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NEUROIMAGING

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Can behavioural therapy influence neuromodulation?

Abstract This paper reviews non-invasive behavioural approaches – broadly construed as cognitive, affective, behavioural and psychophysiological interventions – and examines whether they can impact central, peripheral or autonomic nervous system components responsive to pain in general and headache in particular. It focuses on two developing bodies of literature – neurophysiology of migraine and fMRI studies of pain networks. The available literature suggests behavioural interventions can affect neuromodulation, although further research is clearly warranted.

Key words Behavioural therapy • Neuromodulation • Migraine • Pain

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The International Neuromodulation Society defines neuromodulation as "the reversible therapeutic interaction of activity of the central, peripheral and autonomic nervous system with electrical or centrally applied pharmacological agents". This paper departs from the intervention approaches standard to neuromodulation (e.g., peripheral and percutaneous nerve stimulation, spinal cord stimulation, deep brain stimulation, cranial nerve stimulation, cerebral cortex stimulation, intrathecal drug delivery and functional electrical stimulation). Rather, it focuses upon non-invasive behavioural approaches – broadly construed as cognitive, affective, behavioural and psychophysiological interventions – and asks whether they too can impact central, peripheral or autonomic nervous system components responsive to pain in general and headache in particular. Our review focuses on two developing bodies of literature – neurophysiology of migraine and fMRI studies of pain networks[1].

CNV response and migraine

In migraine, certain neurophysiological abnormalities occur in temporal relation to the attack, and it is believed that these characteristics make migraineurs more susceptible to migraine-provoking agents. The contingent negative variation (CNV) response, a slow cortical event-related potential that is recorded from the scalp between two stimuli while a person is waiting for the second event and preparing for task performance [2], is used to investigate these aspects. This potential is related to the level of cortical excitability following activation in the striato-thalamo-cortical loop and reflects different stages of information processing [3]. Various components can be measured: early, late, postimperative negative variation (PINV) and total. Migraineurs reveal increased amplitudes and reduced habituation of the CNV, both reflecting excitability of cortical networks, particularly with regards to its early component [4–6]. Repeated presentations of a stimulus typically lead to habituation, but this is not so for individuals diag-

[1] For a discussion of related aspects – pain and brain plasticity – see Flor and Andrasik [1]

nosed with migraine[2]. The CNV seems to reflect anticipation of an attack because its amplitude and habituation patterns change during the headache-free interval. CNV abnormalities gradually increase in the days before a migraine attack, with the most pronounced changes (maximal negativity and loss of habituation) occurring just prior to an attack [8].

A recent study of ours provides clearer support for this view [9]. Forty-five patients with migraine (33 women, 12 men; 30 without aura, 15 with aura) were studied, along with 20 healthy non-migraine medical student controls. The migraine patients had been subjected to repeated CNV recording sessions, during rest and stress, prior to them participating in various past clinical trials. In a re-analysis, data records were searched to find migraineurs whose CNV had been recorded (1) 1–3 days before their migraine attack (termed pre-attack), (2) 1–3 days following an attack (termed post-attack) and (3) outside of these periods (termed "headache-free interval group "). When compared to the healthy controls, migraine patients revealed an increase in the early CNV and a marked loss of the early CNV habituation prior to a migraine attack. This pattern of findings is shown in Figure 1.

Findings from this and related studies lead to a series of questions. Can these CNV abnormalities be modified and does that in turn lead to clinical improvement? Secondarily, if CNV abnormalities are pivotal to migraine onset, can these abnormalities be treated in other ways (or are they currently being affected, but are just not the subject of study)? With respect to the first set of questions, preliminary evidence suggests it may be possible to do so. Ten children experiencing migraines without aura were each provided 10 sessions of biofeedback to regulate the CNV response [10]. Children were trained both to increase and to decrease negativity. Examination of neurophysiological data revealed the children could indeed regulate the CNV response during provision of feedback by the end of training, but their abilities to accomplish this when feedback was not present were variable. We suspect that a greater amount of training is needed to control this response in the absence of feedback. More importantly, though, tonic levels of CNV negativity changed as a function of treatment, such that the migraineurs were indistinguishable from a sample of healthy controls (i.e., their cortical excitability had been reduced) after treatment was completed. The limited training provided resulted in significant improvements for most of the headache parameters that were recorded, relative to a comparison group of child migraineurs who served as wait-list controls. This study is by no means definitive, but it is suggestive of the neuromodulatory effects of CNV biofeedback and that training may serve to normalise the CNV response.

