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CORRESPONDENCE

Functional coupling between chronic pain and the autonomic nervous system revealed by neuromodulation techniques. Comment on 'Effect of neuromodulation for chronic pain on the autonomic nervous system: a systematic review' (*BJA Open* 2024; 11: 100305)

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Editor—We read with interest the article published by Billet and colleagues[1] on the effects of neuromodulation therapy for pain concomitantly produced on autonomic nervous system (ANS) parameters. This systematic review showed heterogeneous effects of different types of neuromodulation techniques on various ANS tests. The authors especially highlighted a possible decrease in sympathetic activity produced by dorsal root ganglion stimulation, an approach currently proposed for the treatment of complex regional pain syndromes (CRPS),[2] which is a typical example of the pathophysiological interactions between pain and ANS.[3] However, at least one study concerning implanted spinal cord stimulation (SCS) and two important recent works of noninvasive brain stimulation were omitted from this literature review.

First, in 20 patients successfully treated with SCS for lower limb pain as a result of failed back surgery syndrome (persistent spinal pain syndrome type 2), we showed[4] that plantar sympathetic cutaneous responses (SSRs) were facilitated (increased amplitude and decreased latency) in the 'ON-stimulation' condition compared with the 'OFF-stimulation' condition. This rather suggests an increase in sympathetic activities, contrary to what could be expected. However, SSRs assess sympathetic cholinergic innervation of sweat glands, whereas SCS-induced vasodilation is mainly mediated by adrenergic pathways.[5]

Second, in 33 patients with CRPS, we assessed[6] the effects produced on pain intensity measured on a visual numerical scale (VNS) and sympathetically-mediated electrochemical skin conductance (ESC) measured by Sudoscan® of three different noninvasive neuromodulation techniques: transcutaneous spinal direct current stimulation (tsDCS), anodal transcranial direct current stimulation (tDCS), and high-frequency repetitive transcranial magnetic stimulation (rTMS). These last two types of stimulation were delivered on the primary motor cortex, while tsDCS was delivered over the cervical or lumbar spine. In all cases, a series of 23 stimulation sessions were performed over 5 months with a 1-month follow-up after the end of treatment. The weekly ongoing pain intensity scored on the VNS was significantly reduced at all time points by tsDCS, at the end of the 5-month stimulation period up to 1 month later by rTMS, while tDCS produced no analgesic effect. Regarding sympathetic ESC measures, the subgroup of patients responding to treatment (at least 30% reduction in VNS pain intensity score) had ESC values in the affected limb that were lower than those of non-responders at baseline, but increased after the intervention, tending towards a return to normal values. In a secondary analysis of the subgroup of patients treated with motor cortex rTMS, we found[7] that this increase in ESC was correlated with the

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analgesic effect (decrease in VNS score). One month after treatment, a covariance of both variables (ESC and VNS) with fMRI activation of a brain region in the primary somatosensory cortical region (S1) was observed, revealing rTMS effects on the functional autonomic-pain brain coupling in CRPS patients. This specific S1 region could be the Brodmann Area (BA) 3a part of S1, a 'transition zone' located between M1 and S1 in the depth of the central sulcus and probably engaged in the sympathetic response to nociceptive stimuli.[8] However, the modulation of sympathetic sudomotor activities expressed by ESC changes was rather correlated with changes in fMRI activation of other brain regions, such as the middle frontal gyrus and temporo-parietal junction.[7]

The second work was based on the use of low-intensity focused ultrasound (LIFU), an emerging noninvasive neuromodulation strategy, delivered to the dorsal anterior cingulate cortex (dACC)[9] or the anterior or posterior parts of the insula[10] in healthy volunteers receiving acute noxious thermal stimuli. In both studies, all active LIFU procedures reduced pain-evoked responses to acute noxious thermal stimuli compared with a sham procedure,[9,10] while only LIFU of the dACC[9] and anterior insula (but not posterior insula)[10] increased heart rate variability measured on the electrocardiogram (ECG). This effect was accompanied by an increase in the power of low-frequency ECG signal, or even in the low-frequency/high-frequency ratio, thus rather in favour of an increase in the sympathetic components of heart rate variability. Other autonomic tests (i.e. electrodermal response and blood pressure), were not significantly modified by LIFU neuromodulation.[9,10]

These works based on different approaches of neuromodulation and cortical targeting (rTMS or LIFU) highlight the interest of various brain areas, such as S1, dACC or anterior insula, in the process of coupling neuronal activities between nociceptive information and autonomic control. These critical cortical regions, superficial or deeper, thus appear as promising therapeutic targets of neuromodulation for patients suffering from chronic pain, by acting on the autonomic components of nociception in a manner possibly associated with the interoceptive sensory system.

Declarations of interest

The authors declare that they have no conflicts of interest.

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