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Cerebello-striatal interaction mediates effects of subthalamic nucleus deep brain stimulation in Parkinson's disease

Henrike Hanssen[a,b,1], Julia Steinhardt[a,c,1], Alexander Münchau[c], Arkan Al-Zubaidi[a], Elinor Tzvi[d], Marcus Heldmann[a,e], Peter Schramm[f], Alexander Neumann[f], Dirk Rasche[g], Assel Saryyeva[h], Jürgen Voges[i,j], Imke Galazky[k], Lars Büntjen[i], Hans-Jochen Heinze[k], Joachim K. Krauss[h], Volker Tronnier[g], Thomas F. Münte[a,e], Norbert Brüggemann[a,c,*]

[a] Department of Neurology, University of Lübeck, Lübeck, Germany
[b] Institute of Neurogenetics, University of Lübeck, Lübeck, Germany
[c] Department of Internal Medicine, University of Lübeck, Lübeck, Germany
[d] Department of Neurology, University of Leipzig, Leipzig, Germany
[e] Institute of Psychology II, University of Lübeck, Lübeck, Germany
[f] Institute of Neuroradiology, University of Lübeck, Lübeck, Germany
[g] Department of Neurosurgery, University of Lübeck, Lübeck, Germany
[h] Department of Neurosurgery, Medical School Hanover, MHH, Hanover, Germany
[i] Department of Stereotactic Neurosurgery, University Hospital Magdeburg, Magdeburg, Germany
[j] Leibniz Institute of Neurobiology, Magdeburg, Germany
[k] Department of Neurology, University Hospital Magdeburg, Magdeburg, Germany

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ABSTRACT

Background: In Parkinson's disease (PD), dopamine replacement therapy (DRT) enhances the effective connectivity of the prefrontal cortex (PFC) and supplementary motor area (SMA). The clinical effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) go beyond DRT effects including highly beneficial tremor suppression.

Objectives: Here, we aimed to determine DBS-related changes of a motor network using resting state fMRI in PD patients with chronic STN DBS.

Methods: In a repeated-measurement design, 26 medicated PD patients (60.9 years (SD 8.9)) were investigated using resting state fMRI while bipolar STN stimulation was (i) active or (ii) switched off, and dynamic causal modelling was subsequently performed.

Results: DBS improved the MDS-UPDRS-III score by 26.4% (DBS ON/Med ON vs. DBS OFF/Med ON). Active stimulation resulted in an increased effective connectivity from cerebellum to putamen ($p = 0.00118$). In addition, there was a stronger coupling from PFC to cerebellum ($p = 0.021$), as well as from cerebellum to SMA ($p = 0.043$) on an uncorrected level. Coupling strength from PFC to cerebellum correlated with the DBS-related change of the resting tremor subscore ($r = 0.54$, $p = 0.031$). Self-connections increased as a function of DBS in the right PFC, PMC, SMA, M1, thalamus and left cerebellum.

Conclusions: DBS-related improvement of Parkinsonian signs appears to be driven by an interaction between the cerebellum and the putamen. Resting tremor suppression may be related to an enhanced prefronto-cerebellar network. Activation of the mesial premotor loop (PFC-SMA) as seen in DRT may thus be secondary due to the primary modulation of cerebellar networks.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an important therapeutic option in patients with Parkinson's disease (PD) and clinically relevant motor fluctuations, drug-resistant tremor, or intolerable side effects of Antiparkinsonian drugs. As one of

* Corresponding author. Dept. of Neurology and Institute of Neurogenetics, University of Lübeck; Ratzeburger Allee, 23538, Lübeck, Germany.
E-mail address: norbert.brueggemann@neuro.uni-luebeck.de (N. Brüggemann).
[1] These authors contributed equally.

