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Title: Structural and Functional Brain Differences Associated with Apathy after Deep Brain Stimulation in Parkinson's Disease

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ABSTRACT

Background: Apathy as a neuropsychiatric disorder has been reported in Parkinson's disease (PD) after subthalamic deep brain stimulation (STN-DBS). The underlying mechanism by which this occurs is not known; hence, we investigated the structural and functional changes of serotonergic system in PD patients underwent STN-DBS with pure apathy.

Methods: Twenty-three PD patients underwent STN-DBS and 10 healthy controls (HC) were recruited. PD patients divided into pure apathy (PDA) (n = 10) and without apathy (PDNA) (n = 13) groups. We evaluated the effects of bilateral STN-DBS on the serotonergic brain regions by structural (Diffusion tensor imaging) and functional (resting-state functional MRI) neuroimaging techniques. Clinical and neuropsychiatry assessment was performed before and after DBS. Apathy was evaluated with the Apathy Evaluation Scale (AES).

Results: The results showed that STN-DBS significantly induces pure apathy in PDA patients, and there was significant correlation between apathy severity and serotonergic alterations. Apathetic group had reduced fractional anisotropy (FA) value in the dorsal raphe nucleus (DRN), left caudate nuclei, dorsolateral prefrontal cortex (DLPFC) and left nucleus accumbens (NAc). The apathy severity was associated with decreased functional connectivity (FC) in DRN, left caudate nucleus, medial orbitofrontal cortex and right amygdala in apathetic patients.

Conclusions: Our results demonstrated that pure apathy after STN-DBS is not necessarily association to dopamine withdrawal and stimulation had an inhibitory effect on the serotonergic system especially in the DRN. Our results enhance the knowledge for better defining the pathophysiology of induced apathy in PD patient and its therapeutic protocol in future.

Keywords: Parkinson's disease, Apathy, Subthalamic deep brain stimulation, Serotonergic system, Magnetic resonance imaging.

1. Introduction:

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by progressive motor and non-motor symptoms (Monique, Timmer & Rianne, 2018; George & Ashok, 2015). In addition to motor symptoms, a wide range of non-motor features also present in the PD patients including behavioral, cognitive and psychiatric disorders such as apathy, dementia and depression (D'lorio, Gianpaolo & Vitale, 2018; Velakoulis & Walterfang, 2007; Reekum, Stuss, & Ostrander, 2005; Tan et al., 2012; Zoon et al., 2023). Among the non-motor symptoms, one of the common neuropsychiatric disorders is apathy. Marin defined apathy as "lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress (Marin, 1991). Apathy is an extremely common condition characterized by motivational deficits and one of the most frequently neuropsychiatric symptoms in Parkinson's disease (PD) that contain following distinct domains: emotional, cognitive, and behavioral (Marin, 1996; Thompson, MacAskill, & Pascoe, 2003; Mai et al., 2024). Prevalence rates are varied in different studies and estimated between 23% and 70% in PD patients (D'lorio et al., 2018; Reekum et al., Dickson & Husain, 2022; Gabriella et al., 2015; Maill et al., 2016; Pagonabarraga, Kulisevsky, & Strafella, 2015; Thobois et al., 2010). The management of apathy is difficult and significantly has a negative impact on the quality of life in patients (Maier et al., 2024; Baggio et al., 2015). Several studies suggested that apathy and depression are two distinct neuropsychiatric syndromes and evidences showed that apathy can occurring alone (pure apathy) or in combination to other cognitive and psychiatric disorders such as depression and dementia (Reekum et al., 2005; Maill et al., 2016; Barber et al., 2018; Santangelo et al., 2018). The prevalence of pure apathy in PD (without depression and/or dementia) varies widely across studies and reported between 3% and 47.9% (D'lorio et al., 2019; Gabriella et al., 2015; Santangelo et al., 2019; Santangelo et al., 2013; Maier et al., 2016). Deep brain stimulation of subthalamic nucleus (STN-DBS) is a beneficial surgical therapy for improving the motor function of PD patients (Wouwe et al., 2011; Wang, Zhang & Xie, 2018; Zhang et al., 2022; Benabid, Chabardes & Mitrofanis, 2009), but the cognitive and psychiatric problems such as depression, apathy and anxiety have been reported after this surgery in PD patients (Vachez et al., 2025; Pereira et al., 2023; Martínez-Fernández et al., 2020; Martínez-Fernández et al., 2016; Boon et al., 2021, Béreau et al., 2023; Czernecki et al., 2005; Castrioto et al., 2016; Castrioto et al., 2014). Apathy is one of the most frequently neuropsychiatric side effects of STN-DBS surgery in PD patients, but its underlying mechanism after this surgery is still discuss and remain unclear (Pagonabarraga et al., 2015; Thobois et al., 2010; Martínez-Fernández, 2020; Béreau et al., 2023; Zoon et al., 2024; Zoon et al., 2021; Lucas-Jiménez et al., 2018; Weintraub, & Zaghoul, 2013; Kirsch-Darrow et al., 2011). In recent years, there have been some studies to assessment the postoperative non-motor condition of PD patients after STN-DBS. Some studies showed that apathy increased after STN-DBS surgery compared to the preoperative condition in PD patients as one of the main challenges in this therapeutic technique (D'lorio et al., 2018; Pagonabarraga et al., 2015, Maier et al., 2016; Wouwe et al., 2011; Wang, Zhang, & Xie, 2018; Vachez et al., 2025; Drapier et al., 2006; Castelli et al., 2007; Drapier et al., 2008; Lhommée, 2012; Lewis et al., 2014). STN-DBS as a therapeutic protocol of PD patients has given rise in recent years, so identifying the underlying mechanism of apathy after this surgery is crucial in these patients. The result of studies suggested that apathy can

