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Neurotransmitter activity is linked to outcome following subthalamic deep brain stimulation in Parkinson's disease

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ABSTRACT

Introduction: While the mechanisms underlying the therapeutic effects of deep brain stimulation (DBS) in Parkinson's Disease (PD) are not yet fully understood, DBS appears to exert a wide range of neurochemical effects on the network level, thought to arise from activation of inhibitory and excitatory pathways. The activity within the primary inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmitter systems may therefore play an important role in the therapeutic efficacy of DBS in PD. The purpose of this study was to investigate abnormalities in GABA-ergic and glutamatergic neurotransmission in PD, and to examine the link between neurotransmitter levels and outcome following DBS.

Methods: Magnetic resonance spectra were acquired from the pons and basal ganglia in sixteen patients with PD and sixteen matched control participants. GABA and glutamate levels were quantified with LCModel, an automated spectral fitting package. Fourteen patients subsequently underwent DBS, and PD symptoms were evaluated with the MDS-UPDRS at baseline and six months after surgery. The efficacy of DBS treatment was evaluated from the percentage improvement in MDS-UPDRS scores.

Results: Basal ganglia GABA levels were significantly higher in PD patients relative to control participants ($p < 0.01$), while pontine glutamate + glutamine (Glx) levels were significantly lower in patients with PD ($p < 0.05$). While GABA levels were not significantly related to outcome post-surgery, basal ganglia glutamate levels emerged as a significant predictor of outcome, suggesting a possible role for glutamatergic neurotransmission in the therapeutic mechanism of DBS.

Conclusion: GABAergic and glutamatergic neurotransmission is altered in PD, and glutamatergic activity in particular may influence outcome post-surgery.

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1. Introduction

The world-wide prevalence of Parkinson's Disease (PD) is projected to reach 9 million by the year 2030 [1,2]. While most of the motor symptoms of PD can be improved by dopamine replacement therapy, some patients demonstrate inadequate symptom control and/or medication-related complications such as levodopa-induced dyskinesias. For such patients, deep brain stimulation (DBS) can provide safe and effective improvement of motor symptoms and quality of life [3,4].

While the neurochemical and neurobiological effects of DBS are not yet fully understood, neurotransmitter activity appears to play an important role in the therapeutic mechanism of DBS [5]. Recent reports from animal microdialysis studies suggest that one of the effects of high frequency stimulation of the subthalamic nucleus (STN) is an increase in extracellular gamma-amino butyric acid (GABA) concentration, suggesting that the efficacy of DBS may be at least partially dependent on the activation of GABAergic neurons close to the STN [6], including the GABAergic afferents from the globus pallidus externus. However, mounting evidence suggests that DBS exerts a wide range of effects on the network level as well as locally [7].

Cerebral neurotransmitters like glutamate and GABA are fundamental to brain physiology since they maintain the balance between neuronal excitation and inhibition, and a neurotransmitter imbalance is thought to be central to the pathophysiology of a number of neurodegenerative diseases including PD [8,9]. The

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basal ganglia structures which comprise a central hub of the motor network are innervated by and project glutamatergic and GABA-ergic neurons, which are modulated by the dopaminergic projections from the substantia nigra pars compacta to the striatum. In PD, a loss of these nigrostriatal dopaminergic neurons causes an increase in inhibitory outflow of the basal ganglia, resulting in increased inhibition of the thalamus. As a result, the thalamocortical (glutamatergic) neurons innervating the motor cortex are less likely to be activated, resulting in decreased glutamate in the cortex and a disruption of the cortico-basal ganglia-thalamo-cortical loops. In parallel, the loss of nigrostriatal neurons causes increased excitation of the GABA-ergic efferents from the globus pallidus interna and the substantia nigra to the pontine nuclei [10], resulting in elevated GABA levels in the pons, which may in turn inhibit the activity of noradrenergic and serotonergic neurons projecting to the substantia nigra, further suppressing the activity of the dopaminergic neurons projecting to the striatum. This decrease in dopaminergic activity results in less inhibition of the STN, causing hyperactivity of the STN [11] and culminating in a vicious circle which may be manifested as clinical progression in PD (for review see Ref. [12]). In this context, one potential therapeutic mechanism of DBS may be to reduce the STN hyperactivity by increasing GABA release via stimulation of the GABAergic neurons close to the STN. GABA and glutamate concentrations in the region of the STN or striatum may therefore be important indicators of the potential clinical efficacy of DBS.

