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Editorial

Acupuncture and the CNS: What can the brain at rest suggest?

While the mechanisms of acupuncture are unclear, its use for short term and prolonged analgesia and as a therapy for many other diseases and disorders is widespread. It is evident that acupuncture analgesia requires the stimulation of primary afferent nociceptive fibres (reviewed by Wang et al. [13]), and several brain-imaging studies have demonstrated the neural correlates of acute acupuncture. An obstacle to imaging (e.g. with functional MRI (fMRI)) the effects of acupuncture is isolating the concurrent brain activity related to the sensory stimulation from the brain activity associated with the therapeutic effect resulting from the same stimulation. However, because acupuncture must provide relief beyond the time it is being performed, its effects on brain networks after the therapy has ended (i.e. the sustained, rather than acute, effects) are of interest. In this issue of *Pain*, Dhond and colleagues [7] used fMRI to examine the effects of verum acupuncture on resting-state brain networks. The application of resting-state brain imaging could provide major benefits for pain research.

Resting-state networks (RSNs) are distributed patterns of brain regions whose activity time courses are inter-correlated, while the subject is performing no task (i.e. resting). Several RSNs have been identified, such as a network that is consistently deactivated during performance of a task, known as the default mode network (DMN), and cognitive, sensorimotor, visual, and other networks [6,10]. Dhond et al. [7] compared resting-state brain activity in 15 healthy individuals at four time points: pre-intervention (baseline); after sham (simulated needling and twirling, without insertion) acupuncture; after at least another 15 min had elapsed (second baseline); and after verum (insertion of a needle at an acupoint, with twirling) acupuncture (the order of verum and sham conditions was randomized). They also used an indirect measure of autonomic tone, heart rate variability (HRV), to determine how changes in these resting-state networks reflect autonomic output. They reported that verum acupuncture, but not the sham condition, led to increased connectivity of the default mode network, with recruitment of additional emotion-, memory-, and affect/reward-related brain regions. Furthermore, the sensorimotor network (SMN) had increased connectivity with cingulate cortex. The authors also reported that connectivity strength between the hippocampus and the rest of the DMN correlated with parasympathetic ouput during the acupuncture procedure.

One brain region of particular interest is the anterior cingulate cortex (ACC). Dhond et al. [7] reported increased connectivity of the ACC with the DMN and with the SMN. Considering the proposed role of the ACC for conflict monitoring, awareness, motor planning, and pain modulation, an intriguing question is how the heightened connectivity of the ACC in these resting-state networks reflects behaviour. This statement underscores a limitation of the present study: while resting-state network activity is changed, the exact meaning of this change is yet unresolved. There are many possibilities; for example, resting state activity in the ACC has been reported to predict subsequent responses to noxious stimuli [2]. Thus, while the approach of using resting state activity to determine brain functional differences across states is useful for testing and generating broad hypotheses, further work is needed to elucidate the role of modulating such networks. The best approach to these questions is to combine tightly controlled behavioural and multi-modal imaging (e.g. EEG, MEG, fMRI of spinal cord and brain) designs.

There is increasing evidence for the autonomic mechanisms of acupuncture analgesia, such as increased parasympathetic and decreased sympathetic activity and related increased electroencephalograph activity [8,9,11]. This is especially interesting in light of evidence that some chronic pain conditions have a sympathetic component [e.g. 12] and the hypothesis that pain is a sympathetic homeostatic emotion [4]. While Dhond et al. [7] examined brain activity associated with para/sympathetic output, conspicuously absent from the results was the insula cortex, which has been reported to have a role in autonomic awareness [5]. Yet, because the insula is not typically part of the DMN or SMN, as Dhond et al. point out it is not surprising that connectivity of the insula to these networks was not modulated by autonomic output, perhaps another limitation of the RSN approach. Instead, Dhond et al. reported that connectivity between

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the hippocampus and the DMN correlated with parasympathetic output in the verum condition. This suggests that acupuncture analgesia may operate via the effects of autonomic brain changes, since the hippocampus has connections to brainstem autonomic nuclei [3]. Again, this needs be tested explicitly by modulating hippocampal activity/connectivity via autonomic output, and seeing how this affects a given behaviour, such as pain ratings.

The Dhond et al. study brings to the fore the need to implement different imaging paradigms and techniques to explore analgesic and other types of pain modulation. A strength of analysing resting-state brain activity for clinical research in general is the ability to probe brain function without imposing highly restrictive constraints. For example, a recent study reported differences in DMN function in people with chronic pain compared to controls, and the authors proposed that this difference in resting-state brain activity might reflect the cognitive and affective complications of chronic pain [1]. Likewise, Dhond and colleagues conclude that the sustained effects of sensory stimulation on RSNs may be different in people with chronic pain and healthy controls, something they plan to test. It will be interesting to see how the RSNs of people with chronic pain – already having abnormal resting activity – will be affected by acupuncture, compared with pain-free controls. A growing body of evidence supports the view that chronic pain is a multi-system disease with long-term effects not only on sensory perception and pain, but also on cognitive and affective function. RSN analysis will help us better understand the long-term effects of pain on brain function as well as the potential benefits of various treatments.

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