CHAPTER

13 The Nonspatial Side of Spatial Neglect and Related Approaches to Treatment

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Abstract

In addition to deficits in spatial attention, individuals with persistent spatial neglect almost universally exhibit nonspatially lateralized deficits in sustained and selective attention, and working memory. However, nonspatially lateralized deficits in neglect have received considerably less attention in the literature than deficits in spatial attention. This is in spite of the fact that nonspatially lateralized deficits better predict the chronicity and functional disability associated with neglect than spatially lateralized deficits. Furthermore, only a few treatment studies have specifically targeted nonspatially lateralized deficits as a means to improve spatial neglect. In this chapter, we will briefly review several models of spatial attention bias in neglect before focusing on nonspatial deficits and the mechanisms of nonspatial–spatial interactions and implications for treatment. Treatment approaches that more completely address nonspatial deficits and better account for their interactions with spatial attention will likely produce better outcomes.

Keywords

spatial neglect, hemineglect, neglect, spatial attention, sustained attention, rehabilitation

1 INTRODUCTION

Approximately one-third of all individuals suffering unilateral brain injury exhibit a complex, debilitating array of neurological deficits known as the *neglect syndrome* (Halligan et al., 2003; Heilman et al., 1987, 1993; Mesulam, 1990). This collection of

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spatial and nonspatially lateralized attention deficits vary greatly in presentation and severity (Appelros et al., 2002; Buxbaum et al., 2004; Pedersen et al., 1997), and endure more often following right hemisphere damage (Ringman et al., 2004; Stone et al., 1993). The most apparent problem is failure, or dramatic slowing, of response to stimulation presented to the side of space opposite the lesion (Azouvi et al., 2003; Driver and Vuilleumier, 2001; Heilman et al., 1985; Hornak, 1992; Ishiai et al., 2006; Mattingley et al., 1998). Although less obvious, deficits that are not spatially lateralized (Danckert and Ferber, 2006; Husain et al., 1997; Robertson et al., 1997a; Van Vleet and Robertson, 2006) are also fundamental to persistent neglect. In fact, the severity of nonspatial deficits is a stronger predictor of the chronicity of spatial neglect in the post-acute phase of recovery than the spatial deficits themselves (Duncan et al., 1999; Hjaltason et al., 1996; Husain et al., 1997; Peers et al., 2006; Robertson et al., 1997a).

In this chapter, we will briefly review several models of spatial attention bias in neglect before focusing on nonspatial deficits and the mechanisms of nonspatial/spatial interactions and implications for treatment. We contend that treatment approaches that more completely address nonspatial deficits and account for nonspatial/spatial interactions will produce better outcomes and may eventually lead to effective, practical treatments for this debilitating disorder that currently has no widely accepted standard of care.

2 SPATIAL DEFICITS IN NEGLECT

In the acute phase of recovery, patients suffering from neglect commonly present with a bias in spontaneous orienting and motor initiation toward the side of their lesion (ipsilesional), *neglecting* the side opposite their lesion (contralesional). Performance on tasks requiring volitional or goal-directed spatial attention reveal a graded contralesional bias centered on direction of gaze, head, or body (egocentric neglect), with the most contralesional locations showing the worst performance.

Individuals with neglect may also present with spatial deficits that manifest within object-centered reference frames, known as *allocentric* neglect (List et al., 2008, 2011). Some reports suggest that ego- and allocentric neglect rarely co-occur clinically and may be dissociated anatomically (Medina, 2009; Verdon et al., 2010). However, more recent findings (Rorden et al., 2012) suggest a strong association between egocentric and allocentric neglect (see also Yue et al., 2012). In particular, allocentric behavioral deficits were only observed in conjunction with egocentric deficits and both deficits were shown to have considerable functional anatomical overlap.

In the post-acute phase of recovery (>3 months), pronounced biases in spontaneous orienting and motor initiation typically resolve, especially in patients with neglect caused by left hemisphere lesions. However, spatially lateralized deficits in goal-directed spatial attention typically persist after neglect caused by right hemisphere lesions. For example, several studies report deficits in components of goal-directed attention such as visual search and disengagement of attention

(e.g., disengaging from rightward stimuli to attend to leftward stimuli) several years post-insult (Johnston and Diller, 1986; List et al., 2008; Posner et al., 1984). Over the last 40 years, several theories have been proposed to account for these goal-directed spatial attention deficits in neglect, many of which are not mutually exclusive. While a review of these theories is beyond the scope of this chapter, we briefly describe several popular theories below.

3 THEORETICAL ACCOUNTS OF LATERALIZED SPATIAL DEFICITS IN NEGLECT

3.1 Anatomical Models

3.1.1 Hemispheric Rivalry and Synchrony

One classic theory of neglect emphasizes the importance of balanced interhemispheric activation in goal-directed spatial attention. According to Kinsbourne, spatial neglect may best reflect the influence of disrupted interhemispheric activity on spatial attention (He et al., 2007; Kinsbourne, 1977; Kinsbourne and Bruce, 1987). The resulting imbalance in attention is thought to result from relative hyperexcitation of the intact hemisphere due to release of inhibition from the damaged, hypoactive hemisphere (Corbetta and Shulman, 2002; Corbetta et al., 2005; Koch et al., 2008a). Interestingly, additional damage to the intact hemisphere can sometimes remediate hemispatial neglect, perhaps through rebalancing interhemispheric competition (Vuilleumier et al., 1996). Likewise, recent studies employing transcranial magnetic stimulation (TMS) to functionally deactivate the intact hemisphere can significantly reduce neglect (Brighina et al., 2003; Koch et al., 2008b, 2012; Oliveri et al., 2001) (see more on this below). Recent studies of resting state network activity have also shown that interhemispheric connectivity, particularly in posterior parietal cortex, is disrupted in the acute phase of recovery but in recovered patients is fully restored. This further confirms the importance of interhemispheric communication and balance in successful goal-directed spatial attention (Carter et al., 2010; He et al., 2007).

3.1.2 Right Hemisphere Pays Attention to Both Sides of Space, Left Pays Attention to the Right Side of Space

Another traditional and popular theory of neglect postulates that the right hemisphere controls goal-directed attention to both sides of space, while the left hemisphere only controls attention to the right side of space (Mesulam, 1981). According to this theory, damage to the right hemisphere is associated with more severe spatial attention impairments (as the left cannot compensate), whereas after left hemisphere damage the right hemisphere is able to successfully compensate (i.e., attend to both sides of space). There has not been a wealth of neuroimaging support for this theory; in fact, studies in healthy controls generally show that brain regions involved in goal-directed spatial attention (e.g., intraparietal sulcus, IPS) are sensitive to the opposing side of space in an equal and opposite fashion (Silver et al., 2005; Snyder and

Chatterjee, 2004). However, a recent report has shown that with increasing visual short-term memory load, an asymmetry does in fact emerge: left IPS regions show load effects for the right side of space whereas right IPS regions show load effects for both sides of space (Swisher et al., 2007). This suggests that asymmetries in attention may only be pronounced during demanding tasks (e.g., searching for items in a cluttered array) and further suggests a crucial link between spatial attention and the cognitive load of a task, which we will expand upon below.

3.2 Cognitive Models of Attention in Neglect

3.2.1 Hyperattention/Increased Salience Detection to Ipsilesional Stimuli

Lateralized failure in *detection* of stimuli is often discussed with regard to salience, the sensory distinctiveness and behavioral relevance of an object relative to other objects. Hyperattention (Bartolomeo and Chokron, 1999) accounts of neglect contend that events occurring in ipsilesional space "override" co-occurring events in contralesional space. This abnormally high salience of ipsilesional stimuli may prevent them from being filtered when they are task-irrelevant (Bays et al., 2010; Shomstein et al., 2010; Snow and Mattingley, 2006) or lead to repeated re-fixations during search tasks (Husain et al., 2001). Allowing individuals with neglect to erase targets rather than marking them in a cancellation paradigm so that they are no longer salient or no longer compete for attention improves search performance. However, some individuals continue to neglect the remaining items (Ishiai et al., 2006).

