# Rightward exogenous attentional shifts impair perceptual memory spatial locations in patients with left unilateral spatial neglect

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# Rightward exogenous attentional shifts impair perceptual memory of spatial locations in patients with left unilateral spatial neglect

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## RESUME

Memory for a spatial location's representation is impaired in patients with left unilateral spatial neglect following a rightward gaze-shift, but not a leftward one. This is attributed to the loss of spatial representations normally transferred to the right hemisphere during spatial remapping, a process normally ensuring the updating and integration of successive retinal images in the parietal cortex. Because attentional and oculomotor processes may share partly similar brain circuits, we hypothesized that attentional displacements without overt eye movements might suffice to remap spatial locations' representations. We found a deficit in spatial locations' memory following an exogenous attentional shift caused by a flash in the right periphery in seven neglect patients (mean age 54 ±11.63 SD) comparing with matched non-neglect patients (mean age 65 ±10.21 SD) and healthy controls (mean age 65 ±7.69 SD). Results support the role of a remapping deficit in unilateral spatial neglect, which impairs the maintaining of spatial representations leftward to the direction of gaze or attention.

*Des déplacements attentionnels exogènes vers la droite perturbent la mémoire perceptive des localisations spatiales chez des patients avec une négligence spatiale unilatérale gauche*

Le maintien de la représentation d'une localisation spatiale est perturbé chez des patients avec une héminégligence gauche suite à une saccade vers la droite, mais pas vers la gauche. Ceci est attribué à la perte des représentations spatiales normalement transférées à l'hémisphère droit durant le 'remapping' spatial, un processus assurant normalement la mise à jour et l'intégration des images rétiniennes successives dans le cortex pariétal. Du fait que les processus attentionnels et oculomoteurs partagent certains circuits cérébraux, nous avons émis l'hypothèse que des déplacements attentionnels sans mouvements oculaires pourraient suffire au 'remapping' des représentations des localisations spatiales. Un déficit en mémoire de localisations spatiales suite au déplacement attentionnel exogène provoqué par un flash dans le champ périphérique droit a été observé chez sept patients négligents (âge moyen 54 ±11.63), absent chez des patients appariés non-négligents (âge moyen 65 ±10.21 SD) et des sujets sains (âge moyen 65 ±7.69 SD). Les résultats supportent le rôle potentiel d'un déficit de 'remapping' spatial dans l'héminégligence, qui perturbe le maintien des représentations spatiales à gauche de la direction du regard ou de l'attention.

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# 1. INTRODUCTION

Unilateral spatial neglect (USN) is a frequently observed syndrome following unilateral brain damage, in which patients act as if the contralesional side of space did not exist. USN is commonly defined as “a failure to report, respond, or orient to stimuli that are presented contralateral to a brain lesion, provided that this failure is not due to elementary sensory or motor disorders” (Heilman & Valenstein, 1979). USN can be observed in spontaneous behavior as well as in response to external stimulation. The lack of awareness of such incapacity, anosognosia, often accompanies neglect. Patients often believe that they normally perceive the environment.

Debate is still open about the mechanisms of USN. Different theories try to explain its underlying neuroanatomical basis and cognitive components, but no unanimity is yet established. What is certainly assumed is that neglect is not a unitary syndrome.

USN is most often observed following stroke (15-85% during the acute phase, 30-40% after 3 months), either ischemic or hemorrhagic. In general, USN is more frequent (twice as frequent in the acute phase) and persistent following right- than left-hemisphere damage (Vuilleumier & Saj, 2013). This is thought to be due to the right hemisphere dominance in spatial processing: while the left parietal cortex controls attention in the right hemifield, the right hemisphere controls attention bilaterally (Posner, 1980; for a review see Vuilleumier, 2013). From now on the ‘neglect’ term will only refer to left neglect following a right lesion. USN is also thought to be more severe following right than left damage. However, Suchan, Rorden, and Karnath (2012) found that neglect in the acute phase is equally severe following right or left damage.

The core deficit of USN concerns the orientation of attention in space. Patients show a rightward attentional bias, accompanied by a deviation of the eyes and head toward the ipsilesional side of space. Many different clinical symptoms, concerning attentional and spatial deficits, can be observed in USN patients. For example, patients don’t see objects on their left, don’t eat the left half side of their plate, don’t shave the left side of their face, don’t hear a voice coming from their left, don’t turn left across an open door, or read only the right side of lines in books. Another typical symptom is perceptual extinction: patients fail to perceive and report a stimulus placed on the left side if presented simultaneously with another stimulus placed on the right side, but they can correctly perceive it if presented alone (Vuilleumier, 2013).

Neglect can affect perception, but also mental imagery (Bisiach & Luzzatti, 1978) and motricity, with underuse or no-use of the contralesional arm (Rode & Pisella, 2011). Perceptual neglect can affect different sensory modalities (visual, auditory, olfactory, somatosensory), different parts of space (personal, peripersonal or near, extrapersonal or

far) and different spatial reference frames (egocentered, object-centered) (Vallar, 2001; Vuilleumier & Saj, 2013).

Concerning USN manifestations, it is also important to note the link between biases in attentional processing and intentional planning of movements. Perceptual and motor neglect cannot be easily distinguished, since action and perception interact constantly: a perceived stimulus will influence exploratory behavior toward it, and goal-directed behavior determines the stimuli that will be perceived. This underlies the potential role of associative areas in USN, areas responsible for spatial, attentional and intentional processing (Vuilleumier & Saj, 2013).

In the light of such a number of distinct and dissociable clinical manifestations, a unitary interpretation of USN appears impossible, since distinct cognitive impairments can result from damage to different neuronal regions and networks of the right hemisphere.

Two categories of explanatory models try to explain USN: attentional hypotheses, considering neglect as a disorder of the orientation of attention in space, and spatial hypotheses, considering neglect as a specific disorder of space organization or interpretation. There still isn't any hypothesis unanimously accepted by researchers; in fact, an integrated approach, combining functional and clinical data, seems to be more useful and less reductionist in the understanding of neglect, particularly in the light of spatial and attentional deficits coexisting in patients (Chokron, Bartolomeo, & Siéroff, 2008).

## Neuroanatomy of USN

USN patients often show large lesions in the right hemisphere, which might impair multiple functional modules. Lesions superposition among neglect patients has more often highlighted the implication of the temporoparietal junction (TPJ) and inferior parietal lobule (IPL), the superior temporal gyrus (STG), and the ventrolateral prefrontal cortex (Karnath & Rorden, 2012; Mort et al., 2003; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010).

Studies based on functional MRI (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Umarova et al., 2011) showed that injury to the right temporoparietal junction could induce functional imbalance in the right and left superior parietal lobules (structurally intact), involved in the orienting of attention, with the consequence of a rightward orientation bias.

Many studies that focused on white matter lesions also brought evidence for the implication of the superior longitudinal fasciculus (SLF), linking frontal and parietal lobes (Thiebaut de Schotten et al., 2012; Verdon et al., 2010). Thiebaut de Schotten et al. (2012) used diffusion tensor imaging to investigate the white matter pathways implicated in USN, and found that damage to the second branch of the SLF is most correlated with neglect symptoms. The authors also proposed that damage to different portions of the SLF could

account for different clinical neglect manifestations, since they could be associated with different specific disconnections of shorter white matter pathways within the frontal or parietal lobes. The inferior longitudinal fasciculus (ILF) could also be implicated in USN (Bartolomeo, 2011). A disconnection between cortical regions due to white matter injury, besides structural damage to specific areas, could then also produce USN. This can be further accompanied by 'diaschisis', the metabolic dysfunction of a cerebral intact area due to its disconnection from the damaged area.

Lesions restricted to subcortical regions can also produce neglect (Chokron et al., 2008), in particular lesions to the caudate nucleus, the putamen and the thalamic pulvinar. Cognitive deficits following such lesions appear to be caused by a metabolic indirect effect: a reduced perfusion in the cortical intact areas as noted above (diaschisis). A dysfunction of the cortical perisylvian network is however the first cause of USN.

Verdon et al. (2010), performing factorial analysis, highlighted the existence of three components of neglect (egocentric/visuospatial, exploratory/visuomotor and allocentric/object-centered), related respectively to parietal, frontal and temporal lobes. Saj, Verdon, Vocat, and Vuilleumier (2012) confirmed the same results and found that the three components remained similar in the acute and the chronic stage, despite changes in neglect severity.

## Spatial Remapping

According to some authors (Pisella & Mattingley, 2004; Vuilleumier et al., 2007), a deficit in spatial remapping could contribute to USN.

Every saccade projects a new visual image on the retina; the visual input in the occipital visual cortex changes all the time. Spatial remapping is the process, operating in posterior parietal cortex, which allows the integration and updating of visual information in oculocentric coordinates: the stimulus' location is 'remapped' across saccades in terms of distance and direction from the fovea. Spatial remapping "provides spatial constancy of visual perception and a spatial buffer for working memory" (Pisella & Mattingley, 2004, p. 181).

In 1992, Duhamel, Colby and Goldberg found neurons in the monkey's posterior parietal cortex that seem to play a crucial role in the stabilization of the visual image, or the dynamic linkage of successive retinal images. Using a single-cell recording technique, the authors highlighted some neurons in the macaque's lateral intraparietal area (LIP), which have retinocentric receptive fields and whose activation reflects the predicted perceptual consequences following a just-to-begin saccade. Such neurons activate as if the stimulus was already in their receptive field, even if the saccade has just to begin and the stimulus

image is actually not yet seen on the new retinal location. This finding has been interpreted as the neural basis of a mechanism supporting perceptual stability in visual behavior and spatial awareness. In other words, these neurons 'remap' their receptive field anticipating the saccade, and thus predict sensory input based on the expected retinal position after the saccade.

