Deep brain stimulation and dopamine medication enhance free choice preference in Parkinson's disease

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Abstract

Human decisions are frequently explained as the balancing of potential rewards and punishments, such as food, money, or lost time. However, rational models of decision making based on this idea often fail to accurately predict human behavior. Humans and other animals appear to base decisions on value estimation that is often not clearly linked to extrinsic outcomes. For example, humans prefer to choose, even when doing so has no clear impact on impending rewards or punishments. Thus, choice opportunities may be intrinsically rewarding. There is limited evidence about the mechanisms underlying intrinsic rewards, and it is unclear how deficits in motivation for intrinsic rewards manifest themselves following impairment of brain networks involved in reward processing such as the dopaminergic and cortico-basal ganglia systems. Here we seek to understand how extrinsic and intrinsic rewards act together to guide decisions. We designed a decision-making task that separates the intrinsic value of free choice from the value of extrinsic rewards received for correct performance. We investigated the neural mechanisms underlying choice preference by asking Parkinson's disease patients to perform the task ON and OFF treatment. We tested two groups of patients to explore the effects of dopamine medication and potential modulation of wider cortical areas by deep brain stimulation. One group was treated with acute dopamine replacement therapy, and another group was treated with subthalamic nucleus deep brain stimulation. On average, patients ON dopaminergic treatment preferred to choose even when they risked losing extrinsic rewards (z=3.736, P=0.004). However, we found a significant interaction with the level of *chronic* levodopa therapy (z=2.643, P=0.008); patients with low doses of levodopa treatment in their daily lives did not prefer to choose (z=0.901, P=0.60), nor was this indifference modulated by acute levodopa administration (z=0.227, P=0.996). Deep brain stimulation patients were similarly indifferent to choice opportunities when OFF stimulation (z=-0.95, P=0.339). Like patients with low chronic levodopa treatment in the first group, all deep brain stimulation patients received low-dosage chronic levodopa treatment, which is one of the principal effects of this surgical intervention. Interestingly, in deep brain stimulation patients, choice preference could be re-established by subthalamic nucleus stimulation (z=3.07, P=0.011). This was associated with increased structural connectivity between subthalamic nucleus stimulation sites and the medial frontal cortex (including Brodmann areas 8, 9, and 32; P<0.05 corrected for multiple comparisons). In contrast to healthy humans who typically prefer choice, patients with the most severe dopamine depletion (advanced disease together with low chronic dopamine replacement therapy) did

not prefer to choose. Our results suggests that higher levels of chronic dopamine medication or deep brain stimulation can increase motivation to seek choice opportunities. This is likely due to different mechanisms, with dopamine medication affecting sensitivity to all rewards and deep brain stimulation affecting impulsivity. These results advance our understanding of intrinsic reward and its interplay with general motivational processes associated with behavioral impairments observed in Parkinson's disease and other neuropsychiatric disorders involving the dopaminergic system.

Abbreviations: AC/PC = anterior commissure and posterior commissure; Ago- = without dopaminergic agonist medication; Ago+ = with dopaminergic agonist medication; CT = computerized tomography; DOPA = dopaminergic treatment; DA = dopamine; DBS = deep brain stimulation; DWI = diffusion weighted imaging; FLAIR = fluid attenuated inversion recovery; FOD = fiber orientation diffusions; FWE = familywise error; GLMM = generalized linear mixed models; LEDD = Levodopa Equivalent Daily Dose; LMM = linear mixed model; LOESS = locally estimated scatterplot smoothing; Mg = milligrams; Mm = millimeters; MoCA = Montreal cognitive assessment; Ms = milliseconds; ON = on treatment; OFF = off treatment; P = reward probability; PaCER = precise and convenient electrode reconstruction; PALM = permutation analysis of linear models; RT = reaction time; SD = standard deviation; SIFT = spherical informed filtering technique; STN = subthalamic nucleus; STN-DBS = treatment by deep brain stimulation of the subthalamic nucleus; TD = track density; TFCE = threshold-free cluster enhancement approach; TRAC/CORE = trajectory reconstruction and contact reconstruction; UPDRS = Unified Parkinson's disease Rating Scale; VAT = volume of activated tissue

Introduction

Although Parkinson's disease is characterized by prominent motor symptoms, non-motor symptoms are increasingly recognized as an important component of the disease. These include neuropsychiatric manifestations which can be alleviated, aggravated or even triggered by treatments such as dopamine replacement therapy and deep brain stimulation (DBS) of the subthalamic nucleus (STN) within the basal ganglia [1–3]. For instance, administration of dopaminergic medication in Parkinson's disease patients influence value-based learning. Dopamine (DA) neurons encode a positive, null or negative reward prediction error signal that provides information from stimuli that respectively provide more, equal or less reward that expected [8,9]. In Parkinson's disease, DA replacement therapy may alters this prediction error to enhance learning from positive rewards and reduce learning from negative outcomes [10–12]. On the other hand, STN hyperactivity resulting from DA loss can be restored by DBS. While STN-DBS improves motor symptoms, it can lead to alterations in decision making, such as impulsive choices. Indeed, patients show faster responses when choosing between two stimuli with similar values, or more generally when distinctions between stimuli are perceptually close, that is in conflictual situations [29–31]. This response to conflict is associated with the direct projections of cortical regions to the STN (the "hyperdirect" pathway) that allows fast inhibitory control of decisional processes [30,32]. DBS induces a more permissive decisional threshold with distinct motor and non-motor effects in relation to the functional organization of the STN [33] through the modulation of STN response and its distinct cortical projections. Precisely, while posterior regions are involved in sensorimotor functions, the most anterior regions are related to limbic and associative processes [34,35].

While these manipulations highlight the role of DA and associated basal ganglia circuits in outcome-based decision-making, they focus exclusively on extrinsic outcomes (i.e., feedback indicating correctness or explicit outcomes such as money or points earned). Decisions may also be intrinsically motivated, that is, driven by an inherent satisfaction distinct from extrinsic rewards or punishments [13]. For example, several species prefer access to opportunities to choose, even when this has no impact on immediate extrinsic outcomes [14–17]. Although choice preference appears economically irrational, it is proposed that opportunities to choose are intrinsically rewarding because they offer potential control over ones' environment [13,15]. Personal control is central in numerous psychological theories, where constructs such as autonomy [13,18], controllability [19,20], personal causation [21], effectance [22],