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the primary actions, STN DBS improves PD motor and non-motor symptoms that also respond to dopaminergic medication with long-term efficacy whereas axial signs as seen in later disease stages do not respond [1]. Aside from the effects that mimic dopamine replacement therapy (DRT), STN DBS also effectively alleviates resting tremor that frequently does not sufficiently respond to Anti-Parkinsonian medication [1]. Further evidence that DBS-related effects go beyond the effect of DRT is provided by the observation that DBS improves sequence learning whereas DRT does not affect learning performance [2]. The improvement was associated with increased activity in a broad neuronal network including the lateral cerebellum, dorsal premotor cortex, and supplementary motor area suggesting that improvements are related to changes in a premotor-cerebellar network as a function of STN DBS but not of DRT. In keeping, a recent fMRI study revealed an increased interconnectedness in the left and right cortex and an increase of connectivity with the thalamus and cerebellum as a result of active DBS but not of levodopa [3]. These findings collectively argue for DBS-related effects independent of actions that simply mimic DRT.

The mechanisms that are involved in the facilitating effects of STN DBS in PD are not well understood and complicated by the fact that the STN is connected to several different brain regions, including the prefrontal-subthalamic hyperdirect pathway [4], basal ganglia, thalamus, substantia nigra, brainstem [4], and the cerebellum [5,6]. In line with the complexity of DBS actions, the response to STN DBS is predicted by the localization of the DBS lead in the STN and the related connectivity profile to remote brain regions [4,7]. Structural connectivity between the active electrode and a widespread network including the superior frontal gyrus [4,7] and the SMA [7], but also the thalamus [4] and the cerebellum [7] predicted a beneficial outcome of DBS. The findings on a role of the cerebellum in mediating DBS-related effects is corroborated by animal data reporting increased cerebellar activity in hemiparkinsonian rats due to STN DBS [8]. Recent PET studies and a single fMRI study in a limited number of PD patients confirmed DBS-related changes of the cortico-basal ganglia network but also an involvement of the cerebello-thalamic pathway [9–12].

Here, we performed two sessions of resting state functional MRI (rs-fMRI) in medicated PD patients with chronic bilateral STN DBS and compared neural network dynamics between active stimulation and inactive stimulation conditions. According to strong hypotheses on changes in basal ganglia-thalamo-cortical and cerebello-thalamo-cortical circuits as a function of active DBS, we used resting state fMRI to study DBS effects *in vivo* without the influence of motor preparation, action control, and movement execution during the execution of a motor task.

2. Materials and methods

2.1. Patients and study design

Thirty-seven patients diagnosed with idiopathic PD according to the clinical diagnostic criteria of the Movement Disorder Society were recruited. Stereotactic bilateral DBS electrode implantation was performed at University hospitals in Lübeck, Hannover, and Magdeburg. MRI data from 11 patients had to be excluded for the reasons mentioned below. Therefore, MRI datasets of 26 patients had a sufficient quality for further analysis (eTable 1). Twenty-four of the 26 patients took dopaminergic medication with a levodopa equivalence dose of 552 ± 351 mg/day. All patients continued to take their dopaminergic medication throughout the study. Bilateral STN DBS had been performed 3–78 months prior to the study (mean 25.5 ± 20.8). In all patients, pulse generators of the Medtronic Activa series were implanted (PC or RC). As we were interested in the DBS-related effects on resting state connectivity, we investigated the patients under two conditions in counterbalance: (i) with active stimulation (ON) and (ii) while stimulation was switched off (OFF). For the head motion, there was no significant difference between ON and OFF measurements.

Table 1
Regions selected for the left and the right hemisphere for DCM analysis based on T-statistic testing for evoked responses in the motor task. Regions are defined as contiguous voxels in SPM, surviving a threshold of $p < 0.001$ (uncorrected) within 4 mm of the locations. The anatomical designations are according to the AAL Atlas.

