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REVIEW

Unilateral Spatial Neglect After Stroke: Current Insights

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Introduction: Unilateral spatial neglect (USN) is a disorder of contralesional space awareness which often follows unilateral brain lesion. Since USN impairs awareness of contralesional space/body and often of concomitant motor disorders, its presence represents a negative prognostic factor of functional recovery. Thus, the disorder needs to be carefully diagnosed and treated. Here, we attempted to present a clear and concise picture of current insights in the comprehension and rehabilitation of USN.

Methods: We first provided an updated overview of USN clinical and neuroanatomical features and then highlighted recent progresses in the diagnosis and rehabilitation of the disease. In relation to USN rehabilitation, we conducted a MEDLINE literature research on three of the most promising interventions for USN rehabilitation: prismatic adaptation (PA), non-invasive brain stimulation (NIBS), and virtual reality (VR). The identified studies were classified according to the strength of their methods.

Results: The last years have witnessed a relative decrement of interest in the study of neuropsychological disorders of spatial awareness in USN, but a relative increase in the study of potential interventions for its rehabilitation. Although optimal protocols still need to be defined, high-quality studies have demonstrated the efficacy of PA, TMS and tDCS interventions for the treatment of USN. In addition, preliminary investigations are suggesting the potentials of GVS and VR approaches for USN rehabilitation.

Conclusion: Advancing neuropsychological and neuroscience tools to investigate USN pathophysiology is a necessary step to identify effective rehabilitation treatments and to foster our understanding of neurofunctional bases of spatial cognition in the healthy brain.

Keywords: unilateral spatial neglect, rehabilitation, spatial attention, stroke

Introduction

The first attempt to define Unilateral Spatial Neglect (USN), a neuropsychological disorder of spatial awareness that often follows unilateral brain lesion, was made in the second half of the 19th century.[1] A remarkable number of studies of USN have been published towards the end of the 20th century and the beginning of the current century. However, the last 10–15 years have witnessed a relative decrement in the number of neuropsychological papers investigating this syndrome. The reason might be twofold. Firstly, the advancement of neuroimaging and, more recently, brain stimulation methodologies has driven the interest (and preference) of cognitive neuroscientists toward the use of these innovative techniques to investigate the neurofunctional bases of spatial cognition in the healthy brain. Secondly, medical advances in the treatment of acute stroke have significantly improved individuals' clinical and neuropsychological conditions. Nonetheless, USN is quite frequent

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since it occurs in about 25–30% of all stroke individuals and over 90% of people with USN have right-hemisphere lesions.[2] In the acute phase, USN occurs in 43% of individuals with right-hemisphere lesion (RHL) and 20% of those with left-hemisphere lesions (LHL). At 3 months, it is still present in 17% and 5% of RHL and LHL individuals, respectively.[3] Neglect per se, rather than overall stroke severity, predicts poor outcome in functional recovery.[4] It may indeed entail longer hospitalization, functional dependency, long-term disabilities in activities of daily living and increased risk of falls.[5,6]

Thus, USN is an important neuropsychological condition that needs to be carefully diagnosed and treated. Here, we attempt to provide a clear and concise picture of current insights in the comprehension and rehabilitation of USN. We briefly overview USN clinical and neuroanatomical features and then highlight recent progresses in the diagnosis and rehabilitation of USN. In relation to the latter topic, we review recent findings on three of the most promising interventions for USN rehabilitation: prismatic adaptation (PA), non-invasive brain stimulation (NIBS), and virtual reality (VR).

Clinical Manifestations

Individuals affected by USN fail to explore, orient or respond to contents of the contralesional side of somatic and extrasomatic space.[7,8] In the acute phase, they show an ipsilesional deviation of the head and the eyes and may respond to stimuli presented in the contralesional side as if they were in the "intact" side. During everyday activities, they may eat food only from the ipsilesional side of the plate, bump into objects located in the contralesional side when walking, and wash, shave, or apply cosmetics only to the ipsilesional side of the face/body.[1]

USN Is a Complex Syndrome

There is a broad consensus among researchers on the heterogeneity of USN symptoms that is thought to reflect the complexity of neural correlates of spatial attention/representation. Building a coherent representation of space entails a complex integration of different sensory inputs and output-related factors, in relation to different portions of space and coordinates systems. Coherently with this assumption, USN symptoms can dissociate across sensory modalities,[9] sectors of space (i.e., personal, peri-personal and extra-personal space[10–14]), reference frames (egocentric vs allocentric neglect[15–17]), and tasks.[18] An often neglected dissociation concerns symptoms affecting perceptual and output stages of spatial processing.[19–23] Some USN individuals are affected by a perceptual bias reflecting lateralized impairments in spatial representation/attention. However, in other individuals, USN reflects a "reluctance" to orient the response contralesionally.[19,24] This type of neglect that has been called directional hypokinesia or intentional neglect,[25,26] response bias[19,20] or premotor neglect[24] is rarely assessed, likely because it can only be detected by using few specific tasks, the most well-known being the landmark task.[19,21] Another symptom affecting output stages of stimulus processing is motor neglect, whereby a dramatic reduction in the spontaneous use of contralesional limbs is not explained by motor impairment.[27] Finally, not only the type of task[18] but also task demands[28–31] have been found to affect neglect severity.

Given the complexity of USN symptomatology, there is the need to use comprehensive assessment tools that minimize the risk to overlook its presence. The most reliable and commonly used assessment tests are two "paper and pencil" tasks: the line bisection[32] and cancellation[28] tasks. On these tasks, individuals with USN are asked to bisect a horizontal line or to search for spatially distributed targets. They mark the center of the line ipsilesionally and/or search exclusively for ipsilesional targets. Administration of both tasks is critical because USN can dissociate across them.[18] Furthermore, other variables need to be kept into account when using these tasks. For example, line bisection performance is affected by the length of the line and by contextual factors.[32] Lines of at least 18 or 20 degree of visual angle are necessary to reliably assess neglect. Short lines and very short lines produce a contralesional bisection bias that may even overshoot the end of the line (i.e., the crossover effect;[32] see also Chatterjee et al[33] for crossover effects in non-spatial tasks). Cancellation tasks are significantly affected by stimuli characteristics[34] and task demands.[29,30] USN tests or batteries (e.g., the Behavioral Inattention Test[35]) often include also reading, copying and drawing tasks. In all these tests, individuals with USN omit (or may also "confabulate") contents of contralesional space. However, canonical tests may not be sensitive enough to detect contralesional space disorders in subacute and chronic stages of the disease and more appropriate (and demanding) tasks are necessary to reveal their presence.[30,36] For example, computerized methods may be more effective in detecting subtle symptoms than static paper-and-pencil tests.[22,37–41] In addition, conventional evaluation tests might not provide conditions consistent with real-life situations.

