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Resting state oscillations suggest a motor component of Parkinson's Impulse Control Disorders

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HIGHLIGHTS

- Impulse Control Disorders (ICDs) are associated with abnormal resting state β-power.
- Beta power changes in the Supplementary Motor Area (SMA) predict ICDs severity.
- Impulsivity in ICDs patients might partly rely on motor dysfunctions.

ABSTRACT

Objectives: Impulse control disorders (ICDs) in Parkinson's disease (PD) have been associated with cognitive impulsivity and dopaminergic dysfunction and treatment. The present study tests the neglected hypothesis that the neurofunctional networks involved in motor impulsivity might also be dysfunctional in PD-ICDs.
Methods: We performed blind spectral analyses of resting state electroencephalographic (EEG) data in PD patients with and without ICDs to probe the functional integrity of all cortical networks. Analyses were performed directly at the source level after blind source separation. Discrete differences between groups were tested by comparing patients with and without ICDs. Gradual dysfunctions were assessed by means of correlations between power changes and clinical scores reflecting ICD severity (QUIP score).
Results: Spectral signatures of ICDs were found in the medial prefrontal cortex, the dorsal anterior cingulate and the supplementary motor area, in the beta and gamma bands. Beta power changes in the supplementary motor area were found to predict ICDs severity.
Conclusion: ICDs are associated with abnormal activity within frequency bands and cortical circuits supporting the control of motor response inhibition.
Significance: These results bring to the forefront the need to consider, in addition to the classical interpretation based on aberrant mesocorticolimbic reward processing, the issue of motor impulsivity in PD-ICDs and its potential implications for PD therapy.

Abbreviations: ACC, Anterior Cingulate Cortex; BIS-11, Barratt Impulsiveness Scale; BDI, Beck Depression Inventory; BSS, blind source separation; BA, Brodmann area; DA, Dopaminergic; EEG, Electroencephalography; FAB, Frontal Assessment Battery; gBSS, group Blind Source Separation; H&Y, Hoehn & Yahr scale; ICDs, Impulse Control Disorders; IC, independent component; ICA, independent component analysis; iFG, inferior frontal gyrus; LEDD, Levodopa Equivalent Daily Dose; MIDI, Minnesota Impulsive Disorders Interview; MMSE, Mini Mental State Examination; mPFC, medial Prefrontal cortex; NA, Noradrenergic; PD, Parkinson's Disease; 5HT, Serotoninergic; SMA, Supplementary Motor Area; SOS, Second Order Statistics; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

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1. Introduction

Impulse control disorders (ICDs) are debilitating neuropsychiatric disorders that include hypersexuality, pathological gambling, compulsive eating and compulsive shopping, and concern up to 46% of patients with Parkinson's disease (PD) (Avanzi et al., 2006; Grosset et al., 2006; Voon et al., 2006; Weintraub et al., 2010; Vela et al., 2016; Antonini et al., 2017; Corvol et al., 2018). ICDs in PD are associated mainly with cognitive impulsivity, also termed choice or decisional impulsivity. Cognitive impulsivity reflects dysfunctions in various aspects of decision making and motivation involving the reward system (Czernecki et al., 2002; Abler et al., 2009; Cilia and van Eimeren, 2011; Aarts et al., 2012; Antonelli et al., 2014; Piray et al., 2014; Santangelo et al., 2017; Dawson et al., 2018; Meyer et al., 2019). These dysfunctions can lead to irrational preference for immediate small rewards rather than delayed large rewards (temporal discounting), anticipated decision without enough accumulation of available evidence (reflection impulsivity), and/or biased evaluation of probabilistic gains and losses (probabilistic discounting). ICDs are considered as a side-effect of dopamine replacement therapy (Dodd et al., 2005; Weintraub et al., 2010; Leroi et al., 2013; Antonelli et al., 2014; Lopez et al., 2017; Voon et al., 2017). Thus, their management mainly involves discontinuing or decreasing dopamine agonists (Samuel et al., 2015; Cossu et al., 2018). But this is not a satisfactory therapeutic option since this can cause a worsening of motor symptoms or a dopamine agonist withdrawal syndrome (Evans et al., 2004; Rabinak and Nirenberg, 2010; Pondal et al., 2013; Samuel et al., 2015), and even does not guarantee symptoms remission at follow-up (Ávila et al., 2011; Cilia et al., 2016). A better understanding of these disorders is mandatory to develop more efficient therapeutic strategies (Grall-Bronnec et al., 2018).

Actually, the cognitive and neural bases of ICDs in PD have not been completely elucidated to date. Results of neuroimaging studies are largely inconsistent (see Meyer et al., 2019 for recent review). They show numerous possible abnormalities in the mesocorticolimbic circuits consistent with various dysfunctions of object and action valuation caused by biased probability estimation or reward processing, indeed. But abnormalities are also frequently observed in many other brain regions (Cilia et al., 2008, 2011; Frosini et al., 2010; Rao et al., 2010; van Eimeren et al., 2010; Voon et al., 2011; Politis et al., 2013; Carriere et al., 2015; Imperiale et al., 2017; Tessitore et al., 2017; Petersen et al., 2018). In addition, these studies have limitations. First, influential papers focused only on decision-making by means of tasks probing specifically risk-taking and motivation, or by means of region of interest approaches centered on the decisional circuit (Frosini et al., 2010; Rao et al., 2010; van Eimeren et al., 2010; Kassubek et al., 2011; Voon et al., 2011; Politis et al., 2013). These studies did not test the possibility of response inhibition dysfunctions (motor impulsivity). Yet, studies of impulsivity in psychiatric conditions (Dalley and Robbins, 2017) as well as neuropsychological and behavioral investigations in PD (Nombela et al., 2014; Voon, 2014) suggest that multiple modes of impulsivity are likely to develop in ICDs. Second, neuroimaging studies mostly used fMRI or SPECT/PET, although blood flow changes are only indirect measures of neural activity. Critically, these studies cannot disentangle concurrent excitatory and inhibitory mechanisms (Logothetis, 2008), which is crucial for discriminating the neural events that contribute to the imbalance between excitatory and inhibitory activity in impulsivity.