3.2.2 Feature Integration

Distinct from *detection* of salient items, accurate *discrimination* of more complex stimuli (i.e., searching for your car in a parking lot full of cars) may rely on the proper integration of elementary features such as color and shape (Eglin et al., 1989; Robertson et al., 1988; Treisman and Gelade, 1980; Van Vleet and Robertson, 2009). Thus, according to feature integration theory, spatial neglect may result from a failure to properly bind or conjoin features of an object located in contralesional space. This theory is bolstered by the fact that early visual mechanisms such as contrast sensitivity (Spinelli et al., 1990), image segmentation based on low-level features (Driver and Mattingley, 1998), and visually evoked responses in occipital cortex are typically intact in *neglected* space (Di Russo et al., 2008; Rees et al., 2000; Watson et al., 1977). For example, Pisella et al. (2004) demonstrated that individuals with neglect could detect of color and shape changes in the neglected field but were impaired in detecting more complicated location changes in a matrix of four objects. Further, a study examining implicit attention in neglect showed that feature priming in neglected space does not appear dependent on explicit attention, as feature primes presented at undetectable levels in neglected space influenced speeded detection on subsequent probe trials (Van Vleet and Robertson, 2009). Priming dependent on the combination of two features (i.e., conjunction) in neglected space was only effective if explicitly attended, suggesting that individuals with neglect require spatial attention to bind elementary aspects of complex objects (Eglin et al., 1989; Kristjánsson et al., 2005; Treisman and Gelade, 1980; Van Vleet and Robertson, 2009).

In addition to these popular models, other models contribute to explaining the lateralized spatial deficits in neglect. For example, Posner and colleagues characterize neglect as an impairment in the ability to disengage attention from ipsilesional events (i.e., deficit in reorienting to contralesional events) (Posner et al., 1984). Still others argue that local processing bias (Robertson et al., 1988) is an important component of neglect, as hemispheric specialty for attention to global or local aspects of an object or scene have shown that the right hemisphere is biased toward global processing and the left toward local processing (Delis et al., 1986; Eglin et al., 1989; Robertson et al., 1988). While this deficit is not strictly lateralized (i.e., can occur in intact space), patients' resulting local bias following right hemisphere lesion could increase the tendency to search near the current focus of attention, exacerbating a bias to attend to ipsilesional locations.

Characterizing the mechanisms of all the component spatial deficits, the heterogeneity in presentation of these deficits across patients (e.g., intentional neglect, allocentric neglect, egocentric neglect), and the brain regions that cause these deficits has been the major objective of neglect research over the last 40 years. In spite of this robust body of research, better understanding of nonspatial deficits and their interaction with spatial deficits may hold more promise to improving functional outcomes in patients suffering from neglect.

4 NONSPATIALLY LATERALIZED DEFICITS IN NEGLECT AND NONSPATIAL/SPATIAL INTERACTIONS

In addition to deficits in spatial attention, individuals with persistent neglect almost universally exhibit nonspatially lateralized deficits in sustained attention, selective attention/attention to transient events, and spatial working memory (Battelli et al., 2001; Duncan et al., 1999; Malhotra et al., 2005, 2009; Robertson et al., 1997a). As mentioned, nonspatial deficits are stronger predictors of chronic spatial neglect and related functional disability than are the spatially lateralized deficits themselves (Duncan et al., 1999; Hjaltason et al., 1996; Husain et al., 1997; Peers et al., 2006; Robertson et al., 1997a). This is likely because lesions that produce persistent neglect typically damage brain regions that support nonspatially lateralized attention. Considering the conspicuous spatial biases typical of neglect, this pattern of neglect lesions presents a paradox: brain areas associated with goal-directed lateralized spatial attention are typically spared (Corbetta and Shulman, 2002) while brain mechanisms that support nonspatially lateralized attention are much more commonly damaged.

Although it has been suggested that nonspatially lateralized deficits are not essential to the neglect disorder and simply exacerbate neglect symptoms (Husain and Rorden, 2003), we contend that because neglect producing lesions implicate nonspatial regions and because nonspatial deficits predict the functional outcomes of neglect as well as or better than spatial deficits that nonspatial deficits should be considered a core feature of the disorder. Below we review several component nonspatially lateralized deficits common to neglect and consider models that account for the interaction of spatial and nonspatial deficits.

4.1 Arousal and Alertness

One critical nonspatial deficit accompanying neglect is difficulty maintaining focused engagement. This impairment manifests as decreased physiological arousal (Heilman et al., 1978) and/or poor sustained attention (Bartolomeo and Chokron, 1999) and may also be related to slowed updating of visual working memory (Husain et al., 1997; Van Vleet and Robertson, 2006), poor temporal resolution (Battelli et al., 2001), and slow response times (Samuelsson et al., 1998).

Diminished physiological arousal is particularly evident in individuals with right hemisphere lesion-induced neglect (Hjaltason et al., 1996; Robertson, 2001; Samuelsson et al., 1998), who commonly present as disengaged. Consistent with this presentation, neglect resulting from right hemisphere damage has shown to result in reduced galvanic skin responses to electrical stimulation (Heilman et al., 1978) and a failure to show normative heart rate fluctuation following a target-related cue (Yokoyama et al., 1987). More persistent deficits in cognitive alertness have shown to significantly affect spatially lateralized attention (Robertson et al., 1995, 1998). In two seminal studies, Robertson and colleagues demonstrated that increases in either phasic (Robertson et al., 1998) (moment-to-moment) or tonic (sustained) alertness (Robertson et al., 1995) decreased or transiently eliminated neglect (see additional discussion below). Further supporting the association between alertness and spatial bias, a recent report demonstrated that reducing alertness via administration of a sedative results in the immediate re-emergence of spatial neglect symptoms in recovered patients (Lazar et al., 2002). Additionally, increased alertness via implementation of time pressure during the performance of standard measures of spatial bias (e.g., cancellation task) has shown to significantly improve performance in detecting leftward targets (George et al., 2008).

4.2 Sustained Attention

Distinct from physiological arousal or alertness (Heilman et al., 1978), which may be more sensitive to manipulations of novelty or unexpected events (i.e., effects driven from the *bottom-up*), deficits in sustained attention to a goal (i.e., from the *top-down*) may better account for chronic difficulties in neglect patients (Singh-Curry and Husain, 2009; Van Vleet et al., 2011). For example, deficits in sustained attention have been shown to undermine more complex cognitive functions such as short-term memory and executive control functions, which may particularly impair everyday functioning.

Sustained attention to spatial location may be particularly impaired in neglect. A series of experiments that examined the ability of right hemisphere patients with neglect to sustain attention found deficits even for simple detection of stimuli presented at central fixation (Malhotra et al., 2009). Follow-up experiments demonstrated even more pronounced deficits when neglect patients were required to attend to spatial location over time, showing a much steeper vigilance decrement (decrement in performance over time) than when sustaining attention to letters. Thus, sustaining attention to spatial locations appears to be particularly affected in neglect.

4.3 Selective Attention/Attention to Transient Events

Deficits in speeded selective attention in neglect have been shown in studies examining the processing limits of the visual system. For example, performance on the attentional blink task provides a measure of the temporal dynamics of selective attention—the time taken by the visual system to identify two visual stimuli occurring closely in time. Patients with neglect have shown to have a significantly protracted attentional blink (>1000 ms) compared to controls (~400 ms) and the length of the attentional blink has shown to correlate with the severity of spatial neglect (Husain et al., 1997). Recent studies by Battelli et al. (2001) also show deficits in temporal resolution in neglect, as reflected in performance in apparent motion paradigms. Unlike low-level motion detection, apparent motion is the perception of illusory motion such as when two lights are flashed sequentially at separate locations producing a clear impression of motion. The deficit in apparent motion in neglect is likely due to a bilateral deficit in the temporal resolution of attention to transient events. Additional evidence that neglect patients have particular deficits in attending to transient events is from studies that show sub-second and multisecond time perception deficits (Basso et al., 1996; Danckert et al., 2007; Harrington et al., 1998).

4.4 Spatial Working Memory

In addition to difficulties in sustaining attention and detecting transient events, neglect has also been associated with deficits in holding spatial information in working memory (for a comprehensive review, see Striemer et al., 2013). Spatial working memory deficits may explain why patients with neglect revisit previously attended (marked) ipsilesional locations during cancellation tasks (Husain et al., 2001). Follow-up studies demonstrate that revisiting behavior may be at least partially due to patients' difficulty updating spatial locations across successive eye movements (i.e., saccadic remapping) (Husain et al., 2001). Additionally, patients with neglect may show spatial span deficits (Malhotra et al., 2005). For example, patients with neglect exhibited poor spatial short-term memory for stimuli presented centrally along the vertical meridian. These deficits in short-term memory increased with increasing span and correlated with severity of neglect on cancellation tasks (particularly neglect resulting from damage to parietal cortex and/or insula) (Malhotra et al., 2005).