Duhamel and colleagues used fixation-saccade tasks to demonstrate two main findings: firstly, concerning predictive remapping, they observed that LIP's neurons whose receptive field will be placed at the location of a visual stimulus only after a saccade, respond to that stimulus just before the saccade begins (80 ms in advance). On the contrary, if the same neuron is currently stimulated (at fixation), but the predicted just-to-come saccade will take its receptive field away from the stimulus, its activity will decrease earlier and quicker than in the condition of normal fixation on the stimulus. To say it with the authors' own words: "the cortical representation shifts first, and then the eye catches up" (Duhamel, Colby, & Goldberg, 1992, p. 90). Secondly, these authors observed that almost all LIP neurons show no such anticipatory remapping, but respond when a saccade brings their receptive field where a stimulus has *previously* been presented. This happens even if the neuron has never been directly stimulated by that input before. Such updating (or remapping) of retinal coordinates seems to represent a mechanism sensible to remembered spatial locations, supporting some kind of 'spatial memory'. The authors concluded that "the visual memory trace is coded in a retinotopic format that is updated with each eye movement" (Duhamel, Colby, & Goldberg, 1992, p. 91).

These two remapping mechanisms together, anticipation of retinal consequences and updating of new retinal coordinates, may allow our subjective perception of the visual environment to be stable and coherent. Representation of stimulus location is always kept updated in short-term memory in terms of its distance and direction from the fovea (gaze direction). This dynamic integration of visual information over time may support a construction of gaze-centric representations of visual space.

Interestingly, Reuschel, Rösler, Henriques, and Fiehler (2012) showed that the modulation of gaze-shifts (saccades) on spatial remapping develops early in life on the basis of visual experience and is still observed in late-blind subjects. This suggests that this mechanism is a very fundamental process mediated by higher non-visual associative areas.

We know that representations are created in a gaze-centric format since remapping happens across saccades: the posterior parietal cortex combines retinal information coming from successive eye positions with the extraretinal information (like motor commands) relative to the intervening saccades, in order to constantly update visuospatial representations (Colby, Duhamel, & Goldberg, 1995). The latter authors argued that "spatial locations are defined not by a stimulus or by a movement, but by the spatial vector that could

describe either; remapping is the means by which a coordinate transformation is effected from retinotopic to oculocentric coordinates" (Colby, Duhamel, & Goldberg, 1995, p. 475).

Following studies on the monkeys that identified neurons in the posterior parietal cortex (LIP) responsible for spatial remapping in a gaze-centered frame, Medendorp, Goltz, Vilis, and Crawford (2003) highlighted an analogous region in the human posterior parietal cortex, which updates spatial representations across saccades in a gaze-centered frame (and not, for example, in a head- or body-centered frame). The authors tested six healthy subjects in the fMRI, who performed two tasks: a delayed-movement task, where subjects had to make either a saccade or a pointing movement toward the remembered location after a delay, and an intervening-saccade task. During the delayed-movement task, a medial zone of the intraparietal sulcus (IPS) in left and right hemisphere responded to contralateral stimuli, both for saccades and pointing movements. Results from the intervening-saccade task suggested that this area represents and updates location information in a gaze-centered frame, since location of the second target remained stable relative to the head and body position, but needed to be updated correctly relative to the new ocular coordinates following the first intervening saccade. In this task, two sequentially flashed visual targets (at different eccentricities but in the same hemifield, either left or right) are sequentially fixated by the subject, after starting from a central fixation point. The two targets disappear before the first saccade is performed. This means that the subject has to integrate oculomotor information (the first-saccade vector) to update the spatial-retinotopic information about the second target and predict its new position relative to the new eye position. Remapping mechanisms are thus required to correctly perform the second saccade. Similarly to the first task, results showed a gaze-centered remapping pattern: when the location of a remembered target shifted from left to right (or vice-versa) relative to the new fixation point, dynamic shifts of activity were observed between the two hemispheres. For example, in the condition where the first target was flashed on the left hemifield and the second on the right of the first target (but still on the left hemifield), the left parietal cortex increased its activation following the first saccade (when the second remembered target was situated contralaterally relative to the new gaze-direction), while activation in the right hemisphere decreased.

Some years before, Ingle (1992) had already highlighted the importance of interhemispheric transfer in remapping mechanisms and integration of spatial information. The author tested five callosotomised (split-brain) patients in a pointing task toward memorized targets after passive turns of the body: performance was impaired when an interhemispheric transfer of spatial locations was necessary to operate correct remapping.

Van Koningsbruggen, Gabay, Sapir, Henik, and Rafal (2009) showed a hemispheric asymmetry in spatial remapping in a TMS (transcranial magnetic stimulation) study. They inactivated the left or right anterior intraparietal sulcus after a saccade: only inactivation of

the right hemisphere induced incorrect remapping (incorrect updating of a spatial location). This was true independently of whether the saccade occurred toward the left or the right visual field, and independently of the hemifield where the stimulus had appeared. The authors therefore concluded that the right parietal cortex is responsible of maintaining a saliency map (remapping the salience of visual stimuli) across saccades, but is not only implicated in sending corollary (motor) extra-retinal signals about intervening saccades to update such salience map. These observations are congruent with clinical observations on USN patients: the right hemisphere seems to be more implicated than the left in processing visuospatial information.

A few years later, Pisella et al. (2011) supported the existence of a specialized network for spatial remapping that is lateralized in the right hemisphere, centered on the TPJ. They tested a patient (not affected by USN) with a lesion touching the right posterior parietal cortex (PPC) and part of the corpus callosum in a double-step saccade task (DSST, see *Spatial Remapping and USN* part). The patient showed an impaired performance only when the second saccade had to be directed to the right, which is supposed to be processed by the intact left hemisphere. The authors concluded that such impairment couldn't result solely from the PPC lesion, since the direction of the first saccade didn't influence the second, but rather from damage to the corpus callosum: the right remapping network couldn't send locations' information, necessary to execute correct saccades, to the oculomotor regions in the left hemisphere. The patient's impairment thus seemed to be due to a deficit in interhemispheric transfer rather than to a remapping deficit per se.

Apart from automatic spatial remapping, operating across saccades in order to provide a stable and coherent perception of the visual world, we also need spatial remapping in order to correctly interact with the environment. In the case of reaching movements we talk about intentional remapping. Blangero, Khan, Rode, Rossetti, and Pisella (2011) proposed that both types of remapping (automatic and intentional) implicate the PPC, but in a different manner: the interhemispheric transfer of visual information necessary to automatic remapping could be sustained by more posterior regions (like the TPJ or extrastriate areas), while the interhemispheric transfer of visuomotor information necessary to intentional remapping could be sustained by the PPC itself or by more anterior regions (like the prefrontal cortex). Interestingly, a very recent study (Schütz, Henriques, & Fiehler, 2013) showed that if gaze-independent allocentric information (landmarks) is available in the environment, the brain combines it with gaze-dependent representations (spatial remapping) to guide reach movements.

## Spatial Remapping and USN

Besides directional deficits in the deployment of attention, many other cognitive deficits contribute to the heterogeneous collection of USN manifestations (Vuilleumier & Saj, 2013). Among them, there are non-lateralized deficits that could interact with the rightward directional biases in determining the deployment of attention and exacerbating left neglect. A deficit in spatial working memory or remapping, allowing the brain to maintain track of spatial locations across eye movements, could contribute in keeping spatial exploration biased toward the ipsilesional side of space.

Husain et al. (2001) firstly brought evidence for such a deficit: in exploratory tasks, besides neglecting the left side, patients re-fixate targets that have already been detected, showing an apparent defect in remembering locations after only a few saccades or seconds. Interestingly, other non-spatial deficits (like vigilance or sustained attention) could also interact with a spatial working memory deficit in USN: patients show a reduction of performance over time in maintaining in memory two locations presented vertically, while they show a normal performance for letters or other visual stimuli (Malhotra, Coulthard, & Husain, 2009).

Other authors have subsequently investigated the potential role of a remapping deficit from another perspective: the updating of spatial representation during exploration of visual scenes.

Sapir, Hayes, Henik, Danziger, and Rafal (2004) tested five patients with right unilateral damage touching the intraparietal sulcus and twelve control subjects using inhibition of return (IOR). IOR (Posner & Cohen, 1984) is the phenomenon whereby a recently stimulated visual location is transiently inhibited, with subjects responding slower to a target being presented in such location (after an interval of around 300 ms), a phenomenon that should allow more efficient visual search by facilitating exploration of new locations. In Sapir et al.'s paradigm (2004), four boxes formed a virtual square on the screen (slightly shifted to the left or the right side of the screen): one of the boxes was flashed as a visual clue at the beginning of each trial, and a target stimulus was to be detected as soon as possible in one of the four boxes. The cue wasn't predictive of the target location. The task comprised two conditions: fixation (fixation was maintained at the center, environmental and retinal cue's locations were identical) and eye movement (a saccade needed to be executed toward a marker during the delay between the cue and the target, so that the target could fall on either the environmental location of the cue, the retinal location of the cue, or at one of the two uncued locations). The authors predicted that control subjects would show IOR at the environmental location of the cue due to parietal remapping mechanisms, while patients would be unable to remap environmental locations after a saccade and would show IOR at

the retinal instead of the environmental cue location. Results confirmed the authors' predictions, showing an absence of spatial remapping in patients. Moreover, patients didn't remap environmental cue locations independently of the direction (ipsi- or contra-lesional) of the saccade. This suggested that the parietal circuit that remaps locations in a dynamic way across saccades could also be responsible for encoding inhibitory tags in environmental coordinates. In other words, it seems that inhibitory tags (enabling efficient visual search) are remapped across saccades in healthy subjects, like it's done for stimuli locations. The posterior parietal cortex could be responsible of this updating of visual saliency maps across saccades.

