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LETTER TO THE EDITOR

Does Tonic Spinal Cord Stimulation Really Influence the Medial Pain System?

To the Editor

With interest we read the paper by Deogaonkar and colleagues, "Spinal Cord Stimulation (SCS) and Functional Magnetic Resonance Imaging (fMRI): Modulation of Cortical Connectivity With Therapeutic SCS" (1). This is a very interesting and well performed study. The authors are to be congratulated on the methods used to gaining a better understanding of the supraspinal mechanisms involved in SCS. Analyzing the brain's involvement in pain suppressing obtained by SCS is essential if the neuromodulation community wants to improve its understanding of the underlying pathophysiology of different pain syndromes and how these can be treated by SCS. Ultimately the conscious percept of pain is generated in the brain, even if the trigger is peripheral and/or maintained by abnormal spinal cord activity as proposed by the pain gate model (2). Indeed, all unconscious states, such as anesthesia, coma and deep sleep are associated with an absence of pain, even if the pain cannot be suppressed during a waking state. Thus without an awake brain there is no pain percept. This can be explained by considering the brain as a complex adaptive system.

To qualify as a complex adaptive system, a system, whether internet, economy, ant society or brain, has to fulfill only two criteria (3). It needs to have a small world topology and has to embed noise (3). The brain fulfills these criteria as it has a small world topology (4,5), and is intrinsically noisy, albeit that the noise is structured, generally following a power law distribution (6). This means that it has memory, and can carry information, in contrast to white noise (7), and chronic neuropathic pain can be conceptually seen as a persistent abnormal memory trace. Thus, such a system can learn, while still maintaining stability. All complex adaptive systems share common characteristics, and emergence is one of the most important characteristics (8,9). Emergence is a process whereby larger entities, patterns, and regularities arise through interactions among smaller or simpler entities that themselves do not exhibit such properties (10). All parts of car do not make a car. Only when all those parts are put together in a very specific way, are (functionally) connected in a very specific way does a functioning car emerge. In a similar way, pain can be considered an emergent property of a "pain network," and this implies one has to study pain as a network phenomenon by using connectivity analysis, as the authors have done in their study.

However, using novel functional imaging technologies, such as seed based and whole brain functional connectivity, also brings the risk of giving too much meaning to empirical data, if these data are seen in isolation. Furthermore, it is always good to have a conceptual view of what functional connectivity and activity measurements in the brain might actually reflect or mean.

One should not forget that there is a fundamental difference between functional connectivity and activity. Whereas the former relates to communication between areas, the latter describes how active an area is. To put it in plain and simple words: functional connectivity looks at how brain areas talk to each other, whereas activity describes how silent or loud a brain area whispers/shouts its message. This is of importance, as the authors conclude the following based on their functional connectivity analysis: "This suggests that effective SCS reduces negative emotional processing associated with pain, allowing somatosensory areas to become more integrated into default mode activity and normalization of brain networks." The weakness of this conclusion is that it is not data-driven, as the authors do not provide data on bother/distress/unpleasantness. The authors only analyzed pain intensity, but accept the assumption that a change in functional connectivity between somatosensory cortex and dorsal anterior cingulate cortex/limbic areas is by definition associated with a change in negative emotional processing in pain.

This is not a mere semantic discussion for the following reason. Pain unpleasantness/annoyance and pain intensity are separable both clinically and at functional imaging level, the former processed by the medial pain system, which includes the dorsal anterior cingulate cortex/limbic areas and the latter by the lateral pain pathways which includes the somatosensory cortex (11–13). It is however important to know that the affective component of pain is related to activity changes in the brain as shown by fMRI (14), positron emission tomography (PET) (15), and electroencephalography (EEG) (14). However, there are no data (yet) to support a correlation between functional connectivity and pain unpleasantness. Furthermore, the anterior cingulate cortex is not only involved in the affective component of pain. Boly and coworkers have shown in a PET study that high baseline activity in the pain-related dorsal anterior cingulate cortex and insula predicts a sensation of higher pain intensity in response to painful laser stimuli (16). The activity in the dorsal anterior cingulate cortex is also related to attention to pain (17). In other words, the activity in the dorsal anterior cingulate cortex is not only involved in the affective component of pain, but also in pain intensity processing, and attention to pain.

Based on these data it is likely that the decreased functional connectivity between somatosensory cortex and cingulate areas indeed reflects a decrease in pain as the authors demonstrate, but that the remaining pain might be equally bothersome/distressing/unpleasant as without the SCS. It suffices that the activity in the

The authors have no conflict of interest to report relating to this letter to the editor, but Dr. De Ridder has IP on burst stimulation, which has been shown to modulate the medial pain system.

dorsal anterior cingulate cortex/limbic areas is unaltered for the patient to perceive the same pain unpleasantness/distress/bother. Or alternatively, the change in functional connectivity could only reflect a change in attention to pain, thereby decreasing the pain intensity.

This different interpretation can be easily tested by performing a correlation analysis between functional connectivity and pain unpleasantness scores. If, as the authors claim, tonic SCS does indeed reduce negative emotional processing associated with pain, then there should be a correlation between the decrease in functional connectivity and pain unpleasantness scores. If however, pain unpleasantness is not correlated to a functional connectivity change between somatosensory cortex and dorsal anterior cingulate cortex/limbic areas, then the authors should demonstrate that tonic SCS reduces activity in the cingulate area, associated with a decrease in unpleasantness.

As long as these studies have not been performed we think it is premature to conclude that tonic stimulation does indeed exert its effect on pain suppression by modulating the emotional processing of pain. It is more plausible that the pain improving effect of tonic SCS is related to activation of the descending pain inhibitory network, as demonstrated by pregenual anterior cingulate activity in a fMRI correlation analysis (18). It is of interest that the dorsal anterior cingulate cortex in this fMRI study did not change in activity in tonic SCS, suggesting that the medial pain pathways (if processing emotional processing in pain) are in fact not modulated by tonic SCS.

In sum, we believe that the conclusions drawn in this manuscript are not sufficiently supported by the data, and kindly propose the authors to do a follow up study that proves or disproves their statement that tonic SCS exerts its effect by altering emotional pain related processing.

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