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THE INTERACTION OF EMOTION AND PAIN IN THE INSULA AND SECONDARY SOMATOSENSORY CORTEX

TAGE I. ORENIUS,[a]* TUUKKA T. RAIJ,[b,c] ANTTI NUORTIMO,[d] PETRI NÄÄTÄNEN,[e] JARI LIPSANEN[d] AND HASSE KARLSSON[f]

[a] *ORTON Orthopaedic Hospital Ltd., ORTON Foundation, Helsinki, Finland*

[b] *Department of Psychiatry, Helsinki University Hospital, Finland*

[c] *Department of Neuroscience and Biomedical Engineering and Advanced Magnetic Imaging Centre, Aalto Neuroimaging, Aalto University School of Science, Espoo, Finland*

[d] *Institute of Behavioural Sciences, University of Helsinki, Finland*

[e] *Helsinki University Central Hospital, Finland*

[f] *Department of Psychiatry and Turku Brain and Mind Centre, University of Turku and Turku University Hospital, Finland*

Abstract—Pain is processed in a large neural network that partially overlaps structures involved in emotion processing. Despite the fact that pain and emotion are known to share neural regions and interact in numerous clinical conditions, relatively little is known about the interaction of pain and emotion at the neural level. This study on healthy adults aimed to investigate the interaction between negative and positive emotional stimuli and experimental pain in an essential pain processing network. Sixteen healthy young adult subjects were exposed to pictures from the International Affective Picture System (IAPS) with negative, neutral or positive valence, along with laser pain stimuli. The stimuli were pseudo-randomly arranged in three 15-min experiment series comprising 49 stimuli each (picture, laser or simultaneous picture and laser stimuli). The whole-brain blood-oxygen-level-dependent (BOLD) signal was acquired using 3T functional magnetic resonance imaging (fMRI). As expected, the pain stimulus elicited activation in the secondary somatosensory cortex (SII), insula and anterior cingulate cortex (ACC) when compared to the baseline. The interaction of negative emotion and laser stimuli related to the activation of the left SII. The interaction of positive emotion and pain stimuli led to bilateral activation of the SII and left insula. These findings reveal interaction in parts of the pain processing network during simultaneous emotion and physical pain. We demonstrated a valence-independent interaction of emotion and pain in SII.

Key words: pain, emotion, interaction, pain processing network.

INTRODUCTION

Pain is an unpleasant and intrusive sensory and emotional experience, warning of actual or potential tissue damage (Merskey and Bogduk, 1994). Brain imaging has demonstrated the involvement of a network of multiple brain structures (earlier referred to as the pain matrix) in the neural processing of acute pain. This network mainly comprises the primary somatosensory (SI) and the secondary somatosensory (SII) cortices, the insula, the anterior cingulate cortex (ACC), the prefrontal cortex (PFC) and the thalamus (Apkarian et al., 2005). The network has occasionally been divided into medial and lateral pain circuitries based on the projection sites from medial or lateral thalamic regions to cortical areas. Nociceptive information conveyed to the SI, SII and posterior insula relates to sensory-discriminative aspects of pain (Derbyshire et al., 1997; Apkarian et al., 2005; Raij et al., 2005). Spinal pathways to limbic structures and medial thalamic nuclei provide inputs to the emotion-related brain areas like the ACC and the insula, the amygdala and the PFC, and regions processing the affective-motivational dimension of the pain experience (Derbyshire et al., 1997). A more recent meta-analysis of neuroimaging data indicates that the motor cortex, the cerebellum and the midbrain are also likely to be activated by experimental pain stimuli (Duerden and Albanese, 2013).

Emotion processing and somatosensory circuits are reciprocally interconnected, providing pro- and anti-nociceptive modulations of pain by cognitive and emotional factors (Price, 2000). This enables a necessary survival function by allowing alteration of the pain experience according to the situation rather than allowing pain to dominate (Bingel and Tracey, 2008).

Using subjective and physiological measures, Meagher et al. (2001) found that unpleasant emotional states enhanced cold-pain perception, whereas pleasant emotional states attenuated it. This finding agrees with

*Corresponding author. Address: Tenholantie 10, 00280 Helsinki, Finland. Fax: +358-9-2419706.
E-mail addresses: tage.orenius@orton.fi (T. I. Orenius), raijtu@neuro.hut.fi (T. T. Raij), antti.nuortimo@helsinki.fi (A. Nuortimo), petri.naatanen@hus.fi (P. Näätänen), jari.lipsanen@helsinki.fi (J. Lipsanen), hasseka@utu.fi (H. Karlsson).

Abbreviations: ACC, anterior cingulate cortex; BOLD, blood-oxygen-level dependent; fMRI, functional magnetic resonance imaging; FWE, familywise error; ISI, inter-stimulus interval; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; PFC, prefrontal cortex; ROI, regions-of-interest; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; VAS, visual analogue scale.

