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Differential contributions of the globus pallidus and ventral thalamus to stimulus–response learning in humans

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ABSTRACT

The ability to learn associations between stimuli, responses and rewards is a prerequisite for survival. Models of reinforcement learning suggest that the striatum, a basal ganglia input nucleus, vitally contributes to these learning processes. Our recently presented computational model predicts, first, that not only the striatum, but also the globus pallidus contributes to the learning (i.e., exploration) of stimulus–response associations based on rewards. Secondly, it predicts that the stable execution (i.e., exploitation) of well-learned associations involves further learning in the thalamus.

To test these predictions, we postoperatively recorded local field potentials (LFPs) from patients that had undergone surgery for deep brain stimulation to treat severe movement disorders. Macroelectrodes were placed either in the globus pallidus or in the ventral thalamus. During recordings, patients performed a reward-based stimulus–response learning task that comprised periods of exploration and exploitation. We analyzed correlations between patients' LFP amplitudes and model-based estimates of their reward expectations and reward prediction errors.

In line with our first prediction, pallidal LFP amplitudes during the presentation of rewards and reward omissions correlated with patients' reward prediction errors, suggesting pallidal access to reward-based teaching signals. Unexpectedly, the same was true for the thalamus. In further support of this prediction, pallidal LFP amplitudes during *stimulus* presentation correlated with patients' reward *expectations* during phases of low reward certainty — suggesting pallidal participation in the learning of stimulus–response associations. In line with our second prediction, correlations between *thalamic* stimulus-related LFP amplitudes and patients' reward expectations were significant within phases of already high reward certainty, suggesting thalamic participation in exploitation.

1. Introduction

The ability to learn associations between stimuli and responses is a vital capacity when trying to maximize rewards. Animals and humans therefore constantly adapt their responses to changes in reward contingencies. Learning of stimulus–response associations via rewards relies on the basal ganglia and their synaptic target, the ventral thalamus (Knowlton et al., 1996; Komura et al., 2001; Featherstone and McDonald, 2004; Pasupathy and Miller, 2005). In which ways these two structures may differentially contribute to learning, however, has not yet been reported. To investigate this, we recorded local field potentials (LFPs) from deep-brain electrodes in patients with severe movement disorders.

The basal ganglia receive massive cortical inputs and project to the ventral thalamus (Fig. 1). Additionally, they are targeted by dopaminergic midbrain neurons from the substantia nigra compacta (SNc) and ventral tegmental area (VTA; Beckstead et al., 1979) that likely encode reward prediction errors (e.g., Hollerman and Schultz, 2003; Bayer and Glimcher, 2005). These prediction errors function as teaching

Abbreviations: BGHAT, Basal Ganglia Human Area Template; CT, computer tomographic; DBS, deep brain stimulation; FWER, family-wise error rate; GPi, globus pallidus internus; LFP, local field potential; MNI, Montreal Neurological Institute; MR, magnetic resonance; SNc, substantia nigra compacta; Vim, ventral intermediate nucleus of the thalamus; VTA, ventral tegmental area.

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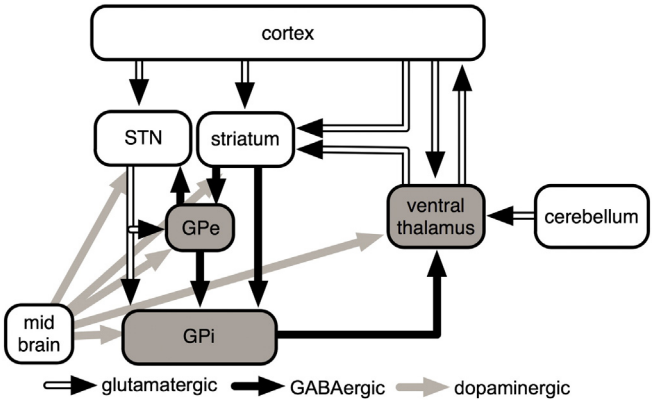

Fig. 1. Connections of the globus pallidus (comprising external and internal segments, GPe and GPi) and ventral thalamus with relevant other parts of the brain. The pallidum receives its inputs primarily from the striatum; the ventral thalamus primarily from the internal segment of the pallidum, from the cortex and the cerebellum. Both the pallidum and ventral thalamus receive dopaminergic afferents from the midbrain.

signals within the basal ganglia (Schultz, 1998; Morris et al., 2004), specifying which pathways should be strengthened and which depressed (Shen et al., 2008). The striatum, an input nucleus of the basal ganglia, uses these teaching signals to establish associations between stimuli and rewarded responses (e.g., Joel et al., 2002; O'Doherty et al., 2003; Pasupathy and Miller, 2005; Horvitz, 2009; cf. Barto, 1995; Houk et al., 1995). Computational models by our group recently predicted that not only the striatum but all nuclei of the basal ganglia, including the pallidum and subthalamic nucleus, contribute to the learning of stimulus–response associations (Vitay and Hamker, 2010; Schroll et al., 2012; Schroll et al., 2014). Moreover, our most recent model predicts that the execution of well-learned stimulus–response associations relies on the establishment of cortico–thalamo–cortical connectivity that bypasses the basal ganglia to accelerate processing (Schroll et al., 2014; Schroll et al., 2015; cf. Ashby et al., 2007; Antzoulatos and Miller, 2011; Waldschmidt and Ashby, 2011).