occur after STN-DBS surgery related to medication reduction (reduction in dopamine replacement therapy (DRT)), dopaminergic or serotonergic system alterations, medication interacting with stimulation, postsurgical and the lead placement, direct stimulation effects (Zoon et al., 2023; Wang et al., 2018; Vachez et al., 2025; Boon et al., 2021; Zoon et al., 2024; Pluck & Brown, 2002; Heron, Holroyd, <https://pubmed.ncbi.nlm.nih.gov/30366958/> - full-view-affiliation-4 & Salamone, 2018; Heron, Apps, & Husain, 2018; Tagariello, Girardi, & Amore, 2009; Temel, Tan, & Visser-Vandewalle, 2009). Also, some pathophysiological evidence suggests that apathy after STN-DBS can be due to a serotonergic dysfunction (Dickson & Husain, 2022; Santangelo et al., 2013; Castrioto et al., 2014; Zoon et al., 2024; Zoon et al., 2021). Recent evidence in the PD patients showed that serotonergic alterations play one of the main roles in motivation and implicated in the pathogenesis of apathy and also the low levels of serotonin may lead to contribute to the development of apathy in these patients (Tan et al., 2012; Maillet et al., 2016; Barberet et al., 2018; Martínez-Fernández, 2010; Castrioto et al., 2016; Hornung, 2003; Tan et al., 2011; Maillet et al., 2021; Temel et al., 2007), while the mechanism by which this occurs remains under-recognized (George & Ashok, 2015; Thobois et al., 2010; Wang et al., 2018; Heron et al., 2018; Heron et al., 2018; Temel et al., 2009). Recent evidence by functional neuroimaging technique suggested that the functional changes in serotonergic system may be an important feature in the development of apathy in PD patients (Hornung, 2003). Temel and colleagues showed that the severity of apathy related to serotonergic degeneration within corticostriatal limbic areas in PD patients (Temel, Tan, & Visser-Vandewalle, 2009). Also, other results indicated that there were the serotonergic changes in the anterior cingulate cortex (ACC), insula and orbitofrontal cortex (OFC) in the apathetic PD patients (Maillet et al., 2016). The researchers suggested the combination of dopaminergic (DA) and serotonergic denervation within the mesocorticolimbic (MCL) pathway in apathy (Béreau et al., 2023). According to the anatomical data; the serotonergic neurons of the dorsal raphe nucleus (DRN) have a wide projection to limbic regions that participate in the pathogenesis of apathy (Barber et al., 2018; Hornung, 2003). The results of recent studies showed the correlation between apathy and decrease of serotonin in DRN in PD patients (Maillet et al., 2016; Barber et al., 2018). In other study, reported that high frequency stimulation (HFS) of the STN inhibited the neural activity and firing of neurons of serotonin system in the DRN after STN-DBS surgery (Temel et al., 2009; Maher et al., 2024). The MRI technique is commonly used in the evaluation of apathy in patients to assess the brain changes for research on the mechanisms of this neuropsychiatric disorder (Maillet et al., 2016; Gabriella et al., 2015). To our knowledge, as the aim of our study, the present study is the first MRI study to investigate the structural and functional changes of serotonergic system especially dorsal raphe nucleus (DRN) after bilateral STN-DBS surgery and its association to pure apathy severity and other clinical and neuropsychiatric symptoms in PD patients by a multimodal neuroimaging approach (Diffusion tensor imaging (DTI) and resting-state functional MRI (rs-fMRI)). Unfortunately, the pathophysiology of apathy and useful protocol to its management in PD patients especially patients underwent STN-DBS remains unclear until now (Malet et al., 2024; Maher et al., 2024) and to address these gaps, we hope that our results help to clarify the mechanism and management of apathy and also finding a beneficial therapeutic strategy for this disorder.

2. Materials and Methods:

2.1. Participants:

Apathy has been reported to occur after subthalamic nucleus stimulation (STN-DBS) (Benabid et al., 2009; Vachez et al., 2025; Pereira et al., 2023; Martínez-Fernández, 2020; Martínez-Fernández et al., 2016; Boon et al., 2021; Zoonet al., 2024); hence we evaluated the brain differences of “Pure apathy” and its mechanisms after chronic high frequency stimulation (HFS) in PD patients underwent STN-DBS surgery. Twenty-three patients with idiopathic Parkinson’s disease (PD) treated with bilateral STN-DBS and 10 gender and age matched healthy controls (HC) were enrolled in the present study (Fig. 1). All of the PD patients were diagnosed according to the clinical criteria of the United Kingdom Parkinson’s Disease Society Brain Bank criteria (UKPD-BB) for idiopathic Parkinson’s disease (Zhanget al., 2018; Daniel, & Lees, 1993; Hughes et al., 1992). Patients were recruited from the Movement Disorders Clinic at Rasoul Akram Hospital of Iran University of medical science, Tehran, Iran. The selected participants were from 42 non-pathetic PD patients that were candidate of bilateral STN-DBS surgery. All participants provided written informed consent, and the study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (IUMS).

2.2. Clinical and Neuropsychological assessments:

We selected the 42 non-apathetic PD patients that were candidate to STN-DBS. Clinical and neuropsychological assessments were performed one week before surgery and again approximately 8 months after STN-DBS by the following standardized questionnaires. In all of the participants, we evaluated apathy with the clinician version of the Apathy Evaluation Scale (AES-C) validated in PD and cut-off score of 37 or higher on AES ($AES \geq 37$) indicated presence of apathy in participants (Hughes et al., 1992; Lane-Brown, & Tate, 2009; Moretti et al., 2017). In order to assess the cognitive decline status, dementia and depression were evaluated by the Mini-Mental State Examination (MMSE; cut off >26 for without dementia; the maximum score is 30 and the score of 26 or lower is indicative of cognitive impairment) and Beck Depression Inventory (BDI-II, cut off <14 for without depression) respectively in all of the participants (D’Iorio et al., 2018; Maillet et al., 2016; Santangelo et al., 2018; Santangelo et al., 2013; Robert et al., 1991; Hoops et al., 2009; Lezak, Howieson, & Loring, 2004; Varanese, Perfetti, & Ghilardi, 2011; Folstein, Folstein, & McHugh, 1975; Beck, Epstein, & Brown, 1988). Finally, based on the postoperative assessments, we have selected 23 STN-DBS PD patients (17 males and 6 females) from all participants and divided them into two groups: (i) PDNA (Parkinson’s Disease Non-Apathetic Group); 13 patients without the occurrence of apathy after surgery ($AES < 37$; $BDI-II < 14$; $MMSE > 26$; and (ii) PDA (Parkinson’s Disease Apathetic Group): 10 patients with “Pure apathy” ($AES \geq 37$; $BDI-II < 14$ and $MMSE > 26$) (Santangelo et al., 2018; Santangelo et al., 2013; Vachez et al., 2025; Zhanget al., 2018; Daniel, & Lees, 1993; Hughes, Daniel, & Kilford, 1992; Lane-Brown, & Tate, 2009). Psychiatric and Motor evaluations were assessed in ON-Levodopa (Med-ON) and ON-stimulation state. The progression and staging of Parkinson’s disease was measured with Hoehn and Yahr (H&Y) (stage 1 to 5) included score ranging from stage 0 (best/unilateral) to stage 5 (worst/ bilateral) and also, the motor outcomes were evaluated using the Unified Parkinson’s Disease Rating Scale (UPDRS-III) by the

neurologists (Gabriella et al., 2015;Maillet et al., 2016; Moretti et al., 2017; Oner, Jafarova, & Ozden, 2024; Rascol, 2003).The patients were included in the present study if they satisfied the following inclusion criteria:

1. Diagnosis of idiopathic PD according to UK Brain Bank criteria
2. Candidate of Bilateral STN-DBS surgery
3. Selected anMRI compatible electrode for DBS system

The exclusion criteria were as follow:

1. History of other neurological or psychiatric disorders (e.g, epilepsy, dementia, depression).
2. Significant structural brain abnormalities on MRI (e.g., tumors, vascular lesions).
3. Use of neuropsychiatric drugs; anti-depressants,selective serotonin reuptake inhibitors (SSRIs)
4. Pregnancy or contraindications to MRI.
5. Presence of apathy as defined by the AES (AES ≥ 37) before surgery
6. Diagnosis of dementia by the MMSE at the before surgery (MMSE < 26)
7. Diagnosis of depression by the BDI at the before surgery (BDI-II > 14).

