Hemispatial Neglect: Clinic, Pathogenesis, and Treatment

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Abstract

Hemispatial neglect is characterized by a failure of awareness on the side of space and body opposite the site of injury, has been extensively studied for its theoretical interest in revealing brain mechanisms of awareness and attention. More recently, it has become apparent that hemispatial neglect reflects not only damage of specific anatomical regions, but also the large-scale dysfunction of networks of brain regions specialized in attention, motor, and multimodal sensory processing. Finally, although previous studies showed that the symptoms of hemispatial neglect could be effectively, albeit transiently, improved by a variety of behavioral, pharmacological, and physical interventions, only recently have treatment studies begun to show long-lasting therapeutic effects. Future advances will require the integration of advanced brain imaging methods to identify abnormal brain circuitries and—in combination with sensory, cognitive, and neural stimulation—methods to modulate activity in those circuitries.

Keywords
- attention
- stroke
- networks
- rehabilitation
- TMS

Nearly 75 years have passed since the first description of hemispatial neglect.[1] Hemispatial neglect is the most common cognitive disorder following right hemisphere injuries. Patients with hemineglect manifest some of the most spectacular and unusual symptoms in neurology, such as shaving only half of their face, eating from only half of their plate, and apparently ignoring half of their body. These disorders of spatial and body awareness may be associated, but not always, with disorders of primary sensation of vision and/or touch. Abnormalities of spatial and body awareness can also be associated with problems of insight, such as a lack of concern about being ill (anosognosia), about being paralyzed (hemisomatognosia), or a denial of ownership of one's own body, at times attributing to someone else nearby (somatoparaphrenia).

In stroke, approximately 30% of all patients will manifest some signs of hemispatial neglect in the acute stage.[2] Neglect can also be present in cases of tumor, and more subtly in cases of acute trauma. By 3 months poststroke, the majority of patients have improved, and florid signs of neglect are rare. However, subtle signs can still be elicited,[3] and these deficits impact long-term outcome.[4–6] Any activity that requires attention to both sides of space, such as driving or working on a cluttered desk, will be affected by hemispatial neglect; similarly, lack of attention to the body contralateral to the stroke may significantly impair motor rehabilitation.

Because the syndrome is heterogeneous and includes perceptual, motor, sensory, and cognitive signs and symptoms, a good understanding of the underlying pathophysiology is critical to treat hemispatial neglect more effectively. Current interventions include compensatory strategies during activities of daily living (ADLs), pharmacological treatment of arousal disorders, and experimental treatments, both behavioral and through magnetic stimulation, aimed at improving the perceptual–motor spatial bias.

Clinical Case

A 58-year-old male truck driver developed confusion and left-sided weakness while at a barbecue with his family. He was brought to the hospital for evaluation against his wishes because he was convinced that nothing was amiss. On first

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appearance, his affect was flat and his vigilance was reduced; his responses were grammatically accurate but delayed, and when asked "What was the matter?," he replied he was not sure why he had been brought in. On examination, his visual fields were normal but his gaze was deviated to the right spontaneously. When presented with two objects, one in each visual field, he always looked first to the right object and denied the presence of the object on the left. However, when asked, he was able to move his eyes to the left and reported seeing that object. Overall, he was very slow in reporting stimuli even in his right visual field. When searching blindfolded for objects scattered on a table with either the left or right hand, he explored mainly the right side of the table, and his search progressed to the center only when objects on the right were removed. Touches on the right hand were easily reported and localized, while touches to the left hand were inconsistently detected. Occasionally, he reported touches to the left hand as belonging to the examiner. Motor function was decreased on the left side, especially in his upper extremity. On closer inspection, his strength was better than what was apparent because he was reluctant to use his left hand unless forced. Head MRI showed a region of diffusion restriction in the right inferior and middle frontal gyrus and anterior insula extending to the ventral white matter, consistent with an acute ischemic stroke.

After a brief admission to an acute stroke unit, he was transferred to an inpatient rehabilitation stroke unit where he spent the next 2 weeks. He was trained on ADLs with an emphasis on "paying attention" to his left visual field and body including the use of sensory "anchors"; he wore a mitten on his right hand to force movements of his left side during ADLs and meals. He was also trained on a protocol involving prismatic adaptation. Finally, after the first week, due to slowness and poor vigilance, he was started on a small dose of methylphenidate that was continued after discharge.

On follow-up at 3 months, his reluctance to move his left side had improved. Gaze was now mostly centered at midline, but was still slightly attracted to the right of two stimuli presented simultaneously, one in each visual field. Awareness of visual targets on his left side had returned, but he was still missing about one-fourth of targets when attention was divided between visual fields. Left touch sensation was also normal. Vigilance and speed were much improved, but his family reported important problems with memory and the initiation of novel tasks, as well as his ability to stay on task for prolonged periods. He reported fatigue and took naps regularly in the afternoon, after which he felt better. He was not back to work or driving, and he was attending an outpatient rehabilitation program 3 days a week.

Analysis of Clinical Symptoms and Signs

Spatial Bias

Acutely, this patient clearly suffered from primary sensory and motor deficits. He was paretic but not plegic on his left side, and he had problems with sensation in his left hand. Even though not explicitly tested, vibratory and joint position senses were also likely affected, as is frequent in these cases. His main motor problem was a reluctance to use his left hand even though force was relatively spared. These signs indicate dysfunction, either structural or functional, of fibers and/or cortical/subcortical regions involved in movement and sensation. However, the fact that the symptoms were subtle, involved mainly his intention to move, and recovered completely at 3 months indicate that the damage was transient and secondary to other factors. These could include edema of the internal capsule from the frontal/insular stroke, or secondary functional effects either metabolic or neurally based. The visual fields were intact to confrontation, indicating that his primary visual cortex and optic pathways to the occipital lobe were spared.

However, there were clear signs of a spatial bias in multiple sensory and motor domains. These included a "magnetic gaze" to the right, that is, an automatic orienting of the eyes to the right when presented with bilateral visual objects; "extinction" to double simultaneous visual or tactile stimulation, that is, lack of awareness for stimuli presented in the left visual field or the left side of the body, especially when presented in conjunction with right visual field or body stimuli; a spontaneous rotation of the eyes and body toward the right even at rest; a rightward exploratory manual bias even when searching blindfolded; and motor neglect of the left hand, that is, a reluctance to use the left hand spontaneously.

