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A critical review of the role of impaired spatial remapping processes in spatial neglect

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Abstract

Objective: Unilateral spatial neglect is a multi-faceted syndrome that arises from brain lesions, typically in the right hemisphere, and is characterized by the failure to attend or respond to stimuli in contralesional space. Here, we expand on the proposal that one deficit contributing to the diverse symptoms in neglect involves spatial remapping processes. Spatial remapping is required to maintain a stable visual representation despite frequent eye movements that change the retinal image. Neglect patients' lesions may disrupt the transfer of this representation across saccades, resulting in the loss of spatial information in working memory or even awareness of an object's presence.

Method: In this review, we will characterize the neglect syndrome and its anatomical origins, describe spatial remapping in healthy individuals, then focus on how impairments of remapping and spatial working memory could contribute to some reported neglect symptoms. Finally, we will discuss the effectiveness of a rehabilitation method known as prism adaptation for alleviating visual spatial symptoms in neglect patients in relation to spatial remapping performance.

Conclusions: The heterogeneity of spatial neglect makes it difficult to pinpoint a single underlying dysfunction or causal lesion. Given the number of brain regions that may be damaged across neglect patients, it is likely that many different processes contribute to the manifested attentional symptoms. In this review, we highlight the role of spatial remapping mechanisms subserved by posterior parietal cortex as one of the underlying deficits leading to visual spatial neglect.

Unilateral spatial neglect is a multi-faceted syndrome that arises from brain lesions, often following stroke, and refers to the failure of an individual to attend or respond to stimuli in the contralesional part of space, despite intact primary sensory cortices (Bartolomeo, 2007; Corbetta and Shulman, 2011; Danckert and Ferber, 2006; Driver and Vuilleumier, 2001; Vuilleumier, 2013). Chronic neglect results most often from lesions in the right hemisphere and typically is considered a deficit in attention allocation or visual exploration of the left part of space, yet many cases present examples of symptoms that defy this simple explanation, such as re-marking of visual targets within non-neglected space (Mannan et al., 2005). Another deficit possibly contributing to these diverse symptoms involves spatial remapping processes (Husain et al., 2001; Pisella and Mattingley, 2004; Vuilleumier et al., 2007). Spatial remapping or updating is required to maintain a stable visual representation of the environment despite frequent eye movements that change the retinal image (Bays and Husain, 2007; Melcher and Colby, 2008; Prime, Vesia, & Crawford, 2008). Neural activity for a visual stimulus within a certain receptive field will be shifted in anticipation of a planned saccade to the appropriate post-saccadic retinotopic coordinates in order to sustain a reliable signal for that location/object (Colby, Duhamel, & Goldberg, 1995; Klier and Angelaki, 2008; Merriam, Genovese, & Colby, 2003). Some neglect patients' lesions may disrupt the transfer of this representation during eye movements, resulting in the loss of spatial information in working memory or awareness of an object's identity.

In this review, we will characterize briefly the neglect syndrome and its anatomical origins, then we will report recent empirical studies that refine the proposal first outlined systematically by Pisella and Mattingley (2004) regarding spatial remapping deficits in neglect. While a remapping deficit cannot account for all symptoms falling under the heterogeneous label of neglect, we argue that the inability to update spatial information across saccades contributes to critical visual attention problems for many patients. Finally, we

will discuss the effectiveness of one potential rehabilitation method, prism adaptation, and how it might alleviate the remapping deficit in neglect patients by targeting spatial processing in parietal cortex.

Symptoms of spatial neglect

To assess neglect symptoms in patients following a brain lesion [due to stroke or an acquired brain injury (Bonnì, Mastropasqua, Bozzali, Caltagirone, & Koch, 2013; Paterson and Zangwill, 1944)], a battery of neuropsychological tests is administered that may include: line bisection, cancellation, copying or drawing figures, reading/writing, and indices of personal neglect in daily life (Azouvi et al., 2006; Azouvi et al., 2003; Bailey, Riddoch, & Crome, 2000; Hartman-Maeir and Katz, 1995; Menon and Korner-Bitensky, 2004; Rousseaux, Allart, Bernati, & Saj, 2015; Rousseaux et al., 2001; Vuilleumier and Saj, 2013; Wilson, Cockburn, & Halligan, 1987). These tests assess various classes of neglect symptoms and different patients may show deficits in different subsets of tests. In line bisection tasks, patients must indicate the midpoint of lines of varying length and tend to show an ipsilesional bias, as if they cannot perceive the full length of the opposite side of the line (Guariglia, Matano, & Piccardi, 2014; Schenkenberg, Bradford, & Ajax, 1980; Sperber and Karnath, 2016). In cancellation tasks, patients must mark all the items distributed across a sheet of paper that fall into a given category such as line segments, letters, or shapes (Albert, 1973; Ferber and Karnath, 2001; Gauthier, Dehaut, & Joanette, 1989; Halligan, Marshall, & Wade, 1989). They frequently omit items on the contralesional side and may re-mark items previously visited (Husain, et al., 2001; Manly, Woldt, Watson, & Warburton, 2002; Mannan, et al., 2005; Wojciulik, Rorden, Clarke, Husain, & Driver, 2004). In copying figures, patients ignore the left half of objects or scenes and may attempt to transpose features from the neglected part of space into the half of the figure they do complete (Ogden, 1985; Gainotti

and Tiacci, 1970). In daily activities, patients may fail to dress the contralesional side of the body or not eat food from the contralesional side of a plate. On these tests and in daily life, patients neglect the left half of the visual field or of individual objects and may limit use of the left side of the body, despite normal motor capabilities. They may be able to identify objects to their left when presented alone or if they are specifically directed to do so, yet disregard these items when competing stimuli are shown in the right visual field, an effect known as extinction (Baylis, Driver, & Rafal, 1993; Danckert and Ferber, 2006; Di Pellegrino, Basso, & Frassinetti, 1997; Vossel et al., 2011). Based on such assessments, a clinical diagnosis of neglect is determined by the rate of error commission (the threshold for which is specified by the clinician (Saj, Verdon, Vocat, & Vuilleumier, 2012; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010).