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a study by Ploghaus et al. (2001) that suggested pain intensity is enhanced by pain-relevant anxiety. Roy et al. (2009) found that emotions induced by pleasant or unpleasant images modulated responses to painful electrical stimulations in the right insula, the paracentral lobule, the parahippocampal gyrus, the thalamus and the amygdala. Furthermore, Villemure and Bushnell (2009) found that positive mood changes induced by pleasant odors decreased activity related to pain and unpleasantness within the ACC, the medial thalamus and the SI and SII cortices. According to Duquette et al. (2007), such modulatory effects might indicate interaction between emotional and nociceptive systems in the PFC and the cingulate cortex, the ventral striatum, the amygdala and the hippocampus. Attentional and emotional states affect the sensory and emotional aspects of pain perception differently, suggesting the involvement of different neural circuits (Villemure and Schweinhardt, 2010).

Emotional components seem to influence the pain chronification process. A brain imaging study revealed that in a group of patients with persistent lower back pain, activity diminished in sensory pain regions but increased in emotion-related circuitry compared to the group of recovered patients (Hashmi et al., 2013). Properties of the brain's emotional learning circuitry can predict the transition to chronic pain. Apkarian et al. (2013) found the strength of functional connectivity between the medial prefrontal cortex (mPFC) and nucleus accumbens (i.e. the reward center) to be highly predictive of individuals who subsequently transition to chronicity within one year.

Thus, emotional components are highly relevant in pain processing during states progressing from acute pain to pain chronicity. In everyday life, pain states usually occur in an emotional context and therefore an understanding of the interaction between emotional states and the pain on a neural level is important. Interaction can be defined as the effects of two or more factors being non-additive, i.e. the sum of the effects of A and B occurring alone does not equal the effects of A and B occurring simultaneously. If there is an interaction effect, the brain activation during simultaneous A and B = A + B + A*B, where A*B is the interaction term. The interaction effects of pain and emotion are clinically highly relevant due to (1) the high comorbidity of pain and emotional disturbances; (2) the contribution of pain to emotional experiences; and (3) the contribution of emotions to the pain experience. However, the neural basis of the interaction between pain and emotion (hereafter referred to as pain $\times$ emotion), remains poorly understood. Only a few functional imaging studies have addressed the effect of emotion on pain-related brain activation (Ploghaus et al., 2001; Roy et al., 2009; Villemure and Bushnell, 2009), and to our knowledge, no studies have controlled for the main effect of emotion to focus on the emotion x pain interaction per se.

Consequently, this study sought to investigate the interaction between negative and positive emotional states and experimental pain in the essential pain processing network.

EXPERIMENTAL PROCEDURES

Subject selection

The study subjects were 16 healthy, pain-free young adult male students, aged 20–26 years, mean 22 (1.9) years. They were selected from a sample of engineering students at Helsinki Metropolia University of Applied Sciences. One subject was excluded due to excessive ($>2^{\circ}$) head rotation during imaging.

The exclusion criteria were depression and alexithymia, because emotion-related neural activation can be divergent in these states (Karlsson et al., 2008; Diener et al., 2012; van der Velde et al., 2013). The 21-item Beck Depression Scale, second version (BDI-II) (Beck et al., 1996, 2004) was used to screen for depressive symptoms. No participant exceeded the reference value for mild depression (BDI $\geq$ 14), which was the exclusion limit (Beck et al., 2004). The Toronto Alexithymia Scale (TAS-20) was used to screen for alexithymia, a deficit in the cognitive processing of emotions (Taylor et al., 1992; Joukamaa et al., 2001). No participant exceeded the reference limit (score > 60) for alexithymia. Other exclusion criteria were past or present prolonged pain, diagnosed psychiatric disorder, regular medication of any kind and magnetic object in the body. No clinical psychological or psychiatric examinations were carried out. Subjects were asked about, but no participants reported, either a history of psychiatric or neurological disorders or the current use of any psychoactive medications.

Pain stimuli

Painful stimuli were delivered with a Thulium-YAG stimulator (Baasel Lasertech, Starnberg, Germany) with a 2000 nm wavelength, pulse duration of 1 ms and spot diameter of 6 mm. The laser beam was led through an optical fiber from outside into the magnetic resonance imaging (MRI) room. The laser stimulation was delivered onto the dorsum of the left hand by the research assistant, who was trained and instructed to slowly move the laser over an area of about 10 cm^2 in order to prevent skin burning injuries and adaptation. The laser pulses heat the skin up to $>45\ ^{\circ}C$, activating selectively nociceptive Aδ and C afferents without significant activation of tactile receptors (Arendt-Nielsen and Chen, 2003). Before taking the measurements, the participants' individual pain thresholds were defined and the laser energy calibrated to equal 1.8-fold the pain threshold. The calibration of the laser energy corresponds to earlier studies using a Thulium-laser with a 1.5–2 $\times$ subjective sensory threshold (Cruccu et al., 2003; Raij et al., 2005).

Emotional stimuli

Employing a passive viewing task, emotions were elicited by utilizing stimuli from the standardized International Affective Picture System (IAPS; Lang et al., 1997, 2005) consisting of a series of emotional, normative and internationally accessible pictorial stimuli. Considered to be a