4.5 Attentional Capacity

Some researchers have interpreted the nonspatial deficits above as reflecting a general reduction in the capacity of their attention and working memory (Driver and Vuilleumier, 2001). An influential study by Peers et al. (2006) showed that dual tasks, which significantly tax attention and working memory capacity, cause a general biasing of attention to the right, similar to effects of low arousal (Peers et al., 2006). A recent study suggests that this rightward bias during dual-tasks particularly affects neglect patients, possibly due to their reduced attention/working memory capacity (Bellgrove et al., 2013).

5 THEORETICAL ACCOUNTS OF NONSPATIAL DEFICITS AND NONSPATIAL/SPATIAL INTERACTIONS

Compared to the numerous models accounting for the spatial deficits in neglect, there are far fewer models of nonspatial deficits that account for nonspatial/spatial interactions, likely because these deficits have only been discovered or re-examined in the last 20 years. We briefly review two models, one that proposes that neglect damages alertness and sustained attention mechanisms that are largely unique to the right hemisphere, and another that proposes that patients with neglect have a reduced attentional capacity. Like models of spatial deficits, it should be noted that these models of nonspatial deficits are not mutually exclusive.

5.1 Right Hemisphere Is Specialized for Alertness and Sustained Attention

Though patients' nonspatial symptoms are apparent on a variety of tasks, one aspect that they all have in common is they require maintenance of adequate levels of alertness and task engagement. One of the key neurotransmitters involved in arousal and alertness is norepinephrine, which is primarily synthesized in the locus coeruleus in the brainstem and has projections throughout the cortex. Damage to the right hemisphere may be particularly detrimental to alertness because the right hemisphere has shown to have a higher number of noradrenergic receptors (particularly in inferior parietal regions) compared to the left hemisphere (Foote et al., 1983).

Regarding the interaction of nonspatial and spatial deficits, this model contends that reductions in alertness are associated with decreased activity in right inferior frontoparietal regions (alertness network). This alertness network has shown to partially overlap/interact with more dorsal frontoparietal regions involved in goal-directed spatial attention (e.g., frontal eye fields, IPS), particularly overlapping in lateral frontal regions (He et al., 2007). The mechanism of this interaction and reasons why these networks interact is currently unknown and a key question for future neglect research. The result of this decreased interaction between the alertness network and the spatial attention network is an imbalance favoring the left hemisphere, resulting in a rightward spatial bias (for a more in-depth review of these mechanisms, see Corbetta and Shulman, 2011).

Right hemisphere dominance in the regulation of alertness and the interaction between alertness and spatial bias has also been demonstrated in healthy individuals as well as those with attention deficit hyperactivity disorder (ADHD, see Klingberg et al., 2005). This suggests that the alertness–spatial attention interaction is a general characteristic of the brain rather than a neglect-specific phenomenon. For example, studies in healthy individuals show a slight tendency to attend to the left side of an object (Nicholls et al., 1999) and that this slight leftward bias is reduced or shifted to the right under conditions of low arousal (Bellgrove et al., 2004; Manly et al., 2005; Matthias et al., 2009) or when taxing sustained attention (Newman et al., 2013;

Russell et al., 2004). Further, recent studies suggest that children with ADHD exhibit lateralized attention deficits similar to neglect (though typically smaller in magnitude) and that this is ameliorated by ADHD-targeted medications that boost the ability to sustain attention (Bellgrove et al., 2013).

5.2 Attentional Capacity

This model suggests that patients suffering from persistent spatial neglect have significantly reduced attentional capacity (Driver and Vuilleumier, 2001) (i.e., limited resources to perform attention-demanding tasks), which may underlie many of their nonspatial deficits such as a protracted attentional blink (Battelli et al., 2001; Husain et al., 1997; Robertson et al., 1998). This limited attentional capacity may affect goal-directed spatial attention mechanisms in an analogous manner as diminished alertness, however, with important differences. In particular, evidence suggests that attentional resources may be lateralized to right ventral frontoparietal regions that, as Corbetta and Shulman (2011) have recently demonstrated, interact with dorsal frontoparietal regions involved in spatial attention. Reduction in available attentional resources, as required in dual-task paradigms, may *decrease* right ventral frontoparietal (network subserving attentional resources) and dorsal frontoparietal (spatial attention) network interactions, producing increased rightward spatial bias. A key difference is that the attentional capacity model better accounts for the exacerbation of lateralized attention biases in patients during dual-task performance. In contrast, the alertness model would suggest that dual-task performance, which is significantly more stressful/arousing than single-task performance, would be associated with lesser rather than greater rightward spatial bias (George et al., 2008).

Though future work is imperative to better characterize these models, particularly with regard to the mechanisms of the interactions between nonspatial and spatial attention, even in their current form they highlight the importance of nonspatial–spatial interactions in understanding and treating neglect.

6 TREATMENTS FOR NEGLECT

Because of the disability associated with persistent neglect, there is a pressing need to develop effective treatments. In particular, neglect is associated with poor motor recovery, higher disability and poor response to rehabilitation in general (Buxbaum et al., 2004; Cherney et al., 2001; Katz et al., 1999; Paolucci et al., 2001). Compared to other patient groups with similar lesion extent, patients with neglect consistently score lower at both admission and discharge on established measures of functional ability, and activities of daily living (Denes et al., 1982; Jehkonen et al., 2001; Kalra et al., 1997). Patients with neglect represent a considerable challenge to rehabilitation efforts as, compared to others with acquired brain injury, they demonstrate significantly more denial (anosagnosia; Adair et al., 1995) or apathy toward their deficits.

Though several treatment approaches have been developed over the last 30-years (for a review, see Luauté, 2006), these approaches have collectively shown limited success. Furthermore, the majority of treatment studies have judged treatment success as the amelioration of spatial deficits only, largely ignoring nonspatial deficits. Because nonspatial deficits are a fundamental aspect of chronic neglect and may underlie (and perpetuate) spatial deficits, we argue and provide evidence that addressing these deficits first or in concert with spatial deficits may produce better treatment outcomes. Below we review several neglect spatial and nonspatial treatments and suggest ways that these treatments can be developed and intelligently combined to produce better outcomes in patients suffering from neglect.

6.1 Treatments That Target Spatially Lateralized Cognitive Mechanisms

The most effective neglect therapies to emerge that have targeted spatially lateralized mechanisms have been visual scanning training (Pizzamiglio et al., 1990; Weinberg et al., 1977) and prism adaptation (Rossetti et al., 1998). Some have argued that treatments such as vestibular stimulation, contralesional limb activation, optokinetic stimulation, and neck muscle vibration also directly shift lateralized spatial awareness, though it could be argued that their improvements simply stem from enhanced alertness or general engagement of the right hemisphere. Furthermore, the evidence of the long-term effectiveness of these treatments is less clear.

Visual scanning training is one of the oldest and most commonly used approaches to treat neglect. The aim of visual scanning training is to have patients actively and consciously pay attention to stimuli on the contralesional side during various detection, reading, writing, and copying tasks. The advantages of this training are that it has shown significant improvements when used for an extended period (e.g., 28 h over 4 weeks) (Weinberg et al., 1979). However, its therapeutic effects have shown quite a bit of individual variation and may not be appropriate with patients with more severe issues with deficit awareness (Adair et al., 1995). Further, others have questioned the ability of scanning training to generalize outside the training environment (Robertson and Halligan, 1999).

Compared to visual scanning training, prism adaptation training sessions are much shorter (20 min session) and rely more on a "bottom-up" mechanism. Prism adaptation treatments involve the patient learning to accurately point to targets (50 trials or more) while wearing right-deviating prisms (which feels like one is reaching to the left side to hit a right target). The therapeutic effect (e.g., improved ability to move to contralesional space) occurs after the prisms are removed and can accumulate after performing many sessions over a period of weeks. Though prism adaptation has shown to consistently improve spatial aiming in contralesional space, it may not affect perceptual or representational aspects of neglect (Barrett et al., 2012). Together, these treatments targeting spatially lateralized deficits offer some relief for patients suffering from neglect. However, on their own, they are relatively incomplete and offer only limited prospects for recovery of function.