Assessing resting state brain activity is essential for identifying clinically relevant brain dysfunctions (Eidelberg, 2009). This allows probing simultaneously the functional integrity of a variety of networks which specific dynamics can only be assessed separately in various functional imaging studies. Here, we analyzed resting state oscillations with high-density electroencephalography (EEG) in PD patients with and without ICDs. Indeed, EEG provides better cortical functional discrimination power than blood flow-derived measures often privileged for resting state studies since frequency-specific activity provides markers of particular cognitive functions, even at rest (e.g., Siegel et al., 2012; Cohen, 2017). This discrimination power is essential for separating multiple neural activities that might be confounded otherwise. This is especially true if spectral analyses are performed directly at the source level after blind source separation –BSS-, and might for instance be helpful for disentangling excitatory from inhibitory activity through analyses of alpha activity (Klimesch et al., 2007; Lorincz et al., 2009; Jensen and Mazaheri, 2010; Mathewson et al., 2011). In order to investigate all cortical networks potentially involved in ICDs' impulsivity, we performed whole-brain analyses without a priori about the anatomofunctional origins of the disorder.

Although we are here testing more specifically the neglected motor hypothesis, it is worth mentioning that the cognitive and motor hypotheses make distinct predictions not only about the anatomy of the circuits displaying cortical activity changes at rest, but also about the spectral signatures of these changes. The cognitive account of impulsivity predicts differences in the mesocorticolimbic system, the orbitofrontal and the lateral prefrontal cortices (e.g., Aracil-Bolaños and Strafella, 2016; Marques et al., 2018; Vriend, 2018), mainly expressed in the delta and theta bands (van Wingerden et al., 2010; Knyazev, 2012; Nacher et al., 2013; Cavanagh, 2015; Pinner and Cavanagh, 2017; Fatahi et al., 2018). The motor account of impulsivity predicts differences in a medial network composed of the medial prefrontal cortex (mPFC), the dorsal anterior cingulate (dACC), the inferior frontal gyrus (iFG), the precuneus and the supplementary motor area (SMA) (Aron, 2011; Criaud and Boulinguez, 2013; Manza et al., 2016; Criaud et al., 2017), mainly expressed in the alpha and beta bands (Supplementary Table 1) (Zhang et al., 2008; Criaud and Boulinguez, 2013; Huster et al., 2013; Kilavik et al., 2013; Hwang et al., 2014; Fonken et al., 2016; Liebrand et al., 2017). Importantly, we will perform whole brain and large spectrum analyses in order not to miss the potential contribution of unpredicted brain regions/frequency bands.

2. Methods

2.1. Participants

Twenty-seven PD patients with current ICDs (ICDs+) and 22 PD without ICDs (ICDs−) were enrolled at the Parkinson Institute in February 2016. The presence of any ICDs was assessed with the Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease (QUIP score ≥ 1 for ICDs+, i.e., one ICD or more (Weintraub et al., 2009)). Considering that ICDs+ patients may underestimate, or even lie about and voluntarily deny any behavioral disturbance (Cilia et al., 2014), caregivers were independently interviewed. For ICDs−, the absence of any behavioral disturbance during the whole disease course (i.e., QUIP score = 0) was stated and confirmed by the caregiver. The sample size was determined on the basis of the results of previous studies using EEG to assess inhibitory dysfunction in PD (e.g. Spay et al., 2018). The estimated sample size n was calculated as the solution of:

$$n = \frac{\left(t_{n-1,\frac{\alpha}{2}} + t_{n-1,\beta}\right)^2}{d^2}$$

where d = delta/standard deviation, α = alpha (the probability of a type I error), $\beta = 1 -$ power (the probability of a type II error) and $t_{v,\,p}$ is a Student t quantile with v degrees of freedom and probability p. Based on former EEG data assessing power modulations associated with inhibitory dysfunction in PD patients (Spay et al., 2018), the expected difference (delta) in normalized spectral power was set at 0.2, with a standard deviation of 0.2. Setting the alpha risk at 5% and the expected power at 95%, the minimum number of patients per group to highlight the expected difference (n) is 18. This sample size was also determined in agreement with former specific recommendations regarding EEG group blind source separation analyses (Lio and Boulinguez, 2018). Indeed, optimal performance of source separation and subsequent source localization does not require the inclusion of large samples of subjects (n < 20) when applying second order statistics (SOS)-based algorithms that use source spectral diversity. These algorithms can identify and gather sources that have similar functional properties despite variable location and orientation due to inter-individual neuroanatomical variability.