An accurate diagnosis of the specific symptoms that affect individuals with USN is fundamental to design tailored rehabilitation programs that may effectively overcome the limits posited by disrupted spatial awareness to functional recovery.

Theoretical Models

USN is not caused by elementary sensory or motor deficits and dissociates from deficits of intermediate vision.[22,42–44] It is thought to derive from disruption of higher level spatial attention/representational processes.[7,8] *Attentional theories* propose that USN is accounted for by a rightward lateralized bias in the orientation of spatial attention. Kinsbourne's hemispheric rivalry account[45] posits mutual transcallosal inhibition between hemispheres in the normal brain and disruption of this balance in USN. It assumes the existence of two antagonist attentional vectors directed by each hemisphere toward the contralateral hemispace. In physiological conditions, the left-hemisphere vector is stronger than the right-hemisphere one. A brain lesion would disrupt interhemispheric balance and symptoms would be explained not only by the inactivity of the lesioned area but also by the increased activity of homologous regions of the opposite hemisphere that are released by contralateral inhibition. Given the asymmetric strength of the attentional vectors, only a right-hemisphere lesion would produce a dramatic, lateralized ipsilateral bias in attentional orienting. Heilman and colleagues[8] propose a complementary model, according to which the right hemisphere would direct attention to both hemispaces, while the left hemisphere exclusively to the right one. As a consequence, a right-hemisphere lesion would more frequently cause USN.[8] *Representational accounts* of neglect instead propose that USN is a disorder of mental space representation,[46] consisting in a left–right pathological anisometry of the medium for space representation: the left-side would be more relaxed and the right-side would be more contracted/compacted.[46] The contralesional relaxation of the medium might still sustain "conscious" representation of contents in space, albeit with a horizontal size distortion. Beyond a critical point, the overrelaxed medium no longer sustains conscious representations. Bisiach's theory[46] also foresees that in some individuals, the disorder affects response level of stimulus processing (i.e., response bias). Another account referring to altered mechanisms of space representations is the *transformational hypothesis*.[47,48] It suggests that USN is due to a failure of the transformation of sensory input into motor output, which is generally based on different reference frames. Since such coordinate transformation mainly occurs in the parietal cortex,[49,50] a parietal lesion might impair this process.[47] As a result, the egocentric representation of the surrounding environment would be deflected towards the ipsilesional side.

Neural Correlates

Early clinical observations pointed to damage to the right posterior parietal cortex (PPC), as the most likely correlate of USN symptoms.[51] Anatomo-clinical correlation studies, based on CT or MRI, confirm a predominant role of the right inferior parietal lobule in association with USN symptoms,[52,53] particularly of the angular gyrus (AG). Other findings suggest the right superior temporal gyrus (STG) as the main neural correlate for USN symptoms.[54] Finally, USN is also observed after lesions to frontal and subcortical structures that are functionally connected to the posterior parietal lobe.[55] Recently, neuroscientists have shifted their interest from trying to identify a single brain area to investigations of brain areas that are involved as sub-components of a more complex network, responsible for space attention and representation (see Hillis et al[55] for a review). Studies using advanced neuroimaging techniques have concluded that USN symptoms heterogeneity can be explained by differences in the structures or circuit affected by the lesion. For instance, using PWI and DWI, Medina and colleagues[56] found that functional inactivation of the right-supramarginal gyrus was most predictive of egocentric neglect, inactivation of posterior inferior temporal and lateral occipital areas was most predictive of stimulus-centered neglect, and, posterior middle/inferior temporal regions of object-centered neglect. Damage to intraparietal sulcus (IPS) and the temporoparietal junction (TPJ) have been further associated with egocentric and allocentric neglect, respectively.[57] Finally, motor-intentional USN correlates to lesions of basal ganglia.[19,23] Breakdown of functional connectivity between parietal and frontal regions linked by the superior longitudinal fasciculus (SLF) has been shown to play a critical role in the occurrence, severity and chronicity of egocentric USN symptoms.[2,57–62]

Rehabilitation Methods

It is possible to distinguish between two types of neglect treatments: top-down and bottom-up approaches.[63] The main difference between them concerns the extent of an individual's awareness and active involvement. The former approach aims to improve perceptual and behavioural bias by acting on disrupted awareness, thus on higher-level cognitive processes. Given USN features, this approach might be difficult to be applied in individuals with severe neglect. The latter is a physiological approach that aims to affect the sensory-motor level through passive sensorial manipulations or visuomotor adaptation. In this way, it is possible to override central awareness deficit and reach higher cognitive levels of spatial and action representation.[64] Given that USN is a disorder of spatial awareness, bottom-up approaches have more frequently been proposed and investigated.

The most widely used top-down approach is *visual scanning training (VST)*, during which the therapist encourages individuals to pay attention to and explore portions of space contralateral to the brain lesion. The standard procedure consists of different training tasks, such as visual search, digit detection, figure copying, picture exploring, reading and writing. The exploratory behaviour of contralesional contents of space is systematically strengthened by visual and verbal reinforcements, as well as compensatory strategies. Despite a wide variability of response to VST, overall, significant improvement of neglect has been reported following this intervention[65] (for a review see Luauté et al[66]). Some studies, comparing the efficacy of VST to that of bottom-up approaches, did not find any significant difference between them.[67–69] Nonetheless, some RCT and single-case studies suggest that VST beneficial effects might be enhanced by the combination of this intervention with other techniques, such as, for example, left-hand somatosensory stimulation,[70] limb activation[71] or transcranial Direct Current Stimulation.[72]

