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Topical review

Pain, body, and space: what do patients with complex regional pain syndrome really neglect?

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1. Introduction

Space is an important dimension in perception. It helps to perceive the relative position between objects including one's own body in order to guide interaction with the outer world. The brain is able to process spatial information according to different frames of reference. A first dissociation can be made between egocentric and allocentric representations [28]. The egocentric, subject-centered frame of reference enables spatial representations of objects depending on their position relative to the perceiver's body. In this case, left and right are defined according to the midline of the body or of specific body parts. In representations that depend on an allocentric frame of reference, the perception of position in space is independent of the observer. Space is then perceived in terms of positions between objects or between parts of the same objects. Another important distinction is the dissociation between personal, peripersonal and extrapersonal spaces [30]. Personal space corresponds to the space of the body, peripersonal space to the immediate space surrounding the body allowing direct manipulation of proximal objects, and extrapersonal space to the far space in which objects are reached by limb movements.

In humans, these dissociations have been documented by the neuropsychological investigations of patients affected by hemispatial neglect or hemineglect syndromes [1,9,10,23]. Hemineglect is an attentional deficit after damage to one hemisphere characterized by an inability to explore and report stimuli on the side of space contralateral to the damaged hemisphere, in the absence of sensory and motor deficits [40]. The term *hemi* denotes the main feature of the disorder, stressing that hemineglect is not a global deficit of space perception. It can affect different sensory systems and motor functions, in isolation or together [40].

2. An impaired body representation in complex regional pain syndromes

It has been proposed that nociceptive stimuli can also be perceived according to different spatial frames of reference [15]. Indeed, the fact that nociceptive processing is greatly influenced by selective spatial attention [14] and by proprioceptive and proximal visual inputs [8,18,20] supports the idea that nociceptive information is integrated in multimodal and peripersonal representations of the body [15]. Evidence is also proposed by the clinical observation of neglect-like behaviors in patients with complex regional pain syndromes (CRPS) [21]. In addition to the major characteristics of CRPS—i.e., pain, swelling, and skin changes in the affected limb—some of these patients tend to ignore or have an altered mental representation of the affected limb (somatoparaphrenia); movements are smaller and less frequent (hypokinesia), and they take conscious effort [5–7,16]. They have difficulties recognizing their own limb [24] and estimating its position [17], its size [25], and its orientation [34]. Stimulation of the affected limb is difficult to be perceived when the unaffected limb is concurrently stimulated [26] (Table 1). These clinical observations and self-administered surveys have led to the hypothesis that sensory-motor symptoms observed in CRPS could be due to more than pain.

3. An impaired perception of space in CRPS

But do the neglect-like symptoms observed in CRPS parallel those observed in patients with brain damage and hemineglect [4]? Which spatial coordinates are able to explain the neglect-like symptoms in CRPS, and more importantly, what can we learn about the spatial perception of pain from these patients? The neglect symptoms of CRPS patients are modified by vision of the limb [17,27]. Patients show mislocalization of the affected and sometimes also of the unaffected limbs [17]. Moseley et al. [26] have shown that during concurrent stimulations of the two limbs in the absence of vision, the attentional bias away from stimulations of the affected limb observed in normal posture is surprisingly reversed when the limbs are crossed: patients tend to neglect stimulations of the unaffected limb. These data strongly suggest that cortical impairment of CRPS does not constitute a simple

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Table 1
Deficits in body representation and spatial perception observed in CRPS patients.