To test our predictions, we here used the unique opportunity to directly record LFP activity from the human globus pallidus and the ventral thalamus during patients' execution of a reward-based stimulus–response learning task. This approach allows differentiation of stimulus- and reward-related activity patterns from these two deep brain structures that are otherwise not accessible in awake humans. Based on our first prediction that the pallidum takes part in the reward-based learning of stimulus–response associations, we expected to find i) significant correlations between pallidal LFP activity during feedback presentation and patients' reward prediction errors, implying pallidal access to reward-based teaching signals and ii) significant correlations between pallidal stimulus-locked LFP activity and patients' reward expectations during phases of low reward confidence, implying pallidal access to learning progress in relatively exploratory phases of learning. Based on our second prediction that the thalamus contributes to the exploitation of previously learned associations, we expected to find iii) significant correlations between thalamic stimulus-locked LFP activity and patients' reward expectations during phases of high reward confidence.

2. Experimental methods

2.1. Patients, surgery, and electrode localization

38 patients (mean age 50.6 years) undergoing deep brain stimulation (DBS) for different movement disorders were recorded on our paradigm. Of these, 19 were included in our analyses as specified in Sub-Section 2.5. Twelve of these included patients were operated at Charité — University Medicine Berlin, seven patients at Hannover University Hospital. Clinical and demographic information on these patients is given in Table 1. The study was approved by the local Ethics Committee; patients gave informed consent prior to participation. Recordings took place between one and six days after operations.

Twelve patients suffered from idiopathic dystonia (mean age: 40.0 years; mean disease duration: 9.8 years; detailed disease classification is given in Table 1), six from essential tremor (mean age: 67.8 years; mean disease duration: 15.8 years) and one from idiopathic Parkinson's disease (age: 74 years; disease duration: 14 years). All six essential tremor patients were implanted bilaterally in the ventral intermediate nucleus of the thalamus (Vim) which is located between ventral lateral and ventral posterior thalamic nuclei, ten of twelve dystonia patients bilaterally in the posteroventral lateral "motor" part of the globus pallidus internus (GPi), the remaining two dystonia patients bilaterally in both the GPi and Vim due to prominent dystonic tremor, and the Parkinsonian patient unilaterally in the Vim to treat severe resting tremor.

Electrode positions were confirmed postoperatively using custom-built software (Horn and Kühn, 2015). For the patients operated in Berlin, electrode locations were reconstructed based on postoperative magnetic resonance (MR) images; for the patients operated in Hannover, localization was based on postoperative stereotactic computer tomographic (CT) images aligned with preoperative MR scans. Postoperative images were first normalized linearly into standard Montreal Neurological Institute (MNI) space in a three-step procedure that increasingly focuses on the sub-cortical target area across steps (cf. Schönecker et al., 2009). Electrodes were then localized using LEAD-DBS software (www.lead-dbs.org, Horn and Kühn, 2015) relative to the Basal Ganglia Human Area Template (BGHAT) atlas (Prodoehl et al., 2008) and an atlas of the human thalamus (Krauth et al., 2010; Jakab et al., 2012). All reconstructed electrode locations are visualized in Fig. 2. Any contact pairs where both contacts lay outside the pallidum (internal or external segments) or outside the ventral thalamus, respectively, were excluded from further analyses leaving on average 85% of all thalamic and 78% of all pallidal contact pairs in our analyses based on electrode localizations (SDs: 23% and 23%, respectively).

For the patients operated in Berlin, macroelectrode models 3389 (Medtronic Neurological Division, MN, USA) and 6147 (St. Jude Medical, MN, USA) were used for pallidal implants, while macroelectrode 3387 (Medtronic Neurological Division, MN, USA) was used for thalamic implants; for all patients operated in Hannover, model 3387 (Medtronic Neurological Division, MN, USA) was used. Macroelectrodes 3387 and 3389 contain 4 platinum–iridium contacts of cylindrical shape (diameter: 1.27 mm; length: 1.5 mm) with contact-to-contact distances of 1.5 mm and 0.5 mm, respectively. Macroelectrode 6147, in contrast, has a contact-to-contact distance of 0.5 mm and a contact diameter of 1.4 mm; its lowermost contact extends into the tip of the electrode, resulting in a total length of 3 mm for this contact and a deviation from cylindrical shape at the tip.

2.2. Setup and procedure

Patients were seated in a comfortable armchair in a well-lit chamber. A response tablet with two force-sensitive response buttons (Tactilus Free Form®; Sensor Products Inc., NJ, USA) was placed on a desk in front of the patients such that they could comfortably press the left button with their left index finger and the right button with their right index finger. Buttons were spaced 13 cm apart from each other. A laptop with a 15.4 in. screen was placed on the desk behind the response tablet, such that the screen had a distance of approximately 100 cm from the participants' eyes.

Before recordings began, patients were made familiar with the setup, recording equipment and procedure of our study and were instructed that they could interrupt or stop their participation whenever they felt uncomfortable. Bandages covering the externalized electrodes were then removed and electrodes were connected to the recording equipment. Finally, the task was explained.