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Am I safe? The ventrolateral prefrontal cortex 'detects' when an unpleasant event does not occur

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The ventrolateral prefrontal cortex (VLPFC) is implicated in contingency detection and the evaluation of emotionally significant stimuli. However, the mechanisms whereby an individual can effectively avoid painful or unpleasant events are not well understood. We therefore examined whether the *absence* of an unpleasant somatosensory stimulus could evoke a response in the human VLPFC as a correlate of contingency detection (the feeling that "I am safe") without any immediately preceding stimulus. In a differential trace-conditioning paradigm, the unpleasant stimulus followed the partially reinforced stimulus in 50% of trials after 3 s; it never occurred after the nonreinforced stimulus. High-resolution DC electroencephalography, current source density mapping, and spatio-temporal source analysis were performed.

After the nonreinforced stimulus, a highly significant negativity over the VLPFC began about a second after the time for the unpleasant stimulus to occur had passed. We concluded that the VLPFC can be activated merely by a sequence of stimuli (with long interstimulus intervals) without any directly preceding stimulus, provided that this sequence creates the expectation that at a certain time an unpleasant stimulus might occur. This mechanism might allow for the detection of conditions under which harmful events could be avoided.

Moreover, in reinforced trials, we found a highly significantly lateralized negativity (N700) that outlasted the strong, unpleasant somatosensory stimulus for about a second. Topography and source analysis pointed to prolonged activation of the somatosensory system. This processing stage preceded activation of the VLPFC. We concluded that N700 might provide important insights into the time course of somatosensory memory traces.

Keywords: Ventrolateral prefrontal cortex; Contingency establishment; Somatosensory event-related potential; Lateralization; Current source density; Source analysis

Introduction

We all need to detect and avoid conditions that might harm us. For example, children who cannot feel pain repeatedly injure themselves. But apart from mere nociception, we must be able to detect circumstances that may lead to rewards as well as those that may cause us to be hurt or punished. This is the role of the "contingency detection system." It is possible, moreover, that a defective contingency detection system may play a role in the pathogenesis of depression (Tremblay et al., 2005). A better understanding of the cerebral mechanisms that enable us to recognize when harmful stimuli do not occur seems essential to the optimization of already existing cognitive strategies of pain control (Apkarian et al., 2005; Seminowicz et al., 2004) and to the elucidation of the cortical mechanisms of learning. The circuitry involved in the perception of pain (which differs importantly from that involved in non-painful somatosensory perceptions) (Davis, 2000) has been well established, and important pioneering work has been done to explain the mechanisms whereby we evaluate stimuli and their salience (Downar et al., 2002, 2003). However, as yet relatively little is known about how we detect the failure of "bad" stimuli to occur.

The ventrolateral prefrontal cortex (VLPFC) plays an important role in contingency reversal learning and the evaluation of (emotionally relevant) stimuli (Morris and Dolan, 2004; Roberts, 2006; Rolls, 2000), as animal model research and functional neuroimaging have shown. However, in order to establish the conditions under which harmful events can be avoided, we need to detect not only when stimuli occur but also when aversive stimulation is absent. Whether the ventrolateral prefrontal cortex also plays an important role in the process of establishing the contingencies when stimuli are absent is not yet understood. Moreover, different functions of the orbitofrontal cortex – such as stimulus evaluation and contingency establishment – are not easily separated (O'Doherty et al., 2003), as changes in stimulus–reward contingencies go along with changes in the affective meaning of a

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conditioning stimulus: when a conditioning stimulus is suddenly followed by a reward, its affective meaning is also changed.

Thus, in the present paper, we address the question whether the absence of an unpleasant stimulus in a sequence of stimuli with long interstimulus intervals – i.e., contingency evaluation *without* any preceding stimulus to be evaluated – might suffice to evoke activation of the VLPFC.

An alternative candidate region for the detection of an omitted stimulus in a sequence of stimuli could be the anterior cingulate, which has been shown to be necessary to discriminate between stimuli and to monitor actions and errors (Cardinal et al., 2003; Gehring and Fencsik, 2001).

