Brain Stimulation 10 (2017) 657–663

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

The human globus pallidus internus is sensitive to rewards – Evidence from intracerebral recordings

Thomas F. Münte [a, b, *, 1], Josep Marco-Pallares [c, d, 1], Seza Bolat [a], Marcus Heldmann [a], Götz Lütjens [e], Wido Nager [f], Kirsten Müller-Vahl [g], Joachim K. Krauss [e]

[a] Department of Neurology, University of Lübeck, Lübeck, Germany
[b] Institute of Psychology II, University of Lübeck, Lübeck, Germany
[c] Department of Basic Psychology, University of Barcelona, Barcelona, Spain
[d] Cognition and Brain Plasticity Group, Bellvitge Biomedical Research Institute - IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[e] Department of Neurosurgery, Medical School Hannover, Hannover, Germany
[f] Schön Klinik Eilbek, Hamburg, Germany
[g] Department of Psychiatry, Medical School Hannover, Hannover, Germany

ARTICLE INFO

Article history:
Received 3 September 2016
Received in revised form
18 December 2016
Accepted 7 January 2017
Available online 14 February 2017

Keywords:
Globus pallidus internus
Deep brain stimulation
Reward
Oscillations
Local field potentials

ABSTRACT

Background: The globus pallidus internus (GPi) is the final output relay of the basal ganglia for the control of movements but has also been shown to belong to a second pathway projecting to the lateral habenula. This latter pathway is related to reward processing.
Method: This prompted us to record, in eight patients receiving deep brain stimulation of the GPi for the alleviation of various movement disorders, local field potentials (LFP) while these patients performed a lottery task. The task entailed choosing between a higher and a lower number, which changed their color after the patient's choice with red (green) signaling a loss (win, in Euro cents) corresponding to the chosen number.
Results: Surface recordings showed a feedback related negativity from a frontal midline site, while time domain averages in the GPi showed differential modulation depending on the valence of the stimulus with polarity inversion indicating that this reward-modulated activity was indeed generated locally. Furthermore, wavelet decomposition of the LFP showed a reward-related response in the high beta/low gamma range.
Conclusion: We conclude that human GPi is involved in reward processing, possibly in relation to the lateral habenula.

1. Introduction

The globus pallidus internus (GPi) is the final output relay of the basal ganglia (BG) for the control of movements [1,2]. The "standard model" of the BG posits that two main projections from the striatum team up to facilitate the appropriate cortical motor command, while suppressing competing response tendencies [3,4]. Both, the direct and the indirect pathway converge on the GPi which in turn projects to the motor part of the thalamus which connects to cortical output areas as well as to subcortical motor structures [5]. The motor functions of the GPi are undisputed and in fact this structure has become a target for deep brain stimulation (DBS) in a variety of motor disorders such as Parkinson's disease [6], dystonia [7], and more recently Huntington's disease [8]. In PD and dystonia, DBS effectively ameliorates motor dysfunctions likely by modifying altered neuronal activity. Recently, a number of investigations in macaque monkeys have targeted another pathway passing through the GPi [9] which is related to reward processing. Besides to the thalamus, the GPi also projects to the lateral habenula (LHb) located medially over the posterior thalamus [10]. The seminal studies of Hikosaka and co-workers [11,12] have demonstrated that this pathway is used to encode nonmotor signals linked to expected rewards. Using antidromic stimulation, Hong and Hikosaka first

Abbreviations: LFP, local field potential; GPi, globus pallidus internus; DBS, deep brain stimulation.

* Corresponding author. Department of Neurology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.
E-mail address: Thomas.muente@neuro.uni-luebeck.de (T.F. Münte).

[1] Equal contribution.

http://dx.doi.org/10.1016/j.brs.2017.01.004
1935-861X/

identified GPi neurons that projected to the LHb. In a second step, the behavior of these neurons was studied in a saccade task involving rewards. Indeed, LHb-projecting GPi neurons showed firing patterns that varied as a function of expected rewards. Anatomical studies in monkeys have suggested that LHb-projecting neurons are distinct from other motor-related GPi neurons [13]. According to these studies, LHb projecting neurons amount to about 10% of the total neuronal population of the GPi. Using a different approach, Karadi and co-workers [14,15] recorded single neuron activity of the GP in rats and rhesus monkeys to the administration of glucose, as well as gustatory, and olfactory stimuli. In monkeys, visual presentation of food and nonfood objects was also used. In rats as well as monkeys about 15% of the GPi neurons were glucose-sensitive, while 19% and 16% of the cells responded to gustatory and olfactory stimulation, respectively. Obviously, these responses can be viewed as being reward-related and the location of glucose-sensitive neurons was similar to the LHb-projecting GPi neurons identified by Hong and Hikosaka [11,12].