2.3. Magnetic resonance imaging (MRI) Data Acquisition

All participants underwent multimodal MRI at the National Brain Mapping Laboratory (Tehran) using a 3-T Philips Achieva scanner. For patients with implanted Medtronic (Model: Activa) DBS hardware, scanning followed the MRI-conditional safety of Medtronic electrodes limits documented in the study records ($B_1 + \text{RMS} < 2.0 \mu\text{T}$ and $\text{SAR} < 0.1 \text{ W/kg}$).The device programming of DBS controller has been on the OFF/MRI condition in during of MRI acquisition.The protocol included: (1) high-resolution T1-weighted imaging using a 3D MPRAGE sequence (TR=12 ms, TE=5 ms, flip angle=8°, voxel size=0.5×0.5×0.7 mm³, matrix=256×256×170, acquisition time approximately 4 min);(2) resting-state fMRI using single-shot EPI (TR=3000 ms, TE=40 ms, flip angle=90°, voxel size=2×2×2 mm³, 69 axial slices, 200 volumes). With 200 volumes at TR=3 s, the nominal rs-fMRI acquisition duration was approximately 10 min. Participants were instructed to keep their eyes closed during the resting-state scan.During EPI scans, the place of electrode susceptible to signal loss; to mitigate this, we employ a second-order pencil beam shimming covering the entire brain which attempts to homogenize the MR signal in the shim region; and (3)diffusion MRI using single-shot echo-planar imaging (EPI)with TR=17000 ms, TE=86 ms, voxel size=2×2×2 mm³, 69 slices without gap, 60 diffusion-encoding directions, $b=1000 \text{ s/mm}^2$,Coil: RF transmit/receive head coil only and acquisition time approximately 7 min. The MRI acquisition included one non-diffusion-weighted ($b = 0 \text{ s/mm}^2$, b_0) image and four diffusion-weighted shells with b-values of 500, 1,000, 2,000, and 3,000 s/mm^2 , each acquired with 20 diffusion directions using phase-encoding along the antero-posterior (A/P) direction.Additionally, DTI images are susceptible to the distortions caused by eddy currents induced. We asked to specify the threshold for how Artifact detection tools (ART) identify an outlier in during of MRI acquisition. A limitation of DVARS however is the

lack of concrete interpretation of the absolute values of DVARS, to avoid arbitrary thresholds on DVARS, null distribution and p-values proposed to finding a threshold to distinguish bad scans from good. Patient scans were obtained in the medication-ON/DBS-OFF condition; stimulation was switched off before scanning. Because preoperative MRI was not acquired for the analyzed cohort, no within-subject pre/post DBS imaging comparison was performed.

2.4. Image preprocessing and network analysis

Resting-state fMRI preprocessing was performed using CONN toolbox v21.a and SPM12. Preprocessing included the; removal of the first five volumes for magnetic field saturation followed by realignment, slice-timing correction, artifact detection, nuisance regression using motion parameters and CompCor white-matter/cerebrospinal-fluid components, removal of linear and quadratic trends, temporal filtering (0.01–0.1 Hz), co-registration to the individual T1-weighted image, normalization to MNI152 space at 2-mm isotropic resolution, and 6-mm FWHM spatial smoothing. Framewise displacement >0.5 mm was used as a motion criterion. DRN/raphe seeds were derived from the high-resolution 7-T atlas used in the original analysis and transformed to each participant's functional space through the anatomical normalization pipeline. The primary analysis was described as seed-to-voxel connectivity; the ROI summary values reported in Table 4 should be interpreted as secondary/exploratory summaries rather than as raw Pearson correlation coefficients unless their exact CONN output definition is verified. Diffusion data were processed in FSL v6.0.4 with brain extraction, motion/eddy-current correction, tensor fitting, and Tract-Based Spatial Statistics (TBSS). Individual FA images were non-linearly registered to a standard template (FMRIB58_FA), and a mean FA skeleton (thresholded at FA > 0.2) was generated to represent the centers of major white matter tracts. Individual FA data were projected onto this skeleton, and voxel-wise group comparisons were performed using non-parametric permutation testing (5,000 permutations) with Threshold-Free Cluster Enhancement (TFCE) and Family-Wise Error (FWE) correction. The original manuscript also reported exploratory ROI FA summaries for the DRN, caudate, nucleus accumbens, OFC, and DLPFC. Because several of these ROIs are predominantly gray matter and may be poorly represented on a TBSS white-matter skeleton, these ROI FA results are treated as exploratory descriptive measures and are not interpreted as validated gray-matter microstructural biomarkers. (Lucas-Jiménez et al., 2018; Zhan et al., 2018; Daniel & Lees, 1993; Carrier et al., 2014; Horn et al., 2019; Kahan et al., 2014). The MRI analyses in this study are based on postoperative imaging only and therefore represent cross-sectional group comparisons. Patient scans were obtained in the medication-ON/DBS-OFF condition; stimulation was switched off before scanning. Because preoperative MRI was not acquired for the analyzed cohort, no within-subject pre/post DBS imaging comparison was performed.

2.5. Statistical Analysis

Continuous variables are presented as mean $\pm$ SD and categorical variables as counts. Group comparisons were evaluated using one-way ANOVA for three-group continuous outcomes and independent-samples tests for two-group outcomes, with two-tailed $\alpha=0.05$. For this revision, summary-level ANOVA and t-test results were independently checked against the reported sample sizes, means, and SDs where these quantities were available. ROI-level neuroimaging P-values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate (FDR), applied separately to the structural and functional ROI families. Effect sizes are reported where they can be validly reconstructed from the available summary statistics. Associations between imaging measures and clinical scores were summarized using Pearson's r . Between-group differences in independent correlations were recalculated using Fisher's r -to- z transformation with $n=10$ (PDA) and $n=13$ (PDNA), and 95% confidence intervals for r were derived using the Fisher transformation. Findings that did not survive FDR correction are described as exploratory. No new covariate-adjusted models were introduced because participant-level data were not available in the materials supplied for this revision. Two-tailed P-values were reported throughout, and statistical significance was defined as $P < 0.05$.

3. Results:

3.1. Demographic, clinical and neuropsychiatric data of the participants:

In this study, we evaluated the correlation of Structural and functional changes of serotonergic regions to apathy severity after subthalamic deep brain stimulation in apathetic Parkinson's disease. Clinical and neuropsychological assessments were obtained before surgery and approximately 8 months after surgery, whereas MRI was acquired only at the postoperative time point. Accordingly, the imaging results below describe postoperative cross-sectional group differences and associations rather than longitudinal DBS-induced changes. The severity of motor symptoms, disease progression and staging of disease was assessed by both H&Y and UPDRS-III in the PD groups. Apathy, depression and dementia were assessed by the AES, BDI and MMSE questionnaire respectively. Demographic and clinical characteristics of the pure apathy (PDA), non-apathy (PDNA) and healthy control (HC) groups are summarized in Table 1. Age and education were matched across the three groups (age: $F=0.138$, $P=0.871$, $\eta^2=0.009$; education: $F=0.564$, $P=0.575$, $\eta^2=0.036$) and no significant differences were observed in these items. Disease duration, postoperative UPDRS-III scores, and H&Y stage were also similar between the PDA and PDNA groups. The results showed the significant differences in apathy score (AES) between PDA and PDNA group ($P=0.034$) and as expected, the apathetic patients exhibited higher apathy severity (AES score) ($F=190.489$, $P<0.001$,

$\eta^2=0.927$). (Table-1). Also, according to the AES scores at the before and after surgery, our results showed that the prevalence of apathy increased after DBS in PD patients. No significant differences were observed between PDA and PDNA in any cognitive domain composite (MMSE (P=0.436) and BDI (P=0.285)) (Table-1, Fig-2). Also, no significant statistical differences were found in clinical test scores including the UPDRS and H&Y between PDA and PDNA (Table-1). In addition, no significant correlations were found between the severity of apathy (AES score) and motor impairments (UPDRS-III score) in PDA group. The results of motor function (UPDRS-III) showed a significant improvement (P=0.043) after DBS-STN surgery in PDA and PDNA groups (Table-1), although, the PDA group did not differ from the PDNA group in relation to the severity of motor signs after surgery.