Several important principles can be deduced from a functional analysis of the spatial bias. First, the bias was multimodal, affecting both visual and tactile (and auditory) stimuli, as well as involving motor representations coordinating eye and hand/arm responses. Therefore, the underlying dysfunction must involve widely distributed sensory and motor representations across the brain independent of the vascular distribution of the stroke.[7–9] The posterior cerebral artery (PCA) feeds the occipital visual cortex, while the middle cerebral artery (MCA) feeds somatosensory and auditory cortices. Similarly, dorsal branches of the MCA vascularize regions in frontal and parietal cortices specialized in eye movements (i.e., eye fields). Finally, regions in the lateral and medial frontoparietal cortices selective for reaching and grasping functions receive blood from dorsal branches of MCA, PCA, and ACA branches. In this patient, the stroke was located in the right inferior frontal/anterior insula cortex that is vascularized by anterior ventral MCA branches.

This mismatch between the location of stroke and symptoms is the rule rather than the exception, in agreement with the notion that hemispatial neglect reflects not only the structural damage, but also the metabolic or neural disruptions provoked by the stroke on distributed cortical/subcortical systems. The physiological underpinnings of such widespread dysfunction will be considered in the next section.

A second important principle is that the spatial bias includes both negative and positive deficits. The negative deficits correspond to a failure of detection and response to stimuli on the left side of the visual field and/or the reluctance to use the left arm for exploration or manipulation. These

deficits coexist with positive deficits of automatic "attraction" to stimuli on the right side of space and a strong rotational bias toward the right that is evident not only during movements but also at rest.[10] The presence of both negative and positive components on opposite sides of the visual field/body suggests that an important mechanism in hemispatial neglect is the disruption of the normal interhemispheric balance of activity that regulates everyday perception and action.[11,12]

The ability of any organism to maintain spatially centered behavior with a good alignment of sensory and motor representations depends on the reciprocal interaction between the left and right sides of the central nervous system (CNS). This interaction occurs at any level from the spinal cord to the cerebral cortex. For instance, a normal sense of balance depends on inputs from both vestibular systems cross-inhibiting each other. Stimulation of one vestibular system leads to slow eye movements in the opposite direction of the stimulated ear (e.g., right direction for left-ear stimulation), accompanied by a tendency to fall in the same direction. Inactivation of one vestibular system leads to eye movements toward the inactivated side and falls in the same direction (e.g., right direction for right-ear inactivation). Eye movements and body responses in the direction of the inactivated ear depend on relative hyperactivity arising from the normal ear. Hence, balanced activity from both sides of the CNS is necessary for gaze, head, and body positions that are on average centrally aligned. The same occurs in the frontal lobe when measuring activity in the left and right frontal eye fields (FEF) and saccadic eye movements. A lesion in the frontal lobe will cause a tonic deviation of the eyes toward the lesion, resulting from an uninhibited contralateral frontal eye field. This balance is gently modified during behavior, allowing for the exploration of the environment while at the same time not upsetting the overall central stance of an organism. Analogously, perceptual systems are also in balance across the midline under normal conditions because of mechanisms that integrate and compare information across both visual fields, and select on a moment-by-moment basis important information based on either internal signals (e.g., goals, motivations, behavioral relevance, memory) or external inputs (sensory distinctiveness).[13,14]

In patients with hemispatial neglect, the normal perceptual, body, and motor midline balance is broken.[15] At rest, the rightward rotation of gaze, head, and body reflects either relative inactivation of the right brain or an overactivation of the left brain. This bias is independent of sensory information or actions and is likely present at multiple levels in the CNS from the brainstem to the thalamus/basal ganglia to the cortex. Similarly, when patients explore space blindfolded, the tendency to search and perseverate on the right side of space indicates a rightward directional motor bias. Finally, during perceptual tasks, the rightward bias leads to an automatic orienting toward right visual field stimuli and to the generation of patterns of eye movements that perseverate onto objects in right-field locations. These observations strongly indicate that neural abnormalities in neglect regard not only the damaged side of the brain, but the balance of activity with the undamaged side (see the Mechanisms and Pathogenesis section).

Finally, a third important principle is that the rightward spatial bias can be modified at any moment by the same internal or external signals that modulate in the healthy brain the balance of activity between hemispheres during perception and action. In other words, the severity of hemispatial neglect is not fixed, but can be dynamically modified by cognitive or environmental information. In this respect, hemispatial neglect may be different from other neurologic deficits like weakness or aphasia that do not fluctuate in their severity, but this issue has not been systematically explored.

Several cognitive signals lessen neglect. Hemispatial neglect is momentarily improved when patients voluntarily direct attention and actions toward the left side of space/body. This instruction works momentarily and is commonly used in therapy,[16] but its efficacy is counteracted by the inability of patients to maintain attention to the left for prolonged periods (deficit of sustained attention) and by the rightward perceptual pull that comes from objects in the right visual field. Expected rewards, such as money, can also induce patients to explore the left side of space more effectively.

There are many sensory, motor, and body tricks that can improve neglect. In general, these maneuvers can be classified as either ways to enhance activity on the damaged side of the brain, decrease activity on the normal side of the brain, or decrease the relative imbalance between hemispheres. For instance, decreasing the saliency or number of objects in the right visual space during visual search can improve leftward search and decrease rightward perseveration.[17] The dependency on number of objects in the right visual space is also observed during blindfolded tactile exploration. This trick decreases the amount of competing sensory information on the right side. Similar effects have been reported with patching the right eye to suppress retinal input to the left hemisphere.[18]

Increasing activity in the damaged brain can also work transiently. For instance, excitatory galvanic or caloric stimulation of the ear on the side of the affected brain can transiently improve motor and perceptual biases. A similar effect is obtained by vibrating the neck tendon on the right side.[19] In the motor domain, movements of the affected hand can improve perceptual neglect.[20] Conversely, limiting movements of the normal hand may also be beneficial, especially in cases of left motor neglect.[21,22] All of these maneuvers have been tried in the therapeutic setting, but their effect is limited to the time the intervention is applied and do not extend long term (see the Treatment and Clinical Management section).