Pisella and Mattingley (2004) focused on the role of the parietal cortex in spatial remapping and put on the idea that unawareness for left space, revisiting behavior during search and other clinical signs of USN that are still not understood could be explained by such a deficit. Based on results from the double-step saccade task (DSST) (similar to the intervening-saccade task, see *Spatial Rremapping* part), Pisella and Mattingley (2004) proposed the theoretical model of a remapping deficit in neglect patients. In the DSST, two sequentially flashed visual targets (A, on the left, and B, on the right) are sequentially fixated by the subject, after starting from a central fixation point (FP), such that the subject has to make two consecutive saccades: from FP to A, and from A to B. While the first saccade is performed, the two targets disappear. This means that the subject has to integrate oculomotor information (the first-saccade vector) to update the spatial-retinotopic information about target B and predict its new position relative to the new eye position. Remapping mechanisms are thus required to correctly perform the second saccade toward target B. USN patients with damage to the right posterior parietal cortex (PPC) cannot correctly execute the second rightward saccade toward target B when target A is flashed on the left (contralesional, neglected) hemifield. The authors suggested that the position of the right target couldn't help being overwritten when another target in the neglected field had previously been fixated. In other words, a saccade toward target B in the ipsilesional (right) hemifield is impaired by a failure of the remapping mechanism (operating in the injured right PPC) to correctly update B's position with incoming oculomotor information from the first saccade to target A. On the contrary, there is no impairment when target A is on the right (ipsilesional) hemifield and a leftward saccade toward target B follows; in this case, a saccade toward the contralesional (neglected) hemifield can be correctly performed thanks to the intact remapping mechanism operating in the left PPC. In left-injured neglect patients the opposite pattern of performance at the DSST was found. In case of right injury, though, performance is affected even when doing intra-hemifield (left) saccades, while in case of left injury performance is affected only following inter-hemifield saccades. Results show the crucial role of interhemispheric transfer for spatial remapping and integration of information

coming from both hemifields. The authors explained this asymmetric pattern as a consequence of the hemispheric parietal asymmetry: the right posterior parietal cortex is in charge of remapping locations in both hemifields, while the left posterior parietal cortex remaps only locations in the right hemifield.

Based on these findings, Pisella and Mattingley (2004) proposed the following model of a remapping deficit in USN patients (see Figure 1). In right-injured patients, representations of spatial locations concerning the whole visual field would be lost or 'overwritten' by the new incoming information following a leftward (contralesional) saccade. Differently, a rightward (ipsilesional) saccade would only affect locations in the previous left hemifield. In left-injured patients, rightward or leftward saccades would only overwrite locations on the opposite hemifield relative to saccade direction. According to this model, in case of left or right injury representation of the left hemifield is overwritten similarly following a rightward saccade. Following a leftward saccade, right-injured patients lose not only representation of the right hemifield (like left-injured patients), but of the whole visual scene.

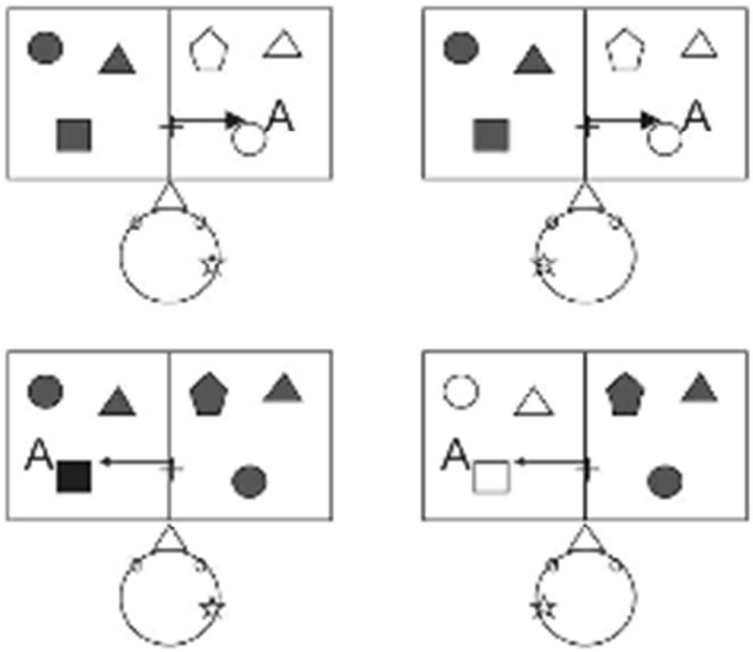


*Figure 1.* The objects in black represent objects that will not be correctly remapped in spatial representations following a saccade according to Pisella and Mattingley's theoretical model (2004); such objects depend on lesion side (star) and saccade direction (arrow) toward point A (taken from Pisella & Mattingley, 2004).

The authors speculated that such a lack of visual coherence (loss of position, identity and number of previously fixated objects in the visual scene) could result in the frequently observed anosognosia for neglect. Moreover, they think that rightward saccades could be

further promoted by typical attention biases in right-injured patients, what makes the overwriting of left hemifield always bigger and could explain many symptoms of USN (like extinction behavior).

Pisella and Mattingley (2004) proposed their model based on theoretical assumptions. Few years later, Vuilleumier et al. (2007) decided to experimentally test a related hypothesis. The authors made up a new experimental paradigm to test the role of spatial remapping on gaze-centric representations in USN. More than strictly on oculomotor behavior, the authors focused on spatial memory: their hypothesis was that right-injured neglect patients would show a deficit in maintaining spatial locations for several seconds across saccades. This was based on a work by Umeno and Goldberg (2001), who showed that neurons in monkeys' frontal eye field could maintain activation even after the stimulus in their receptive field had disappeared, if the location of that stimulus remained task-relevant. Moreover, dynamic remapping could operate on such activation: when a saccade brings that location into the receptive field of another neuron, this one will activate in response to the memory trace of that relevant location, even if it has never been directly stimulated. Medendorp et al. (2003), as we saw above, observed the same activity modulation in humans' parietal and prefrontal cortex. It thus seems that maintaining locations across saccades doesn't involve a unique neurons' population, but rather relies on a dynamic process involving changeable patterns of neurons. According to this view, Vuilleumier et al. proposed that

for a location initially encoded at fixation, a rightward gaze-shift should remap it leftward in gaze-centric terms, and so presumably into neuronal subpopulations of the contralateral right hemisphere. […] However, such remapping might be severely disturbed in a neglect patient, for whom right hemisphere damage could destroy some of the neuronal populations representing leftward locations within gaze-centric maps. […] The trace of the remembered location should become degraded or lost in neglect patients; hence, not be remappable out of the 'black-hole' of the gaze-centric map, even if gaze subsequently returned to the initial fixation. (2007, p. 1391)

This paradoxical prediction is opposite to the one of Pisella and Mattingley (2004), and contrasts with findings in the double-step saccade task (DSST), where deficits have been attributed to the loss of efference copies predicting saccades. However, Vuilleumier et al. (2007) tested explicit spatial memory: efference copy should therefore not play a role in such longer delays, since different neural circuits (than those implicated in faster and automatic oculomotor reactions) can potentially be recruited here. Moreover, if the loss of efference copies played a role, the authors would find results opposite to their predictions.

In Vuilleumier et al.'s study (2007), 7 USN patients affected by right unilateral stroke and 7 control subjects without brain lesions were tested. The task was to tell the color (red or green) of a dot appearing on the left or the right side of a computer screen by fixating it, after what the dot disappeared for a few seconds. During this 2-seconds delay, two conditions were tested. In the 'no-remapping' condition, nothing happened and the screen remained blank. In the 'remapping' condition, a small letter was presented on the far right or left of the screen, which had to be fixated and named by subjects. This condition imposed thus a gaze-shift either leftward or rightward. At the end of the 2-seconds delay, a second colored dot appeared on the screen, either at the same position as before or slightly shifted to the left or right. At the end of the trial, subjects had to tell whether the second dot appeared at the same position as the first one or not (same/different judgment). The authors predicted that left-neglect patients would show impaired spatial memory performance (in maintaining the representation of target location) only when a rightward saccade occurred. Results supported precisely this hypothesis, and thus contrasted with Pisella and Mattingley's model (2004) according to which spatial memory should be impaired after any leftward gaze-shift, due to an 'overwriting' of all previous locations' representations. More precisely, results showed that neglect patients' performance after rightward gaze-shifts (implying remapping of the remembered dot location on the left in gaze-centric representations, thus operating in the right parietal cortex) was identically impaired whether dots were presented on the left or on the right side of the screen. In other words, the direction of gaze-shifts has an asymmetric effect on spatial memory (or, presumably, on the remapping processes allowing spatial memory) independently of whether the location to be remembered is on the neglected or in the non-neglected side of space.

