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Apomorphine-induced reorganization of striato-frontal connectivity in patients with tremor-dominant Parkinson's disease

Salvatore Nigro[a,1], Cécile Bordier[b,i,1], Antonio Cerasa[c], Rita Nisticò[c], Giuseppe Olivadese[c], Basilio Vescio[d], Maria Giovanna Bianco[e], Antonino Fiorillo[e], Gaetano Barbagallo[f], Marianna Crasà[c], Andrea Quattrone[f], Maurizio Morelli[f], Gennarina Arabia[f], Antonio Augimeri[d], Carlo Nicolini[b], Angelo Bifone[b,g,*], Aldo Quattrone[c,h,**]

[a] Department of Experimental and Clinical Medicine, Magna Graecia University, Catanzaro, 88100, Italy
[b] Center for Neuroscience and Cognitive Systems, Istituto Italiano di Tecnologia, Rovereto, TN, Italy
[c] Institute of Molecular Bioimaging and Physiology, National Research Council, 88100, Catanzaro, Italy
[d] Biotecnomed S.C.aR.L, Catanzaro, 88100, Italy
[e] Department of Health Sciences, Magna Graecia University, Catanzaro, 88100, Italy
[f] Institute of Neurology, Department of Medical and Surgical Sciences, University "Magna Graecia", 88100, Catanzaro, Italy
[g] Department of Molecular Biotechnologies and Health Sciences, University of Torino, Torino, Italy
[h] Neuroscience Centre, University "Magna Graecia", 88100, Catanzaro, Italy
[i] In-vivo Imaging and Functions core facility, Lille University and Lille University Medical Centre, Lille, France

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ABSTRACT

Introduction: Apomorphine is a dopamine agonist used in Parkinson's disease (PD), which matches levodopa in terms of the magnitude of effect on the cardinal motor features, such as tremor and bradykinesia. The beneficial effect of this treatment on PD patients with tremor-dominant has widely been demonstrated, although the underlying neural correlates are unknown. We sought to examine the effects of apomorphine on topological characteristics of resting-state functional connectivity networks in tremor-dominant PD (tdPD) patients.

Methods: Sixteen tdPD patients were examined using a combined electromyography-functional magnetic resonance imaging approach. Patients were scanned twice following either placebo (subcutaneous injection of 1 mL saline solution) or 1 mg of apomorphine injection. Graph analysis methods were employed to investigate the modular organization of functional connectivity networks before and after drug treatment.

Results: After injection of apomorphine, evident reduction of tremor symptoms was mirrored by a significant increase in overall connectivity strength and reorganization of the modular structure of the basal ganglia and of the fronto-striatal module. Moreover, we found an increase in the centrality of motor and premotor regions. No differences were found between pre- and post-placebo sessions.

Conclusion: These results provide new evidence about the effects of apomorphine at a large-scale neural network level showing that drug treatment modifies the brain functional organization of tdPD, increasing the overall resting-state functional connectivity strength, the segregation of striato-frontal regions and the integrative role of motor areas.

1. Introduction

The standard pathophysiological model of Parkinson's disease (PD) claims that decreases in striatal dopamine modulate the network from a healthy to the parkinsonian state by destabilizing the normal communication between subcortical striatal regions with cortical motor and premotor cortices [1]. Dopaminergic medication normalizes this abnormal neural firing acting at a variety of sites within and beyond the striato-frontal pathways [2]. Levodopa and apomorphine are both still considered the gold standard therapy for treatment of PD. While the clinical and neurobiological effects of levodopa treatment have widely been described [3] the apomorphine history is characterized by several

* Corresponding author. IBFM-CNR, Catanzaro, Italy.
** Corresponding author. Center for Neuroscience and Cognitive Systems, Istituto Italiano di Tecnologia, Corso Bettini, 31, 38068, Rovereto, Italy.
E-mail addresses: quattrone@unicz.it (A. Bifone), angelo.bifone@iit.it (A. Quattrone).
[1] These authors equally contribute to this work.

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contrasting findings [4].