Left hemisphere	Region of Interest	Location (mm)		
CB	(Contralateral) Cerebellum	−27	−45	−24
M1	Primary motor cortex	36	−18	54
PMC	Premotor cortex	42	−12	54
PFC	Prefrontal cortex	42	42	27
SMA	Supplementary motor area	12	6	45
Put	Putamen	22	3	5
Thal	Thalamus	13	−14	2
Right hemisphere	**Region of Interest**	**Location (mm)**		
CB	(Contralateral) Cerebellum	27	−57	−21
M1	Primary motor cortex	−33	−17	57
PMC	Premotor cortex	−33	−9	57
PFC	Prefrontal cortex	−33	39	24
SMA	Supplementary motor area	−3	3	45
Put	Putamen	−30	−3	6
Thal	Thalamus	−18	−12	6

Some patients had greater head movement during the ON condition, others more during the OFF condition. Before an MRI session, patients were neurologically examined by a movement disorders specialist according to the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III). The examinations were videotaped and additionally rated by a second movement disorder specialist (A.M.) blinded to the stimulation mode. For rigidity, the ratings from the onsite examiner were used. After both MRI sessions, the stimulation parameters were set to the initial settings and treatment impedances were tested. The neurological examination was repeated to confirm that patients had returned to their initial clinical baseline. Handedness was assessed using the Edinburgh Handedness scale. Cognitive functions were tested by using Montreal Cognitive Assessment. The study was approved by the local ethics committee of the University of Lübeck, Germany (AZ15-212), and all participants gave their written consent prior to their inclusion.

2.2. Dynamic causal modelling

Information on exclusion criteria, MRI data acquisition, fMRI preprocessing and ROI selection are described in the Suppl. Material (eMethods 1) and in Table 1. We used spectral DCM to estimate a motor network consisting of regions of interest (ROIs) that were previously implicated in PD pathophysiology (Fig. 1, eMethods 2). In contrast to classical DCM, spectral DCM aims to reveal intrinsic connectivity from resting state fMRI data without task-related input. We decided against Bayesian Model Selection for the following reasons: (i) both states of the experimental factor (DBS) could not be applied during the same MRI session, (ii) concatenation of both fMRI time series that allowing the combination of both experimental states was problematic due to a break of 60 min between both sessions, (iii) the input region (STN) could not be defined due the loss-of-signal artefact and (iv) the interactions between our seven selected ROIs is highly complex resulting in an enormous number of possible models, of which many may be biologically plausible.

We thus decided to analyze a full spectral DCM model which means that all endogenous connections (DCM.A) were estimated and analyzed except for connectivity between PFC and M1. This approach allowed us to evaluate DBS-related connectivity changes in the basal ganglia-thalamo-cortical and cerebello-thalamo-cortical circuits and to determine their interactions.

To minimize loss-of-signal artefacts by DBS electrodes and extension cables we analyzed both hemispheres separately. In nine patients, both