The attentional dysfunction in neglect can bias perception and/or action towards the ipsilesional side along a gradient with a gradual shift from left to right, rather than with a hard transition such as occurs with sensory impairment (Corbetta and Shulman, 2011; Karnath, 2015; Vuilleumier and Saj, 2013). This ipsilesional bias also may be associated with a horizontally displaced center of the body representation – when asked to align a rod with the perceived body midline, patients shift the rod towards the ipsilesional side, often with a slight counterclockwise vertical rotation (Karnath, 2015; Rousseaux, Honore, & Saj, 2014). Even when sitting without a task, patients may orient their body and/or eyes towards the right and have difficulty in sustaining spatial attention and general arousal (Corbetta and Shulman, 2011; Malhotra, Coulthard, & Husain, 2009). Neglect patients also may have a local attention bias that causes them to focus on a narrower region of space than healthy individuals (Bultitude, Rafal, & List, 2009; Halligan and Marshall, 1994; Marshall and Halligan, 1995; Pisella and Mattingley, 2004; L. Robertson and Delis, 1986). Interestingly, patients struggle with temporal order judgments as well: stimuli displayed to the right are perceived as

occurring earlier than simultaneous stimuli to the left, likely because of the spatial attention bias (Berberovic, Pisella, Morris, & Mattingley, 2004; Danckert and Ferber, 2006; I. H. Robertson, Mattingley, Rorden, & Driver, 1998; Rorden, Li, & Karnath, 2018; Rorden, Mattingley, Karnath, & Driver, 1997). Patients may even deny the presence of their own symptoms (anosognosia), displaying a lack of self-awareness of their perturbed perceptions and actions (Bisiach, Vallar, Perani, Papagno, & Berti, 1986; Rousseaux, et al., 2015; Saj, Vocat, & Vuilleumier, 2013, 2014; Vossel, Weiss, Eschenbeck, & Fink, 2013).

The array of tasks described above that are used for diagnosis and the constellation of symptoms observed across individuals illustrate the heterogeneity of the neglect syndrome and the difficulty in identifying a single cause. Indeed, there may be several significantly unique subtypes of neglect (Bisiach, Geminiani, Berti, & Rusconi, 1990; Buxbaum et al., 2004; Chechlacz et al., 2010; Committeri et al., 2007; Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990; Danckert and Ferber, 2006; Halligan and Marshall, 1991; Mesulam, 1999; Mizuno et al., 2013; Vaessen, Saj, Lovblad, Gschwind, & Vuilleumier, 2016) that load onto perceptual, visual motor, and object-based symptoms (Saj, et al., 2012; Vaessen, et al., 2016; Verdon, et al., 2010). These subtypes may combine or occur singly in individual patients, perhaps depending on the location of the underlying lesions that disrupt function in various nodes of a spatial attention network (Chechlacz, Rotshtein, & Humphreys, 2012).

Anatomy of neglect

In classic studies of the anatomical substrates of neglect, the syndrome has been associated most reliably with right parietal lesions (McFie, Piercy, & Zangwill, 1950; Mort et al., 2003; Vallar and Perani, 1986). The diffuse nature of lesions and the heterogeneity of the syndrome, however, make it difficult to pinpoint a single location that causes a single symptom. Nonetheless, recent advancements in imaging capabilities and technical analyses,

including voxel-wise lesion symptom mapping, have allowed more precise investigations of neglect-related lesions across the brain (Rousseaux, et al., 2015; Saj, et al., 2012; Verdon, et al., 2010). With these advancements, multiple gray and white matter regions have been identified that contribute to components of neglect, suggesting a crucial role of disconnection within and across visual spatial attention networks (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Danckert and Ferber, 2006; Karnath and Rorden, 2012; Mesulam, 1981; Mort, et al., 2003; Verdon, et al., 2010; Vuilleumier, 2013).

Within parietal cortex, studies have proposed the inferior parietal lobule, intraparietal sulcus, angular gyrus, supramarginal gyrus, and temporal-parietal junction as potential causal regions for neglect (Karnath and Rorden, 2012; Vossel, et al., 2011), particularly with respect to perceptual components (Verdon, et al., 2010). Inferior parietal cortex and the temporal-parietal junction are part of a ventral attention network that is critical for orienting to behaviorally salient or unexpected stimuli (Corbetta and Shulman, 2002). This right-lateralized attention hub connects with the dorsal attention network in intraparietal sulcus and frontal cortex that controls voluntary attention. The intraparietal sulcus also putatively corresponds to the lateral intraparietal area reported in non-human primate studies to house remapping mechanisms and spatial priority maps (Konen and Kastner, 2008; Merriam, et al., 2003; Sereno, Pitzalis, & Martinez, 2001); see below), although this homology remains uncertain (Pisella et al., 2011). As such, damage to right inferior parietal cortex may lead to general spatial attention deficits of a perceptual nature by disrupting the functional input to the dorsal network (Corbetta and Shulman, 2011), while avoiding the motor deficits associated with structural damage to the dorsal network (Verdon, et al., 2010). Furthermore, a study using transcranial magnetic stimulation (TMS) over posterior parietal cortex in healthy individuals resulted in spatial attention biases similar to those observed in neglect (Hilgetag, Theoret, & Pascual-Leone, 2001).

