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Slow cortical potentials in human aversive trace conditioning

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ABSTRACT

The aim of the present study was to better understand the cortical structures and neuronal processes involved in aversive differential trace conditioning in healthy subjects. According to previous findings in literature, we tested whether the stimulus preceding negativity (SPN) in an emotional trace-conditioning paradigm shows a frontocentral maximum reflecting affective anticipation, e.g. in the anterior cingulate, or a centroparietal maximum reflecting time estimation and sensory anticipation. Two distinct SPN intervals were analyzed, one during the presentation of the CS (comparable to delay conditioning) and another one after CS offset (trace conditioning).

In the CS+ condition, where subjects anticipated the onset of an aversive electrical stimulus after CS+ offset, a significantly larger negativity than in the unpaired (CS−) condition was present. SPN revealed a sustained midcentral and posterior parietal negativity during both SPN intervals. Differences between the two analyzed SPN intervals pointed towards occipital activity being found in the first interval (delay), but not in the second (trace). Aversive conditioning paradigms with longer trace intervals seem to rely upon a similar activation pattern as cognitive stimulus anticipation.

1. Introduction

Classical conditioning, based on Pavlovs experiments (Pavlov, 1927), became one of the most influential scientific concepts of the 20th century which formed our understanding of basic learning processes and inspired the clinically highly successful behavioral therapy. A neutral stimulus, which is paired with a biologically significant stimulus (unconditioned stimulus, US), soon evokes a behavioral reaction that appears independently from the emergence of the biologically relevant stimulus, with the former neutral stimulus becoming a conditioned stimulus (CS) (Pavlov, 1927). There are different ways of conditioning: Delay conditioning, where the CS and US coterminate, and trace conditioning, where the US appears some time after the offset of the CS, therefore requiring the establishment of a memory trace. One of the main neural mechanisms to form associations between two events is long-term potentiation (LTP), which requires neurons to be simultaneously activated. The special feature about trace conditioning is that subjects have to mentally bridge the gap between the offset of the CS and the onset of the US in order to establish a connection between these stimuli. Some authors have postulated that this process involves an activation of the declarative memory circuit: They found awareness of the contingencies to be necessary in trace, but not in delay conditioning (Clark et al., 2001; Clark and Squire, 1998; Gabrieli et al., 1995). In differential trace conditioning, only one of two distinct stimuli (CS+) is paired with the US, whereas the other one (CS−) never is. Thereby, it is possible to compare subject's reaction to the presentation of CS+ with subject's response to the appearance of CS−. In this respect, CS− serves as a control condition.

Elucidating the biological basis of learning promotes a better understanding of the neuropsychological correlates. Electroencephalography (EEG) records distinct brain activation with a high temporal resolution. In order to explore trace conditioning in more detail, we focused on the analysis of slow cortical potentials (SCP) which develop in trace conditioning.

The classical CNV (contingent negative variation) paradigm is an S1–S2 paradigm with a motor response. In a CNV paradigm, a warning stimulus (S1) is followed by an imperative stimulus (S2). The subject has to respond by a motor reaction. The resulting slow cortical potentials are named early and late contingent negative variation, one appearing shortly after S1 (early CNV), the other one before S2 onset (late CNV).

The equivalent to late CNV in motor paradigms is stimulus preceding negativity (SPN) in non-motor paradigms. In the thalamic gating model (Brunia, 1993; Brunia, 1999; Brunia and van Boxtel, 2001), SPN is considered as modality-specific selective anticipatory

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attention. Modality-specific relay nuclei act as gates that can be opened non-selectively by the brainstem reticular formation and can be closed selectively by the (pre)frontal cortex. Some studies could not find modality-specific distributions of SPN (Böcker et al., 1994, Bastiaansen and Brunia, 2001), and pointed towards influences of supramodal parietal attention-shifting processes (Gomez et al., 2007). SPN has also been considered an indicator of response timing and attention (Brunia and van Boxtel, 2001). All these interpretations agree that an information-conveying stimulus (with an affective or motivational valence) is sufficient to evoke an SPN (Lang et al., 1990).

Non-paired stimuli (as well as S1 in non-motor S1–S2 paradigms) are followed by a frontal late negative wave (Rohrbaugh et al., 1979, 1980). This slow negative wave was considered to represent an unspecific orienting response to S1 (Simons et al., 1979), as well as a correlate of late S1 processing, early response selection and task anticipation processes (Bender et al., 2004; Rockstroh et al., 1989). The underlying activity (at least in CNV paradigms) seems to arise from frontal regions (Ruchkin et al., 1986) like the anterior cingulate cortex (ACC) and the frontocentral supplementary motor area (SMA) (Bender et al., 2005; Gomez et al., 2003; Nagai et al., 2004).

We considered our CS+ – US interval as an equivalent of a non-motor S1–S2 paradigm, with the CS being the warning (S1) and the US being the "imperative" (S2) stimulus. In the following, the terms early negative slow wave and SPN are applied for the early and the late negative slow waves following CS (S1). In delay conditioning paradigms, this design has been applied before in several studies (Lumsden et al., 1986; Pierson et al., 1987; Regan and Howard, 1995).

