Brain Research Bulletin 130 (2017) 75–80

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Electroencephalographic frontal synchrony and caudal asynchrony during painful hand immersion in cold water

Joshua Levitt[a], Hyunwoo J. Choo[b], Kelsey A. Smith[c], Brian W. LeBlanc[d], Carl Y. Saab[d,*]

[a] Center for Biomedical Engineering, Brown University, Providence, RI, USA
[b] Warren Alpert Medical School, Brown University, Providence, RI, USA
[c] Department of Neuroscience, Brown University, Providence, RI, USA
[d] Department of Neurosurgery, Rhode Island Hospital, and Department of Neuroscience, Brown University, Providence, RI, USA

ARTICLE INFO

Article history:
Received 19 October 2016
Accepted 20 December 2016
Available online 23 December 2016

Keywords:
Electroencephalography
Cold pressor
Power
Synchrony
Connectivity

ABSTRACT

Recent studies in our laboratory showed that cortical theta oscillations correlate with pain in rodent models. In this study, we sought to validate our pre-clinical data using EEG recordings in humans during immersion of the hand in ice cold water, a moderately noxious stimulus. Power spectral analysis shows that an increase in pain score is associated with an increase in power amplitude within a frequency range of 6–7 Hz at the frontal (Fz) electrode. These results are consistent with our previous pre-clinical animal studies and the clinical literature. We also report a novel reduction in power at the caudal (O1) electrode within a broader 3–30 Hz rand and decreased coherence between Fz and C3, C4 electrodes within the theta (4–8 Hz) and low beta (13–21 Hz) bands, while coherence (an indirect measure of functional connectivity) between Fz and O1 increased within the theta and alpha (8–12 Hz) bands. We argue that pain is associated with EEG frontal synchrony and caudal asynchrony, leading to the disruption of cortico-cortical connectivity.

1. Introduction

Pain is known to modulate cortical synchrony, defined as rhythmic 'oscillations' between neuronal ensembles constituting nodes within a network (Buzsáki et al., 2012). In chronic pain patients, increased electroencephalographic (EEG) spectral power (Sarnthein et al., 2006; Stern et al., 2006), an indirect measure of cortical synchrony, is attributed to a disruption in functional connectivity between thalamic and cortical structures, otherwise known as thalamocortical dysrhythmia (Llinás et al., 1999; Walton et al., 2010). However, the subjects recruited in these and other similar studies often represent a heterogeneous group of individuals with varying pain degrees, etiologies, and treatment regimens. Hence, although several laboratories have investigated pain-induced changes in the time frequency domain of the EEG (Chen et al., 1989; Ohara et al., 2006), a consistent map representing cortical synchrony under well controlled nociceptive states has been elusive, owing to several confounding variables in the study designs including type and duration of the noxious stimulus, source localization models, clinical history and designation of the experimental control condition.

In order to limit experimental variables encountered in clinical studies and to investigate the mechanisms of cortical synchrony, our laboratory was first to show pain-induced cortical synchrony using animal models with stereotypic pain behaviors (LeBlanc et al., 2014). Invasive intracortical recordings of the local field potential (LFP)(LeBlanc et al., 2014) and epicranial EEG in rats (LeBlanc et al., 2014) localized cortical synchrony to somatosensory cortex and prefrontal cortex, mostly in the theta range (4–8 Hz), and further showed that thalamic burst firing contributes to cortical synchrony and pain behavior (LeBlanc et al., 2016a). Choi et al. and Chang et al. have more recently produced similar findings (Chang et al., 2016; Choi et al., 2016). Recently, we reported that pain-induced cortical synchrony is attenuated using clinically effective medications in rat models of neuropathic and inflammatory pain (LeBlanc et al., 2016b).

Hence, in addition to modulating cortical oscillations we hypothesized that pain disrupts connectivity between cortical structures. Our aim was first to validate our pre-clinical data regarding coupling between pain and cortical oscillations by generating a map for power distributuion in humans, and second to measure signal coherence between EEG electrodes manifesting differential power modulation during pain, using a portable, wireless, single-

* Corresponding author at: 593 Eddy Street, Aldrich 402, Providence, RI 02903, USA.
E-mail address: Carl_Saab@Brown.edu (C.Y. Saab).

http://dx.doi.org/10.1016/j.brainresbull.2016.12.011
0361-9230/

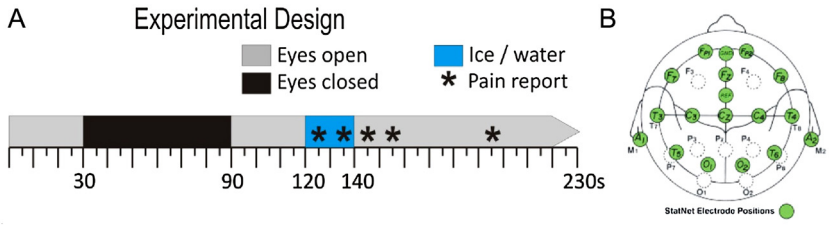

Fig. 1. (A) Subjects were instructed to rest comfortably with their eyes open for 30 s, closed for 60 s, open for 30 s, submerge their hand for 20 s, return to the starting position for 90 s, and report their pain at five time points (asterisks). (B) Montage of the portable, wireless 16 electrode EEG system.

