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Painful engrams: Oscillatory correlates of working memory for phasic nociceptive laser stimuli

Elia Valentini[a,b,c,*], Valentina Nicolardi[a,b], Salvatore Maria Aglioti[a,b]

[a] Department of Psychology and Centre for Brain Science, University of Essex, England, UK
[b] Sapienza Università di Roma, Dipartimento di Psicologia, Italy
[c] Fondazione Santa Lucia, Istituto di Ricovero e Cura a Carattere Scientifico, Italy

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ABSTRACT

Research suggests that working memory (WM) is impaired in chronic pain. Yet, information on how potentially noxious stimuli are maintained in memory is limited in patients as well as in healthy people. We recorded electroencephalography (EEG) in healthy volunteers during a modified delayed match-to-sample task where maintenance in memory of relevant attributes of nociceptive laser stimuli was essential for subsequent cued-discrimination. Participants performed in high and low load conditions (i.e. three vs. two stimuli to keep in WM). Modulation of EEG oscillations in the beta band during the retention interval and in the alpha band during the pre-retention interval reflected performance in the WM task. Importantly, both a non-verbal and a verbal neuropsychological WM test predicted oscillatory modulations. Moreover, these two neuropsychological tests and self-reported personality measures predicted the performance in the nociceptive WM task. Results demonstrate (i) that beta and alpha EEG oscillations can represent WM for nociceptive stimuli; (ii) the association between neuropsychological measures of WM and the brain representation of phasic nociceptive painful stimuli; and (iii) that personality factors can predict memory for nociceptive stimuli at the behavioural level. Altogether, our findings offer a promising approach for investigating cortical correlates of nociceptive memory in clinical pain conditions.

1. Introduction

Research pinpointed a recurrent link between clinical pain and memory deficits, with particular reference to verbal and non-verbal working memory (WM; e.g. Munoz & Esteve, 2005; Oosterman, Derksen, van Wijck, Veldhuijzen, & Kessels, 2011; Schnurr & MacDonald, 1995). WM is crucial for keeping active the task-relevant features of target stimuli for the needs of the ongoing behavioural demands (Luck & Vogel, 2013). Clinical studies, for example, reported memory impairments in a number of diseases where chronic pain is a symptom (Moriarty, McGuire, & Finn, 2011), as in fibromyalgia syndrome (Glass, 2009). A meta-analytic study on the link between WM deficits and pain shows that, despite high across-studies variability, WM performance is moderately but significantly better in healthy controls than in chronic pain patients (Berryman et al., 2013). Understanding the process of short-term maintenance and manipulation of sensory information may help scholars to explain how maladaptive memory for potentially noxious stimuli takes place in the central nervous system in a wide variety of chronic pain conditions (Flor, 2012).

Surprisingly, there is limited evidence on how WM for nociceptive stimuli operates, and eventually influences the outcome of pain experience. In fact, only a few studies have thus far attempted to investigate the maintenance in memory of nociceptive and painful stimuli. Functional magnetic resonance imaging (fMRI) studies showed memory-specific activity linked to thermal painful stimuli in primary somatosensory, posterior parietal cortex and anterior insula (Albanese, Duerden, Rainville, & Duncan, 2007; replicated by Lotsch et al., 2012). Oshiro and colleagues carried out two model-driven studies whereby they investigated how the brain processes spatial (Oshiro, Quevedo, McHaffie, Kraft, & Coghill, 2007), i.e. stimulus location, and non-spatial (Oshiro, Quevedo, McHaffie, Kraft, & Coghill, 2009), i.e. stimulus intensity, features of nociceptive input. They concluded that, similar to neurobiological evidence gathered in the visual modality, spatial information is actively stored in a “dorsal stream” involving the posterior parietal cortex and the dorsolateral prefrontal cortex, whereas non-spatial features are processed by a more “ventral stream” associated with activity in the temporal lobe and ventral portions of the prefrontal cortex (Oshiro et al., 2009).

Yet, no study has explored thus far the electroencephalography

* Corresponding author at: Centre for Brain Science, Department of Psychology, University of Essex, Wivenhoe Park, Colchester CO4 3SQ, UK.
E-mail address: evalent@essex.ac.uk (E. Valentini).

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(EEG) correlates of the cortical representation of memory for nociceptive stimuli. This is particularly important as there is abounding evidence showing how oscillatory EEG responses may provide both specific and aspecific representation of pain perception in the brain. For instance, amplitude modulation in the theta and gamma range has been associated with both bottom-up and top-down attentional modulations of nociceptive processing (Chien, Liu, Kim, Markman, & Lenz, 2014; Hauck, Domnick, Lorenz, Gerloff, & Engel, 2015; Iannetti, Hughes, Lee, & Mouraux, 2008; Schulz et al., 2015; Tiemann et al., 2015; Zhang, Hu, Hung, Mouraux, & Iannetti, 2012). Amplitude modulation in the alpha and beta range has also been associated with processing of phasic painful nociceptive stimuli (Babiloni, Vecchio, Bultrini, Luca Romani, & Rossini, 2006; Hu, Peng, Valentini, Zhang, & Hu, 2013; May et al., 2012; Mouraux, Guerit, & Plaghki, 2003; Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2006; Raij, Forss, Stancak, & Hari, 2004). However, it is yet to be clarified whether these activities can have a functional role also in memorisation of nociceptive stimuli.

