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Structural and functional correlates of subthalamic deep brain stimulation-induced apathy in Parkinson's disease

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ABSTRACT

Background: Notwithstanding the large improvement in motor function in Parkinson's disease (PD) patients treated with deep brain stimulation (DBS), apathy may increase. Postoperative apathy cannot always be related to a dose reduction of dopaminergic medication and stimulation itself may play a role.
Objective: We studied whether apathy in DBS-treated PD patients could be a stimulation effect.
Methods: In 26 PD patients we acquired apathy scores before and >6 months after DBS of the subthalamic nucleus (STN). Magnetoencephalography recordings (ON and OFF stimulation) were performed ≥6 months after DBS placement. Change in apathy severity was correlated with (i) improvement in motor function and dose reduction of dopaminergic medication, (ii) stimulation location (merged MRI and CT-scans) and (iii) stimulation-related changes in functional connectivity of brain regions that have an alleged role in apathy.
Results: Average apathy severity significantly increased after DBS ($p < 0.001$) and the number of patients considered apathetic increased from two to nine. Change in apathy severity did not correlate with improvement in motor function or dose reduction of dopaminergic medication. For the left hemisphere, increase in apathy was associated with a more dorsolateral stimulation location ($p = 0.010$). The increase in apathy severity correlated with a decrease in alpha1 functional connectivity of the dorsolateral prefrontal cortex ($p = 0.006$), but not with changes of the medial orbitofrontal or the anterior cingulate cortex.
Conclusions: The present observations suggest that apathy after STN-DBS is not necessarily related to dose reductions of dopaminergic medication, but may be an effect of the stimulation itself. This highlights the importance of determining optimal DBS settings based on both motor and non-motor symptoms.

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Abbreviations

STN	subthalamic nucleus
dlPFC	dorsolateral prefrontal cortex
antCC	anterior cingulate cortex
medORB	medial orbitofrontal cortex
HPI	head position indicator
MDS-UPDRS-III	Movement Disorders Society Unified Parkinson's Disease Rating Scale (motor part)
tSSS	temporal extension of signal space separation
AAL	automated anatomical labelling
ROI	region of interest
cAEC	corrected amplitude envelope correlation
ANT	advanced normalization tools
MNI	Montreal Neurological Institute
LEDD	levodopa equivalent daily dose
NMSS	non motor symptom scale

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for Parkinson's disease (PD) patients with disabling fluctuations in motor symptoms [1–3]. Despite excellent effects on motor symptoms, emotional, behavioural and cognitive disturbances associated with STN-DBS have been reported [4–7]. Apathy is a frequently observed symptom after STN-DBS in PD (prevalence ~25%) and is associated with a decrease in the quality of life [8–11].

Apathy can be defined by a lack of motivation, diminished goal-directed behaviour and decreased emotional involvement [12]. Apathy after DBS has been attributed to mesolimbic denervation [10] and dose reductions in dopaminergic medication [13], although a consistent correlation with the latter has not been found [10,14,15]. The results of a recent animal study suggest that impaired motivation may be an effect of the brain stimulation itself [16]. Moreover, in DBS-treated PD patients apathy scores correlated with the position of active DBS contacts [4,17,18], as well as with DBS-related changes in cortical glucose metabolism [15]. However, a study in which the functional effects of deep brain stimulation (DBS-ON versus DBS-OFF) are related to apathy scores is currently lacking.

In the current study, we selected three bilateral brain regions that have an alleged role in apathy: the dorsolateral prefrontal cortex (dlPFC), the anterior cingulate cortex (antCC) and the medial orbitofrontal cortex (medORB). Functional changes in the antCC and the medORB appear to be related to emotional-affective apathy [10,19], whereas functional changes in the dlPFC are associated with cognitive apathy (mostly via executive cognitive dysfunction) [20,21].

In a previous magnetoencephalography (MEG) study, we demonstrated that DBS has widespread effects on oscillatory brain activity and functional connectivity and that changes in the latter correlate with DBS-related improvement in motor scores [22]. Based on this observed correlation between functional connectivity changes and motor effects, we decided to study apathy-related functional connectivity changes. Specifically, in this MEG study using a DBS ON-OFF setup, we aimed to determine whether change in pre-to-post-DBS apathy score correlated with (i) the dose reduction of dopaminergic medication, (ii) the stimulation location and (iii) changes in functional connectivity of the three pre-selected bilateral cortical brain regions. In line with a previous case-report from our group [4], we hypothesized that postoperative apathy can be an effect of stimulation of the ventral (limbic) STN, affecting brain regions involved in emotional-affective processing.

Materials and methods

Patients

A total of 33 PD patients who had undergone bilateral STN-DBS implantation between 2016 and 2018 at Amsterdam UMC, location AMC, participated in this study (after consecutively approaching eligible patients) and underwent MEG recordings at least 6 months after DBS electrode placement (range 6–17 months; median 7 months). Inclusion and exclusion criteria were previously described [22]. In the context of standard clinical care, the stimulation parameters were individually determined for optimal therapeutic efficacy (regarding motor effects) and monopolar stimulation was applied. All patients were implanted with a Boston Scientific Vercise directional stimulation system (Valencia, CA, USA). Of the 33 PD patients included in this study, five patients were excluded from further analysis due to excessive noise in more than ~13 MEG channels during the ON-stimulation recording, which prevented the use of the temporal extension of Signal Space Separation (tSSS; see MEG data preprocessing). One patient was excluded because of missing clinical data (pre-DBS apathy score) and one patient as a consequence of excessive tremor during the OFF-stimulation recording. This led to a final study sample of 26 patients. The research protocol describing the MEG, psychiatric and neuropsychological data collection was approved by the medical ethical committee of Amsterdam UMC, location VUmc. Ethics review criteria conformed to the Helsinki declaration. All patients gave written informed consent before participation.