perceived behavioral control [23] or self-efficacy [19] are key for motivating behaviors that are not economically rational or easily explained as satisfying basic drives such as hunger, thirst, sex, or pain avoidance [24]. The DA and basal ganglia networks may be important in the processing of both extrinsic and intrinsic rewards. This is supported by the observation that midbrain DA neurons encode the inferred value of visual cues that are informative, without changing the rate of extrinsic reward [25]. Striatal activation is also enhanced when subjects can choose freely (compared to forced selections of equivalent value), or even simply when subjects know that free choice is available [26,27]. In addition, some evidence suggests that specific polymorphism in genes involved in the DA signal transduction is related to enhanced preference for freely chosen items compared to items that are forced to sample [28]. However, it remains unclear whether intrinsic rewards such as the opportunity to choose are altered by dysfunction of the DA and basal ganglia system. To investigate both the role of DA and basal ganglia networks in the intrinsic motivation for choice opportunities, we designed a task where participants revealed their preference by selecting between free- and forced-choice options. We explored the involvement of the dopaminergic and basal ganglia systems in free choice preference by testing two separate groups of Parkinson's disease patients: one treated with dopamine replacement therapy alone and one treated by STN-DBS. We tested both groups with and without treatment. Patients ON dopaminergic treatment preferred opportunities to choose, and this preference was not changed by acute levodopa administration. Interestingly, choice preference was absent in a subgroup of patients treated with low-dosage chronic levodopa therapy. In STN-DBS patients, where chronic dopamine replacement therapy was lowered following surgery, choice preference was also absent OFF stimulation. However, choice preference was re-established when turning ON stimulation, which was associated with increased connectivity between the subthalamic nucleus and the medial frontal cortex.

Materials and methods

Participants

We recruited 45 patients through the neurology and neurosurgery services at the Pitié-Salpêtrière Hospital (Paris, France). Parkinson's disease was diagnosed following the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [36]. Exclusion

criteria included the presence of a significant cognitive impairment (MoCA <= 25) or concomitant significant neurological or psychiatric disease. For the first group of patients (DOPA group, *n* = 25, 7 females), inclusions were assessed during a visit at the hospital for evaluation of eligibility for DBS surgery. Patients who already underwent STN-DBS surgery constitute the second group (STN-DBS group, *n* = 20, 9 females) and were recruited (delay after surgery: 15 months +/-5.3 SD) during a routine follow-up visit. Eight were implanted with Medtronic 3389 electrode (Medtronic Inc., Minneapolis, MN, USA) and the remaining twelve were implanted with Boston Vercise Cartesia directional electrode (Boston Scientific, Marlborough, MA). Among the latter, five had steering current on at least one of the two electrodes (one electrode per hemisphere for all patients). Details of stimulation parameters are provided in Supplementary Table 1. The sample size was chosen based on previous studies investigating the value of free choice[15,37]. All the patients were fully informed of the study approved by the local ethics committee and gave consent in accordance with the Declaration of Helsinki and.

Task description

Patients were seated in front of an LCD screen (15,6 inches, resolution 1920 x 1080) and were told that they would be presented with different pairs of fractal images (targets), which were associated with different probabilities of being rewarded. The goal of the task was to accumulate the maximal amount of reward symbolized by a virtual green euro (€) on the screen. Patients could select these fractal targets in two different ways: either by choosing themselves (*free*) or by performing a computer-selected action (*forced*). They received oral and written instructions and before starting the task they performed a dozen trials to familiarize themselves with the task structure. Patients used their preferred hand to select targets with the left and right buttons on the computer keyboard.

The task consisted of a series of trials each with a two-stage structure. For each trial, during the first stage, two image targets were displayed on the screen representing the *free* or *forced* options and patients had to make an initial selection. At the second stage, two different targets were displayed. In the *free* option, patients could choose either of the two second-stage targets, while in the *forced* option they were obliged to select the one that was preselected by the computer. This mandatory second-stage forced target was indicated by a grey V-shape above the image. During this *forced* condition, the computer always selected the same target and selection of the other image was disabled. During both stages, after

pressing one of the two keys, patients received a visual cue displayed above their selected target (red V-shape) that confirmed their selection. After selecting the second-stage target, the reward outcome was displayed and could be either the green euro symbol when the trial was rewarded or a black zero when the reward was absent (Figure 1).

Importantly, before each testing phase, patients performed a training phase to learn the contingencies between the different targets and their associated reward probabilities. During this phase patients did not choose between *free* or *forced* options and they therefore performed mandatory *free* of *forced* trials in succession (e.g., 48 forced then 48 free trials or 24 trials in free and forced when the reward delivery were deterministic, see below). Patients were explicitly informed that the stimuli remained identical between training and testing phases.

We varied reward contingencies in three different blocks, a block being defined as one training follow by one testing phase (48 trials) with the same reward probability. In one block the reward delivery was stochastic, and all the second-stage targets were associated with a reward probability of P = 0.5. In another block, the probabilities of reward for the forced second-stage target and the most rewarded second-stage target in the *free* option were set at P = 0.75, and at 1-P for the less rewarded target. In the last block, reward delivery was deterministic and selecting the target in forced or the most rewarded in free always led to a reward (P=1) while choosing the other target in free led systematically to its absence (P=0). Thus, because, in *forced* option, the computer always selected the most rewarded target (when P > 0.5), reward contingencies were identical between the *free* and *forced* options. However the target images were different between options as well as in all the different blocks. The task was written using the Psychophysics Toolbox (http://psychtoolbox.org/) running MATLAB (Natick, Massachusetts: The MathWorks Inc).

Procedure

Patients in both the DOPA and STN-DBS groups performed the task twice, ON and OFF treatment. The patients in the STN-DBS group were OFF medication for both sessions to focus on the effect of stimulation. All the target images were also different between the OFF and ON sessions.

The acute dopaminergic challenge and ON/OFF testing of DBS patients were part of standard clinical follow-up for the included patients. For the DOPA group, OFF sessions took place

following discontinuation of levodopa treatment for 12 hours and dopamine agonist treatments for 72 hours. This procedure was implemented to wash-out antiparkinsonian pharmacological treatments. ON sessions took place the same day, 45 minutes after taking the levodopa equivalent dose of their usual morning treatment plus 50 mg of levodopa.

For the STN-DBS group, the wash-out of pharmacological treatments for both ON and OFF sessions were the same as for the DOPA group. ON sessions (stimulation ON) took place first and OFF sessions start at least an hour after stimulation was stopped.

Patients could discontinue the experiment at any time. In the STN-DBS group, 18 out of 20 patients performed the P=1 and P=0.5 block. In the DOPA group, 13 out of 25 patients performed the P=0.5 block and 20 out of 25 patients performed the P=1 block. All patients in both groups performed the P=0.75 block.