Over the years, a number of different techniques have been proposed to rehabilitate neglect symptoms. A large number of studies have been published for each approach. Since this is not a systematic review of neglect treatments, we will focus on the most promising recently proposed rehabilitation methods, although other effective – but less employed – techniques have been investigated to treat the disorder, such as eye-patching,[73] caloric vestibular stimulation,[74] visuomotor imagery,[75] mirror therapy,[76] TENS,[77] Optokinetic Stimulation[78–80] and the Constraint-induced movement therapy.[81,82] Specifically, we conducted a MEDLINE literature research on the use of prismatic adaptation, non-invasive brain stimulation and virtual reality in USN rehabilitation. To this end, we used the following combinations of words: “neglect”, “rehabilitation”, “prism adaptation”, “tDCS”, “galvanic vestibular stimulation”, “TMS”, “TBS”, “Virtual reality”. Reference lists from identified articles were also reviewed. Studies were selected according to the following exclusion criteria: nonintervention studies; theoretical, descriptive, or review papers; papers without adequate specification of interventions; subjects other than persons with stroke and USN; non-English language papers. The identified studies were classified according to the strength of their methods based on Cicerone et al[83] recommendations. Specifically, three main levels of evidence were established. Studies were considered Class I evidence if they had well-designed, prospective, randomized controlled trials. Prospective studies with “quasi-randomized” assignment to treatment conditions were designed as Class Ia studies. Class II studies comprised prospective nonrandomized cohort studies, retrospective, nonrandomized case–control studies, or clinical series with well-designed controls (eg, multiple baseline across subjects). Studies were considered as Class III evidence if they consisted of clinical series without concurrent controls, or single-case studies with appropriate single-subject methods. All classifications were based on the agreement of at least two authors. The disagreement between reviewers was resolved by the evaluation of a third author.

Prismatic Adaptation

Prismatic Adaptation (PA) is one of the most widely studied and used bottom-up procedure for USN rehabilitation. Since the literature on this topic is very extensive and several reviews on this procedure have been published, here, we will present a non-exhaustive overview of recent relevant studies on PA for the treatment of USN (see Table 1). Standard PA procedure foresees that subjects wear the prismatic goggles, producing a visual shift, and perform different tasks to reach visual targets (e.g., pointing, reaching or throwing). These tasks are initially failed because of the deviation caused by the shift of the visual field that generates a mismatch between the perceptive object position and the arm movement trajectory. After a series of trials with visual feedback, the subjects adapt to optical displacement, improving their performance. After removing the prisms, movement trajectory deviates in the direction opposite to the visual shift, indicating a negative aftereffect. PA effects have been initially interpreted as due to a correction of the biased egocentric representation, in line with the transformational hypothesis. However, some studies suggested that PA may mainly affect motor-intentional “aiming” (response) neglect rather than perceptual levels of space representation.[84] Finally, some

Table 1 Prism Adaptation Studies

Study	Patients	Control	Protocol	Number of Sessions	Test	Assessment	Results	Design	Classification
Frassinetti et al,[63]	7 RH	6 RHI	10° RPA	20	BIT; Bell cancellation; Reading; Fluff test; Room description; Object reaching	Pre, Post, Follow-up (2 days, 1 week and 5 weeks later)	Improvement after RPA, at least for 5 weeks	NRCT	Class II
Priftis et al,[67]	31 RH	None	10° RPA, or VST (visual scanning training), or LAT (limb activation treatment)	20	Comb and razor test; Fluff test; Picture scanning; Reading; Coin sorting; Ecological scale; Room description; CBS	Pre, Post, Follow-up (2 weeks later)	Improvement after each treatment, at least for 2 weeks later	Quasi-RCT	Class Ia
Spaccavento et al,[69]	20 RH	None	10° RPA or VST	20	Fluff test; Personal neglect scale; BIT; Extrapersonal neglect scale; CBS; FIM	Pre, Post (4 weeks later)	Improvement after both treatments in each test, except in the extrapersonal neglect scale	Pilot	Class III
Fortis et al,[84]	5 RH	None	12,4° RPA	1	LBT; Pointing	Pre, Post	Improvement on "aiming", but not on "where" spatial bias	Pilot	Class III
Pisella et al,[85]	2 RH	None	10° RPA	1	Straight-ahead; LBT	Pre, Post, Follow-up (72 hrs later)	Improvement at least for 4 days	Pilot	Class III
Rossetti et al,[87]	Exp1: 8 RH Exp2: 6 RH	5 Healthy subjects 6 RHI	10° RPA and LPA	1	LBT; Cancellation test; Copying; Drawing from memory; Reading	Pre, Post, Follow-up (2 hrs later)	Improvement after RPA, at least for 2h	RCT	Class I
Farné et al,[88]	6 RH	None	10° RPA	1 2 (for 4 patients)	Line, bell and letter cancellation; LBT; Visual scanning; Object-naming; Reading	Pre, Post, Follow-up (1 day and 1 week later)	Improvement after RPA, at least for 1 day	Pilot	Class III

(*Continued*)

Table 1 (Continued).

Study	Patients	Control	Protocol	Number of Sessions	Test	Assessment	Results	Design	Classification
Serino et al,[89]	21 RH	None	10° RPA	10	BIT; Bell cancellation; Reading; Fluff test; Room description; Object reaching; Tactile extinction test; Proprioceptive sensibility and standardized mobility scale	Pre, Post (1 week later); Follow-up (1, 3 and 6 months later)	Improvement in visuospatial abilities, tactile modality, but not for proprioception and motor functions. Persisted for 6 months	Pilot	Class III
Serino et al,[90]	10 RH	10 RH	10° RPA and NP (neutral pointing)	10	BIT; Bell cancellation; Reading	Pre, Post, Follow-up (1 month later)	Improvement after RPA and NP, but stronger after RPA. Persisted for 1 month after RPA	Quasi-RCT	Class Ia
Vaes et al,[91]	21 RH	22 RH	10° RPA or Placebo	7	Digital visuospatial neglect test battery	Pre, Post, Follow-up (3 months later)	Improvement after RPA in drawing and bisection, navigation, visual extinction and non-motor memory Improvement in navigation, drawing and memory persisted 3 months later	RCT	Class I
Mizuno et al,[92]	20 RH	18 RH	12° RPA or Neutral glasses	20	BIT; CBS; ADL; FIM	Pre, Post, Follow-up (discharge)	Improvement in FIM and CBS in mild USN-patients after RPA. Improvement in FIM in prism group at the discharge	RCT	Class I
Nys et al,[93]	1 RH	None	10° RPA	4	Star cancellation; Figure copying	Pre, Post (after each session)	Improvement of neglect severity, but worsening of perseveration behaviour	Pilot	Class III
Turton et al,[94]	16 RH	10 RH	6° RPA or neutral glasses	10	CBS; BIT	Pre, Post, Follow-up (8 weeks later)	Improvement of pointing bias, but not in CBS and BIT	RCT	Class I