6.2 Treatments That Target Hemispheric Asymmetry

Over the last 15-years, several studies have utilized noninvasive brain stimulation (e.g., TMS) in attempts to re-balance hemispheric asymmetries in excitability and improve symptoms of neglect. One of the first reported studies by Oliveri and colleagues (1999) used TMS to temporarily deactivate left posterior parietal regions and found that this lessened the neglect symptom of extinction, the phenomenon where patients with unilateral brain damage fail to report a stimulus delivered to the side contralateral to the lesion when an ipsilateral stimulus is delivered simultaneously (Oliveri et al., 2001). More recent TMS studies targeting similar regions in patients with neglect have utilized higher frequency trains of pulses (continuous theta burst TMS) over multiple sessions in an attempt to create longer-lasting deactivation of the intact posterior parietal regions (Koch et al., 2012). Indeed, these studies have shown both significant improvements in standard neglect batteries (which assess spatially lateralized deficits) and in daily functioning. Though promising, it is still unclear if these effects can be sustained and if this approach can also ameliorate patients' nonspatially lateralized deficits.

6.3 Treatments That Target Nonspatially Lateralized Mechanisms

At this point it should be clear that there are several reasons to specifically target nonspatially lateralized deficits in the treatment of neglect. First, treatments that target nonspatially lateralized mechanisms, such as sustained attention would potentially benefit most patients, as these deficits affect nearly all patients suffering from persistent neglect (DeGutis and Van Vleet, 2010). Also, treating sustained attention deficits may enable patients to be more alert, fully engaged, and derive greater benefit from other treatments and therapies (e.g., occupational therapy). Second, treating nonspatial attention deficits may guard against the re-emergence of neglect symptoms, such as when a recovered patient is experiencing low arousal or decreased attentional capacity. Finally, training to improve nonspatial deficits may help re-balance spatially lateralized attention mechanisms, which may make subsequent training of spatial attention (e.g., prism adaptation training) more effective. Below we briefly review current treatments that target nonspatial deficits and suggest future directions for the development of more effective treatments for neglect.

6.3.1 Pharmacological Interventions

Pharmacological interventions for neglect have shown some success in treating deficits in alertness, although results have been generally less successful than behavioral treatments (e.g., prisms, sustained attention training). These studies have examined the effects of these interventions to improve alertness and/or spatial attention (Buxbaum et al., 2004; Danckert et al., 2007).

Despite mixed results in prior studies examining the effects of dopaminergic agonists to treat neglect (Barrett et al., 1999; Fleet et al., 1987; Geminiani et al., 1998; Grujic et al., 1998), a recent study examining rotigotine, a complete dopamine agonist, was associated with a significant increase in the number of contralesional targets identified in the Mesulam shape cancellation task, as well as a decrease in the pathological rightward spatial bias (Danckert et al., 2007). However, rotigotine did not affect performance on measures of working memory, sustained attention or motor performance. Analogous results obtained in a rodent model of neglect suggest that beneficial effects of dopaminergic agonists in neglect are brain-location-specific (Van Vleet et al., 2003), therefore systemic administration may produce mixed results.

Similarly, administration of the noradrenergic agonist, guanfacine, a selective alpha 2A receptor agonist has been shown to be useful for treating alertness impairments in patients with neglect (Buxbaum et al., 2004). In two patients with spared right prefrontal cortex, guanfacine extended the time spent searching for relevant targets resulting and an increase in the number of targets found. A third patient with damage to the right prefrontal/inferior frontal cortex and neglect did not benefit from the drug. In general, while drug therapies have shown promise, their effects may be too nonspecific with the goal of treatment to simply increase the baseline level of alertness rather than promoting greater intrinsic regulation (i.e., do not specifically address the core mechanisms of neglect dysfunction). Further, drug therapies may be dependent on the functional integrity of remaining brain areas and may not be suitable for a large number of patients with neglect. Finally, drug therapies often produce unwanted side effects and may negatively interact with other medications.

6.3.2 Behavioral Treatments

One of the first reported therapist-administered behavioral treatments to target nonspatial deficits in neglect employed strategies that teach patients to increase alertness through periodic self instruction (e.g., "attend") (Gorgoraptis et al., 2012; Robertson et al., 1995). While these methods produced improvements in spatial attention, they rely on adequate recall of the behavioral strategy, which may not be conducive for patients with deficit awareness issues, and may not generalize beyond the training environment (Robertson and Halligan, 1999).

As a result of these concerns, computerized behavioral training methods have largely eclipsed top-down, therapist-administered treatments. Computerized treatments that target nonspatial deficits in neglect have taken a distinctly different approach, providing systematic and adaptive challenges tailored to individual patient's specific level of deficit. This bottom-up approach to treatment (i.e., no explicit strategy required) provides many hundreds to several thousands of learning trials presented within multiple (albeit virtual) contexts to more fully engage natural mechanisms of plasticity. In general, computerized treatments to improve nonspatial deficits have targeted sustained attention or intrinsic alertness and have exploited two well-characterized properties of the brain's alertness-control machinery: *tonic*

and *phasic* alertness. As mentioned previously, Tonic alertness refers to the ongoing state of intrinsic readiness that fluctuates on the order of minutes to hours, and is intimately involved with sustaining attention and also provides the cognitive tone necessary for performing more complicated functions such as working memory and executive control (Harvey et al., 1995; Matthias et al., 2010). In contrast, phasic alertness is the rapid modulation in alertness due to any briefly engaging event, and is vital for operations such as orienting and selective attention (Matthias et al., 2010).

To improve tonic alertness, computerized interventions for neglect have required patients to maintain attentional engagement over prolonged time periods. For example, an intervention referred to as AIXTENT (Sturm et al., 2006; Thimm et al., 2006) challenges individuals with neglect to continuously drive a virtual car while responding to cues to slow down (e.g., virtual traffic lights). Studies of AIXTENT in individuals with neglect have shown benefit. In one study, six out of seven neglect patients improved on at least one spatial neglect test (e.g., line bisection, cancellation tasks, visual search tasks, drawing tasks); improvements persisted for 4 weeks after training was terminated in two patients. Further, for those patients showing behavioral improvement, neuroimaging revealed partial restoration of the right hemisphere functional network known to subserve intrinsic alertness in healthy individuals, especially in the right dorsolateral or medial frontal cortex. Individuals that did not improve showed an increase of activation only in the left hemisphere, suggesting that training did not fully re-engage the damaged hemisphere in some patients.

In contrast to attempts to enhance tonic alertness, experimental interventions aimed at improving the efficiency of phasic alertness in neglect have utilized extrinsic, unexpected alerting events (e.g., unexpected tone) (Robertson et al., 1998). However, due to the short-acting effect of extrinsic alerting and the close relationship between phasic and tonic alertness, recent studies have examined phasic alertness in the context of tonic alertness, and thus utilize paradigms that require continual monitoring of successive stimuli for behaviorally relevant events (e.g., phasic spike in alertness to infrequent and unexpected appearance of a target stimulus) (DeGutis and Van Vleet, 2010a; Sturm et al., 2006; Thimm et al., 2006; Van Vleet and DeGutis, 2013). This top-down approach to phasic alertness may engage similar but distinct mechanisms (Singh-Curry and Husain, 2009) from bottom-up approaches. Electrophysiological studies have shown that bottom-up approaches may have a frontal source (Comerchero and Polich, 1999), whereas top-down approaches may have a more posterior, parietal source (Herrmann and Knight, 2001).

