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P50 suppression in human discrimination fear conditioning paradigm using danger and safety signals

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ABSTRACT

Auditory P50 suppression, which is assessed using a paired auditory stimuli (S1 and S2) paradigm to record the P50 mid-latency evoked potential, is assumed to reflect sensory gating. Recently, P50 suppression deficits were observed in patients with anxiety disorders, including panic disorder, post-traumatic stress disorder and obsessive–compulsive disorder, as we previously reported. The processes of fear conditioning are thought to play a role in the pathophysiology of anxiety disorders. In addition, we found that the P50 sensory gating mechanism might be physiologically associated with fear conditioning and extinction in a simple human fear-conditioning paradigm that involved a light signal as a conditioned stimulus (CS+). Our objective was to investigate the different patterns of P50 suppression in a discrimination fear-conditioning paradigm with both a CS+ (danger signal) and a CS− (safety signal). Twenty healthy volunteers were recruited. We measured the auditory P50 suppression in the control (baseline) phase, in the fear-acquisition phase, and in the fear-extinction phase using a discrimination fear-conditioning paradigm. Two-way (CSs vs. phase) Analysis of variance with repeated measures demonstrated a significant interaction between the two factors. Post-hoc LSD analysis indicated that the P50 S2/S1 ratio in the CS+ acquisition phase was significantly higher than that in the CS− acquisition phase. These results suggest that the auditory P50 sensory gating might differ according to the cognition of the properties (potentially dangerous or safe) of the perceived signal.

1. Introduction

Fear conditioning is a type of associative learning that involves the formation of linkages between a neutral stimulus and a stimulus with innate behavioral significance (Sanders et al., 2003). In a simple fear-conditioning paradigm, a conditioned stimulus (CS), such as a light signal or a tone, and an aversive unconditioned stimulus (US), such as an electric shock, are repeatedly and consistently paired. The CS alone begins to elicit a conditioned response (CR) in anticipation of presentation of the US (Cheng et al., 2006; Rosen et al., 1998; Wolpe, 1981). In humans, a CR is often assessed by measuring the skin-conductance responses (SCR). Fear extinction refers to the weakening of the CR through the repeated presentation of the CS in the absence of the US with which it was previously paired. It has been hypothesized that extinction does not erase the original memory (a previously established CS–US association) but rather forms a new memory of safety that inhibits fear expression (a newly established CS–no US association) (Myers and Davis, 2007). This behavioral model has been widely used for both basic (animal) and clinical (human) studies that investigate the pathophysiology of anxiety-related disorders, in which the core symptoms are excessive fear and anxiety that are hardly attenuated by extinction; in such disorders, deficits in the inhibitory control of the brain are considered to play a role (Sotres-Bayon et al., 2006).

In the discrimination fear-conditioning paradigm, the CSs that have been adopted are known as the CS+ (danger signal) and CS− (safety signal) (Hofmann, 2008). Discrimination learning in the respondent conditioning is indexed as the difference between the CRs to the CS+ and CS− (Lissek et al., 2005). Healthy adults should be able to suppress the fear response during CS− presentations and show higher rates of discrimination learning. If patients fail to inhibit fear in the presence of safety cues during fear conditioning, they might display the fear response to both the CS+ and the CS−, leading to low levels of discrimination learning even if these patients actually have the fear response to the CS+. In a meta-analytic review by Lissek et al., it was concluded that patients with anxiety disorders were more conditioned to danger cues (CS+) than were control subjects, and their inhibitory conditioning to safety signals (CS−) was impaired (Lissek et al., 2005). For example, Michael et al. reported that patients

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with panic disorder (PD) could not reduce their SCRs to the CS- in the extinction phase as the healthy subjects could (Michael et al., 2007). Blechert et al. reported that patients with post-traumatic stress disorder (PTSD) showed delayed extinction of SCR to the CS+ and heightened SCR to the CS− during the acquisition phase compared to healthy participants who were not exposed to trauma (Blechert et al., 2007). Clinically, the above-mentioned finding in discrimination fear conditioning suggested that in anxiety disorders, the inability to distinguish the external stimulus seemed to be physiologically associated with a failure of the habituation to irrelevant sensory input.

Sensory gating is defined as the habituation to irrelevant sensory input, which might be an important function for the human brain as the central information-processing organ of the body. The failure of sensory gating might be associated with mental disturbances. A well-established method for sensory gating assessment is the suppression of an auditory evoked potential (AEP) of P50, which is a positive waveform of small amplitude that occurs 40–70 ms after an auditory stimulus. Using two paired auditory stimuli, P50 suppression is evaluated using the ratio of the amplitude of the second to the first stimulus response (S2/S1 ratio) or using the decrease from the 1st to the 2nd stimuli in terms of microvolts (Fuerst et al., 2007; Rentzsch et al., 2008b). Deficits in P50 suppression have been mainly demonstrated in clinical studies of schizophrenia, but these deficits have also been reported in patients with anxiety disorders, such as PTSD (Karl et al., 2006) and panic disorder (Ghisolfi et al., 2006a). In addition, we have found P50 suppression deficits in patients with obsessive–compulsive disorder (OCD) (Hashimoto et al., 2008). These data suggest that P50 suppression deficits may have considerable interest as a putative biomarker or endophenotype for the vulnerability to anxiety disorders.