Mancuso et al,[95]	13 RH	9 RH	5° RPA or Neutral glasses	5	Line and bells cancellation; Line orientation; LBT; Copying drawings; Finding objects; Dealing playing cards	Pre, Post	No statistical difference between the two groups	RCT	Class I
Rode et al,[96]	10 RH	10 RH	10° RPA or Neutral glasses	4	Straight ahead; Open Loop Pointing; FIM; BIT	Pre, Post, Follow-up (1, 3 and 6 months later)	Improvement in the straight-ahead test, but no difference between the two groups 6 months later	RCT	Class I
Ten Brink et al,[97]	34 RH	35 RH	10° RPA or neutral glasses	10	CBS; Mobility Assessment Course; Shape cancellation	Pre, Post (1, 2, 3, 4, 6 and 12 weeks later)	No difference between the two groups	RCT	Class I

Abbreviations: RH, Right Hemisphere; RPA, Rightward Prism Adaptation; LPA, Leftward Prism Adaptation; LBT, Line Bisection Task; BIT, Behavioural Inattention Test; FIM, Functional Independence Measure; CBS, Catherine Bergego Scale; ADL, Activites of Daily Living; RCT, Randomized Control Trial; NRCT, Non-Randomized Control Trials.

authors proposed that PA improves spatial cognition by inhibiting the PPC contralateral to the prismatic deviation, restoring, as a result, interhemispheric balance,[85,86] in line with USN rivalry account.[45] Although it is not clear yet the exact nature of the mechanisms underlying beneficial effects of PA in USN, this non-invasive procedure has showed its effectiveness in several studies and therefore researchers are currently exploring its potentials. For example, single rightward-PA sessions can improve USN from 2 hrs[87] to few days.[85,88] Likewise, two daily sessions of PA-treatment for 2 weeks may produce beneficial effects persisting for 1 to 6 months.[63,89] Although several Randomized Control Trials (RCTs) have been published, the evidence supporting a systematic efficacy of PA for neglect rehabilitation is still controversial. For example, three studies reported a significant improvement in 51 individuals with USN treated by PA compared to a placebo control group, both in standard neglect tests[90,91] and in functional independence measures.[92] Positive outcomes were also observed in studies comparing PA to VST, whereby the effectiveness of both approaches was found.[67,69] However, mixed results have been reported in a brain-damaged woman suffering from USN who showed amelioration soon after 4 days of PA treatment,[93] but not after 1 month at follow-up. Moreover, no beneficial effects by PA were observed in four RCT-studies treating overall 72 individuals affected by USN.[94–97] A possible explanation of negative findings might be that visuomotor adaptation (ie, aftereffect) has to reach a critical threshold to affect performance in other tasks.[98] Given the high intra- and interindividual variability of individuals with USN, visuomotor adaptation induced by low power prisms (i.e., shifting the visual field of 5°, 6° or 10°) – as those used in RCT studies that did not find any beneficial outcomes after PA[94–97] – might be too small to produce detectable effects in all patients. The fact that the critical threshold can only be reached with prisms of high power (i.e., shifting the visual field of 10° or 12°, as those used in the above studies that found significant PA effects) might explain some negative findings. Another suggestive possibility is that, as demonstrated by Fortis and collaborators,[84] PA is more effective when USN affects response level of stimulus processing. However, with the exception of few investigations,[67,84] studies on PA never disentangle the two components of USN, not making possible to understand whether PA efficacy may depend on the stage (input vs output) affected by the lesion. Future investigations on PA rehabilitation (but also on other types of interventions) need to provide information on whether USN occurs at perceptual or response stages of stimulus processing. Besides the power of prismatic goggle also this variable might explain the heterogeneity of findings. In general, tailoring PA treatment to specific forms of USN may result in a more successful rate of improvement. As shown in Table 1, on the basis of Cicerone et al[83] classification, 9 out of 16 of selected works on PA were classified as class I (or Ia) studies.

Non-Invasive Brain Stimulation

NIBS may be effective in ameliorating cognitive and motor disorders in individuals affected by stroke[99,100] or by other neurological disorders.[101–103] The first attempts to treat neuropsychological symptoms using NIBS were made in individuals with USN.[104,105] In line with the hemispheric rivalry account of neglect,[45] according to which symptoms are not solely due to inactivity of the lesioned area, but also to increased activity of homologous regions of the opposite hemisphere, therapeutic effects in USN are typically obtained by down-regulating the PPC of the intact hemisphere and/or up-regulating the PPC of the affected hemisphere. It is worth noticing that the first NIBS studies for USN rehabilitation have been published less than 20 years ago. In Tables 2 and 3 are reported studies investigating the efficacy of different Non-Invasive Brain Stimulation (NIBS) techniques and protocols for the treatment of USN. The number and quality of studies reported in these Tables index a fast-growing interest and literature on this topic.

Transcranial Magnetic Stimulation (TMS)

In a proof of concept study, Brighina and collaborators were the first to apply a low-frequency (1 Hz) rTMS treatment (seven sessions over 2 weeks) to the healthy hemisphere of three individuals suffering from visuospatial neglect.[104] Participants showed significant improvement on different tasks (landmark, line bisection, clock drawing) lasting up to 15 days from the intervention. Subsequent pilot[105–108] and NRCT studies[110] administering low-frequency rTMS to the left-hemisphere in small groups of individuals with left USN confirmed and extended preliminary findings. Furthermore, two RCT-studies corroborated the above outcomes.[111,112] In recent years, researchers have also successfully applied inhibitory continuous Theta Burst Stimulation (cTBS) to the healthy hemisphere of individuals with USN in NRCT,[113,114] as well as in RCT-studies[115–118] observing long-lasting improved performance. Interestingly, Yang and colleagues[119] conducted a RCT study to compare behavioural and brain plasticity effects in USN individuals undergoing low-frequency rTMS, high-frequency rTMS, or cTBS. The cTBS group exhibited the best outcome at 1 month after the end of treatments, followed by the low-frequency and high-frequency group. Interestingly, DTI evaluation showed a connectivity enhancement of the white matter tract network related to visual attention in the cTBS group.[119] Table 2 reports TMS studies of USN treatments. On the basis of Cicerone et al[83] classification, 50% of these studies (8 out of 16) were scored as high-quality studies (class I or Ia).

