we aimed to further understand the relationship between horizontal and vertical spatial asymmetries. In two experiments, we asked healthy participants to carry out a line bisection task (Experiment 1a) and a landmark task (Experiment 1b) both in the horizontal and vertical orientations. In both experiments, participants completed the task in a single- and dual-task condition (e.g. while concurrently performing a secondary auditory working memory task). Our results demonstrated that the increased cognitive load similarly modulates horizontal and vertical spatial asymmetries, thus demonstrating that horizontal and vertical biases might be driven by only partially separated functional mechanisms. Interestingly, this finding challenged the idea previously reported that linked spatial asymmetries under load to an alteration of hemispheric asymmetries, since only horizontal attentional biases have been demonstrated to depend on differences in the activations between the two hemispheres. Indeed, vertical attentional biases seem to rely on asymmetries in the contribution between ventral and dorsal visual stream (Drain & Reuter-Lorenz, 1996; Post et al., 2006).

Another interesting result of Study 1 regards the different effect of cognitive load found between line bisection (Experiment 1a) and landmark tasks (Experiment 1b). Indeed, whereas spatial asymmetries were reduced in the dual-task condition of the line bisection task, an increased attentional bias was found for the landmark task. Although surprising at first, these results are in line with prior evidence showing that the two tasks might rely on separate mechanisms and that different strategies are used to perform them (Cavenzian et al., 2012; Cicek et al., 2009; Learmonth et al., 2015). Therefore, our data, in line with prior evidence (Golob et al., 2017; Kim et al., 2005) also suggest that the modulation of spatial asymmetries under load depend on the specific task adopted, with line bisection and landmark tasks possibly engaging distinct processes.

Another issue in the pseudoneglect literature that requires further investigations is how the development of spatial asymmetries depend on a normal visual input and how a lack (or an alteration) of a normal visual experience affects them. On this regard, blindfolded healthy individuals show a leftward deviation in haptic rod bisections tasks, thus demonstrating that attentional biases are independent of any visual input. More importantly, blind participants showed a leftward bias, similar to the one of sighted individuals, both in haptic rods and number bisection task (Cattaneo et al., 2011a, b; see Chapter 3 for more evidence), thus suggesting that a normal visual experience is not critical to the development of the right-hemispheric dominance for visuospatial processing (Gougoux et al., 2005; Renier et al., 2014; Ricciardi & Pietrini, 2011). However, the total lack of visual input may have different effects on lateralization patterns compared to a distorted visual input, as suggested by studies on strabismic amblyopes, with a distorted binocular vision, which show a rightward bias in visual line and number bisection tasks (Mohr et al., 2010; Thiel & Sireteanu, 2009). Moreover, an extreme case of loss of binocularity is that of individuals with monocular blindness, which has been shown to impact on many visual functions (Cattaneo et al., 2014; Moro et al., 2019; Kelly et al., 2013; Steeves et al., 2002, 2004; Vecchi et al., 2006). On these grounds, in Study 2 we investigated whether distorted binocular vision that leads to alterations in typical visuospatial attention asymmetries (Mohr et al., 2010; Thiel & Sireteanu, 2009) also affects spatial attention in the haptic modality, thus shedding light on the difference between line bisection across modalities. To this aim, in Study 2 we compared the performance of normally sighted, strabismic and early monocular blind participants in a visual and a haptic line bisection task. In visual line bisection, in line with prior evidence (Thiel & Sireteanu, 2009), strabismic individuals tended to err to the right of the veridical midpoint, in contrast with normally sighted participants who showed pseudoneglect. Monocular blind participants exhibited high variability in their visual performance, with a tendency to bisect toward the direction of the functioning eye. In turn, in haptic bisection, all participants consistently erred towards the left of the veridical midpoint. Therefore, our data demonstrated that a normal binocular experience is important for a right-hemispheric dominance to emerge only when visual feedback is available; with no visual feedback, an altered binocular vision has no effect. Taken together, our findings support the view that pseudoneglect in the visual and haptic modality relies on different functional and neural mechanisms.

