The effect of dopamine on response inhibition in Parkinson's disease relates to age-dependent patterns of nigrostriatal degeneration

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ABSTRACT

Introduction: Motor but also non-motor effects are modulated by dopamine (DA) in Parkinson's disease (PD). Impaired inhibition has been related to dopamine overdosing of the associative striatum. We compared effects of dopaminergic medication on inhibitory control in patients with young (age at onset <50 years, YOPD) and late onset PD (LOPD) and related them to nigrostriatal degeneration.

Methods: 27 patients (10 YOPD, 17 LOPD) underwent a Go/NoGo paradigm comprising a global and specific NoGo condition ON and OFF DA. The ratio of dopamine transporter availability (DAT) in the associative relative to the sensorimotor striatum according to [^{123}I]FP-CIT SPECT was compared between YOPD and LOPD (n=8/12). Neuro-computational modeling was used to identify pathway activation during Go/NoGo performance.

Results: Patients made more errors ON compared to OFF in the global NoGo. This DA effect on global NoGo errors correlated with disease duration ($r=0.489$, $p=0.010$). YOPD made more errors in the specific NoGo ON-OFF compared to LOPD ($p=0.015$). YOPD showed higher associative-to-sensorimotor DAT ratios compared to LOPD ($p<0.001$). Neuro-computational modeling revealed DA overdosing of the associative striatum in YOPD resulting in excess activation of the direct basal ganglia pathway triggering incorrect responses.

Conclusions: Depending on the age of symptom onset, DA differentially modulated inhibition in PD with detrimental effects on specific NoGo performance in YOPD but increased performance in LOPD. YOPD showed relatively less degeneration in the associative striatum suggesting DA overdosing that is supported by our neuro-computational model. Reduced inhibition in the global NoGo condition suggests different pathway activation.

INTRODUCTION

In Parkinson's disease (PD), nigrostriatal degeneration proceeds from dorsal/caudal to anterior/ventral, i.e. from motor to associative and limbic striatal areas. Dopaminergic drugs alleviate most motor symptoms but can also result in impaired inhibition and increased impulsivity. These side-effects are commonly interpreted in the light of the dopamine (DA) overdose theory [1]: While dopamine loss primarily affects motor areas of the basal ganglia (BG) and spares associative and limbic parts, DA treatment is delivered systemically and therefore results in overdosing of intact areas of the brain [2,3].

Interestingly, both the pattern of DA loss and the occurrence and nature of side-effects of the dopaminergic treatment depend on the patients' age at symptom onset [4] . Young onset (YOPD, onset age <50 years) and late-onset PD patients (LOPD) show different phenotypes. Schrag and Schott describe that a young age of onset is associated with a better prognosis, slower progression and less cognitive impairment [5] . Moreover, Kempster and colleagues showed that YOPD patients progress to advanced stages of the disease after a relatively long interval of several decades, whereas LOPD patients reach advanced stages much faster [6] . Furthermore, later age at onset of PD is associated with lower DAT binding in [^{123}I]FP-CIT SPECT [7].

YOPD patients show a higher risk of neuropsychiatric side-effects of dopaminergic treatment than LOPD, especially impulse control disorders (ICDs) such as pathological gambling, hypersexuality, binge eating and excessive shopping [8] . These symptoms can have serious implications for the quality of life. Apart from DA equivalent doses (LED), DA agonists are another risk factor for the development of ICDs [9] which are associated with increased DA function in the associative and limbic brain regions [10–12] .

Experimentally, deficits in response inhibition can be measured via Go/NoGo paradigms. These tasks require to respond fast in Go trials but to suppress prepotent responses in NoGo trials. Hereby, global (simple) NoGo and specific (complex) NoGo conditions can be distinguished that show different brain network activation pattern in fMRI [13] with a large overlap between the 'core' NoGo brain network activated in most paradigms using global NoGo and auxiliary networks related to working memory and executive functions for specific NoGo.

In order to compare effects of dopaminergic medication on inhibitory control in patients with YOPD and LOPD and its relation to nigrostriatal degeneration we related the behavioral results from novel Go/NoGo paradigm comprising both global and specific NoGo conditions to the patterns of motor, associative and limbic FP-CIT binding in both groups [^{123}I]FP-CIT SPECT. Additionally, we performed simulations in a neuro-computational model of the basal ganglia. Such simulations have been used widely in recent years, offering the opportunity to manipulate parameters that are empirically not accessible [14] .

