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OSCILLATORY EEG ACTIVITY INDUCED BY CONDITIONING STIMULI DURING FEAR CONDITIONING REFLECTS SALIENCE AND VALENCE OF THESE STIMULI MORE THAN EXPECTANCY

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Abstract—Imaging studies have described hemodynamic activity during fear conditioning protocols with stimulus trains in which a visual conditioned stimulus (CS+) is paired with an aversive unconditioned stimulus (US, painful laser pulse) while another visual stimulus is unpaired (CS−). We now test the hypothesis that CS Event Related Spectral Perturbations (ERSPs) are related to ratings of CS Expectancy (likelihood of pairing with the US), Valence (unpleasantness) and Salience (ability to capture attention). ERSP windows in EEG were defined by both time after the CS and frequency, and showed increased oscillatory power (Event Related Synchronization, ERS) in the Delta/Theta Windows (0–8 Hz) and the Gamma Window (30–55 Hz). Decreased oscillatory power (Event Related Desynchronization – ERD) was found in Alpha (8–14 Hz) and Beta Windows (14–30 Hz). The Delta/Theta ERS showed a differential effect of CS+ versus CS− at Prefrontal, Frontal and Midline Channels, while Alpha and Beta ERD were greater at Parietal and Occipital Channels early in the stimulus train. The Gamma ERS Window increased from habituation to acquisition over a broad area from frontal and occipital electrodes. The CS Valence and Salience were greater for CS+ than CS−, and were correlated with each other and with the ERD at overlapping channels, particularly in the Alpha Window. Expectancy and CS Skin Conductance Response were greater for CS+ than CS− and were correlated with ERSP at fewer channels than Valence or Salience. These results suggest that Alpha ERSP activity during fear conditioning reflects Valence and Salience of the CSs more than conditioning per se. **© 2017 The Author(s). Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).**

Key words: EEG, event-related synchronization, fear conditioning, human, painful laser stimulus, salience.

INTRODUCTION

Fear conditioning of a neutral stimulus (conditioned stimulus, CS+) by pairing with an aversive stimulus (unconditioned stimulus, US) is a widely accepted probe to perturb the nervous system and examine neural processes for fear and anxiety (Phelps and LeDoux, 2005; Milad et al., 2006; Palazzo et al., 2008; Liu et al., 2011a; LeDoux, 2014). Studies of the amygdala in rodents have led to a neuroanatomical model of fear conditioning in which the CS+ and US produce signals which arrive in the lateral nucleus and converge there or in the basal nuclear group. The resulting signal is transmitted to the central nucleus, which is an output structure (Davis, 1992; Pare et al., 2004; Rauch et al., 2006; Sotres-Bayon et al., 2006). Recordings from these structures during surgery for epilepsy demonstrate that the amygdala and Frontal lobe structures are activated and interact with each other during fear conditioning (Liu et al., 2010, 2011c,d, 2015a).

The involvement of human forebrain structures in fear conditioning is well described by fMRI studies (Sehlmeyer et al., 2009). The amygdala and hippocampus show a contrast of CS+ versus CS− related BOLD signals during the interval between the end of the CS+ and beginning of the US in a trace protocol. This contrast is related to the Skin Conductance Response (SCR), an autonomic expression of conditioned fear with tolerable painful or 'annoying' nonpainful USs (Carter et al., 2006; Cheng et al., 2006; Milad et al., 2007) and with a loud auditory US (Buchel et al., 1999). In a different kind of (delay) protocol, the CS+ is presented first and the US begins before the end of the CS+ so that there is an interval during which both stimuli are delivered together. In delay protocols, the Mid Cingulate Cortex showed this contrast which was related to the SCR in a protocol with a 'highly annoying but not painful' electrical stimulus (Milad et al., 2007; Linnman et al., 2012), while other cortical areas are not commonly involved (Sehlmeyer et al., 2009).

On the contrary, numerous fMRI studies of the anticipation with a painful US have reported that the contrast of CS+ visual stimuli versus rest is *less* common in the amygdala than in cortical areas including Anterior Cingulate Cortex, Prefrontal Cortex, Insula,

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Superior Temporal Gyrus and Inferior Parietal Lobule (Palermo et al., 2015). This anticipation was related to behavioral domains such as sensory perception rather than the SCR (cf (Seifert et al., 2013)). The role of these human cortical structures in the anticipation of pain may be related in part to their role in Salience and Valence of the conditioning stimuli (Anderson and Phelps, 2001; Frankenstein et al., 2001; Longe et al., 2001; Downar et al., 2002; Sander et al., 2003; Apkarian et al., 2005; Vogt, 2005). Finally, widespread BOLD activations occur in response to CSs at cortical sensory areas related to the modality of somatic, auditory and complex visual stimuli (Buchel et al., 1998; Knight et al., 2004; Nitschke et al., 2006), and in cortical association areas. Therefore, cortical areas may play a large but relatively unexplored role in processes for the anticipation of pain.