Finally, the last issue considered in the present dissertation regards the relationship between perceptual and representational pseudoneglect from a neural perspective. Indeed, although an attentional bias toward the same direction (e.g. leftward) might one think that both biases are driven by a right hemispheric dominance, several evidence pointed out to the existence of separate mechanisms between perceptual and representational pseudoneglect (Aiello et al., 2012; Doricchi et al., 2005; Rotondaro et al., 2015; Loetscher and Brugger, 2009; Loetscher et al., 2010). On a neural level, the involvement of a right fronto-parietal network has been demonstrated for both biases; however, recent neuroimaging finding supports the presence of partially separated underlying neural processes (Liu et al., 2019). On this regard, in Study 3, we carried out two experiments where a brain stimulation approach was adopted to investigate the neural correlates of perceptual and representational biases. In particular, we were interested in investigating the role played by the cerebellum in spatial asymmetries. Indeed, despite being typically associated with motor and sensory functions (Manto et al., 2012), the cerebellum has been linked to higher-level cognitive and emotional processes as well (Stoodley & Schmahmann, 2009; 2010). Accordingly, neuroimaging studies demonstrated that both the vermis and the lateral sector of the cerebellum are activated during line bisection tasks (Fink et al., 2000); however, prior brain stimulation evidence reported a cerebellar involvement only in number but not physical line bisections (Oliver et al., 2011). Interestingly, a recent neuroimaging study comparing the two tasks found different cerebellar contributions between perceptual and representational attentional biases (Liu et al., 2019). Therefore, In Experiment 3a participants completed a landmark task in two orientations (horizontal and vertical) while receiving online neuronavigated single-pulse TMS over the cerebellar vermis (lobule VII), the visual cortex and the vertex (control sites). TMS over the vermis did not modulate participants' bias or response times, whereas TMS over the visual cortex delayed response latencies. In Experiment 3b, participants completed a landmark task and a number bisection task while online neuronavigated TMS was delivered over the cerebellar vermis, the left cerebellar hemisphere (Crus I) and the vertex. Neither cerebellar TMS affected participants' performance in the landmark task. Critically, TMS over the left cerebellar hemisphere slowed down participants' response latencies in the number bisection task. Our data suggest that the left cerebellar hemisphere (but not the vermis) is causally implied in spatial attentional mechanisms in numeric intervals, but not physical lines, bisection. Therefore, our findings shed light on the neural underpinning of spatial attentional orienting in the physical and representational space, by showing that the left cerebellar hemisphere (and not the vermis) should be considered, together with right parietal and frontal regions (Brighina et al., 2002; Cicek et al., 2009; Fink et al., 2000, 2001; Foxe et al., 2003; Göbel et al., 2006; Liu et al., 2019; Oliveri et al., 2004; Zago et al., 2017), as part of a cerebello-fronto-parietal network deputed to drive spatial attentional mechanisms at least in mental space.

In conclusion, the studies described in the present dissertation address some of the many unsolved questions on spatial attentional asymmetries. In particular, we demonstrated that horizontal and vertical attentional biases might rely on only partially separated mechanisms, by showing similar effects of cognitive load between the two biases. Moreover, our findings showed that an altered binocular vision affects the allocation of spatial attention resources in the visual modality, corroborating results from previous studies (Thiel & Sireteanu, 2009). Critically, the effects of altered binocular visual development are restricted to the visual modality, as the typical spatial asymmetry towards the left side of space in the haptic modality was presesrved, in line with the notion of right hemispheric dominance in spatial tasks (Jewell & McCourt, 2000). Therefore, in line with previous studies (Eardley et al., 2017) our data suggest that pseudoneglect in the visual and haptic modality rely on different functional and neural mechanisms. Finally, we reported evidence in favour of the involvement of the cerebellum, specifically the left cerebellar hemisphere (crus I), in numbers but not physical line bisections, confirming previous investigations suggesting separate underlying mechanisms between perceptual and representational pseudoneglect. Finally, in line with prior evidence (Fink et al., 2000; Oliver et al., 2011 Liu et al., 2019), we demonstrated that the neural correlates of spatial asymmetries are not restricted to regions in a right fronto-parietal network but extended to the cerebellum. Nevertheless, although our data helped to clarify several open questions, further investigations are necessary to disentangle the many intriguing and fascinating aspects that still need to be addressed on spatial attentional asymmetries both from an experimental and a clinical perspective.

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