Beyond the parietal lobe, damage to frontal cortex (including frontal eye fields and inferior frontal cortex), superior and middle temporal cortex, insula, thalamus, basal ganglia, and the white matter tracts connecting these widespread regions also have been associated with neglect symptoms (Damasio, Damasio, & Chui, 1980; Danckert and Ferber, 2006; He et al., 2007; Saj, et al., 2012; Vaessen, et al., 2016; Vuilleumier, 2013). Frontal eye fields are critically involved in saccade generation (Amiez and Petrides, 2009; Bruce, Goldberg, Bushnell, & Stanton, 1985; Grosbras, Laird, & Paus, 2005) and may contain priority maps of retinotopic space (Jerde, Merriam, Riggall, Hedges, & Curtis, 2012) that when damaged by stroke impair the patient's ability to explore the contralateral visual field (Verdon, et al., 2010). Inferior frontal cortex forms the anterior hub of the ventral attention network responsible for orienting attention to salient stimuli. Lesions encompassing this region or lateral prefrontal cortex have been associated with neglect of extra-personal space (Committeri, et al., 2007; Karnath and Rorden, 2012) and difficulties in resisting distracters (Saj, Verdon, Hauert, & Vuilleumier, 2018).

Superior temporal cortex also has been associated with human neglect cases (Committeri, et al., 2007; Karnath, Ferber, & Himmelbach, 2001), although not as consistently as inferior parietal cortex (Mort, et al., 2003). Temporal lobe lesions within the ventral "what" stream of visual processing may cause more object-based (allocentric) deficits, like ignoring the left side of a clock regardless of its location in space (Danckert and Ferber, 2006; Karnath and Rorden, 2012; Verdon, et al., 2010). In some non-human primate studies, however, superior temporal sulcus was the critical lesion site that caused visual neglect and a lack of exploratory reaching into contralesional space, not the parietal lobe (Luh, Butter, & Buchtel, 1986; Watson, Valenstein, Day, & Heilman, 1994). It currently remains unclear whether this inter-species difference represents an evolutionary shift in brain organization or lack of anatomical precision in human stroke studies (Caminiti et al., 2010).

Finally and perhaps most importantly, damage to the white matter tracts connecting these distributed brain regions determines the functional efficacy of the attention network overall and may be a key cause of the diverse effects observed in neglect as communication between distant regions is disrupted (Bird et al., 2006; Karnath, Rorden, & Ticini, 2009; Urbanski et al., 2011; Vuilleumier, 2013). Specifically, the superior longitudinal, superior occipito-frontal, arcuate, inferior occipito-frontal, uncinate, and middle longitudinal fasciculi connecting inferior frontal, superior temporal, and inferior parietal cortices are proposed to transmit visual spatial attention signals that are degraded or lost in patients with neglect (Chechlacz, et al., 2010; Corbetta and Shulman, 2011; Doricchi and Tomaiuolo, 2003; Karnath and Rorden, 2012; Thiebaut de Schotten et al., 2005). Indeed, a recent longitudinal study reported changes in white matter integrity not only within the damaged hemisphere, but also within *contralesional* visual spatial networks that correlated with chronic behavioral deficits in neglect patients (Umarova et al., 2017). Thus, damage to one gray matter region and its adjacent white matter can impact multiple nodes in the network, even if the distant regions themselves remain intact. Characterizing the functional implications of structural disconnection, therefore, is crucial to identifying the brain changes that cause neglect (Baldassarre et al., 2014; Baldassarre et al., 2016; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008), and research should emphasize how connectivity in visual attention networks is affected rather than focus on isolated damage to cortical regions.

Spatial remapping in healthy individuals

Impairments to the structure and function of visual attention networks evidently lead to neglect symptoms by disrupting many perceptual and motor processes, including spatial remapping during saccades. To understand this deficit in patients, however, we first must describe the functioning of remapping processes in healthy individuals. As mentioned above,

spatial remapping is critical to the maintenance of visual stability across saccades and intimately tied to visual perception. Our perception of the external environment is not an instantaneous, direct translation of sensory input. Instead, the brain constructs an internal representation of visual space that accounts for eye and body movements, reflects the limited capacity of attentional processing, and is guided by prior experience and current goals (Colby and Goldberg, 1999; Melcher and Colby, 2008). Visual input is received from the retina during sequential fixations at spatially disparate locations (Figure 1), with the greatest detail gleaned from objects projecting onto the high-acuity fovea. The information gathered at each fixation must be sustained and combined during subsequent saccades to generate a complete map of space that can be stored and used to guide actions (Klier and Angelaki, 2008; Melcher and Colby, 2008).

Early work in non-human primates investigated how the brain is able to process and respond to this complex, trans-saccadic visual input so effectively. Some neurons in posterior parietal cortex (notably the lateral intraparietal area, LIP) have retinotopic receptive fields tuned to a particular region of the contralateral visual field: when a stimulus appears in the neuron's classic receptive field its firing rate increases (Colby, et al., 1995). Duhamel et al. (Duhamel, Colby, & Goldberg, 1992) demonstrated that the receptive fields of these neurons transiently shift in anticipation of a planned eye movement. Utilizing an efference copy of the impending saccade metrics, neural activity at one location is transferred preemptively to the corresponding post-saccadic location. The first neuron will stop firing for the pre-saccadic stimulus in its classic receptive field and another neuron corresponding to the post-saccadic receptive field will begin firing shortly before the saccade is executed, allowing the brain to establish a functional link between visual input prior to and following eye movements (Bays and Husain, 2007). This transient remapping effect, combined with suppression of blurred

peri-saccadic input, leads to construction of a stable representation of the visual scene without interference from unwelcome jumps in perception.

Spatial remapping additionally may be critical for establishing reference points in spatial working memory. Primate research demonstrated that activity for a briefly flashed stimulus at one location will be remapped to the neuron corresponding to its post-saccadic position, despite no stimulus ever actually appearing in its receptive field, only a memory of the previous stimulation (Colby, et al., 1995; Duhamel, Colby, et al., 1992). The spatial positions of salient objects within the focus of attention in the visual field are assessed relative to the viewer at every fixation; an item that does not match a previous point in the representation must be considered as novel or relocated, depending on whether the identity or location is mismatched, respectively. Spatial remapping helps to ensure that changes in visual input due to one's own eye movements can be distinguished from external motion. Those items that are consistent with the previous representation are perceived as stable and their memory trace strengthened. Attention then can be deployed specifically to goal-relevant objects or salient changes in the scene, with less attention devoted to processing constant background features of the environment, which can be represented on an abstract level requiring fewer neural resources (Melcher and Colby, 2008). Hence, spatial remapping provides a means for integrating visual information from one moment to the next and building a useful mnemonic representation of relevant objects' locations in space (Duhamel, Colby, et al., 1992).