Level of cognitive abstraction	System	Deficits	Frame of reference	Limb/side concerned by deficits
Body representation	Vision	Impaired recognition [24], perception of the size [25], and the orientation of the limb [34]	?	Affected limb
		Impaired perception of limb position [17]	?	Affected and unaffected limbs
	Internal imagery	Distorted mental images of the limb [16]	?	Affected limb
	Proprioception	Trend to somatoparaphrenia [5–7]	?	Affected limb
		Impaired perception of limb position outside of vision [17]	?	Affected and unaffected limbs
	Motor function	Hypokinesia and motor neglect [6,7]	?	Affected limb
Spatial perception	Somatosensory	Impaired identification of fingers to somatosensory stimulation [4]	Egocentric (hand-centered)	Affected limb
		No tactile extinction to double stimulation [4]	Egocentric (trunk-centered)	—
		Trend to tactile extinction in temporal order judgment tasks, dependent of the posture [26]	Egocentric personal	Affected (normal posture) and unaffected (crossed posture) limbs
	Visual	No deficit in line bisection [4]	Egocentric peripersonal	—
		Neglect in straight-ahead estimation tasks only in the dark [35,36,38]	Egocentric extrapersonal	Unaffected side
		Agnosia for object orientation [31]	Allocentric	(Deficits according to the horizontal axis)

?, not tested.

modification of the sensory-motor pathways [33] and involves alterations of more complex and multimodal representations of the bodily space. These data [26] also imply that CRPS patients do not especially neglect the affected limb, but more exactly the side of space where the affected limb normally resides, suggesting an impairment of a reference frame that is not dependent of the somatotopic representation of the body (i.e., personal frame) [13]. It is therefore proposed that neglect-like symptoms in CRPS, and the underlying cortical changes, result from an implicit maladaptive reorganization of the sensory-motor system to avoid provocation of the affected limb, leading to an impaired representation of that limb [21].

4. An impaired perception of space not limited to the side of the affected limb

Puzzling data have revealed that CRPS patients can have an impaired spatial perception of visual stimuli presented far from the body and that the direction of neglect symptoms could be the reverse of that previously observed—i.e., CRPS patients can bias the perception of space toward, and not away from, their affected limb [35,36,38]. Sumitani et al. [36] have used a visual subjective body midline judgment task known to produce errors toward the ipsilesional hemispace in brain-damaged neglect patients [11]. During this task, a light dot was projected on a screen 2 m away from the patients' body, and they were asked, facing the screen, to move the dot to the position they estimated to cross the trunk-centered sagittal midline of their body. To manipulate the spatial frame of reference used to perform the tasks, straight-ahead estimations were performed either in the dark or in the light. While performance in the light relied on both egocentric and allocentric frames, performance in the dark could only rely on an egocentric spatial frame of reference because of the absence of any external visual clues. Subjective judgments closely matched the real objective body midline in the light condition, but conversely, in the dark, judgments were dramatically shifted toward the side of the affected limbs. This pattern of response was not observed in patients with other kind of unilateral pain syndromes [38].

The neglect of CRPS patients observed in the visual subjective body midline judgments might result from an attentional imbalance between the sensory inputs arising from the two hemibodies as a result of "exaggerated information" on the affected side—i.e., unilateral pain [36]. Neglect symptoms reduced after the application of nerve blocks, and a similar trend was noted in healthy participants [36]. In addition, the shift toward the hemispace of the affected limb during visual straight-ahead estimations can be efficiently reduced by prism adaptation [35]. This technique, previously used with brain-damaged neglect patients, consists of modifying visuospatial perception by distorting it through prismatic glasses. Looking through these glasses shifts the visual field ipsilesionally in hemineglect patients. The resulting errors in visually guided reaching force the recalibration of visual and proprioceptive spatial coordinates toward the impaired hemispace, and improve neglect symptoms [32]. As compared to hemineglect consecutive to brain damage, a different strategy was proposed in CRPS: the prism intervention is aimed at shifting spatial frames away from the affected side [35,36]. After prism adaptation, visual body midline judgments erred in the opposite direction, toward the side of the unaffected side [35]. In contrast to previous studies [5–7,16,24,25,34], these latter experiments [35,36,38] demonstrated that the side for which there is a diminished representation of space does not always correspond to that of the affected limb.