Inclusion criteria were: age between 40 and 70 years old, with idiopathic PD, benefiting from a stable antiparkinsonian drug therapy for at least 2 months. Exclusion criteria were: dementia, cognitive impairment (MMSE < 26), other neurologic or psychiatric disease, pharmacological treatment with cerebral or psychic impact, substance abuse according to the criteria DSM-IV-TR (except tobacco smoking). Patients remained on their usual medication during the study. Clinical and neuropsychological assessment included the Mini Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), the Minnesota Impulsive Disorders Interview (MIDI) and the QUIP to assess ICDs, the Barratt Impulsiveness Scale (BIS-11), the Beck Depression Inventory (BDI), the UPDRS-III (Unified Parkinson's Disease Rating Scale part III) and the evaluation of Hoehn & Yahr (H&Y) stage. Data from 10 subjects had to be discarded following technical issues during data collection due to difficulties inherent to bedside acquisition (excessive unfilterable noise, defective electrodes). In the end, two groups of 22 ICDs+ and 17 ICDs− were included in the analysis. Groups were matched for age, disease duration, levodopa equivalent daily dose (LEDD) and UPDRS-III. The main demographic and clinical characteristics of the patients are displayed in Table 1. All patients gave written informed consent before the study, and the protocol was approved by the local Ethical Committee of the Parkinson Institute, Milan (Italy).

2.2. Design and procedure

Resting state activity was recorded over two continuous periods of 10 min. Subjects comfortably sat and were instructed to stay quietly with the eyes closed. The EEG signal was recorded at a sampling rate of 4096 Hz with the BioSemi™ ActiveTwo Mk2 system from 128 electrodes (BioSemi™ ABC system standard locations, electrode offsets < 20 mV). Six supplementary electrodes were used in temporal (Biosemi spherical coordinates: Phi −103.5 Theta −18 −36; Phi 103.5 Theta 18 36) and eye (Phi 103.5–103.5 Theta 81–81) regions. The CMS active electrode and the DRL passive electrode served to create a feedback loop steering the average potential of the participant in the Common Mode voltage.

2.3. Data analyses

A flowchart of methods pipeline is presented in Fig. 1 to summarize data analyses strategy.

2.3.1. Preprocessing

First, the quality of each electrode signal was checked, and spherical interpolation was used when necessary. Data were

Table 1
Patients characteristics.

	PD-ICDs+	PD-ICDs−	p-value
Demographics			
Number	22	17	–
Sex	20 M/2F	16 M/1F	–
Age	62.3 ± 7.0	59.5 ± 7.4	0.23
Disease duration	10.4 ± 4.9	7.9 ± 3.7	0.09
Clinical characteristics			
Total LEDD	815.5 ± 285.3	761.6 ± 199.2	0.51
Levodopa dose	645.8 ± 286.4	451.5 ± 188.8	0.02
DAAs dose (LEDD)	69.4 ± 87.4	249.4 ± 94.3	3.7.10–7
Fluctuations	16 Yes/6 No	4 Yes/13 No	
H&Y stage	1.8 ± 0.7	1.5 ± 0.7	0.63
Predominant type, *type[number of patients]*	[AR]15 [TD]7	[AR]16 [TD]1	
UPDRS-III (ON)	11.7 ± 6.1	10.1 ± 7.2	0.44
Neuropsychological assessment			
MMSE	28.2 ± 2.1	29.6 ± 0.7	Cut-off > 26
FAB	15.4 ± 2.2	16.9 ± 1.2	Cut-off > 13.4
BDI	11.7 ± 8.7	6.9 ± 6.7	0.07
BIS-11	67.8 ± 13.7	63.8 ± 5.6	0.26
QUIP (A), *ICDs #[number of patients]*	[1]10; [2]3; [3]6; [4]3	0	–
QUIP (ABC), *ICBs #[number of patients]*	[1]8; [2]3; [3]6; [4]3; [5]2	0	–
A1 (Pathological gambling)	22	0	–
A2 (Hypersexuality)	7	0	–
A3 (Compulsive Buying)	6	0	–
A4 (Binge Eating)	7	0	–
B (Punding, Hobbyism or Walkabouts)	9	0	–
C (DDS)	2	0	–

Values are given as mean ± SD. ICDs = Impulse Control Disorders, Total LEDD = Total Levodopa Equivalent Daily Dose (mg/day), DAAs = dopamine agonists, H&Y = Hoeh & Yahr scale, AR = Akineto-rigid, TD = Tremor-dominant subtypes of PD patients, UPDRS-III = Unified Parkinson's Disease Rating Scale (part III), MMSE = Mini-Mental State Evaluation, FAB = Frontal Assessment Battery, BDI = Beck Depression Inventory, BIS = Barratt Impulsiveness Scale, QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, ICBs = Impulsive-Compulsive Behaviors, DDS = Dopamine Dysregulation Syndrome.

