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Understanding the mechanisms through which spatial attention acts on nociception

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Abstract

Previous studies have shown that spatial attention can influence the magnitude of brain responses to nociceptive inputs. In their paper, Franz and colleagues expand this observation by showing that spatial attention is further able to modify the chronometry of nociceptive processing by modulating the latency and temporal jitter of the recorded responses. The mechanisms through which attention could possibly modulate nociceptive processing are here discussed, with a particular focus on novel findings and future perspectives.

Neuro Forum

"Somatosensory spatial attention modulates amplitudes, latencies, and latency jitter of laser-evoked brain potentials" by Marcel Franz, Moritz M. Nickel, Alexander Ritter, Wolfgang H. R. Miltner and Thomas Weiss

Pain is a complex experience that emerges, in normal conditions, in response to the activation of peripheral nociceptors. Pain has to be distinguished from the related notion of nociception: although the two concepts are clearly related, they are not the same. This distinction between the activation of a sensory stream (nociception) and the conscious experience of the stimulus (pain), has rendered the study of pain and its cognitive modulations particularly challenging (Wiech et al. 2008). Several studies have shown that attention is able to modulate behavioral and brain responses to noxious inputs (see (Legrain et al. 2012), for a review on event related potentials, ERPs). However, attention is not a unitary construct; indeed different attentional processes have been identified, and a systematic investigation of the physiological mechanisms through which these different processes can shape nociception remains elusive.

In their recent paper, Franz and colleagues (Franz et al. 2015) provide an interesting perspective on the mechanisms through which spatial attention (i.e. attention allocated to a specific spatial location) exerts its modulation on brain responses to nociceptive laser stimuli (i.e. laser evoked potentials, LEPs). The authors aimed to investigate not only the effects of attention on the *magnitude* of the response, but also the effects on the *latency* of the response, with a particular focus on the trial-to-trial variability. By examining the possible effects of attention on the single trial basis, the authors sought to explore as whether differences in the magnitude of the response can be influenced by latency jitters

of the response. Importantly, these latency jitters become irrelevant when performing the analysis on a single trial level.

The authors applied laser stimuli onto the left hand and electrical stimuli onto the right hand. Interspesed with these noxious stimuli, the authors delivered non-noxious air puffs to both hands. In the ‘attend left hand condition’, the authors maximized the effects of spatial attention on the processing of nociceptive stimuli by asking participants to count the number of targets (laser stimuli and air puffs) applied on the left hand. Importantly, attending to the left hand inevitably implied also attending to laser stimuli (‘attend laser stimuli’, ALS), considering that laser stimuli were always applied on the same hand. While receiving laser stimuli on the left hand, participants also received electrical painful shocks (and non-noxious air puffs) on the right hand. Electrical stimuli were matched for intensity with laser stimuli, thereby constituting a control for salient stimuli. Therefore, in the attend electrical stimuli condition (i.e. unattend laser stimuli, ULS), participants had to focus on stimuli of a similar saliency and intensity of those that they should ignore. At high intensities, electrical stimuli are able to induce a painful sensation, without being able to selectively activate nociceptors. Indeed, at present, heat laser stimuli constitute the best available tool to measure brain responses to the activation of type II Aδ peripheral nociceptors without a concomitant activation of low threshold Aβ mechanoreceptors.

LEPs are usually constituted by three main components: an early latency N1 component, peaking at centro-temporal electrodes, followed by a negative (N2), and a positive (P2) component, both maximal at the vertex (Garcia-Larrea et al. 2003). Seminal studies have shown that spatial attention allocated to a body part (the hand) was able to enhance the amplitude of the N1 and N2 components of laser stimuli applied onto that body part (Legrain et al. 2002; 2003). The modulation of the N1 indicated that the effects of spatial

attention on brain responses can occur as early as the first stages of the elaboration of the stimulus (see also (Valentini et al. 2012)). In contrast, the P2 component was found to be largely unaffected by spatial attention *per se*, but influenced instead by the probability of occurrence of the stimulus (i.e. frequent or rare occurrence) (Legrain et al. 2002; 2003). Subsequent studies also showed that the N2 and P2 can be differentially modulated by cognition, pointing to the possibility that the two components reflect functionally different processes (reviewed in (Legrain et al. 2012)).

As an element of novelty in comparison with these previous studies, Franz and colleagues (Franz et al. 2015) analyzed their results with two different approaches: by using a standard across-trials averaging of the responses, and by applying a single-trial based estimation. This second approach allows accounting for the effect of single trial latency jitters, which can influence the amplitude of the response (Mouraux and Iannetti 2008). The authors used the method proposed by Hu and colleagues (Hu et al. 2011), which includes two steps: First, a wavelet time-frequency transform of the data is performed at both the single trial and the average level. Subsequently, a regressor and its temporal derivative are obtained for the multiple linear regression from the across-trial average waveforms. This set is then applied to single trials and allows determining latency and amplitude for each ERP peak. This analysis has been suggested to offer a more accurate and unbiased estimation of ERPs latency and amplitude (Hu et al. 2011).