In the light of their results, Vuilleumier et al. (2007) also put on the idea of a remapping deficit in neglect patients, although they didn't take it as the sole and main deficit in the USN syndrome. However, such deficit might certainly contribute to many symptoms, since rightward saccades are continuously made either in daily life or during clinical testing. For example, revisiting behavior during search tasks (like cancellation tasks), omissions in drawing tasks (like scene copy), rapid forgetting of spatial scenes in familiar settings. Accordingly, the authors found that the remapping deficit shown by patients at the spatial memory task was positively correlated with the severity of USN (measured as average performance at many different clinical tests). Subtraction of brain damaged areas between patients who showed a relatively severe remapping deficit and patients who showed a relatively milder remapping deficit highlighted the implication of the inferior parietal and superior temporal lobe, its underlying white matter and subcortical regions. These regions are well known to be implicated in USN.

In conclusion, Vuilleumier et al. (2007) interpreted the observed impossibility for neglect patients to maintain a spatial location across a rightward saccade as the failure in transiently update such location on the left of their gaze-centric representation, since this cannot be taken in charge by the injured right hemisphere. The spatial representation seems thus to be lost or degraded when it has to be updated by the right hemisphere. These results support studies on monkeys and humans that highlighted a process of dynamic remapping operating on gaze-centric spatial representations. Moreover, they show for the first time the direct impact that a deficit in such dynamic remapping can have on explicit spatial memory, beside than on oculomotor behavior.

It should be noted that a deficit in spatial remapping could also be implicated in other neuropsychological spatial syndromes than USN, like in constructional apraxia (Russell et al., 2010).

## Hypothesis

Since Rizzolatti, Riggio, Dascola, and Umiltá's premotor theory of attention (1987, see *Discussion)*, many studies (Awh, Armstrong, & Moore, 2006; Corbetta et al., 1998; Smith & Schenk, 2012) have highlighted the possible overlapping of neural circuits implicated in spatial attention and oculomotor behavior. Based on this overlapping, it would be interesting to test the same effect observed by Vuilleumier et al. (2007) when a rightward transient shift of attention occurs but does not imply an eye movement. In other words, with USN patients fixating a central point all along the trial and attention being shifted only covertly to the far right of the computer screen. Should the same pattern of performance be observed, a more general 'attention-centric' perspective could account for the hypothesis of a remapping deficit in neglect patients; if, instead, the rightward shift should not impair the maintaining of spatial locations, then a strictly gaze-centric interpretation could better explain the remapping deficit.

The aim of this study was to investigate whether an eye movement is necessary to observe the spatial remapping phenomenon in neglect patients, or an attentional shift alone (without eye movement) could induce the same phenomenon. Our hypothesis was that an attentional stimulation on the right periphery of the visual field impairs the maintaining of the representation of a spatial location, and thus impairs the spatial remapping process, in right-injured patients affected by left USN.

## 2. METHODS

### Subjects

7 patients (mean age 54 ±11.63 *SD*) with right-hemisphere lesions (see Figure 2b) who presented USN symptoms were tested and compared to two control groups. The first was composed of 7 patients (mean age 65 ±10.21 *SD*) with right-hemisphere lesions (see Figure 2a) who did not present USN symptoms, and the other was composed of 7 healthy subjects (mean age 65 ±7.69 *SD*). No significant differences were observed between ages in the three groups (non-neglect vs. neglect patients: $p = .071$; non-neglect patients vs. control subjects: $p = .472$; neglect patients vs. control subjects: $p = .056$). All patients had a right-hemisphere stroke, ischemic or hemorrhagic, demonstrated by MRI or CT scan. The precise location of the lesions in the right hemisphere was not specified.

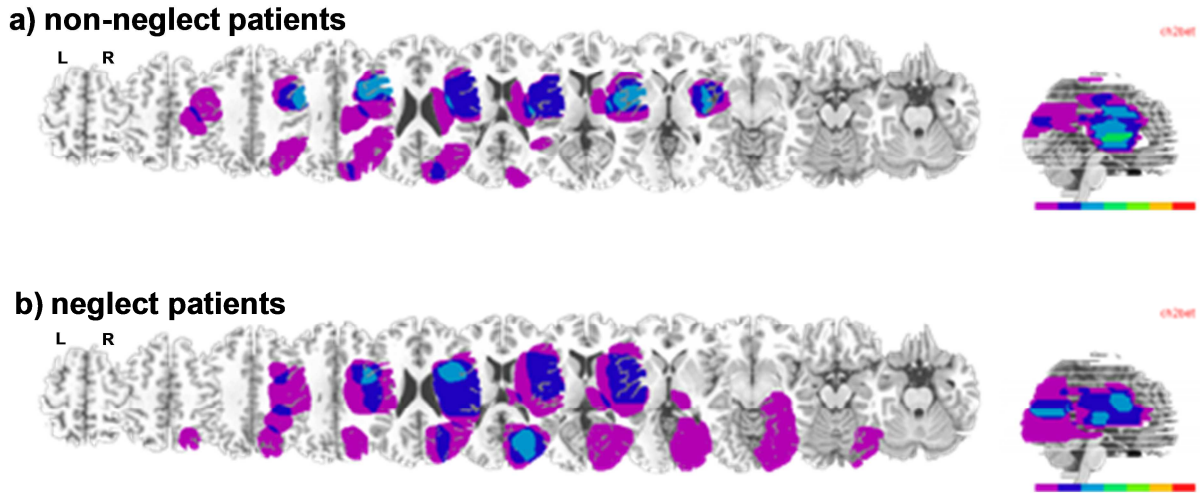


*Figure 2.* Lesion overlap for (a) non-neglect patients and (b) neglect patients. The color range indicates the number of patients presenting a lesion in each pixel (violet = 1 patient, red = 7 patients). L = left, R = right.

All patients were recruited in the Neurology Department, University Hospital of Geneva (HUG). All subjects were right-handed. All patients had their stroke between May 2011 and March 2013, and all subjects were tested between January 2012 and March 2013. Generally, patients were tested a few weeks post-accident (*Mdn* = 12 days for non-neglect patients; *Mdn* = 16 days for neglect patients; no significant difference between the two groups was observed, with $p = .194$).

The presence and severity of USN was assessed using a standard clinical battery composed of the Bells test (Gauthier, Dehaut, & Joanette, 1989), Scene copy (Gainotti, Messerli, & Tissot, 1972), and Line bisection (Schenkenberg, Bradford, & Ajax, 1980) (see Table 1). Patients needed to show a clinical score in at least two out of three tests to be classified as 'neglect'. All patients were also examined with the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), a standardized clinical test used to exclude other major cognitive disorders and dementia (see Table 1).

All subjects gave written informed consent according to the local ethics rules of the University Hospital of Geneva.

Table 1

*Demographic and clinical data of patients*

| **Patient** | **Age** | **Sex** | **Days since stroke** | **Bells test** (omissions) | | | **Scene copy** (score 0-3) | **Line bisection** (% deviation) | **MMSE** (items tested: 1-23) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | L | C | R | | | |
| ***Neglect patients*** | | | | | | | | | |
| EP | 65 | f | 16 | 11 | 4 | 1 | 2 | 13.87 | 22 |
| CM | 57 | m | 9 | 15 | 5 | 8 | 3 | 54.46 | 21 |
| LV | 65 | f | 12 | 15 | 5 | 6 | 3 | 56.03 | 19 |
| MC | 59 | m | 399 | 11 | 1 | 1 | 2 | 49.19 | 20 |
| RM | 50 | m | 16 | 15 | 5 | 3 | 3 | 92.02 | 20 |
| MF | 48 | f | 226 | 7 | 0 | 1 | 2 | 22.40 | 22 |
| ER | 32 | f | 53 | 10 | 0 | 2 | 1 | 26.68 | 23 |
| ***Non-neglect patients*** | | | | | | | | | |
| WG | 48 | m | 14 | 0 | 1 | 1 | 0 | 7.98 | 22 |
| DG | 55 | f | 11 | 1 | 0 | 0 | 0 | 7.36 | 23 |
| PP | 69 | m | 6 | 1 | 0 | 3 | 0 | 8.12 | 21 |
| PO | 76 | m | 7 | 3 | 0 | 1 | 1 | 7.26 | 23 |
| MT | 65 | m | 43 | 1 | 1 | 1 | 0 | 2.61 | 23 |
| MB | 73 | f | 12 | 4 | 0 | 2 | 0 | -6.04 | 23 |
| MR | 71 | f | 31 | 5 | 0 | 2 | 0 | 6.90 | 19 |

*Note.* Scene copy: the scene includes 4 distinct elements from the left to the right of the sheet; performance is coded from 0 (no omissions) to 4 (severe omissions on the contralateral side). Bells test: number of omitted bells in the left (/15), central (/5), and right (/15) parts of the test sheet. Line bisection: mean error in percentage of maximal possible error. MMSE: number of total points (among items 1-23).

## Procedure

The objective of the task was to transitory capture covert attention in the periphery of the computer screen during a discrimination judgment of position. Based on the observations of Vuilleumier et al. (2007), the task was expected to show a modulation of USN patients' behavior as a function of covert attentional capture and laterality of the distractor. The task (see Figure 3) was created with the software E-Prime 1.