Apomorphine is a potent dopaminergic agent that exerts its effect by direct stimulation of presynaptic and postsynaptic dopamine D1 and D2 receptors [5]. This is recognized as an efficacious treatment for motor complications in advanced PD, as well as for counteracting non-motor PD-related symptoms [6] or generally as a rescue medication in PD patients with motor fluctuations during the "off" period. However, it has been demonstrated to be a potent drug also used to alleviate tremor-related symptoms in PD [7], even though its inherent neurobiological effect on PD's brain activity is still obscure.

The pathophysiology of tremor-dominant PD (tdPD) certainly differs from that underlying akinesia/rigidity. Despite the dopaminergic basis of parkinsonian tremor is still unclear, in the last few years, the Helmich's group [8,9] have tried to provide new advances demonstrating that a specific neural pathway, parallel to the well-known nigrostriatal system, is impaired in these patients. These authors called these dual neural degeneration systems as the "dimmer-switch model" [8]. Evidence provided so far suggested that parkinsonian tremor dependent upon the altered activity of the striato-cortical loop, which is primarily affected by dopamine depletion in PD, together with the cerebello-thalamo-cortical circuit, which is also involved in many other tremor disorders [9]. Altered modulation of the cerebello-thalamic-motor system activity by means of the globus pallidum would seem the key mechanism triggering tremor symptoms, which are, in part, significantly restored after levodopa treatment [8].

Investigation of the structure of resting-state functional connectivity (rsFC) brain networks may provide information about the effects of drug treatment at a neural circuit level. Recently, graph analysis methods have been applied to assess the topological features of rsFC networks [10], in which nodes correspond to anatomically defined brain regions and the edges to interregional correlations. Of particular interest is the modular structure of brain networks [10], i.e. the presence of subsets, or clusters, of nodes that are more densely connected among themselves than to nodes in other modules. This feature is thought to reflect the balance between functional segregation and integration in the brain and is critical to interpret and classify the role of nodes within the topology of the network [10]. Advanced connectivity approaches have been recently applied in PD patients for evaluating the effects of levodopa at a large-scale neural network level [11]. They found that levodopa reduced local efficiency in the sensorimotor and frontal cognitively-related neural networks, suggesting that levodopa tends to normalize the disrupted network topology in PD. On the other hand, the modular organization of functional connectivity networks in tdPD patients has never been investigated.

In this study, we sought to explore for the first time the neurobiological correlates of the apomorphine effects on the presumed brain dys-functional organization of tdPD's brain. To this end, we apply Asymptotical Surprise, a graph-theoretic approach recently shown to provide superior sensitivity and resolution [12,13] to investigate and compare the modular structures of rsFC networks before and after administration of apomorphine compared to placebo.

2. Methods

2.1. Patients

We enrolled eighteen right-handed patients with a diagnosis of idiopathic PD in accordance with the UK Brain Bank criteria [14]. Only PD patients with rest tremor were enrolled in the study. In particular, patients with Unified Parkinson Disease Rating Scale (UPDRS) resting tremor score of ≥ 2 for at least one hand during physical examination, and a history of resting tremor were considered eligible for this study [9]. Exclusion criteria were: a) presence of dementia; b) use of psychoactive drugs during 3 months preceding the experiment; c) major depression; d) neurological comorbidity; e) side effects related to drug treatment; f) motion artefacts during fMRI examination and g) abnormal structural MRI of the brain.

All subjects gave written informed consent before participation. All the experimental procedures were conducted according to the policies and ethical principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the University "Magna Graecia" of Catanzaro.

2.2. Experimental procedure

Patients were studied according to a repeated-measures single-blind placebo-controlled study. Patients attended combined fMRI and electromyographic (EMG) examination performed twice in the same morning immediately before (practical OFF-phase: 12 h after last medication [T0]) and after ('ON phase'; [T1]) drug administrations. On the first day, after baseline evaluation, patients received the placebo (i.e. subcutaneous injection of 1 mL saline solution), whereas on the second day we evaluated the neurobiological correlates of the apomorphine (subcutaneous injection of 1 mg). This schedule and dosage allow us to study effects on motor functions approximately at drug peak dose and under a strong postsynaptic pharmacological action [15]. The two treatment conditions were initiated 10 min before scanning session.