In our previous studies, we hypothesized that there was a physiological association between P50 suppression and the mechanism of fear acquisition and extinction; this finding was based on the concept that if there was such an association, then the attenuated P50 suppression (i.e., loosened sensory gating) would manifest as a vulnerability to fear acquisition and a deficit in the inhibitory control of the brain, which could subsequently lead to a delay in the recovery from the fear. Therefore, we combined a P50-suppression measurement with a simple fear-conditioning paradigm, and we reported that the mean P50 S2/S1 ratio in the fear-acquisition phase was significantly more elevated than in the control phase but recovered to the basal level in the extinction phase in healthy participants (Kurayama et al., 2009). In contrast and in support of our hypothesis, the elevation of the P50 S2/S1 ratio, which represents attenuated P50 suppression, was sustained through the fear extinction phase in patients with OCD (Nanbu et al., 2010). These findings suggest a potential link between the processes of the acquisition/extinction of conditioned fear and P50 suppression.

These findings collectively suggest that the deficit in the sensory gating mechanism in the discrimination of safe signals or fear signals might be involved in the pathophysiology of anxiety disorders, but this possibility remained to be elucidated from our previous studies of the single fear-conditioning paradigm. In the current study, we aimed to measure a discriminable change in P50 suppression with the CSs in separate roles by first elucidating the physiological association between the sensory gating and discrimination learning of stimulus properties (potentially dangerous or safe) in healthy persons before proceeding to a study of patients with anxiety disorders.

2. Material and methods

2.1. Participants

This study was performed after approval by the ethics committee at Chiba University Graduate School of Medicine. Written informed consent was obtained from all the participants. Twenty-five healthy volunteers (11 men and 14 women), who ranged in age from 21 to 34 years (mean 27.5, standard deviation [SD] 4.0), were recruited to the study. None of the participants had a history of psychiatric, neurological, or hearing problems, as determined by a non-structured interview. All the participants were non-smokers, but because nicotine and caffeine can affect P50 suppression (Ghisolfi et al., 2006b; Knott et al., 2010), the participants were instructed to abstain from smoking and caffeine-containing products for 12 h prior to the experiment.

2.2. Experimental design and procedure

Though this study was conducted using methods similar to those described in our previous study (Kurayama et al., 2009), one conditioned stimulus (i.e., CS−) was added to the method. We used a red light signal (CS+) or a blue light signal (CS−) for the discrimination fear-conditioning paradigm. Participants were seated in a comfortable recliner and were instructed to relax with their eyes open and to keep viewing the light-emitting diode (LED) lamp that was used as a conditioned stimulus. The intensity of the electric shocks to the wrist (used as the US) was determined by each participant to be "aversive but not painful" (LaBar et al., 1998). The mean voltage of the electrical shock was 83.8 (SD = 19.7, range 41–195 V). Throughout the experiment, the participants were required to look at the LED lamp, which was used as the CS in the acquisition phase, and to listen to auditory clicks, which were used to measure the P50 suppressions. Fig. 1 summarizes the conditioning parameters that were used in the present study. The experiment consisted of the following three phases: phase 1 for control, phase 2 for fear acquisition, and phase 3 for fear extinction. Participants were exposed to 10 repetitive stimuli of each CS+ and CS−, alternating with a 30 ± 25 s intertribal interval throughout the three phases. In phase 2, only CS+ was paired with US, and in phase 3, the CSs were again individually presented. Skin conductance responses were also recorded throughout the three phases. To measure the P50 suppressions, the participants were given 60 pairs of click sounds (S1 as the first stimulus and S2 as the second stimulus) in each phase, independently of the presentation timing of the CSs. Control waveforms of P50 were recorded in phase 1.

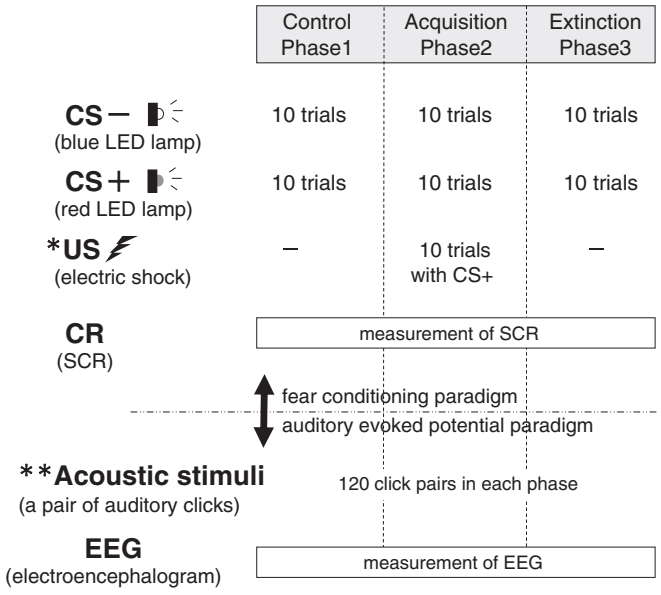

Fig. 1. The conditioning parameters used in the present study. Abbreviations: CS: conditional stimulus (CS−: safety signal, a blue LED lamp; CS+: danger signal, a red LED lamp); US: unconditioned stimulus; CR: conditioned responses; SCR: skin conductance responses; EEG: electroencephalogram. Note: *An acoustic stimulation was delivered as a click tone, the intensity of which was adjusted to 40 dB above the hearing threshold for each subject. **The US intensity was adjusted to the highest value that was aversive but not painful for each participant.