In their results, Franz and colleagues (Franz et al. 2015) observed that, irrespective of the method that was used (standard averaging or single trial analysis), N2 peaks were larger in the attended condition. This would suggest that the effects of spatial attention on the magnitude of the N2 peak are not influenced by possible latency jitters occurring at the single-trial level. In contrast, single trial estimates of the P2 did not allow ruling out

completely an effect of spatial attention on the magnitude of the response. Indeed, although the authors reported that the increase of the single-trial P2 amplitudes did not reach significance, a definitive conclusion should be avoided, as the p value was p=0.051, and estimates of the effect size and/or confidence intervals were not provided. Latencies of the N2 and P2 peaks did not appear to be affected by spatial attention when extracted from the waves obtained by standard-averaging. Conversely, when single-trial analyses were used, the authors observed a reduction of the latency for the attendend N2 and P2 stimuli. In addition, they disclosed reduced latency jitters for the N2 component (expressed as standard deviation), but surprisingly, increased latency jitters for the P2 component.

Finally, the authors did not observe an effect of spatial attention on the perceived painfulness of the stimuli, meaning that attended stimuli were not perceived as more painful as compared to unattended ones.

Altogether, their findings strongly support previous reports indicating that spatial attention can modulate the N2 (Legrain et al. 2002), but less convincingly show that the P2, measured at Cz, cannot be modulated by spatial attention.

At present, it is difficult to be conclusive about which cognitive processes influence the magnitude of the LEP-P2. A possibility is that modulations of the amplitude of the P2 can depend more largely on the characteristics of the task. Previous studies have related the increase in amplitude of the P2 to the detection of rare events (Legrain et al. 2002), linking increased P2 magnitude to possibly bottom-up (i.e. stimulus-driven) capture of attention. In order to minimize the effects of bottom-up capture of attention by laser stimuli in the ULS condition, Franz et al., (Franz et al. 2015) used a new approach. They: i) matched electrical and laser stimuli for saliency and painfulness, ii) applied non-noxious stimuli on both hands, iii) reduced the interstimulus interval between laser and electrical stimuli

(although an ISI of 1 to 3 seconds is possibly not short enough to avoid brief shifts of attention towards the not to be attended hand).

Another possibility is that the effects of spatial attention on the P2 largely depend on the intensity of the incoming stimulus. Indeed, Legrain and colleagues (Legrain et al. 2003) found that the P2 of attended strong stimuli was larger than that of non-attended strong stimuli. Instead, the effects of attention on weak stimuli were observed only when attended stimuli were frequent. Franz and colleagues (Franz et al. 2015) used 'medium' perceived intensities. It would be interesting, in future studies, to investigate the effects of spatial attention on stimuli of different intensities, chosen both by physical properties (e.g. the intensity of the stimulus itself as in (Legrain et al. 2002; 2003)) and by perceived intensity (as in (Franz et al. 2015)).

By showing that spatial attention has an effect on stimulus latency and latency jitter, Franz and colleagues (Franz et al. 2015) provide useful insights on how attention can fluctuate over trials, thereby influencing the chronometry of stimulus processing. Contrary to research in other sensory domains (i.e. vision) in which the relationship between spontaneous fluctuations of attention and perception has been addressed (Romei et al. 2008), research in the pain field has long neglected this possibility. Recently, a very interesting fMRI study, by analysing trial-to-trial brain activity fluctuations, has demonstrated how spontaneous fluctuations of attention towards or away from the painful stimuli modulate brain activity (Kucyi et al. 2013). In detail, the authors observed that attention to pain increased BOLD levels in the insula, midcingulate cortex, primary and secondary somatosensory cortices (contralateral to the side of pain stimulation), and temporo-parietal junction. Attention to pain was also associated with decreased BOLD

levels in areas of the default mode network (DMN), including the posterior cingulate cortex and the medial prefrontal cortex.

Some final observations could be put forward in relation to the study of Franz et al. (Franz et al. 2015). Laser stimuli were always presented on the left hand. In this sense, it cannot be completely ruled out that effects of spatial attention can depend on the dominant side (all participants were right-handed). In addition, considering that ERPs reflect brain responses to the first afferent volley, the inclusion of electrical responses possibly activating Aβ fibers would have provided further insights on the role of spatial attention in non-nociceptive specific responses. We recently showed (Torta et al. 2015) that multisensory interactions between vision (induced by asking participants to look at their hand) and nociception modulate the N2 component of the LEPs, but the P2 component of the electrical responses. One possibility is that multisensory interactions affect functionally distinct processes in nociception and touch. However, it could also be that multisensory (and/or attentional) effects occur around 200 ms after the stimulus has been applied onto the skin. In this sense, the effect observed on the N2 component of the laser would functionally equate those occurring on the P2 of the electrical stimuli.

In conclusion, the strength of the work by Franz et al., (Franz et al. 2015) is to higlight how the effects of spatial attention modify the chronometry of nociceptive processing by modulating the latency and temporal jitter of the recorded responses. Future studies should try to provide more fine-grained characterizations of the role of attentional fluctuations over brain responses to nociceptive stimuli and pain perception in healthy and clinical populations.

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