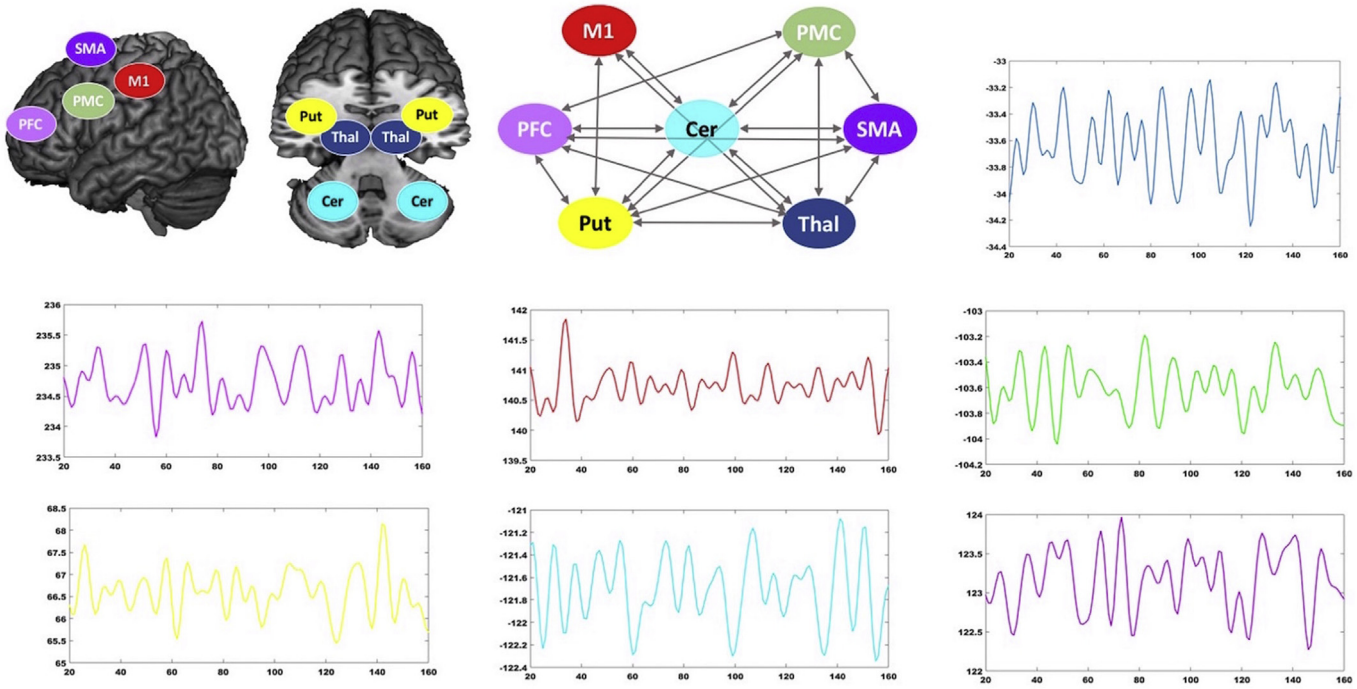

Fig. 1. Illustration of regions of interest, their principal eigenvariates and pre-defined connections for the DCM analysis. The figure shows the selected regions of interest and corresponding time-series represented as principal eigenvariates.

hemispheres could be analyzed, and in the remaining patients only the hemisphere opposite to the extension cable could be used for further analysis. Accordingly, we created two models: one model for the left (model 1; N = 10) and one model for the right hemisphere (model 2; N = 25). We analyzed both hemispheres and considered them separately because (i) PD is an asymmetric disorder, (ii) bilateral DBS may introduce different effects in both hemispheres due to varying stimulation parameters, and (iii) resting state network show an asymmetric distribution upon resting state fMRI.

2.3. Statistical analysis of effective connectivity

After DCM definition and estimation, connectivity parameters from each subject were analyzed. One sample t-tests were conducted to examine the consistency of the coupling parameters (different from 0). If this was the case, paired t-tests were subsequently applied to compare coupling parameters in the ON versus OFF condition. For the primary analysis, Bonferroni correction was applied to account for multiple comparisons taking 42 connections into account ($p < 0.0012$ (0.05/42)). We also report connectivity changes that did not survive multiple comparisons correction ($0.00119 < p < 0.05$). For the separate analysis of DBS-related changes of self-connections, we also applied Bonferroni correction. Given a number of seven ROIs, we defined a p-value < 0.0071 (0.05/7) as significant due to the ROI-based analysis strategy. Since we were specifically interested in the actions of DBS on resting tremor, coupling strengths of DBS-related connectivity alterations were correlated with the MDS-UPDRS-III resting tremor score (item 20). This analysis was done on an exploratory level. Pearson's r is reported as the data is approximately normally distributed (assessed by the Shapiro-Wilk test).

3. Results

3.1. Clinical effects of STN DBS

The MRI procedure was safe in all patients independent of the stimulation mode. After both MRI sessions, no changes were observed in the clinical response to DBS and in the assessment of treatment impedances and current flow. The stimulation amplitude during the MRI session was similar to the therapeutic stimulation amplitude (2.35 ± 0.79 vs 2.39 ± 0.85, p = 0.682, eTable 2). Bilateral STN DBS resulted in a mean improvement of 26.4 ± 15.5% of the total MDS-UPDRS-III score (DBS ON/Med ON vs. DBS OFF/med ON, range −3 to 63%). Resting tremor was present in 15 patients in the DBS OFF state and improved on average by 42.4 ± 43.6% (range −33 to 100%). Active DBS also improved bradykinesia which was present in all 26 patients in the DBS OFF state and rigidity (n = 24 during OFF) by 19.5 ± 17.5% (range −16 to 45%) and 59.6 ± 19.7% (range 30–100%). MDS-UPDRS-III scores of the onsite examiner and the blinded offsite examiner correlated significantly ($p < 0.001$) in both, ON Condition (r = 0.813) and OFF condition (r = 0.912).