Subgroup analyses

We distinguished between the use of dopaminergic agonists and the total amount of remaining treatment (Levodopa Equivalent Daily Dose, LEDD). We used the median LEDD to split patients into those who received low (≤1050 mg, n =13) or high (>1050 mg, n =12) amount of LEDD. We used this transformation instead of continuous LEDD because the quantity of medication was very skewed and followed a bimodal distribution with one peak of LEDD at 971 and another at 1550 mg. Mean LEDD in patients with high LEDD was 1646 and 887 for those with low LEDD (Supplementary Fig. 1). This categorization approach was also performed in a large scale study assessing behavioral changes in Parkinson's disease [38]. Similarly, we considered the use of dopaminergic agonists as a categorical variable because of a quasi-equivalence between users (Ago+, n = 11) and non-users (Ago-, n = 14). One sample Wilcoxon tests for each group compared to the respective peaks of the bimodal distribution showed no statistical difference (high-LEDD: W = 52, P = 0.675, low-LEDD: W = 19, P = 0.126).

Statistical analyses

We used mixed effect models to account for the nested nature of the data (lme4 package, R Core Team, https://www.R-project.org). Generalized linear mixed models (GLMMs) were used for binary variables (first- and second-stage choices). Main effects and interactions of

the models were reported using Wald's z statistics and corresponding *P*-values. For reaction times, we used linear mixed models (LMMs) and reported t-statistics and corresponding *P*-values for main effects and interactions. Patients were treated as a random effect for all models. One slope for each fixed effect was added to the random part of the model when possible; slopes were added to the random component hierarchically until singularity of the model [39,40]. Before analysis, continuous fixed effects were scaled across the whole data and reaction times above 2-fold median absolute deviation across the entire dataset were removed [41]. We included in the model the actual obtained reward probability, calculated as the mean of all the rewarded trials during training and testing, for every programmed reward probability.

Post-hoc statistics were calculated using the *emmeans* packages in R, adjusted for multiple comparisons using Tukey method, and *P*-values were calculated using a *z*-statistic as provided by default in the *emmeans* package in R (https://CRAN.R-project.org/package=emmeans). We used two-sample Wilcoxon tests for demographic statistics.

Image processing

Preoperative MRI volumetric T1-weighted, T2-weighted FLAIR sequences and postoperative CT scans were obtained for the 20 patients of the STN-DBS group. We pre-processed images with LEAD-DBS pipelines [42] using the default settings. We visually checked the outcome at every step of the procedure. CT images were co-registered to MRI T1-weighted sequences using a two-stage linear registration as implemented in Advanced Normalization Tools [43], and MRI FLAIR sequence was linearly co-registered to T1-weighted using SPM12 [44]. Pre- and post-operative acquisitions were spatially normalized into MNI_ICBM_2009b_NLIN_ASYM space[45] using the SyN registration approach as implemented in Advanced Normalization Tools [43], adding two supplementary nonlinear SyN-registrations that consecutively focused on the basal ganglia as defined by subcortical masks in Schönecker et al. (2009).

DBS electrodes localizations were corrected for brainshift in postoperative acquisitions by applying a refined affine transform calculated between pre- and post-operative acquisitions that were restricted to a subcortical area of interest, as implemented in the brainshift-correction module of Lead-DBS software [47]. Electrodes were automatically pre-localized using the precise and convenient electrode reconstruction (PaCER) algorithm [48]. For one patient, the PaCER algorithm failed and TRAC/CORE was used instead [47]. Visual

verification of the reconstruction and manual correction were performed if necessary. For patients with directional leads, orientation was determined using the Direction orientation detection (DiODE) algorithm implemented in LEAD-DBS [49]. Coordinates were then converted from the MNI space into AC/PC coordinates (relative to the posterior commissure point) using LEAD-DBS [50].

After normalization and localization of electrode trajectories, volume of activated tissue (VAT) for each electrode were estimated using a finite element approach based on a four-compartment tetrahedral mesh as detailed in Horn et al. (2017). The resulting estimated E-field was thresholded above 0.2 V/mm to obtain finite volumes.

Tractography analysis

We assessed cortical connectivity with VATs using a high-definition normative Parkinson's disease connectome [51,52] that was created using multi-shell diffusion weighted imaging (DWI) data from a local cohort of 33 patients with Parkinson's disease as explained in our previous study [34]. For each individual DWI data fiber orientation diffusions (FOD) were calculated and using affine and diffeomorphic registration a FOD template was created using MRtrix [53]. We generated whole brain probabilistic tractography using FOD templates, and obtained a weighting factor for each streamline using spherical informed filtering technique (SIFT2) for the quantitative connectivity assessment [54,55]. An anatomical template was also created in the same space as the normative Parkinson's disease connectome for the segmentation of 39 Brodmann areas as explained previously [56].

Each individual VAT mask was reconstructed in the normative PD-connectome space and cortical connectivity of each VAT with the 39 Brodmann areas was extracted from the whole brain tractogram. For each extracted cortico-VAT connectivity, corresponding track density (TD) maps were created using SIFT2 weights for statistical analysis. These density maps are 3D images that reflect the intra-axonal volume within the voxel [54]. We created cortical TD maps by overlapping the TD maps with each binary cortical masks. Those cortical track-density maps correspond to the cortical connectivity of each VAT of each patient were then merged in a 4D volume for statistical analysis.

We performed voxelwise analysis using PALM from FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM) to compute statistical maps using permutation methods. Two-sample *t*-tests were performed for each voxel of the volume, with 1000

permutations. *P*-values were corrected using familywise error (FWE) with the threshold-free cluster enhancement approach (TFCE) that could provide reliable correction at the voxel level[57].

To assess the effect of DBS on preference for choice, we used the difference between preference for choice ON minus OFF treatment, averaged across the reward probabilities. We then split the STN-DBS cohort into patients with low DBS effect (low ON-OFF difference) and those with a high DBS effect using the median. This categorization was justified by the skewed distribution of the ON-OFF difference, with a peak around zero and more distributed values above it. We treated patients in the low ON-OFF free choice difference group as the reference group. The contrast matrix provided two statistical maps: one which contains voxels with positive t-values associated with higher connectivity in the high ON-OFF group and the other associated to the opposite, i.e., positive t-values were associated with higher connectivity in the low ON-OFF group.

Data availability

Anonymized data used for the analyses are available upon reasonable request.

Results

Demographic data

We studied choice preference in two groups of Parkinson's disease patients, one group with DBS of the STN tested, without their dopaminergic treatment, ON and OFF stimulation (STN-DBS group, $n = 20$), and a second group of patients tested OFF and ON acute oral levodopa treatment (DOPA group, $n = 25$). Patient demographics are listed in Table 1. As expected, LEDD was significantly lower for STN-DBS compared to DOPA patients ($W = 494$, $P < 0.0001$). They were comparable for age ($P = 0.226$), disease duration ($P = 0.113$), cognition ($P = 0.087$) and severity as assessed by the UPDRS III during OFF ($P = 0.355$).

