

SCIENTIFIC COMMENTARIES

Lost in space: do somatic symptoms affect the perception of extra-somatic stimuli?

This scientific commentary refers to ‘Space-based bias of covert visual attention in complex regional pain syndrome’, by Bultitude *et al.* (doi:10.1093/brain/awx152).

According to traditional specificity theories, distinct somatosensory modalities (e.g. mechanoreception, thermoception and nociception) generate functionally distinct somatic sensations (touch, warm/cold, pain), in response to specific stimuli encoded by specific receptors and transmitted by specific afferent pathways (see Moayed and Davis, 2013 for a historical review from Descartes’ theory on nerves to Melzack and Wall’s gate control theory on inhibitory processes in spinal relay neurons). It is now more widely acknowledged that somatic sensations result from the convergence of sensory inputs from the different pathways (so-called pattern theories). In particular, pain is described as a percept resulting from the brain’s interpretation of a pattern of activities arising from different nerve fibres (Craig, 2003). However, the neurophysiological investigation of such a convergence has been so far mostly limited to the spinal level (Melzack and Wall, 1965). At the cortical level, only somatosensory modalities are taken into account, while non-somatic modalities, such as vision, are excluded from neuroscientific theories of pain (Craig, 2002). Nonetheless, recent investigations have shown that almost none of the cortical areas responding to painful nociceptive stimuli are truly specific to

nociception since most of them are able to respond also to non-somatic stimuli such as auditory and visual stimuli (Legrain *et al.*, 2011). Therefore, it has been suggested that most of the brain activity sampled when experiencing pain might correspond to a multimodal system giving processing priority to the stimuli that are most meaningful for homeostasis, whatever the sensory modality through which those stimuli are conveyed, in order to prompt adaptive behaviour (Legrain *et al.*, 2011). In accordance with this hypothesis, recent work has shown that the ability to perceive nociceptive stimuli on the skin depends on close interaction between the nociceptive stimuli and visual stimuli presented near the limb on which the nociceptive stimuli are applied (De Paepe *et al.*, 2017; Filbrich *et al.*, 2017). This impact of crossmodal interaction between somatic and extra-somatic inputs on nociception highlights the double function of the nociceptive system as an interoceptive and exteroceptive system (Haggard *et al.*, 2013).

Despite growing evidence of the multisensory nature of nociception and pain, this topic currently has little impact on clinical research on pain. For instance, whereas the pattern theories are widely accepted, clinical assessments of somatosensory systems, including the nociceptive system, have been developed in such a way that somatic sensations are still interpreted as emerging from specific labelled lines. However, the specificity of the somatic nature of chronic pain syndromes has recently been