Subjects were placed at 50 cm from the computer screen (Dell Laptop), on which a central fixation-cross appeared. Subjects were told to never take their eyes away from the cross during the trials. A first dot (red or green) could appear either on the left or the right side of the screen. All dots appeared on the middle of the screen vertically, randomly in the middle of the left (25%) or the right (75%) half of the screen horizontally. Before a second dot (the target-dot) appeared, there was a short interval (1750 ms) during which either a blank screen was presented or a salient stimulus (flash) appeared in the left or right periphery of the screen. Subjects were told not to pay attention to the flash and to always keep their eyes on the fixation cross in the middle of the screen. The flash was expected to induce a transitory displacement of covert exogenous attention (for example as in Posner paradigm, see Sapir et al., 2004). After the interval, the target-dot (red or green) could appear randomly in one of three possible horizontal locations: the same as the first dot, slightly (10%) to its left, or slightly (10%) to its right. This means that the target-dot was always presented on the same side of the screen (left or right) as the first dot. There were in total six possible eccentricities where the target-dot could appear: 15% from the left periphery, 25% from the left periphery and 35% from the left periphery when the first dot appeared on the left; 65% from the left periphery, 75% from the left periphery and 85% from the left periphery when the first dot appeared on the right. There wasn't any variability of position along the vertical axis, with dots always appearing in the middle (at 50% from the bottom) of the screen. The location and the color of the two dots could be either the same or different. At the end of each trial, the questions 'Color?' and 'Position?' appeared on the screen. Subjects had to press two different buttons to indicate whether the color and position of the two dots were the same or different. Once subjects had pressed the button, the next trial began. Healthy subjects pressed the buttons themselves, while patients indicated the answer verbally to the experimenter, who pressed the buttons for them, to simplify their task.

The first dot appeared after 500 ms and stayed on the screen for 1000 ms. The interval lasted 1750 ms (blank screen). In the conditions where the flash appeared, the flash was presented after a blank screen (750 ms) for a duration of 250 ms, followed by another blank screen (750 ms). The target-dot stayed on the screen for 1000 ms. The first question appeared and stayed on the screen until the subject pressed the response button, after what

the second question appeared. Once the subject pressed the response button for the second question, the next trial began. There were 72 trials, for a total duration of about 15 minutes.

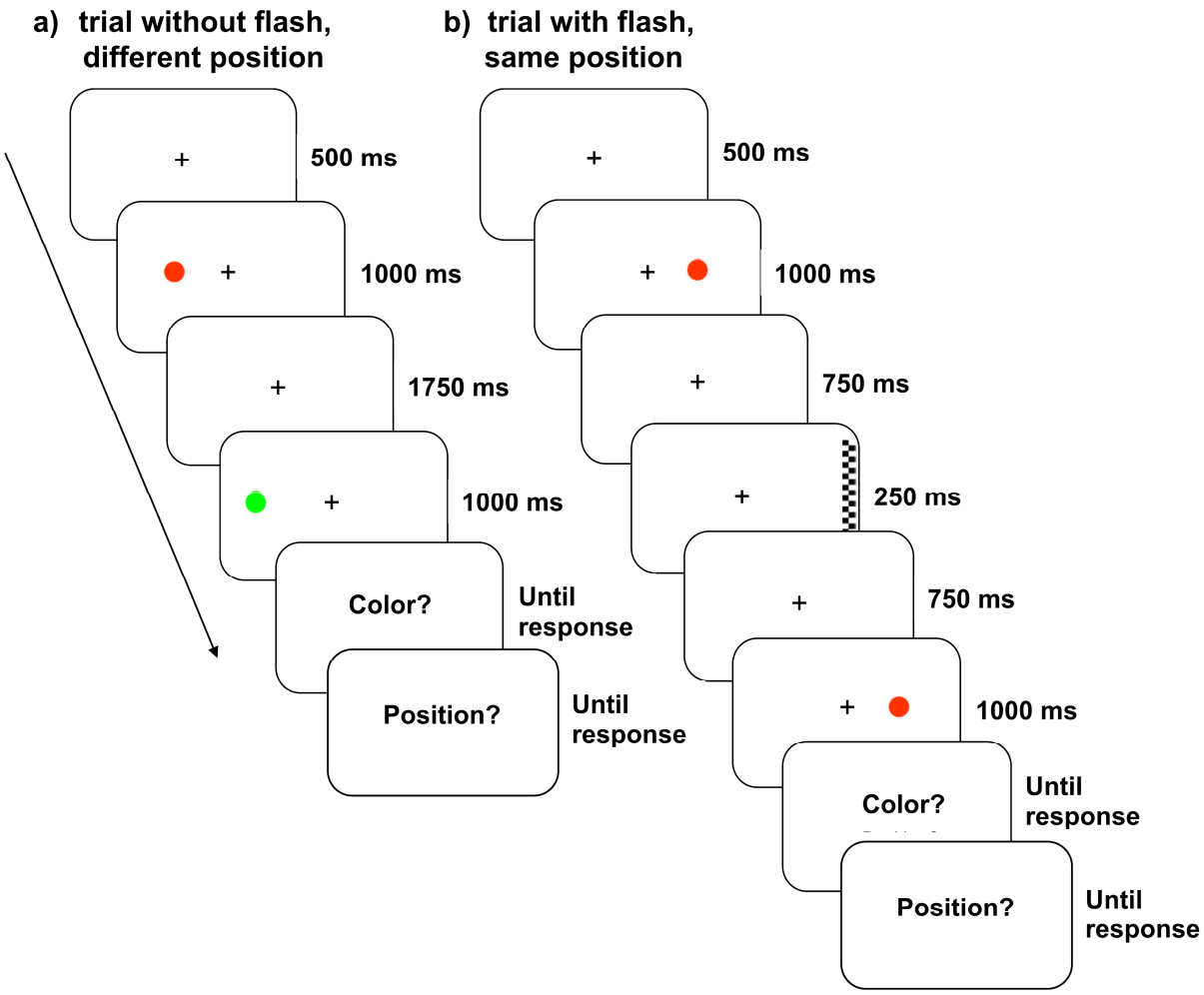


*Figure 3.* Experimental task. Examples of (a) a trial without flash during the interval, with the second dot appearing in a different position than the first; (b) a trial displaying a flash in the right periphery during the interval, with the second dot appearing in the same position as the first.

During the task, eye movements were measured with an eye-tracker (iView X 2.4, Sensomotoric Instruments) in 3 neglect patients, 3 non-neglect patients and 3 control subjects. To verify that subjects did not systematically look at the peripheral flash, we calculated the mean point of gaze during the task. We determined a central square on the screen, and considered that central fixation was maintained if the mean point of gaze didn't fall out of that square.

The square was delimited on the Y axis at ±1/4 of the screen height from the center, and on the X axis at 35% and 65% of the screen length, corresponding to the more central positions where the target-dots could appear in the left and in the right visual field. The laptop screen was setup at 800x600 pixels; in terms of pixels, the central square was delimited at 280 and 520 on the X axis, and at 225 and 375 on the Y axis. The center of the screen (and of the central square that was delimited) was at 400 pixels on the X axis and 300 pixels on the Y axis.

## Statistical Analysis

We distinguished the data into two categories: color responses and position responses. The color-discrimination task was used to make sure that subjects correctly perceived the two dots, and it was expected to be quite easy for all subjects. In fact, Pisella, Berberovic, and Mattingley (2004) showed, using a change-detection task, that the performance of USN patients was specifically impaired in location's memory, but not in color and shape's memory. The position-discrimination task allowed measuring the effect of the transitory displacement of exogenous attention on locations' memory performance. The dependent variable was the number of correct responses (proportion) in both the color and the position tasks.

There were three independent variables: Group (neglect patients, non-neglect patients, control subjects), Flash (interval without flash, flash in the left periphery, flash in the right periphery), Visual field (left half of the screen, right half of the screen). Two more variables were controlled by balanced trials: Dots' color (either red or green and either the same or different between the two successive dots) and Second dot's position (either the same, or 10% shifted to the right or to the left of the first dot). Our assumptions were that neglect patients' performance in the position task when the flash was presented on the right periphery would be significantly impaired compared to that of non-neglect patients and control subjects, independently of the visual field (left or right) on which dots were presented. We didn't expect to observe other significant differences between groups, neither in the position nor in the color task. In particular, flashes in left periphery should not differentially affect spatial memory performance in both groups of patients.

A repeated-measure ANOVA (2x3x3x2) on correct answer proportion was performed using the software Statistica (version 11.0.170.0). Analysis was performed on the variables Task (color or position response), Group, Flash, and Visual field.

# 3. RESULTS

## Eye-Tracker

The mean point of gaze during the task, across all trials, was calculated for each group of subjects, and it never fell out of the central square (see *Statistical Analysis* part, above). The mean point of gaze (pixels), calculated on the [X; Y] axis, was [291.91; 235.83] for neglect patients, [355.50; 278.21] for non-neglect patients, and [322.70; 257.63] for control subjects. We calculated the t-Student to compare these values and found no significant differences between the mean point of gaze of the three subjects' groups, except for the X coordinate of neglect patients and non-neglect patients that was significantly different. Here are the p-values observed for the X coordinates: $p = .249$ between control subjects and neglect patients, $p = .212$ between control subjects and non-neglect patients, $p = .007$ between neglect patients and non-neglect patients. Here are the p-values for the Y coordinate: $p = .137$ between control subjects and neglect patients, $p = .397$ between control subjects and non-neglect patients, $p = .263$ between neglect patients and non-neglect patients.