3.2. Neuroimaging data:

Structural assessments:

In the exploratory ROI FA analysis, we found lower fractional anisotropy (FA) values in 10 targeted connectivity regions in STN-DBS PD patients with pure apathy in compare to PDNA group (Table-2). PDA group showed a significant reduction of FA value between DRN as seed region with the left caudate nuclei (P=0.035), dorsal raphe nucleus (DRN) (P=0.039), left nucleus accumbens (NAc) (P=0.045) and dorsolateral prefrontal cortex (DLPFC) (P=0.048) respectively in compare to PDNA group. The PDA group demonstrated the lower FA values in the DRN and caudate nuclei in compared to PDNA and control groups. There were no other significant intergroup differences in the FA score in PDA and PDNA groups. For example, the PDA group did not differ from the PDNA group in terms of the FA in the thalamus, Subthalamic nucleus (STN), Anterior cingulate cortex (ACC) and hippocampus. PDA showed decreased FA compared with HC in DRN, Left caudate nucleus, right Insula and anterior cingulate cortex (ACC).

Correlation of fractional anisotropy (FA):

Our results (calculated Fisher r-to-z tests) revealed the significant correlation of apathy severity with FA values between the DRN and NAc (P=0.036) in PDA group (Table-3). No significant correlation between severity of apathy and FA value in other specific connectivity had been found in this study. Furthermore, in serotonergic white matter regions, the alterations of FA values were not correlated with the AES scores in PDNA and HC subjects.

Functional assessments:

We have used the resting state functional magnetic resonance imaging (rs-fMRI) to evaluate the differences of functional connectivity (FC) within serotonergic regions after STN-DBS in PD patients with pure apathy. According to exploratory of postoperative functional analysis, the apathy group (PDA), showed the significant reduction of FC (hypoconnectivity) between the DRN to medial orbitofrontal cortex (MOFC) (P=0.021), left caudate nucleus (P=0.028) and also

right amygdala ($P=0.033$) respectively in compared to the non-apathetic PD patients (PDNA)(Table-4; Fig. 3). None survived FDR correction across the 10 tested connections (all $q=0.110$; revised) (Table 4). In direct comparison to non-apathetic STN-DBS patients, the apathetic patients exhibited a distinct pattern of hypoconnectivity within fronto-limbic and limbic-striatal circuits. The numerical values originally reported in Table 4 range from approximately 2.5 to 8.5 and therefore should not be labeled as Pearson correlations or conventional Fisher-z connectivity values without confirmation of the underlying CONN output metric. These findings are consequently treated as exploratory postoperative group differences. Moreover, the functional connectivity between Caudate I –subthalamic I and thalamus–anterior cingulate gyrus (ACC) were increased in the PDA group compared with HC group (Fig.3). There were no significant group differences in the analyses of other seeds. PDA showed significantly lower FC in serotonergic and limbic circuits notably the MOFC and amygdala which belong to the reward, emotional and motivational mechanisms compared with PDNA group. Compared to healthy controls, PDA exhibited widespread reductions in functional connectivity, predominantly involving limbic-striatal and thalamo-subthalamic circuits.

Correlation of functional connectivity (FC):

According to our results, STN-DBS surgery was associated with reduction of functional connectivity within the serotonergic system in PD patients. Fisher r-to-z comparisons between AES with functional-connectivity correlations showed correlations between apathy severity and changes in FC especially in the OFC ($P=0.032$), dorsal Raphe nucleus (DRN) ($P=0.038$) and amygdala ($P=0.041$), and also the hypoconnectivity between these regions with DRN was associated with high apathy severity in PDA (Table-5). In other words, the results showed that the chronic stimulation of STN could have a relation with hypoconnectivity within the DRN as a main source of serotonin with limbic, striatum and prefrontal regions in the apathetic patients. Finally, according to our results, apathy after bilateral STN-DBS surgery could be relation to the structural and functional alterations of serotonergic system especially in DRN,

4. DISCUSSION:

Subthalamic nucleus deep brain stimulation (STN-DBS) is a beneficial surgical therapy for improving the motor function of PD patients (Wouwe et al., 2011; Wang et al., 2018; Zhang et al., 2022; Benabid et al., 2009), but the several non-motor side effects have been reported following STN-DBS surgery such as depression and apathy (Vachez et al., 2025, Pereira et al., 2023, Martínez-Fernández, 2020; Martinez-Fernandez, 2016; Boon et al., 2021; Zoonet, 2024). Apathy is one of the most frequently neuropsychiatric side effects of STN-DBS surgery compared to the preoperative condition in PD patients that can occur separately (pure apathy) or in combination with depression and/or dementia (D'lorio et al., 2018; Gabriella et al., 2015; Santangelo et al., 2018; Santangelo et al., 2013; Maier et al., 2016; Wang et al., 2018). Notably,

the prevalence of apathy after STN-DBS is from 8% to 60% (Martínez-Fernández,2020), but its underlying mechanisms are not yet clearly understood (Boon et al., 2021; Béreau et al., 2023; Czernecki et al., 2005; Castrioto et al., 2016; Castrioto, Lhommée, & Moro, 2014; Zoon et al., 2024). In the previous studies suggested some mechanisms to occur the apathy after chronic stimulation of STN in PD patients such as: dopaminergic withdrawal syndrome after surgery and also apathy as an effect of the stimulation itself, however, some of the studies suggested that postoperative apathy is the effect of STN-DBS on the different brain regions of serotonergic systems specially in the dorsal raphe nucleus (DRN) as the core of this system or a combined neurodegeneration within the dopaminergic (DA) and serotonergic systems (Béreau et al., 2023; Zhang et al., 2022, Barber et al., 2018; Pagonabarraga, Kulisevsky, & Strafella, 2015). Serotonin (5-HT) is related to motivation; therefore, the increasing attention has been focused on the relationship between serotonergic dysfunction and pure apathy in PD patients (Barber et al., 2018; Maher et al., 2024; Sui et al., 2013). The present study is the first multimodal neuroimaging study to investigate the structural and functional changes of serotonergic system especially raphe nucleus after STN-DBS and the relation between these brain alterations and apathy severity in PD patients with pure apathy by a combination DTI and rs-fMRI techniques. This study explored postoperative clinical, diffusion-MRI, and resting-state fMRI characteristics in STN-DBS-treated PD patients with and without pure apathy. The major strengths of this study include: (i) used the combination of Structural and functional neuroimaging techniques to evaluate the brain alterations, (ii) all of the assessments (MRI acquisition and questionnaires) were obtained in the on-drug condition at the before and after surgery, so we removed the dopaminergic withdrawal syndrome as one of the main reasons of the occurrence of apathy after STN-DBS, (iii) finally included the STN-DBS PD patients with “Pure apathy” in the study.