That the severity of neglect is modified with short-term changes in sensory input, motor output, or cognitive states strongly supports the idea that hemispatial neglect symptoms reflect an abnormal distributed (i.e., involving many brain regions) functional state of the brain, and that this state can be transiently modified through activation of structurally intact connections.[9] The hope is that identification of these patterns of physiological dysfunction might lead in the near future to more effective and long-lasting interventions (see

the Experimental Restorative Treatment and Diagnostics section).

There are other aspects of spatial bias that have attracted a great deal of attention in the literature, including the frame of reference in which spatial biases manifest, or the distinction between location-based versus object-based neglect.[23] My personal opinion is that these distinctions are important theoretically, but are not of great clinical significance, at least for the moment. Frames of reference are highly integrated in the brain and during behavior, so that distinctions between patients with different frame of reference deficits will be relative rather than absolute, and any intervention based on one frame of reference is likely to spill over to another. Object-based neglect is a relatively rare problem of object processing[24] that involves position and scale invariant coding of objects rather than directional sensorimotor biases that are the core problems in hemispatial neglect.

Vigilance, Arousal, Sustained Attention

Although spatial bias is what defines the syndrome of hemispatial neglect, there is another set of core deficits that is less evident, but also clinically important. When our patient came to the hospital, he was drowsy and his overall speed of processing was delayed, not only during spatial tasks but also when speaking. During rehabilitation, his inability to stay on task led the clinical team to start him on methylphenidate, a mixed dopaminergic/catecholaminergic agent to improve attention. At 3-month follow-up, the family reported problems with staying on task and low cognitive endurance, with subjective fatigue and a need to take naps throughout the day. These symptoms indicate a failure of vigilance/arousal and sustained attention that are very common in patients with hemispatial neglect.[7,25,26]

Low vigilance must be recognized acutely; potentially dangerous etiologies such as hemorrhagic transformation of an ischemic stroke or brain swelling must be ruled out. Patients with low vigilance may be inappropriately sent to a skilled nursing facility, or worse, a nursing home and not admitted to an inpatient rehabilitation unit (at least in the United States), as their ability to participate in therapy may be underestimated. Chronic difficulties with cognitive function and task maintenance also often relate to low sustained attention.

It is important from a clinical and theoretical standpoint to separate spatial sensory–motor biases from vigilance/sustained attention deficits; they are mediated by different neural mechanisms and are amenable to different interventions. It is also important to recognize that vigilance/sustained attention and spatial attention interact, as transient increases in vigilance can improve spatial bias in neglect[25] and vice versa. This interaction reflects the normal interaction of these processes in the healthy brain. Even though spatial attention and eye movements scan dynamically different locations in the visual field during natural behavior, on average, people spend most of their time exploring the central region of space. Although there are large individual differences, on average, people have a slight bias toward the left that fluctuates throughout the day in a way that correlates with the level of vigilance/sustained attention. Peaks of vigilance/sustained attention late in the morning and late in the evening are associated with a slightly stronger leftward bias, while troughs of vigilance/sustained attention early in the morning or early in the evening after lunch (that is why a siesta is a physiologically supported habit) tend to correlate with a relative rightward shift of the attention midline.[27] This dynamic shift to the right has been also recently shown when people transition from an awake to a drowsy state.[28] In patients, transient increases of vigilance produced either by a strong sensory stimulation or in a more sustained fashion by drugs[29] or training[26] have been shown to ameliorate the rightward spatial bias.

At the level of neural mechanisms, this functional interaction suggests that processes mediating vigilance/sustained attention and spatial attention interact. This interaction affects the midline attention that is controlled by the balance of activity across hemispheres and likely occurs in the right hemisphere, given that increases of vigilance tend to bias attention to the left, whereas decreases of vigilance bias attention to the right.[9] This inference is based on the role that each hemisphere plays in orienting attention and actions toward the contralateral space.

Hemispheric Differences

At this point, it is important to discuss the hemispheric lateralization of hemispatial neglect and more generally in attention. Our patient's deficits were lateralized to the left side of the body and space after a right inferior frontal/insula lesion, hence causing left hemispatial neglect. In general, left hemispatial neglect is thought to be more common than right hemispatial neglect following left-hemisphere lesions, which is one of the facts used to propose a right-hemisphere dominance for attention. Early observations indicated that acutely the relative frequency of left and right neglect was comparable, but in the chronic stage left hemispatial neglect was found to be more frequent than right neglect.[2] More recent studies indicate that even at the acute stage the frequency and severity of left neglect is stronger than right neglect,[30] even though right neglect is by no means rare and can be easily detected through observation.

Two main theories have been offered to explain the right-hemisphere dominance of hemispatial neglect. One idea is that hemispheric differences in neglect underlie hemispheric differences of spatial coding in each hemisphere. Specifically, the right hemisphere contains neural representations for coding both sides of space, whereas the left hemisphere contains representations for coding only the right side of space. Therefore, a lesion in the left hemisphere can be compensated for by the right space representation in the right hemisphere.[14] Some limited experimental evidence for such a theory is provided by neuroimaging studies (see the Mechanisms and Pathogenesis section).

An alternative explanation is that lateralization does not involve spatial representations, but rather vigilance/sustained attention mechanisms. This is consistent with lesion studies which show that sustained attention deficits are more severe after right hemisphere damage. It is also consistent

with the direction of spatial bias under conditions of low/high vigilance reviewed above.[9,31] Finally, it is also consistent with a large body of neuroimaging studies (see the Mechanisms and Pathogenesis section).

Insight and Body Awareness Deficits

In addition to spatial biases and low sustained attention, our patient displayed deficits of insight and body awareness including (1) anosognosia, or lack of concern about his acute change in functional status; (2) hemisomatognosia, or a lack of recognition of his weakness; and (3) somatomotor paraphrenias, or an incorrect attribution of touches to his body to the examiner. These symptoms are of exceptional theoretical interest, as they provide a glimpse into the mechanisms of awareness, but they are in general less frequent than hemispatial neglect symptoms.