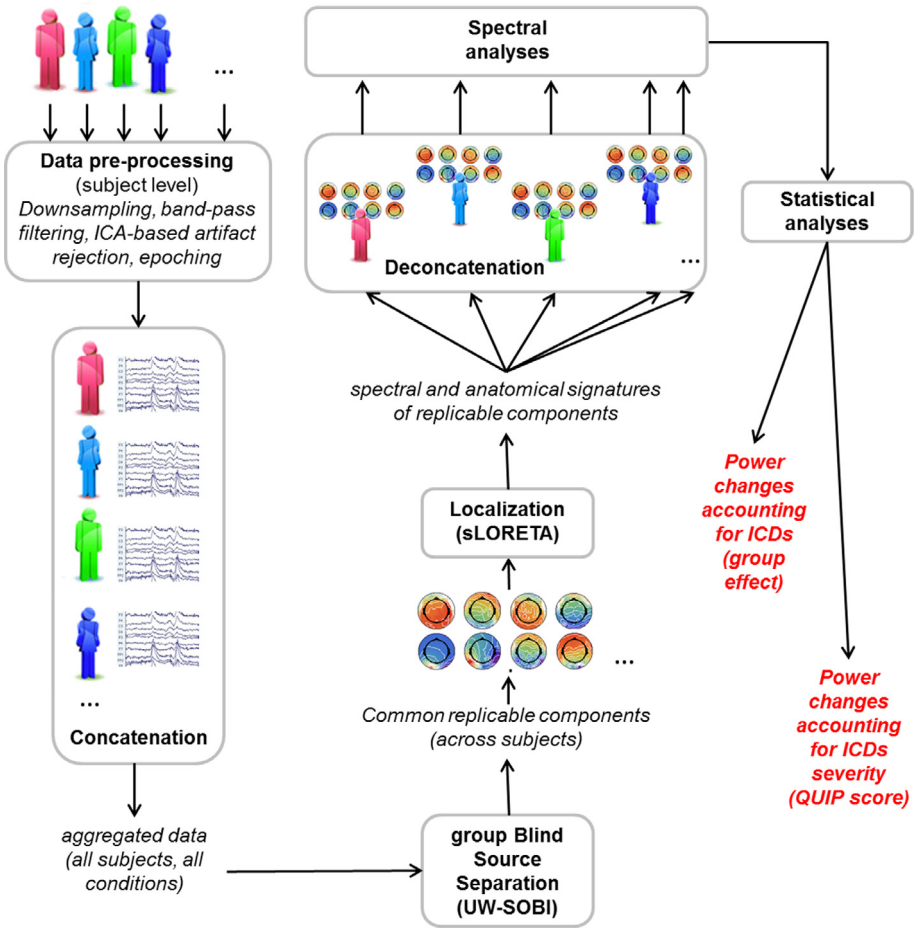

Fig. 1. Overview of data processing and analysis pipeline.

down-sampled at 2048 Hz, filtered (High-pass 0.5–1 Hz; Low-pass 46–48 Hz) and set to average reference. First, artifacts (movement-induced perturbations including especially eye movements, ballistocardiac noise, electrode displacements and other electrical noises) were rejected by means of independent component analysis (ICA)/blind source separation (BSS) (UWSOBI, 300 times delays; (Yeredor, 2000) and the EEGLAB toolbox (Delorme and Makeig, 2004). Second, data were partitioned into epochs of 2 seconds with an overlap of 50% and an automatic rejection procedure for outlier epochs was applied. The Frobenius norm between the covariance matrix of each epoch and the covariance matrix of the mean dataset was calculated. For each dataset, the 5% of the epochs deemed as outliers according to this metric have been rejected.

2.3.2. Group Blind Source Separation (gBSS)

gBSS provides an efficient solution to the issue of multi-subject analysis by concatenating data from all subjects. A unique mixing matrix is therefore obtained for the whole group of subjects, as well as a unique demixing matrix after separation. The main advantage of the method is that gBSS reveals the independent components (ICs) that are consistently expressed across subjects (Eichele et al., 2011; Huster et al., 2015; Huster and Raud, 2018; Lio and Boulinguez, 2018). A potential benefit of this method is a better sensitivity for the identification of substantial sources that might be hidden by the most energetic ones (Sutherland and Tang, 2006). We employed UWSOBI, an algorithm relying on the approximate joint diagonalization of lagged-covariance matrices (SOS). We have recently demonstrated that this class of algorithms is especially adapted to gBSS because it is insensitive to inter-subjects differences in neuroanatomy and does not require deleterious dimension reduction before separation (Lio and Boulinguez, 2018). This method is especially adapted here because it separates the sources on the basis of time-frequency information, not on the basis of data distribution characteristics as classical higher order statistics data-based algorithms do (e.g., FASTICA or INFOMAX, see Lio and Boulinguez, 2013). This is more convenient when searching spectral signatures of cognitive processes, but this is also more convenient because SOS-based algorithms are more robust to the distortions of the mixing matrix that are inevitable in gBSS (Lio and Boulinguez, 2013, 2018). Basically, after a set of matrices of SOS between electrodes has been estimated and made symmetric – time delayed covariance is not symmetric-, a linear transformation that enhances spectral diversity between sources is searched -the mixing matrix is calculated by approximate joint diagonalization of the whole set-. Importantly, the output of the separation provides components that are statistically independent regarding the parameters used for separation (whole spectrum signature). This does not mean that independent components cannot be functionally connected and part of the same neural network, i.e., cannot provide similar or interrelated activation patterns in response to specific events or conditions within specific frequency bands.

For each epoch, 300 lagged-covariance matrices (time delays: 0/2048 s to 300/2048 s) were calculated, averaged across dataset epochs, and finally across subjects. In the end, a total of 600 lagged-covariance matrices have been approximately joint-diagonalized by means of the UWEDGE algorithm (Tichavsky and Yeredor, 2009), leading to the detection of 134 ICs. Thanks to this averaging procedure, inter-epochs and inter-subject variability

was reduced while sources with spectral modifications between ICDs+ and ICDs− were highlighted (Ramoser et al., 2000; Congedo et al., 2008). Brain regions explaining the group effect (ICDs+/ICDs−) were revealed by sorting components by percent of explained variance. Components explaining at least 1% of variance were retained for further analyses (n = 10).