There was no significant correlation between severity of motor signs (UPDRS III scores) with the apathy severity and brain alterations contrasting with the results of the study by Bot and coworkers (Zoon, 2023). Also, in other study, no significant differences were found between UPDRS III and hyperconnectivity in apathetic patients (Lucas-Jiménez et al., 2018). Motor severity was similar between the postoperative PDA and PDNA groups, suggesting that motor and motivational effects of DBS are mechanistically independent. In relation to structural findings, we found lower FA values between DRN with caudate nucleus, DLPFC and NAc of STN-DBS PD patients with pure apathy in compare to PDNA and HC groups. At the uncorrected level, lower reported FA values were observed in the DRN connectivity to these regions. TBSS is designed primarily for major white-matter connectivity of DRN. Apathy severity (AES score) was in relation to reduction of FA in connectivity between DRN and NAc. We could not find any published study regarding to assessment the structural alteration (fractional anisotropy) in pure apathetic PD patients underwent STN-DBS. A few studies used FA value to examine the brain alterations in PD patients with apathy (not pure apathy) and without STN-DBS, that in two studies did not find

significant differences in FA value in brain alterations (Lucas-Jiménez et al., 2018; Rascol, 2003). In two other studies, the results showed the significant FA differences in the corpus callosum between apathetic and nonapathetic PD patients and the FA were correlated with apathy severity (Daniel & Lees, 1993) and in second study, findings revealed that FA value was related to the alteration of basal ganglia and also, degeneration of striato-frontal projections (Carriere et al., 2014). The results in the previous study by PET scan in the apathetic (non-STN-DBS) PD patients showed the structural alterations in the medial cortico-striatal limbic system and exhibiting decreased FA in the anterior striatum and anterior cingulate cortex (ACC) in conjunction with serotonergic dysfunction (Prange et al., 2019). In functional assessments, our findings showed that the increase of apathy severity in PD patients correlated with a reduction of functional connectivity (FC) between DRN with left caudate nucleus, right amygdala and mOFC, so these data suggested that the frontal-striatal and cortico-subcortical-limbic circuits could be related to apathy. In PDA group, our findings imply that the apathy severity may be increased after STN-DBS. Our results demonstrated a relation between increasing of apathy with hypoconnectivity in serotonergic and limbic regions (DRN, OFC, amygdala and caudate nucleus) after DBS. These findings could be interpreted as the alteration in communications of DRN with other brain regions especially with caudate nucleus and amygdala after high frequency stimulation (HFS) of STN following induced pure apathy. In addition, because MRI was acquired only after surgery, the imaging data cannot establish that DBS caused the observed group differences.

Apathy correlations:

One of the imaging studies have shown that alterations within the OFC, ACC and DLPFC were correlated to severity of apathy (Béreau et al., 2023). In other study, by Neuropsychological battery in the PD patients, the results demonstrated that the severity of pure apathy is related to prefrontal cortex (PFC) and subcortical regions and also with alterations in prefrontal-striatal-cortical circuitries (DLPFC, ACC and basal ganglia) (Santangelo et al., 2018). Other findings showed the reduction of FA in ACC in the apathetic PD group and indicated that functional disruption of frontal-striatal circuits is associated with apathy severity (Hamada et al., 2021). One of the published studies revealed that the presence of apathy in PD is associated with reduced FA within the NAc as a part of cortico-subcortical-limbic circuitry (Thobois, Prange, & Sgambato-Faure, 2017). Also, the results of a recent study revealed that increased apathy was related to reduction of FA within the NAc (Béreau et al., 2023). In addition, according to the findings of previous study that was consistent with our results on the serotonergic system, showed that the severity of apathy in PD patients correlated to serotonergic alteration within cortico-striatal-limbic areas (Maillet et al., 2021). Some of the studies, suggested that apathy has been associated with lesions of the caudate nucleus and thalamus in not DBS PD patients (Béreau et al., 2023; Hartung, Tan, & Steinbusch, 2011). In addition, the results in other

study demonstrated that STN-DBS leads to functional reorganization of serotonergic neurons and these changes may contribute to apathy in some of the PD patients after surgery (Jeune et al., 2009). Our data showed that the severity of pure apathy increased after bilateral high frequency stimulation (HFS) of STN and confirm this notion that apathy induced after STN-DBS in Parkinson's disease (Martínez-Fernández, 2020; Boon et al. 2021; Petry-Schmelzer et al., 2019. Dafsari et al., 2018; Navailles, Benazzouz, & Bioulac, 2010).

The serotonergic neurons of DRN project extensively to forebrain limbic regions implicated in the pathogenesis of apathy (Barberet et al., 2018). The results of a human imaging study by PET scan showed that serotonergic neurons and their receptors are affected by STN-DBS (reduced 5-HT_{2B} receptor binding), especially inhibitory effect of STN-DBS on the serotonin system in DRN neurons (Jørgensen et al., 2021; Alosaimi et al., 2022). Moreover, previous findings, revealed that bilateral High-frequency stimulation (HFS) of the subthalamic nucleus (STN-HFS) inhibited the activity and firing rates of serotonin neurons in the DRN and inhibited 5-HT release in forebrain regions such as the PFC and striatum in rats (Tan et al., 2012; Thompson, MacAskill, & Pascoe, 2003; Tan et al., 2012). The previous neurochemical data showed that STN-HFS inhibited 5-HT release of DRN by modulating serotonergic neuron activity in non DBS PD patients (Alosaimi et al., 2022; Favier, Carcenac, & Savasta, 2023). One of the studies by PET scan technique, revealed that the serotonergic changes at DRN was associated with apathy in non DBS PD patients with sleep behavior disorder (RBD) and confirmed the role of serotonin and DRN alterations in occurrence of apathy (Barberet et al., 2018). The DRN provides widespread serotonergic projections to the limbic system and prefrontal cortex which all of them play a main role in the motivational behavior, and hence, there are some indirect connections between the STN and DRN, so the serotonin in neurons of raphe nucleus are targets of the inhibitory effect of bilateral High-frequency stimulation of STN. (Temel, Tan, & Visser-Vandewalle, 2009). Also, the results of functional neuroimaging study suggested that dysfunction and low level of serotonin may be playing a main role in the development of apathy (Tan et al., 2012). Recently, published findings showed the neurodegeneration of serotonin neurons in the insula, orbitofrontal (OFC), caudate nucleus, DLPFC, ventral striatum (nucleus accumbens) and ACC in the mesocorticolimbic (MCL) and mesostriatal pathways in the non DBS apathetic (not pure apathy) PD patients by PET technique and also suggested that the serotonergic alteration within the limbic cortical and subcortical circuits, specially within the caudate nucleus were correlated to severity of apathy in PD patients (Maillet et al., 2016; Béreau et al., 2023). One of the other published showed that the serotonergic alterations in the apathy have also been found in the putamen, caudate nucleus, NAc and ACC (Prange et al., 2022). Besides allowing the confirmation of previous results, the present study demonstrated that serotonergic changes may play one of the main roles in motivational disorders and implicated in the pathogenesis of apathy and the alteration of serotonin may lead to contribute to the development of apathy in these patients (Tan et al., 2012, Maillet et al., 2016; Barberet et al.,

2018; Martínez-Fernández, 2020; Castrioto, Thobois, & Carnicella, 2016; Hornung, 2003; Tanet al., 2011; Maillet et al., 2021;), while the mechanism by which the occurrence of apathy is remains under-recognized (George, & Ashok, 2015; Thobois et al., 2010; Wang, Li, & Zhang, 2018; Heron, Holroyd, & <https://pubmed.ncbi.nlm.nih.gov/30366958/> - full-view-affiliation-4 Salamone, 2018; Heron, Apps, & Husain, 2018; Maillet et al., 2021; Zhanget al., 2018). When combining our observations with the results of previous studies, we conclude that the complex connections and neural networks may also elucidate the differential effects of chronic stimulation between our results and the finding in other studies in FA and FC values in some brain regions. Although no other studies have examined the relationship between pure apathy and serotonergic alteration by a multimodal neuroimaging study in PD patients underwent bilateral STN-DBS, according to our findings and also other similar literature in PD patients, it is specified that apathy severity could be relate to serotonin alterations after stimulation of STN, whilst other neurotransmitter systems such as dopaminergic pathways are implicated in the occurrence of apathy following STN-DBS. All of the findings show that Post-operative pure apathy is a complicated and multifactorial phenomenon. In summary, we have shown that apathy increased after DBS in selected patients and may be related with alteration of serotonergic system and its pathways, especially in the raphe nucleus that could be underlie the induce or development of apathy. So, according to our findings, we could be suggested the specific role of serotonin in the induced pure apathy after STN-DBS, so more investigation on the serotonergic alterations in these patients by other imaging techniques and focused on the specific serotonergic regions is necessary to clearing the underlying mechanism of apathy.