A nurse performed placebo and drug injections. In both conditions patients were informed that they had received a "Parkinsonian therapy", but the patients did not know (single-blind) when they were receiving a placebo or apomorphine (all patients received both treatments). To avoid learning related to the possible side effects, placebo and apomorphine conditions were not applied in a counterbalanced order. All patients were given domperidone (60 mg/daily) for 48 h before the two experimental sessions, in order to prevent apomorphine-induced side effects. No significant side effect was reported in agreement with previous evidence [7]. The clinical response to treatment was objectively evaluated by EMG recordings performed at baseline (T0) and 1 h after treatment (T1) at the end of the scan session. For each patient, the change in the tremor amplitude at the frequency characteristic of PD (3–5 Hz) between T1 and T0 was normalized to value recorded at the basal condition (T0 session), and expressed in percentage units (%).

During fMRI scanning, muscle activity in the most-affected arm of PD patients was also measured using electromyographic (EMG) (Fig. S1). EMG signal was used as a nuisance variable in the graph analysis to limit the influence of movement artifact on the organization of rsFC and then to better characterize the neurobiological correlates of apomorphine in PD patients.

2.3. MRI acquisition and pre-processing

Neuroimaging data were acquired on a 3T Unit with an 8-channels head coil (Discovery MR-750, General Electric, USA). A validated gradient-echo echo planar (EPI) T2*-weighted pulse sequence (TR/TE: 2000/25 ms; slices n° = 39; FOV = 24 mm; thickness/gap = 3/0.8 mm; matrix size = 96 × 96) was used for fMRI investigation. A high-resolution T1-weighted anatomical image was obtained (368 sagittal slices, 1-mm thickness; TR 9.2 msec; TE 3.7 msec; voxel size 1 mm^3). During the functional scan, subjects were asked to simply stay motionless, awake and relaxed with their eyes closed. For information about fMRI pre-processing see Supplementary Materials.

2.4. Graph analysis

For each participant, 638 regional mean time series were computed by averaging the voxel time series within each of the parcellized areas of the Crossley's template [12,16]. Individual parcels were considered as nodes of a graph.

We estimated the connectivity matrix between nodes, i.e. the relation between the time series of each area of the template, by computing pairwise inter-regional Pearson correlation for each individual. To

compute group-level connectivity matrices, individual correlation matrices were Fisher-transformed and averaged for each run. In order to remove the weakest edges, which are the most affected by experimental noise and more likely to contain spurious correlations, we sparsified group-level connectivity matrices using percolation analysis [17].To assess general features of the resulting functional connectivity network, we extracted the distribution of z-score (corresponding to the weighted edges of our network), the local efficiency (which quantifies a network's resistance to failure on a local scale), the global efficiency (which is inversely related to the network characteristic path length) and finally its density (which indicates the ratio between the connections in the matrix and all possible connection [18].

The modular structure of these networks was calculated by maximization of the Asymptotical Surprise fitness function [12]. This recently developed approach is rooted in information theory and aims to encode the relative entropy between the observed intra-cluster density and its expected value as on the basis of a null model [19]. Asymptotical Surprise was shown to be quasi-resolution-limit free, and to provide improved means to resolve the modular structure of complex networks of brain functional connectivity over other methods [13]. Recently, we demonstrated this approach in the context of the analysis of brain connectivity in neuropsychiatric disorders like Schizophrenia [12] (for further information see Supplementary Materials). Additionally, we computed the Participation Coefficient, a measure of the centrality of each node in the integration of the different modules into a cohesive structure.

Finally, we investigated the clinical relevance of brain network properties in our PD cohort. Specifically, we tested the relation between tremor scores and functional connectivity in our patients using the network-based statistic (NBS) approach [20]. NBS analysis was performed on connectivity matrices computed from the entire data-set prior to and after EMG regression.

2.5. Statistical analysis

The analysis for changes in clinical and electrophysiological variables between baseline and after pharmacological treatment was performed using the General linear mixed model (GLM) for repeated measures to test whether these variables differed across time in the groups. Factors were treatment (Apomorphine Vs Placebo) and time (T0 Vs T1) and we obtained effects from each of them together with interaction between group and time for each of the variables. Paired *t*-test was used to assess differences in amplitude percentage change (%Δ) at a tremor frequency between T0 and T1 and between treatments. All analyses had two-tailed alpha levels of 0.05 for defining significance.