2.3.3. Independent components source localization

To identify the neuronal generators of the electrical patterns recorded on the scalp, standardized low resolution electromagnetic tomography was performed with the sLoreta software (Pascual-Marqui, 2002). The cortical distribution of the electric neuronal activity generating each IC on the basis of its topography was estimated (solving the inverse problem). sLoreta uses the current density estimate obtained from the minimum norm estimate, and standardizes it by means of its variance. Here, standardized current source density was calculated at each of the 6239 voxels (resolution: 5 mm) of a head model built on the basis of the boundary element method -BEM- and the MNI152 template (Mazziotta et al., 2001). The 3D solution space was constrained to gray matter, and sLoreta solutions were calculated with an amount of Tikhonov regularization optimized for an estimated Signal/Noise Ratio of 100. The output is a map of current density power (arbitrary units) whose maximum value corresponds to the exact generating dipole location in noise-free conditions.

2.3.4. Blind spectral analysis

We performed analysis of resting state spectral activity without a priori knowledge about anatomical sources or frequency bands. The ICs obtained with group BSS were used as a filter to go back to subject level for spectral analysis (deconcatenation). For each dataset of each PD patient, and each one of the 10 ICs accounting at least for 1% of explained variance (group effect), relative power was estimated. The power spectral density was calculated with the Welch's method for each epoch (with segments of 2048 samples, windowed with a Hamming window, and an overlap of 2000 samples between segments), and averaged across epochs for each dataset. This procedure generated absolute spectra with 1 Hz resolution. Relative spectra were then computed in the 1–45 Hz frequency range with respect to the total power of the component:

$$Power_{rel}(f) = Power_{abs} / \sum_{f=1Hz}^{45\,Hz} Power_{abs}(f)$$

2.3.5. Statistical analyses

Two analyses were performed in order to test our predictions twice: 1) by comparing ICDs+ and ICDs−, assuming discrete differences between groups, and 2) by looking for correlations with a clinical score reflecting ICD severity (QUIP) within the group of PD patients with ICDs, assuming gradual dysfunctions.

2.3.5.1. Group regression analysis. We performed blind analyses and compared mean relative power differences between ICDs+ and ICDs− for all frequency bands and each component. In order to control for clinical characteristics, we performed a correlation matrix including all the dependent variables reported in Table 1. Since most of these variables were significantly correlated to each other (Supplementary Table 2), we selected the two most important variables (best model fitting F) for the subsequent group regression analyses. In other words, we controlled only for motor performance (UPDRS-III) and medication (total LEDD) to avoid collinearity issues.

For each frequency band and each IC, a multiple regression analysis was applied based on one factor of interest (ICDs: ICDs+ vs. ICDs−) and two factors of no-interest (the UPDRS-III score and the LEDD), providing one F-statistic for the quality of the model fitting, and one t-statistic for the modeled factor:

$$Power_{rel}(IC, Freq.) = b_1 . ICDs + b_2 . UPDRS\,III + b_3 . LEDD + b_4$$

where b_1, b_2, b_3 represent the parameters to be estimated for the first, second and third factors, respectively, and b_4 represents the estimated intercept.

2.3.5.2. Oscillatory modulations predicting ICDs severity (QUIP score, ICDs+ only). For each IC and each frequency band, a multiple regression analysis was applied based on one factor of interest (the $QUIP_A$ – ICDs score) and two factors of no-interest (the UPDRS-III score and the LEDD):

$$Power_{rel}(IC, Freq.) = b_1 . QUIP_A + b_2 . UPDRS\,III + b_3 . LEDD + b_4$$

where b_1, b_2, b_3 represent the parameters to be estimated for the first, second and third factors, respectively, and b_4 represents the estimated intercept. The second and the third factors are constants which represent a modulation of the source spectral activity associated with the UPDRS-III motor score and the LEDD that are non-clinically relevant for the ICDs severity (QUIP score). Modeling these effects is essential because motor performance and medication-induced spectral modulations that do not account for ICDs severity are likely. The multiple regression provides an F-statistic for the quality of the model fitting, and one t-statistic for the modeled factor.

Multiple testing correction was performed when appropriate by means of false discovery rate (FDR) estimation.

3. Results

Results (controlled for motor performance -UPDRS-III score- and medication -LEDD-) are summarized in Fig. 2.

3.1. Power changes accounting for ICDs (group effect)

Sources localized in the dACC and the mPFC revealed power modulations of resting state activity in PD patients with ICDs+ compared with ICDs− ($F = 5.78$; $p < 0.05$). The first source (IC 11/BA32) showed increase in low beta (13–14 Hz) and decrease in gamma (33 Hz) mean relative power in ICDs+ compared to ICDs− ($p < 0.001$). The second source (IC 13/BA9), showed increase in low beta ($p < 0.001$). The third source (IC 16/BA32) showed decrease in gamma (32–44 Hz) mean relative power in ICDs+ compared to ICDs− ($p < 10^{-4}$).

3.2. Power changes accounting for ICDs severity (QUIP score)

Only one source (IC 8/BA6) localized in the supplementary motor area (SMA proper) revealed power changes predicting QUIP scores ($F = 11.26$; $p < 0.01$). Within this source, a positive correlation was found between beta band power (18–28 Hz) and ICDs severity.