Since the calculation of the mean point of gaze could be biased and artificially centered due to the presence of an equal number of right and left flashes across the task, resulting in an apparent central position when averaged across all trials, we also decided to compare the mean point of gaze of the three subjects' groups during the intervals between the two dots, as a function of flash position. Interestingly, we found again that the mean point of gaze never fell out of the central square, independently of whether the flash appeared at the left periphery, the right periphery or didn't appear. This was true for each group of subjects. For neglect patients the point of gaze was [398.96; 274.61] in the presence of the right flash, [370.70; 273.00] in the presence of the left flash, and [365.75; 274.63] in the absence of the flash; a three-levels one-way ANOVA confirmed that no significant differences were observed between the point of gaze in the three flash conditions ($F(2, 3) = 0.03$, $p = .971$). For non-neglect patients the point of gaze was [473.64; 451.97] in the presence of the right flash, [452.00; 466.77] in the presence of the left flash, and [456.64; 458.50] in the absence of the flash; a three-levels one-way ANOVA confirmed that no significant differences were observed between the point of gaze in the three flash conditions ($F(2, 3) = 0.13$, $p = .888$). For control subjects the point of gaze was [371.67; 316.20] in the presence of the right flash, [364.02; 316.91] in the presence of the left flash, and [340.33; 327.06] in the absence of the flash; a three-levels one-way ANOVA confirmed that no significant differences were observed between the point of gaze in the three flash conditions ($F(2, 3) = 0.06$, $p = .943$).

## Experimental Task

Repeated-measure ANOVA of the correct response rates showed an effect of Task ($F(1, 18) = 37.72$, $p < .001$), and two interactions: the first between Task*Group ($F(2, 18) = 6.35$, $p = .008$) and the second between Task*Flash*Group ($F(4, 36) = 4.53$, $p = .005$).

The principal effect of Task showed that the performance in color discrimination was globally better in all subjects than in position discrimination (as expected).

The interaction between Task*Group showed that this difference in performance between the two discrimination tasks was more important in the two patients' groups (than in the control subjects' group): a significant difference between color and position discrimination (with performance in color discrimination being globally significantly better than in position discrimination) was only observed in the neglect ($p < .001$) and the non-neglect ($p = .002$) patients' groups, while not in the control subjects' group ($p = .387$). Moreover, neglect patients were significantly worse than control subjects in position discrimination ($p = .015$), but only marginally worse than non-neglect patients ($p = .055$). No significant differences were observed between non-neglect patients and control subjects in position discrimination ($p = .457$).

Finally, the interaction between Task*Flash*Group showed that such difficulty in the position-discrimination task among the neglect patients was particularly important when the peripheral flash appeared on the right side of the screen (see Figure 4). No significant effect of Visual field was found ($F(1, 18) = 0.99$, $p = .334$).

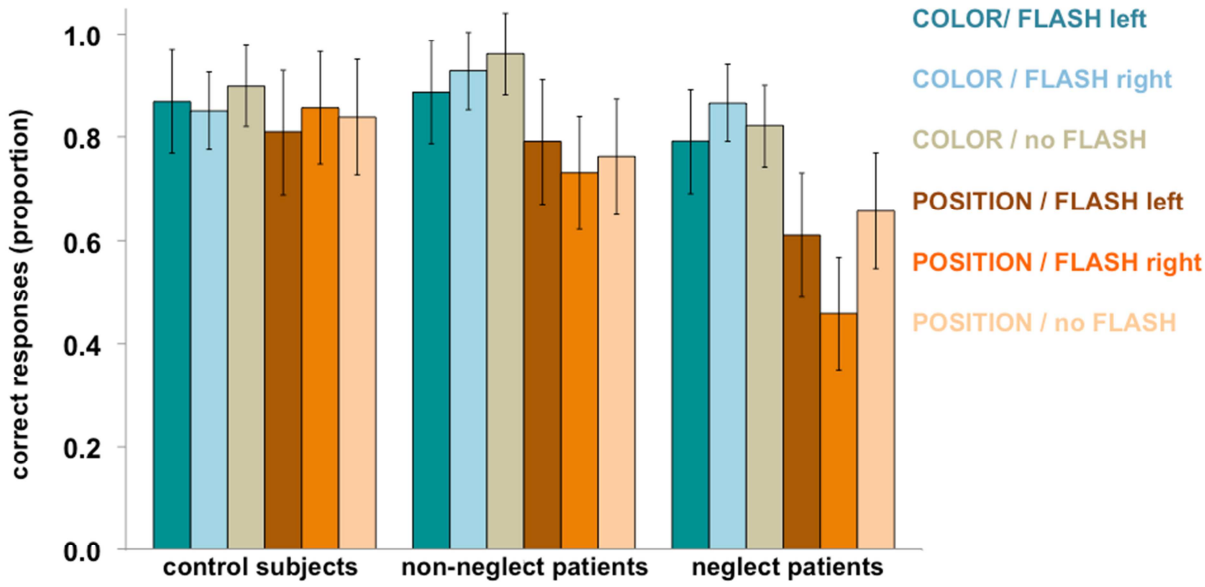


*Figure 4.* Proportion of correct responses at the color- and position-discrimination tasks for the three groups of subjects as a function of flash appearance.

In line with this latter significant interaction, results showed several significant differences between experimental conditions in multiple pairwise comparisons (Duncan test). Neglect patients' performance in position discrimination after a right flash (see Figure 4, orange bars) is significantly worse compared to the same condition in control subjects ($p$ = .014), and marginally worse compared to non-neglect patients ($p$ = .061).

The most interesting result in the light of our predictions is that performance in position discrimination when a right flash is presented is significantly worse than when a left flash ($p$ = .002) or no flash ($p$ < .001) is presented among the neglect patients' group. By contrast, no significant difference was found between the left flash and no flash conditions ($p$ = .292). Furthermore, no significant differences were observed in any other group (neither the non-neglect patients' group, nor the control subjects' group) in position discrimination as a function of the flash position. In particular, right and left flash led to similar performance in non-neglect patients ($p$ = .209) and control subjects ($p$ = .343).

## 4. DISCUSSION

An involuntary attentional shift to the right, without eye movement, impairs the maintaining of a spatial location in neglect patients. This effect is observed independently of the visual field (left or right) where the dots appear, since no principal effect or interaction involving visual field was found.

These findings replicate those of Vuilleumier et al. (2007), but also extend them by suggesting for the first time that spatial remapping can be impaired in neglect patients not only following a rightward gaze-shift, but also following a covert attentional shift, in the absence of eye movements. The memory trace of a spatial location is lost, or degraded, when it has to be remapped on the left in gaze-centric representations (presumably by the injured right hemisphere), and this effect also occurs following a covert attentional shift, without a saccade being executed.

On the contrary, our findings (like Vuilleumier et al.'s, 2007) contradict the theoretical model of a spatial remapping deficit in USN proposed by Pisella and Mattingley (2004), who suggested that a leftward gaze-shift should selectively impair performance of neglect patients.

Our hypothesis is thus supported by our new results: an attentional stimulation on the right periphery of the visual field impairs the maintaining of a spatial location's representation, and thus impairs the spatial remapping process toward the contralesional side, in right-injured patients affected by left USN. This is true independently of the visual field where dots are presented. Our results support once more the role of a potential deficit in spatial

remapping in USN (Pisella & Mattingley, 2004; Vuilleumier et al., 2007), which impairs the maintaining of spatial representations for stimuli presented at the left of gaze direction, and, moreover, at the left of the attentional focus.

A few clarifications need to be done here. 'Attention' is a very large concept that is implicated in many cognitive domains. Without attention our mental resources are just unusable. We are interested here mainly on what is called 'spatial attention': the way we select, perceive, and process information coming from the external environment based on a representation of locations in space. First of all, we must distinguish the different ways in which our attention can be directed and oriented in space, according to two variables: different situations may arise depending on eye movements and voluntary intention of attention displacements (Posner, 1980). Attention can be oriented in space according to two kinds of dichotomic manners: either overtly (accompanied by ocular movement) or covertly (not accompanied by ocular movement, with eyes maintaining fixation), and either endogenously (voluntarily, according to the subject's intentions) or exogenously (automatically, being captured by a salient stimulus independently of the subject's intentions). In Vuilleumier et al.'s task (2007), subjects shifted attention overtly and endogenously. In our task, attention was shifted covertly and exogenously. There are thus two differences in spatial attentional shifts to be considered between the two studies. Since this maximizes the difference between experiments, it reinforces the pervasive role of a remapping deficit in the spatial disturbances associated with USN.

## Endogenous and Exogenous Attention

Attention was captured exogenously in our study by a peripheral flash, while in Vuilleumier et al.'s study (2007) it was endogenously shifted to a peripheral letter that the subjects had to name. Endogenous attention is displaced according to top-down cognitive intentional processes dictated by task-relevant goals (goal-directed), while exogenous attention is displaced according to bottom-up automatic processes dependent on the detection of behaviorally-relevant (like salient or unexpected) stimuli (stimulus-driven).

Many dissociations show that these two types of attention rely on distinct mechanisms: exogenous attention is more often touched in USN, with an ipsilesional bias in orienting, but an impairment to endogenous attention can aggravate symptoms (Chokron et al., 2008). However, Rosen et al. (1999) tested twelve healthy subjects performing a covert-attention task in the fMRI. No significant differences in brain activation were observed between the conditions of endogenous and exogenous shifts of attention. The authors thus concluded that exogenous and endogenous orienting of covert attention depend on a unique attention system, including the dorsal premotor cortex and superior parietal cortex bilaterally,

plus the temporoparietal junction and anterior cingulate cortex/supplementary motor area in the right hemisphere.