In graph analysis, after community detection by Asymptotical Surprise in the four conditions (placebo and apomorphine sessions pre- and post-medication administration), we computed the similarity between the extracted modular partitions in terms of normalized mutual information (NMI) (for further information see Supplementary Materials).

In NBS analysis, family-wise error (FWE)-corrected p values were applied to the resulting networks using a null distribution obtained by 5000 permutations. Only components that survived a network-level threshold of $p < 0.05$ (FWE corrected) were considered significant.

3. Results

3.1. Clinical data

Sixteen tdPD patients were enrolled in this rsFC study. Clinical information has been reported in Table 1.

Apomorphine induced a marked reduction in clinical, as well as, in electrophysiological tremor amplitude (main effect of session, $F_{1,30} = 10.7$; p-level < .002; interactive effect group x session, $F_{1,30} = 3.1$; p-level = .05) (Fig. 1). Post-hoc analysis (Tukey *t*-test), confirmed that after apomorphine treatment, EMG-related amplitude values were significantly reduced with respect to baseline (p-level = .006), whereas the placebo treatment produced a slight clinical improvement without reaching significant threshold (p-level = 0.41). The assessment of motor status by means of amplitude percentage change (%Δ), confirmed the beneficial effect of apomorphine treatment (mean tremor reduction Δ: 53.5%) with respect to placebo (mean tremor reduction Δ: 19%) ($t_{1,15}$-value = 2.5; p-level < .03).

3.2. Graph analysis

A significant overall increase in rsFC strength was observed after apomorphine administration (*t*-test p-value = 2.26×10^{-08}). No significant difference was observed in the placebo session (for further information see Supplementary Materials).

The only significant difference between the two partitions of the apomorphine session was the reorganization of the basal ganglia (BG) nodes (pallidum, putamen and caudate). Before treatment, caudate nodes (6 nodes over 8 in total) were grouped with bilateral superior frontal and anterior cingulate nodes to form a single module (Fig. 2C, in red). Similarly, the pallidum and putamen (Fig. 2C, in blue) and the thalamic nodes were also clustered together (Fig. 2C, in green). After medication the caudate was pooled with the pallidum/putamen (Fig. 2D, in blue), with no involvement of fronto-cortical nodes, while the tightly knit thalamic module was unaffected (Fig. 2D, in green). The pre and post placebo sessions showed a modular organization comparable to the pre-apomorphine acquisition: i.e. a grouping of the caudate nodes (5 and 4 nodes, for pre and post-placebo respectively) with superior prefrontal and anterior cingulate (Fig. 2A and B).

Finally, Fig. 3 shows the statistical comparison in nodal participation coefficient between the two conditions. Fig. 3D shows that the supplementary motor areas, postcentral and precentral gyrus, increased their influence in the integration of the connectivity network after injection of apomorphine. Conversely, nodes in the precuneus as well as several middle and superior frontal nodes showed reduced integrative role after medication. This indicated a reconfiguration of the nodes' role in the networks despite the lack of apparent differences in the cortical modular structure. Nodes presenting a statistically significant difference between the pre- and post-placebo session were scattered and did not comprise large, functionally homogeneous regions (Fig. 3A and B).

3.3. Behavioral correlations

Significant correlations were found between tremor scores and functional connectivity in several pairs of brain regions. Using a highly conservative threshold (t-value > 6) we found a set of significant patterns of correlations which mainly involved the relationship between associative cortical areas with additional involvement of the putamen together with the premotor cortex (see Supplementary Materials Fig. S5 and Table S5). All the detected relationships were positive, thus suggesting that the increase in tremor was associated with increased connectivity between these brain regions. However, it should be borne in mind that this analysis was performed without regression of the EMG signal. Hence, these correlations may reflect contamination of functional data due to the direct effects of tremor on the BOLD signal or to motion artefacts. Indeed, it is well documented that subject motion produces substantial changes in the timecourses of resting state functional connectivity MRI data despite compensatory spatial registration and regression of motion estimates from the data [21]. These changes cause systematic but spurious correlation structures throughout the brain. Indeed, when covarying out EMG signal from fMRI data the vast majority of previous findings disappeared.