Furthermore, the maps in which spatial updating occurs are based not only on visual input, but also on attention and motor intentions, in a combined topographic priority map (Gottlieb, Kusunoki, & Goldberg, 1998). Priority map locations are weighted based on the inherent bottom-up salience of a stimulus, such as its color or shape, as well as the endogenous top-down goal of the individual at that moment, such as the instruction to search

for a triangle (Fecteau and Munoz, 2006; Karnath, 2015; Zenon, Filali, Duhamel, & Olivier, 2010). Parietal cortex priority maps play an important role in attentional selection of target locations for action including saccade or reaching movements and in maintenance of spatial information during a delay task (Bisley and Goldberg, 2010; Hilgetag, et al., 2001; Jerde, et al., 2012; Srimal and Curtis, 2008). Priority maps may also exist in frontal eye fields (Jerde, et al., 2012; Srimal and Curtis, 2008; Zenon, et al., 2010) and superior colliculus (Fecteau and Munoz, 2006), areas directly related to saccade generation and remapping (Bays and Husain, 2007; Colby and Goldberg, 1999), and thus perfectly situated to translate location priority into foveation of that location. Indeed, the interaction of various nodes of a visual attention network (posterior parietal, frontal eye fields, and superior colliculus) is critical for deploying attention to relevant visual input to establish and update priority maps in retinotopic, egocentric, and motor coordinates, and to use those maps to initiate behavioral output. Damaging priority maps in parietal cortex may interrupt the process at earlier perceptual stages and lead to more extensive deficits, while frontal lesions may be restricted to the motor domain (Verdon, et al., 2010).

More recently, the functional correlates of spatial remapping have been studied with functional magnetic resonance imaging (fMRI) and TMS in humans (Hu and Walker, 2011; Medendorp, Goltz, Vilis, & Crawford, 2003; Merriam, et al., 2003; van Koningsbruggen, Gabay, Sapir, Henik, & Rafal, 2010). Merriam and colleagues (Merriam, et al., 2003) presented healthy individuals with a brief visual stimulus in the center of the screen while they fixated a point in the periphery; participants then made a saccade to the opposite visual field while the stimulus was extinguished. The authors reported activation in posterior parietal cortex (within a large area of intraparietal sulcus) corresponding to the post-saccadic receptive field of the visual stimulus; however, no stimulation actually occurred following the saccade. Therefore, the activation could have been generated only by the transfer of the

stimulus' memory trace from the neurons coding for the pre-saccadic location. The stimulus information was remapped from one hemisphere to the other in preparation for the saccade to create a stable representation, although the brief duration of the stimulus in the experiment caused this updating of visual information not to match the actual post-saccadic scene. While these effects were reported bilaterally, TMS studies have shown that remapping may be disrupted especially by stimulation of right posterior parietal cortex (Chang and Ro, 2007; Morris, Chambers, & Mattingley, 2007; Prime, et al., 2008), supporting the right hemisphere's privileged role in spatial processing and neglect (Corbetta and Shulman, 2011). Interestingly, it has been proposed that remapping of spatial information may occur not only for overt eye movements as in these studies, but also for covert shifts of attention [(Pisella and Mattingley, 2004; Vasquez and Danckert, 2008) but see (Duhamel, Colby, et al., 1992)].

Remapping deficits in neglect patients

Several of the deficits associated with neglect could be explained by a failure of the remapping processes described above, and, indeed, the localization of these remapping and priority maps in primates and healthy humans matches several of the regions identified as part of the disrupted visual attention network in neglect. If patients are unable to transfer and maintain spatial information or object identity across eye movements, then their internal representation of the visual scene could quickly become disorganized and inaccurate. Although new retinal information seems to be processed successfully because patients can identify fixated objects, previous objects' locations are not maintained accurately after eye movements (Husain, et al., 2001; Pisella, Berberovic, & Mattingley, 2004; Vuilleumier, et al., 2007). This, in turn, interferes with spatial priority maps and patients' ability to direct attention to appropriate locations (Bays, Singh-Curry, Gorgoraptis, Driver, & Husain, 2010; Heide and Kömpf, 1998).

In a study by Bays and colleagues (2010), neglect patients with parietal lesions were presented with an array of green squares and asked to fixate red X's when they appeared. On certain trials, a change to the salience (orientation, luminance, or timing) of a green square occurred, erroneously drawing gaze for both patients and controls. Importantly, patients demonstrated an equal deficit for fixating left targets and salient distracters relative to control performance. The authors interpreted this effect as a disruption of the priority map in parietal cortex, which similarly impacted top-down and bottom-up biasing of stimulus locations of interest while interacting with an overall bias towards ipsilesional targets (Bays, et al., 2010). For those patients with right parietal lesions, remapping deficits weaken representations for left space within the priority map, encouraging visual exploration and attention allocation only within the more stable right visual field.