Transcranial Direct Current Stimulation (tDCS)

Only a few studies have been conducted using tDCS in the context of USN. Preliminary works administering a single session of excitatory stimulation (ie, anodal or a-tDCS) to the affected hemisphere[120,121] or inhibitory stimulation (ie, cathodal or c-tDCS) to the intact one[120] showed improved performance on line bisection and cancellation/visual search tasks. In a double-blind randomized cross-over study, Sunwoo and colleagues,[122] comparing the effects of a dual-mode protocol (ie, a-tDCS of the affected hemisphere and c-tDCS of the intact hemisphere concurrently) to those of single-mode a-tDCS of the affected hemisphere, found that both single- and dual-mode tDCS were safe and effective for USN rehabilitation. Another double-blind, single-case, cross-over study,[72] using a combined approach of biparietal tDCS (the anode was applied to the right PPC and the cathode to the left PPC) and cognitive training, showed greater USN improvement when using biparietal tDCS than standard therapy alone or sham. Beneficial effects were still observed at 3 months after treatment. However, a subsequent placebo-controlled study[123] did not find any long-term USN improvement after parietal right-anodal and left-cathodal-tDCS of PPC. To our knowledge, only two studies used RCT designs. Yi and colleagues[124] applied a-tDCS to the right-PPC and c-tDCS to the left-PPC and found beneficial effects on left-USN compared to sham-stimulation. The same protocol was applied by Bang & Bong[125] in combination with Feedback Training (FT). Results showed greater improvement of symptoms after tDCS combined with FT than FT alone. In a recent NRCT study, Turgut and collaborators[126] compared the efficacy of biparietal tDCS combined with optokinetic stimulation (eight sessions over 2 weeks) to that of a standard cognitive training, in 10 individuals with LHL and 6 with RHL suffering from USN. The authors showed greater efficacy of tDCS compared to standard treatment. Interestingly, RHL-participants showed improvement of allocentric

Table 2 TMS Studies

Study	Participants	Protocol	Control	Stimulation	Coil	Number of Sessions	Tests	Assessment	Results	Design	Classification
Brighina et al,[104]	3 RH	LF-rTMS over P5	None	900 pulses 1 Hz 90% MT	Figure-of-eight	7	LBT; Length judgment; Clock drawing	Pre (2 weeks); Post, Follow-up (2 weeks later)	Improvement at least for 15 days	Pilot	Class III
Oliveri et al,[105]	5 RH 2 LH	HF-rTMS over contralesional hemisphere, P5 and P6	Sham	300 pulses 25 Hz 115% MT	Figure-of-eight	1	LBT; Length judgment	Pre, Post;	Improvement after stimulation compared to sham	Pilot	Class II
Shindo et al,[106]	2 RH	LF-rTMS over P5	None	900 pulses 0.9 Hz 90% MT	Figure-of-eight	6	BIT; BRS; BI; MMSE	Pre (2 weeks), Post; Follow-up (2, 4 and 6 weeks later)	Improvement in BIT and activities of daily living at least for 6 weeks	Pilot	Class III
Koch et al,[107]	12 RH N+ 8 RH N- 10 Healthy participants	LF-rTMS over P3	None	600 pulses 1 Hz 90% MT	Figure-of-eight	1	Visual Chimeric Test	Pre, Post	LH hyperexcitability reduced in N+ patients; reduction of left-side omissions	Pilot	Class II
Song et al,[108]	7 RH (TMS) 7 RH (Control)	LF-rTMS over P3	None	450 pulses 0.5 Hz 90% MT	Figure-of-eight	20 (twice a day)	LBT and Cancellation Task	Pre (2 weeks), Post; Follow-up (2 weeks later)	Improvement in both tasks up to 2 weeks	Randomized controlled Pilot	Class Ia
Lim et al,[109]	7 RH (TMS +BT) 7 RH (BT)	LF-rTMS over P5	Behavioural Therapy (BT)	900 pulses 1 Hz 90% MT	Figure-of-eight	10	LBT task; Albert Test	Pre (2 weeks), Post	Improvement in the line bisection task	Controlled open-label pilot	Class II
Agosta et al,[110]	6 RH	LF-rTMS over P3	Sham Coil	600 pulses 1 Hz 90%	Figure-of-eight	2	Visual tracking task; unilateral and bilateral task	Pre, Post, Follow-up (30 mins)	Improvement of sustained attention in the left visual field after rTMS, but not after sham	Crossover	Class II

(*Continued*)

Table 2 (Continued).

Study	Participants	Protocol	Control	Stimulation	Coil	Number of Sessions	Tests	Assessment	Results	Design	Classification
Kim et al,[111]	9 RH (HF-group) 9 RH (LF-group) 9 RH (sham-group)	LF-rTMS over P3 + Standard Therapy *or* HF-rTMS over P4 + Standard Therapy	Sham Coil + Standard therapy	LF: 1200 pulses 1 Hz 90% MT HF: 1000 pulses 10 Hz 90% MT	Figure-of-eight	10	Motor-Free Visual Perception Test; LBT; Cancellation test; CBS; K-MBI	Pre (2 weeks), Post	HF-group improved in line bisection task. Both the HF- and LF-groups improved in K-MBI	RCT	Class I
Cha & Kim,[112]	15 RH (rTMS) 15 RH (Sham)	LF-rTMS over P3 + Standard therapy	Sham Coil + Standard therapy	1200 pulses 1 Hz 90 Hz	Figure-of-eight	20	LBT; Box and block; Albert test; Grip strength test	Pre (4 weeks), Post	Improvement in every test after rTMS but not after sham stimulation	RCT	Class I
Cazzoli et al,[113]	5 RH (cTBS) 5 RH (Sham) 3 RH (Both)	cTBS over P3	Sham Coil	276 bursts (each contained 3 pulses at 30 Hz, repeated at 6 Hz) 100% MT	Round	2	Visual search and two cancellation tasks with high *or* low attention load; Eye-tracking	Pre, Post	Improvement of neglect severity. Redeployment of visual fixations to the contralesional visual field;	RCT Crossover	Class Ia
Hopfner et al,[114]	12 RH (SPT alone, SPT + cTBS, SPT + Sham) 6 RH (cTBS alone)	cTBS over P3	Sham Coil + SPT	801 pulses 267 bursts (each including 3 pulses at 30 Hz, repeated at 6 Hz) 100% MT	Round	1 (2 cTBS each day)	Bird cancellation task;	Pre, Post	Improvement of detection and cancellation score after cTBS + SPT compared to other conditions	NRCT Crossover	Class Ia
Cazzoli et al,[115]	8 RH (cTBS + Sham) 8 RH (Sham + cTBS) 8 (No stimulation)	cTBS over P3	Sham Coil	801 pulses 30 Hz ISI 100 ms 100% MT	Round	2 (4 cTBS each)	CBS; Vienna test system; Picture test; Munich reading texts; short aphasia checklist	Pre (1 week); Post (1, 2 and 3 weeks later)	Improvement in every test only for real cTBS at least for 3 weeks	RCT	Class I