Data acquisition

Study visits took place after an overnight withdrawal of dopaminergic medication (practically defined off-state). MEG data were recorded using a 306-channel whole-head system (Elekta Neuromag Oy, Helsinki, Finland) in an eyes-closed resting-state condition, with a sample rate of 1250 Hz and online anti-aliasing (410 Hz) and high-pass (0.1 Hz) filters. The head position relative to the MEG sensors was recorded continuously using the signals from five head position indicator (HPI) coils. For each subject, the total MEG recording time was 55 min, consisting of 11 trials of 5 min. In each trial different DBS stimulation settings were used. The first recording was during bilateral stimulation with the standard DBS-settings of the individual patient (DBS-ON). Subsequently, nine recordings took place in randomized order, eight of which consisted of unilateral stimulation using a single electrode contact (data not presented) and one recording during DBS-OFF. The eleventh and last recording was, again, performed during stimulation using the standard DBS-settings of the individual patient (DBS-ON2; data not presented). Further details on the MEG acquisition can be found in Boon et al. [22].

Anatomical images of the head were obtained in the context of standard pre-operative imaging up to 6 months before surgery using a 3T magnetic resonance imaging (MRI) scanner (Philips Ingenia, Best, the Netherlands) and a 16-channel receiver coil. We acquired post-gadolinium volumetric T1-weighted scans (TR 8.8–9.1 ms; TE 4.0–4.2 ms; flip angle (FA) 8°; field of view (FOV) 256 × 256 mm; slice thickness 1.0 mm; 1.0 × 1.0 mm; 169 slices) and T2-weighted scans using a slab covering the brain from the superior cerebellar peduncle to the top of the lateral ventricles (TR 4000.0–5233.2 ms; TE 80.0–87.7 ms; FA 90°; FOV 432 × 432/560 × 560 mm; slice thickness 2 mm; 0.5 × 0.5 mm; 46–80 slices). For 21 patients, on the postoperative day, a multidetector CT-scan

of the head was acquired (Philips Medical System, Best, The Netherlands; slice thickness 1–2 mm; FOV 512 × 512 mm; 56–169 slices). For the five remaining participants, an intra-operative CT-scan was acquired using a Medtronic O-arm O2 (high definition mode; 20 cm FOV; 192 slices; 120 kV; 150 mAs; Medtronic Inc., Minneapolis, MN, USA).

Apathy scores reflecting the last 4 weeks [23] were obtained from the patient (helped by the patient's relative or caregiver, if possible) using the patient-based version of the Starkstein apathy scale [24], both at baseline (several days before DBS placement) and after DBS placement (several days before the study visit) with patients on medication and ON stimulation in the standard settings of the individual patient. This validated apathy scale ranges from 0 to 42 and patients with an apathy score ≥14 were considered apathetic (in line with [24]). Hamilton Depression Scores and Hamilton Anxiety Scores [25] were also obtained at baseline and during the study visit. Neuropsychological tests of executive functioning (Trail Making Test A and B; Stroop Test 1–3) were performed before DBS placement and after six months of DBS therapy by a licensed clinical neuropsychologist on medication and ON stimulation. Motor function was scored by trained nurses using the motor part of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) both at baseline and, approximately six months after DBS placement, during DBS-ON and DBS-OFF, off medication.

Data processing

MEG data

MEG channels that were malfunctioning or noisy were ignored after visual inspection of the data. Thereafter, the temporal extension of Signal Space Separation (tSSS [26,27]) in MaxFilter software (Elekta Neuromag Oy, version 2.2.15) was applied with a subspace correlation-limit of 0.8 to suppress the strong magnetic artefacts [22]. MEG data of each patient were co-registered to their T1 MRIs using a surface-matching procedure, with an estimated accuracy of 4 mm [28]. A single sphere was fitted to the outline of the scalp as obtained from the co-registered MRI, which was used as a volume conductor model for the beamformer approach described below.

The automated anatomical labelling (AAL) atlas was used to label the voxels in 78 cortical and 12 subcortical regions of interest (ROIs) [29,30]. We used each ROI's centroid as representative for that ROI [31]. Subsequently, an atlas-based beamforming approach [32] was used to project broad-band (0.5–48 Hz) filtered sensor signals to these centroid voxels, resulting in broad-band time series for each of the 90 ROIs (see Hillebrand et al. [33] for details). The source-reconstructed MEG data were visually inspected (by LIB) for tremor-, motion- and stimulation-related artefacts and drowsiness. The MEG data were cut into ~22 epochs per (5 min) recording. Epochs were then downsampled from 1250 Hz to 313 Hz (4x) and contained 4096 samples (13.12 s). For each recording, the 50% epochs with the lowest peak frequency (estimated within the 4–13 Hz frequency range using automatic quantification) were discarded in order to minimize the risk of including episodes with drowsiness. For each condition, 10 epochs with the best quality (visual selection based on the absence of artefacts and drowsiness) were selected for further analysis. Spectral and functional connectivity analyses were performed using BrainWave (version 0.9.152.12.26; CJS, available from https://home.kpn.nl/stam7883/brainwave.html). For frequency band-specific analyses, epochs were filtered in five frequency bands (delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz) and beta (13–30 Hz), using a Fast Fourier Transform. The gamma band was not analysed as we had observed stimulation-related artefact peaks in this band in a previous study [22]. For each epoch, frequency band-specific functional connectivity was estimated using the corrected Amplitude Envelope Correlation (cAEC), an implementation of the AEC [34] corrected for volume conduction/field spread, using a symmetric (pairwise) orthogonalisation procedure [34,35]. The cAEC was calculated for all possible pairs of ROIs, leading to a 90x90 adjacency matrix.

Imaging data

To determine the stimulation locations after placement of the DBS system, the electrode trajectories were reconstructed using Lead-DBS (Lead-DBS, version 2.2; http://www.lead-dbs.org [36]). To this end, the post- or intra-operative CT-scan was co-registered to the pre-operative MR image using a two-stage (rigid and affine) registration as implemented in Advanced Normalization Tools (ANT [37]). In three cases in which only an intra-operative CT-scan was available, the co-registration failed using ANT. In these cases, co-registration was successfully performed using FSL FLIRT. Co-registration was followed by a semiautomatic localization of the electrode positions on the CT data in patient space.

The electrode stimulation positions were then transformed from patient space to Montreal Neurological Institute space (MNI ICBM 2009b NLIN ASYM space) to facilitate group-level analyses. The DISTAL Minimal atlas [38] was used as outline of the STN. Next, the midpoints of stimulation positions were projected on a vector running through the longitudinal axis of the STN (from ventromedial to dorsolateral), leading to one scalar value to indicate each stimulation position, where negative values indicated more ventromedial stimulation positions.