From a phenomenological perspective, these symptoms suggest a disconnection between parts of the brain that report verbally on the subjective experience and parts of the brain that code for the body or motor actions. Consistent with this idea, they always occur when patients have severe sensory or motor function loss. In the case of paraphrenias, primary touch and deep perception are typically abnormal. Patients can still have a faint perception of being touched, but typically have major problems with joint position sense and tactile localization, such as in reporting the location of touches on the body. Therefore, "far echoes" of detection may remain, but discriminatory mechanisms are always affected. Similarly, in the case of denial of hemiplegia, patients always have severe motor deficits. A plausible explanation for denial of hemiplegia is that premotor signals or corollary discharge (i.e., forward motor plans) are still felt in the absence of any movement or deteriorated sensory feedback. This can be shown by asking patients who have been blindfolded to "lift" their hemiplegic arm and then reproduce that position with the normal arm. The normal arm will move to the position of the hemiplegic arm's intended position. Accordingly, denial of hemiplegia has also been reported after lesions of the premotor areas of the brain, where premotor or corollary signals are presumably generated.[32,33] This situation is nearly opposite to motor neglect, in which patients who have relatively good strength do not use their arm, presumably due to a failure of activation of premotor representations. However, motor signals are normal once the motor plans are activated.

From a clinical perspective, it is important to recognize these deficits, as they can impair motor rehabilitation. Improvement of body awareness can be facilitated by several measures (e.g., passive sensory stimulation, body position awareness exercises, discussions about a patient's lack of insight, visual orienting to the ignored arm, etc.). However, none of these methods has been formally evaluated.

A complication not infrequently associated with loss of primary sensation and syndromes of lack of insight is the development of allesthesia or allodynia, that is, abnormal painful sensations coming from an anesthetized arm that is partially recovering feeling. Although central pain is often associated with thalamic lesions, cortical/subcortical lesions of the right hemisphere can also cause neuropathic pains that typically emerge after the first few weeks poststroke. Central pain syndromes can occur in the setting of abnormal or supernumerary body part syndromes, including phantom limbs, and may be difficult to treat (see the Experimental Restorative Treatment and Diagnostics section).

Mechanisms and Pathogenesis

►**Fig. 1** shows a summary of the main mechanisms behind hemispatial neglect. Hemispatial neglect is observed with damage to different parts of the brain, including the temporoparietal junction, the inferior frontal gyrus, the superior temporal gyrus, the medial frontal cortex, the thalamus, and basal ganglia (reviewed in[15]). The syndrome is worse for large lesions and lesions that go deep into the white matter. Experimental lesions in monkeys disconnecting the frontoparietal white matter cause more severe neglect than lesions that affect the frontal or parietal cortex alone.[34] Because fiber-tract white matter pathways connect sensory posterior to motor anterior regions of the brain, the white matter damage is likely responsible for the multimodal sensory and motor impairment in hemispatial neglect.[35]

In other words, neglect is a syndrome of disrupted integration between multiple regions of the brain. In humans, the region of the white matter more closely associated with severe neglect include the dorsal periventricular white matter that contain fibers of the superior longitudinal fasciculus (SLF, branches I–III) connecting dorsal prefrontal (e.g., frontal eye field) with parietal regions (e.g., intraparietal sulcus [IPS]), ventral prefrontal regions (e.g., inferior frontal gyrus) with ventral (e.g., temporoparietal junction [TPJ]) and dorsal parietal (e.g., IPS) regions. These cortical regions are part of two cortico–cortical networks involved in the control of attention and whose dysfunction plays a critical role in the pathogenesis of neglect (see below).[9]

It is important to underscore that symptoms of hemispatial neglect can be similar for damage to different locations in the brain. Our patient's symptoms in the right inferior frontal/anterior insula cortex may be indistinguishable from those of patients with lesions in the basal ganglia or temporoparietal region. This suggests two important insights. First, hemispatial neglect is a "network" problem, whereby a similar abnormal behavior emerges when damaging different parts of the brain connected as a network (►**Fig. 1**). That is why damage to the white matter, by disconnecting multiple nodes of the network, causes more severe neglect than just cortical damage.

This leads to the second insight, that some behavioral manifestations of neglect reflect the physiological disruption induced by the injury onto structurally normal regions. There is extensive support for this notion. We discussed above how the multimodal and multieffector deficits of neglect do not match the vascular location of the stroke. Experimental studies in animals show that lesions in frontal and parietal cortex cause widespread changes in the metabolic rate of many structurally normal cortical and subcortical regions and that this hypometabolism improves over time.[36]