A recent series of treatment studies from our lab using a computer-based task that targets *both* tonic and phasic alertness (tonic and phasic alertness training, TAPAT) has shown promising results (DeGutis and Van Vleet, 2010a; Van Vleet and DeGutis, 2013). TAPAT was designed to challenge patients to better intrinsically sustain attention via prolonged training epochs (3×12-min blocks per session). TAPAT training involves performing visual and auditory continuous performance tasks with key elements to foster sustained attention. First, the tasks employed jittered interstimulus intervals, shown to improve response control in other clinical

populations, such as ADHD (Bouret and Sara, 2005; Wodka et al., 2009). The training also included numerous rich, novel and colorful stimuli (particularly in the visual TAPAT) to further engage attention (Schultz et al., 1997). Further, participants were required to respond via button press to frequent and centrally presented images or tones while trying to inhibit their response to an infrequent and randomly presented target stimulus (a unique target image or target tone was committed to memory prior to each 12-min training epoch), similar to other go-no-go paradigms (Comerchero and Polich, 1999; Robertson et al., 1997a,b). The unexpected presentation of the target image (or tone), which informed participants to inhibit the execution of the pre-potent motor response, was particularly salient (i.e., producing a strong phasic modulation in alertness) (Aston-Jones and Cohen, 2005). Finally, all stimuli in TAPAT were presented at central fixation, which ensured that patients with visual field deficits could also benefit.

Following only limited training (5 h over 9 days), patients with neglect improved their intrinsic alertness as reflected in improvements in accuracy on go and/or no-go trials in all but 2 of 20 patients. Further, improvements in target accuracy (i.e., inhibitory control/phasic alertness) across TAPAT training was significantly correlated with improvements on sensitive measures of spatial attention following only limited training (5 h over 9 days) (DeGutis and Van Vleet, 2010a; Van Vleet and DeGutis, 2013). Specifically, individuals with neglect that trained on TAPAT versus a spatial search training task (utilizing the same stimuli used in TAPAT) showed group-level performance improvements on a sensitive conjunction search task (List et al., 2008); post-training, the time required to locate targets on the left versus the right side of the search array was not different. Benefits in spatial attention (i.e., absence of spatial bias) were also evident on an alternate, novel conjunction search array and an adaptive landmark task in patients that completed TAPAT training versus spatial search training. These effects are notable as it clearly demonstrates that patients with neglect are capable of re-regulating intrinsic alertness, thereby normalizing spatial attention. Figure 1 shows performance from a representative patient on the conjunction search task, delivered at the end of each TAPAT training session and daily for several weeks post-training in this case. The distribution shows a clear evolution of the treatment effect over several sessions and its impact following 2 weeks without additional training.

Finally, as mentioned, all training was conducted at central fixation; thus, the results show a clear transfer of training-related benefit (i.e., greater intrinsic alertness) to untrained tasks of spatial attention. In addition, TAPAT training versus control resulted in normative performance (i.e., performance was not different from an age-matched healthy control group) on a nonspatially lateralized, visual working memory updating task (attentional blink) (Husain et al., 1997; Pattyn et al., 2008; Van Vleet and Robertson, 2006). Outcomes on all measures examined were most improved in those patients with worse neglect at baseline.

Taken together, these results support models of neglect that advance the critical role of alertness and sustained attention to affect not only spatial attention, but also other nonspatial functions such as selective attention/attention to transient events.

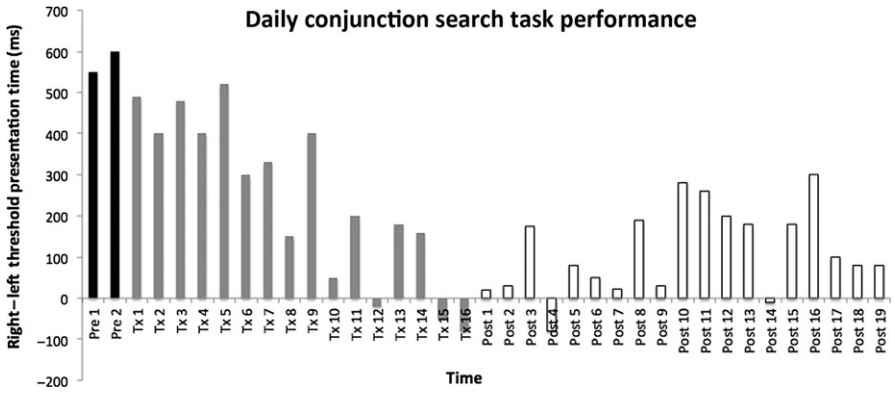

FIGURE 1

Daily performance on a sensitive conjunction search task (List et al., 2008) for a representative patient with neglect following right parietal damage (DW). Figures show performance pre, during and post TAPAT training. Differences in threshold presentation times (TPT) for right targets–left targets are shown. A score of zero represents symmetrical target detection, positive values represent a rightward bias and negative values leftward bias.

The results from behavioral treatment studies that target nonspatial deficits clearly show the influence of plasticity, as these nonspatial mechanisms are shown to be remediable rather than permanently damaged (even in very chronic patients; Van Vleet and DeGutis, 2013).

7 FUTURE DIRECTIONS

As the other chapters in this volume detail, many studies now show that the processing machinery of the brain is plastic, remodeled throughout life by learning and experience, enabling the strengthening of skills or abilities or the acquisition of new skills, at any age. These studies show that continual engagement in goal-directed and rewarded behaviors is advantageous to sustaining efficient brain operations, engaging targeted brain structures and causing the release of specific neurotransmitters that enable, amplify, and shape plasticity in the adult brain. This rich body of literature offers numerous insights that can be applied to the proper development of treatment methods to more efficiently drive the extensive, requisite, and generalized changes required for significantly improving neurological syndromes such as neglect (see Chapter 9).

As discussed throughout this chapter, recent advances in knowledge regarding the influence of nonspatially lateralized deficits on spatial attention in neglect require future rehabilitation efforts to consider novel approaches that directly address these functions. The successes of such simple nonspatial treatments such as TAPAT are promising, but represent only the beginning of this exciting area of rehabilitation

research. For example, a number of studies have shown that task complexity and spatial working memory load contribute to the magnitude of spatial deficits in neglect. Thus, intervention strategies that target spatial working memory capacity for example, shown effective in other clinical populations (Klingberg et al., 2005), may be beneficial for patients suffering from neglect (see Striemer et al., 2013 for expanded discussion). Additionally, first person action video game training has shown to significantly enhance selective attention and detection of transient events in healthy individuals. By modifying these games for patients suffering from neglect (e.g., slowing down the action and making adjustments for contralesional hypokinesia), it may be possible to boost arousal and potentially improve nonspatial and spatial symptoms. In addition, future research on the nature of spatial–nonspatial attention interactions will enable the development of more effective and targeted treatments for neglect.

Finally, two additional considerations for future development of treatments for neglect. First, treatments that more comprehensively and completely engage nonspatial mechanisms may prove more useful or longer lasting if combined with spatial therapies (e.g., prism adaptation to also improve directional hypokinesia). Combined therapies may also prove synergistic. As discussed, a number of recent studies have shown benefits in spatial attention following TMS of the intact hemisphere. Combined computerized training targeting nonspatially lateralized deficits (e.g., sustained attention) may bolster these TMS effects, driving behaviorally specific alterations in the underlying neural mechanisms. Alternatively, computer-based training paired with transcranial direct current stimulation that excites peri-lesional right-sided regions and dampens homologous regions in the left hemisphere may produce more pronounced and longer-lasting improvements in neglect symptoms.

Second, future rehabilitation efforts should also consider the "real-world" implications of treatment. For example, "statistical learning" deficits, (Shaqiri et al., 2013) or poor ability to implicitly ascertain properties of a particular environment (i.e., appreciate elements that occur more often than others), can affect decision making capacity in neglect. The statistical learning model suggests that neglect is a breakdown in the accurate construction of mental models of the environment, in which future predictions or decisions are based. This multilevel conceptualization of neglect takes into account a number of nonspatially lateralized deficits (e.g., temporal misperceptions, spatial working memory deficits) that contribute to functional disability. Consideration of the cumulative effects of nonspatially lateralized dysfunctions in neglect can inspire the development of more comprehensive rehabilitation interventions designed to improve functional abilities. For example, treatments that target deficits in temporal perception and spatial working memory may also improve patient's future predictions about the location of relevant events. Ultimately, improvements in functional ability or transfer of training-related benefits to untrained real-word functions, is the most important aim of neglect rehabilitation. A multimodal, cognitive neuropsychological approach, which capitalizes on known properties of neuroplasticity is the best method to achieve this goal.

References

Adair, J.C., Na, D.L., Schwartz, R.L., Fennell, E.M., Gilmore, R.L., Heilman, K.M., 1995. Anosognosia for hemiplegia: test of the personal neglect hypothesis. Neurology 45, 2195–2199.