METHODS

Patients: Thirty PD patients underwent motor and cognitive examination ON and OFF dopaminergic medication after having given their written informed consent. Study procedures were approved by the ethics committee of the Charité - Universitätsmedizin Berlin. None of the patients suffered from ICDs. None of the patients investigated in this study underwent deep brain stimulation during study enrolment but 3 YOPD and one LOPD patient after having completed the study. All patients were withdrawn from their individual dopaminergic medication for a minimum of 2 halftimes of their specific substances but at least 12h for the OFF-medication session. Standardized assessment of motor symptoms was conducted using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS III). Three patients were excluded from further analysis because i) motor improvement in UPDRS III did not reach 30% (OFF-ON; n=1), ii) 2 patients showed error rates exceeding the average by more than three standard deviations (SD; mean overall errors > 8,5%). The temporal sequence of ON and OFF study sessions was randomized. The cohort partly overlaps with the one of our previous study on overall cognitive performance and DAT availability [15] .

The YOPD group was approximately 20 years younger at study participation with 48.9±3.2 ys in comparison to the LOPD group with 68.0±6.0 ys (Z=-4.278, p=0.000). The age at symptom onset differed accordingly with 44.3±3.5 ys in the YOPD group and 63.0±6.4 ys (Z=4.275, p<0.001) in the LOPD group. Importantly, disease duration did not differ across subgroups (Z=-0.102, p=0.941). Detailed demographic and clinical data can be found in Table 1.

Neuropsychological assessment included the Montréal Cognitive Assessment (MoCA), Beck Depression Inventory [16] (BDI-II), Short Form 36 Health Survey Questionnaire [17] (SF-36) and Barratt Impulsiveness Scale [18] (BIS-11). Patients had no clinically relevant cognitive deficits or affective disturbances (details shown in Supplementary Table 1). Subscores of the SF-36 showed reduced self-ratings of different aspects of health-related quality of life. Scales of the BIS-11 indicated normal states and traits of impulsivity.

Paradigm: Our Go-NoGo paradigm contains a global Go and specific Go as well as a global and specific NoGo condition (Figure 1). In each trial, an arrow is presented with red and green squares right and left of it. The participant's task is to press a button on the side that the arrow points to whenever a green square is presented on that side and to withhold the button press whenever a red square is presented on that side. Each trial lasted for a maximum of 3500ms but disappeared as soon as a button press occurred. Between trials, a fixation cross was presented (500ms ± 200ms). A total of 280 trials (70% global Go, 10% specific Go, 10% global NoGo and 10% NoGo trials) were presented in randomized order. Responses and reaction times were recorded (MATLAB R2014b, MathWorks Inc.)

[^{123}I]FP-CIT SPECT: [^{123}I]FP-CIT SPECT was performed in 20 patients according to common guidelines [19] . SPECT acquisition was performed with a dual head SPECT camera, either a Symbia S (Siemens Healthcare, Hoffman Estates, USA) or a Millenium VG-Hawkeye (GE Healthcare, Haifa, Israel), equipped with low-energy, high-resolution, parallel-hole collimators. The acquisition started 3-4 hours after intravenous injection of about 180

MBq [^{123}I]FP-CIT following blocking of the thyroid gland by oral administration of perchlorate. A 128x128 matrix was used and an energy window of 20% centered at the photopeak of I-123 at 159keV. Three-dimensional SPECT images were reconstructed by filtered back-projection with a Butterworth filter (harmonized between the two SPECT cameras). Post reconstruction uniform attenuation correction was performed using Chang's method with linear attenuation coefficient $\mu = 0.11$/cm. No scatter correction was applied. Quantitative analysis of FP-CIT uptake was performed using a fully automated processing pipeline using the SPM software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). First, the patient's [^{123}I]FP-CIT SPECT image was stereotactically normalized (affine transformation) into the anatomical space of the Montréal Neurological Institute (MNI) using SPM's normalize tool and a custom-made FP-CIT template [20] . Mean FP-CIT uptake was extracted separately from the left and right limbic, associative and sensorimotor parts of the striatum as described in [15] using regions of interest (ROI) provided by the Oxford-GSK-Imanova Striatal Connectivity Atlas [21] with three subregions based on cortico-striatal anatomical connections. Whole brain without striata, thalamus and brainstem was used as reference region for the quantitative analysis of striatal FP-CIT uptake [22,23] . The specific FP-CIT binding ratio (SBR) in a ROI was computed as SBR = mean FP-CIT uptake in ROI / mean FP-CIT uptake in reference region - 1. The SBR of the whole striatum was obtained as the volume weighted average of limbic, associative and sensorimotor SBR and bilateral SBR values were obtained by volume weighted averaging over left and right hemispheres. In order to take the temporospatial gradient of nigrostriatal degeneration into consideration, we calculated the associative-to-sensorimotor ratio of FP-CIT binding.

To visualize the localization of differential DAT binding between YOPD and LOPD, a voxel-based analysis using a general linear model implemented in SPM was conducted. The analyses were restricted to the striatum (regions showing SBR $\geq$1.5 in the in-house FP-CIT template). 8mm full-width-at-half-maximum Gaussian kernel was used for spatial smoothing to improve the signal-to-noise ratio.