3.2. DBS OFF

In DBS OFF state, the one sample *t*-test revealed significant self-connections in the left cerebellum and right PFC, PMC, SMA, M1, putamen and thalamus (all $p < 0.001$). In the left hemisphere, the same trend was present for PMC (p = 0.048) and thalamus (p = 0.040).

During DBS OFF effective connectivity was significant at a trend level from left cerebellum to right putamen (p = 0.040), left cerebellum to right SMA (p = 0.01), right M1 to right thalamus (p = 0.009), right PFC to left cerebellum (p = 0.021), PMC to thalamus (p = 0.039), with mean values lower than zero. In contrast, we found significant effective connectivity on trend level from left putamen to M1 (p = 0.047), with mean values greater than zero. Please note that these changes did not survive p-value correction for multiple comparisons. Details are shown in eTable 3 and Fig. 2.

3.3. DBS on

In DBS ON state, the one sample *t*-test showed significant self-connections in the PFC, PMC, SMA, M1, thalamus and cerebellum bilaterally and right putamen (all $p < 0.005$). There was a similar trend for the left putamen (p = 0.0096). Significant effective connectivity on

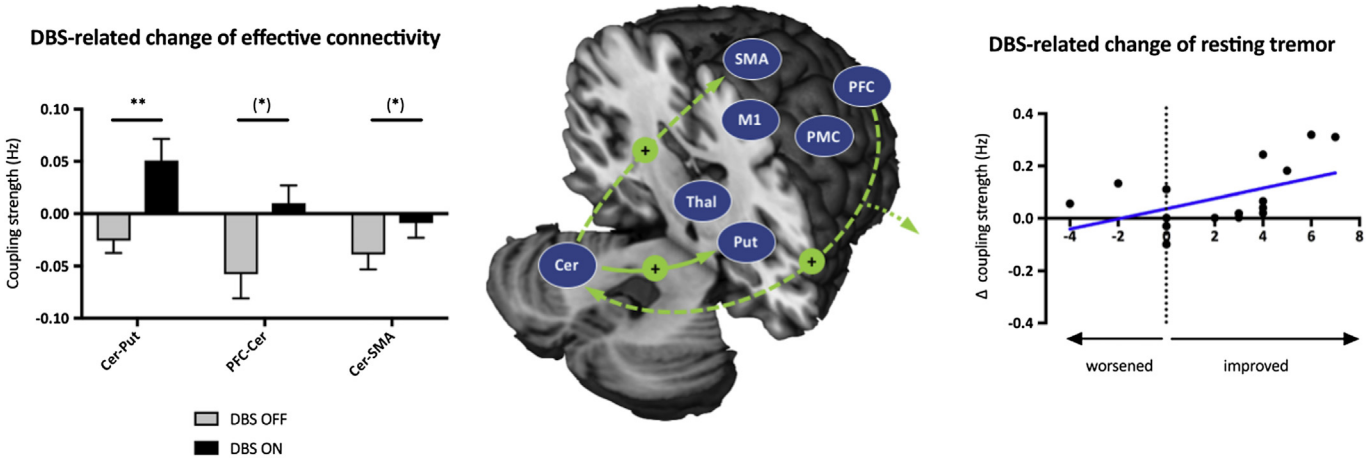

Fig. 2. DBS-related changes of effective connectivity in the right hemisphere. STN DBS resulted in an increased coupling between the cerebellum and putamen (solid line). Cerebello-SMA output and PFC-cerebellar connectivity were also increased on an exploratory level (dotted line). The quantitative changes in effective connectivity are plotted on the left side. The diagram on the right side demonstrates that resting tremor improved with increasing coupling between PFC and cerebellum. Bars are presented as mean ± SEM. ** p < 0.01, * p < 0.05, () uncorrected for multiple comparisons.

trend level was observed from right cerebellum to left PFC (p = 0.021), SMA (p = 0.048), putamen (p = 0.023) and M1 (p = 0.034), with mean values lower than zero, as well as from the left cerebellum to right putamen and from M1 to PMC in both directions (p = 0.016/0.049) with mean values greater than zero. Please note that these changes did not survive p-value correction for multiple comparisons. Details are shown in eTable 3 and Fig. 2.