Appelros, P., Karlsson, G.M., Seiger, A., Nydevik, I., 2002. Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. J. Rehabil. Med. 34 (5), 215–220.

Aston-Jones, G., Cohen, J.D., 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu. Rev. Neurosci. 28, 403–450.

Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., Tesio, L., 2003. Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Bergego Scale. Arch. Phys. Med. Rehabil. 84 (1), 51–57.

Barrett, A.M., Crucian, G.P., Schwartz, R.L., Heilman, K.M., 1999. Adverse effect of dopamine agonist therapy in a patient with motor-intentional neglect. Arch. Phys. Med. Rehabil. 80 (5), 600–603.

Barrett, A.M., Goedert, K.M., Basso, J.C., 2012. Prism adaptation for spatial neglect after stroke: translational practice gaps. Nat. Rev. Neurol. 8 (10), 567–577.

Bartolomeo, P., Chokron, S., 1999. Left unilateral neglect or right hyperattention? Neurology 53 (9), 2023–2027.

Basso, G., Nichelli, P., Frassinetti, F., di Pellegrino, G., 1996. Time perception in a neglected space. Neuroreport 7, 2111–2114.

Battelli, L., Cavanagh, P., Intriligator, J., Tramo, M.J., Hénaff, M.A., Michèl, F., Barton, J.J., 2001. Unilateral right parietal damage leads to bilateral deficit for high-level motion. Neuron 32 (6), 985–995.

Bays, P.M., Singh-Curry, V., Gorgoraptis, N., Driver, J., Husain, M., 2010. Integration of goal- and stimulus-related visual signals revealed by damage to human parietal cortex. J. Neurosci. 30 (17), 5968–5978.

Bellgrove, M.A., Dockree, P.M., Aimola, L., Robertson, I.H., 2004. Attenuation of spatial attentional asymmetries with poor sustained attention. Neuroreport 15 (6), 1065–1069.

Bellgrove, M.A., Eramudugolla, R., Newman, D.P., Vance, A., Mattingley, J.B., 2013. Influence of attentional load on spatial attention in acquired and developmental disorders of attention. Neuropsychologia 51 (6), 1085–1093.

Bouret, S., Sara, S.J., 2005. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 28 (11), 574–582.

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., La Bua, V., Daniele, O., Fierro, B., 2003. 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. Neurosci. Lett. 336 (2), 131–133.

Buxbaum, L.J., Ferraro, M.K., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., et al., 2004. Hemispatial neglect: subtypes, neuroanatomy, and disability. Neurology 62 (5), 749–756.

Carter, A.R., Astafiev, S.V., Lang, C.E., Connor, L.T., Rengachary, J., Strube, M.J., et al., 2010. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Ann. Neurol. 67 (3), 365–375.

Cherney, L.R., Halper, A.S., Kwasnica, C.M., Harvey, R.L., Zhang, M., 2001. Recovery of functional status after right hemisphere stroke: relationship with unilateral neglect. Arch. Phys. Med. Rehabil. 82 (3), 322–328.

Comerchero, M.D., Polich, J., 1999. P3a and P3b from typical auditory and visual stimuli. Clin. Neurophysiol. 110 (1), 24–30.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3 (3), 201–215.
Corbetta, M., Shulman, G.L., 2011. Spatial neglect and attention networks. Annu. Rev. Neurosci. 34, 569–599.
Corbetta, M., Kincade, M.J., Lewis, C., Snyder, A.Z., Sapir, A., 2005. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat. Neurosci. 8 (11), 1603–1610.
Danckert, J., Ferber, S., 2006. Revisiting unilateral neglect. Neuropsychologia 44 (6), 987–1006.
Danckert, J., Ferber, S., Pun, C., Broderick, C., Striemer, C., Rock, S., Stewart, D., 2007. Neglected time: impaired temporal perception of multisecond intervals in unilateral neglect. J. Cogn. Neurosci. 19 (10), 1706–1720.
DeGutis, J., Van Vleet, T.M., 2010a. Tonic and phasic alertness training: a novel behavioral therapy to improve spatial and non-spatial attention in patients with hemispatial neglect. Front. Human Neurosci. 4, 1–16.
Delis, D.C., Robertson, L.C., Efron, R., 1986. Hemispheric specialization of memory for visual hierarchical stimuli. Neuropsychologia 24, 205–214.
Denes, G., Semenza, C., Stoppa, E., Lis, A., 1982. Unilateral spatial neglect and recovery from hemiplegia: a follow-up study. Brain 105, 543–552.
Di Russo, F., Aprile, T., Spitoni, G., Spinelli, D., 2008. Impaired visual processing of contralesional stimuli in neglect patients: a visual-evoked potential study. Brain 131 (3), 842–854.
Driver, J., Mattingley, J.B., 1998. Parietal neglect and visual awareness. Nat. Neurosci. 1 (1), 17–22.
Driver, J., Vuilleumier, P., 2001. Perceptual awareness and its loss in unilateral neglect and extinction. Cognition 79 (1–2), 39–88.
Duncan, J., Bundesen, C., Olson, A., Humphreys, G., Chavda, S., Shibuya, H., 1999. Systematic analysis of deficits in visual attention. J. Exp. Psychol. Gen. 128 (4), 450–478.
Eglin, M., Robertson, L.C., Knight, R.T., 1989. Visual search performance in the neglect syndrome. J. Cogn. Neurosci. 4, 372–381.
Fleet, W.S., Valenstein, E., Watson, R.T., Heilman, K.M., 1987. Dopamine agonist therapy for neglect in humans. Neurology 37 (11), 1765–1770.
Foote, S.L., Bloom, F.E., Aston-Jones, G., 1983. Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. Physiol. Rev. 63 (3), 844–914.
Geminiani, G., Bottini, G., Sterzi, R., 1998. Dopaminergic stimulation in unilateral neglect. J. Neurol. Neurosurg. Psychiatry 65 (3), 344–347.
George, M.S., Mercer, J.S., Walker, R., Manly, T., Brain, R., Buxbaum, L.J., et al., 2008. A demonstration of endogenous modulation of unilateral spatial neglect: the impact of apparent time-pressure on spatial bias. J. Int. Neuropsychol. Soc. 14 (1), 33–41.
Gorgoraptis, N., Mah, Y.H., Machner, B., Singh-Curry, V., Malhotra, P., Hadji-Michael, M., Husain, M., 2012. The effects of the dopamine agonist rotigotine on hemispatial neglect following stroke. Brain 135 (8), 2478–2491.
Grujic, Z., Mapstone, M., Gitelman, D.R., Johnson, N., Weintraub, S., Hays, A., et al., 1998. Dopamine agonists reorient visual exploration away from the neglected hemispace. Neurology 51 (5), 1395–1398.
Halligan, P.W., Fink, G.R., Marshall, J.C., Vallar, G., 2003. Spatial cognition: evidence from visual neglect. Trends Cogn. Sci. 7 (3), 125–133.
Harrington, D.L., Haaland, K.Y., Knight, R.T., 1998. Cortical networks underlying mechanisms of time perception. J. Neurosci. 18, 1085–1095.
Harvey, M., Milner, A.D., Roberts, R.C., 1995. An investigation of hemispatial neglect using the landmark task. Brain Cogn. 27, 59–78.