Statistical analysis

We tested the differences in proportion of apathetic patients (pre-versus post-DBS) using a chi-square test, change in apathy score, MDS-UPDRS-III score, and levodopa equivalent daily dose (LEDD)-score using paired *t*-tests (all pre-DBS versus post-DBS). Correlations between the change in apathy score and change in LEDD, change in MDS-UPDRS-III score, stimulation positions, change in depression score, change in anxiety score, and change in executive functioning (difference in T-scores (mean of 50 ± 10), normed by age and education) were estimated using Pearson correlations. Next, in order to explore the possibility of confounding variables explaining change in apathy scores, the abovementioned variables were combined into a single hierarchical linear regression model using a backward elimination method (in which change in apathy score functioned as dependent variable).

For each patient, stimulation condition and frequency band separately, functional connectivity matrices were averaged over 10 epochs. Next, we obtained the average functional connectivity between one ROI and the rest of the brain by averaging functional connectivity values over each column of the matrix. We then calculated the change in functional connectivity (DBS-ON versus DBS-OFF) for three pre-selected cortical brain regions, the dlPFC (AAL-region: middle frontal gyrus, as previously used by Pretus and co-workers [39]), antCC and medORB, and correlated these values with the change in pre-to-post-DBS apathy score. As the functional connectivity data was not normally distributed (despite attempts to transform the data) this was done using Spearman correlations.

All analyses were performed using the SPSS Statistics 20.0 software package (IBM Corporation, New York, USA), using a significance level of 0.05 (two-tailed). Bonferroni correction was applied for the number of seed regions in the Spearman correlations between change in apathy score and change in functional connectivity. Due to the exploratory nature of the study, we did not correct for the number of frequency bands used for the functional connectivity estimates.

Data availability statement

The data and codes used in this study are available from the corresponding author, upon reasonable request.

Results

Patients

26 DBS-treated PD patients, whose characteristics are summarized in Table 1, were included in this study. DBS significantly improved off-dopamine motor function with a mean change of 51.2% in MDS-UPDRS-III score ($t(25)$=9.21; $p < 0.001$) and the LEDD was significantly lowered after DBS placement ($t(25)$=8.01; $p < 0.001$; see Table 1). The mean number of excluded MEG channels before running tSSS was 9 for DBS-ON recordings (range: 4–13) and 6 for DBS-OFF recordings (range: 2–12).

Apathy

In 24 of the 26 PD patients apathy severity increased after DBS and the number of apathetic patients increased from 2 pre-DBS to 9 post-DBS (X^2 (1,26) = 4.093, $p = 0.043$). Apathy severity scores were significantly higher during follow-up than at baseline (pre-DBS versus post-DBS; $t(25)$=6.47, $p < 0.001$). Increase in apathy severity did not correlate with decrease in LEDD, neither taking all dopaminergic medication into account ($p = 0.157$; SupplementaryFig A.1), nor dopamine agonists alone ($p = 0.503$; Supplementary Fig A.2). Change in apathy severity did not correlate with improvement in motor function (MDS-UPDRS-III; $p = 0.518$; Supplementary Fig A.3). Change in apathy severity did also not correlate with change in depression severity ($p = 0.443$; Supplementary Fig B.1), change in anxiety severity ($p = 0.710$; Supplementary Fig B.2), nor with change in executive functioning ($p = 0.693$; Supplementary Fig B.3). Lastly, as a recent paper shows that motor asymmetry can predict emotional outcome of STN-DBS [40], we compared the change in apathy score for patients with left- and right-sided onset of motor symptoms, but there was not difference ($t(25) = 0.68$, $p = 0.501$).

Apathy and DBS localization

In Fig. 1A, the midpoints of the stimulation positions of all active contact points are depicted in standard MNI space relative to an atlas representation of the STN. Increases in apathy scores are color-coded, ranging from no increase (green/yellow) to a strong increase (dark red) in apathy severity. There was a significant correlation between a more dorsolateral stimulation position (along a vector) and increase in apathy severity post-DBS for the left side ($p = 0.010$), but not for the right side ($p = 0.491$; Fig. 1B). In contrast, there was no relationship between stimulation position (along the same vector) and the degree of improvement in total motor score (UPDRS-III; Supplementary Fig E).

Next, we performed a hierarchical linear regression model using a backward elimination method to study the relationship between stimulation location and change in apathy score, including the following covariates: pre-to post-operative change in executive functioning, depression score, anxiety score, LEDD total, LEDD of dopamine agonist, and motor function. For the left side this resulted in the following model: $R^2 = 0.465$; change in depression score, β(standardized) = 0.587, $p = 0.039$; stimulation position, β(standardized) = 0.727, $p = 0.015$. For the right side no statistically significant model could be fitted.

Apathy and functional connectivity

The three *a priori* selected cortical brain regions are depicted in Fig. 2A. The centroid voxel was taken as representative for each individual brain region, and its time-series was used for the estimation of functional connectivity. A significant negative correlation was found between the pre-to-post-DBS change in apathy score and the stimulation-related change in functional connectivity of the bilateral dlPFC with the rest of the brain (alpha1, $p = 0.006$; alpha level was adjusted to 0.05/3 to correct for multiple comparisons as three seed regions were studied; Fig. 2B). A reduction in stimulation-related functional connectivity was related to an increase in post-operative apathy. In contrast, no significant correlations were found for the medORB (alpha1, p=0.298), as well as for the antCC (alpha1, p=0.163). Correlations with functional connectivity in the other frequency bands can be found in Table 2.

As a post-hoc visualization, both for patients with weaker ($\leq$5) and patients with stronger (>5) increase in apathy severity (based on a median split of the data) we showed the distribution of stimulation-related changes in alpha1 functional connectivity of individual connections linked to the dlPFC (Fig. 3). In line with the correlation previously shown, we observed a stimulation-related lowering in functional connectivity in patients with a stronger increase in apathy severity. Furthermore, stimulation-related functional connectivity changes in both groups mostly involved connections with frontal brain regions. Functional connectivity matrices and functional connectivity of the three seed regions (alpha1; both DBS-OFF and DBS-ON) averaged over all subjects are provided in Supplementary Fig. C and D.