Following advances in magnetic resonance spectroscopy (MRS) methodology, it is now possible to measure both glutamate and GABA in vivo noninvasively. Previous MRS studies in PD have reported decreased cortical glutamate [13], increased GABA concentrations in the pons and putamen [14], increased GABA in the thalamus [15], and an increased GABA/glutamate ratio in the substantia nigra [16], consistent with increased inhibitory outflow of the basal ganglia and decreased glutamatergic excitation of the cortex. In addition to neurotransmitter changes, MRS studies have also revealed alterations in other neuro-metabolites, such as N-acetyl aspartate (NAA), Creatine (Cr), Choline-containing compounds (Cho), and myo-inositol (mI) in PD patients [17–19]. Interestingly, the pattern of neurotransmitter abnormalities reported in PD is indicative of a progressive caudo-rostral degeneration [14], consistent with the well-described caudo-rostral progression of alpha-synuclein deposition [20], leading some authors to suggest that neurotransmitter abnormalities may represent a biomarker for disease progression in PD [13,14,21].

The purpose of the present study was to investigate abnormalities in GABA-ergic and glutamatergic neurotransmission in patients with PD, and to examine the link between neurotransmitter concentrations and the efficacy of DBS treatment. Based on reports from the literature, we hypothesize that patients with PD will show elevated GABA levels in the basal ganglia [13,14,16] and reduced glutamate in the basal ganglia and pons, since reduced cortical glutamate would be expected to result in less excitation of the glutamatergic projections from the cortex to the basal ganglia and the pontine nuclei [10]. Since the progressive loss of nigrostriatal neurons would be expected to exacerbate the imbalance of GABA and glutamate, we hypothesize that neurotransmitter concentrations may represent a predictive biomarker for the efficacy of DBS treatment.

2. Methods

2.1. Participants

Sixteen patients with PD (3 female, mean age 65 years, range 54–75, Hoehn and Yahr ≥2, mean disease duration 10 years, range 3–18 years), were recruited from the Neurology Department at the University Hospital of Zürich, Switzerland (see Table 1 for demographics). Seven patients showed the initial manifestation of Parkinson's symptoms on the right side. Patients were classified as akinetic rigid (n = 10) or tremor dominant (n = 6) type [22]. Fourteen patients subsequently underwent DBS surgery targeting the bilateral subthalamic nucleus, with a mean reduction in levodopa equivalent dose (LED) of 64% (range 11%–100%) [22,23] and a mean improvement in the motor part (III) of the Unified Parkinson's Disease Rating Scale of the Movement Disorders Society (MDS-UPDRS) [24] scores on medication of 39% (range 17%–69%). Preoperatively, nine patients were treated with levodopa medication without dopamine agonists, while seven were treated with levodopa medication in combination with dopamine agonists (see Supplementary Table 1 for a list of medications). Sixteen healthy control participants with no history of neurological or psychiatric illness were also recruited (4 Female, mean age 62 years, range 28–78). All participants gave verbal and written informed consent to participate in the study, which was approved by the cantonal ethics committee of the Canton of Zürich, Switzerland.

2.2. MR data acquisition

MR Imaging and Spectroscopy (MRS) investigations were performed with a 3T GE MR750 MRI scanner, using an 8 channel receive only head coil. The MRI protocol included a high-resolution axial T1-weighted spoiled gradient echo scan used for planning the MRS voxels (TR = 10 ms; TI = 600 ms; FOV = 256 × 192 mm^2; acquisition matrix = 256 × 192; reconstruction matrix = 256 × 256; flip angle = 8°; slice thickness = 1 mm; 172 slices).

Single-voxel GABA-edited spectra were acquired from a 30 mL voxel centred on the left basal ganglia using the MEGAPRESS method [25] (see Supplementary Fig. 1 for voxel position). In total 320 spectral averages were acquired with a repetition time (TR) of 1800 msec, an echo time (TE) of 69 msec, and an eight-step phase cycle. MEGA-editing was achieved with 16-msec Gaussian editing pulses applied at 1.9 ppm and 7.5 ppm in alternate spectral lines. For each metabolite spectrum, 16 unsuppressed water reference lines were also acquired as part of the standard PROBE acquisition, resulting in a total acquisition time of 10 min. To achieve a consistent voxel position between participants, voxels were prescribed on an axial plane where the putamen was widest in the lateral (right-left) direction, such that the anterior and medial borders of the voxel were aligned with the anterior and medial margins of the head of the caudate nucleus.

Single voxel PRESS spectra were acquired from a 3.4 mL (15 × 15 × 15 mm^3) voxel in the pons, with TE = 35 ms, TR = 3000 ms, and 128 spectral averages. In a similar manner as for the MEGAPRESS spectra, 16 unsuppressed water reference lines were acquired as part of the standard PROBE acquisition, resulting in a total scan time of 7 min (see Supplementary Fig. 1 for voxel positions).

All MRI/MRS examinations were performed while patients were in the OFF medication state, confirmed by neurological evaluation immediately prior to the scan.

2.3. MRS data analysis

Water-scaled GABA, glutamate (Glu), and glutamine (Gln) concentrations were derived from the edited basal ganglia MEGA-PRESS spectra, and Glu and Gln concentrations were derived from the pontine PRESS spectra with LCModel version 6.3-1H, a fully automated spectral fitting package [26], using a fit range between 1.9 and 4 ppm. For GABA quantification, the control parameter

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