4. Discussion

The hypothesis of a contribution of motor impulsivity to ICDs in PD (Nombela et al., 2014; Palermo et al., 2017) has mostly been ignored in neuroimaging studies (Frosini et al., 2010; Rao et al., 2010; Politis et al., 2013; Aracil-Bolaños and Strafella, 2016; Voon et al., 2017; Marques et al., 2018) or rejected in behavioral studies (e.g., Rossi et al., 2009; Bentivoglio et al., 2013; Leroi et al., 2013; Yoo et al., 2015; Pineau et al., 2016; Ricciardi et al., 2017) up to date. Here, we used a resting state design and EEG to probe the functional integrity of all the cortical networks that

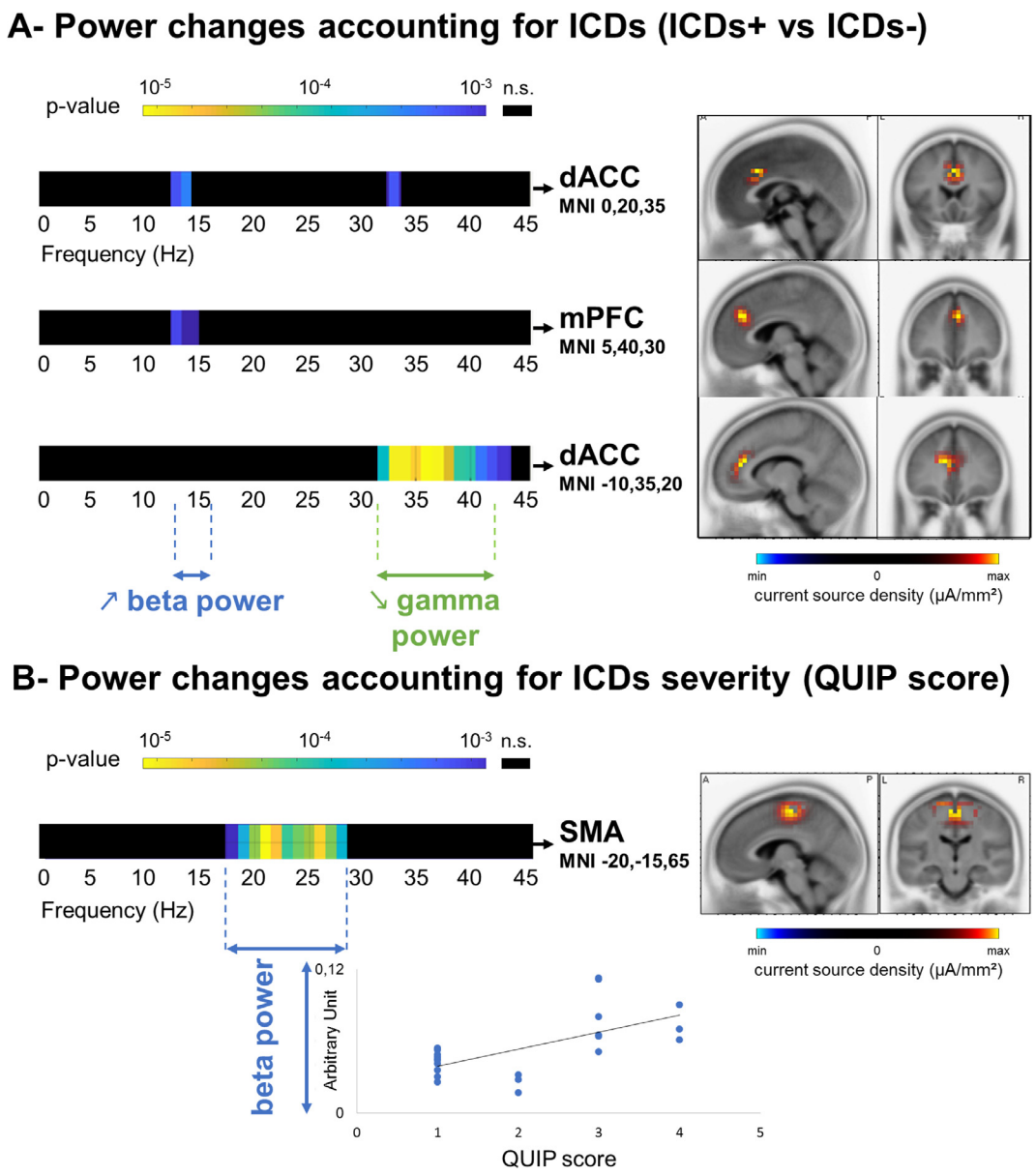

Fig. 2. Resting state cortical oscillatory activity (spectral power) predicting impulse control disorders. (A) Group effect, controlled for UPDRS-III and LEDD. The left side of the figure displays the frequency bands in which significant differences are observed for each one of the identified sources. The right side of the figure shows the location (current density map obtained with sLoreta) of the corresponding source. (B) Power changes correlating with ICDs severity (as indexed by QUIP scores), controlled for UPDRS-III and LEDD. The left side of the figure displays the frequency bands in which significant differences are observed. The right side of the figure shows the location (current density map obtained with sLoreta) of the unique source revealing power changes predicting ICD severity.

might be dysfunctional in ICDs in the hope of finding a proof of concept for the contribution of motor impulsivity to PD-ICDs. First, by contrast with blood flow imaging studies, EEG provides a direct measure of neural activity and a fair functional discrimination power. Indeed, cognitive processes have spectral signatures (Siegel et al., 2012; Keitel and Gross, 2016). Second, as it is challenging to test specifically all mechanisms involved in motor impulsivity (e.g., Criaud et al., 2017), and as brain activity during tasks (i.e., the functional architecture of cortical networks) is partly already reflected in intrinsic activity at rest (Raichle, 2015), this is an ideal starting point to probe resting state activity for the analysis of general brain function (Keitel and Gross, 2016). As illustrated in Supplementary Table 1, our original approach exploits the observation that the motor and the decisional hypotheses of impulsivity make distinct predictions regarding the cortical and spectral origins of ICDs.