We asked these patients to perform the behavioral task. They had to make a first decision between the opportunity to choose from two terminal actions (*free*) or to perform a mandatory computer-selected terminal action (*forced*), which they then actualized in the second stage (Figure 1).

Choice behaviors

First-stage preference for free choice

We examined first-stage choice preference by looking at how often patients selected the *free* option in the first stage of the task (Figure 2A). We used a GLMM to test for an interaction between patient group (STN-DBS or DOPA), treatment (ON or OFF), and reward probability (calculated using obtained rewards over each block). We found a significant two-way interaction (group x treatment, z = -2.12, P = 0.034), while the three-way interaction (group x treatment x reward probability) was not significant (z = -0.57, P = 0.570). The main effect for reward probability was marginal (z = 1.95, P = 0.051). Post-hoc tests revealed that STN-DBS patients preferred the *free* option more when ON DBS compared to OFF DBS, (63% vs. 44%, z = 3.07, P = 0.011). Indeed, the average choice preference OFF DBS was not significantly different from chance level (44% vs. 50%, z = -0.95, P = 0.339). By contrast, the free choice preference in the DOPA patient group was significantly greater than 50% for all reward probabilities (z = 3.736, P = 0.004), and acute levodopa challenge did not affect this preference (72 % OFF vs. 71% ON, z = 0.227, P = 0.996). Comparison between patient groups revealed that free choice preference was significantly greater OFF DOPA compared to OFF DBS (z = 2.78, P = 0.032) and ON DOPA compared to OFF DBS (z = 3.00, P = 0.014), but was not significantly different between ON DOPA compared to ON DBS (z = 0.89, P = 0.810).

We next investigated the evolution of first choice behavior over the course of the different blocks over which the programmed reward probability was constant. For each block, the average percentage of *free* selections was approximately constant for both the STN-DBS and DOPA groups and did not vary over time with treatment (Figure 2B). Notably, when present, free choice preference was immediately expressed from the beginning of the testing phase.

Second-stage target selection during free choice

We next investigated behavior at the second-stage of the task to determine whether differences in obtained rewards could explain free choice preference. For example, for two blocks (P=0.75 and P=1) one of the second-stage targets was more highly rewarded in the *free* option, and patients may have exhibited choice avoidance because they failed to learn the

reward contingencies and therefore earned fewer rewards compared to the computer-selected action (which always led the higher-rewarded target).

We assessed patients' understanding of reward contingencies at P=0.75 and P=1 by looking at how frequently they selected the more highly rewarded target in the second-stage during the test phase. We used a GLMM to test for an interaction between patient group (STN-DBS or DOPA), treatment (ON or OFF), and reward probability (obtained reward over block). We found a significant two-way interaction (group x treatment, z = -3.98, P < 0.001), and the three-way interaction (group x treatment x reward probability) was not significant (z = 1.326, P = 0.185). Post-hoc analysis revealed that both patient groups preferred the more highly rewarded target (DOPA=82%, z = 7.32, P < 0.0001; DBS=81%, z = 6.91, P < 0.00001), indicating that they learned the reward contingencies. Looking at specific blocks by treatment condition, we observed that the DOPA patient group performed worse ON DOPA compared to OFF DOPA during the P=0.75 block (74% vs 88%, z = -1.992, P = 0.046). By contrast, patients OFF DBS performed worse than when they were ON DBS at P=0.75 only (83% vs 94%, z = 3.37 P = 0.001). We also examined how selection of the most rewarded target in free option changed across the blocks where the programmed reward probability was held constant at P=0.75 and P=1. The temporal dynamic of second-stage choices shows that while patients in the STN-DBS group increased selection of the highly rewarded targets over the block, this did not appear to be associated with first-stage choice preference (Supplementary Fig. 2).

Reaction times

First-stage reaction time differences while choosing free and forced options

We examined whether patients were faster or slower for selecting the *free* or *forced* options at the first stage. We used a LMM to test for an interaction between patient group (STN-DBS or DOPA), treatment (ON or OFF), and first-stage choice (*free* or *forced*). We found a significant three-way interaction (group x treatment x first-stage choice, t = 3.46, P = 0.0006). Post-hoc tests revealed that DBS patients were faster when selecting *free* compared to *forced* when they were ON DBS (-230ms, z = 4.37, P = 0.0001), and were faster ON compared to OFF when they were selecting *free* (196 ms, z = 2.70, P = 0.035; Figure 3). There was no main effect for group (t = -0.210, P = 0.834) or group x treatment (t = -0.434, P

= 0.666), indicating that DBS patients were not generally faster at making a first-stage choice compared to DOPA patients.

Second-stage reaction times during target selection

We used the same LMM to examine second-stage reaction times. We found significant main effects for treatment (t = -2.788, P = 0.007) and reward probability (t = -2.993, P = 0.005), with no significant interactions with patient group (P > 0.176). Post-hoc tests revealed that reaction times were significantly faster ON treatment compared to OFF treatment (-92 ms DBS, -31 ms DOPA, z = 2.681, P = 0.007), and faster when reward probability was higher (-36 ms DBS for P = 0.50 vs. P = 1, - 41.5ms DOPA, z = 2.993, P = 0.003).

Tractography results in STN-DBS patients

The coordinates of active stimulation contacts were not different between left and right hemispheres (two-sample: W = 771, P = 0.477), nor did they differ along the dorso-ventral axis (W = 802, P = 0.298). We found a significant difference in the antero-posterior axis with right electrodes being slightly more anterior than left (left: y = 10.2; right: y = 10.8; W = 431, P = 0.004); Left and right VAT volumes were not statistically different, although right VATs were bigger on average (left: 74 mm^3, right 95 mm^3, W = 155, P = 0.231).

Voxelwise analysis highlighted a subregion of the right dorsomedial prefrontal cortex and anterior cingulate cortex (total volume significant voxels: 436 mm^3) where connectivity with VATs was significantly higher in STN-DBS patients who selected the *free* option more ON compared to OFF (Figure 4, upper panels). We did not observe any significant voxels with the inverse contrast, i.e., voxels with higher connectivity in patients who selected more the *forced* option ON compared to OFF.

This difference in connectivity between the STN and the prefrontal cortex represents the difference in the electrode STN implantation sites between patients. Indeed, while the targeted area within the STN is at the edge of the sensorimotor and associative territories of the STN, small differences of contact localisation in the x,y and z axis existed between patients (Supplementary Fig. 3).