Computational simulations: We implemented a simple neuro-computational model of BG pathway functions to investigate whether empirically observed error rates in specific NoGo trials could be explained by patterns of dopaminergic degeneration in the associative striatum. The model was based on previous work from our group by Schroll [24] and Neumann [25] and comprised of a cortico-BG-thalamic loop containing direct, indirect and hyperdirect BG pathways. Of these, the direct pathway is assumed to select specific responses (Go function), the indirect pathway inhibits specific responses (NoGo function) and the hyperdirect pathway globally withholds responding in the case of a response conflict. In detail, the model is determined by the differential equations depicted in Supplementary Methods.

Statistical analysis: Mean reaction times and error rates were compared using Wilcoxon signed-rank tests for within-subject comparisons and Mann Whitney-U test for between-group comparisons. Results are given including Z-scores and two-sided p-values <0.05 were considered significant. Correlations were tested by Spearman's rho method. Subgroups were delineated according to age at onset, i.e. YOPD (<50 ys) and LOPD ($\geq$50 ys) patients. The effect of DA on behavioral data was calculated as the differences in the global and specific NoGo errors ON-OFF. This relative change was correlated with age at onset, disease duration,

disease duration until the begin of therapy, LED and FP-CIT binding in the striatum (entire striatum, associative subregion and associative-to-sensorimotor ratio). Statistical analyses were performed with IBM SPSS Statistics version 24 (SPSS Inc., Chicago).

RESULTS

Behavioral data: The overall error rate averaged across trial types and medication conditions was 2.3±2.2 % (minimum: 0.9 %, maximum: 8.5 %). The mean reaction time in the Go conditions was 607±120 ms and did not differ between ON and OFF. According to our aim of studying response inhibition, we focused our analysis on specific NoGo trials (further details on Go responses can be found in Supplementary Table 2).

Global NoGo: Patients made more errors during the dopaminergic ON as compared to the OFF state in the global NoGo condition (2.7±3.3 % vs. 1.5±3.4 %, Z=-2.132, p=0.033). The difference in error rates in the global NoGo condition ON-OFF correlated with disease duration (r=0.489, p=0.010) but not with disease duration until therapy (r=0.090), age (r=0.061, p=0.764) or age at symptom onset (r=-0.187, p= 0.350). Correlations between error rates in the global NoGo condition ON-OFF with LED did not reach significance (r=0.359, p=0.066) and were also not significant when using LED derived from DA agonists only (r=0.128, p=0.600). No difference in global NoGo error rates occurred between subgroups of YOPD and LOPD (1.2±2.5 % vs. 1.2±3.3%, Z=-0.406, p=0.711).

Specific NoGo: No overall difference was revealed between ON and OFF DA in the specific NoGo condition (2.6±2.4 % vs. 2.7±3.3 %, Z=-0.261, p=0.794). There was a significant correlation between the difference in error rates in the specific NoGo condition ON-OFF and age at symptom onset (r=-0.481, p=0.011) and age at study participation (r=-0.463, p=0.015). In contrast, there were no significant correlations between the difference in specific NoGo errors ON-OFF and disease duration (r=-0.155, p=0.441), LED (r=-0.050, p=0.803) or LED derived from agonists only (r=-0.208, p=0.393). The YOPD group made significantly more errors than the LOPD group in the specific NoGo condition ON-OFF (1.7±2.2% vs. -0.12±0.31%, Z=2.398, p=0.015; Figure 2A).

[^{123}I]FP-CIT SPECT: The SBR in the striatum was 1.67±0.15 (1.33-1.95) in the sensorimotor part, 2.23±0.24 (1.71-2.61) in the associative part and 2.14±0.23 (1.47-2.54) in the limbic part. When comparing FP-CIT binding between YOPD and LOPD, there was a highly significant difference in the associative-to-sensorimotor DAT ratio (1.41±0.04 vs. 1.28±0.07, Z=3.626, p<0.001; Figures 2B and 2C). No such group difference was found when comparing the entire (6.14±0.50 vs. 6.00±0.65, Z=0.772, p=0.473) or the associative striatum (2.31±0.21 vs. 2.17±0.25, Z=-1.389, p=0.181). The associative-to-sensorimotor DAT ratio of FP-CIT binding correlated negatively with age at symptom onset (r=-0.748; p<0.001) as well

as age (r=-0.771; p<0.001). However, there was no significant correlation between error rates in the NoGo conditions ON-OFF and FP-CIT binding.