The latter question has been addressed in an investigation that examined whether the mechanism of a medical treatment, the beta-blocker metoprolol, might involve alteration of the CNV response [11]. With this in mind, we treated a small group of patients, all of whom were experiencing migraine without aura. These patients were treated in a double-blind study with random assignment either to metoprolol-CR or placebo. Metoprolol (and placebo) was administered in the morning in steps of 50 mg (1/2 tablet) per week, to a maximum dose of 200 mg by the fourth week. Treatment was continued for two additional months, at which time a gradual reduction programme was instituted (also in steps of 50 mg). CNV was recorded on five separate occasions: at the beginning and the end of the 1-month baseline and at the end of each month of treatment. Metoprolol did lead to significant improvement on all 3 outcome parameters, when compared to placebo (see Fig. 2). By the end of treatment, CNV

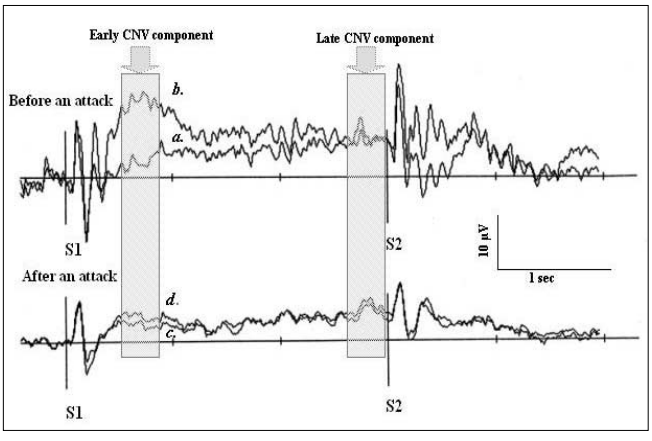

Fig. 1 CNV, early and late components, in participants experiencing migraine without aura. **a** CNV recorded 1 day prior to a migraine attack, during rest. **b** CNV recorded 1 day prior to a migraine attack, during stress. **c** CNV recorded 2 days following a migraine attack, during rest. **d** CNV recorded 2 days following a migraine attack, during stress

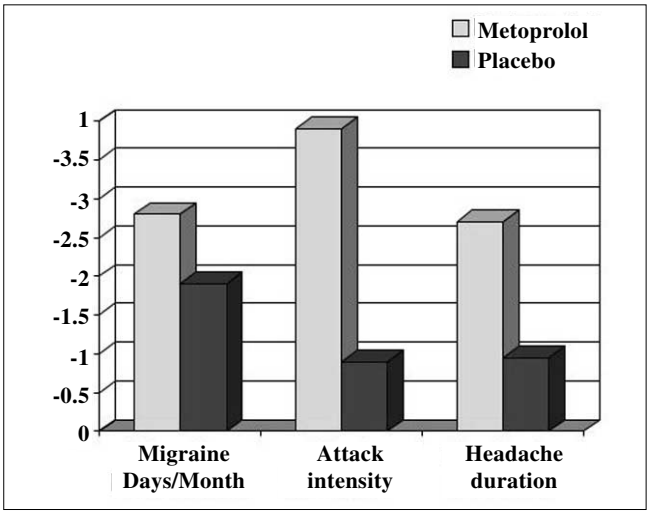

Fig. 2 Clinical efficacy of metoprolol-CR. Aggregated *z*-values of ARIMA analyses (headache diary, baseline *vs.* treatment) indicate a significant reduction for all 3 measures comparing metoprolol to placebo [11]

[2] A brainstem migraine generator has been proposed as well because alterations in brain stem activity have regularly been found during migraine attacks [7].

measures of amplitude (total and PINV) and habituation were improved for patients receiving metoprolol, but not for those receiving placebo. Thus, CNV biofeedback may be an effective neuromodulator for migraine and exert its effects in a manner that is similar to that of beta-blockers [12–14].

Functional magnetic resonance imaging and pain networks

Real-time functional magnetic resonance imaging (rtfMRI) allows researchers and clinicians to observe brain activity as it occurs. Neural activity is measured with a blood oxygenation level-dependent (BOLD) signal [15]. There is a natural haemodynamic delay of the signal of approximately 3–6 s [16]. Additional delays in the signal depend on the equipment and computer processing techniques used for imaging (for a review of rtfMRI development, see Bagarinao et al. [17]).

