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Human centromedian-parafascicular complex signals sensory cues for goal-oriented behavior selection

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ABSTRACT

Experimental research has shown that the centromedian-parafascicular complex (CM-Pf) of the intralaminar thalamus is activated in attentional orienting and processing of behaviorally relevant stimuli. These observations resulted in the hypothesis that the CM-Pf plays a pivotal role in goal-oriented behavior selection. We here set out to test this hypothesis with electrophysiological recordings from patients with electrodes implanted in CM-Pf for deep brain stimulation (DBS) treatment of chronic neuropathic pain. Six patients participated in (1) an auditory three-class oddball experiment, which required a button press to target tones, but not to standard and deviant tones and in (2) a multi-speaker experiment with a target word that required attention selection and a target image that required response selection. Subjects showed transient neural responses (8–15 Hz) to the target tone and the target word. Two subjects additionally showed transient neural responses (15–25 Hz) to the target image. All sensory target stimuli were related to an internal goal and required a behavior selection (attention selection, response selection). In group analyses, neural responses were greater to target tones than deviant and standard tones and to target words than other task-relevant words that did not require attention selection. The transient neural responses occurred after the target stimuli but prior to the overt behavioral response. Our results demonstrate that in human subjects the CM-Pf is involved in signaling sensory inputs related to goal-oriented selection of behavior.

Introduction

It is vital for flexible goal-oriented behavior that we adaptively select appropriate behavior when goal-relevant sensory input signals arrive. Such goal-oriented behavior may include overt or covert attention selection and the selection of overt or covert goal-appropriate motor or non-motor responses. Several studies have investigated goal-oriented attention and motor action selection at the cortical level (Fan, 2014; Knight, 2007; Mesgarani and Chang, 2012) and the cortical control of action selection in the basal ganglia (Jahfari et al., 2012). Evidence for an involvement of the thalamic centromedian-parafascicular complex (CM-Pf) in processing of relevant sensory events has been derived primarily from experimental studies in non-human primates (Minamimoto and Kimura, 2002; Weigel and Krauss, 2004) and rodents (Kato et al., 2011). However, little is known about the putative role of the CM-Pf in goal-oriented behavior selection in humans.

Anatomically, the CM-Pf constitutes the major part of the intralaminar thalamus in rodents and primates. It belongs to the higher-order thalamus and receives inputs from different brainstem nuclei and cortical areas (Krout et al., 2002; Redgrave et al., 2010; Sadikot and Rymar, 2009). The CM-Pf provides strong glutamatergic excitatory inputs to the striatum, its main target structure (Doig et al., 2014; Lapper and Bolam, 1992; Nanda et al., 2009). The CM-Pf additionally provides excitatory inputs to two other basal ganglia structures, the pallidum and subthalamic nucleus, as well as to the cerebral cortex

Abbreviations: CM-Pf, centromedian-parafascicular complex; DBS, deep brain stimulation; FDR, false discovery rate; LFP, local field potential

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(Lanciego et al., 2009). The excitatory input to the striatum seems to play an essential role in behavioral flexibility (Brown et al., 2010), goal-directed motor action (Bradfield et al., 2013) and attention shifting (Ding et al., 2010). A possible mechanism by which this thalamo-striatal input is modulating cortico-striatal-thalamo-cortical processing is the synchronization of networks of cortical neurons. By synchronizing multiple cortical regions, cortical information transmission may be controlled (Saalmann, 2014).

Earlier studies in non-human primates suggested a role of the CM-Pf in attentional orienting (Minamimoto and Kimura, 2002) and processing of behaviorally relevant stimuli from different sensory modalities, particularly audition (Matsumoto et al., 2001). A goal-oriented component in CM-Pf signaling is suggested by findings in non-human primates showing that the CM-Pf responds strongest to unexpected, undesired stimuli, which nevertheless require an action linked to an internal goal (Minamimoto et al., 2014, 2005). In mice, the PF is a homologue of the human CM-Pf (Groenewegen and Berendse, 1994), and disruption of the pathway from the PF to the dorsolateral striatum leads to a decrease in correct button presses to visual stimuli in a two-choice reaction time task (Kato et al., 2011). These results provide support for the notion that the CM-Pf is important for goal-oriented response selection to behaviorally relevant stimuli. The CM-Pf's putative role in goal-oriented overt and covert selection of behavior is also in accordance with its reciprocal connections with the motor and premotor cortices and cortical areas of the attention and cognitive control networks (frontal eye field, prefrontal and anterior cingulate cortices; (Sadikot and Rymar, 2009).