Computational Modeling: We hypothesized that the empirical findings, i.e. more specific NoGo errors ON-OFF and less associative striatal DA loss in YOPD compared to LOPD patients were related to one another. Specifically, we assumed that less DA loss in the associative striatum in YOPD patients, via DA overdosing, causes stronger behavioral impairments ON relative to OFF DA. Since our empirical findings did not allow for this conclusion, we performed neuro-computational simulations to investigate whether the assumed causality was indeed plausible. Therefore, we varied the degree of DA loss in the associative striatum and investigated whether this variation reproduced the modulation of error rates in specific NoGo trials ON-OFF. The results are depicted in Figure 3. Indeed, we found a negative correlation between error rates ON-OFF and dopamine loss in the associative striatum suggesting a causal effect between associative DA loss and error rates ON-OFF DA in specific NoGo trials. Notably, this effect was related to hyperactivation of the associative-striatal direct pathway ON DA. Detailed computational results on associative striatal DA loss and the activities of direct and indirect pathways ON and OFF DA are depicted in the Supplementary Methods and Supplementary Figure 1.

DISCUSSION:

We were able to demonstrate that YOPD and LOPD patients without ICDs show opposite dopaminergic effects in the specific NoGo condition: YOPD patients committed more errors in the specific NoGo when ON medication whereas LOPD patients seem to benefit from dopaminergic treatment in terms of reduced error commission rates in the specific NoGo condition ON medication. YOPD and LOPD patients also differed significantly in the associative-to-sensorimotor DAT ratio reflecting a relatively intact associative striatum in the YOPD group. However, the behavioral findings did not correlate directly with striatal DAT binding as suggested by the DA overdose hypothesis.

By means of simulations in a neuro-computational model of the cortico-BG-thalamic loop, we were able to show that differential performance between YOPD and LOPD patients in specific NoGo trials could indeed be explained by smaller associative striatal DA loss and subsequent overdosing in the YOPD group. As a methodological advantage of these simulations, we were able to directly manipulate associative striatal dopamine levels and observe their effect on specific NoGo performance. In YOPD patients (who show less associative relative to sensorimotor dopaminergic loss than LOPD patients), direct pathway activity is larger ON DA than in LOPD patients causing a relative facilitation of unwanted responses (i.e., increased error rates). The model approved that more dopaminergic degeneration in the associative striatum resulted in reduced error rates in the specific NoGo condition ON-OFF. Moreover, the model predicted that YOPD patients' direct basal ganglia pathway has a larger relative excess activation ON dopamine than LOPD patients'. It further

suggested that this excess activation explains YOPD patients' increased error rates in specific NoGo trials ON-OFF dopamine: In (specific) NoGo trials, response facilitation (as performed by the direct pathway) is unwanted and results in increased error rates. These results do not suggest a causal role of the indirect basal ganglia pathway in YOPD patients' increased error rates ON-OFF in specific NoGo trials.

Our findings are in line with the clinical observation that overdosing phenomena occur more often in young PD patients [9,26]. In our cohort, the YOPD and LOPD group differed in age by approximately 20 years with no significant difference in disease duration or other demographic or other relevant clinical characteristics like LED and the use of DA agonists.

In a previous study by our group [27] , DA overdosing effects in a Flanker's task and respective changes in error-related deep brain activity were also found to be associated with the patients' age: A younger group of PD patients (age 51±13 ys) performed worse with DA than without in contrast to an older group of PD patients (age 64±4 ys) that showed better performance during the dopaminergic ON.

Liu and colleagues showed that DAT imaging patterns of YOPD and LOPD differ anatomically: In their study, the caudate-to-anterior putamen ratio was significantly higher in YOPD than in LOPD patients both ipsi- and contralateral to the clinically more affected side [28] . This finding was supported by a negative correlation between age of PD onset and the caudate-to-anterior putamen ratio. DAT binding in the putamen correlated negatively with disease duration and UPDRS motor scores. Using functionally defined ROIs in our study, we also found a negative correlation between DAT binding in the associative striatum and age. This can be interpreted as a superimposition of normal ageing and PD pathology independent of disease duration. Pagano and colleagues, however, pointed out that PD duration might be underestimated in the elderly [7] .

In the global NoGo condition, more errors were committed ON as compared to OFF DA, independent of patients' age or age at onset. The DA effect on global NoGo performance correlated with disease duration but no relationship to age or FP-CIT binding was detected which suggests a different mechanism unrelated to overdosing phenomena. It is more likely that this finding may relate to DA sensitization and malplasticity as previously discussed by Voon and colleagues [29] . The authors attributed the development of ICDs in the presence of advanced nigrostriatal degeneration to an increased sensitivity to DA due to a decreased uptake and clearance from the synaptic cleft. Other studies showing increased DA release in response to ICD-related stimuli in PD with ICDs [10,11] support this view. PD patients with ICDs may present a varying sensitivity to regulatory mechanisms of DAT expression by chronic dopaminergic medication dependent on mono- or combination therapy as well as age at disease onset. In contrast to our cohort of YOPD and LOPD patients without ICDs, Voon's ICD patients were younger than those without ICDs but had a longer disease duration. Also, baseline impulsivity trait differences [30] , premorbid personality traits and the psychiatric history have to be taken into account. Confounding factors like comorbidities, social environment and psychological influences are notable and can be avoided by testing patients ON and OFF dopaminergic medication serving as their own controls, as employed in our approach.