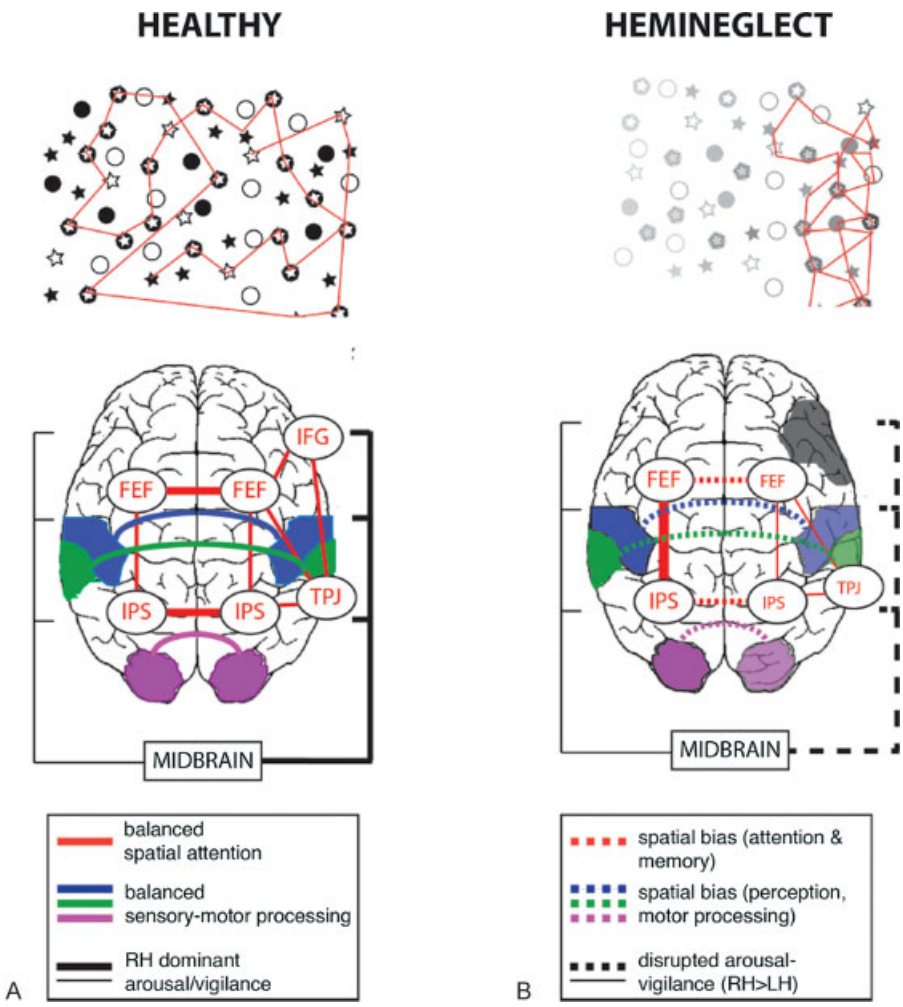

Fig. 1 (**A**) Healthy: Normal exploration pattern by eye movements of visual stimuli. Activity and interhemispheric connections are in dynamic balance between the two hemispheres. Attention regions (*red*) include dorsal areas in frontal eye field (FEF) and intraparietal sulcus (IPS) and ventral areas in inferior frontal gyrus (IFG) and temporoparietal junction (TPJ). Dorsal areas are bilateral and specialized for spatial attention, and eye and arm movements. Ventral areas are lateralized to the right hemisphere and are involved in vigilance/arousal and reorienting of attention. Somatomotor (*blue*), auditory (*green*), and visual (*purple*) regions are also in balance. Interhemispheric interactions may involve reciprocal inhibition. The lateralization of arousal/vigilance may reflect an asymmetric input to cortex from the midbrain. (**B**) Hemineglect: The pattern of eye movements, attention, and perception is biased to the right (left hemineglect). Anatomical damage in right IFG extends into the white matter, damaging connection with dorsal attention areas and posteroanterior communication. The damage causes "network" dysfunction in multiple regions including dorsal attention, and related sensorimotor regions in the lesioned hemisphere. At the acute stage, decrements of activity have been observed in the lesioned hemisphere[12] whereas imbalance of activity between left- and right-hemisphere regions has been associated with severity of neglect.[12] Reductions of interhemispheric interactions, not only in attention but also sensorimotor regions, have been noted that also correlate with the severity of neglect.[30,40] Finally, vigilance/arousal are reduced especially after left-hemisphere lesions, possibly reflecting either damage of cortical areas involved in these functions (e.g., IFG) or decreased input from midbrain.

Metabolic abnormalities in circuits involved in spatial orienting, like the parietal cortex and the superior colliculus, are especially relevant, as are interhemispheric asymmetries between damaged and undamaged regions.[37,38] Subcortical lesions (white matter, thalamus, or basal ganglia) cause widespread cortical hypoperfusion, whose reversal has been associated with neglect recovery.[39] Finally, more recent studies show an association between visuospatial biases—impaired perception in the left as compared with the right visual field—imbalances of activity during visual attention task in left- and right- hemisphere regions specialized for visuospatial attention,[12] and disrupted interhemispheric synchronization at rest between regions involved in attention, vision, auditory perception, and motor functions.[30,40] Therefore, these results clearly indicate that focal damage to one part of the brain causes multinetwork changes in metabolism, level of task activation and synchronization, and that interhemispheric imbalances appear to be strongly related to spatial biases in perception.

Selective deficits in sustained attention occur instead for damage to the right inferior frontal cortex and the right temporoparietal junction, independent of the spatial bias.[41,42] Other studies have proposed an association between frontal or basal ganglia lesion and motoric aspects of hemispatial neglect,[43,44] and damage to the temporoparietal junction and superior temporal gyrus with the multimodal

integration of sensory information including vestibular cues responsible for the indwelling rotation bias observed at the acute stage.[15] Therefore, these studies indicate that some nodes of a large-scale network of brain regions may be partly specialized for components of attention.

The above information leads to a neuroanatomical model of hemispatial neglect that can serve as a basis for future intervention studies.[9,15] Cortical lesions causing neglect tend to occur in the ventral frontal/insula or temporoparietal cortex (TPJ, superior temporal gyrus (STG)) and underlying white matter, especially superior longitudinal fasciculus (SLF). These regions are part of a ventral attention network (VAN) specialized for sustained attention/vigilance, and reorienting that is lateralized to the right hemisphere. For instance, in our patient, direct damage to the right inferior frontal/anterior insula cortex is likely responsible for deficits of vigilance/arousal early on and sustained attention at follow up (►**Fig. 1**). These regions (TPJ/STG) are important for the multimodal integration of visual, auditory, tactile, and vestibular inputs.

In contrast, sensorimotor spatial biases are likely due to abnormalities in dorsal frontoparietal cortex and related sensorimotor regions (►**Fig. 1**). These regions (e.g., IPS, FEF) contain maps of space, attention, eye movements, and arm/hand responses that are organized in retinotopic coordinates: preferential coding of contralateral visual field locations. There is also evidence of cross-inhibitory interactions between left- and right-hemisphere maps. These regions form a dorsal attention network (DAN), whose damage in isolation does not cause the full-blown hemispatial neglect but more specific deficits in saliency and visual search.

However, ventral lesions through white matter disconnection can physiologically affect these dorsal maps by altering their balance, specifically decreasing activity in the right DAN and impairing the normal interhemispheric balance between the left and right DAN. Our patient's damage extended in the white matter, possibly disconnecting the anterior component of the VAN (IFG) with the right DAN (right FEF, right IPS) and posterior component of the VAN (TPJ). Therefore, his sustained attention deficits due to structural damage to the VAN were augmented by the spatial biases due to VAN-DAN disconnection with secondary imbalance between left and right DAN. Spatial biases in perception and movement generated in attention areas (i.e., the DAN) can feed back onto primary and secondary sensory and motor regions through extensive feedback pathways, hence accounting for the multimodal nature of hemispatial neglect. Activity in these sensorimotor regions has been shown to be depressed at the acute stage.[12] This model provides a sensible framework to interpret the current evidence and to identify targets for novel interventions.