On the contrary, a few years later, Corbetta and Shulman (2002) distinguished a bilateral dorsal frontoparietal network and a separate ventral frontoparietal network that is strongly lateralized in the right hemisphere. The first is composed of the intraparietal sulcus (IPS) and the intersection of the superior frontal sulcus and precentral sulcus (SF-PrCes), while the second is composed of the temporoparietal junction (TPJ) and the inferior frontal gyrus (IFG). The human IPS is considered as analogous to the monkey's LIP, and the SF-PrCeS as analogous to the monkey's FEF. The two attentional frontoparietal networks are interconnected: the dorsal network controls the allocation and maintenance of spatial attention (endogenous attention), while the ventral network is responsible for detecting salient external stimuli (exogenous attention) and can thus modulate activity in the dorsal network in case of new or unexpected stimuli.

Corbetta, Kincade, and Shulman (2002) tested thirteen healthy subjects in the fMRI while operating covert shifts of attention, and found that the same two regions (IPS and Pr-CeS) were activated when first allocating attention to a spatial location as well as when maintaining that location in memory during a time interval. The authors thus concluded that the dorsal network controls both the allocation (shift) and the maintenance of endogenous visuospatial attention, and might thus be involved in spatial working memory.

Corbetta et al. (2002) also explained USN as reflecting dysfunction in both systems following structural damage limited to the ventral network, whose anatomy and lateralization matches the anatomy of neglect: according to this view, the right ventral system acts as a 'circuit breaker', a sentinel system reacting rapidly (within 50 ms) to cues triggering exogenous attention and then alerting the dorsal regions for the reorienting and control of endogenous attention. Following a right ventral lesion, this (non-spatial) alerting system for the spatial orienting of attention is impaired and reorienting signals are no more sent to the dorsal system, which as a consequence impairs the allocation of spatial attention toward the contralesional side.

Indeed right lesions to the ventral network (mainly to the TPJ) are strongly correlated with USN manifestations (rightward bias and reorienting deficit). Corbetta et al. (2005) showed in an fMRI study that structural damage to the TPJ induces dysfunctional activation in other regions of the ventral and dorsal networks (structurally intact). Structural ventral damage directly impairs non-spatial attention functions (exogenous detection) and indirectly impairs spatial attention (endogenously controlled), mediated by the dorsal network. These results allow explaining the prevalence of USN following right lesions and the deficit in automatic stimulus detection, while intentional orientation toward the left (neglected) space is

usually preserved. At the same time, they provide support to the idea that USN could result from dysfunction in both the ventral and dorsal interacting networks.

The authors highlighted four points in support to such hypothesis: first, non-lateralized problems of attention and vigilance are frequently observed in neglect patients. Second, the typical rightward sensory-motor bias could be a spatial deficit resulting from the inactivation of the right IPS (coding for the left space) due to absence of reorienting signals coming from the right TPJ (damaged), what creates a spatial imbalance in favor of the ipsilesional (right) space. Third, such effect could be exacerbated in case of damage to the right IPS or FEF, coding for bilateral spatial locations. Four, at a behavioral level, USN patients' performance is worse in exogenous (stimuli-driven) orienting and can be facilitated with verbal cues (like 'go to the very left side of the paper before starting reading') and cognitive (endogenous) control.

As it will be fully discussed later (see *Overt and Covert Attention* part), brain regions that compose the dorsal frontoparietal attentional network overlap with oculomotor areas. Endogenous attention and overt eye movements might thus be expected to have the same effect on spatial remapping. If gaze-shifts (as tested by Vuilleumier et al., 2007) induce spatial remapping and recruit brain areas in IPS partly overlapping with oculomotor areas, remapping might also be observed in case of endogenous shifts regardless of whether endogenous attention is shifted overtly or covertly, due to preparatory eye movements. However, since no overlap is observed between oculomotor areas and the ventral network responsible of exogenous attention as conceived by Corbetta and Shulman (2002), an exogenous shift of attention shouldn't be expected to produce spatial remapping in case of a covert shift. To probe a more different case than endogenous attention, we decided thus to test exogenous attention, which is relevant to USN given that neglect is often associated with more severe exogenous deficits and ventral lesions (mainly to the TPJ and adjacent inferior parietal lobule (IPL)).

Interestingly, a recent review on exogenous-endogenous attention (Chica, Bartolomeo, & Lupianez, 2012) pointed out that stimulus-driven reorienting (processing of task-relevant stimuli) is a different concept than exogenous attention (involuntary capture by salient or unattended stimuli). Following this conceptual dissociation, the dorsal frontoparietal network could be responsible of both endogenous and exogenous orienting of attention, while the ventral network could be responsible of stimulus-driven reorienting. According to this view, salient and unattended stimuli could capture exogenous attention without activating the reorienting (ventral) network. Moreover, some exogenous effects independent of the ventral attention system have been reported by other authors in response to emotional stimuli and driven by distinct neural systems (Dominguez-Borràs & Vuilleumier, 2013; Vuilleumier, 2005).

According to Chica et al. (2012), however, in the light of the behavioral dissociations observed after brain lesions or TMS, it seems unlikely that exogenous and endogenous attention are sustained by the same neural system. The authors suggest that the fMRI's poor temporal resolution might constrain neuroanatomical conclusions. A recent TMS study (Chica, Bartolomeo, & Valero-Cabré, 2011) showed that the IPS is involved in both endogenous and exogenous orienting of attention, while the TPJ is involved, more than in stimulus-driven reorienting alone, in exogenous attention also. Endogenous and exogenous attention could then be sustained by partially overlapping brain regions, perhaps particularly those encoding spatial locations for perceptual selection or eye movement.

If exogenous attention is also controlled in part by the dorsal frontoparietal network (Chica et al., 2012), a neural overlap could then exist also between exogenous attention and oculomotor areas. Exogenous attention (like endogenous attention) and overt eye movements might thus be expected to have the same effect on spatial remapping. According to this view, an attentional task implying endogenous (as tested by Vuilleumier et al., 2007) or exogenous (as tested here) shifts may elicit similar remapping deficits in USN patients. Vuilleumier et al.'s results (2007) could thus be comparable to the results observed here. Moreover, Corbetta et al. (2005) showed that structural damage to the ventral network in USN patients impairs the intact dorsal network too. Remapping deficits in neglect patients could thus be explained on this account even in the absence of structural damage to the IPS or SF-PrCes (dorsal network).

## Overt and Covert Attention

Attention was shifted covertly in our task, while it was shifted overtly in Vuilleumier et al.'s task (2007). This was the target manipulation of our experiment. In overt attention, an eye movement accompanies the attentional shift. A saccade is executed to fixate the focus of attention; gaze direction and attention direction correspond. In covert attention, an eye movement does not accompany the attentional shift. Ocular fixation is maintained while a displacement of the focus of attention takes place; gaze direction and attention direction do not correspond.

Rizzolatti et al. (1987) were interested in understanding why stimuli at unattended locations are detected much slower than attended ones. They measured reaction time in a covert-attention task and showed that stimuli are detected faster when a valid cue prepares subjects to direct attention to the location where the target would actually appear. In contrast, stimuli are detected much slower when such cue is invalid and prepares subjects to direct attention to a wrong location. More interestingly, the authors found that the incongruent-cue cost increases proportionally as the distance between the actual and cued location increases

itself. The cost was even bigger when locations where opposite relative to a central midline, either vertical or horizontal, respectively implying or not an interhemispheric transfer in information processing. These authors proposed the premotor theory of attention, according to which “attention is oriented to a given point when the oculomotor program for moving the eyes to that point is ready to be executed. Attentional cost is the time required to erase one ocular program and prepare the next one” (Rizzolatti et al., 1987, p. 31), and they supposed that

[…] overt and covert orienting of attention are controlled by common [neural] mechanisms and that the absence of eye movements in case of covert orienting is a consequence of a peripheral inhibition, which leaves unchanged the central programming. In other words, the program for orienting attention either overtly or covertly is the same, but in the latter case the eyes are blocked at a certain peripheral stage. (Rizzolatti et al., 1987, p. 37)

The authors explained the observed effects of midline-crossing and cue-target distance costs in terms of motor programming: when the stimulus appears in a different location than the cue, but in the same hemifield, a modulation of distance parameters in muscular commands is required, what takes time. However, in case of midline crossing, a more important direction change in muscles programming as well as a visual-information transfer between the two hemispheres are required, what should take more time than a simple adjustment in distance.

Since 1987, several neuroimaging studies have supported this theory, most notably by reporting a neural overlap in activation during a covert or overt shift of attention (Corbetta et al., 1998). Nevertheless, other more recent single-cell studies (on the monkey) found distinct neurons’ populations within these overlapping regions, most notably in the frontal eye field (FEF), responding to either covert or overt shifts (Awh et al., 2006).