4. Discussion

In this study, we used graph-based analysis and rsFC to investigate

Table 1
Clinical, radiological and electrophysiological features.

tdPD at the enrollment (n° = 16)	
Sex, M/F	13/3
Age, y	66.1 ± 7.2
MMSE	27.4 ± 1.6
Age at onset, y	61.9 ± 8.1
Disease duration, y	4.7 ± 3
LEDD, mg/die	165 [0–600]
DAT-SPECT: Contralateral putamen	2.31 ± 0.47
DAT-SPECT: Ipsilateral putamen	2.7 ± 0.53

Clinical variables	Drug treatment		Placebo treatment		p value [a]
	OFF	ON	OFF	ON	
UPDRS-ME	22.6 ± 7.3	16.6 ± 7.3	22.8 ± 7.1	19.8 ± 8.04	*$p < .001$
Tremor Subscore	5.1 ± 2.1	2.2 ± 1.2	5 ± 2.2	3.7 ± 2.4	*$p < .002$

Abbreviations – tdPD = tremor-dominant Parkinson's disease. EMG = electromyography. UPDRS-ME = Unified Parkinson's Disease Rating Scale-Motor Examination. Tremor subscore refers to the resting tremor subscore of the UPDRS item n°21.

[a] ANOVA F-test test.

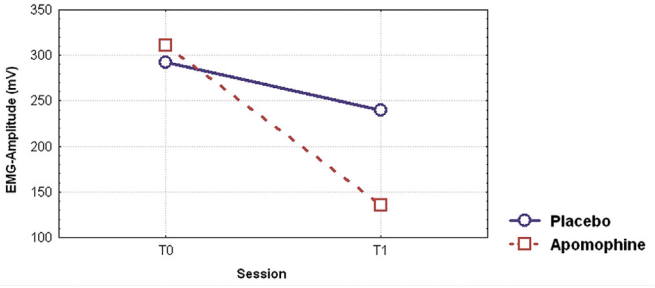

Fig. 1. Differences in EMG-related tremor amplitude after apomorphine and placebo administrations in tdPD patients.

the impact of dopaminergic therapy on functional brain network organization in tdPD patients. We found that after injection of apomorphine, evident reduction of tremor symptoms was mirrored by a significant increase in overall connectivity strength and a reorganization of the modular structure of the BG and of the fronto-striatal module. An increase in participation coefficient was found in motor-premotor regions. These findings provide the first evidence that apomorphine modulates functional connectivity organization in the brain of tdPD patients.

The normalization of altered brain connectivity after dopaminergic replacement is a milestone of PD-related pathophysiology [1]. According to the well-known pathophysiological model of PD in the OFF-condition [22], neurodegeneration of dopamine modulates the network from a healthy state to a parkinsonian state by destabilizing the normal