In an interesting approach, Böcker et al. (2001) recently focused on the role of orientation towards and anticipation of stimuli in a combined threat of shock and selective attention experiment, in order to clarify which cortical sources were involved. In the threat of shock condition, they found negativity located over frontocentral areas. The authors concluded that this negativity was a manifestation of affective anticipation (most likely involving activation of the anterior cingulate gyrus), because it was absent in the selective attention paradigm. The authors argued in favour of a pre-S2 SPN compared to manifestations of an early negative slow wave ("O-wave") evoked by S1, but, since the stimulus duration was not sufficiently long to separate the two negative components (early slow wave; "O-wave" and stimulus anticipation; SPN), they could not exclude that the activation was "an O-wave modulated by the affective valence of this particular S1" (Böcker et al., 2001).

So far, there is no study analyzing slow negative waves in trace conditioning with a trace interval of more than 1 s, although this paradigm seems to be much closer to the original S1–S2 paradigms due to the gap between the stimuli. In the study at hand, a continuous presentation of the CS for 7 s as well as a 3 s trace interval before the onset of the unconditioned aversive stimulus provided the opportunity to analyze two distinct intervals where an SPN can be detected: one interval prior to the offset of the CS (a situation similar to the one in delay conditioning where the gap between stimulus onset and the US is bridged by the continuing stimulus, SPN1) and another interval prior to the onset of the US but after the CS offset (trace conditioning: the gap between the stimuli is not bridged by the CS, SPN2). An interesting question is now whether these two SPN rely upon the same underlying mechanism or whether they show distinct topographies due to different required brain areas.

Possible differences between SPN1 and SPN2 could be

1. The presence or absence of the physical visual stimulus that might provide a perceptual "bridge" between CS onset and CS offset, so the cortical mechanisms of contingency establishment and expectation of the US might differ comparing SPN1 and SPN2 (in analogy to differences between delay and trace conditioning).
2. The affective state of the subject: during SPN1 a feeling of security might be induced, since the subjects learn that as long as the visual stimulus persists, no aversive electric stimulus will be presented. In the second interval (SPN2), the visual stimulus is absent and the affective state could change to insecurity. This should be the case for the CS+ condition only, provided that subjects learned the connection between CS+ and US.

In the present study we prolonged the stimulus duration in order to separate the negative slow wave following the onset of the visual stimulus from both analyzed SPN intervals. This approach could provide new information with respect to the functional and topographical aspects of the analyzed SCPs. The hypotheses regarding the appearance of the negative slow wave and/or both SPN (SPN1/SPN2) in the study at hand were the following:

1.1. Presence and absence of both SPN courses (SPN1 and SPN2)

Both SPN should be present in the CS+ condition, provided that the contingency between CS+ and US was learned by the subjects. In the CS− condition, due to the lack of an S2 equivalent, no SPN should be established by the participants.

To register the subjective guess of contingency, a subjective rating of probability concerning the co-occurrence of CS+/CS− and US was performed by each subject.

1.2. Presence, absence and topography of the early negative slow wave

An early negative slow wave should be present in both conditions if it represented mainly a late supramodal response component to the sensory stimulus (Rohrbaugh et al., 1979: "negative after wave"; Rohrbaugh et al., 1980). If it represented early stimulus anticipation processes (in analogy to early response preparation, Gomez et al., 2003), it should be more prominent in the CS+ condition.

We hypothesized that the early negative slow wave shows a frontal maximum around Fz (Bender et al., 2004; Gomez et al., 2003) which might be weaker than in an acoustic paradigm, since visual stimuli often evoke a weaker early CNV (Gaillard, 1976; Ritter et al., 1980; Rohrbaugh and Gaillard, 1983).

1.3. Main hypothesis: Differences in topography and function between SPN1 and SPN2

Do both analyzed SPN-components rely upon the same underlying neuronal mechanism although SPN1 is influenced by the persisting visual stimulus? Or are SPN1 and SPN2 two individual potentials with different topographies due to distinct underlying neuronal generators? Which role does the affective state of the subject play? As a correlate of affective anticipation of the unpleasant stimulus, i.e. in the case of sustained activity in the anterior cingulate cortex (Baas et al., 2002; Böcker et al., 2001), "SPN" before the unconditioned stimulus would be expected to show a frontal maximum around Fz. A more central maximum around the vertex and behind (Cz, Pz) would be expected as a correlate of predominant sensory anticipation/time estimation reflecting widespread activation involving supplementary motor, posterior parietal and somatosensory areas summing up over the vertex (Brunia and van Boxtel, 2004; Ruchkin et al., 1986; Waschulewski-Floruss et al., 1994). This kind of SPN often shows a right hemisphere preponderance (Brunia and Damen, 1988). These hypotheses were taken from results in delay conditioning experiments. We contrasted these hypotheses in a first step by *t*-tests for significant activation at either frontal (ACC, Fz) or centroparietal electrode sites (SMA, somatosensory parietal cortex, Cz/Pz) against baseline and the CS− condition.

In order to examine possible topographic differences between both SPN intervals a multivariate ANOVA (factors area, hemisphere and SPN interval — see Materials and methods for details) was calculated.