Subgroup analyses of the DOPA patients

We next investigated whether heterogeneity in pharmacological therapy could influence choice preference in the DOPA patient group. We split patients in the DOPA group by dosages of dopamine agonist and other dopamine replacement therapy (see Materials and methods). We then used a GLMM to model choice preference, including factors for levels of long-term dopaminergic medication and their interaction (high or low, dopamine agonist [Ago] or other dopamine replacement [LEDD]). We found a significant interaction of LEDD x Ago (z = -2.53, P = 0.01). Post-hoc tests revealed that for patients without agonists (Ago-), those with high LEDD selected the *free* option significantly more than those with low LEDD (80% vs. 54%, z = 3.55 P = 0.002; Figure 5A). Furthermore, among patients with high LEDD, Ago- patients selected the *free* option significantly more than Ago+ patients (80% vs. 69%, z = -2.69, P = 0.036; Figure 5A). Interestingly, acute levodopa treatment did not interact with any terms of the model (P > 0.216), nor did we find a significant main effect of the reward probability (z = -0.594, P = 0.55).

We also examined first-stage reaction times by DOPA patient subgroups, finding significant two-way interaction (LEDD x treatment, t = -2.71 P = 0.01), and a marginal three-way interaction (Ago x LEDD x treatment, t = 1.94, P = 0.059). Post-hoc analyses revealed that among patients without dopamine agonists (Ago-), patients with high LEDD and were faster ON compared to OFF acute levodopa treatment (z = 2.06, P = 0.044). Also, ON patients were faster if they received high LEDD compared to low LEDD (z = 2.572, P = 0.010, Figure 5B). Although patients with high LEDD were faster than those with low LEDD this effect was not significant (876 ms vs 1003 ms, t = 0.270, P = 0.789).

Discussion

Intrinsic motivation is a construct used to explain behavior that an agent apparently performs independently of extrinsic outcomes [13]. Neural mechanisms underlying intrinsic motivation remain unclear, and no direct evidence exists regarding whether such behaviors are impaired in neurodegenerative disorders with neuropsychiatric symptoms like Parkinson's disease. Because the preference for choice opportunities is well established in humans, we used it as a type of intrinsic reward to investigate these questions. We used a paradigm that allowed participants to choose between the opportunity to choose again or to make a computer-selected action, and we characterized how intrinsic motivation is impaired in Parkinson's

disease. For the first time, while keeping extrinsic reward equal between options with or without choice opportunity, we were able to characterize conditions that diminish intrinsic preference for choice at a group level. Indeed, our results shows that chronic low level of levodopa diminished preference for choice opportunity in patients that either were treated with dopaminergic or STN-DBS therapies. However, either high doses of chronic levodopa, dopaminergic agonists, or stimulation of the STN-MF cortex network reestablishes this preference.

STN stimulation reestablishes intrinsic motivation for free choice opportunity

We observed that Parkinson's disease patients OFF DBS were indifferent between the *free* and *forced* options, while ON DBS they increased their free choice preference to a level close to that observed in healthy humans using similar experimental designs [15,37]. This improvement in choice preference was associated with increased connectivity between medial frontal cortical (MFC) and the VATs constructed with individual parameters of each patient side by side. The cortical areas involved included Brodmann's areas 8, 9, and 32, consistent with the current knowledge about the connectivity of the STN with non-motor cortical areas [35,56]. These MFC regions have been classically related to the processing of conflicting information and generation of voluntary action as well as response inhibition in stimulated patients[58]. For example, a STN-DBS-induced decrease in cerebral blood flow in this region is correlated with more impulsive responses [29,59]. Computational modeling in Parkinson's disease patients revealed that stimulated patients had a more permissive decision threshold during conflict [31,60], which was also related to the MFC in an EEG study [30].

Alternatively, MFC including the dorsal anterior cingulate cortex also appears important during value-based decision making [61–63]. Although these studies focused on extrinsic rewards (e.g., money or fluids), it is possible that MFC is involved in encoding intrinsic value, consistent with work indicating that this region is important for the sense of agency associated with voluntary decisions [64,65]. It might be the case that DBS antidromically activates projections from the MFC to the STN, reestablishing the sense of agency associated with voluntary actions leading to positive consequences. An improved sense of agency, and no better performance per se, is supported by the observation that patients correctly learned the reward contingencies both OFF and ON DBS.

DBS may also have additional effects besides the modulation of cortico-STN fibers[66]. One possibility is modulation of neurons within the STN itself. Recordings in the STN show sub-populations of neurons responding to distinct rewards, encoding their aversive or appetitive character as well as motivational information [67–69]. Similar results have been obtained in Parkinson's disease patients during neuronal recordings and analysis of local field potentials showing that STN activity is correlated with motivation to obtain a monetary reward as well as the subjective value of rewarded stimuli [70,71]. It has also been shown that STN-DBS promotes incentive of reward-based actions [71,72]. This raises the possibility that a pro-motivational effect could come from activation of widespread dopaminergic axons projecting to the STN [73–75], consistent with well-established role of the dopaminergic system in extrinsic reward processing [76,77] as well as the intrinsically rewarding property of information [25]. Thus, STN-DBS in Parkinson's disease could reestablish free choice preference by activating the dopaminergic terminals found in the STN. This motivational effect is consistent with STN stimulation leading to faster reaction times specifically when patients selected the *free* option.

A role for dopamine is further suggested by the observation that STN-DBS patients OFF stimulation were indifferent between the *free* and *forced* options. This could be due to the substantial reduction of dopaminergic medication in this specific group.

Chronic low doses of levodopa impair free choice preference

To further investigate the role of dopamine in intrinsic motivation, we asked whether dopamine replacement therapy modulates choice preference in a second group of Parkinson's disease patients. We found that on average patients in the DOPA group preferred choice at a similar level to healthy humans [15,37], independent of acute levodopa treatment. However, chronic medication type can influence behavioral (dys)functions in distinct manners [3,78]. For example, both dopaminergic agonists and high doses of levodopa could lead to different forms of impulsive and compulsive behaviors [38,79–81]. Therefore, we asked how different chronic pharmacological therapies affected choice preference. We found that patients with the lowest amount of dopaminergic treatment (low LEDD and Ago-) were indifferent between the *free* and *forced* options. By contrast, patients with increased dopaminergic treatment, be it through levodopa or dopamine agonists, preferred free choice like healthy humans. These findings in the DOPA group rejoin those of the STN-DBS group since in both groups a lower level of chronic dopaminergic treatment yielded indifference between free and forced choice. This suggests that dopaminergic depletion is involved in motivation for

intrinsic reward although acute dopaminergic treatment was not sufficient to reestablish this preference. Additionally, Ago-/low LEDD patients produced the slowest first-stage reaction times compared to the other DOPA subgroups. The sustained choice preference in DOPA group patients is interesting since they did not always select the most rewarded target in the second-stage (although they performed well above chance). This is economically irrational since it decreases the expected value of the *free* option compared to the *forced* option where the computer always selected the most rewarded target. This is strictly true during the deterministic block (P=1) where the forced second-stage target was always rewarded, and the clear choice preference in this block rules out the possibility that patients incorrectly undervalued the *forced* option.