3.4. Specific actions of DBS (DBS on vs. OFF)

Active STN DBS resulted in stronger coupling from left cerebellum to right putamen (p = 0.00118, Fig. 2, eTable 3). Effective connectivity also tended to increase from right PFC to left cerebellum (p = 0.021), as well as from left cerebellum to right SMA (p = 0.043) (Fig. 2, eTable 3). Self-connections tended to increase as a function of DBS in the left PFC, PMC, SMA, M1, thalamus and left cerebellum (all p < 0.05, Fig. 3, eTable 4).

To check to which degree the changes in effective connectivity can predict the clinical outcome of DBS treatment, coupling strength from PFC to the cerebellum was correlated with the DBS-related change of the resting tremor subscore. Indeed, patients with stronger coupling between PFC and cerebellum showed a higher degree of resting tremor improvement (r = 0.54, p = 0.031, Fig. 2). No such changes in resting tremor severity or total MDS-UPDRS-III scores were observed for the other significant connections.

4. Discussion

Investigating the mechanisms of DBS in movement disorders including PD contributes not only to a better understanding of DBS-related changes in neural networks, but also provides an avenue for gaining insights into the underlying disease. Here, we performed resting state fMRI in medicated PD patients in whom STN DBS was previously established and used effective connectivity in a pre-specified model of the motor network to unravel neural connectivity changes as a result of DBS. Active STN DBS resulted in various changes in network connectivity that collectively argue for an interaction of prefronto-cerebellar, striato-thalamic, intracerebellar, and cerebello-striatal circuits. These complex interactions add to previous evidence of an increased connectivity between cortex and both, thalamus and cerebellum due to

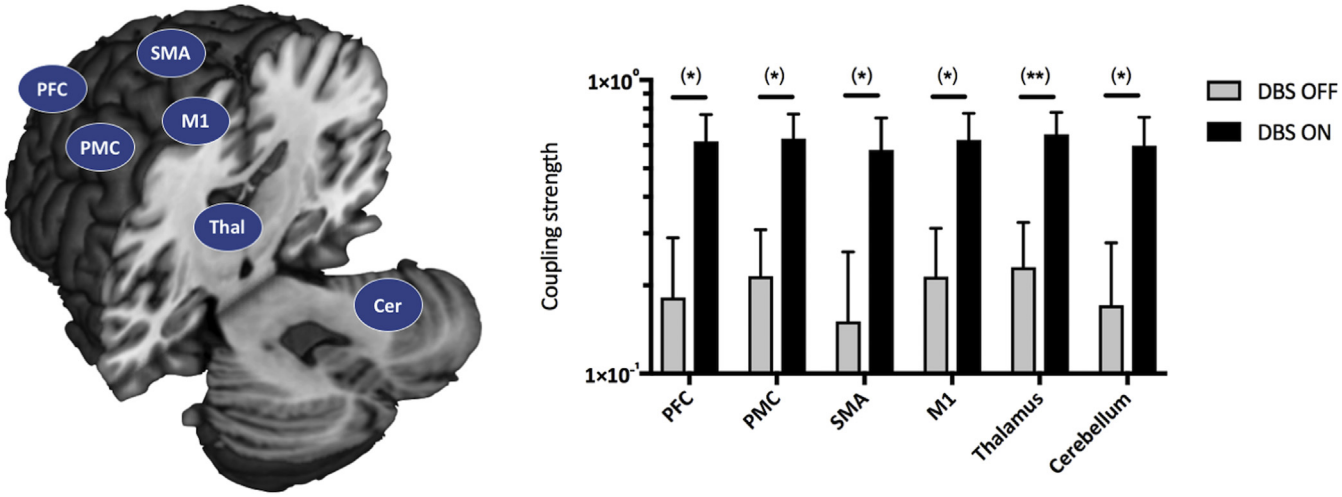

Fig. 3. DBS-related changes on the 'within region' ROI connectivity. The self-connections of the left PFC, PMC, SMA, M1, thalamus and right cerebellum clearly increases when the neurostimulator is switched on (DBS ON vs. DBS OFF). Bars are presented as mean ± SEM. ** p < 0.01, * p < 0.05, () uncorrected for multiple comparisons.