Discussion

In this study, we investigated apathy after STN-DBS treatment in patients with PD, in particular the relationship between DBS-related increase in apathy severity and stimulation location, as well as the association between DBS-related increase in apathy severity and stimulation-induced changes in functional connectivity. Our results confirm the notion that apathy severity increases after STN-DBS in PD and that the stimulation itself may play a role in this increase [15,17,18]. The pre-to-post-DBS increase in apathy severity was associated with a more dorsolateral position of the stimulation for the left hemisphere, as well as a stimulation-related reduction in alpha1 band functional connectivity of the bilateral dlPFC with the rest of the brain. The latter could be interpreted as a stimulation-related loss in connectedness (functional communication) of this brain region with the rest of the brain in patients who became apathetic.

We found no significant correlation between the increase in pre-to-post-DBS apathy score and the degree of reduction of dopaminergic medication in the present study. Reintroduction of dopaminergic medication has previously been shown to improve post-operative apathy [13] suggesting a causal role for dopamine withdrawal in the occurrence of apathy. However, a recent animal study has demonstrated that impaired motivation caused by deep brain stimulation itself can also be reversed by a dopamine agonist [16]. We acknowledge that post-operative apathy is a complex and multifactorial phenomenon in which adjustments of dosages of dopaminergic medication, degeneration of dopaminergic neurons [41], as well as the stimulation itself may have a role.

The STN occupies a central role in several functionally different basal ganglia circuits and comprises specific motor (dorsolateral), associative (central) and limbic (ventromedial) regions [42,43]. The influence of the stimulation location in or around the STN on the occurrence of post-DBS apathy is as yet unclear. Two case-studies have described the induction of apathy by stimulation of the zona

Table 1
Patient characteristics.

Patient	Age (years)	Sex	Disease duration (years)	Side disease onset	Stimulation parameters (stimulation side; contact; intensity (mA))	Pulse width and frequency of stimulation	LEDD pre-DBS (mg/day)	LEDD study visit (post-DBS (mg/day))	Motor UPDRS (III)			Starkstein apathy score	
									Pre-DBS Med off	Med off/ DBS-OFF	Med off/ DBS-ON	Pre-DBS	Post-DBS (DBS-ON)
1	38	M	8	Right	L; DM; 2.9 R; VM; 3.4	60 μs 179 Hz	Total: 1644 DA: 320	Total: 996 DA: 80	73	54	31	3	8
2	63	F	5	Right	L; DM; 1.7 R; DM; 1.7	60 μs 130 Hz	Total: 495 DA: 150	Total: 567 DA: 315	43	16	11	2	3
3	65	F	27	Left	L; VM; 2.7 R; DM; 1.5	60 μs 130 Hz	Total: 500 DA: -	Total: 400 DA: -	33	20	19	24	25
4	49	F	10	Left	L; Dors; 1.9 R; Dors; 2.5	60 μs 130 Hz	Total: 797 DA: 240	Total: 536 DA: 120	35	37	22	12	20
5	69	M	12	Right	L; DM; 2.1 R; DM; 2.1	60 μs 130 Hz	Total: 1830 DA: 360	Total: 150 DA: -	56	24	14	12	18
6	60	M	8	Left	L; DM; 3.2 R; DM; 1.3	60 μs 179 Hz	Total: 1200 DA: 75	Total: 300 DA: -	57	65	38	4	19
7	53	M	11	Right	L; DM; 2.9 R; DM; 1.9	60 μs 130 Hz	Total: 1567 DA: 240	Total: 1043 DA: 160	60	44	30	2	6
8	66	F	8	Left	L; VM; 2.2 R; DM; 1.8	60 μs 130 Hz	Total: 1226 DA: 160	Total: 753 DA: 120	47	37	33	6	5
9	45	M	5	Left	L; Dors; 1.7 R; DM; 1.7	60 μs 130 Hz	Total: 1410 DA: -	Total: 283 DA: -	50	80	44	14	19
10	70	F	25	Left	L; DM; 2.1 R; DM; 2.4	60 μs 130 Hz	Total: 1590 DA: 450	Total: 555 DA: 37.5	46	33	15	4	12
11	66	M	10	Left	L; DM; 2.5 R; DM; 1.8	60 μs 149 Hz	Total: 750 DA: -	Total: 575 DA: -	38	54	27	6	12
12	55	M	8	Right	L; DM; 2.7 R; DM; 2.6	60 μs 130 Hz	Total: 950 DA: -	Total: 775 DA: -	42	31	15	5	15
13	57	M	11	Left	L; VM; 1.6 R; VM; 1.6	60 μs 130 Hz	Total: 1134 DA: 320	Total: 606 DA: 80	38	21	7	0	12
14	61	M	7	Left	L; VM; 1.5 R; VM; 2.1	60 μs 130 Hz	Total: 1000 DA: -	Total: 375 DA: -	30	27	11	3	16
15	60	M	14	Left	L; DM; 2.0 R; VM; 2.5	60 μs 130 Hz	Total: 1073 DA: -	Total: 425 DA: -	55	27	7	6	14
16	57	M	12	Left	L; VM; 3.1 R; VM; 2.3	60 μs 130 Hz	Total: 1380 DA: 480	Total: 720 DA: 120	80	52	26	4	9
17	61	M	8	Left	L; DM; 1.8 R; DM; 2.3	60 μs 130 Hz	Total: 1726 DA: 360	Total: 946 DA: 80	56	52	21	3	11
18	56	M	12	Right	L; DM; 1.4 R; VM; 1.3	60 μs 130 Hz	Total: 2131 DA: 240	Total: 1245 DA: 45	45	20	10	5	6
19	58	M	16	Left	L; VM; 1.9 R; DM; 1.9	60 μs 130 Hz	Total: 2032 DA: 160	Total: 613 DA: 80	35	38	14	11	12
20	57	M	12	Left	L; VM; 3.0 R; VM; 3.2	60 μs 130 Hz	Total: 1170 DA: 150	Total: 533 DA: -	38	51	33	8	11
21	71	F	17	Right	L; VM; 1.8 R; VM; 1.7	60 μs 130 Hz	Total: 1940 DA: -	Total: 791 DA: -	56	59	42	3	9
22	57	F	14	Left	L; DM; 1.7 R; DM; 2.0	60 μs 130 Hz	Total: 1080 DA: 480	Total: 660 DA: 160	50	40	21	5	12
23	54	F	6	Left	L; DM; 2.2 R; DM; 2.4	60 μs 130 Hz	Total: 1600 DA: -	Total: 883 DA: -	71	69	44	6	4
24	55	M	12	Left	L; VM; 2.9 R; DM; 2.9	60 μs 130 Hz	Total: 1344 DA: -	Total: 679 DA: -	30	50	17	0	1
25	64	M	22	Left	L; DM; 3.7 R; DM; 3.2	60 μs 130 Hz	Total: 2100 DA: 150	Total: 780 DA: 150	59	59	39	13	27
26	48	M	6	Right	L; DM; 2.0 R; DM; 1.7	60 μs 130 Hz	Total: 990 DA: 320	Total: 110 DA: 80	14	14	12	5	10
Mean (SD)	58 (8)	M, n = 18; F, n = 8	12 (6)		L; 2.3 (0.61) R; 2.1 (0.58)		Total: 1369 (490)	Total: 627 (273)	47.6 (14.8)	41.3 (17.7)	23.2 (11.8)	6 (5)	12 (7)