Some limitations for our study have to be considered: the overall error rate was small in our paradigm which reduces the statistical power of our results. Although the difference in PD phenotypes with respect to age at disease onset is attracting increasing interest, defined cut-offs are lacking and their definition still seems arbitrary [4] . An additional group with patients suffering from ICDs would be helpful to clarify the development from impaired inhibition to ICDs. Unfortunately, the availability of patients who are willing to undergo the dopaminergic OFF state is small. As to the computational simulations, the simplifications of the cortico-BG-thalamic loop aim at the interplay of direct and indirect pathways in a stable (i.e. non-learning) model. As a consequence, the model does not allow inferences on the role of various more complex phenomena like beta oscillations and synaptic plasticity.

The clinical implications of age-dependent DA overdose effects are clear: They have to be considered when choosing an individual therapeutic strategy aiming at a balance between motor and cognitive dopaminergic effects. Here, we show that YOPD patients are at risk of increased facilitation of unwanted responses under dopaminergic treatment.

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Competing interests: Nothing to report.

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LEGENDS OF FIGURES

Figure 1: Scheme of the Go/NoGo paradigm consisting of four different conditions presented in a randomized order. In between trials a fixation cross is delivered.

Figure 2: Comparison of LOPD and YOPD **A:** Errors in the specific NoGo condition ON-OFF. **B:** Associative-to-sensorimotor ratio of FP-CIT binding. Lines indicate mean and SEM. * indicates $p<0.05$, ** indicates $p<0.005$. **C:** Ratio of striatal to sensorimotor SBR controlling for age and disease duration. Cluster-level FWE-corrected $p<0.05$ at height-threshold $p<0.001$.

Figure 4: Main computational results on the causal relationship between associative striatal DA loss and the percentage of specific NoGo errors ON-OFF. **A:** Varying the degree of striatal DA loss reveals a negative correlation between DA loss in the associative striatum and error rates in specific Nogo trials ON-OFF. **B:** These results are attributed to reduced direct pathway activity ON-OFF dopamine with advanced associative dopamine loss (see Supplementary Figure 1 for more details).

REFERENCES

[1] D. Vaillancourt, D. Schonfeld, Y. Kwak, N. Bohnen, R. Seidler, Dopamine overdose hypothesis: Evidence and clinical implications, Movement Disorders. 28 (2013) 1920–1929.

[2] A. MacDonald, O. Monchi, K. Seergobin, H. Ganjavi, R. Tamjeedi, P. MacDonald, Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function, Movement Disorders. 28 (2013) 153–160.

[3] E. Aarts, A. Nusselein, P. Smittenaar, R. Helmich, B. Bloem, R. Cools, Greater striatal responses to medication in Parkinson′s disease are associated with better task-switching but worse reward performance, Neuropsychologia. 62 (2014) 390–397.

[4] S.-M. Fereshtehnejad, R. Postuma, Subtypes of Parkinson's Disease: What Do They Tell Us About Disease Progression?, Curr Neurol Neurosci. 17 (2017) 34.

[5] A. Schrag, J. Schott, Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism, Lancet Neurology. 5 (2006) 355–363.

[6] P. Kempster, S. O'Sullivan, J. Holton, T. Revesz, A. Lees, Relationships between age and late progression of Parkinson's disease: a clinico-pathological study, Brain. 133 (2010) 1755–1762.

[7] G. Pagano, N. Ferrara, D. Brooks, N. Pavese, Age at onset and Parkinson disease phenotype, Neurology. 86 (2016) 1400–1407.

[8] D. Weintraub, J. Koester, M. Potenza, A. Siderowf, M. Stacy, V. Voon, et al., Impulse Control Disorders in Parkinson Disease: A Cross-Sectional Study of 3090 Patients, Archives of Neurology. 67 (2010) 589–595.

[9] Vela, J.C. Castrillo, G. Ruiz, Gasca-Salas, M. Macías, P. Fernández, et al., The high prevalence of impulse control behaviors in patients with early-onset Parkinson's disease: A cross-sectional multicenter study, J Neurol Sci. 368 (2016) 150–154.

[10] T. Steeves, Miyasaki, Zurowski, Lang, Pellecchia, V. Eimeren, et al., Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study, Brain. 132 (2009) 1376–1385.

[11] S. O'Sullivan, K. Wu, M. Politis, A. Lawrence, A. Evans, S. Bose, et al., Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours, Brain. 134 (2011) 969–978.

[12] J. Joutsa, K. Martikainen, S. Niemelä, J. Johansson, S. Forsback, J. Rinne, et al., Increased medial orbitofrontal [18F]fluorodopa uptake in Parkinsonian impulse control disorders, Movement Disord. 27 (2012) 778–782.