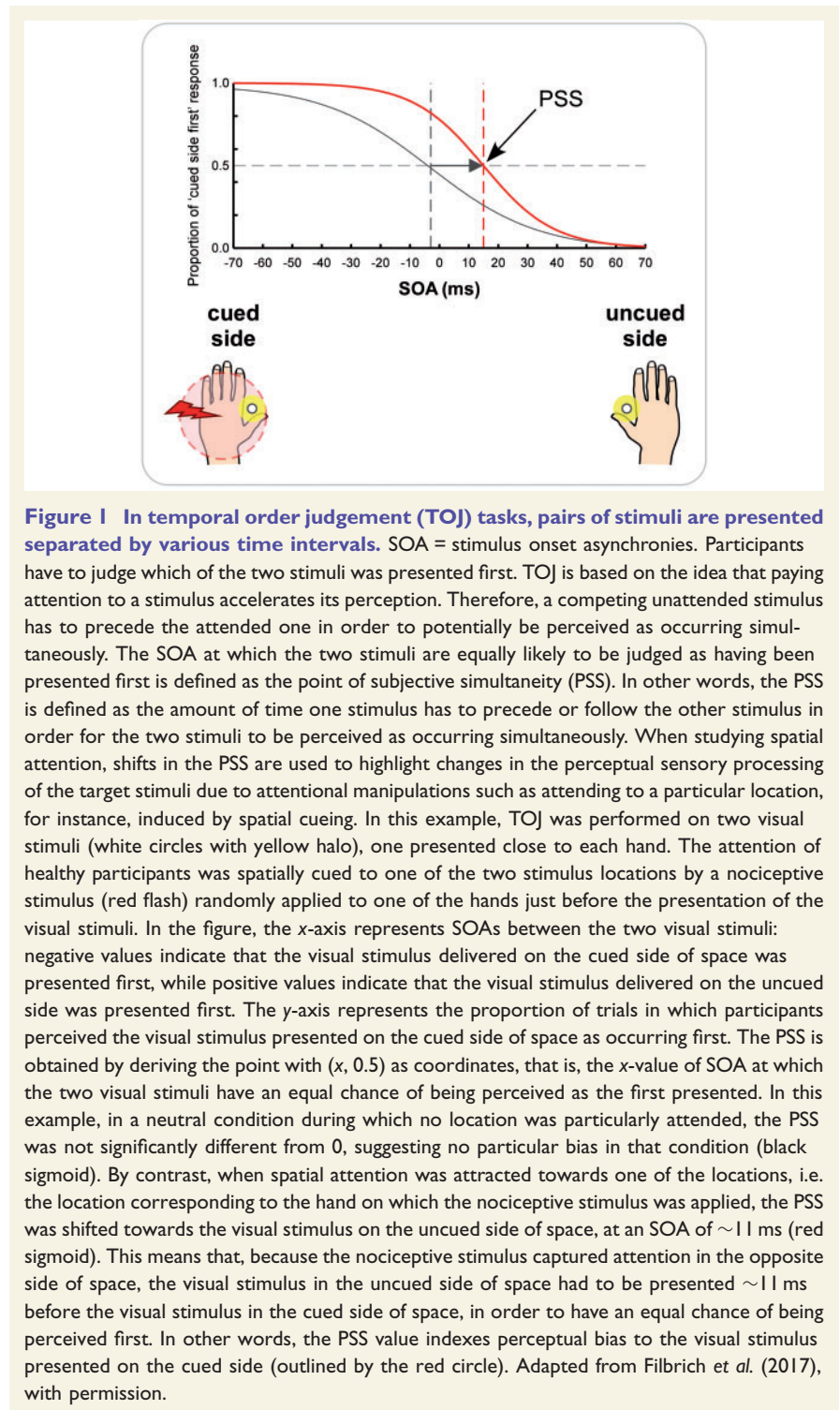
challenged by studies examining the behaviour of patients with complex regional pain syndrome (CRPS). CRPS is a chronic pain disease associating sensory, vegetative, trophic and motor symptoms of one limb. Cognitive impairments have also been reported, characterized by an altered ability to represent, perceive and use the affected limb. These cognitive symptoms emphasize the involvement of cortical mechanisms in the pathophysiology of CRPS. Nevertheless, the exact nature of the cognitive deficits is still a matter of debate (Legrain *et al.*, 2012).

One important issue is whether CRPS-related cognitive symptoms might be linked to those observed in hemispatial neglect, an attentional disorder consecutive to a lesion in one hemisphere and characterized by the inability to explore and report stimuli in the side of space contralateral to the damaged hemisphere. Whereas hemispatial neglect has been mainly (but not exclusively) characterized by, and even diagnosed according to, deficits in perceiving extra-somatic space, e.g. visual space, cognitive deficits in CRPS are thought to be limited to somatic stimuli or body-related information (Reid *et al.*, 2016). In this issue of *Brain*, Bultitude *et al.* provide compelling evidence that CRPS can also affect the perception of visual space (Bultitude *et al.*, 2017).

