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Editorial comment

Objective measurement of subjective pain-experience: Real nociceptive stimuli versus pain expectation

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In the present issue of *Scandinavian Journal of Pain* Meyer-Friessem and co-workers report from a study on using brain oxygen delivery-consumption balance (**BODCB**) for measurements during experimental electrical pain, both expected and non-expected pain [1].

1. Cerebral oxygen consumption: related to pain experience? (Expectation of pain does not always aggravate pain-experience?)

In a crossover design in volunteers, real electrical pain stimulation was given without warning and then with warning of upcoming pain. Also, warning was given without any pain stimuli to follow, on one test followed by a gentle skin spray and one occasion without anything to follow at all. The numerical rating of pain was recorded, as well as the concomitant change in oxygen delivery-consumption balance, as measured by near-infrared technology in the forehead. As the verbal NRS scores of pain-intensity behaved predictively, increased similarly by both unexpected and expected real pain and not by the other tests, the results of the **BODCB** were non-specific. Thus, disappointingly, **BODCB** appears not to be a new method for objective pain measurement.

However, the results are still interesting as they demonstrate the impact of expectations on brain neuronal activity, and that expectations can overrule the subjective pain-experience (as expressed by NRS) from real pain stimuli, in this kind of experiment [1].

2. Objective measurement of subjective pain-experience – searching for a holy grail?

The authors have indeed a very brave project, attempted by a vast number of scientists throughout many decades: Is it feasible to find a way to measure pain objectively when pain is defined as a person's subjective experience? Although acute pain perception is usually based on tissue destruction and subsequent physiologic signals mediated by nociceptive pathways, the measurement of the experience is hard to do. We know that a standardized repetitive nociceptive pain response may change abruptly to the better when a person is positively distracted and to the worse when the same person is subjected to anxiety or fear. The question is whether we ever will be able to objectively and quantitatively measure this change in psychological modulation of the nociceptive signal as revealed by the final "pain experience".

3. Nocicepto-meters are not specific for pain-experience

We already have many "nocicepto-meters" i.e. more or less specific ways of measuring the nociceptive activation. In animal models direct measurement of electrical currents and firing in neurons and across receptors and synapses is possible. In clinical practice we may use changes in EEG or changes in sympathetic outflow to target organs, such as heart rate variability, pupilometer, muscle tension or sweating, as indirect indicators of nociceptive load [2]. The problem with these "nocicepto-meters" is a low specificity and poor correlation with clinical experienced pain. While cutaneous sweating correlates very well with nociceptive stimulation during low dose general anaesthesia, the signals will be totally non-specific in the awake person [3]. A strong sound, or even some disturbing thoughts, may produce the same response as pain, or may be even stronger.

4. Functional magnetic resonance imaging (fMRI) and positive emission tomography (PET)

However, if there should be any ways of objectively measure the psychological process of pain perception, the cortical brain is a logical place to look for specific changes. We know that strong feelings, thoughts, stress etc. increase the neuronal firing in cortical brain, and increased neuronal firing increases the oxygen consumption. Old experiments show that the oxygen delivery, i.e. local blood flow, increases beyond the oxygen demand in such situations [4]. This observation has been the base of using functional magnetic

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resonance imaging (fMRI) of blood-flow changes in the brain as a tool to characterize whether neuronal activity increases or decreases [5]. Different modifications of fMRI to study blood flow, blood volume, oxygen content or even other aspects of neuronal activity, such as glucose metabolism or neurotransmitter activity have been very successful in experimental settings [5]. Also the use of radiolabelled ligands and subsequent mapping in positive emission tomography (PET) has shed important light on pain mechanisms within the brain [5]. However, the fMRI and PET methods of exact mapping of neuronal activities in small, specified areas of the brain do not render themselves for everyday clinical use. They are based on cumbersome, time-consuming and very expensive technology. Thus, the potential use of a disposable electrode set on the fore-head for non-invasive, online measurements seems to be a very attractive alternative to exploit, such as in the present study of Meyer-Friessem and coworkers [1].

5. Near-infrared spectroscopy technology (NIRS) in the present study: alternative to fMRI and PET?

NIRS has been shown to reliably measure increased regional cerebral tissue oxygen consumption in clinical situations of nociception [6,7]. Then why does the method not come out with proper sensitivity and specificity in the present report? The authors point to a number of sensible reasons in their paper [1], such as the small and maybe not fully relevant part of the frontal brain being monitored. Further, the experimental character of the electrical stimulus may be important; not being calibrated, strong, continuous or fully representative for clinical pain.

6. Conclusions and implications

Still, while being negative and in that aspect disappointing; the study provides a number of interesting information and learning points about pain and arousal: In awake persons, we know that emotions and even thoughts, may result in more sympathetic outflow than modest experimental pain. It has been shown with the sweat response, which works most specifically for nociception when the patient is asleep and not disturbed by other stimuli or emotions [8]. In the present study of awake volunteers, the expectation of a painful stimulus seemed to abolish the response, whether pain-stimuli or just a gentle skin spray followed it. However, and interestingly; when no stimuli came at all there was an increase in BODCB when expectation was not fulfilled. This latter curve was not significantly different from the increase seen when pain stimuli came unexpectedly.

In spite of the lack of specificity for the unexpected pain stimuli, there was an increase in BODCB in 17 out of 20 persons. This may suggest that in a model with stronger pain combined with either more extensive or more anatomical focused monitoring of oxygen delivery consumption balance in relevant brain structures, the method may be of interest. Still, the emotional overlay from other brain activities than pain may be a problem, pointing towards the value of objective nociceptor activity measurements being best in non-communicating patients. Heavily sedated patients and patients in the intensive care setting may be other interesting areas for future research into this exciting area.

Conflict of interest

None declared.

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