Long-term effects of levodopa are well-known clinically. For example, Parkinson's disease patients show a certain degree of persistent motor improvement after stopping levodopa treatment [82]. This long term response can be observed for days to weeks, which indicates that it is independent of levodopa pharmacokinetics (half-life ~3 hours) [83–85].

Chronic dopaminergic treatment is also responsible of enhanced incentive-based behavior. For example, impulse control disorders are defined as "behavioral addictions" [80] like pathological gambling, hypersexuality, binge eating or compulsive buying. These pathological behaviors are closely related with dopamine agonist intake and to a lesser extent, with levodopa use [38,79]. Other pathological behaviors are rather induced by chronic amount of levodopa like punding, hobbyism, or compulsive use of dopamine replacement therapy [80,86]. Experimental evidences showed that patients with impulse control disorders have enhanced reward sensitivity [87] and are biased toward more risky choices [88]. Interestingly, difference between ON and OFF medication on such behavior seems to be lower than those observed in Parkinson's patients without impulse control disorders, reflecting long term changes independent of the acute dopaminergic status. The mechanisms of such chronic effect on both motor and behavioral changes could be postsynaptic like neuroplasticity inducing enhancement of spine density on striatal neurons[89–91], hypersensitization of striatal D2 receptors [83,92] or increase of firing range of remaining dopaminergic cells presumably due to downregulation of D2-autoreceptors [78,93]. Because dopamine neurons activity can signal congruency of action with expected outcome, that is if ones given action is coherent with specific internal goals [94,95], the potential consequence of such structural modifications is an increase of response rates to actions with higher values. This is due to the enhanced tonic dopaminergic signaling driven by sustained exogenous dopamine levels [89,96].

Regarding dose effects of LEDD on behavioral disorders, observational studies yield contrasting results on impulse control disorder, with significant, weak or no effect of total LEDD on the emergence or severity [38,79,86,97]. This heterogeneity may be due to the inclusion of patients with less advanced disease progression and lower LEDD doses compared to our cohort. However, decreasing LEDD alleviates behavioral symptoms and could induce in extreme cases a withdrawal syndrome defined by the emergence of hypodopaminergic behavioral features like apathy, mood disorders and anxiety [98,99]. This is mostly the case after STN-DBS, which frequently allows for a substantial decrease in oral medication intake. Thus this effect is generally considered as unmasking lesions of the mesolimbic pathway present in more advanced stages of Parkinson's disease patients eligible for STN-DBS [99–101]. Therefore, this could account for choice preference for the OFF DBS patients and lower LEDD patients in the DOPA group. Indeed, both groups were indifferent to free choice opportunities, consistent with a level of dopaminergic treatment insufficient to compensate for impairment in processing of incentive-based stimulus.

Conclusion

Altogether our results support the idea that a hypodopaminergic state can reduce intrinsic motivation. This lack of motivation can however be reestablished with different therapeutic strategies such as the stimulation of specific sub-cortical-prefrontal network or by high chronic doses of levodopa or DA agonists. Our results suggest that, in this experimental context, value of intrinsic reward was not processed similarly to the value of extrinsic reward. Indeed second-stage selection of the most rewarded target was quite similar ON and OFF treatments whereas first-stage preference varied. This might be the case because the intensity of extrinsic rewards was sufficiently high to be efficiently processed either by the remaining dopaminergic system or compensated by other mechanisms.

More generally our results also suggest that depletion of DA and associated impairment of the STN alters intrinsic motivation for choice opportunities. Further investigation should address whether some general motivational deficits in patients could be better explained by a lack of intrinsic motivation in addition to impaired motivation for extrinsic rewards.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

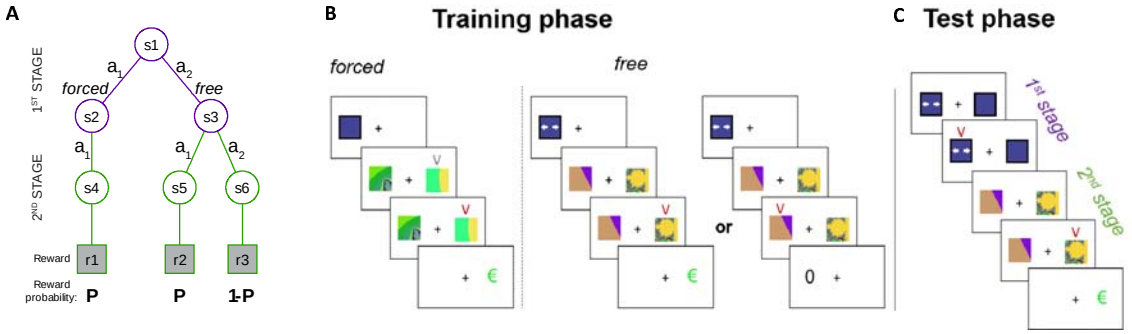

Figure 1 Two-stage task structure. (A) State diagram illustrating the 6 possible states (s), actions (a) and associated extrinsic reward probabilities (e.g., P = 0.5, 0.75 or 1 for blocks 1 to 3, respectively); s2 and s3 were represented by two different 1st-stage targets (e.g., colored squares with or without arrows for free and forced trials, respectively) and s4 to s6 were associated to three different 2nd-stage targets (fractals). **(B)** Illustration of typical trials during the training phase. For each probability block, participants learned the reward contingencies (green euro symbol) associated to the second-stage targets in forced and free option. When training for forced choice, participants had to select the target indicated by a V-shape grey symbol. When training for free choice, participants could freely select one of the two targets.

V-shape red symbol indicated participant's selection after keypress. **(C)** Schematic illustration of a trial during test phase. At first-stage, participants had to select if they wanted to perform the trial either in the free or forced option.