Treatment and Clinical Management

On admission to the stroke rehabilitation unit, our patient was positioned in a room with the left side of the bed oriented toward the door. Because behaviorally relevant individuals (nurses, doctors, visitors) entered from the left (and the television was to his left), he was forced to attend to that side throughout the course of his stay. Relatives were invited to speak to him from his left side and touch his left body for increased awareness. His initial drowsiness improved, but he continued to have problems staying on task and participating, an indicator of overall low sustained attention. His spatial orienting, while in the hall or moving from the room to the gymnasium, was highly disrupted by automatic orienting to any stimulus entering his right visual field (people walking down the hall, other patients, etc.). Therefore, he was retrained in a low-noise environment to decrease distractibility and by positioning the right side of his body next to a blank wall. On day 5 he was started on a low dose of methylphenidate (5 mg twice daily, given at 8 AM and 1 PM), which was then changed to a slow-release preparation. Over a 1-week period, his vigilance and participation had improved. Before his second dose, he was allowed to take a brief nap prior to his afternoon therapy session.

His therapy evaluation included (1) a standardized assessment of motor function including functional tasks, like the Arm Research Action test; (2) sensory function, including superficial, deep, and pain sensation; (3) balance, including the Berg test; (4) cognition, including verbal and spatial memory; and (5) hemispatial neglect, including the Behavioral Inattention Test, Mesulam unstructured search, Posner computerized visual orienting, and Catherine Bergego Scale (CBS) including anosognosia. The Mesulam unstructured and Posner visual field difference scores have been found to be highly accurate in diagnosing even mild neglect at the chronic stage, while the CBS is a sensitive functional scale of neglect. Functional outcome was measured with the Functional Independence Motor and Activity Scales (FIM, FAM). This battery was given at admission and discharge from the rehabilitation floor.

Physical therapy concentrated on gait and balance, transfers, positioning, and awareness of the left body. Task-specific exercises, such as reaching and pointing to real objects of different sizes and in different locations, were performed with the left hand. The right hand was placed in a mitten during therapy and meals to enforce use of the left side. Motor neglect improved significantly over the course of 2 weeks. Occupational therapy focused on ADL training (bathing, showering, object manipulation, etc.), with and without vision. They also trained him on visual scanning therapy by forcing him to localize and touch lights on an electronic board spanning a large expanse of the visual field, searching for natural objects, or reading text in the left visual field. Visual scanning therapy is an effective method for retraining the search impairment in neglect, but does not generalize well to other tasks.[16] Speech therapy performed a dysphagia assessment with emphasis on increasing awareness to not pocket food on the left side of the mouth.

Experimental Restorative Treatments and Diagnostics

Prismatic Adaptation

Prismatic adaptation (reviewed in[45]) is a procedure by which patients are asked to perform visuomotor tasks like reaching

to an object with their hand while looking through prisms that displace the light path, by for instance 10 degrees to the right/left. The effect of the prisms is to induce a pointing error in the direction of the light displacement. If patients have the possibility to see their final hand position within 10 to 15 minutes of repeated movements, an adaptation occurs such that the hand position is eventually realigned with the target. When the prisms are removed, an aftereffect of the adaptation can be measured for a relatively short time (typically 10 minutes in healthy individuals). Patients tend to point in the opposite direction (left for rightward prisms), but this error quickly wanes as patients continue to point, eventually realigning their hand and target location.

In healthy individuals this adaptation is remarkably motor specific, such that adapting an upper hand throw does not generalize to a lower hand throw. Lesion data indicate the importance of the olivocerebellum in establishing this adaptation.[46,47] A seminal observation by Rossetti and colleagues showed that in neglect patients this procedure induces approximately 1 hour of improvement on multiple deficits including cancellation, drawing, mental scanning, wheelchair navigation, and postural stability.[48] Repeated exposures have been shown to have longer lasting effects.[49] At our institution, patients with hemispatial neglect undergo 2 weeks of daily 30-minute sessions of prismatic adaptation and visual reaching to multiple locations. As in the original Rossetti protocol, movements are performed with the right arm in open loop (without visual feedback of the arm), and at least 100 movements are performed in each session. This repetitive protocol has been shown to improve neglect up to 1 month. In general, the current evidence indicates that the adaptation has to be repeated over several sessions (i.e., 2 weeks), involve a high number of pointing responses in each session, and the prisms must be strong (at least 10 degrees). The effect of add-on interventions such as neck vibration or smooth pursuit stimulation is being tested (see reviews[19,50]).

The neural mechanisms targeted by prismatic adaptation are not clear. The adaptation is thought to change the gain of the gaze position with a tonic displacement toward the left side (after right-field adaptation) that counteracts the ipsilesional rightward bias in neglect. This predicts a stronger effect for larger prismatic displacements, a result that has been partially confirmed. Interestingly, the generalizable effect of prismatic adaptation to many tasks in a damaged brain contrasts with the strong movement specificity in healthy individuals. This indicates that the lesion causes a loss of selectivity of the adaptation that spills over to many circuitries from the original focal changes in cerebellum and posterior parietal cortex. In one study on neglect patients, improvement in left-side detection was correlated with increases in blood flow in the right cerebellum and left temporal cortex.[45]

Optokinetic Stimulation

Optokinetic stimulation–stimulation with large fields of stripes or dots moving right to left, induces smooth pursuit eye movements in the direction of the movement as well as illusory rotation of the body. This stimulation has been shown to transiently improve neglect.[19] More recently, bedside stimulation has been performed with small field of views on computer screens, a set-up that emphasizes smooth-pursuit eye tracking. In a recent randomized trial, Kerkhoff and colleagues compared the effects of smooth pursuit eye movement training (SPT) and visual scanning training (VST).[51] Twenty-four participants with acute neglect were randomly allocated to either SPT or VST ($n = 12$ each). They received 20 treatment sessions lasting 30 minutes each at the bedside over 4 weeks. Outcomes included measures of neglect and unawareness. Smooth-pursuit eye movement training produced greater improvement over VST at the end of the trial and the benefits persisted 2 weeks later.