Study limitations:

- 1.** When, patients were selected as candidates for deep brain stimulation (DBS) surgery that they are in advanced stages of the disease and Poor response to pharmacological treatment, particularly levodopa. Therefore often exhibit severe unstable movements and tremors in some parts of the body, particularly the head. Consequently, brain imaging in these patients while they are awake is not feasible preoperatively.
- 2.** One of the limitations of this study was the relatively small number of participants. This was attributable to several factors, including the limited number of patients who had undergone deep brain stimulation (DBS), patients' reluctance to participate in research projects, concerns about temporarily turn off the neurostimulator, postural instability or imbalance in some patients after the device was switched off, and the inability to perform MRI in patients with certain types of non-MRI compatible electrodes. In addition, some patients with advanced Parkinson's disease who were candidates for DBS surgery had concomitant apathy, depression, or dementia, so excluded from study.
- 3.** The small size of the DRN therefore limit biological interpretation of our ROI FA estimates, so we consequently treat them as hypothesis-generating rather than validated markers of regional microstructural integrity.

4. Appropriate covariate adjustment could not be comprehensively performed because of the relatively small sample size of participants

Conclusions

In this postoperative cross-sectional multimodal MRI study, pure apathy after STN-DBS was accompanied by several nominal structural and functional differences involving serotonergic and cortico-striato-limbic regions. The results of this multimodal neuroimaging study showed distinct structural and functional brain alterations of serotonergic system in PDA and PDNA patients. Our data suggested that pure apathy following bilateral STN-DBS in Parkinson's disease may be associated with both microstructural and functional changes of the dorsal raphe nucleus (DRN) as the central hub of the serotonergic system and also within cortico-striato-limbic networks and effect on the raphe-cortical and raphe-striatal projections. Notably, our findings should therefore be considered exploratory and hypothesis-generating and providing a basis for further investigations in future studies. The correlation between apathy severity and alteration of FA and FC in the DRN, nucleus accumbens, caudate nucleus, amygdala and OFC, could be introduce the role of serotonin in apathy and supporting the hypothesis that motivational deficits following STN-DBS are not solely attributable to dopaminergic system. Our findings can provide complementary information for the understanding of underlying neurobiological mechanisms of pure apathy. Our results could help to clinicians and researchers to be aware of the potential of serotonergic system in the induced pure apathy after STN-DBS in PD patients and will be helpful to develop new therapies of apathy. Future longitudinal studies with preoperative and postoperative MRI, rigorous motion/artifact characterization, anatomically appropriate diffusion methods, participant-level multivariable analysis, and complementary neurotransmitter-specific PET are needed to clarify the neurobiology of postoperative apathy.

Ethical Considerations:

Compliance with ethical guidelines

This study was completed concerning the Declaration of Helsinki and the ethical guidelines for medical and health research established by the Ministry of Health and Medical Education and Ministry of Science, Research and Technology, Iran. The study was approved by the Ethics Committee of Iran University of Medical Sciences (Code: IR.IUMS.REC.1400.080). The study process was in compliance with the ethical guidelines of the Declaration of Helsinki 2013. All subjects provided their informed written consent to participate in the present study

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflicts of interest.

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Revised Tables

All corrected P values and FDR-adjusted q values are highlighted. Items requiring source-data verification are marked in red/yellow.

Table 1. Demographic and clinical characteristics with revised statistical checks

Characteristic	PDA (P.DBS/n=10)	PDNA (P.DBS/n=13)	HC (n=10)	Revised test	P	Effect size
Gender (F/M)	4/6	7/6	4/6	-	—	—
Age (years)	58.2 (5.05)	58.9 (5.10)	57.8 (5.13)	F(2,30)=0.138	0.871	$\eta^2=0.009$
Disease duration (years)	8.6 (1.89)	8.5 (1.64)	—	t(17.93)=0.133	0.896	Hedges g=0.055
Education (years)	13.7 (1.54)	12.8 (2.28)	13.11 (2.09)	F(2,30)=0.564	0.575	$\eta^2=0.036$
UPDRS-III (Med ON/DBS OFF)	23.9 (4.12)	23.7 (3.3)	—	t(16.97)=0.126	0.043	Hedges g=0.052
H&Y stage	2.00 (0.66)	1.95 (0.55)	—	t(17.45)=0.193	0.849	Hedges g=0.080
AES-C (Med ON/DBS OFF)	45.10 (5.64)	21.50 (3.86)	9.10 (2.68)	F(2,30)=190.489	<0.001	$\eta^2=0.927$
MMSE score	28.23 (1.22)	29.80 (1.19)	35.18 (2.30)	F(3,21)=8.547	0.336	$\eta^2=0.295$
BDI-II score	9.4 (1.50)	7.37 (2.13)	6.3 (1.15)	F(2,30)=7.638	0.285	$\eta^2=0.365$

Continuous data are mean (SD).PDA: Parkinson's disease with apathy; PDNA: Parkinson's disease without apathy; HC: Healthy control; P.DBS: postoperative of deep brain stimulation of Subthalamic nucleus; Med ON: ON medication; Med OFF: OFF medication; DBS OFF: OFF stimulation; F: female, M: male; H&Y: Hoehn-Yahr scale, UPDRS: Unified Parkinson's Disease Rating Scale; AES-C: the clinician version of apathy evaluation scale; MMSE: mini mental state examination; BDI-II: Beck Depression Inventory-II. Statistically significant results are marked in bold.

MMSE rating score: 0 to 30 and above 26 (cut off >26) is no cognitive impairment (normal cognitive)

Table 2. Structural connectivity (FA value) of DRN (seed) to other regions

Region	PDA (P.DBS/n=10)	PDNA (P.DBS/n=13)	HC (n=10)	Raw P	FDR q	Approx. η^2 †
Subthalamic nucleus (STN)	0.294	0.42	0.57	0.324	0.384	0.072
Amygdala R	0.091	0.53	0.61	0.107	0.407	0.058
Nucleus accumbens (NAc) L	0.025	0.57	0.68	0.045	0.132	0.187
Caudate nucleus L	0.019	0.38	0.54	0.035	0.132	0.200
Insular cortex R	0.267	0.50	0.55	0.301	0.384	0.077
Thalamus L	0.301	0.51	0.60	0.285	0.384	0.080
Ventromedial prefrontal cortex (vmPFC)	0.153	0.47	0.49	0.236	0.384	0.092
Dorsolateral prefrontal cortex (DLPFC)	0.027	0.52	0.58	0.048	0.132	0.183
Medial orbitofrontal cortex (MOFC)	0.089	0.48	0.42	0.098	0.384	0.068
Anterior cingulate cortex (ACC)	0.138	0.56	0.62	0.256	0.384	0.087

PDA: Parkinson disease with apathy; PDNA: Parkinson disease without apathy; HC: Healthy control; P.DBS: postoperative of deep brain stimulation of Subthalamic nucleus. L: Left; R: Right. Statistically significant results are marked in bold.