4.1. Power modulation in brain regions supporting global motor inhibition

We clearly identified power modulations accounting for ICDs in a medial ensemble of areas including the mPFC, the dACC and the SMA (Fig. 2). These areas have repeatedly been found to form a functional network supporting global motor inhibition in task-based imaging studies (Jaffard et al., 2008; Criaud et al., 2017) and to be disrupted in PD-ICDs (Cilia et al., 2011). It is especially involved in proactive inhibition, an executive function that inhibits movement-triggering processes in anticipation of stimulation to prevent automatic and potentially inappropriate responses (Ballanger et al., 2009; Boulinguez et al., 2009; Criaud et al., 2012, 2016). Because this locking state is the default state of executive control (Criaud et al., 2012), it was found to be tonically active at rest (Jaffard et al., 2008). The observation that the

network of brains sources whose activity at rest predicts ICDs coincides with the proactive inhibitory network is thus consistent with the hypothesis according to which dysfunctions of motor inhibition account for ICDs (Rubia et al., 2001; Jaffard et al., 2008; Brevers et al., 2012; Criaud and Boulinguez, 2013; Albares et al., 2014; Manza et al., 2016).

4.2. Power modulation in frequency bands associated with motor processes and executive control

Although in some instances the ACC and the mPFC have been associated with decision making (Paus, 2001; Botvinick, 2007; Gasquoine, 2013; Shenhav et al., 2016; O'Doherty et al., 2017), the present spectral data are more consistent with the predictions of the motor hypothesis (Supplementary Table 1). Indeed, the oscillatory activity associated with reward processing in the context of decision making in these regions involves theta and delta frequency bands (Wacker et al., 2009; Park and Moghaddam, 2017). Here, raw differences between groups of patients with and without ICDs or gradual differences indexing ICDs severity were found in beta and low gamma frequency bands (Fig. 1). The beta rhythm has been extensively studied in the sensorimotor system, and was broadly linked to motor processes and executive control (Kilavik et al., 2013; Zhang et al., 2008). Consistent with the inhibitory interpretation, beta activity over the motor cortex during movement preparation is suppressed prior to and during movement (Baker, 2007), and increases when movement is voluntarily suppressed (Zhang et al., 2008). Beta oscillations are also considered as a marker of inhibitory cortical transmission mediated by GABA (Feshchenko et al., 1997). It is of interest to note that a broad increase in beta rhythm is a hallmark of PD (Oswal et al., 2013; Stein and Bar-Gad, 2013). In addition, some studies have also associated low gamma waves to executive and motor control (Engel and Fries, 2010; Karch et al., 2012; Gaetz et al., 2013; Stein and Bar-Gad, 2013; Iijima et al., 2015; Fonken et al., 2016) and to cortical inhibition (Jensen et al., 2012, 2014; Bonnefond and Jensen, 2013; Cheng et al., 2016). It is therefore likely that the power changes observed here in the dACC, mPFC and SMA are related to the control of motor inhibition.

Taken together, these anatomical and spectral data contrast with the dominant idea that ICDs in PD do not involve motor impulsivity (Voon et al., 2017; Weintraub and Claassen, 2017). They rather suggest that inhibitory dysfunction might contribute to some of the motor and non-motor symptoms observed in various movement and psychiatric disorders (Jahanshahi et al., 2015a, 2015b; Jahanshahi and Rothwell, 2017). Interestingly, our observation that ICDs severity is related to motor impulsivity is reminiscent of a study on pathological gambling in non-PD patients (Brevers et al., 2012) according to which both cognitive and motor inhibition underlie the presence of ICD, but only motor impulsivity determines its severity. Motor impulsivity is indeed acknowledged in ICDs in the general population (Chowdhury et al., 2017).

4.3. Limitations and open issues

It is important to emphasize, however, that our positive results do not contradict the role of cognitive impulsivity in PD-ICDs. Indeed, although particularly useful to detect problems with self-initiation and task-set maintenance in Parkinson's disease (Ko et al., 2013; Tinaz et al., 2016), resting state oscillations can just inform incompletely about the functional integrity of neural networks. The fact that intrinsic activity at rest reflects only to some extent brain activity during tasks (Raichle, 2015) is certainly critical when considering reward-related cognitive mechanisms whose dysfunctions expected for instance in the orbitofrontal or lateral prefrontal cortex have been mainly associated with neural activity induced by cues or signals (Frosini et al., 2010; Voon et al., 2010; Politis et al., 2013). In other words, our data can provide only some clues, but a comprehensive map of dysfunctional cortical networks cannot be expected from resting state studies. In addition, EEG does not provide easy access to subcortical activity, and is therefore blind to substantial activity of the mesocorticolimbic system. Again, the lack of evidence of involvement of the reward system in the present data does not rule out the major hypothesis of mesocorticolimbic dysfunctions. Further, another issue related to patient's demographics must be acknowledged for critical appraisal: Group differences were observed for several clinical variables (Table 1). Most were expected because they are either inherent in disease management or a common comorbidity of ICDs like, respectively, medication status (e.g., Samuel et al., 2015; Cossu et al., 2018; Mamikonyan et al., 2008) and depression (Antonini et al., 2017; Martini et al., 2018). But the fact that patients with ICDs may have shorter disease duration ($p = 0.09$) represents a potential bias.