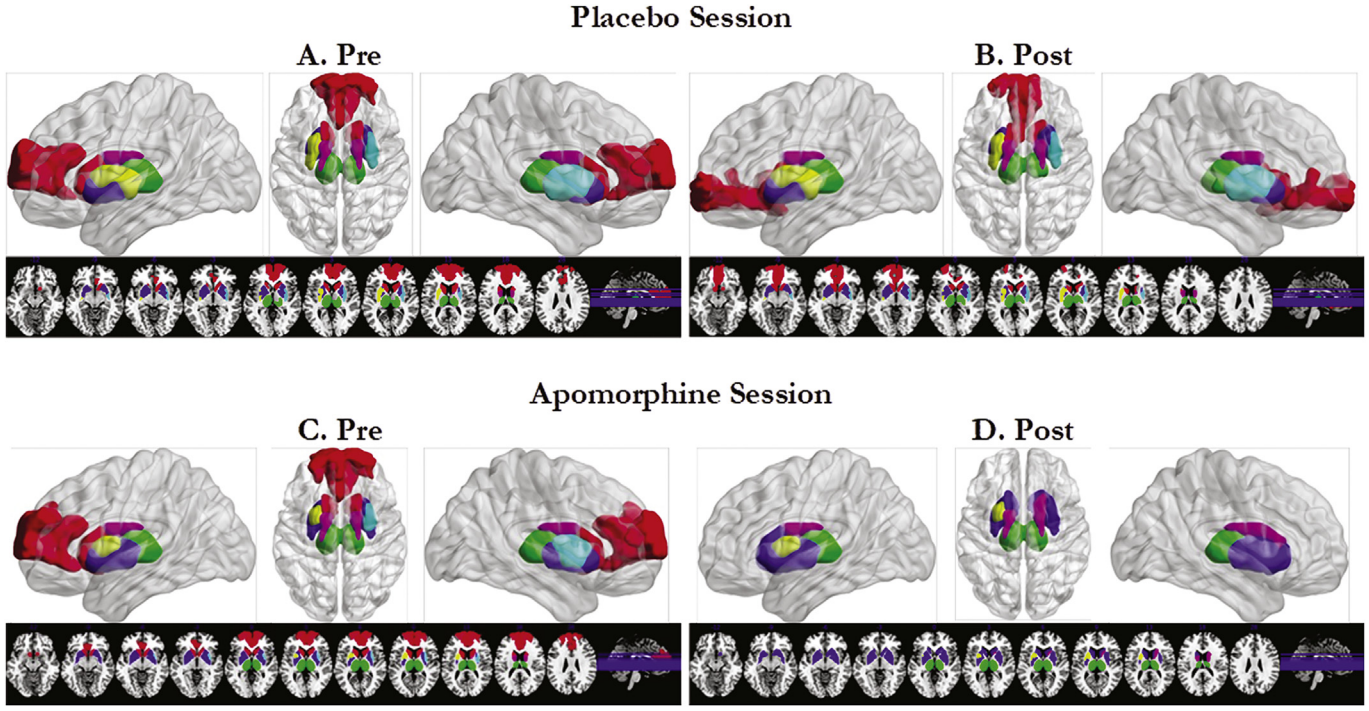

Fig. 2. Modules containing caudate, pallidum, putamen and thalamus nodes in the four sessions. (A) At baseline, before injection of placebo, the majority of the caudate nodes are grouped with the orbitofrontal areas. (B) Placebo administration does not affect the modular organization of these structures. Conversely, administration of apomorphine breaks up the fronto-striatal module (D), compared to baseline (C). Anatomical representation was obtained with BrainNet viewer (https://www.nitrc.org/projects/bnv/) and MRIcron toolboxes (http://people.cas.sc.edu/rorden/mricron/index.html).