mA, milliampère; μs, microseconds; LEDD, Levodopa Equivalent Daily Dose; DA, dopamine agonist; mg, milligrams; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale motor ratings; DBS, Deep Brain Stimulation; M/F, male/female; L/R, left/right; D/DM/VM, Dorsal/Dorsomedial/Ventromedial; Med, medication.

incerta [13,44], located dorsally from the STN, whereas another case study demonstrated that apathy resolved by switching from a ventrally located contact point to a more dorsal contact point [4]. By contrast, in one study cohort (analysed in two publications [17,18]), apathy scores (non-significantly) decreased in PD patients after STN-DBS placement. Above-average decreases in apathy scores were related to stimulation around the ventral border and the sensorimotor subregion of the STN and below-average decreases were related to stimulation dorsal to the STN [17,18]. A potential explanation for the fact that decreases rather than increases in

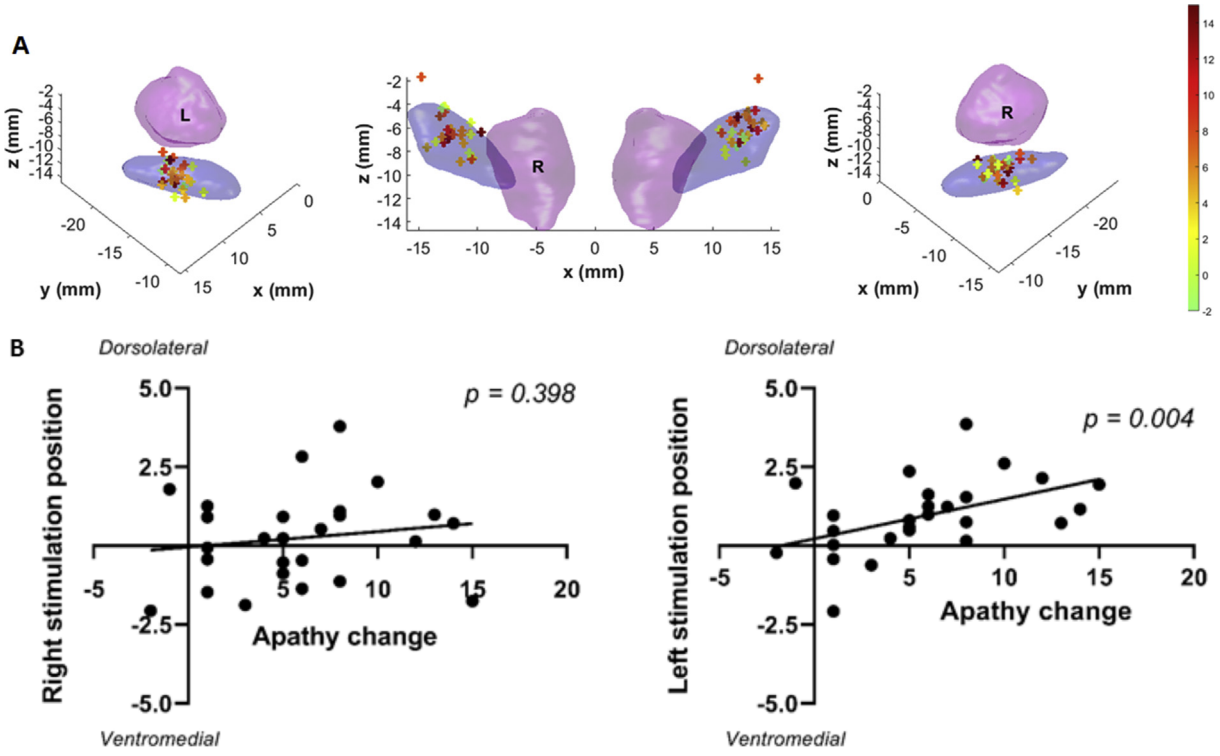

Fig. 1. Stimulation locations of contact points in relation to change in apathy severity
A) Stimulation locations in MNI-space (viewed from respectively dorsolateral right, anterior and dorsolateral left). The subthalamic nucleus (blue) and red nucleus (red) were added for reference purposes. Increases in apathy severity are color-coded, ranging from no increase (green/yellow) to strong increase (dark red).
MNI, Montreal Neurological Institute; R, right; L, left.
B) Stimulation locations were projected on a vector through the longitudinal axis of the STN, where negative values indicated more ventromedial stimulation positions. There was a significant correlation between stimulation position and increase in apathy severity for the left side ($r(24) = 0.498$, $p = 0.010$), but not for the right side ($r(24) = 0.141$, $p = 0.491$).

apathy severity were found in the latter study is that subscores related to apathy derived from the Non Motor Symptom Scale were used as a measure of apathy, which is not recommended for the assessment of apathy in PD [23].