Proposed pain network and associated areas

A number of fMRI, rtfMRI and other neuroimaging studies have revealed brain structures involved with the experience of pain. Apkarian et al. [18] performed a meta-analysis of these studies and reported six structures were repeatedly activated in the "pain network" of the brain (see Table 1). Of these structures, the anterior cingulate cortex (ACC) has shown a strong involvement across various pain stimuli and imaging techniques. The ACC, a component of the limbic system, is believed to have distinct regions influencing both cognitive-evaluative and affective responses to pain [19, 20]. Bantick and associates [21] found that when participants were distracted by a cognitive task while simultaneously undergoing a painful thermal stimulus, activation in the rostral-ventral anterior cingulate cortex (rACC), the subdivision of the ACC considered to influence affect, increased compared to a non-distracting condition. In contrast, activation in the dorsal anterior cingulate cortex (dACC), the subdivision believed to influence the cognitive processing of pain, decreased. Activation in other structures of the pain network also decreased. Additionally, the participants' pain intensity ratings decreased during the distraction task. This study demonstrates that cognitive state can serve as a neuromodulator for pain.

Table 1 Structures activated in the "pain network" of the brain [18]

Those structures activated most often
Primary and secondary somatosensory cortices
Anterior cingulate cortex (ACC)
Insula
Thalamus
Prefrontal cortex
Those structures activated less often:
Primary and supplementary motor cortices
Posterior parietal cortex
Posterior cingulate
Basal ganglia
Hypothalamus
Amygdala
Parabrachial nuclei
Periaqueductal grey (PAG)

Apkarian et al. [18] point out that other areas are often associated with pain, as well (see Table 1). Valet and colleagues [22] assert that the ACC and orbitofrontal cortex relay information to the PAG regarding pain. Pain stimulation alone does not appear to activate the PAG, but it is believed that this brain region modulates pain perception. Although an increase in activation during distraction tasks results in self-reported decreases in pain perception [23], it may have more than one role in pain. Activation of the PAG has also been implicated in the anticipation of pain [24] and anxiety associated with pain [25]. The anticipation of pain and the activation of the PAG prior to an expected painful stimulus may account for the enhanced sensitivity to pain shown by patients with chronic pain [24].

Apkarian et al. [18] also found differences in brain activity response to acute pain in healthy populations compared to chronic pain populations. Healthy populations show consistent activity in the brain structures of the pain network with the application of a painful stimulus, whereas chronic pain populations have a decrease in activity in most of these prominent structures with the same stimulus. Chronic pain patients appear to have more activity in the prefrontal cortex compared to their healthy counterparts. The authors proposed that chronic pain patients may have a reduction in sensory information processing and heightened emotional and/or cognitive processing of pain. Borsook and Becerra [26] note that such neuronal changes in chronic pain patients may account for the high incidence of depression, anxiety and amotivation in this population.

Imaging techniques provide opportunities to identify brain structures involved in the pain network. It is evident that this network of brain regions and varying connections are complex. Localised areas in the brain may have a number of functions with regards to pain, as demonstrated by studies of the ACC and PAG. Some of these functions are seemingly contradictory in the perception of pain. Currently, rtfMRI neurofeedback is being investigated for clinical applications. A handful of studies have revealed the potential of volitional control or neuromodulation over the activation of brain regions.

rtfMRI neurofeedback studies and considerations

Voluntary control of physiological responses, such as muscle tension, electrodermal activity, hand temperature, heart rate and brain waves has been established [27]. In an fMRI study, a decrease in electrodermal response through intentional relaxation biofeedback was found to activate the ACC, insula, somatosensory cortices and amygdala [28]. Instead of using the conventional signals for feedback, some researchers have conducted studies using regions of interest (ROIs) in the brain as a signal for feedback with rtfMRI.

Yoo and Jolesz [29] analysed whether 5 participants would be able to alter their own cortical activity through rtfMRI feedback. The ROIs were the left motor and somatosensory areas of the brain. The investigators showed the participants these locations on a brain image. Participants completed eight reference trials with index finger movements. In the following eight trials, participants were instructed to increase the activation of the ROIs in relation to the reference image. The reference and feedback images were functional maps of the brain. The feedback was processed and updated approximately every minute. Through trial and error, participants learned to increase their activation by engaging more fingers in tapping, with the intensity of tapping, and other similar strategies. The investigators reported that all five participants attained a 3-fold increase in activation compared to the reference image by the third trial.

Posse et al. [30] examined activation in the amygdala in participants who were presented with sad and neutral faces. The participants were instructed to self-induce feelings of sadness when the sad faces were presented. They rated their level of sadness on a scale of 1–5, where 1 was not at all sad and 5 was intensely sad. After the self-rated sadness, the investigators gave verbal feedback to the participants about their level of amygdala activation, where 1 was no activation and 5 was maximum activation. This study revealed a correspondence between self-rated sadness and amygdala activation. Participants' volitional control of the amygdala, however, was not assessed in this experiment, leaving this form of neuromodulation as just an intriguing possibility.