Koch et al,[116]	9 RH (cTBS) 9 RH (sham)	cTBS over P3	Sham Coil	600 pulses 50 Hz ISI 200 ms 80% MT	Figure-of-eight	10 (2 cTBS each day)	BIT	Pre (2 weeks), Post, Follow-up (2 weeks later)	Improvement in BIT and reduced hyperexcitability of LH only after real cTBS for up to weeks after.	RCT	Class I
Fu et al,[117]	10 RH (cTBS) 10 RH (Sham)	cTBS over P5	Sham cTBS + Standard Therapy	Three-pulse burst at 30 Hz 80% MT	Figure-of-eight	56 (4 cTBS each day)	Star cancellation task; Line Bisection Task	Pre (14 consecutive days), Post, Follow-up (4 weeks)	Improvement in both tasks after cTBS, but not after Sham cTBS, at least for 4 weeks	RCT	Class I
Fu et al,[118]	6 RH (cTBS) 6 RH (active control)	cTBS over P3	cTBS over P3 40% MT	600 pulses (200 bursts at 5 Hz. Each burst contained 3 pulses at 30 Hz) 80% MT	Figure-of-eight	40 (4 cTBS each day)	Star cancellation; LBT; fMRI	Pre (10 days), Post	Improvement in every test in both groups cTBS group showed lower connectivity in VAN after stimulation	RCT	Class I
Yang et al,[119]	9 RH (LF-rTMS) 10 RH (HF-rTMS) 9 RH (cTBS) 10 Controls (Sham)	LF-rTMS *or* HF-rTMS *or* cTBS over P3 + Standard Therapy	Sham rTMS + Standard Therapy	LF-rTMS: 656 pulses, 1 Hz, 80% MT; HF-rTMS: 1000 pulses, 10 Hz, 80% MT; cTBS: 801 pulses, in bursts of 3 pulses at 30 Hz, 80% MT	Figure-of-eight	28	Star cancellation task; Line Bisection Task; DTI	Pre, Post, Follow-up (1 month)	cTBS group displayed the best curative effect followed by 1 Hz and 10 Hz group; Enhanced connections in VAN after cTBS	RCT	Class I

Abbreviations: RH, Right Hemisphere; LF, Left Hemisphere; N+, Patients with Neglect; N+, Patients without Neglect; BT, Behavioural Therapy; rTMS, repetitive TMS; cTBS, continuous TBS; HF, High Frequency; LF, Low Frequency; MT, Motor Threshold; SPT, Smooth Pursuit eye movement Therapy; LBT, Line Bisection Task; BIT, Behavioural Inattention Test; BRS, Brunnstrom Recovery Stage; BI, Barthel Index; MMSE, Mini Mental State Examination; K-MBI, Korean version of Modified Barthel Index; CBS, Catherine Bergego Scale; DTI, diffusor tension imaging; RCT, Randomized Control Trial; NRCT, Non-Randomized Control Trial.

Table 3 tDCS and GVS Studies

Study	Patients	Protocol	Control	Stimulation	Number of Sessions	Tests	Assessment	Results	Design	Classification
	tDCS									
Brem et al,[72]	1 RH	Single Mode: Anodal DC over P4	Sham DC	1 mA 20 min	10 (5 combined with standard therapy)	Covert attention test; LBT; cancelation and copy figures; ADL	Pre, Post, Follow-up (3 months)	Improvement in every test immediately after the treatment. Improvement only in ADL at the follow-up	Crossover	Class III
Ko et al,[120]	15 RH	Single Mode: Anodal DC over P4	Sham DC	2 mA 20 min	1	Cancellation task; LBT	Pre, Post	Improvement in every test	Crossover	Class I
Sparing et al,[121]	10 RH	Cathodal over P3 or Anodal over P4 or Anodal over P3	Sham DC	1 mA 10 min	1	Subtests of Test Battery of Attentional Performance LBT	Pre, Post	Improvement in LBT after Cathodal over P3 and Anodal over P4	Crossover	Class II
Sunwoo et al,[122]	10 LH	Dual Mode: Anodal DC over P4 and Cathodal DC over P3	Sham DC	1 mA 30 min	1	LBT; Star cancellation task	Pre, Post	Improvement in every test for dual and single mode. Dual mode was more effective than single	Crossover	Class I
Smit et al,[123]	5 RH	Dual Mode: Anodal DC over P4 and Cathodal DC over P3	Sham DC	2 mA 20 min	5	Conventional tasks of BIT	Pre, Post, Follow-up (1 months)	No difference between the stimulation and sham condition	Placebo-controlled	Class I
Yi et al,[124]	30 RH	Single Mode: Anodal DC over P4 or Cathodal DC over P3 + Standard therapy	Sham DC + Standard therapy	2 mA 30 min	15	Motor-free visual perception test (MVPT); LBT; Star cancellation task; CBS; m-BI	Pre, Post (1 weeks)	Improvement in MVPT, SCT, and LBT was greater in the anodal and cathodal groups than in the sham group	RCT	Class I

Bang and Bong,[125]	12 RH	Dual Mode: Anodal DC over P4 and Cathodal over P3 + FT	FT alone	2 mA 20 min	15	MVPT; LBT; m-BI	Pre, Post	tDCS + FT decreased the symptoms of visuospatial neglect significantly more than FT alone	RCT	Class I
Turgut et al,[126]	20 RH 12 LH	Dual Mode: Anodal DC over ipsilesional P4 and Cathodal DC over contralesional P3 + OKS	Standard therapy	1.5–2.0 mA 20 min	8	Spontaneous body orientation; LBT; Apples cancellation task; Clock drawing test; ADL	Pre, Post, Follow-up (6 days)	Improvement in spontaneous body orientation and in Clock Drawing Test	NRCT	Class II
	GVS									
Saj et al,[130]	7 RH (N+) 5 RH (N-) 8 Healthy participants	RC-GVS and LC-GVS	Sham GVS	1.5 mA (task time)	1	Subjective Vertical (SV)	Pre, Post	GVS induced a deviation toward the side opposite to the cathode in the three groups. LC-GVS stimulation can reduce the SV of N+	NRCT Crossover	Class II
Nakamura et al,[131]	7 RH	RC-GVS and LC-GVS	Sham GVS	Below the ST (0.4–2.0 mA) 20 min	1	Line cancellation task	Pre, Post (10 min), Follow-up (20 min)	Improvement of cancellation score after LC-GVS at least for 20 mins	NRCT Crossover	Class II
Schmidt et al,[132]	7 RH (N+) 15 RH (N-) 10 Healthy participants	RC-GVS and LC-GVS	Sham GVS	Below the ST (mean: 0.6 mA) 20 min	1	Horizontal Arm Position Sense (APS)	Pre, Post, Follow-up (20 min)	N+ showed impaired APS at baseline, which was improved after LC-GVS	NRCT Crossover	Class II
Zubko et al,[133]	2 RH	RC-GVS	None	1 mA and 1.5 mA 20 min	5	Letter and Star cancellation task	Pre, Post, Follow-up (3 days)	Improvement in both tasks at least for 3 days	Pilot	Class III
Utz et al,[134]	6 RH (N+) 11 RH (N-)	RC-GVS and LC-GVS	Sham GVS	1.5 mA 20 min	1	LBT	Pre, Post	Both RC-GVS and LC-GVS lead to a reduction of rightward bias in N+ compared to N-, but it was larger after RC-GVS	NRCT Crossover	Class II

(*Continued*)

Table 3 (Continued).