Optokinetic stimulation drives superior colliculus and cortical neurons involved in motion perception along the dorsal stream visual pathway. The response is always stronger during active tracking that engages visual attention and enhances sensory responses. Active tracking induces both eye and attention movements to the left with a possible rebalancing of saliency signals in dorsal frontal and parietal maps. It also recruits the vestibular system, possibly with a rebalancing effect on the ipsilesional rotation bias.

TMS and tDCS Stimulation

An imbalance in interhemispheric activity is also suggested by experimental and clinical work aimed at either suppressing activity on the left hemisphere or enhancing activity on the right hemisphere using transcranial magnetic stimulation (TMS) or transcranial direct-current stimulation (tDCS). The first studies focused on stimulation of the left parietal cortex using high-frequency (25 Hz)[52] or low-frequency (1Hz) stimulation,[53] and transient improvements in neglect scores were reported. Current evidence indicates that benefits can be obtained both with anodal (excitatory) stimulation of the right hemisphere (left neglect) or cathodal stimulation of the left hemisphere.[54] However, a large parameter space of stimulation frequency, duration, number of sessions, and experimental measures must be explored before setting on a specific protocol in the clinic.

More recently, there has been proof-of-concept evidence for the efficacy of theta burst stimulation (TBS), an inhibitory protocol with longer lasting effects possibly induced by long-term potentiation and depression.[55] Two randomized clinical trials have found long-term efficacy with repeated sessions. Kock et al used continuous TBS over 2 weeks and showed a 20% increase in neglect scores at 1 month.[56] Cazzoli et al applied TBS over 2 consecutive days and showed a 37% increase on a functional assessment of neglect (Catherine Bergego Scale) that persisted at 3 weeks.[57]

Computer Game Stimulation

Based on the work of Van Vleet and DeGutis, patients with hemispatial neglect may improve their visual field bias by training sustained attention and inhibitory control through computer games presented on a home computer through the web.[58] Researchers in San Francisco, California, St. Louis, Missouri, and Boston, Massachusetts are now testing this home-based intervention for 3 months in chronic neglect

patients in a multicenter randomized phase II trial sponsored by the National Institutes of Health.

Whole Brain Mapping of Disrupted Functional Connections

A final advance that will certainly change the way we treat patients with hemispatial neglect is the ability to map in much greater detail the functional/structural effects of stroke on the rest of the brain. In the case of neglect, recent studies have shown a disruption of interhemispheric synchronization in attention, sensory, and motor areas.[30] These changes can be now visualized at the level of single patients[59] and may be targetable through neuronavigation systems by TMS or tDCS methods.

Conclusions

Hemispatial neglect is a fascinating and to a great extent, still mysterious cognitive disorder that widely impacts behavior. It has served as a fundamental model to understand attention and awareness; recently, much work has been dedicated to treating it. The efficacy of current interventions, mainly developed either pragmatically or based on currently outdated models of anatomical/physiological principles of strict modularity, could be much enhanced by developing novel intervention guided by network theories of brain function and a more precise mapping of dysfunctional circuitries.

References

1 Brain WR. Visual disorientation with special reference to lesions of the right cerebral hemisphere. Brain 1941;64:244–272
2 Stone SP, Halligan PW, Greenwood RJ. The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. Age Ageing 1993;22(1):46–52
3 Rengachary J, d'Avossa G, Sapir A, Shulman GL, Corbetta M. Is the posner reaction time test more accurate than clinical tests in detecting left neglect in acute and chronic stroke? Arch Phys Med Rehabil 2009;90(12):2081–2088
4 Pedersen PM, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Hemineglect in acute stroke—incidence and prognostic implications. The Copenhagen Stroke Study. Am J Phys Med Rehabil 1997; 76(2):122–127
5 Ringman JM, Saver JL, Woolson RF, Clarke WR, Adams HP. Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. Neurology 2004;63(3):468–474
6 Buxbaum LJ, Ferraro MK, Veramonti T, et al. Hemispatial neglect: Subtypes, neuroanatomy, and disability. Neurology 2004;62(5): 749–756
7 Heilman KM, Valenstein E. Mechanisms underlying hemispatial neglect. Ann Neurol 1979;5(2):166–170
8 Mesulam M-M. A cortical network for directed attention and unilateral neglect. Ann Neurol 1981;10(4):309–325
9 Corbetta M, Shulman GL. Spatial neglect and attention networks. Annu Rev Neurosci 2011;34:569–599
10 Fruhmann-Berger M, Karnath HO. Spontaneous eye and head position in patients with spatial neglect. J Neurol 2005;252(10): 1194
11 Kinsbourne M. Mechanisms of unilateral neglect. In: Jeannerod M, ed. Neurophysiological and Neuropsychological Aspects of Spatial Neglect. Amsterdam, The Netherlands: Elsevier Science; 1987: 69–86
12 Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci 2005;8(11):1603–1610
13 Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3(3):201–215
14 Mesulam MM. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos Trans R Soc Lond B Biol Sci 1999;354(1387):1325–1346
15 Karnath HO, Rorden C. The anatomy of spatial neglect. Neuropsychologia 2012;50(6):1010–1017
16 Weinberg J, Diller L, Gordon WA, et al. Visual scanning training effect on reading-related tasks in acquired right brain damage. Arch Phys Med Rehabil 1977;58(11):479–486
17 Eglin M, Robertson LC, Knight RT. Visual search performance in the neglect syndrome. J Cogn Neurosci 1989;1(4):372–385
18 Smania N, Fonte C, Picelli A, Gandolfi M, Varalta V. Effect of eye patching in rehabilitation of hemispatial neglect. Front Hum Neurosci 2013;7:527
19 Kerkhoff G, Schenk T. Rehabilitation of neglect: an update. Neuropsychologia 2012;50(6):1072–1079
20 Robertson IH, North N. Active and passive activation of left limbs: influence on visual and sensory neglect. Neuropsychologia 1993; 31(3):293–300
21 Sampanis DS, Riddoch J. Motor neglect and future directions for research. Front Hum Neurosci 2013;7:110
22 Wu CY, Wang TN, Chen YT, et al. Effects of constraint-induced therapy combined with eye patching on functional outcomes and movement kinematics in poststroke neglect. Am J Occup Ther 2013;67(2):236–245
23 Behrmann M, Tipper SP. Attention accesses multiple reference frames: evidence from visual neglect. J Exp Psychol Hum Percept Perform 1999;25(1):83–101
24 Marsh EB, Hillis AE. Dissociation between egocentric and allocentric visuospatial and tactile neglect in acute stroke. Cortex 2008; 44(9):1215–1220
25 Robertson IH, Mattingley JB, Rorden C, Driver J. Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. Nature 1998;395(6698):169–172
26 Robertson IH, Tegnér R, Tham K, Lo A, Nimmo-Smith I. Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. J Clin Exp Neuropsychol 1995;17(3):416–430
27 Matthias E, Bublak P, Costa A, Müller HJ, Schneider WX, Finke K. Attentional and sensory effects of lowered levels of intrinsic alertness. Neuropsychologia 2009;47(14):3255–3264
28 Bareham CA, Manly T, Pustovaya OV, Scott SK, Bekinschtein TA. Losing the left side of the world: rightward shift in human spatial attention with sleep onset. Sci Rep 2014;4:5092
29 Malhotra PA, Parton AD, Greenwood R, Husain M. Noradrenergic modulation of space exploration in visual neglect. Ann Neurol 2006;59(1):186–190
30 Baldassarre A, Ramsey L, Hacker CL, et al. Large-scale changes in network interactions as a physiological signature of spatial neglect. Brain 2014. pii: awu297. [Epub ahead of print]
31 Husain M, Rorden C. Non-spatially lateralized mechanisms in hemispatial neglect. Nat Rev Neurosci 2003;4(1):26–36
32 Garbarini F, Rabuffetti M, Piedimonte A, et al. 'Moving' a paralysed hand: bimanual coupling effect in patients with anosognosia for hemiplegia. Brain 2012;135(Pt 5):1486–1497
33 Garbarini F, Piedimonte A, Dotta M, Pia L, Berti A. Dissociations and similarities in motor intention and motor awareness: the case of anosognosia for hemiplegia and motor neglect. J Neurol Neurosurg Psychiatry 2013;84(4):416–419
34 Gaffan D, Hornak J. Visual neglect in the monkey. Representation and disconnection. Brain 1997;120(Pt 9):1647–1657
35 Bartolomeo P, Thiebaut de Schotten M, Doricchi F. Left unilateral neglect as a disconnection syndrome. Cereb Cortex 2007;17(11): 2479–2490