Weiskopf et al. [31] conducted a preliminary case study with rtfMRI. The ROI was the rACC and the dACC. The participant was provided feedback in the form of analogue scrolling curves from the two ACC areas, with signals being processed in less than 2 s. The participant was instructed to alternatively increase both curves for a period of time, then to decrease both curves. He used his own strategies to accomplish this task. In 8 sessions, the participant achieved improved control of the rACC, the affective subdivision of the ACC. He also improved his control over the dACC, the cognitive subdivision of the ACC, but the results were not statistically significant. The investigators of this case study assert that a learning effect occurred from this feedback.

deCharms and associates [32] investigated activation in the somatomotor cortex (SMC) based on actual motor movements and imagined motor movements. Nine participants practised specific finger movements and imagined these movements for an hour before rtfMRI feedback. A baseline measure of SMC activation was obtained for actual finger tapping. All of the participants were instructed to increase their SMC activation while imagining the tapping of their index finger and receiving feedback. In addition to measuring the ROI, the investigators measured EMG activity of the index finger to ensure actual finger movements were not confounding the imagined activation results. The feedback was presented as a scrolling curve in addition to a video image of a weight lifter bringing the weight up as SMC activation increased and bringing the weight down as the activation decreased. The haemodynamic delay is approximately 2 s and the computer processing was approximately 2 s, providing peak feedback in 4–6 s. Six of the participants were provided actual feedback, whereas 3 control participants were provided random sham feedback. Although there is generally some activation of the SMC during imagined movements, the experimental group receiving actual feedback significantly increased their SMC activation over the course of three 20-min sessions compared to the control group. After the 3-session training, the investigators tested all the participants on the same task in the absence of rtfMRI feedback. The experimental group continued to show increased SMC activation, whereas the control group maintained a much lower level of activation. These results suggest that the participants receiving actual feedback were able to exert self-regulation of the targeted ROI.

deCharms and associates [33] carried out subsequent research with the rACC as the ROI. All of the participants were provided with information on strategies to control activation of the rACC. Healthy participants, receiving actual or pseudo-feedback from rtfMRI, were presented a scrolling curve of rACC activation and a video display of a fire with increasing and decreasing flames corresponding to rACC activation, with a delay of approximately 4–7 s. Training occurred for three 13-min sessions and a painful thermal stimulus was applied during these sessions. Over the course of the training, participants receiving actual feedback demonstrated increased volitional control of rACC activation and pain perception ratings decreased. The control groups not receiving any feedback or receiving sham feedback did not demonstrate these effects. The investigators also assessed potential training effects in chronic pain patients. A similar protocol to that for the healthy participants was utilised. However, an acute thermal pain application was not used and the control group received conventional biofeedback information on their electrodermal activity, heart rate and respiration. The chronic pain patients were also able to learn voluntary control of the rACC with decreased ratings in pain perception

using rtfMRI feedback, whereas the pain ratings for the controls remained the same. It is of note to point out that this is the first experiment to use rtfMRI neurofeedback for individuals with chronic pain [26].

While the research using sophisticated rtfMRI feedback training is in its infancy, the results from these aforementioned studies are promising for clinical applications. The use of rtfMRI feedback is not yet standardised, where different equipment and computational processing has been used [17]. This needs consideration when comparing studies [26]. Additionally, artefacts, resulting from head movements and respiration patterns, can confound the results of rtfMRI research [16]. There are also individual differences in brain structure and processes that can threaten the validity of rtfMRI research [18]. Likewise, the various roles of a given brain structure, as described with the ACC and PAG, can affect the interpretation of activation in these areas.

Weiskopf and associates [16] outline optimal training considerations in rtfMRI feedback based on operant learning principles. These include the feedback delay and feedback presentation. The more immediate the feedback, the more likely training can take place. In the deCharms et al. studies [32, 33], the feedback was provided in a matter of seconds. The feedback modality can also impact the facilitation of learning. For instance, it may be difficult for participants to detect slight changes in activation with the brain image. Translating this activation in scrolling curves allows participants to visualise slight changes in the increasing and decreasing patterns of activation. Furthermore, video images may have a more reinforcing property than the scrolling curves. For example, using images of a weight lifter [32] or a flaming fire [33] in addition to the scrolling curves may enhance learning. While this research has only scratched the surface, the findings to date suggest that components of the pain network can be affected by noninvasive voluntary self-regulation and that this may indeed constitute a new set of neuromodulators.

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