The disruption of priority maps due to deficient spatial remapping processes exhibits a close relationship with spatial working memory in neglect patients (Pisella, et al., 2011; Pisella, Berberovic, et al., 2004; Pisella and Mattingley, 2004). Patients are unable to properly maintain spatial information over delays, even in the non-neglected ipsilesional visual field, although object feature information may be preserved (Ferber and Danckert, 2006; Husain, et al., 2001; Pisella, Berberovic, et al., 2004; Striemer, Ferber, & Danckert, 2013). Pisella and Mattingley (2004) proposed a relationship between spatial remapping and neglect, citing an early study by Duhamel and colleagues (Duhamel, Goldberg, Fitzgibbon, Sirigu, & Grafman, 1992) in which a chronic neglect patient performed a double step saccade task. In this task, two sequential targets are presented briefly and the participant is instructed to saccade to each target in turn (Becker and Jurgens, 1979; Hallett and Lightstone, 1976). Once the eyes move to the first target, a saccade to the original retinal position of the second target would be inaccurate. To perform the task correctly and quickly, the position of the second target must be updated in retinotopic coordinates based on the trajectory of the first

saccade plan. For the neglect patient in Duhamel et al. (1992), the spatial accuracy of the saccades depended on the location of the two targets in visual space and the order of saccades to those targets. The first saccade was accurate when the target was in right, non-neglected visual space, but fell somewhat short of the correct location when the target was in left, neglected space, consistent with performance in a simple visually-guided task. For the second saccade, however, the patient was unable to correctly update the target location only when the first saccade was leftward and the second saccade was rightward, and thus failed to reach the target location despite it being in the non-neglected visual field.

The authors concluded that this deficit was due to disruption of the saccade corollary discharge in right parietal cortex from the initial leftward saccade (Duhamel, Goldberg, et al., 1992), whereas Pisella and Mattingley (2004) suggested that the errant second saccade was caused by the loss of the second target location during remapping for the leftward saccade. The lesioned right parietal cortex was unable to perform spatial remapping, instead reconstructed the entire visual representation following the leftward saccade, and consequently mislocalized the second target (Pisella and Mattingley, 2004). This pattern was replicated in several patients with parietal lesions (Heide, Blankenburg, Zimmermann, & Kompf, 1995; Heide and Kömpf, 1998) and a more recent study confirmed the slowed saccade generation to the contralesional field in a comparable saccade paradigm requiring remapping (Van der Stigchel, Rafal, & Bultitude, 2013). Additionally, similar double step saccade task errors were observed in healthy participants when the right posterior parietal cortex was transiently inhibited with TMS (Morris, et al., 2007; van Donkelaar and Muri, 2002), supporting the role of this region in integrating extraretinal signals to perform spatial remapping of saccade targets.

To address the functioning of spatial remapping in neglect in a simple spatial working memory task, Vuilleumier and colleagues (2007) presented patients with two sequential

colored dots located along the horizontal axis and asked them to report whether the position of the second dot matched that of the first. In the seconds between the presentation of the first and second dots, however, a peripheral letter was presented, which required a saccade to its location to report its identity. The results indicated that when the letter appeared on the right side of the screen, patients' spatial memory was impaired, putatively because the rightward saccade initiated remapping of the first dot's location into the left visual field, regardless of its initial location. The lesioned right parietal cortex responsible for leftward remapping was unable to perform this transformation, causing the first dot's position to be degraded and thus not compared correctly to the second dot (Vuilleumier, et al., 2007). These findings illustrated how simple eye movements to examine a scene or object could interfere with the patient's internal representation of space. If spatial information about an object is lost during saccades, particularly for the left visual field, the patient may appear to forget its existence altogether and direct attention further towards the intact right visual field.

The results of Vuilleumier et al. (2007) at first appear contradictory to the double step saccade task results (Duhamel, Goldberg, et al., 1992; Heide, et al., 1995; Heide and Kömpf, 1998), in which a leftward initial saccade disrupted performance. These two tasks, however, made different perceptual and motor demands over a different time scale. In the double step saccade task, two sequential saccades must be programmed rapidly with the second saccade metrics updated based on the efference copy of the planned motor command for the first saccade. This efference copy may be sent to a representation map close to motor output in order to efficiently update the second saccade plan. For Vuilleumier and colleagues' spatial memory task, the critical remapping was performed on a perceptual/attentional target with several seconds delay before recall. Thus, no rapid updating of a motor command was required and any damage to the leftward saccade efference copy may have been irrelevant to the perceptual shift of the dot's location to the right visual field over the delay. Instead

remapping had to occur within a visual representation map maintaining salient perceptual stimuli, where the error occurred following a rightward saccade that put the stimuli into left visual field. The manner in which the remapping deficit manifests, therefore, depends on the specific task demands placed on the patient with potentially diverging effects on rapid motor plans and slower perceptual representations.

Disruption of perceptual representations also could account for another behavioral irregularity in neglect: revisiting during cancellation tasks, where patients re-fixate and re-mark items already attended as if they were new items (Husain, et al., 2001; Mannan, et al., 2005; Pisella and Mattingley, 2004). Performing the visual search for targets induces frequent remapping of the items' positions on the page during exploratory saccades and results in overwriting of spatial maps, which presumably hinders patients' ability to recognize previously marked items. An ipsilesional attention bias would direct patients' gaze towards the right, remapping most of the items into damaged left visual field representations, effectively erasing the memory trace of recently fixating those locations. These reports of re-fixation when no mark remains visible, however, may correspond to a separate phenomenon from motor perseveration also associated with some cases of neglect (Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009). In the latter type of perseveration, patients will continue to select cancellation targets with visible marks and add unnecessary elements in drawing tasks (Gainotti and Tiacci, 1970; Manly, et al., 2002; Rusconi, Maravita, Bottini, & Vallar, 2002). Nonetheless, spatial remapping may contribute to perseveration [in combination with a frontal/motor defect (Rusconi, et al., 2002) or transposition of left targets to the right side (Halligan, Marshall, & Wade, 1992; Manly, et al., 2002)] since cancellation and drawing tasks also require a high degree of visual exploration (Ronchi, et al., 2009).