36 Deuel RK, Collins RC. The functional anatomy of frontal lobe neglect in the monkey: behavioral and quantitative 2-deoxyglucose studies. Ann Neurol 1984;15(6):521–529
37 Payne BR, Lomber SG, Rushmore RJ, Pascual-Leone A. Cancellation of visuoparietal lesion-induced spatial neglect. Exp Brain Res 2003;150(3):395–398
38 Lomber SG, Payne BR. Perinatal-lesion-induced reorganization of cerebral functions revealed using reversible cooling deactivation and attentional tasks. Cereb Cortex 2001;11(3):194–209
39 Hillis AE, Newhart M, Heidler J, Barker PB, Herskovits EH, Degaonkar M. Anatomy of spatial attention: insights from perfusion imaging and hemispatial neglect in acute stroke. J Neurosci 2005;25(12):3161–3167
40 He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 2007; 53(6):905–918
41 Rueckert L, Grafman J. Sustained attention deficits in patients with lesions of posterior cortex. Neuropsychologia 1998;36(7): 653–660
42 Rueckert L, Grafman J. Sustained attention deficits in patients with right frontal lesions. Neuropsychologia 1996;34(10):953–963
43 Mattingley JB, Bradshaw JL, Bradshaw JA, Nettleton NC. Recovery from directional hypokinesia and bradykinesia in unilateral neglect. J Clin Exp Neuropsychol 1994;16(6):861–876
44 Sapir A, Kaplan JB, He BJ, Corbetta M. Anatomical correlates of directional hypokinesia in patients with hemispatial neglect. J Neurosci 2007;27(15):4045–4051
45 Pisella L, Rode G, Farnè A, Tilikete C, Rossetti Y. Prism adaptation in the rehabilitation of patients with visuo-spatial cognitive disorders. Curr Opin Neurol 2006;19(6):534–542
46 Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. I. Focal olivocerebellar lesions impair adaptation. Brain 1996;119(Pt 4):1183–1198
47 Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. Brain 1996;119 (Pt 4):1199–1211
48 Rossetti Y, Rode G, Pisella L, et al. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 1998;395(6698):166–169
49 Frassinetti F, Angeli V, Meneghello F, Avanzi S, Làdavas E. Long-lasting amelioration of visuospatial neglect by prism adaptation. Brain 2002;125(Pt 3):608–623
50 Làdavas E, Bonifazi S, Catena L, Serino A. Neglect rehabilitation by prism adaptation: different procedures have different impacts. Neuropsychologia 2011;49(5):1136–1145
51 Kerkhoff G, Bucher L, Brasse M, et al. Smooth Pursuit "Bedside" Training Reduces Disability and Unawareness During the Activities of Daily Living in Neglect: A Randomized Controlled Trial. Neurorehabil Neural Repair 2014;28(6):554–563
52 Oliveri M, Bisiach E, Brighina F, et al. rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. Neurology 2001;57(7):1338–1340
53 Brighina F, Bisiach E, Oliveri M, et al. 1. Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. Neurosci Lett 2003; 336(2):131–133
54 Sparing R, Thimm M, Hesse MD, Küst J, Karbe H, Fink GR. Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. Brain 2009;132(Pt 11):3011–3020
55 Nyffeler T, Cazzoli D, Hess CW, Müri RM. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 2009;40(8):2791–2796
56 Koch G, Bonnì S, Giacobbe V, et al. θ-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. Neurology 2012;78(1):24–30
57 Cazzoli D, Müri RM, Schumacher R, et al. Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. Brain 2012;135(Pt 11):3426–3439
58 Van Vleet TM, DeGutis JM. The nonspatial side of spatial neglect and related approaches to treatment. Prog Brain Res 2013; 207:327–349
59 Siegel JS, Snyder AZ, Metcalf NV, et al. The circuitry of abulia: insights from functional connectivity MRI. NeuroImage: Clinical 2014;6:320–326