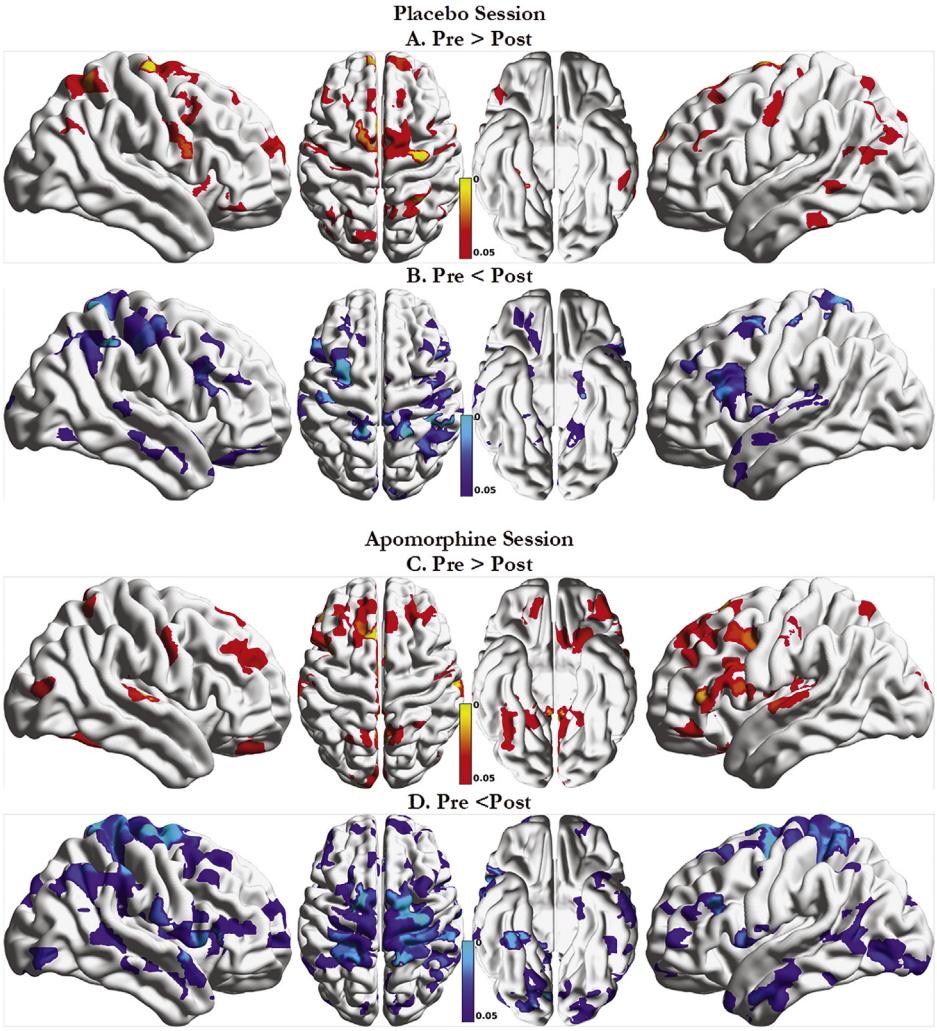

Fig. 3. Anatomical distribution of statistically significant node-wise differences in Participation Coefficient between pre-post conditions, Bonferroni corrected. A. Nodes with larger participation coefficient at baseline compared to post placebo administration session; B. Nodes with lower participation coefficient at baseline compared to post placebo administration session; C. Nodes with larger participation coefficient at baseline compared to post apomorphine administration session; D. Nodes with lower participation coefficient at baseline compared to apomorphine administration session.

functional activity of the striato-cortical loop. This destabilization results in abnormal activity in the motor cortices, mainly accounting for tremor, rigidity, and bradykinetic symptoms. Dopaminergic treatment reverses this parkinsonian state directly (or indirectly) acting at a variety of sites within the network, leading to normalization in the activity of the primary motor pathway [1,22].

The impact of levodopa is the most investigated dopaminergic treatment either in animal or human, whereas few studies have evaluated the effects of other medications, such as apomorphine. Apomorphine is a mixed D1/D2 dopamine receptor agonist with a very appreciable efficacy for motor and nonmotor disorders in PD patients [23]. Previous pharmacological MRI studies in animal and human models demonstrated a robust response to apomorphine administration in several neural hubs extending beyond the classical striato-frontal loop. An $H_2{}^{15}O$ PET study revealed that apomorphine induced in idiopathic PD a fast and widespread activation in the BG, thalamus, sensorimotor cortex, and cerebellum [24]. Animal studies have provided a deeper understanding of apomorphine effects on the neural oscillation of the globus pallidus and subthalamic nuclei. This dopaminergic drug acts by regulating abnormal firing rate and repairing functional imbalance with the prefrontal cortex [25].

However, how dopaminergic treatment acts in vivo on the tdPD's brain has been hardly investigated with respect to bradykinetic or akinetic PD-related phenotypes. This lack of data is due to intrinsic limitations of MRI when applied to these patients, namely the contamination of functional data due to motion artefacts. The large part of studies has been provided by the Helmich's group, which proposed the “dimmer-switch” model [8]. According to this model, cerebral dysfunctional activity related to parkinsonian resting tremor first starts in the striatal nuclei then propagating to the cerebello-thalamo cortical circuit by means of the pallidal modulation (the tremor's interrupter). Levodopa medication influences thalamic activity by potentiating its self-inhibition, which ultimately reduces cerebral activity related to tremor changes in the pallidum [8].