5. An impaired perception of space not limited to egocentric frames of reference

These data show that CRPS patients can neglect sensory information that is neither in direct nor proximal (i.e., peripersonal) contact with the body, assuming, however, that only an egocentric frame of reference is used to perceive the outer world. In other words, neglect symptoms in CRPS patients seem to be determined by a spatial mapping system that uses the body as the coordinate of reference. Very recent data are further complicating the interpretation of the pattern of neglect symptoms of CRPS patients. Robinson et al. [31] have reported a single case of CRPS with impaired knowledge of spatial orientation for external objects. The patient was able to recognize and to name objects, but was unable to judge whether their orientation was canonical or not and was unable to reorient objects from noncanonical to canonical orientation. Surprisingly, this was especially marked along the horizontal axis (i.e., up vs down). The patient could correctly copy objects, but his copies were most of the time mirror reversed, as if, as outlined by the authors, the internal structure of visual objects was maintained but the main orientation axis was absent. This case is

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puzzling because the deficits of the patients cannot be explained by the opposition between affected vs. unaffected sides, nor by an impaired egocentric representation of space in which the viewer's body is the main coordinate frame.

6. Physiological and clinical implications

The data reviewed here lead us to carefully address the role of the posterior parietal cortex, not only in the pathogenesis of CRPS [19], but more largely in the cortical integration of nociceptive information in the perspective of programming the most efficient action in response to external sensory events [15], especially those threatening the physical integration of the body. Damage to the posterior parietal cortex is involved in hemineglect [39], and this area plays an important role in the integration of sensorimotor and multimodal inputs in order to form multiple representations of space and to guide appropriate actions [3,12]. This suggests that the parietal areas are of primordial importance in nociceptive processing. On the other hand, stressing the role of space perception in nociceptive processing and pain generation outlines the fact that pain is more than just *an unpleasant sensory and emotional experience*, but a signal warning the presence of a potential threat mobilizing the cognitive system in order to localize, identify and respond to this threat. The acknowledgment of distorted spatial processes is also highly relevant for the clinical management of pain. Indeed, Sumitani et al. [35] have shown that prism adaptation can additionally decrease pain and other CRPS symptoms after 2 weeks of treatment. These data were replicated by Bultitude and Rafal [2], who confirmed in one patient that daily prism adaptation could alleviate CRPS symptoms such as pain, swelling, and hand motricity after 10 days. Other techniques based on similar conceptions are also potentially relevant. Moseley et al. [27] have demonstrated modification of the perception of pain in CRPS by distorting the visual size of the affected hand. Other teams [2,22,37] have tried to cure CRPS patients with mirror rehabilitation [29]. With this technique, synchronous movements of the two limbs are made while the affected limb is hidden behind a mirror that gives to the subject the image of the unaffected limb as if it was the affected one. The subject *sees* the reflected image of the unaffected limb in the space occupied by the affected one, giving the illusion of a healthy moving limb, and this change in visual input is helpful in alleviating CRPS symptoms after several days of treatment [2,22,37].

7. Conclusion

The studies presented in this review do not allow us to conclude that the neglect-like symptoms of CRPS patients simply result from an *implicit* defensive mechanism to avoid confronting the affected body part to increased pain, but instead suggest a deficit of spatial perception, which is not always restricted to the space of the affected limb. It also seems evident that CRPS does not affect a simple somatotopic mental schema of the body represented in primary somatosensory cortex, but instead multiple representations of space that are multimodal and not specifically limited to direct sensory inputs of the body. Dissociated impairments to distinct space representations in CRPS are yet to be demonstrated. This stresses the need to pursue neuropsychological testing of spatial perception in CRPS patients to illuminate how various reference frames are affected by CRPS. The study of nociceptive processing and pain perception in relationship to spatial perception is highly relevant, not only for understanding the role of pain in the cortical processes that underlie the coordination between detection of threat and defensive action, but also for developing new neuropsychological techniques to treat chronic pain.

Conflict of interest statement

The authors report no conflict of interest.

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