We found a significant increase in apathy severity after STN-DBS. In addition, we observed a significant correlation between increase in pre-to-post DBS apathy score and a more dorsolateral stimulation location relative to the STN for the left hemisphere, but not for the right hemisphere. As the occurrence of apathy has previously not been related to laterality of DBS [45,46], we refrain from drawing any conclusions from this left-right difference. Despite the fact that dorsolateral stimulation positions in the motor part of the STN are considered as the optimal STN target resulting in the best clinical motor effects (and hence a stronger reduction in dopaminergic medication dose) [47,48], increased apathy severity was not associated with a stronger improvement of motor symptoms. In addition, we did not find a relation between stimulation position and the degree of improvement in motor score (Supplementary Fig E), contrasting with the results of the study by Bot and coworkers [48]. Our study differed in several aspects though, including the method of localizing the electrodes (patient versus standard space), method of quantifying the stimulation location (vector through the longitudinal axis of the STN versus Euclidian distance to the medial STN border), and the motor scores used (overall UPDRS-III versus unilateral motor score).

When combining our observations with those of previous studies [13,17,18,44], we conclude that, in contradiction with the previously proposed mechanism (and our own hypothesis) [4,49], stimulation in the ventral part of the STN (the limbic regions) does not necessarily induce apathy. Our findings even suggest that apathy may worsen by a stimulation location in proximity to the motor region of the STN. Moreover, the fact that increase in apathy severity did not correlate with improvement in motor symptoms leads us to conclude that finding an optimal stimulation location, striking a balance between the least apathy and the best motor response, seems feasible. Future longitudinal studies using a within-subject design in which the stimulation in case of post-DBS apathy is switched to an alternative (more ventral) contact point may shed further light on this matter. In addition, studies that take into account individual differences in the division of subregions using structural connectivity profiles of the STN (using high-resolution MRI techniques) could guide the search for an optimal stimulation position.

The fact that we found stimulation-related changes in functional connectivity of the dlPFC to be associated with the pre-to-post-DBS increase in apathy severity, suggests an (executive) cognitive substrate, rather than an emotional-affective type of apathy (which is more related to the antCC and medORB). However, recent findings by Irmen and coworkers suggest a structural link between DBS stimulation, the left prefrontal cortex and depressive symptoms [50]. Moreover, in our study increases in apathy severity were not associated with changes in executive functioning, whereas in the multiple regression model there was a relation between improvement in depression scores and better apathy scores after surgery (in the context of left-sided stimulation). It remains to be determined whether the occurrence of apathy after DBS has a cognitive or emotional-affective basis.

Our results on stimulation-related changes in functional connectivity were most outspoken for the alpha1 band (8–10 Hz). A direct functional loop of resting-state alpha band coherence has

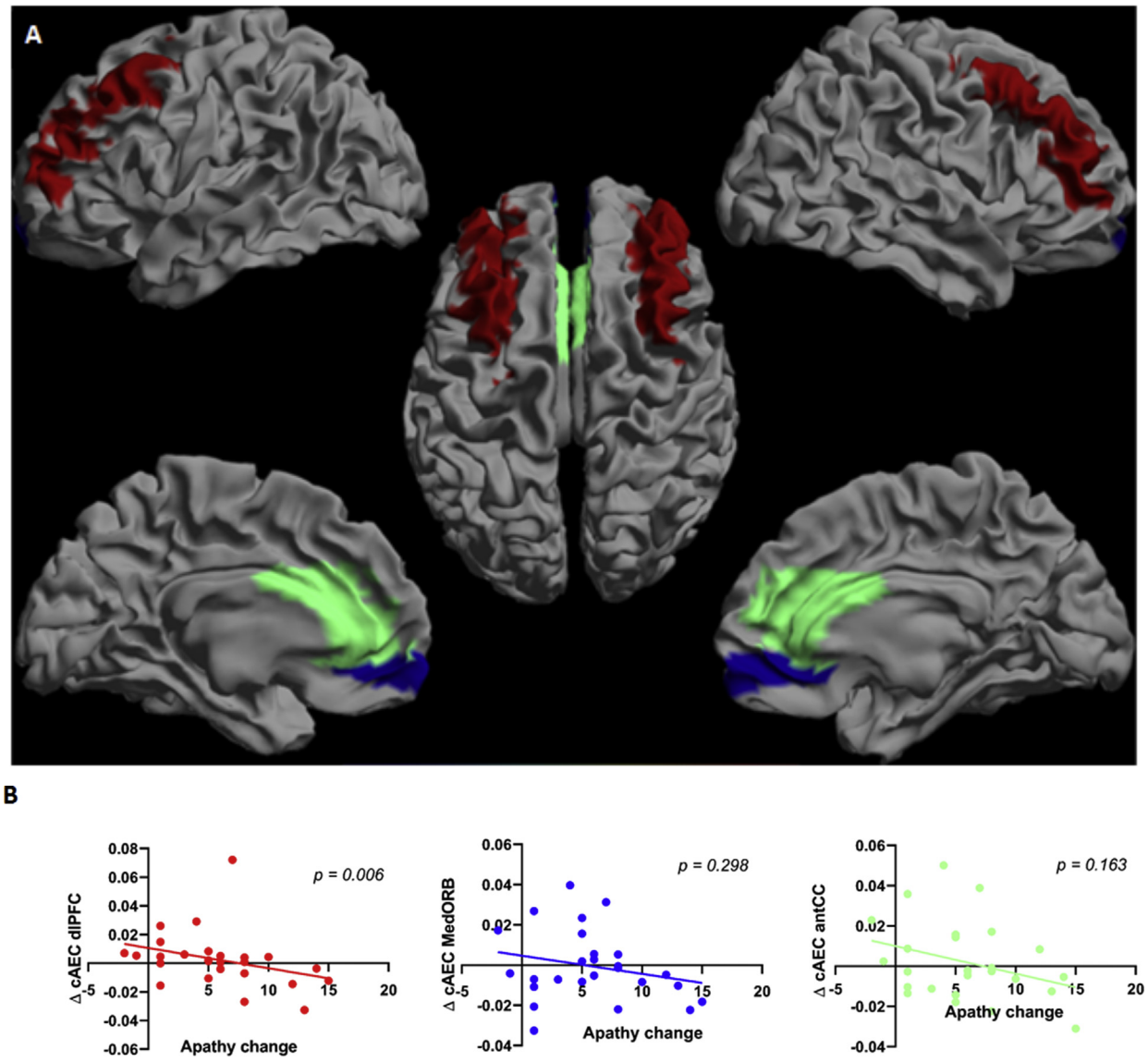

Fig. 2. Correlations between regional changes in functional connectivity (alpha1) and change in apathy severity
A) Distribution of the bilateral cortical brain regions studied, the dlPFC (red), medORB (blue) and antCC (green) displayed on a parcellated template brain viewed from, in clockwise order, the left, top, right, left midline and right midline.
B) Scatter plots of pre-to-post-DBS change in apathy severity and alpha1 functional connectivity change (DBS-ON − DBS-OFF), averaged for each of the three regions of interest. Statistics can be found in Table 2.dlPFC, dorsolateral prefrontral cortex; medORB, medial orbitofrontal cortex; antCC, anterior cingulate cortex.