use, 16-electrodes EEG system in human subjects (Grant et al., 2014). Compared to other EEG studies in humans, we sought to minimize confounding variables by recruiting adult, healthy subjects with no prior history of pain or neurologic disorders, and used the cold pressor test as a reliable stimulus for inducing tonic, moderately intense pain (Chang et al., 2002; Chen and Rappelsberger, 1994; Chen et al., 1998; Dowman et al., 2008; Ferracuti et al., 1994; Gram et al., 2015). This is a widely-used protocol that does not evoke excess psychological distress, a potential confounding variable. Our goal in this study, therefore, was to limit confounding variables resulting from incongruent experimental conditions (i.e. water temperature) by making longitudinal comparisons in response to the same noxious stimulus resulting in dynamic pain ratings within subjects. Consistent with our previous studies in animal models, we focused on oscillations in the 3–30 Hz frequency range (LeBlanc et al., 2016a; LeBlanc et al., 2014) within the following common bands: theta (4–8 Hz), alpha (8–12 Hz), low beta (13–21 Hz), and high beta (21–30 Hz).

Results show significant frontal (Fz) synchrony and occipital (O1) *a*synchrony, as well as increased Fz-O1 coherence, in subjects reporting higher pain rating, suggesting enhanced fronto-caudal connectivity.

2. Methods

2.1. Recruitment of subjects and randomization

This research was conducted under the supervision of the Institutional Review Board at Rhode Island Hospital. Twenty five healthy volunteers participated; none reported significant medical history. The mean age of the subjects was 26.8 years (Standard deviation = 10.0 years). All were right handed, except one. Fifteen subjects were randomly assigned to the ice water group (ice; 0–4 °C), and 10 were assigned to the room temperature (RT) water group. Data from 5 subjects (3 ice, 2 RT) were excluded due to poor EEG quality. Subjects were blinded to group randomization.

2.2. Experimental procedure

After obtaining consent, each subject was asked to complete a demographics and screening questionnaire. A researcher then fitted the subject to the EEG, which was connected by Bluetooth to a laptop computer. EEG recordings were performed using the MicroEEG and Statnet system (BioSignal Group, Acton, MA; see Fig. 1b for electrode names and positions), an FDA-approved portable EEG platform. Once the EEG system was properly applied, subjects were asked to sit, facing a blank wall, with hands on their thighs, and a water-filled bucket adjacent on their right covered by a cloth to conceal its contents. Subjects were prompted by the researcher to remain in this position with eyes open for 30 s, then asked to close the eyes for 60 s, and open them again for 30 s. Next, subjects were verbally instructed to insert their right hand into the bucket through a slit in the cloth up to the wrist and to remain in this position for 20 s. Subjects were then prompted by the researcher to indicate pain level on a scale of 0–5 by raising digits of the left hand, after 5 and 15 s in ice or RT, with 0 indicating no pain and 5 the worst pain they could imagine. Finally, the subjects were instructed to return the hand to the starting position and to remain this way for 90 s (see Fig. 1a). Additional pain reports were collected at 1, 10, and 60 s after returning to this 'rest' position. Please see supplementary methods section for a more comprehensive description of the experimental procedure.

2.3. Data analysis

A neurologist, EEG specialist was consulted to ascertain the quality of our EEG recordings (Dr. Julie Roth; see acknowledgement). Data were analyzed using Spike2 (Cambridge Electronic Design, UK), Microsoft Excel, and EEGLab (Matlab, Mathworks, MA, USA; for documentation of how to implement EEGLab analyses please see https://sccn.ucsd.edu/eeglab/). Care was taken to avoid eye blink artifacts when selecting 5–15 s long waveforms during each stage of the procedure (eyes open, eyes closed, eyes open, ice/RT stimulus, eyes open). Fast Fourier transform was performed to compute power spectral densities (PSD) with a bin size of 1 Hz. PSDs were normalized by dividing each bin by the sum of the power of all frequency bins from 3 to 30 Hz, then multiplying by 100 to yield percentages. EEG source localization was modeled using *"Plot Channel Measures"* tool in the *"Study"* menu in EEGLab. Using *'COHER'* script in Spike 2, coherence was calculated between the following pairs of electrodes: Fz-C3, Fz-C4, C3-C4 and Fz-O1. Coherence between two signals x and y for a given frequency f, is equal to the square of the cross-spectral density between x and y at f, divided by the autospectral density of each signal at f. Time points used for coherence analysis were identical to those used to compute power spectra. Mean and standard error of the mean (SEM) were calculated across subjects for each frequency bin per study condition. In addition, power spectra for the *"eyes open"* and *"eyes closed"* in order to determine if the power increase from 8 to 10 Hz typically associated with closing the eyes was present, as a form of quality control.

3. Results

We computed power spectra from channel O1, which was significantly increased as predicted in the 8–12 Hz range during *'eyes closed'* compared to *'eyes open'* ($n = 19$, $P < 0.0001$; Fig. 2A–C), indicating appropriate EEG montage (Andersen and Andersson, 1968).

Two pain scores were collected from each subject during ice/RT stimulus. Among subjects in the ice group ($n = 12$), the later pain score (i.e. 15 s after hand submersion; mean = 1.53) was significantly higher compared to the earlier score (i.e. 5 s after hand submersion; mean = 0.78; $p = 0.0015$; Fig. 2D). This was also confirmed in the qualitative post-test survey responses, which indicated that the ice stimulus became more painful toward the end of submersion in 8 subjects in the ice group. Thus, we performed