Corbetta et al. (1998) were the first to describe a neural basis for the premotor theory of attention. They used functional magnetic resonance imaging and surface-based representations of brain activity to highlight in six healthy subjects a neural overlap in parietal, frontal and temporal regions: the same regions responded during two distinct tasks, one involving overt shifts of attention and the other involving covert shifts. Subjects were asked to detect a visual target. In the covert task, subjects shifted attention endogenously according to a 100% predictive series of box locations while maintaining ocular fixation. In the overt task, the only thing that changed was that subjects shifted fixation sequentially together with attention. Regions that responded in both tasks included the superior temporal sulcus (STS), the intraparietal sulcus (IPS) and near transverse occipital sulcus (TOS), the precentral sulcus (PrCeS, considered as the homolog of monkey’s FEF) and a region of the medial frontal gyrus (MeFG). The authors concluded that “the overlap reflects both

attentional modulations of the visual response and preparatory oculomotor activity associated with covert shifts of attention" (Corbetta et al., 1998, p. 768). However, such anatomical data do not completely prove the premotor theory of attention, since distinct neurons' populations could be active in the same cortical areas, and fMRI doesn't allow seeing that due to insufficient spatial resolution.

Besides evidence about a causal role of oculomotor circuits in the shifting of spatial attention, some other studies have thus focused on the possible existence of different neurons' populations among overlapping regions found by fMRI studies, responsible of either overt or covert attention. Awh et al. (2006) reviewed the neurophysiologic literature on this subject and pointed out that dissociations at a single-cell level can be observed in the monkey's FEF and superior colliculus (SC): purely visual (responding only to covert attentional selection) and purely motor (responding only to saccade control and execution) neurons can be distinguished. Some visuomotor neurons, responding in both cases, can also be identified. Different neurons working simultaneously seem thus to exist on a continuum of functions between spatial attention and eye movements.

Steinmetz and Moore (2012) suggested that the neural mechanisms sustaining covert and overt shifts of attention could be at the same time 'lumped' and 'splitted'. The authors argued that the debate depends essentially on what is conceived as 'mechanisms': brain structures or single neurons being part of those structures, or circuits of different neurons within and between areas? The authors concluded that the two kinds of neurons (visual or motor) found by neurophysiologic studies among overlapping regions contribute together to both covert and overt shifts of attention, but, at the same time, single cells make different work. It seems thus appropriate to consider the two attentional functions as overlapping in terms of brain structures or 'networks' of structures, but on another level (the one of underlying neuronal contributions) it seems on the contrary appropriate to split them. Steinmetz and Moore (2012) made the point on the problem: covert and overt shifts of attention share the same neural circuitry (even if not completely), but the question would be to know at what stage such circuitry diverges in the control of different forms of attention deployment.

Smith and Schenk (2012) reviewed the literature that followed the premotor theory of attention, according to which "planning an action is both necessary and sufficient for a shift of spatial attention" (Smith & Schenk, 2012, p. 1104). As we have seen, studies are controversial for what concerns a common neural basis for covert and overt shifts of attention: a neural overlap seems to exist, but at the same time a single-cell differentiation between visual selection (responding only to covert shifts) and motor control (responding only to overt shifts) seems also to exist. The authors came here to a conclusion by differentiating endogenous and exogenous deployment of attention. They reviewed the

literature on ophthalmoplegic patients (affected by eyes paralysis) comparing endogenous and exogenous shifts of attention: these patients seem to be impaired in exogenous but not endogenous attention. Exogenous attention seems to strictly rely on the activation of the oculomotor system, while not endogenous attention. Smith and Schenk (2012) thus concluded that endogenous attention could be dissociated from saccade preparation, while not exogenous attention. According to this view, the premotor theory of attention should in part be rejected (for what concerns endogenous attention), and could be tenable only for what concerns exogenous attention. The main problem with ophthalmoplegic patients is that we know that they aren't able to execute an eye movement, but we don't know how impaired is the ability to prepare that movement (for example to generate an intention without an actual movement), which makes it weak evidence against the premotor theory of attention.

Recently, Smith, Schenk, and Rorden (2012) confirmed such findings on ophthalmoplegic patients using a peripheral-cueing task. They prevented healthy subjects from programming and executing saccades, and observed that exogenous attention is dependent on saccade preparation toward a cued location (since no attentional facilitation is observed for locations that cannot be attended by a saccade), while endogenous attention is independent of oculomotor control, as well as IOR (what shows moreover its independence from exogenous attention).

On this basis, Smith and Schenk (2012) argued that the premotor theory of attention, claiming that all covert shifts of spatial attention depend on saccade preparation, should be in part rejected (in the case of covert endogenous attention) and could only in part be conserved (in the case of covert exogenous attention). To conclude on the debate around the premotor theory of attention, Smith and Schenk proposed that

during exogenous cueing, the sudden appearance of the cue briefly increases the physical salience of the cued location and triggers the preparation of a saccade, creating a powerful bias in the visual and oculomotor system toward the cued location. This bias propagates through the perceptual-motor system and facilitates processing of subsequent visual events at the cued location (i.e. the cued location becomes attended). However, when the ability to represent spatial locations as the goal of a movement is compromised, either by a lesion to the oculomotor system or an experimental manipulation, such as eye-abduction, the onset of the cue does not create a bias in the oculomotor system. As a consequence, visual events from the cued location are not prioritised in the visuomotor system so no cueing effect is observed. In contrast, during an endogenous-cueing task the participant knows that the cue accurately predicts target location and can use top-down cognitive processes that are independent of the eye-movement system to bias the visual system toward the cued location. (2012, p. 1112)

Finally, distinct neurons' populations are likely to be mixed in the FEF (thus not distinguished by neuroimaging), suggesting that covert attention is partly independent of motor control, even if the two systems clearly interact (Petersen & Posner, 2012). However, it's important to remember that besides purely motor and purely visual neurons, visuomotor neurons have also been identified. The existence of these distinct neurons could thus at the same time contradict and support the premotor theory of attention and the coupling between oculomotor control and covert attentional selection (Awh et al., 2006). Consequently, the debate remains open for what concerns the neural basis of covert and overt shifts of attention. Further investigation differentiating endogenous and exogenous covert attention could clarify the extent of neural overlap between spatial covert attention and oculomotor control, since the premotor theory of attention could be tenable only for what concerns exogenous covert attention (Smith & Schenk, 2012).

## Conclusion

When they proposed their model of a remapping deficit in USN, Pisella and Mattingley (2004) postulated that similar remapping mechanisms might be involved in covert and overt shifts of attention, based on behavioral and anatomical data. First, they took the results of Corbetta et al. (2002) as anatomical evidence, which provide evidence for a possible overlap in the dorsal parietal cortex (intraparietal sulcus, IPS) between two types of representations: those allowing spatial memory by integrating retinal and extra-retinal information, and those directing endogenous attention to selected locations. Pisella and Mattingley (2004) took another study as experimental support for their hypothesis that covert and overt shifts of attention may share the same remapping mechanisms: the work of Deubel, Schneider, and Paprotta (1998), who observed anticipatory remapping when subjects had to point toward peripheral targets while maintaining ocular fixation. Finally, Pisella and Mattingley (2004) also took the behavioral evidence coming from the phenomenon of change blindness during ocular fixation in healthy subjects as support for their remapping hypothesis. Change blindness is known as the incapacity to detect even large changes in a visual scene when two successive images are separated by a blank interstimulus interval (ISI), a saccade, an occluding object or a camera cut. Such phenomenon has also been observed when subjects maintain ocular fixation (Becker, Pashler, & Anstis, 2000), across blinks, flickers or movie cuts, and not only across saccades. Pisella and Mattingley (2004) thus suggested that remapping of visual representations might follow both overt and covert attentional shifts.

As predicted by Pisella and Mattingley (2004), but by different means, we showed here that spatial remapping is impaired in USN patients not only following overt shifts of attention, but also following covert shifts. Our results support the existence of a neural overlap between attentional and oculomotor processes. Moreover, the effects observed on remapping in neglect patients following eye movements (Vuilleumier et al., 2007) could possibly be accounted for by the attentional shifts that accompany them.

IPS's neurons are surely implicated in creating saliency maps, coding the spatial locations of relevant stimuli. Since such maps could integrate not only endogenous/top-down (Corbetta & Shulman, 2002), but also exogenous/bottom-up (Chica et al., 2012) influences, we could expect as a consequence that a stimulus' salient position is remapped similarly following either an eye movement, or an exogenous attentional shift, or even an endogenous shift without eye movement. This might possibly be the reason why in our study we observed the same results as Vuilleumier et al. (2007).

However, based on recent studies (Smith et al., 2012; Smith & Schenk, 2012), it seems that a neural overlap between overt and covert attention might exist at the single-neuron level for exogenous attention, but not for endogenous attention. This might also alternatively be the reason why in our study, characterized by covert exogenous shifts of attention, we observed the same results as in Vuilleumier et al.'s study (2007), where attention was shifted overtly and endogenously.

In the future, it would be interesting to test the effect on remapping in USN patients in case of covert endogenous shifts of attention, for example following a preparatory period to shift attention even without any overt eye movement. If these (endogenous) mechanisms are less related to oculomotor processes, a deficit in spatial remapping could in this case not be observed. To complete the frame of spatial attention, overt exogenous attention should also be tested.

In the future, it would also be interesting to replicate our position-discrimination task in the fMRI with healthy control subjects on one hand, and to perform lesions mapping in neglect and non-neglect patients on the other hand, to highlight the cerebral regions implicated in spatial remapping and covert exogenous attention. Lesions mapping could be of particular interest in patients with chronic (at least 6 months after stroke) USN, whose lesion delimitation is better defined than in acute patients. This would allow investigating key-regions to the symptoms and cognitive processes implicated in neglect.

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