[13] M. Criaud, P. Boulinguez, Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review, Neuroscience & Biobehavioral Reviews. 37 (2013) 11–23.

[14] H. Schroll, F. Hamker, Basal Ganglia dysfunctions in movement disorders: What can be learned from computational simulations, Movement Disorders. 31 (2016) 1591–1601.

[15] D. Kübler, H. Schroll, R. Buchert, A. Kühn, Cognitive performance correlates with the degree of dopaminergic degeneration in the associative part of the striatum in non-demented Parkinson's patients, Journal of Neural Transmission. 124 (2017) 1073–1081.

[16] M. Hautzinger, [The Beck Depression Inventory in clinical practice]., 62 (1991) 689–96.

[17] M. Bullinger, German translation and psychometric testing of the SF-36 Health Survey: Preliminary results from the IQOLA project, Social Science & Medicine. 41 (1995) 1359–1366.

[18] A. Hartmann, W. Rief, A. Hilbert, Psychometric Properties of the German Version of the Barratt Impulsiveness Scale, Version 11 (Bis–11) for Adolescents, Perceptual and Motor Skills. 112 (2011) 353–368.
[19] J. Darcourt, J. Booij, K. Tatsch, A. Varrone, T. Borght, Ö. Kapucu, et al., EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands, version 2, European Journal of Nuclear Medicine and Molecular Imaging. 37 (2010) 443–450.
[20] C. Lange, A. Seese, S. Schwarzenböck, K. Steinhoff, B. Umland-Seidler, B. Krause, et al., CT-Based Attenuation Correction in I-123-Ioflupane SPECT, PLoS ONE. 9 (2014) e108328.
[21] A. Tziortzi, S. Haber, G. Searle, C. Tsoumpas, C. Long, P. Shotbolt, et al., Connectivity-Based Functional Analysis of Dopamine Release in the Striatum Using Diffusion-Weighted MRI and Positron Emission Tomography, Cerebral Cortex. 24 (2014) 1165–1177.
[22] Kupitz, Apostolova, Lange, Ulrich, Amthauer, Brenner, et al., Global scaling for semi-quantitative analysis in FP-CIT SPECT., Nuklearmedizin. Nuclear Medicine. 53 (2014) 234–41.
[23] R. Buchert, A. Kluge, L. Tossici-Bolt, J. Dickson, M. Bronzel, C. Lange, et al., Reduction in camera-specific variability in [123I]FP-CIT SPECT outcome measures by image reconstruction optimized for multisite settings: impact on age-dependence of the specific binding ratio in the ENC-DAT database of healthy controls, European Journal of Nuclear Medicine and Molecular Imaging. 43 (2016) 1323–1336.
[24] H. Schroll, J. Vitay, F. Hamker, Dysfunctional and compensatory synaptic plasticity in Parkinson's disease, European Journal of Neuroscience. 39 (2014) 688–702.
[25] W.-J. Neumann, H. Schroll, A. de Marcelino, A. Horn, S. Ewert, F. Irmen, et al., OUP accepted manuscript, Brain. 141 (2018) 2655–2669.
[26] A. Rana, W. Mansoor, S. Hussaini, A. Mosabbir, M. Rahman, L. Rahman, Factors associated with the development of impulse compulsive disorders in Parkinson patients, Int J Neurosci. 123 (2013) 503–506.
[27] S. Siegert, M. Ruiz, C. Brücke, J. Huebl, G.-H. Schneider, M. Ullsperger, et al., Error signals in the subthalamic nucleus are related to post-error slowing in patients with Parkinson's disease, Cortex. 60 (2014) 103–120.
[28] S.-Y. Liu, J.-J. Wu, J. Zhao, S.-F. Huang, Y.-X. Wang, J.-J. Ge, et al., Onset-related subtypes of Parkinson's disease differ in the patterns of striatal dopaminergic dysfunction: A positron emission tomography study, Parkinsonism & Related Disorders. 21 (2015) 1448–1453.
[29] V. Voon, A. Rizos, R. Chakravartty, N. Mulholland, S. Robinson, N. Howell, et al., Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels, Journal of Neurology, Neurosurgery & Psychiatry. 85 (2014) 148–152.
[30] V. Voon, C. Napier, M. Frank, V. Sgambato-Faure, A. Grace, M. Rodriguez-Oroz, et al., Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update, The Lancet Neurology. 16 (2017) 238–250.