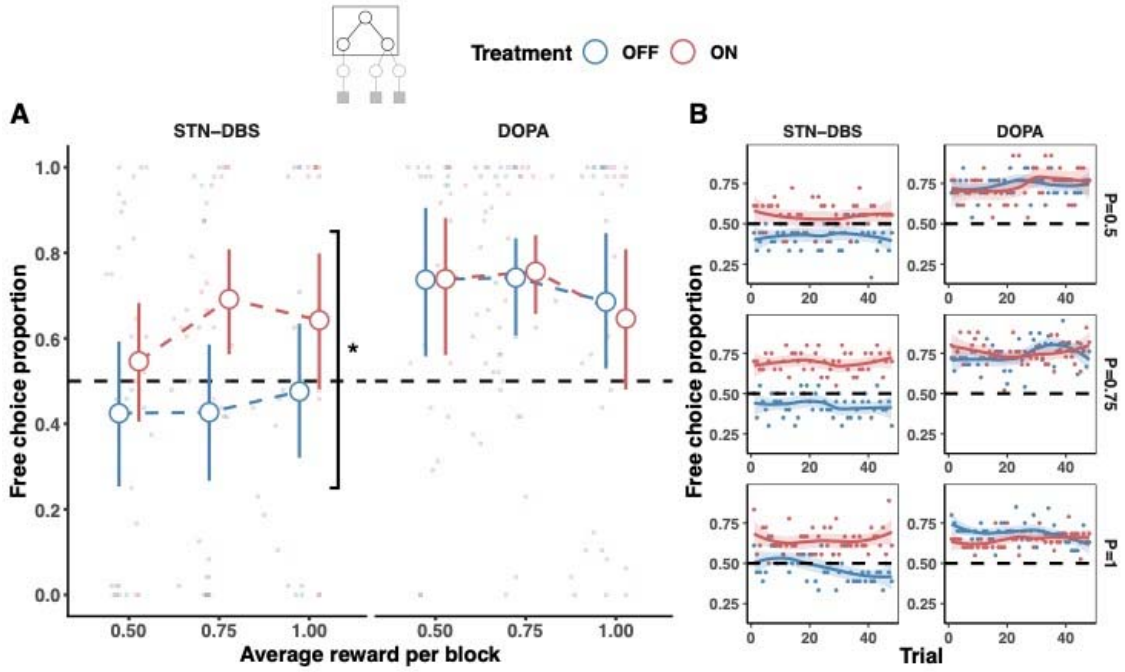

Figure 2 Free choice preference at the first-stage. (A) Free choice preference in the STN-DBS (left) and DOPA (right) groups of Parkinson's disease patients. Small colored dots represent the mean free choice preference for each patient, plotted against the mean obtained reward. Large empty circles represent the mean free choice preference per block among all patients by group (STN-DBS and DOPA). Red and blue for ON and OFF sessions respectively. Error bars correspond to the 95% confidence interval. The asterisk and black vertical line represent the significant difference between ON and OFF patients (*P*=0.011). **(B)** Temporal dynamic of free choice preference across the task per block in the two groups of Parkinson's disease patients. Small dots represent mean free choice preference at the trial level among all patients. Lines represent LOESS smoothing and their respective standard errors. The horizontal dashed lines represent chance level.

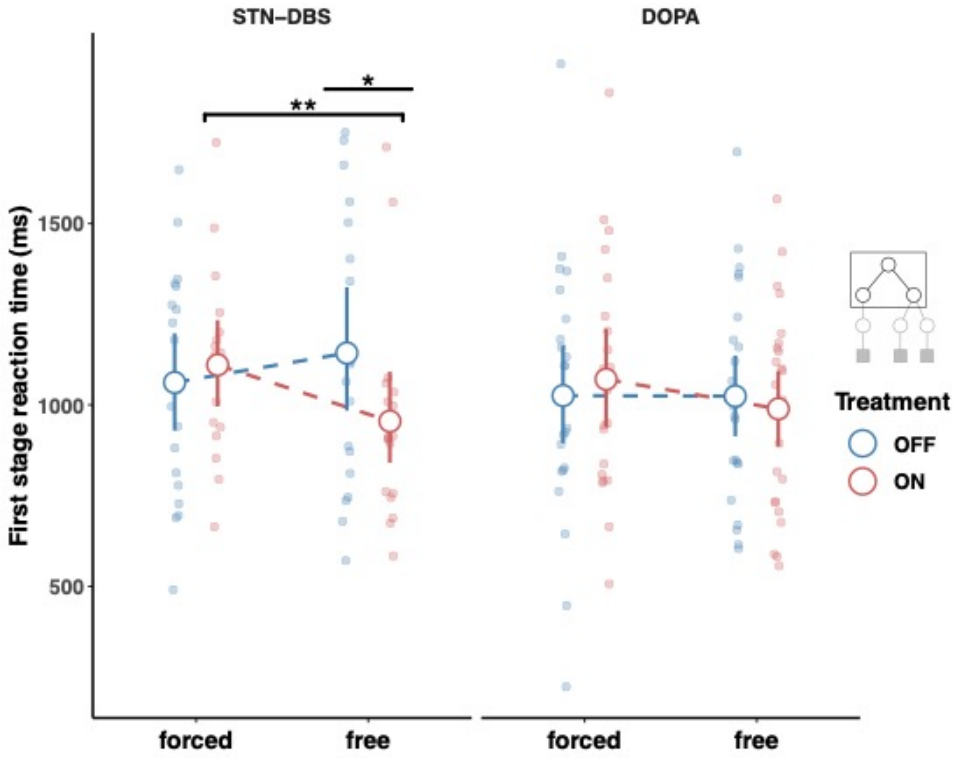

Figure 3 Reaction times (RT) during first-stage selection. Red (ON) and blue (OFF) dots represent the mean individual RT of STN-DBS (left) and DOPA (right) Parkinson's disease patients while selecting forced or free option. Large empty circles represent the mean RT. Errorbars correspond to 95% confidence interval. For the STN-DBS group, the bracket with two asterisks on top represents a significant difference between free and forced options for ON patients (*P*=0.0001). The horizontal line with one asterisk represents the significant difference between ON and OFF sessions for STN-DBS patients selecting free option (*P*=0.035).