To this aim, the authors used a temporal order judgement (TOJ) task, which entails discriminating the

temporal order of two sensory stimuli presented in rapid succession. Patients with CRPS were asked to judge which of two visual stimuli, separated by various and randomly selected time intervals, was delivered first. One of the two visual stimuli was presented on the side of space corresponding to the pathological limb, the other on the side of the healthy limb. An important measure that can be extracted from this task is the estimated interval at which the two stimuli are equally likely to be perceived as having been presented first (Fig. 1). Under normal conditions, this point of subjective simultaneity (PSS) equals 0, indicating that no particular perceptual bias applies to the perception of the stimuli. Bultitude *et al.* observed that this was not the case in patients with CRPS. Analysis of their judgements revealed instead a cognitive bias impeding the perception of visual stimuli presented on the side of space corresponding to the pathological limb. Indeed, for the two stimuli to be perceived as simultaneous, the visual stimulus presented on the side of the affected limb had to precede the visual stimulus presented on the side of the unaffected limb. This shows that cognitive biases in CRPS are not limited to the representation and perception of the body, but also extend to extra-body space.

The findings of Bultitude *et al.* suggest that the pathophysiological processes of CRPS might underlie more than low-level sensory-motor dysfunctions, but also complex impairments in the patients' ability to perceive and act in their environment with the pathological limb. Difficulties in perceiving and exploring extra-somatic space might reflect altered functioning of cortical areas such as the supplementary motor and posterior parietal areas (Maihöfner *et al.*, 2007), which are also involved in the multisensory representation of the body and the perception of space. Now, one of the main questions remaining to be addressed is which specific spatial abilities are affected in CRPS. Indeed, although space is perceived as a unitary phenomenon, this subjective unitary



experience comes from the integration of different frames of reference, that is, different coordinate systems involved in particular spatial dimensions (e.g. our body space and the space around us). For instance, in the study by Bultitude *et al.*, because the side of visual space impaired in patients with

CRPS is related to which limb is affected, and because it depends on the actual spatial position of that limb, it can be hypothesized that CRPS affects a particular cognitive representation of external space that integrates also the somatic space. Moreover, since the different spatial frames of reference are

Glossary

Labelled lines theories: Physiological theories according to which a sensation is generated by the activation of a specific coding and transmitting system. Defenders of a labelled lines theory of pain propose that pain is a specific modality with its own receptors and fibres.

Pattern theories: Physiological theories according to which the different sensations result from distinct spatiotemporal patterns of activation of nerve impulses, rather than from the activation of distinct and specific afferents. Defenders of a pattern theory propose that pain results from the intense activation of receptors and pathways that are unspecific to pain.

hypothesized to shape motor planning (Rizzolatti *et al.*, 1997), the perceptual disabilities of patients with CRPS may be relevant to the disturbances in using the pathological limb that are particularly characteristic of these patients. Such studies offer a new theoretical framework for the investigation of cognitive rehabilitation as a potentially effective technique to treat clinical pain. To summarize, the study of Bultitude *et al.* illustrates the current dynamics of pain research, reflecting recent contributions from the theories and methods of cognitive neuropsychology.

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Stereotypical activation of hippocampal ensembles during seizures

This scientific commentary refers to ‘Involvement of fast-spiking cells in ictal sequences during spontaneous seizures in rats with chronic temporal lobe epilepsy’, by Neumann *et al.* (doi:10.1093/brain/awx179).

In addition to affecting a person’s behaviour and risk of accidents, seizures are believed to result in various neurophysiological changes that disrupt nervous system integrity. Although anti-epileptic treatments exist, they are not always effective and in some epilepsy syndromes, such as temporal

lobe epilepsy, a large proportion of patients are pharmacologically resistant. In order to develop seizure-preventing treatments, researchers have been trying to identify the neurological processes leading to seizures. In this issue of *Brain*, Neumann and co-workers use extracellular electrophysiological recordings to determine the temporal evolution of neuronal activity preceding and during spontaneous temporal lobe seizures in rats (Neumann *et al.*, 2017). They provide evidence that ictal discharges preferentially recruit specific cell ensembles

firing in stereotypical sequences. In contrast to the classic view that seizures result from excessive runaway excitation, they show that the predominant cell types activated during ictal discharges are fast-spiking, putative inhibitory interneurons.

Two concepts have traditionally been put forward as fundamental to epilepsy pathology: excitation–inhibition balance and hypersynchrony. The concept of excitation–inhibition balance is based on the assumption that normal brain function depends on the perfect balance between