Another recent study examined how deficits in spatial remapping in neglect contribute to the ability to learn and anticipate sequences of stimuli (Saj, et al., 2018). Patients were

presented with a series of dots appearing at five locations across a screen in progression from either right to left, left to right, or randomly; they were required to respond manually when an infrequent red dot appeared. To correctly perform this task, patients needed to maintain the previous dot locations in spatial memory despite the saccades to each new dot that necessitated remapping of the locations to construct an updated representation of the task's visual scene. Those with lesions in the frontal lobe demonstrated a reduction in reaction time for the predictable sequences over the course of the experiment, whereas patients with parietal lesions showed no learning effect over time. Evidently, the parietal patients' ability to store and utilize spatial information in working memory was impaired, preventing them from improving behavior based on the past appearances of the visual stimuli. This deficit in working memory appears to be restricted primarily to the spatial domain: Pisella and colleagues tested patients on a working memory task requiring identification of a color, location, or shape change and found that after a one-second delay patients with parietal lesions were impaired specifically on the location response [(Pisella, Berberovic, et al., 2004), see also (Denis, Beschin, Logie, & Della Sala, 2002; Ferber and Danckert, 2006; Kristjansson and Vuilleumier, 2010)]. These two studies imply that spatial remapping and spatial working memory deficits may occur primarily in neglect patients with damage impacting the posterior parietal cortex.

Further evidence of spatial remapping deficits in neglect has been demonstrated in a task using covert attentional shifts rather than overt saccades to the periphery (Saj, Pierce, Caroli, & Vuilleumier, under review). In this study, seven neglect patients were tested on a paradigm similar to Vuilleumier et al. (2007), except that instead of identifying peripheral letters, patients were instructed to maintain central fixation while a peripheral checkerboard briefly flashed, presumably capturing attention due to its inherent visual salience. The authors reported a similar pattern of results to Vuilleumier et al. (2007) with rightward covert

attention shifts eliciting poorer performance on location judgements in neglect patients than leftward or no attention shift conditions. These findings support earlier work on the relationship between covert attention and spatial remapping (Pisella and Mattingley, 2004; Vasquez and Danckert, 2008) as well as the notion of an obligatory relationship between the ocular motor and visual attention systems (Deubel and Schneider, 1996; Hoffman and Subramaniam, 1995; Rizzolatti, Riggio, Dascola, & Umilta, 1987), with attention shifts triggering remapping processes as preparation for an upcoming eye movement. Neglect patients thus may show degradation of spatial memory signals when they "refresh" remapping representations (Pisella and Mattingley, 2004) following attention wandering in daily activities, even when few eye movements are produced.

Overall, remapping deficits in neglect contribute to poor spatial attention and working memory, impairing behavior in many tasks that require updating of visual representations. Recognizing this deficit may supplement other major theories of neglect, without necessarily supporting one view over another. One prominent theory suggests that neglect arises from primarily ventral lesion sites corresponding to a ventral attention network responsible for orienting and arousal (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Corbetta and Shulman, 2011; Karnath, 2015). Damage to this stimulus-driven network and the loss of reorienting functions then disrupt the goal-driven dorsal attention network (Corbetta and Shulman, 2011). A remapping deficit could be compatible with such a view, assuming that the intraparietal priority maps are impaired following functional disconnection with the ventral attention hub around the right superior temporal gyrus and temporal-parietal junction. Attention might then be deployed unevenly across visual fields for salient stimuli, with leftward stimulus locations failing to be maintained following saccadic remapping, exacerbating the apparent attentional bias and discouraging voluntary visual exploration of the left visual field.

Another important theory of neglect emphasizes interhemispheric competition and proposes that right and left hemisphere attentional networks favor exploration of contralateral visual locations while suppressing ipsilateral locations (Kinsbourne, 1977; Szczepanski and Kastner, 2013; Szczepanski, Konen, & Kastner, 2010). This competition is normally balanced so that attention is centered straight ahead and the whole visual field can be prioritized. In spatial neglect, however, the right-sided lesions leave the left hemisphere driving attention only towards the right. If this proposal is extended to remapping mechanisms, the intact left hemisphere biases visual exploration towards the right visual field and impaired updating of left visual field representations in the right hemisphere hinders spatial memory for and exploration of those locations. Furthermore, right lateralization of spatial attention processes may lead to the inability to remap left locations specifically while the opposite might not be observed with left hemisphere lesions if the right hemisphere is able to represent and remap the full visual field on its own (Corbetta and Shulman, 2011; Mesulam, 1981). Additional research with left lesion patients with right neglect could clarify whether a lateralized remapping deficit is present or what other attentional mechanisms are dysfunctional in these less common cases.

Towards rehabilitation

The combined impact of the spatial remapping and attention deficits described in the preceding sections clearly makes persistent visual spatial neglect a debilitating condition that disrupts daily functioning for many patients and adds to the burden of caregivers. Unfortunately, few practical rehabilitation options have been developed that provide significant, enduring reductions of neglect symptoms, and the efficacy and generalizability of any specific treatment varies by patient. One particularly promising method for improving spatial neglect symptoms is prism adaptation (Rossetti et al., 1998), a treatment in which the

patient wears wedge lenses that shift visual input towards the ipsilesional side. This results in a contralesional adjustment in visual-spatial bias that can last well beyond the training sessions (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Làdavas, Bonifazi, Catena, & Serino, 2011; Nijboer, Nys, van der Smagt, van der Stigchel, & Dijkerman, 2011; Redding and Wallace, 2006; Saj, Cojan, Vocat, Luaute, & Vuilleumier, 2013; Serino, Barbiani, Rinaldesi, & Làdavas, 2009), although some studies reported no lasting improvements in symptoms (Morris et al., 2004; Nys, de Haan, Kunneman, de Kort, & Dijkerman, 2008; Rode et al., 2015; Rousseaux, Bernati, Saj, & Kozlowski, 2006; Ten Brink et al., 2017; Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010). This technique may be specifically helpful for neglect patients with spatial remapping deficits because it targets visual-spatial transformation processes (Rossetti, et al., 1998) supported by parietal-based functional networks (Chapman et al., 2010), is non-invasive, and generalizes to a broader range of tasks more effectively than other training regimens (Newport and Schenk, 2012).