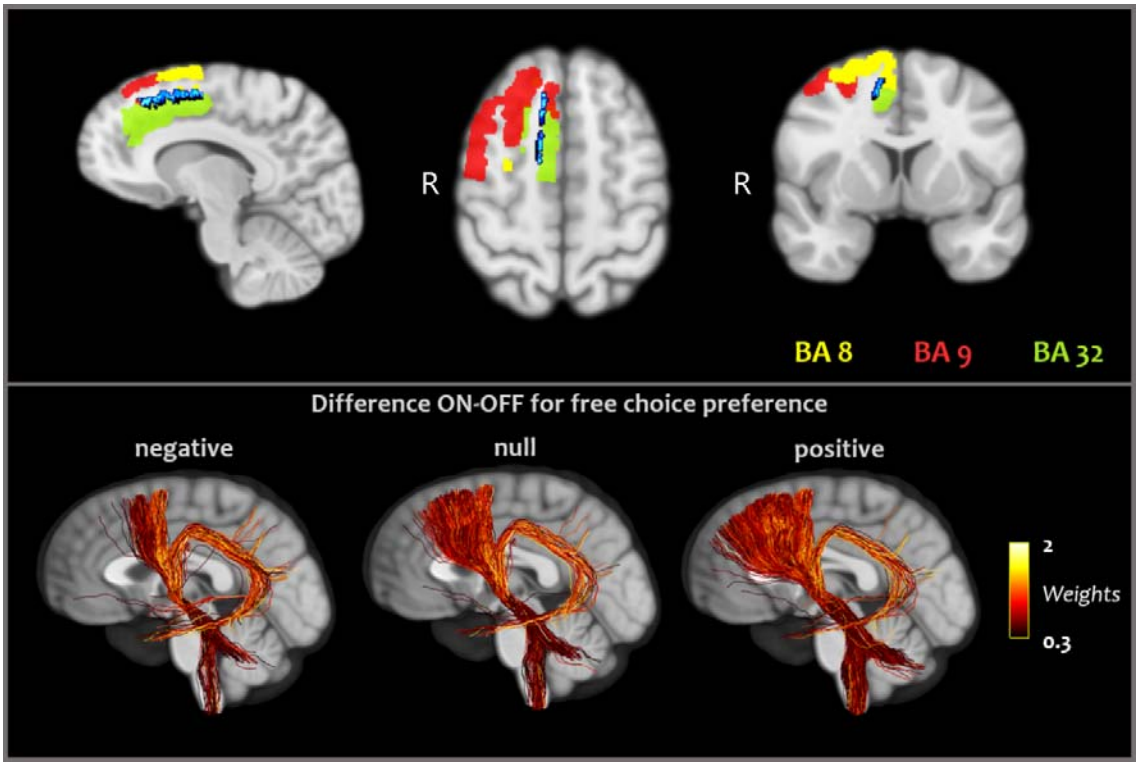

Figure 4 Voxelwise analysis between low and high ON-OFF free choice preference in the STN-DBS group. (Top) The blue region corresponds to the statistical map with a threshold of $P<0.05$ (FWER-TFCE) overlaid on a T1 volume of the template. Yellow, red and green regions correspond to the Brodmann area 8, 9 and 32 respectively. **(Bottom)** Illustrations of connectivity in three patients with different effects of DBS on free choice preference. Left to right represent streamlines projections of individual patients with negative (-0.23), null and positive (0.97) effect of the stimulation on free choice preference. The images are displayed using the radiological orientation (R: right).

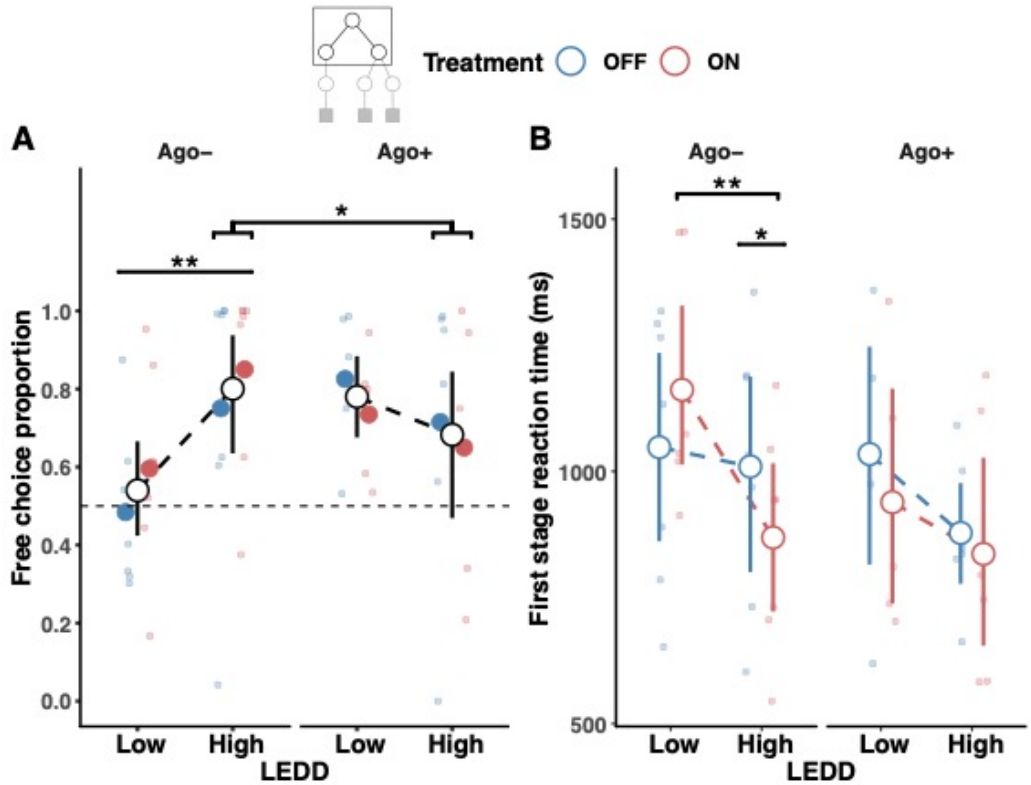

Figure 5 First-stage free choice preference and reaction times (RT) of the DOPA group. (A) Free choice preference plotted as a function of LEDD doses (Low, i.e. ≤1050 *versus* High, i.e. >1050 mg) and dopaminergic agonist (Ago– or Ago+) medication. Small red (ON) and blue (OFF) dots represent the average preference for free choice at the individual level. Medium red and blue dots represent the average across all patients, respectively for ON and OFF conditions. Empty large black circles represent mean free choice performance across all patients against LEDD doses and whether they took agonists (Ago+, right) or not (Ago-, left). Horizontal dashed line represents chance level. Horizontal line with one asterisk represents the significant difference between low LEDD and high LEDD among Ago- patients (P=0.002). Brackets with one asterisk represent the significant difference between Ago- and Ago+ among high LEDD patients (P =0.036). Error bars represent the confidence interval at 95%. **(B)** First stage RT plotted against LEDD doses. Small blue and red dots represent mean individual RT for ON and OFF conditions respectively. Large blue and red circles represent mean RT across all patients. Brackets with two asterisks represent the statistical RT difference between patients with high LEDD and those with low LEDD during ON session in the Ago- group (P =0.010). Horizontal line with one asterisk represents the statistical RT difference between ON and OFF with high LEDD in the Ago- group (P =0.044).

Table

Table 1 Statistical comparison of demographic data in the two groups of patients.

Patient groups	DOPA	STN-DBS	Wilcoxon's test (*P* value)
	Mean (standard deviation)	Mean (standard deviation)	
Age (years)	56.8 (8.6)	54.2 (7.8)	303.5 (0.226)
MoCA (/30)	28.2 (1.4)	27.5 (1.5)	324 (0.087)
Duration (years)	10.4 (4.3)	12.3 (3.3)	180.5 (0.113)
UPDRS III (OFF)	43.5 (14.5)	47.7 (16.3)	209 (0.355)
LEDD (mg)	1355.2 (525)	404.6 (224.3)	**494 (<0.0001)**