Very few studies have investigated the functional role of the CM-Pf in humans due to its relative inaccessibility in the intralaminar thalamus. However, humans can perform much more complex cognitive tasks and require a negligible amount of training compared to any animal model. Interestingly, a PET study found greater regional blood flow in the intralaminar thalamus when subjects were performing an attention-demanding task compared to a relaxed awake state (Kinomura et al., 1996). Similarly, the intralaminar thalamus was activated during covert shifts in visual attention in a recent fMRI study (Hulme et al., 2010). The temporal resolution of fMRI and PET is, however, on the order of seconds, which means that the temporal dynamics of neural responses in the human CM-Pf could not be determined in these imaging studies. The CM-Pf has been introduced as a target for DBS in the treatment of chronic pain both with regard to its functional connectivity and the previous experience with radio-frequency lesioning (Andy, 1980; Hariz and Bergenheim, 1995; Krauss et al., 2002; Sims-Williams et al., 2016; Weigel and Krauss, 2004). DBS in CM-Pf for treatment of chronic pain appears to modulate the affective and motivational dimensions of pain perception (Weigel and Krauss, 2004). In stroke patients, CM-Pf lesions result in deficits on the Wisconsin Card Sorting Test, which measures the ability to flexibly adjust behavior to changing rules (Liebermann et al., 2013). Thus, there is some evidence that the CM-Pf complex is relevant for attentional shifting and cognitive and behavioral flexibility in humans.

Given these findings in non-human primates and limited evidence from human lesion and imaging studies, we hypothesized that in humans the CM-Pf is involved in signaling the occurrence of sensory events that are relevant for a current goal and request overt or covert behavior selection, for example covert attention selection or response selection. In our study we set out to characterize the signatures of CM-Pf responses with respect to this hypothesis. Therefore, direct electrophysiological recordings were obtained in patients with CM-Pf DBS electrodes while they performed tasks in which sensory cues signaled the need for behavior selection to achieve the task goal. As tasks we selected a three-class auditory oddball and a multi-speaker paradigm (Mesgarani and Chang, 2012; Polich, 2007). In oddball paradigms, subjects are presented with frequent standard stimuli and infrequent stimuli that differ in some, typically relatively simple, feature (Sandmann et al., 2009; Verleger et al., 2016, 2014). Here, a three-class auditory oddball paradigm was used, in which subjects were presented with two infrequent tones designated target and deviant tone, which differed in their frequency from a frequent standard tone (Polich, 2007). The goal was to press a button only after target tones and not after deviant and standard tones. Therefore, only the target tones required an overt response selection. Typically, this task is used to measure attentional processes with EEG, which shows enhanced responses around 300 ms after the infrequent stimuli. In general, this enhanced deflection over fronto-parietal cortical regions reflects higher-level processing such as the evaluation of a task-relevant event and updating of working memory (Kok, 2001; Verleger, 2008, 1997; Vogel et al., 1998). In the multi-speaker task two realistic speech streams were presented simultaneously. The goal was to correctly report two task words from a target speaker stream. The relevant speaker stream was indicated by a target word uttered by the target speaker. The two task words appeared later in the target speaker stream and had to be reported after a visual target indicated to the subjects that they should now press the buttons corresponding to the two task words. This task required a covert attention selection after the target word, but not after the two task words, and overt response selection after the target image. Moreover, using a visual target to cue the response selection allowed us to investigate whether the CM-Pf responds to both auditory and visual cues for goal-oriented behavior selection. Thus, the oddball and multi-speaker task consist of target stimuli, which require different forms of behavior selection (attention selection, response selection) and other sensory events that do not require a behavior selection.

The reviewed studies suggest a behavior selection related plus a goal oriented component in CM/Pf responses to external stimuli. Therefore, we expected that CM/Pf responds to all target stimuli (target tone, target word, target image) because these were the sensory events that required a behavior selection. We also expected neural responses to target stimuli to be greater than responses to other task events which do not require a behavior selection. In particular, we expected greater responses to the target tone compared to the deviant and standard tone and to the target word compared to the two task words.

Materials and methods

Subject information

Informed consent was obtained from all subjects under the auspices of the ethics committee of Hannover Medical School. Six patients with chronic neuropathic pain (2 women, age range 25–57, mean age 48, SD 12 years; five subjects were right handed and one subject was left handed) participated in an auditory oddball experiment and a multi-speaker experiment. The patients were implanted with quadripolar DBS electrodes in the right CM-Pf (S1-S3, S6), the left CM-Pf (S5) or bilateral CM-Pf (S4) for treatment of their pain syndromes. A summary of the clinical background for the individual patients is provided in Table 1.

Electrode implantation and recording

Patients were implanted unilaterally, and in one case bilaterally, with quadripolar DBS electrodes (Medtronic 3387, Minneapolis, MN, USA) both in the CM-Pf and the somatosensory thalamus (ventral posterolateral or ventral posteromedial depending on pain distribution) guided by stereotactic surgery as outlined in detail previously (Weigel and Krauss, 2004). DBS electrodes were longitudinally spaced at distances of 1.5 mm (1.27 mm diameter, 1.5 mm length). A stereotactic head frame was attached to the patients head under local anesthesia. Based on stereotactic computer tomography (CT) imaging combined with a preoperative magnetic resonance image (MR), the anterior (AC) and posterior (PC) commissures were identified to calculate coordinates for the targets. Post-surgical stereotactic CT scans were performed to document placement of DBS electrodes.