In the standard procedure, participants are asked to point to visual targets before, during, and after wearing the prism goggles for as little as five to ten minutes (Rossetti, et al., 1998). While wearing the prisms, pointing initially is offset with the direction of the prism shift. With continued exposure, however, participants adjust their visual-manual coordination by accounting for the altered visual input and ultimately can point to the correct location. This adjustment occurs both due to an intentional strategy to minimize the mismatch and an unconscious adaptation within the sensorimotor system (Chapman, et al., 2010), though the former effect may be weaker in patients (Pisella et al., 2004; Redding and Wallace, 2006). After the prisms are removed, this proprioceptive realignment results in immediate after-effects where individuals point in the opposite direction of the original prism shift (Newport and Schenk, 2012; Pisella, Rode, Farne, Tilikete, & Rossetti, 2006). For healthy participants,

these sensorimotor aftereffects are typically short-lived and occur with either rightward or leftward deviating prisms.

Several studies have investigated the impact of prism adaptation on visuospatial behavior in healthy controls. For example, Bultitude and colleagues (2013) tested healthy individuals on the double step saccade task following prism adaptation. When the prisms shifted the visual scene towards the right, behavior on the saccade task reflected the anticipated leftward compensation. When the prisms shifted the visual scene towards the left, however, behavior on the task differed based on whether the second target (that required remapping) initially appeared in the left or right visual field. Second targets in the right visual field showed the anticipated rightward aftereffect, but those in the left visual field did not. The authors proposed that this deviation reflected impaired spatial remapping processes in the right hemisphere, induced by the leftward prism shift's effect on parietal cortex. This caused the left visual field second targets to be directed towards the original retinal location, cancelling out the rightward prism aftereffect. As such, they further suggested that since leftward prisms induce remapping deficits, rightward prisms should counteract remapping deficits in neglect patients (Bultitude, Van der Stigchel, & Nijboer, 2013).

Furthermore, in two fMRI studies of healthy individuals, prism adaptation activated parietal cortex (Chapman, et al., 2010; Luaute et al., 2009), supporting the role of parietal lesions or disconnection in visual-spatial deficits observed in neglect and the appropriateness of this therapy for such patients. In these studies, left anterior intraparietal sulcus, parietal occipital sulcus (Luaute, et al., 2009), right superior parietal lobule, and anterior inferior parietal lobule (Chapman, et al., 2010) were associated with visual-motor error detection and correction, which would allow for strategic, but coarse, adjustment of pointing direction to match the visual shift caused by the prism (Chapman, et al., 2010; Luaute, et al., 2009; Pisella, Michel, et al., 2004). Right anterior inferior parietal lobule, angular gyrus, and

cerebellum activation, on the other hand, were consistent with a role in fine-tuning motor control over the course of prism training (Chapman, et al., 2010; Luaute, et al., 2009). Activation in superior temporal sulcus also was reported for the later phase of prism adaptation, potentially indicating a sustained impact on broader spatial cognition (Luaute, et al., 2009). Together these results support the use of prism adaptation for neglect patients, as it may target visual spatial processes that are impaired by parietal damage or disconnection from the attention network, and encourage other nodes (i.e., cerebellum, temporal or frontal cortex) to compensate for the lack of parietal input (Jacquin-Courtois et al., 2013; Pisella, et al., 2006). Alternatively, prism adaptation rehabilitation may require sufficiently intact parietal cortex for recovery to occur, making patients with large parietal lesions less likely to be successful. Indeed, one group has reported that only patients with frontal lesions benefitted from their prism adaptation procedure, which targeted motor aiming mechanisms rather than perceptual processing (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Goedert, Chen, Foundas, & Barrett, 2018).

In studies of the effects of prism adaptation on neglect patients, lasting improvements were reported for several common neglect measures like visual search, line bisection, cancellation, reading, temporal order judgement, and subjective straight ahead (Berberovic, et al., 2004; Bultitude and Rafal, 2010; Frassinetti, et al., 2002; Nijboer, et al., 2011; Saj, Cojan, et al., 2013; Sarri et al., 2008; Serino, et al., 2009; Vangkilde and Habekost, 2010). Patients generally showed less attentional bias towards the ipsilesional part of space and were able to create and use a more balanced internal visual representation. Importantly, these reported measures do not assess simple visual-manual coordination that would be impacted directly by the pointing training, but instead require higher-level visual spatial processing, indicating a broader impact on brain function than simple motor training (Sarri, et al., 2008). Furthermore, prism adaptation may reduce the local attention bias often observed in neglect patients

(Bultitude, et al., 2009; Redding and Wallace, 2006) and encourage visual exploration of contralesional space (Shiraishi, Yamakawa, Itou, Muraki, & Asada, 2008).

Patient studies that utilized multiple training sessions and prisms with strong visual shifts reported significant benefits on neglect tests, even in chronic patients months after training (Jacquin-Courtois, et al., 2013; Keane, Turner, Sherrington, & Beard, 2006; Newport and Schenk, 2012; Serino, et al., 2009; Vaes et al., 2016; Vangkilde and Habekost, 2010). Plasticity of neural circuitry may allow healthy brain regions to compensate for parietal or adjacent white matter damage and improve deployment of spatial attention or remapping mechanisms after prism adaptation (Pisella, et al., 2006). Nonetheless, as with most rehabilitation protocols, the findings on prism adaption have been equivocal, with some studies showing a lack of improvement in neglect symptoms (Morris, et al., 2004; Nys, et al., 2008; Rousseaux, et al., 2006; Ten Brink, et al., 2017; Turton, et al., 2010), possibly due to the intensity of the training regimen or the type of patients included. Ultimately, many factors can influence the effectiveness of a rehabilitation protocol for a given patient, and future research is necessary to determine whether prism adaptation is particularly effective for neglect patients with spatial remapping deficits.