A postimperative negative variation (PINV) has been described in paired stimulus paradigms (Eikmeier and Lodemann, 1994; Klein et al., 1998; Rockstroh et al., 1999; Wagner et al., 1996) under conditions of loss or gain of control: that is, when, for example, a painful imperative stimulus could suddenly no longer be switched off or, the other way around, suddenly could be (Elbert et al., 1982; Kathmann et al., 1990). A PINV was also described when subjects could not be certain whether their response after the second (imperative) stimulus was correct (Klein et al., 1996a,b). The PINV, which is distributed over anterior scalp regions, has thus been interpreted as a correlate of the detection of changes in contingency (Klein et al., 1998; Rockstroh et al., 1999). We have described two subcomponents of PINV: an early motor PINV maximum over the contralateral central area (N700; motor/proprioceptive post-processing), and a later maximum over ventrolateral prefrontal areas, which might be related to contingency detection (Bender et al., 2004, 2006). Since the VLPFC has been shown to be important in contingency reversal learning, as mentioned above (Morris and Dolan, 2004; Roberts, 2006; Rolls, 2000), an equivalent of PINV over the ventrolateral prefrontal areas could develop after the non-reinforced stimulus in a differential trace conditioning paradigm, indicating that the brain has detected the non-occurrence of the unconditioned stimulus.

We examined such a differential trace conditioning paradigm with an unpleasantly strong somatosensory stimulus following a partially reinforced visual stimulus in 50% of trials after a fixed interval of 3 s, while it never occurred after the nonreinforced visual stimulus. We hypothesized that

- a late negativity over the ventrolateral prefrontal areas (Bender et al., 2004, 2006) would also occur after the nonreinforced stimulus when the time for the unpleasant stimulus to occur has passed. This ventrolateral prefrontal activation after an "absent" stimulus would indicate that the subject had noted that no unpleasant stimulus had occurred at the crucial time point after the nonreinforced stimulus. The high time-resolution of dense-sensor-array DC EEG would allow imaging of the temporal sequence of cortical activation.
- contingency awareness (Tabbert et al., 2006) would influence VLPFC activation. We tested for differences between the first block of the recording session, when subjects might still not be aware or fully aware of the correct contingencies and the following blocks when subjects might have already learned the contingencies in our differential trace conditioning paradigm (which stimulus indicated that they were "safe" and which stimulus indicated that they would receive an unpleasant electrical stimulus with a probability of 50%).

Shorter time intervals (short-term integration of somatosensory feedback through sensory memory) might be bridged by different cortical mechanisms. We recently discovered post-processing in secondary motor areas before activation of the prefrontal cortex (motor PINV) (Bender et al., 2004, 2006). This post-processing in secondary cortical areas might occur within the motor system (post-processing of reafferent proprioceptive input), while also representing a general mechanism of brain functioning that is valid for different modalities. A precategorical short-term sensory memory for the visual modality has already been suggested by early psychological investigation (iconic memory) (Sperling, 1963, 1967). There have also been discussions about the duration of sensory memory (e.g., Purdy and Olmstead, 1984). So far, no direct neurophysiological correlate of sensory memory has been described apart from indirect hints from mismatch negativity (MMN) in the auditory modality (Deouell et al., 2006; Matuoka et al., 2006). However, one of the basic principles in associative learning is long-term potentiation, which requires two neurons to be simultaneously active in order to establish a connection of increased strength (Hebbian learning) (Cooper, 2005). Short time gaps between subsequent stimuli need to be bridged. This can be done by deliberate attention and working memory. However, many forms of conditioning have been shown to work automatically, especially for short delays. Late modality-specific cortical post-processing could represent the neurophysiological equivalent of short-term sensory memory, which would be supported by our finding of a comparable component ("N700") after visual stimulation as well (Bender et al., submitted). By analyzing the topography of lateralized potentials, we have been able to eliminate temporal overlaps of widespread endogenous potentials such as P300 and the LPC to a large extent (Bender et al., 2006). We examined possible lateralized activation of primary and secondary somatosensory areas (SI, SII) during the N700 time interval (500 to 1000 ms after stimulus offset according to our previous findings), when the short, rare, strong, unpleasant but not painful somatosensory stimulus had already terminated.

With respect to N700, we hypothesized that

- A significant lateralized N700 component would appear in the same latency range as for the motor and visual modality (about 500 to 1000 ms after somatosensory stimulation).
- This lateralized somatosensory N700 would differ in its topography from the visual or motor N700 and would be compatible with an activation of secondary somatosensory areas. Late activation of the secondary cortical areas of the corresponding modality might represent a mechanism of the sensory memory valid for a variety of modalities.
- No comparable lateralized N700 would be evoked by a visual warning stimulus presented in the center of the visual field.

Materials and methods

Subjects

Twenty-seven healthy adult right-handed (according to the Edinburgh Handedness Inventory) (Oldfield, 1971) subjects (15 females, 12 males) between 20 and 58 years of age (mean