previously been observed between the STN and the ipsilateral temporal cortex [51–53], but not the dlPFC. This could suggest that the dlPFC is indirectly influenced by DBS via downstream effects on the thalamus, although there may also be direct antidromic stimulation effects via the hyperdirect pathway (albeit the latter mechanism would be more likely for the medial prefrontal cortex than for the dlPFC [54,55]). The complex balance between downstream (via the thalamus) and antidromic stimulation effects (hyperdirect pathway) may also explain the differential effects of stimulation; an increase in FC in some patients and a decrease in FC in others.

The present study has some limitations that need to be addressed. (i) We correlated change in apathy severity over a time interval of ≥6 months with differences in functional connectivity between ON-DBS and OFF-DBS conditions recorded on the same day. Nevertheless, we believe that studying DBS effects (ON versus OFF) on the same day offers the advantage of a better insight into the effect of brain stimulation *itself* (in which we interpret the DBS-ON setting, and not turning off, the stimulation as the intervention), without any bias of disease progression or change in the dose of (dopaminergic) medication over time. The occurrence of apathy is generally assessed over a period of four weeks and can therefore not be tested in a DBS-ON versus DBS-OFF setup [23,24]. However, since we lacked an ON-OFF paradigm in the apathy scores, we must be cautious in drawing conclusions on causality beyond the observed correlation. (ii) We correlated the change in apathy scores obtained on medication with MEG recordings recorded off medication. The off-medication state of the subjects may have influenced the MEG signals. However, as the subjects served as their own controls in this DBS ON-OFF setup, we expect the influence of the off-medication state on our results to have been minimal. (iii) The correlation between the position of stimulation and the change in apathy severity was based on the position of the stimulation sites along a vector running through the longitudinal axis of the STN,

Table 2
Correlations of functional connectivity changes with change in apathy severity.

Region	Frequency band	Spearman's rho
Dorsolateral prefrontal cortex	Delta	0.231 ($p = 0.256$)
	Theta	−0.261 ($p = 0.290$)
	Alpha1	**−0.520 ($p = 0.006$)**
	Alpha2	−0.393 ($p = 0.047$)
	Beta	−0.241 ($p = 0.235$)
Medial orbitofrontal cortex	Delta	0.044 ($p = 0.829$)
	Theta	−0.151 ($p = 0.461$)
	Alpha1	−0.212 ($p = 0.298$)
	Alpha2	−0.124 ($p = 0.545$)
	Beta	−0.247 ($p = 0.224$)
Anterior cingulate cortex	Delta	−0.105 ($p = 0.609$)
	Theta	−0.110 ($p = 0.593$)
	Alpha1	−0.282 ($p = 0.163$)
	Alpha2	−0.108 ($p = 0.599$)
	Beta	−0.243 ($p = 0.231$)

Correlations between the changes in cAEC upon stimulation and increase in apathy severity (Starkstein apathy scale) between baseline (pre-DBS) and follow-up (post-DBS). The correlations are expressed as a Spearman's rho. To account for the fact that three seed regions were compared, alpha levels were adjusted such that *p*-values smaller than 0.05/3 (using Bonferroni correction) were considered to be statistically significant, marked in bold.
cAEC, corrected Amplitude Envelope Correlation; DBS, deep brain stimulation.

from the ventromedial tip in a dorsolateral direction. Although this correlation analysis does not provide information on the optimal position of stimulation in 3D, it does give an intuitive idea of the different stimulation positions throughout the functional subdivision of the STN. (iv) Previously, we described the potential effects of monopolar DBS on MEG signals [22]. Despite the ability of tSSS and beamforming to effectively suppress artefacts [56,57], two sharp peaks remained in the power spectrum during stimulation, at ~27 Hz and ~35 Hz. As the peaks did not appear to affect the alpha1 band, we consider the influence of stimulation artefacts on our results to be limited. Furthermore, the estimation of (changes in) functional connectivity may be influenced by modulation of the signal to noise ratio in the seed regions [58]. It is unlikely that our results can be explained by such modulations, since there was no relation between change in absolute alpha1 band power and change in functional connectivity in the three seed regions (Supplementary Fig D). (v) Instead of focusing on the functional effects of stimulation in all brain regions, we chose to select only three (literature-based) brain regions, which prevented us from testing an abundance of other possible correlations. In addition, our MEG analysis lacked the spatial resolution to study subcortical brain regions such as the nucleus accumbens, which has previously been associated with apathy in PD [59]. As a consequence, we may have missed brain regions that may be associated with the occurrence of apathy. However, we assume that, in accordance with a previous PET-study in DBS-patients with apathy [15] the stimulation-related change in the dlPFC specifically reflects the increased apathy severity and does not represent a global phenomenon such as stimulation-related vigilance affecting background alpha-activity. To verify this in a *negative control* brain region, we tested whether stimulation-related changes in functional connectivity of the bilateral inferior occipital lobe correlated with the change in apathy severity and this was not the case (alpha1, Spearman's $\rho(24) = -0.227$; $p = 0.265$).

Important strengths of this study include the DBS ON-OFF setup taking place on the same day. Second, the use of MEG (instead of EEG) in source-space, in combination with a leakage-corrected connectivity measure (cAEC), offers good spatial resolution, enabling interpretation of the findings in an anatomical context. Last, the Starkstein apathy scale used in our study has very high intra- and interrater reliability [24]. Regarding the scores on post-DBS apathy, we consider our study sample as representative for the STN-DBS population, as the average apathy scores were comparable to those in a large longitudinal cohort [11,60].