Table 1

	all subjects	YOPD	LOPD	LOPD vs. YOPD
number of subjects	27	10	17	
gender (m/f)	15 / 12	6 / 4	9 / 8	
	mean (SD)	**mean (SD)**	**mean (SD)**	**p**
age (ys)	61.0 (10.7)	48.9 (3.2)	68.0 (6.0)	**<0.001****
education (ys)	15.4 (3.0)	15.1 (3.6)	15.5 (2.6)	0.570
age at symptom onset (ys)	56.1 (10.7)	44.3 (3.5)	63.0 (6.4)	**<0.001****
disease duration (ys)	4.9 (3.9)	4.6 (3.8)	5.0 (4.0)	0.941
disease duration until treatment (ys)	2.0 (2.2)	1.9 (1.8)	2.1 (2.4)	0.573
disease duration until fluctuations / LID (ys)	5.9 (3.6)	6.3 (4.5)	5.7 (3.6)	0.628
UPDRS III ON	11.8 (6.5)	10.2 (5.0)	12.7 (7.2)	0.359
UPDRS III OFF	26.6 (13.0)	25.9 (11.0)	27.0 (14.3)	0.980
LED (mg)	580 (365)	615 (368)	559 (374)	0.473
LED agonists only (mg)	214 (150)	166 (120)	250 (165)	0.238
DA agonist (y/n)	18 / 9	7 / 3	11 / 6	
motor type (TD/ART/EQ)	5 / 13 / 9	0 / 6 / 4	5 / 7 / 5	

Table 1: Patient sample and comparison of the YOPD and LOPD groups

YOPD: young onset Parkinson's disease **LOPD:** late onset Parkinson's disease, **m:** male, **f:** female, **SD:** standard deviation, **ys:** years, **LID:** Levodopa-induced dyskinesias (present in 4 YOPD and 6 LOPD patients), **TD:** tremor dominant, **ART:** akinetic-rigid type, **EQ:** equivalent motor type of PD, **y**: yes, **n:** no, **LED:** Levodopa equivalent dose[34].

Figure1
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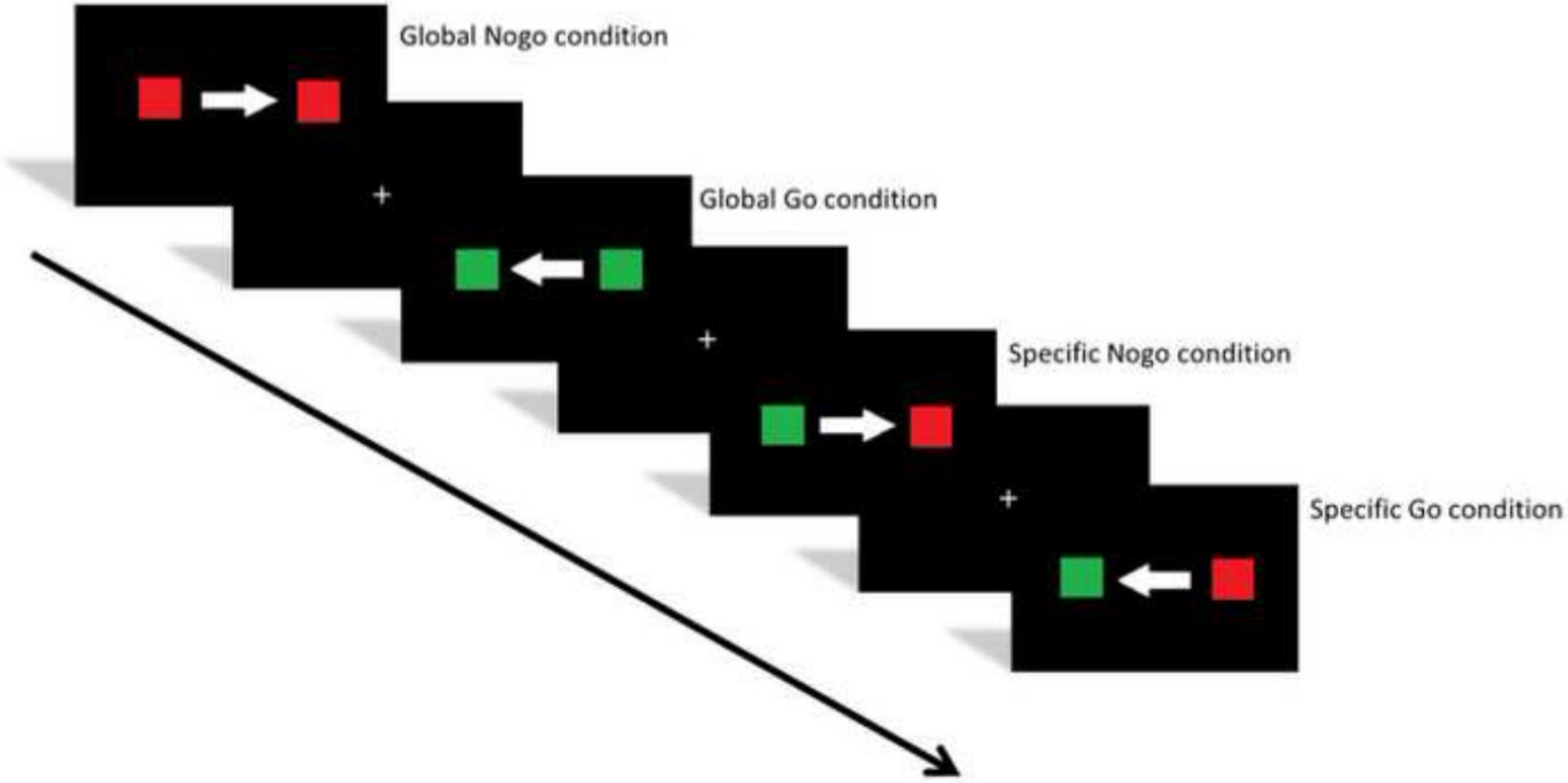