STN DBS [3]. Our study additionally corroborates previous functional studies showing changes of both, the cortico-basal ganglia and the cerebello-thalamic pathway [9–12]. It may help to better understand the magnitude of interactions between the basal-ganglia-thalamo-cortical and the cerebello-thalamo-cortical circuits and changes in those interactions as a result of STN DBS. Moreover, our results argue for a direct interaction between both circuits deemed to successfully implement goal-directed actions. These findings challenge the concept of two distinct pathways that modulate thalamo-cortical output in isolation. Given the direct structural connections between basal ganglia and cerebellum, these two systems should be understood as acting in close coordination, both in the healthy brain and in the context of movement disorders.

4.1. Basal ganglia-cerebellar crosstalk

The traditional concept of basal ganglia and cerebellar loops stipulates an indirect link between both circuits due to converging projections to distinct thalamic nuclei, and an interaction between striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways only on the neocortical level. This view has been challenged by the evidence of direct anatomical connections between basal ganglia and cerebellum in animals [13,14] and humans [6]. Transneuronal transport of Rabies viruses demonstrated disynaptic pathways between the dentate nucleus and the striatum [14], as well as the STN and cerebellar cortex [13] in brains of Macaque monkeys. The connections were shown to be dense and to affect both, motor and non-motor domains of the basal ganglia and the corresponding regions in the cerebellum. Recently, the presence of connections between STN and cerebellar cortex was confirmed in humans using DTI [5,6]. Connections were also found between the dentate nucleus and both, the substantia nigra and pallidum, highlighting that reciprocal connections between both circuits exist and that cerebellar output may have a direct impact on basal ganglia functions and operations. In addition, recent fMRI studies using DCM in healthy subjects demonstrated a relationship between increased coupling of the putamen and the cerebellum with M1 and movement speed [15] and striato-cerebellar interactions during encoding of a motor sequence task [16]. The close interaction of the cortico-basal ganglia and the cerebello-thalamic pathway is furthermore supported by the observation that patients with essential tremor and thalamic DBS had more beneficial DBS outcome when a specific cluster within the cerebello-thalamo-cortical tract was targeted [17]. Moreover, patients following thalamotomy showed an increased coupling between the frontal eye field and the cerebellum [18].

With regard to PD, functional connectivity of the cerebellum with the striatum is reported to be increased in drug-naïve PD patients or medicated patients during the OFF state [19,20], although unchanged connectivity was also seen in comparison to healthy controls [21]. L-dopa exposure reduced striato-cerebellar connectivity to levels which were comparable with healthy controls [20] or resulted even in decreased connectivity [22]. The degree of connectivity between the posterior putamen and the cerebellum was strongly associated with motor performance [20,23], independent of whether L-dopa was given or not [20]. These findings suggest that the increased coupling between striatum and cerebellum during the OFF state represents a compensatory mechanism that counteracts dopaminergic depletion in PD. In our study, we were able to show that the connectivity between cerebellum and striatum was strengthened as a function of STN DBS. Using DCM, we were furthermore able to demonstrate a causal relationship, namely, that the cerebellum exerted an influence on the striatum. Increased cerebellar output due to DBS could either represent a normalization of cerebellar connectivity with re-connection of a functionally 'disconnected' cerebellum or a distinct effect of DBS that goes beyond restoration of a more physiological state in a PD-diseased brain. As the patients were medically treated during the study it cannot be concluded that the findings are specific for DBS as the medication effect may have the same direction but to a smaller degree. Further, given the lack of a control group, we were not able to show differences in cerebellar-striatal connectivity across PD patients and controls. In addition to the cerebellar involvement as shown here, DBS also modulates the connection between cortex and basal ganglia including the direct and indirect pathway as well as the hyperdirect, cortico-subthalamic projection [12]. In this previous resting state fMRI study, DCM was used with the difference that different a priori models were compared and the cerebellum was not considered.