Cortical structures and processes can be examined in healthy subjects by EEG activity induced by CSs during fear conditioning, which has not previously been studied to our knowledge. These recordings have high temporal resolution, which can be used to measure the timing of emotional responses (Esslen et al., 2004), and the frequency of cortical processes (Pfurtscheller and Lopes da Silva, 1999; Neuper et al., 2006; Bardouille et al., 2010; Lachaux et al., 2012). We now test the hypothesis that ERSP following conditioning stimuli will be related to the behavioral response to those stimuli including the Valence, Salience, and Expectancy, and that the painful US is related to the CSs. The results of this study may enable development of combined fMRI and EEG techniques for the study of fear conditioning, and illuminate the mechanism of the fear of pain (Vlaeyen and Linton, 2000; Asmundson et al., 2004; Crombez et al., 2013).

EXPERIMENTAL PROCEDURES

Participants and EEG recordings

Seven participants with no active medical or psychiatric disease (five men and two women; aged 23–58 years) were recruited for this study. The protocol for this study was approved by an Institutional Review Board of the Johns Hopkins University School of Medicine. All participants signed an informed consent form for participation in this study. EEG signals were recorded using a high density EEG cap (Quik-cap) with 128 electrodes placed on the scalp with a reference of linked earlobes (Fig. 3)(Jasper, 1958). EEG signals were amplified and digitized at the sampling rate of 1000 Hz (NeuroPort, Blackrock Microsystems). These signals were subsequently band-pass filtered with a low-pass cutoff of 300 Hz and a high-pass cutoff of 0.1 Hz. Trials with artifacts were excluded based upon visual inspection. The timing for the onset of the laser and electrical stimuli were acquired and digitally embedded in the recordings through a data acquisition module (Model: NI USB-6212 BNC, National Instrument, Austin, TX, USA).

Event-Related Spectral Perturbations (ERSPs) were calculated through EEGLAB (Delorme and Makeig, 2004). An epoch extended from 2 s before to 2 s after an event, and the ERSP calculation used the whole 2 s before the epoch as a baseline (*newtimef.m* function in EEGLAB toolbox (Delorme and Makeig, 2004) in Matlab (Mathworks). The significance threshold was set to $p < 0.05$ with false discovery rate correction for multiple comparison (*fdr.m* function in EEGLAB toolbox (Delorme and Makeig, 2004) in MATLAB). The randomization procedures were carried out by the use of a standard random number generator (*randperm.m* function in Matlab Mathworks, Natick, MA).

Experimental design

The fear conditioning paradigm included Habituation (Hab) and Acquisition (Acq) phases in the sequence shown in Fig. 1. Hab was composed of One Block while Acquisition was composed of two sequential blocks, Acq 1 and Acq 2. There were breaks between phases during which psychophysical measures of the CS and US were obtained during each break and at the end of Acquisition. A trial consisted of the presentations of contexts (CXs), which were pictures of either a living room or study room which were displayed as described below (see next section Experimental Stimuli . . .), where the onset and end of the contexts is indicated by the red and blue underlines in Fig. 1A and B. In each room there were two lamps; one produced yellow light and the other green light when lit. The yellow and green light from the lamp in the CX were the CSs as represented by colored blocks in Fig. 1A and B. If the yellow light was designated the dangerous cue (CS+), then the green light would designate the safe cue (CS−, Fig. 1B). The CS and CX designations were assigned at random and counterbalanced across subjects.

The Hab phase consisted of 20 trials, with each CS presented 5 five times in the each context. The order of presentation of each combination of Context and CS was randomized and the approximate durations of stimuli, contexts and intervals during Habituation is illustrated in Fig. 1A. At the start of each 15 s trial, the CXs are presented alone for 6 s and then with the CS for 6 s, followed by CXs alone for the remaining 3 s. The inter-trial interval is set to between 2 and 4 s. The lamp colors of the CS+ and CS− and the rooms of the CXs were assigned at random and counterbalanced across subjects.

The Acq phase consisted of two blocks, Acq 1 and Acq 2 (Fig. 1C), for a total of forty trials. In each block, 20 CS+ and 20 CS− trials were ordered at random and presented within CX+. Each trial was 21 s long and the inter-trial interval was 5–7 s. When a trial started, the CX+ was presented alone for 6 s and then CSs were on within the CX+ for 6 s. The US (laser duration 1 ms, see section on Experimental Stimuli . . .) were delivered 3 s after the CS+ offset in 80% of CS+ trials. The time between blocks was set to 5 min. The timing of image presentation and triggers were controlled through a computer program Psychtoolbox in a MATLAB (MathWorks Inc., Natick, MA) environment. The intensity of laser pulse US was adjusted to produce a pain level of 5 out of 10 for each subject before the Hab phase.

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