He, B.J., Snyder, A.Z., Vincent, J.L., Epstein, A., Shulman, G.L., Corbetta, M., 2007. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53 (6), 905–918.
Heilman, K.M., Schwartz, H.D., Watson, R.T., 1978. Hypoarousal in patients with the neglect syndrome and emotional indifference. Neurology 28 (3), 229–232.
Heilman, K.M., Bowers, D., Coslett, H.B., Whelan, H., Watson, R.T., 1985. Directional hypokinesia: prolonged reaction times for leftward movements in patients with right hemisphere lesions and neglect. Neurology 35, 855–859.
Heilman, K.M., Bowers, D., Valenstein, E., Watson, R.T., 1987. Hemispace and hemispatial neglect. Adv. Psychol. 45, 115–150.
Heilman, K.M., Bowers, D., Valenstein, E., Watson, R.T., 1993. Disorders of visual attention. Baillieres Clin. Neurol. 2 (2), 389–413.
Herrmann, C.S., Knight, R.T., 2001. Mechanisms of human attention: event-related potentials and oscillations. Neurosci. Biobehav. Rev. 25 (6), 465–476.
Hjaltason, H., Tegner, R., Tham, K., Levander, M., Ericson, K., 1996. Sustained attention and awareness of disability in chronic neglect. Neuropsychologia 34 (12), 1229–1233.
Hornak, J., 1992. Ocular exploration in the dark by patients with visual neglect. Neuropsychologia 30 (6), 547–552.
Husain, M., Rorden, C., 2003. Non-spatially lateralized mechanisms in hemispatial neglect. Nat. Rev. Neurosci. 4 (1), 26–36.
Husain, M., Shapiro, K., Martin, J., Kennard, C., 1997. Abnormal temporal dynamics of visual attention in spatial neglect patients. Nature 385 (6612), 154–156.
Husain, M., Mannan, S., Hodgson, T., Wojciulik, E., Driver, J., Kennard, C., 2001. Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. Brain 124 (5), 941–952.
Ishiai, S., Koyama, Y., Seki, K., Hayashi, K., Izumi, Y., 2006. Approaches to subjective midpoint of horizontal lines in unilateral spatial neglect. Cortex 42 (5), 685–691.
Jehkonen, M., Ahonen, J.P., Dastidar, P., Koivisto, A.M., Laippala, P., Vilkki, J., Molnar, G., 2001. Predictors of discharge to home during the first year after hemisphere stroke. Acta Neurol. Scand. 104 (3), 136–141.
Johnston, C.W., Diller, L., 1986. Exploratory eye movements and visual hemi-neglect. J. Clin. Exp. Neuropsychol. 8, 93–101.
Kalra, L., Perez, I., Gupta, S., Wittink, M., 1997. The influence of visual neglect on stroke rehabilitation. Stroke 28 (7), 1386–1391.
Katz, N., Hartman-Maeir, A., Ring, H., Soroker, N., 1999. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. Arch. Phys. Med. Rehabil. 80 (4), 379–384.
Kinsbourne, M., 1977. Hemi-neglect and hemisphere rivalry. Adv. Neurol. 18, 41–49.
Kinsbourne, M., Bruce, R., 1987. Shift in visual laterality within blocks of trials. Acta Psychol. 66 (2), 139–155.
Klingberg, T., Fernell, E., Olesen, P.J., Johnson, M., Gustafsson, P., Dahlström, K., Westerberg, H., 2005. Computerized training of working memory in children with ADHD-A randomized, controlled trial. J. Am. Acad. Child Adolesc. Psychiatry 44 (2), 177–186.
Koch, G., Oliveri, M., Cheeran, B., Ruge, D., Gerfo, E.L., Salerno, S., et al., 2008a. Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain 131 (12), 3147–3155.
Koch, G., Del Olmo, M.F., Cheeran, B., Schippling, S., Caltagirone, C., Driver, J., Rothwell, J.C., 2008b. Functional interplay between posterior parietal and ipsilateral

motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward contralateral space. J. Neurosci. 28 (23), 5944–5953.
Koch, G., Bonnì, S., Giacobbe, V., Bucchi, G., Basile, B., Lupo, F., et al., 2012. Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. Neurology 78, 24–30.
Kristjánsson, Á., Vuilleumier, P., Malhotra, P., Husain, M., Driver, J., 2005. Priming of color and position during visual search in unilateral spatial neglect. J. Cogn. Neurosci. 17 (6), 859–873.
Luauté, J., Michel, C., Rode, G., Pisella, L., Jacquin-Courtois, S., Costes, N., Cotton, F., et al., 2006. Functional anatomy of the therapeutic effects of prism adaptation on left neglect. Neurology 66 (12), 1859–1867.
Lazar, R.M., Fitzsimmons, B.F., Marshall, R.S., Berman, M.F., Bustillo, M.A., Young, W.L., et al., 2002. Reemergence of stroke deficits with midazolam challenge. Stroke 33 (1), 283–285.
List, A., Brooks, J.L., Esterman, M., Flevaris, A.V., Landau, A.N., Bowman, G., Stanton, V., Van Vleet, T.M., Robertson, L.C., Schendel, K., 2008. Visual hemispatial neglect, reassessed. J. Int. Neuropsychol. Soc. 14, 243–256.
List, A., Landau, A.N., Brooks, J.L., Flevaris, A.V., Fortenbaugh, F.C., Esterman, M., et al., 2011. Shifting attention in viewer-and object-based reference frames after unilateral brain injury. Neuropsychologia 49 (7), 2090–2096.
Malhotra, P., Jäger, H.R., Parton, A., Greenwood, R., Playford, E.D., Brown, M.M., et al., 2005. Spatial working memory capacity in unilateral neglect. Brain 128 (2), 424–435.
Malhotra, P., Coulthard, E.J., Husain, M., 2009. Role of right posterior parietal cortex in maintaining attention to spatial locations over time. Brain 132 (3), 645–660.
Manly, T., Dobler, V.B., Dodds, C.M., George, M.A., 2005. Rightward shift in spatial awareness with declining alertness. Neuropsychologia 43 (12), 1721–1728.
Matthias, E., Bublak, P., Costa, A., Müller, H.J., Schneider, W.X., Finke, K., 2009. Attentional and sensory effects of lowered levels of intrinsic alertness. Neuropsychologia 47 (14), 3255–3264.
Matthias, E., Bublak, P., Müller, H.J., Schneider, W.X., Krummenacher, J., Finke, K., 2010. The influence of alertness on spatial and nonspatial components of visual attention. J. Exp. Psychol. Hum. Percept. Perform. 36 (1), 38–56.
Mattingley, J.B., Husain, M., Rorden, C., Kennard, C., Driver, J., 1998. Motor role of human inferior parietal lobe revealed in unilateral neglect patients. Nature 392 (6672), 179–182.
Medina, J., et al., 2009. Neural substrates of visuospatial processing in distinct reference frames: evidence from unilateral spatial neglect. J. Cogn. Neurosci. 21 (11), 2073–2084.
Mesulam, M., 1981. A cortical network for directed attention and unilateral neglect. Ann. Neurol. 10 (4), 309–325.
Mesulam, M.M., 1990. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann. Neurol. 28 (5), 597–613.
Newman, D.P., O'Connell, R.G., Bellgrove, M.A., 2013. Linking time-on-task, spatial bias and hemispheric activation asymmetry: a neural correlate of rightward attention drift. Neuropsychologia 51 (7), 1215–1223.
Nicholls, M.E., Bradshaw, J.L., Mattingley, J.B., 1999. Free-viewing perceptual asymmetries for the judgement of brightness, numerosity and size. Neuropsychologia 37 (3), 307–314.

Oliveri, M., Rossini, P.M., Traversa, R., Cicinelli, P., Filippi, M.M., Pasqualetti, P., Tomaiuolo, F., Caltagirone, C., 1999. Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. Brain 122 (9), 1731–1739.

Oliveri, M., Bisiach, E., Brighina, F., Piazza, A., La Bua, V., Buffa, D., et al., 2001. rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. Neurology 57, 1338–1340.

Paolucci, S., Grasso, M.G., Antonucci, G., Bragoni, M., Troisi, E., Morelli, D., et al., 2001. Mobility status after inpatient stroke rehabilitation: 1-year follow-up and prognostic factors. Arch. Phys. Med. Rehabil. 82 (1), 2–8.

Pattyn, N., Neyt, X., Henderickx, D., Soetens, E., 2008. Psychophysiological investigation of vigilance decrement: boredom or cognitive fatigue? Physiol. Behav. 93 (1), 369–378.

Pedersen, P.M., Jørgensen, H.S., Nakayama, H., Raaschou, H.O., Olsen, T.S., 1997. Hemineglect in acute stroke-incidence and prognostic implications: the Copenhagen Stroke Study. Am. J. Phys. Med. Rehabil. 76 (2), 122–127.

Peers, P.V., Cusack, R., Duncan, J., 2006. Modulation of spatial bias in the dual task paradigm: evidence from patients with unilateral parietal lesions and controls. Neuropsychologia 44 (8), 1325–1335.