Conclusions

The neglect syndrome is characterized by a maladaptive ipsilesional attention bias with limited perception and action for the contralesional part of space. Lesions to the right hemisphere attention network in inferior parietal, frontal, and superior temporal cortex and the white matter tracts connecting these regions lead to this diverse condition with a range of behavioral manifestations. Some neglect symptoms may be caused by dysfunction of spatial remapping and spatial working memory processes, and an impaired mental representation of the visual world. Remapping is necessary to establish a consistent representation despite

frequent eye movements and to build memory traces for individual objects and locations. Neglect patients perform poorly on tasks that require a saccade or attention shift while trying to remember or update the location of a visual target. The inability of damaged parietal regions to complete spatial remapping during saccades disrupts the maintenance of spatial information and patients' ability to use this information to guide behavior. Fitting with the heterogeneous nature of neglect and its underlying lesions, this deficit may not occur in all patients or in itself be sufficient to cause full-blown neglect. Remapping deficits may be more common in patients with visual-perceptual symptoms and parietal lesions (Verdon, et al., 2010) encompassing spatial attention representations in the intraparietal sulcus, or lesions to the white matter tracts disconnecting these parietal maps from the rest of the attention network. Prism adaptation is a promising rehabilitation method that seemingly targets spatial processing in right parietal cortex and may attenuate some visual spatial attention symptoms with repeated training. While a general rightward attention bias or misaligned subjective midline may account for many features of visual spatial neglect, the deficit for maintaining left visual field spatial information across eye movements appears specific to a failure of remapping mechanisms.

Disclosure statement

The authors declare no conflicts of interest.

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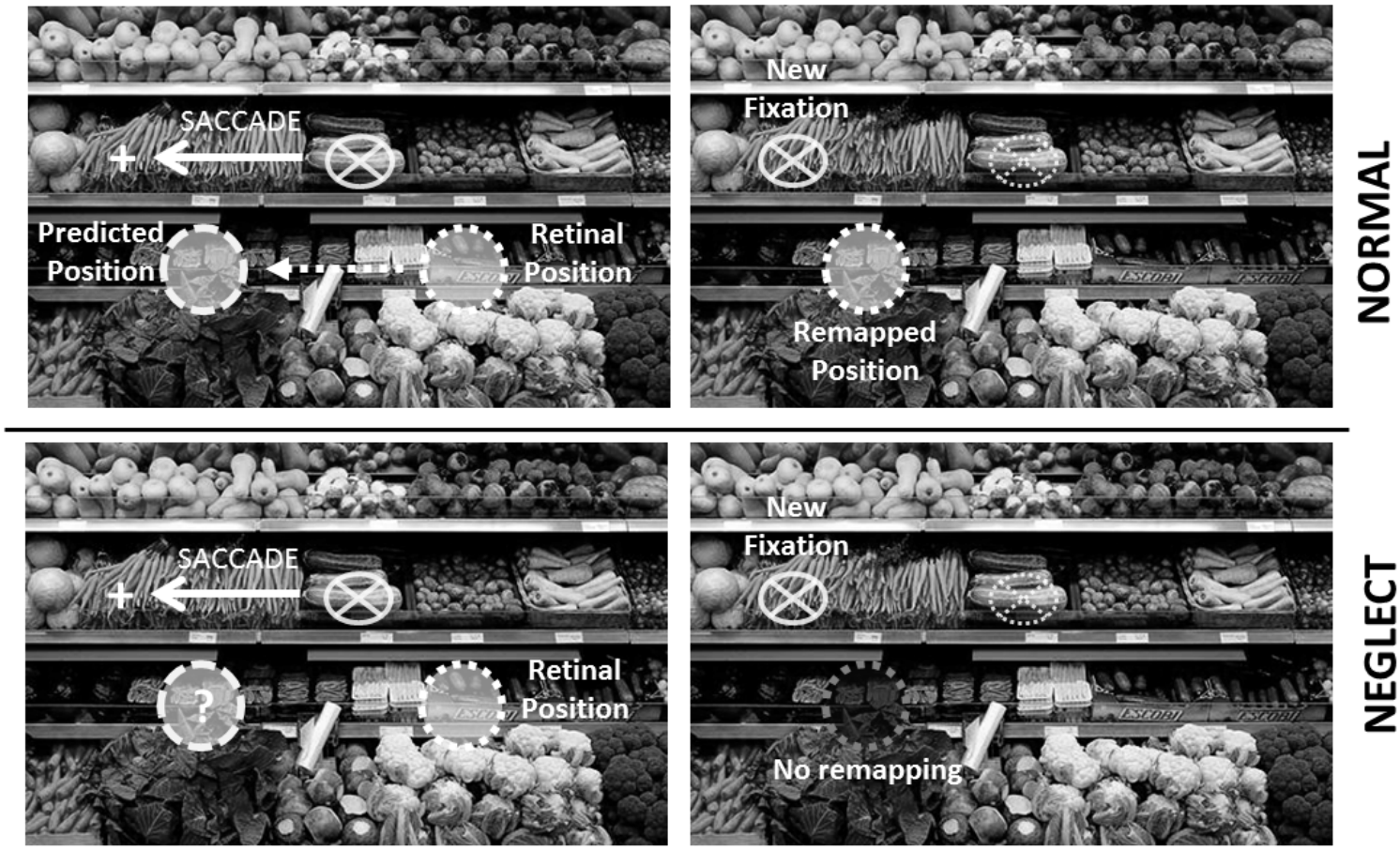

Figure 1. After each saccade the location of a visual target is memorized to maintain a correct representation of the location in space. If the remapping process is normal, the position of the target in the environment will still be available after the saccade. In this example, the remembered location that the subject had previously searched or attended would be updated with respect to the new fixation location (top). In neglect patients, the location of this previously searched location may be lost: the spatial remapping fails, and no stable representation of space is formed (bottom).