Nevertheless, our results allow relaunching the debate on the neglected hypothesis of motor inhibition dysfunctions in PD-ICDs (Antonelli et al., 2011; Kehagia et al., 2014; Nombela et al., 2014; Ye et al., 2015). Further studies are needed to provide direct causal evidence that, among the numerous neural mechanisms involved in response inhibition (Chambers et al., 2009; Verbruggen and Logan, 2009; Aron, 2011; Bari and Robbins, 2013; Criaud and Boulinguez, 2013; Li, 2015; Criaud et al., 2017), some might be dysfunctional in PD-ICDs. In this respect it is noteworthy that the valence of beta power changes observed in the present study are difficult to interpret precisely. Indeed, beta activity is known to be involved in different forms of top-down proactive control. It would directly drive, for instance, local inhibition in targeted motor structures (e.g., Hwang et al., 2014). It could also drive, however, the executive setting of local, automatic, self-inhibitory networks that gate information processing locally in the motor system[1] (Albares et al., 2014). The first mechanism predicts decreased beta power as motor impulsivity increases (see also Lee et al., 2017). The second mechanism predicts increased beta power as motor impulsivity increases (see also Threadgill and Gable, 2018). In addition, it is not possible to determine from these data if brain activity changes are a direct expression of ICDs–related dysfunctions or the manifestation of compensatory mechanisms. Another issue here is the fact that we found no difference in alpha power, a direct physiological marker of active inhibition (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011; Mathewson et al., 2011; Klimesch, 2012; Hindriks and van Putten, 2013). This does not mean that no difference in the activity of local inhibitory populations can account for dysfunctions of motor inhibition in ICDs. We just did not find significant modulations of α oscillations at rest. These issues require further investigations using specific behavioral tasks coupled with appropriate event-related brain imaging protocols (e.g., Verbruggen and Logan, 2009; Hu and Li, 2012; Swann et al., 2012; Huster et al., 2013; Zandbelt et al., 2013; Hwang et al., 2014; Lavallee et al., 2014; Albares et al., 2015; Zhang et al., 2015; Wessel et al., 2016; Bartoli et al., 2018; Wagner et al., 2018).

[1] This is a paradoxical mechanism by which voluntary control of action may be achieved. The ability to provide controlled responses in unpredictable environments would require the automatic activation of the self-inhibitory circuitry within the SMA (i.e., automatic inhibition of automatic responses). Conversely, enabling automatic behavior when the environment becomes predictable would require top-down control to deactivate anticipatorily and temporarily the default and automatic inhibitory set. For this inhibitory mechanism, more control (more β) would mean more automatic (more impulsive) behavior (Albares et al., 2014).

5. Conclusions and perspectives

Our data clearly bring to the forefront the hypothesis that PD-ICDs might partly be due to motor dysfunctions leading to action impulsivity, and not only to cognitive dysfunctions leading to choice impulsivity. Potential implications for PD therapy are substantial. Indeed, recent work on the neural and neurochemical bases of response inhibition, a central function controlling the initiation of any response whatever a complex decision has to be made or not, has questioned the implication of the dopaminergic (DA) system (e.g., Obeso et al., 2011; Favre et al., 2013; Michely et al., 2015), and has identified the key role of the noradrenergic (NA) system (Chamberlain et al., 2006, 2009; Chamberlain and Sahakian, 2007; Robbins and Arnsten, 2009; Chamberlain and Robbins, 2013). In particular, proactive response inhibition, the basic executive function supported by the circuit identified in the present results, has been linked to the NA system and movement initiation dysfunctions in PD (Albares et al., 2015; Criaud et al., 2016; Spay et al., 2018). Other clues point to the involvement of the serotoninergic (5HT) system (Eagle et al., 2008; Pattij and Vanderschuren, 2008; Bari et al., 2009; Paterson et al., 2012; Ye et al., 2016). Dysfunction of specific inhibitory processes in PD patients with ICDs might thus be treated with non-dopaminergic pharmacological agents as suggested by recent experimental data (Kehagia et al., 2014; Ye et al., 2015; Rae et al., 2016). This approach is successful in psychiatric conditions with impulsivity symptoms like Attention Deficit Hyperactivity Disorder (Pattij and Vanderschuren, 2008; Dalley and Robbins, 2017), but is still to be tested in clinical trials for PD-ICDs (Tanwani et al., 2015). Nonetheless, further studies are warranted to identify all possible sources of dysfunction leading to ICDs. This should help defining subtypes of ICDs in PD differently associated with the DA, NA and 5HT systems, as inspired by former work in psychiatric conditions (Del Campo et al., 2011; Dalley and Robbins, 2017).

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

Authors' roles

(1) Research project: A. Conception: P.B., R.C., C.S., B.B.; B. Organization: P.B., R.C., G.P., C.S., G.M.; Execution: C.S., R.C.;
(2) Statistical Analysis: A. Design: P.B., C.S., G.L.; B. Execution: C.S., G.M., G.L.; C. Review and Critique: R.C., G.P., B.B., P.B.;
(3) Manuscript: A. Writing of the first draft: C.S., G.M.; B. Review and Critique: P.B., R.C., B.B; C. Reading and approval of the final version of the manuscript: C.S., G.M., G.L., B.B., G.P., R.C., P.B.

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Appendix A. Supplementary material

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