Figure2
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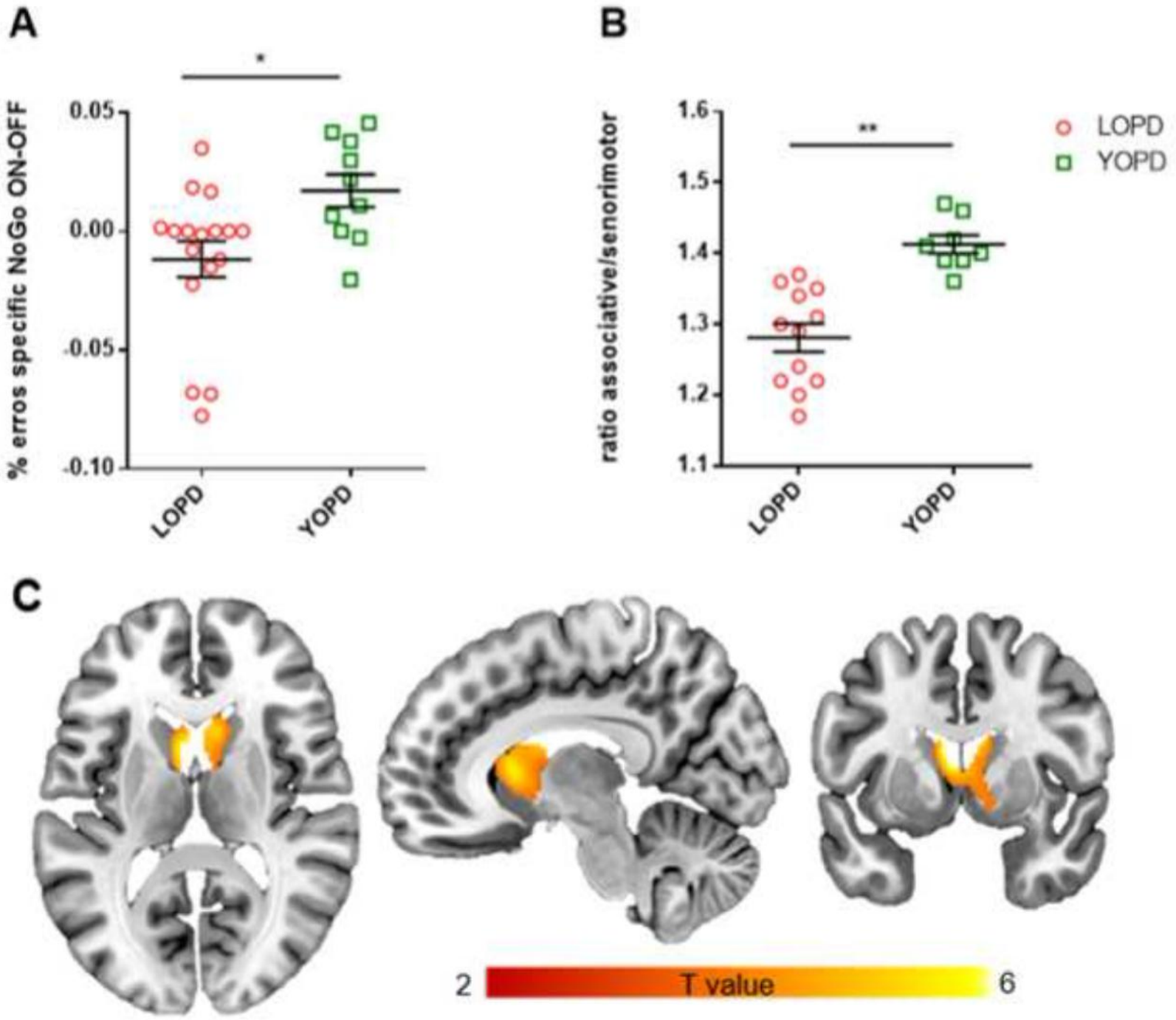

Figure3
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