Study	Patients	Protocol	Control	Stimulation	Number of Sessions	Tests	Assessment	Results	Design	Classification
Wilkinson et al,[135]	15 RH (1 GVS – 9 Sham) 18 RH (5 GVS - 5 Sham) 16 RH (10 GVS)	RC-GVS	Sham GVS	Below the ST (0.5–1.5 mA) 25 min	10	BIT	Pre, Post, Follow-up (1 months)	Improvement after all conditions at least for 1 months	RCT	Class I
Oppenländer et al,[136]	11 RH (N +) 13 RH (N-)	RC-GVS and LC-GVS	Sham GVS	Below the ST (mean: 0.7 mA) 20 min	3 (1 for each condition)	Digit cancellation; text copying; copy of symmetrical figures; LBT	Pre, Post	L-GVS improved egocentric neglect, R-GVS results in an amelioration of the allocentric neglect	NRCT Crossover	Class II
Volkening et al,[137]	24 RH	RC-GVS and LC-GVs + SPT and VST	Sham GVS + SPT and VST	1.5 mA 20 min	10-12	Neglect test, visuo-tactile search task, SV and tactile vertical	Pre, Post, Follow-up (2 and 4 weeks)	Neither SPT nor the combination of SPT, VST and GVS improved neglect symptoms	RCT	Class I
Ruet et al,[138]	4 RH	RC-GVS and LC-GVS	Sham GVS	1.5 mA 20 min	1	LBT and star cancellation task	Pre, Post (after 10 min GVS)	No significant differences in the performance of either task following GVS	RCT crossover	Class I

Abbreviations: RH, Right Hemisphere; LF, Left Hemisphere; N+, Patients with Neglect; N+; Patients without Neglect; DC, Direct Current; OKS, Optokinetic Stimulation; RC= Right Cathodal; LC, Left Cathodal; ST, Sensory Threshold; SPT, Smooth Pursuit eye movement Training; VST, Visual Scanning Training; FT, Feedback Training; LBT, Line Bisection Task; BIT, Behavioural Inattention Test; m-BI, modified Barthel Index; MMSE, Mini Mental State Examination; CBS, Catherine Bergego Scale; ADL, Activities of Daily Life; RCT, Randomized Control Trial; NRCT, Non-Randomized Control Trial.

symptoms, while the ones with LHL improved their egocentric symptoms. Findings from this study indicate that differences between egocentric and allocentric symptoms need to be considered in future brain stimulation studies. As shown in Table 3, 5 out of 8 tDCS studies provide class I (or Ia) evidence.[83]

Galvanic vestibular stimulation (GVS) is a variant of tDCS that consists in applying a weak direct percutaneous current through an anode and a cathode positioned over the right and the left mastoids. Cathodal currents induce an increase and anodal currents a decrease in the firing rate of the vestibular nerve.[127–129] Some NRCT-studies applying R-GVS (ie, right anodal/left cathodal stimulation) showed beneficial effects on perceptual[130,131] and arm-position symptoms[132] of neglect. On the contrary, in other pilots,[133] NRCT-[134] and RCT-studies,[135] L-GVS (ie, left anodal/right cathodal stimulation) has been found to ameliorate USN and the effects persist up to a month when stimulation was applied for several (10) sessions.[135] A recent NRCT-study tested repetitive-GVS in right-brain-damaged people with neglect syndrome, by comparing the effects of R-GVS, L-GVS and sham stimulation.[136] While previous studies showed vestibular stimulation effects on egocentric spatial neglect symptoms, authors interestingly reported that L-GVS significantly improved egocentric neglect (assessed by line bisection and text copying task) whereas R-GVS results in amelioration of allocentric neglect (evaluated by figure copying and digit cancellation tasks). However, two recent RCT-studies, using repeated sessions of stimulations (10–12 sessions)[137] did not observe any post-treatment effects by GVS on neglect symptomatology.[137,138] Future studies are necessary to better understand the specific influence of GVS on disorders of spatial awareness and its potential in neglect rehabilitation. As shown in Table 3, only 3 out of 9 studies were classified as class I investigations.

Virtual Reality

Computerized methods may provide a proper alternative approach to standard methods not only for the assessment but also for the rehabilitation of neglect.[39] One of the most advanced tools recently implemented in clinical treatments is Virtual Reality (VR). In Table 4 are reported the most significant or recent studies on the use of VR for USN treatment. The VR can simulate relevant situations of everyday life and the possibility to control for head, eyes and limbs movements or postural shifts, provide a key feature for an optimal research setting.[41] To our knowledge, the only RCT-study using VR on USN-rehabilitation was conducted by Kim and colleagues.[139] Twelve people suffering from USN were asked to accomplish the following three tasks: 1) “Bird and Ball”, where they had to touch flying balls to turn them into a bird; 2) “Coconut”, where they had to grab a coconut falling down from a tree; and 3) the “Container”, where they had to relocate an object from one side to the other. The authors compared the outcomes of the experimental group to those of a control group undergoing standard training. Treatments were administered for 15 days over 3 weeks. Although both groups showed improvement after intervention, the VR-group had higher scores in star cancellation test and the Catherine Bergego Scale compared to controls. Another contribution to the use of VR in neglect rehabilitation is a single case study using the “Duckneglect” platform,[140] in which the participant was asked to reach various targets in conditions requiring different levels of difficulty. The virtual environment was arranged in ecological settings representing everyday life situations. Authors administered the videogame-like task to a man affected by neglect, 5 days a week for a month. Results showed improvement of neglect on several standard evaluations and in daily-life activities persisting up to 5 months. A third low-cost VR-system for training street-crossing was validated by Navarro and colleagues.[141] Fifteen USN individuals were recruited and compared to 17 post-stroke individuals without USN and 15 healthy participants. Interestingly, results showed that USN-group had more difficulties crossing the street avoiding accidents than the non-USN control group and healthy controls. Furthermore, a correlation between the scores of standard neuropsychological tests and those of the virtual street-crossing system was observed, suggesting the potential of the VR approach for USN rehabilitation. Another novel VR-training method is the RehAtt.[142] The software consisted in visual scanning training with multi-sensory stimulation in a VR-environment. Fifteen post-stroke individuals suffering from chronic neglect were trained for 15 sessions over 5 weeks. Results showed that the VR-training improved visuospatial deficits and activities of daily living.[142] Interestingly, 2 years later, authors used fMRI to evaluate changes in brain activity during Posner′s Cueing Task after RehAtt™ rehabilitation. The amelioration of neglect symptoms was associated with increased brain activity in the pre-frontal and temporal cortex during attentional cueing,[143] suggesting enhancement of top-down strategies, and increased inter-hemispheric resting-state functional connectivity of the dorsal attentional