To investigate WM for nociceptive painful stimuli we used a delayed match-to-sample task that required participants to match the intensity or the location of two nociceptive stimuli in two different memory load conditions (high and low). The task allowed us to record the EEG activity not only during the encoding of phasic thermal nociceptive laser stimuli but also during the maintenance of sensory information until the recall phase. Based on previous research investigating brain activity associated with sensory working memory in the visual (e.g. Myers, Stokes, Walther, & Nobre, 2014) and tactile domain (e.g. Spitzer, Wacker, & Blankenburg, 2010), we expected to observe a modulation of oscillatory activity in the alpha (pre-retention) and beta (retention) EEG bands associated with the different memory loads.

This study also aimed to investigate the association of cognitive and personality variables with nociceptive memory performance and EEG activity. The aforementioned reported association between chronic pain and impaired cognitive functioning (e.g. memory impairment) added to the well-established evidence of bidirectional link between chronic pain and personality dispositions towards anxiety, depression and catastrophizing (Edwards, Cahalan, Mensing, Smith, & Haythornthwaite, 2011; Han & Pae, 2015). Interestingly, studies show that depression, anxiety and catastrophizing personality traits are often linked with the development of chronic postsurgical pain (e.g. Goubert, Crombez, & Van Damme, 2004; Theunissen, Peters, Bruce, Gramke, & Marcus, 2012). It is also worth noting that variations in mood, anxiety and coping have been associated with increased pain perception (Frot, Feine, & Bushnell, 2004; Rhudy & Meagher, 2000, 2003). In addition, studies in healthy individuals show that pain catastrophizing is predictive of cortical responses to pain (Seminowicz & Davis, 2006) and coupled to increased attention to pain (Van Damme, Crombez, & Eccleston, 2004). Emotional decision-making seems compromised in some chronic pain patients too (Apkarian et al., 2004). Therefore, we hypothesised that memory performance and EEG activity would be predicted by neuropsychological tests and personality factors classically associated with chronic pain conditions.

2. Methods

2.1. Participants

Twenty-six right-handed healthy participants (14 males) between 21 and 35 years of age (mean ± SD, 26.1 ± 4.1) were tested. All had normal or corrected-to-normal vision and were not briefed about the purpose of the experiment. None of the participants had a history of neurological or psychiatric diseases or conditions that could potentially interfere with pain sensitivity (e.g. drug intake or skin diseases). Participants gave written, informed consent and were debriefed at the end of the experiment. All experimental procedures were approved by the Fondazione Santa Lucia ethics committee and were in accordance with the standards of the Declaration of Helsinki.

2.2. Nociceptive laser stimulation

The nociceptive heat stimuli were pulses generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (Electronical Engineering, Florence, Italy). Laser pulses selectively and directly activate the Aδ and C-fibre nociceptive terminals located in the superficial layers of the skin (Cruccu et al., 2003). The laser beam was transmitted via an optic fibre and its diameter was set at approximately 6 mm ($\approx 28\ mm^2$) by focusing lenses. Laser pulses, each lasting 4 ms, were delivered on a square area (5 × 5 cm) defined on the left hand dorsum prior to the beginning of the experimental session. To prevent increases in baseline skin temperature and fatigue or sensitisation of the nociceptors, the position of the laser beam was changed after each pulse. An infrared thermometer (precision ± 0.3 °C) was used to measure the temperature of the stimulated skin area before and during the experiment (group-average of 33.39 ± 0.74 °C).

During a familiarisation and calibration procedure on the quality of the sensation associated with radiant heat stimuli, participants were instructed to define the sensation of pain using both a numerical rating scale (NRS) and a visual-analogue scale (VAS). For both of these methods, pain was defined as how intense and how unpleasant the sensation was (i.e. a pricking/burning sensation). Participants were instructed to input their rating on an electronic VAS with five verbal anchors: no pain (0), low pain (25), moderate pain (50), high pain (75) and worst imaginable pain (100). The energy of the stimulus was adjusted using a staircase procedure. The procedure required two ascending series of energy until the most tolerable high pain sensation was reported. Once this energy was seemingly identified then one random series of stimuli with the minimal energy difference of 0.25 Joules (J) were delivered as to eventually confirm the perceptual rating for each energy value.

2.3. EEG recording

EEG recordings (in AC mode) were obtained from 60 tin electrodes (Electro-cap International – ECI) placed according to the 10–20 International System (Fp1, Fp2, Fpz, AF3, AF4, AF7, AF8, F1, F2, F3, F4, F5, F6, F7, F8, FC1, FC2, FC3, FC4, FC5, FC6, FT7, FT8, Cz, FCz, Fz, Oz, POz, Pz, C3, C4, C5, C6, T7, T8, TP7, TP8, CP1, CP2, CP3, CP4, CP5, CP6, CPz, P1, P2, P3, P4, P5, P6, P7, P8, PO3, PO4, PO7, PO8, O1, O2). Three surface electrodes were positioned for the vertical and horizontal electro-oculography (EOG) recordings below the right eye and at the right and left ocular canthi. One electrode was placed at the left mastoid for the electromyography recording (EMG). The reference was on the nose and the ground at AFz. Electrode impedance was kept below 5 kΩ. The EEG signal was amplified and digitised at 1000 Hz.

2.4. Self-reported measures of personality

Due to the important role that emotional and cognitive distress plays in memory complaints in patients with chronic pain (e.g. Eccleston, 2001; Munoz & Esteve, 2005), we assessed individual differences in mood, anxiety and catastrophizing using the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996), State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) and the Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995). The PCS consists of three different subscales: the individual's proneness to ruminate about pain, to magnify pain experience and the feeling of helplessness in managing pain.

2.5. Neuropsychological testing

A number of studies have linked chronic pain to a series of cognitive deficits, including executive function and decision-making, attention and memory (Moriarty et al., 2011). The neuropsychological tests used