In the present investigation, we recorded from DBS electrodes which were temporarily externalized prior to implantation of the pulse generator while the patient is performing a cognitive task. To further investigate the role of the GPi in reward processing, we used a simple lottery task that has been used for electrophysiological and neuroimaging studies [16–20]. This task requires subjects to select the smaller or the greater of two numbers displayed on a computer screen. A change of color of the numbers indicates whether the chosen number led to a monetary win (change to green) or a loss (change to red) for the subject. The change of color, i.e. the feedback signal indicating wins or losses, is the critical reward indicating stimulus in this type of study. In averaged scalp surface event-related potentials (ERPs) losses are associated with a phasic negative component peaking at about 280 ms post onset of the feedback signal, variously termed medial frontal negativity or feedback related negativity (FRN). This FRN is superimposed on a positive going component present for both, wins and losses. Furthermore, time-frequency analyses has revealed an increase of theta power for losses and an increase of beta-power for wins [16,17]To the extent to which the GPi is sensitive to rewards we expected a change both in the oscillatory and averaged local field potential (LFP).

2. Method

All procedures were approved by the ethical review board of Hannover Medical School. The study was performed in compliance with the Declaration of Helsinki.

2.1. Patients, surgery, and electrode localization

Eight patients were included in the study (mean age 35.5, range 17–54). All patients were right-handed. Of these, 4 patients suffered from Tourette syndrome (mean age 32.2, range 19–47, disease duration 4.5–37 years), one had generalized dystonia (age 17, disease duration 17 years), 2 had cervical dystonia (age 17 and 57, disease duration 15 years in one patient, unclear in the other) and one patient had severe dystonic tremor (age 54, disease duration 12 years). In the Tourette patients, the Yale Global Tic Severity Scale (YGTSS) scores were between 12 and 23 for the motor part (maximum possible score: 25) and between 32 and 44 for the total tic score (maximum possible: 50). Medication at the time of the recording included antipsychotics (3 patients), serotonin reuptake inhibitors (2), benzodiazepines (2), and anticholinergics(1).Patients gave informed consent prior to participation in the study which had been approved by the local ethics committee. DBS electrodes were implanted in all patients bilaterally in the posteroventral lateral "motor" portion of GPi guided by CT-stereotactic surgery, magnetic resonance imaging and microelectrode recording. All Tourette patients and two patients with dystonia were implanted under general anesthesia because of the severity of their movement disorder. Preliminary target coordinates were $x = 20$, $y = 3$, and $z = 0$, related to the midcommissural point. In all patients the Medtronic model 3387 (Medtronic Neurological Division, MN, USA) DBS electrode was used which harbors 4 contacts of 1.27 mm diameter and 1.5 mm length spaced 1 mm apart. Postoperative stereotactic CT confirmed appropriate DBS electrode placement with the lowest active contact located at 17.4–22 mm lateral to the intercommissural line, 2–4 mm anterior to, and 2–4 mm below the midcommissural point in standard Montreal Neurological Institute (MNI) stereotactic space coordinates [21]. There were no intraoperative or postoperative adverse events. All patients benefitted from chronic stimulation with improvement in the corresponding scores.

2.2. Stimuli

We used an established gambling task [16,17] in which the numbers 5 and 25 were presented in white on a black background in one of the possible orders, [5 25] or [25 5]. Participants selected one of the numbers by pressing a spatially corresponding button with the left or right index finger. One second after the choice, one of the numbers turned green, while the other changed to red. If the number selected by the participant changed to red (green), this signaled a loss (gain) of the corresponding amount of money (in Euro cents). Two seconds later, a new pair of numbers appeared on the screen for the next trial. Patients were provided with an initial sum of 10 € and were encouraged to gain as much as possible. They were familiarized with the task during a brief practice block. Patients took part in 5–15 blocks of 40 trials each. The probability to win/lose was 50%. The experiment also contained trials in which the numbers not only changed color (to indicate wins and losses) but also doubled in size. These "boost" trials were included to provide unexpected wins and losses (for a similar approach: [17]) which are known from animal experiments to lead to prominent modulations of dopaminergic activity [22]. The boost trials occurred randomly interspersed with standard trials in 12% of the trials. The number of trials was insufficient to compute reliable average LFPs and time-frequency analyses, however. Therefore, we will not report data from the boost trials. Recording sessions differed somewhat in duration between patients, depending on their clinical condition.

2.3. Data acquisition and analysis

We obtained bipolar recordings between different contacts of the DBS-electrodes.[2] Data were sampled at 1000 points/s and data analysis was performed using EEG-Lab [24] and ERP-Lab (http://www.erpinfo.org/erplab/erplab-toolbox) software. To increase signal-to-noise ratio, we averaged over small (5 cents) and large (25 cents) wins and small and large losses, from −100 to 1000 ms after

[2] An important issue with regard to bipolar recordings of LFPs, discussed for example by Herrojo-Ruiz et al. [23], is that polarity cannot be defined due to the measurement of the "differential" electrical potential from 2 contacts located in or near the target structure. Moreover, depending on the precise position of the recording sites, a polarity reversal between subjects might occur. In the present set of data we carefully examined the single patients' data and found that in spite of this potential problem very similar findings could be obtained in the different patients owing to the very stable localization of the contacts. Therefore we found it justified to obtain group averages for the different bipolar derivations.