Using different functional connectivity taxonomy we demonstrated the presence of fragmentation in the BG modules, which matches previous evidence on idiopathic PD patients. Moreover, we found aggregation of the caudate, putamen and pallidum within the same module after apomorphine treatment. The fact that dopaminergic medication improves deficient connectivity in the BG network of PD patients is another hallmark provided in the last years by advanced neuroimaging community [26]. Besides BG re-modulation, apomorphine also induces increased functional participation coefficient in the motor and premotor cortices. This finding is in line with previous fMRI studies showing the normalization of motor/premotor activity by means of either apomorphine or levodopa treatments [27].

The most common model of the BG functioning established that during action, there is a specific enhancement of activity in corticostriatal loops together with concomitant suppression of competing motor networks [28]. The imbalance between Go and NoGo systems described in PD [1] is dependent on the loss of functional segregation of cortical information to the striatum (the so called “direct” and “indirect” pathways). This can be easily revealed by means of neuroimaging of dopaminergic treatment or directly by stimulating motor cortex with transcranial magnetic stimulation. In the hemi-parkinsonian patients [29] stimulation of the asymptomatic motor cortex induces greater dopamine release in the unaffected putamen, whereas an abnormal neural response was detected in the controlateral symptomatic hemisphere. Our results show that this abnormal imbalance may be repaired by dopaminergic treatment which is able to restore functional segregation of striato-frontal regions.

This study presents several advantages and limitations. First of all, the apparent discrepancy with tremor model proposed by Helmich's group [8]. This is strictly dependent on the fact that we used EMG signal to remove tremor-related variance from our data. We adopted this procedure to help control potential spurious correlations resulting from tremor-related head motion, as confirmed by DVARS and frame-wise displacement analysis (Supplementary Materials). Moreover, regression of tremor-related fMRI signals removed downstream effects of the pharmacological intervention that may be related with amelioration of the symptom (tremor), rather than with the primary action of the drug. Although we applied rigorous preprocessing and motion correction to our data, we recognize that this approach did not allow assessing drug-induced changes in the cerebello-thalamo-cortical network. However, it proved important to highlight the effects of apomorphine on functional brain organization ruling out the possibility that inter-session differences in modular structure were dominated by the effects of greater movement in the OFF-condition. Moreover, we did not consider a healthy control group making difficult to attribute a pathological nature to the functional organization of the BG at baseline. However, our results are in line with previous studies showing a reduced connectivity within the BG and cortical motor areas in PD off medication compared to healthy controls [27,30].

5. Conclusions

We provided evidence that putative disturbances in the neurofunctional topology of tdPD's brain are rescued by treatment with dopamine agonist apomorphine. Dopaminergic treatment would seem to act on tremor symptoms by rapidly recovering the functional network organization of the BG related to motor and premotor activity, and by increasing segregation in the fronto-striatal loop. Further studies are required to evaluate if graph analysis might become a reliable biological marker of dopaminergic vulnerability and integrity in patients with other motor sub-phenotype of PD.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The code for the optimization of Asymptotical Surprise is available at https://github.com/carlonicolini/paco.

Declaration of interest

None.

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Author's contribution

Salvatore Nigro: acquisition of data, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and final approval of the version to be submitted.

Cécile Bordier: analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and final approval of the version to be submitted.

Antonio Cerasa: conception and design of the study, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and final approval of the version to be submitted.

Rita Nisticò: conception and design of the study, acquisition of data and final approval of the version to be submitted.

Giuseppe Olivadese: acquisition of data and final approval of the version to be submitted.

Basilio Vescio: acquisition of data and final approval of the version to be submitted.

Maria Giovanna Bianco: acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

Antonino Fiorillo: analysis and interpretation of data and final approval of the version to be submitted.

Gaetano Barbagallo: acquisition of data, drafting the article and final approval of the version to be submitted.

Marianna Crasà: acquisition of data and final approval of the version to be submitted.

Andrea Quattrone: acquisition of data and final approval of the version to be submitted.

Maurizio Morelli: acquisition of data and final approval of the version to be submitted.

Gennarina Arabia: acquisition of data and final approval of the version to be submitted.

Antonio Augimeri: acquisition of data and final approval of the version to be submitted.

Carlo Nicolini: analysis and interpretation of data and final approval of the version to be submitted.

Angelo Bifone: analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and final approval of the version to be submitted.

Aldo Quattrone: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be submitted.

Appendix A. Supplementary data

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