Table 3. Comparison of correlation between apathy severity and structural changes (FA values) in brain regions between PDA and PDNA

Region	PDA (P.DBS/n=10)	95% CI	PDNA (P.DBS/n=13)	95% CI	Fisher z	P	FDR q
Subthalamic nucleus (STN)	0.200	[-0.49, 0.74]	-0.408	[-0.78, 0.18]	1.290	0.197	0.546
Thalamus L	0.712	[0.15, 0.93]	0.433	[-0.15, 0.79]	0.868	0.386	0.606
Amygdala R	0.219	[-0.48, 0.75]	0.392	[-0.20, 0.78]	-0.389	0.697	0.852
Nucleus accumbens (NAc) L	0.284	[-0.07, 0.89]	0.424	[-0.17, 0.79]	0.438	0.036	0.852
Caudate nucleus L	0.019	[-0.62, 0.64]	0.526	[-0.04, 0.83]	-1.148	0.251	0.546
Insular cortex R	-0.225	[-0.75, 0.47]	0.586	[0.05, 0.86]	-1.827	0.068	0.372
Ventromedial prefrontal cortex (vmPFC)	-0.728	[-0.93, -0.18]	0.023	[-0.53, 0.57]	-1.923	0.068	0.372
Dorsolateral prefrontal cortex (DLPFC)	0.451	[-0.25, 0.84]	0.364	[-0.23, 0.76]	0.212	0.832	0.906
Medial orbitofrontal cortex (MOFC)	-0.216	[-0.74, 0.48]	0.290	[-0.31, 0.73]	-1.051	0.293	0.546
Anterior cingulate cortex (ACC)	0.105	[-0.56, 0.69]	0.162	[-0.43, 0.65]	-0.118	0.906	0.906

P values compare two independent correlation coefficients using Fisher's r-to-z transformation. Only one significant correlation indicated after FDR correction across 10 tests. PDA: Parkinson disease with apathy; PDNA: Parkinson disease without apathy; HC: Healthy control; P.DBS: postoperative of deep brain stimulation of Subthalamic nucleus; CI: confidence interval; L: Left; R: Right; Statistically significant results are marked in bold.

Table 4. Exploratory DRN-related functional connectivity: omnibus group tests with FDR correction

Seed	Target	PDA (P.DBS/n=10)	PDNA (P.DBS/n=10)	HC (n=10)	Raw P	FDR q	Approx. η^2 †
DRN	Subthalamic nucleus (STN)	6.84	7.84	7.95	0.231	0.329	0.093
DRN	Amygdala R	2.59	7.90	7.92	0.033	0.110	0.203
DRN	Nucleus accumbens (NAc) L	2.58	8.05	7.91	0.325	0.333	0.072
DRN	Caudate nucleus L	2.46	7.56	8.37	0.028	0.118	0.212
DRN	Insular cortex R	6.96	7.82	8.09	0.207	0.329	0.100
DRN	Thalamus L	7.28	7.32	7.63	0.333	0.333	0.071
DRN	Ventromedial prefrontal cortex (vmPFC)	7.09	8.29	8.25	0.263	0.329	0.085
DRN	Dorsolateral prefrontal cortex (DLPFC)	6.73	7.31	8.36	0.204	0.329	0.101
DRN	Medial orbitofrontal cortex (MOFC)	2.51	8.10	8.15	0.021	0.120	0.227
DRN	Anterior cingulate cortex (ACC)	7.14	8.42	8.51	0.238	0.329	0.091

No connection survives Benjamini-Hochberg FDR correction across 10 tests. The numeric metric (approximately 2.5–8.5) is retained from the source table (identified as Pearson r or conventional Fisher-z connectivity). †Approximate η^2 reconstructed from the reported omnibus P value assuming one-way ANOVA with $df=2,30$. PDA: Parkinson disease with apathy; PDNA: Parkinson disease without apathy; HC: Healthy control; P.DBS: postoperative of deep brain stimulation of Subthalamic nucleus; L: Left; R: Right. Statistically significant results are marked in bold.

The functional analysis similarly showed nominal postoperative group differences involving DRN connections with these regions that participate in motivational and reward processing.

Table 5. Correlation between apathy severity and functional connectivity changes (FC values) postoperative in brain regions PDA and PDNA

Region	PDA (P.DBS/n=10)	95% CI	PDNA (P.DBS/n=13)	95% CI	Fisher z	P	FDR q
Dorsal raphe nucleus (DRN)	0.476	[-0.22, 0.89]	-0.068	[-0.60, 0.50]	1.189	0.038	0.249
Subthalamic nucleus (STN)	0.219	[-0.48, 0.75]	0.036	[-0.53, 0.58]	0.379	0.705	0.849
Thalamus L	-0.128	[-0.70, 0.55]	-0.277	[-0.72, 0.32]	0.316	0.752	0.649
Amygdala R	0.307	[-0.40, 0.88]	0.130	[-0.45, 0.64]	0.378	0.041	0.253
Nucleus accumbens (NAc) L	0.126	[-0.55, 0.80]	0.263	[-0.34, 0.87]	-0.289	0.772	0.849

		0.70]		0.71]			
Caudate nucleus L	0.267	[-0.44, 0.77]	0.727	[0.29, 0.91]	-1.316	0.188	0.849
Insular cortex R	0.151	[-0.53, 0.71]	0.407	[-0.19, 0.78]	-0.568	0.670	0.849
Ventromedial prefrontal cortex (vmPFC)	0.128	[-0.55, 0.70]	0.138	[-0.45, 0.64]	-0.021	0.984	0.984
Dorsolateral prefrontal cortex (dLPFC)	-0.232	[-0.75, 0.47]	-0.622	[-0.87, -0.11]	0.998	0.618	0.849
Medial orbitofrontal cortex (mOFC)	0.227	[-0.47, 0.85]	0.080	[-0.49, 0.60]	0.206	0.032	0.231
Anterior cingulate cortex (ACC)	-0.031	[-0.65, 0.61]	0.261	[-0.34, 0.71]	-0.605	0.545	0.649

P values compare independent correlations with Fisher's r-to-z transformation. PDA: Parkinson disease with apathy; PDNA: Parkinson disease without apathy; HC: Healthy control; P.DBS: postoperative of deep brain stimulation of Subthalamic nucleus; CI: confidence interval; L: Left; R: Right. Statistically significant results are marked in bold.