Table 4 Virtual Reality (VR) Studies

Study	Participants	Control	VR Training	Number of Sessions	Tests	Assessment	Results	Design	Classification
Kim et al,[139]	24 RH (12 VR-Group and 12 Control Group)	Standard therapy	Bird and Ball (touch a flying ball); Coconuts (catch falling coconuts); Container (move a box from one side to another)	15 sessions of 30 mins	Star Cancellation task; LBT; CBS; K-MBI	Pre, Post	Improvement in CBS and in star cancellation task after VR training	RCT	Class I
Mainetti et al,[140]	1 RH	None	Duckneglect (reach targets with an increasing level of difficulties)	20 sessions of 30 mins	Albert Test; Letter Cancellation Test; LBT; MMSE; Attentional Matrices and the Token Test	Pre, Post, Follow-up (5 months later)	Improvement in MMSE, Attentional matrices, Albert test and LBT, at least for 5 months	Single-case	Class III
Fordell et al,[142]	15 RH	None	VST and multi-sensory stimulation	15 of 1 hr	VR-Star cancellation; VR-Baking tray task; VR-LBT; VR-Extinction; VR-Posner Task; CBS	Pre, Post, Follow-up (6 months)	Improvement in Star cancellation, Baking tray, Extinction and Posner Task; Improvement in CBS at least for 6 months	Pilot	Class III
Ekman et al,[143]	12 RH	None	VST and multi-sensory stimulation	15 of 1 hr	VR-Posner Task; fMRI	Pre (1 week), Post (1 weed)	Improvement in Posner performance. Increasement after VR-training in frontal and temporal activity during attentional cueing	Pilot	Class III
Wåhlin et al,[144]	13 RH	None	VST and multi-sensory stimulation	15 of 1 hr	VR-Posner task; rs-fMRI	Pre (1 week), Post (1 week)	Increasement of DAN connectivity	Pilot	Class III

Abbreviations: RH, Right Hemisphere; VST, Visual Scanning Training; LBT, Line Bisection Task; K-MBT, Korean version of Modified Barthel Index; MMSE, Mini Mental State Examination; CBS, Catherine Bergego Scale; DAN, Dorsal Attention Network; RCT, Randomized Control Trial.

network.[144] A final promising protocol was tested in a single-blind dose–response study in healthy subjects, by using VR as an alternative to real prisms.[98] Authors progressively induced a displacement of the visual field following the virtual PA procedure, making difficult for the subject to become aware of the experimental manipulation. Results showed that large rightward deviations may affect sensorimotor performance in healthy participants similarly to neglect patients without generating discomfort linked to the large visual shift. However, results need to be replicated in stroke individuals with USN. Taken together, these studies suggest that VR-systems may represent a suitable alternative to standard rehabilitation techniques. By involving multisensory online feedbacks in real-like situations, virtual approaches may provide novel powerful tools for neglect rehabilitation.[145] As shown in Table 4, only one out of five studies was classified as class I investigation. However, VR is one of the most recent and innovative approaches of USN rehabilitation and, up to now, its potentials have been only minimally explored.

Conclusions and Future Directions

Investigations of USN have provided most of the knowledge we currently have on the neural mechanisms of spatial attention and representation and their interaction with the response system. Nonetheless, correlating brain lesion localization with behavioral impairment presents a series of limitations (i.e., the extent of natural lesions which often involve more than one structure, the effects of the diaschisis and brain reorganization). Moreover, individuals' clinical and cognitive conditions may posit practical constraints on recruitment and testing. In the last 20 years, cognitive neuroscientists have used TMS to induce neglect-like behaviors in healthy volunteers and overcome the above limits. These studies have disentangled previous controversies on neglect neuroanatomy, confirming a causal role of the right PPC in visuospatial attention during performance of stimulus detection[146] and line bisection/landmark [60,147–153] tasks, and a role of superior temporal cortex in the performance of visual conjunction search task.[18] These findings, in line with the observation that USN may dissociate across tasks, further highlight the importance of using diverse types of assessment tools to reliable evaluate neglect symptomatology for both clinical and experimental purposes. Consistent with recent studies on neglect neuroanatomy,[58,154] single-pulse TMS applied to the right PPC inside the scanner, shows that neglect-like bias on the landmark task is associated with decreased activity of right parieto-frontal areas corresponding to those connected by SLFII.[60] In contrast to the rivalry account of USN[45] and in line with Heilmann's hypothesis,[8] these TMS/fMRI findings also show decreased activity of contralateral PPC (see Bagattini et al[155] for similar findings), suggesting that unbalanced inter-hemispheric activity might worsen neglect symptomatology but not be necessary for its emergence. Future TMS and neuroimaging studies in the healthy brain may help to clarify the nature of neglect symptoms and the possibilities offered by brain stimulation, PA and other techniques to modulate them. As described in the present paper, high-quality studies have already demonstrated the efficacy of PA, TMS and tDCS interventions for the treatment of USN. In addition, preliminary investigations are suggesting the potentials of GVS and VR approaches for UNS rehabilitation. However, optimal protocols for USN rehabilitation still need to be defined.

To sum up, the application of advanced neuroimaging and brain stimulation techniques in healthy individuals and in individuals with USN may help to overcome parts of the limits posit by classical neuropsychological studies. On the other hand, only high-quality neuropsychological investigations of individuals with USN may provide unique insights into the syndrome and, consequently, into the mechanisms underpinning conscious space representations in the healthy brain.

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