In conclusion, we found that increase in apathy severity after STN-DBS might well be an effect of the stimulation itself. Increased apathy severity scores correlated with a more dorsolateral stimulation location (left hemisphere) and with reduced functional connectivity of the dlPFC, not with decreases in dopaminergic medication dose. Hence, the occurrence of apathy after DBS might not necessarily be linked to stimulation of the limbic STN, whereas the correlation with dlPFC connectivity suggests that it may even have a cognitive substrate. To further validate this hypothesis, future prospective (within-subject) studies are necessary to determine whether switching stimulation to an alternative, more ventromedially located, contact point can resolve DBS-induced apathy, preferably without losing clinical effectiveness on motor symptoms, along with a normalization of functional connectivity of the dlPFC.

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CRediT authorship contribution statement

Lennard I. Boon: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Wouter V. Potters:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization, Project administration. **Thomas J.C. Zoon:** Investigation, Writing - review & editing. **Odile A. van den Heuvel:** Conceptualization, Validation, Investigation, Writing - review & editing. **Naomi Prent:** Software, Validation, Writing - review & editing. **Rob M.A. de Bie:** Conceptualization, Investigation, Writing - review & editing. **Maarten Bot:** Investigation, Writing - review & editing. **P. Richard Schuurman:** Conceptualization, Validation, Investigation, Writing - review & editing. **Pepijn van den Munckhof:** Investigation, Writing - review & editing. **Gert J. Geurtsen:** Investigation, Writing - review & editing. **Arjan Hillebrand:** Conceptualization, Methodology, Software, Validation, Investigation, Writing - review & editing, Visualization. **Cornelis J. Stam:** Conceptualization, Methodology, Software, Investigation, Resources, Writing - review & editing. **Anne-Fleur van Rootselaar:** Conceptualization, Investigation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Henk W. Berendse:** Conceptualization, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declarations of competing interest

RDB received unrestricted research grants from Medtronic. PRS is consultant on educational activities for Medtronic, Boston Scientific and Elekta. All other authors report no declarations of interest.

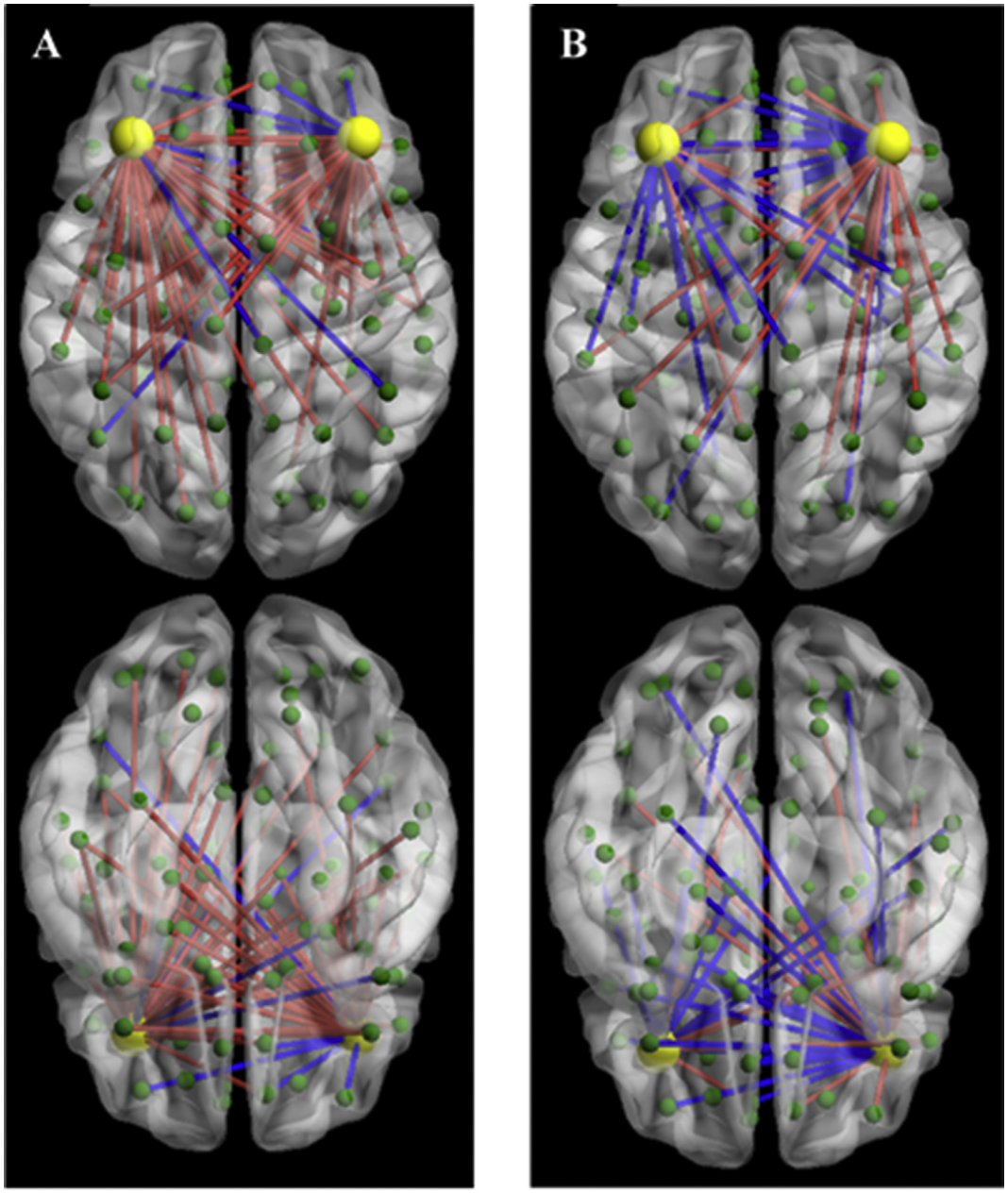

Fig. 3. Functional connectivity changes induced by DBS for individual connections for patients with weaker (≤5; panel A) and with stronger (>5; panel B) increase in apathy severity.
Distribution of alpha1 cAEC differences induced by DBS stimulation for each individual connection linked to the dorsolateral prefrontal cortex (yellow nodes) for patients with weaker (≤5; panel A) and with stronger (>5; panel B) increase in apathy severity. Green nodes represent brain regions, red (blue) connections represent a stimulation-related increase (decrease) in functional connectivity. Top and bottom views of a template brain are shown [61]. For visualization purposes, only links with an absolute t-value larger than 1.00 are shown (arbitrary threshold for visualization purposes).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.12.008.

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