Figures

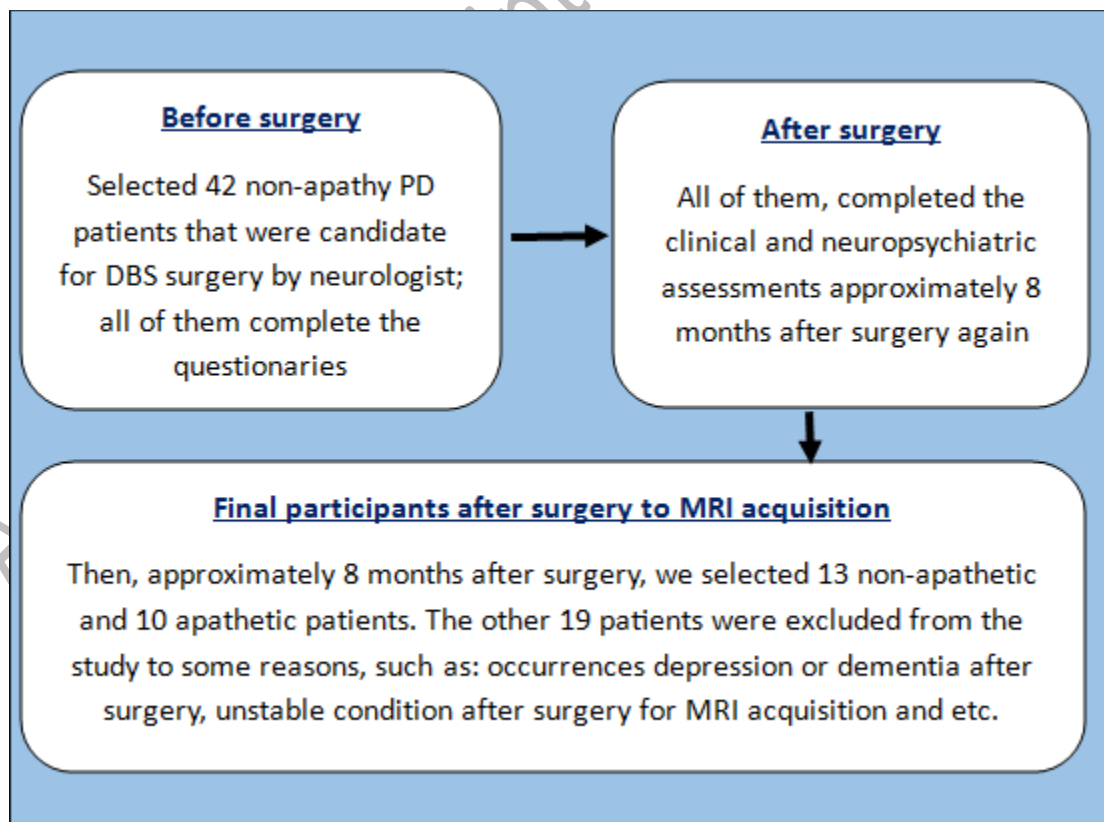


Figure 1: Participant-flow diagram

Figure 1 has been added to provide a more detailed description of the participant selection protocol.

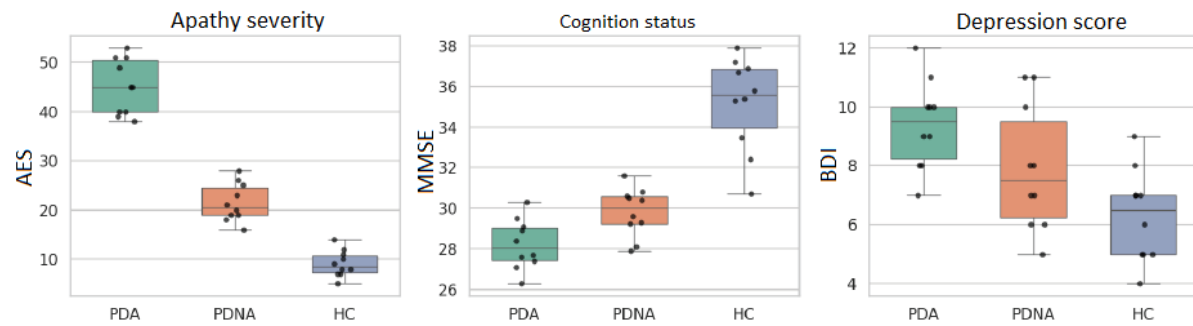


Figure 2: Boxplot comparison of clinical scores among study groups

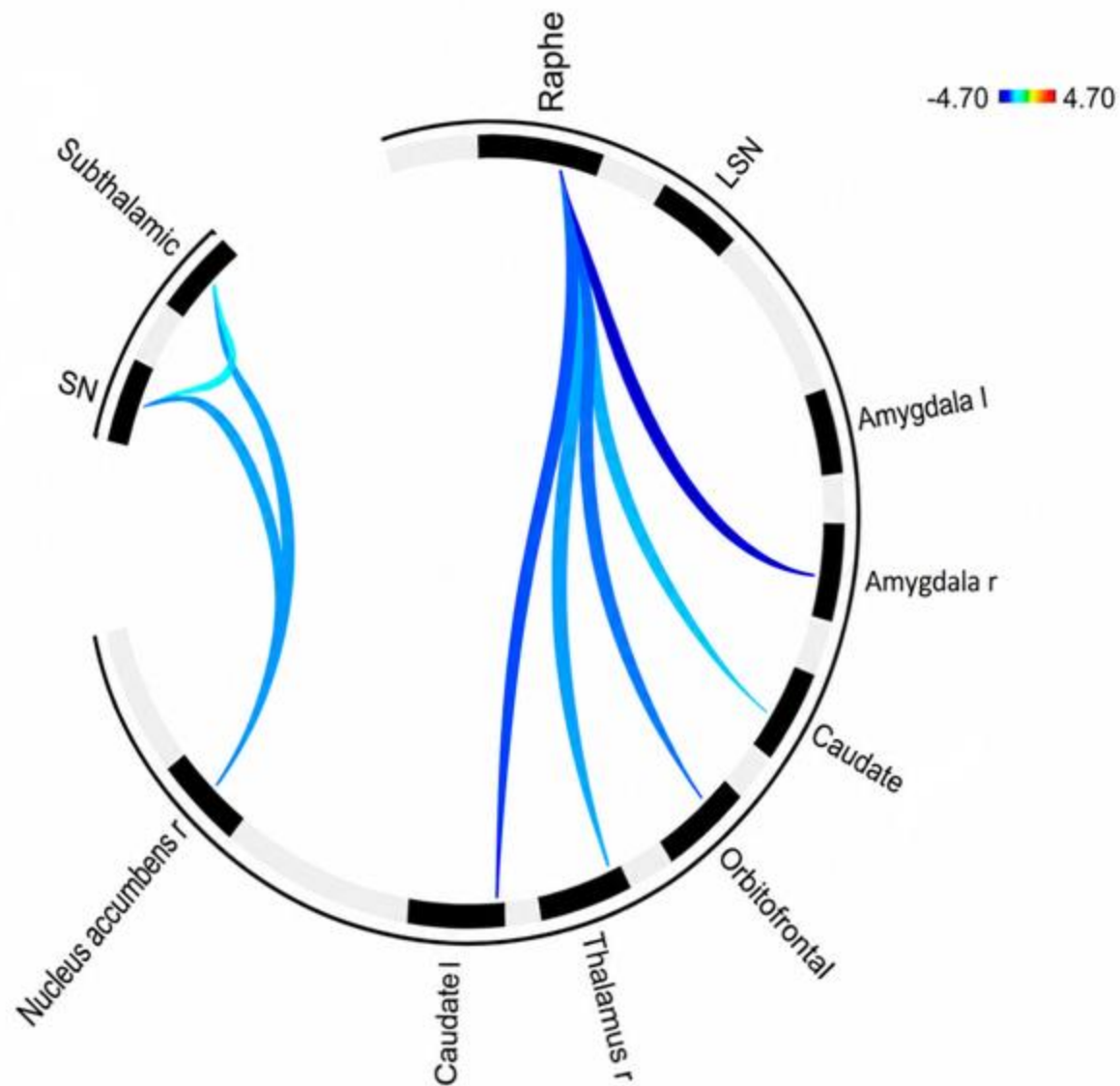


Figure 3. Ringogram showing widespread hypoconnectivity in apathetic Parkinson's disease patients (PDA group) compared to non-apathetic patients (PDA > PDNA). The significant reduction of functional connectivity circuits includes between raphe nucleus with orbitofrontal cortex, caudate nucleus l and amygdala r.

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