4.2. Cerebellar pathology in Parkinson's disease

The source of cerebellar dysfunction and altered intrinsic connectivity in PD remains elusive. Recently, anatomical alterations including gray matter loss in motor and cognitive territories have been described [24,25] that correlated with cerebellar-cortical functional connectivity [24] and seemed to be more pronounced in patients presenting with tremor [26]. In keeping with a neurodegenerative aspect, synuclein pathology was found in the cerebellum of PD brains [27], and loss of cerebellar neurons and synapses was identified in a rat model of PD [28]. Another source of impairment may be due to a direct influence of the dysregulated basal ganglia circuit given the evidence of anatomical connections between striatum, subthalamic nucleus and cerebellum [13,14]. Dopamine deficiency of the striatum could thus indirectly affect cerebellar function and give rise to abnormal network activity that can be restored by the administration of dopaminergic drugs [10–12]. Accordingly, the modulatory influence of the STN on intracerebellar connectivity is thought to be lost in PD as compared to controls [24], and the degree of nigral degeneration correlates with persistent hyperactivation of Purkinje cells [29]. Dopamine deficiency may also have a direct impact on cerebellar function as the cerebellum receives dopaminergic projections from the ventral tegmental area and substantia nigra pars compacta and expresses dopamine D1-D3 receptors [30,31]. Lastly, altered cerebellar activity could correspond to a compensatory mechanism that aims to counteract the progressive dysfunction of the striato-pallido-thalamo-cortical circuit in PD [32].

4.3. Strengths and limitations

Our study benefits from a high number of participants with a wide range of age, disease duration and clinical symptoms. Further, the clinical assessment was highly standardized and the evaluation of motor symptoms was done in a blinded manner. The loss-of-signal artefacts prevented us, however, to use a whole brain approach to independently confirm our results. Further, the patients were scanned while they were still taking their dopaminergic medication. This could have mask actions of DBS similar to DRT, i.e. an influence on the mesial premotor loop and interactions between the striatum and the prefrontal and premotor cortex.

5. Conclusions

Our results highlight distributed effects of STN DBS on Parkinsonian resting motor network activity. DBS-related improvement of Parkinsonian signs, i.e. resting tremor, seemed to be driven by a prefronto-cerebellar network bypassing the striatum. DBS-related modulation of cerebellar activity resulted in an implementation of DBS effects via a cerebello-striatal loop. Activation of the mesial premotor loop may thus be secondary due to the primary modulation of cerebellar networks. Our results strengthen the notion that the striato-pallido-thalamic and the cerebello-thalamic loop are strongly interconnected which is corroborated by animal studies that show direct disynaptic connection between both, STN and putamen and cerebellum.

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The authors do not have any conflict of interest.

Conflicts of interest

The authors report no competing interests.

Author's contribution

1. Research project: A. Conception, B. Organization, C. Execution.
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Henrike Hanssen 1A, 1B, 1C, 2A, 2B, 3B
Julia Steinhardt 1C, 2A, 2B, 2C, 3A
Alexander Münchau 1C, 2C, 3B
Arkan Al-Zubaidi 2A, 2C, 3B
Marcus Heldmann 1A, 1C, 2A, 2C, 3B
Elinor Tzvi 2A, 2C, 3B
Peter Schramm 1B, 2C, 3B
Alexander Neumann 1B, 2C, 3B
Dirk Rasche 1B, 2C, 3B
Assel Saryyeva 1B, 2C, 3B
Jürgen Voges 1B, 2C, 3B
Imke Galazky 1B, 2C, 3B
Lars Büntjen 1B, 2C, 3B
Hans-Jochen Heinze 1B, 2C, 3B
Joachim K. Krauss 1B, 2C, 3B
Volker Tronnier 1B, 2C, 3B
Thomas Münte 1B, 2C, 3B
Norbert Brüggemann 1A, 1B, 1C, 2A, 2B, 3A

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.003.

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