Pisella, L., Berberovic, N., Mattingley, J.B., 2004. Impaired working memory for location but not for colour or shape in visual neglect: a comparison of parietal and non-parietal lesions. Cortex 40 (2), 379–390.

Pizzamiglio, L., Frasca, R., Guariglia, C., Incoccia, C., Antonucci, G., 1990. Effect of optokinetic stimulation in patients with visual neglect. Cortex 26 (4), 535–541.

Posner, M.I., Walker, J.A., Friedrich, F.J., Rafal, R.D., 1984. Effects of parietal injury on covert orienting of attention. J. Neurosci. 4 (7), 1863–1874.

Rees, G., Wojciulik, E., Clarke, K., Husain, M., Frith, C., Driver, J., 2000. Unconscious activation of visual cortex in the damaged right hemisphere of a parietal patient with extinction. Brain 123 (8), 1624–1633.

Ringman, J.M., Saver, J.L., Woolson, R.F., Clarke, W.R., Adams, H.P., 2004. Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. Neurology 63 (3), 468–474.

Robertson, I.H., 2001. Do we need the "lateral" in unilateral neglect? Spatially nonselective attention deficits in unilateral neglect and their implications for rehabilitation. Neuroimage 14 (1), S85–S90.

Robertson, I.H., Halligan, P.W., 1999. Spatial Neglect: A Clinical Handbook for Diagnosis and Treatment. Psychology Press, Hove.

Robertson, L.C., Lamb, M.R., Knight, R.T., 1988. Effects of lesions of temporal-parietal junction on perceptual and attentional processing in humans. J. Neurosci. 8, 3757–3769.

Robertson, I.H., Tegnér, R., Tham, K., Lo, A., Nimmo-Smith, I., 1995. Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. J. Clin. Exp. Neuropsychol. 17 (3), 416–430.

Robertson, I.H., Manly, T., Beschin, N., Daini, R., Haeske-Dewick, H., Homberg, V., Hehkonen, M., Pizzamiglio, G., Shiel, A., Weber, E., 1997a. Auditory sustained attention is a marker of unilateral spatial neglect. Neuropsychologia 35 (12), 1527–1532.

Robertson, I.H., Manly, T., Andrade, J., Baddeley, B.T., Yiend, J., 1997b. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia 35 (6), 747–758.

Robertson, I.H., Mattingley, J.B., Rorden, C., Driver, J., 1998. Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. Nature 395 (6698), 169–172.

Rorden, C., Hjaltason, H., Fillmore, P., Fridriksson, J., Kjartansson, O., Magnusdottir, S., Karnath, H.O., 2012. Allocentric neglect strongly associated with egocentric neglect. Neuropsychologia 50 (6), 1151–1157.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., Perenin, M.T., 1998. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 395 (6698), 166–169.

Russell, C., Malhotra, P., Husain, M., 2004. Attention modulates the visual field in healthy observers and parietal patients. Neuroreport 15 (14), 2189–2193.

Samuelsson, H., Hjelmquist, E., Jensen, C., Ekholm, S., Blomstrand, C., 1998. Nonlateralized attentional deficits: an important component behind persisting visuospatial neglect? J. Clin. Exp. Neuropsychol. 20 (1), 73–88.

Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275 (5306), 1593–1599.

Shaqiri, A., Anderson, B., Danckert, J., 2013. Statistical learning as a tool for rehabilitation in spatial neglect. Front. Hum. Neurosci. 7: 224.

Shomstein, S., Kimchi, R., Hammer, M., Behrmann, M., 2010. Perceptual grouping operates independently of attentional selection: evidence from hemispatial neglect. Atten. Percept. Psychophys. 72 (3), 607–618.

Silver, M.A., Ress, D., Heeger, D.J., 2005. Topographic maps of visual spatial attention in human parietal cortex. J. Neurophysiol. 94 (2), 1358–1371.

Singh-Curry, V., Husain, M., 2009. The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. Neuropsychologia 47 (6), 1434–1448.

Snow, J.C., Mattingley, J.B., 2006. Goal-driven selective attention in patients with right hemisphere lesions: how intact is the ipsilesional field? Brain 129 (1), 168–181.

Snyder, J.J., Chatterjee, A., 2004. Spatial-temporal anisometries following right parietal damage. Neuropsychologia 42 (12), 1703–1708.

Spinelli, D., Guariglia, C., Massironi, M., Pizzamiglio, L., Zoccolotti, P., 1990. Contrast sensitivity and low spatial frequency discrimimation in hemi-neglect patients. Neuropsychologia 28 (7), 727–732.

Stone, S.P., Halligan, P.W., Greenwood, R.J., 1993. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. Age Ageing 22 (1), 46–52.

Striemer, C., Ferber, S., Danckert, J., 2013. Spatial working memory deficits represent a core challenge for rehabilitating neglect. Front. Hum. Neurosci. 7, 334.

Sturm, W., Thimm, M., Kust, J., Karbe, H., Fink, G.R., 2006. Alertness-training in neglect: behavioral and imaging results. Restor. Neurol. Neurosci. 24 (4–6), 371–384.

Swisher, J.D., Halko, M.A., Merabet, L.B., McMains, S.A., Somers, D.C., 2007. Visual topography of human intraparietal sulcus. J. Neurosci. 27 (20), 5326–5337.

Thimm, M., Fink, G.R., Kust, J., Karbe, H., Sturm, W., 2006. Impact of alertness-training in spatial neglect: a behavioral and fMRI study. Neuropsychologia 44 (7), 1230–1246.

Treisman, A., Gelade, G., 1980. A feature-integration theory of attention. Cogn. Psychol. 12, 97–136 [PubMed: 7351125].

Van Vleet, T.M., DeGutis, J., 2013. Cross-training in hemispatial neglect: auditory sustained attention training ameliorates visual attention deficits. Cortex 49 (3), 679–690. http://dx.doi.org/10.1016/j.cortex.2012.03.020.

Van Vleet, T.M., Robertson, L.C., 2006. Cross-modal interactions in time and space: auditory influence on visual attention in hemispatial neglect. J. Cogn. Neurosci. 18 (8), 1368–1379.
Van Vleet, T.M., Robertson, L.C., 2009. Implicit representation and explicit detection of features in patients with hemi-spatial neglect. Brain 132, 1889–1897.
Van Vleet, T.M., Heldt, S.A., Corwin, J.V., Reep, R.L., 2003. Infusion of apomorphine into the dorsocentral striatum produces acute drug-induced recovery from neglect produced by unilateral medial agranular cortex lesions in rats. Behav. Brain Res. 143 (2), 147–157.
Van Vleet, T.M., Hoang-duc, A.K., DeGutis, J., Robertson, L.C., 2011. Modulation of non-spatial attention and the global/local processing bias. Neuropsychologia 49 (3), 352–359.
Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., Vuilleumier, P., 2010. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. Brain 133 (3), 880–894.
Vuilleumier, P., Hester, D., Assal, G., Regli, F., 1996. Unilateral spatial neglect recovery after sequential strokes. Neurology 46, 184–189.
Watson, R.T., Miller, B.D., Heilman, K.M., 1977. Evoked potential in neglect. Arch. Neurol. 34 (4), 224–227.
Weinberg, J., Diller, L., Gordon, W.A., Gerstman, L.J., Lieberman, A., Lakin, P., et al., 1977. Visual scanning training effect on reading-related tasks in acquired right brain damage. Arch. Phys. Med. Rehabil. 58 (11), 479–486.
Weinberg, J., Diller, L., Gordon, W.A., Gerstman, L.J., Lieberman, A., Lakin, P., et al., 1979. Training sensory awareness and spatial organization in people with right brain damage. Arch. Phys. Med. Rehabil. 60 (11), 491–496.
Wodka, E.L., Simmonds, D.J., Mahone, E.M., Mostofsky, S.H., 2009. Moderate variability in stimulus presentation improves motor response control. J. Clin. Exp. Neuropsychol. 31 (4), 483–488.
Yokoyama, K., Jennings, R., Ackles, P., Hood, P., Boller, F., 1987. Lack of heart rate changes during an attention-demanding task after right hemisphere lesions. Neurology 37 (4), 624–630.
Yue, Y., Song, W., Huo, S., Wang, M., 2012. Study on the occurrence and neural bases of hemispatial neglect with different reference frames. Arch. Phys. Med. Rehabil. 93 (1), 156–162.