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Brain oscillations reveal impaired novelty detection from early stages of Parkinson's disease

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ABSTRACT

The identification of reliable biomarkers for early diagnosis and progression tracking of neurodegenerative diseases has become an important objective in clinical neuroscience in the last years. The P3a event-related potential, considered as the neurophysiological hallmark of novelty detection, has been shown to be reduced in Parkinson's disease (PD) and proposed as a sensitive measure for illness duration and severity. Our aim for this study was to explore for the first time whether impaired novelty detection could be observed through phase- and time-locked brain oscillatory activity at early PD. Twenty-seven patients with idiopathic PD at early stages (disease duration < 5 years and Hoehn and Yahr stage < 3) were included. A healthy control group (n = 24) was included as well. All participants performed an auditory involuntary attention task including frequent and deviant tones while a digital EEG was obtained. A neuropsychological battery was administered as well. Time-frequency representations of power and phase-locked oscillations and P3a amplitudes were compared between groups. We found a significant reduction of power and phase locking of slow oscillations (3–7 Hz) for deviant tones in the PD group compared to controls in the P3a time range (300–550 ms). Also, reduced modulation of late induced (not phase locked) alpha-beta oscillations (400–650 ms, 8–25 Hz) was observed in the PD group after deviant tones onset. The P3a amplitude was predicted by years of evolution in the PD group. Finally, while phase-locked slow oscillations were associated with task behavioral distraction effects, induced alpha-beta activity was related to cognitive flexibility performance. Our results show that novelty detection impairment can be identified in neurophysiological terms from very early stages of PD, and such impairment increases linearly as the disease progresses. Also, induced alpha-beta oscillations underlying novelty detection are related to executive functioning.

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease, and is characterized by both motor and non-motor symptoms. The former include tremor, bradykinesia, rigidity, postural instability, and gait impairment; these signs being considered as the cardinal features of the disease. Nevertheless, non-motor symptoms are now widely recognized. These manifestations include gastrointestinal, cardiovascular, genitourinary, and sleep disorders, though neuropsychiatric symptoms and cognitive decline are among the most common (Weintraub and Burn, 2011). Early cognitive deficits in PD represent a risk factor for developing Parkinson's disease dementia (PDD) and psychosis (Litvan et al., 2011; Pedersen et al., 2013). Moreover, cognitive impairment in PD is associated with decreased quality of life and increased burden for caregivers (Marras et al., 2008).

During the last years, identification of reliable biomarkers for early detection and tracking of neurodegenerative diseases has become an important target in clinical neuroscience. Electroencephalography (EEG) derived measures, especially the event-related potentials (ERPs), have been considered among possible biomarkers candidates for different neurodegenerative and neuropsychiatric diseases, due to their direct link to neurotransmission, low cost, reliability, and relatively easy obtainment (Ellger et al., 2002; Jackson and Snyder, 2008; Mondragón-Maya et al., 2013; Nguyen et al., 2010; Prichep, 2007;

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Solís-Vivanco et al., 2015). Additionally, ERPs can be used for cognition assessment in normal aging, as well as in neurologic and psychiatric disorders (Luck et al., 2011). One of the ERPs that have become promising as a possible biomarker for neurodegenerative disorders, especially PD, is the P3a wave (Seer et al., 2016). This ERP is evoked by unexpected auditory or visual stimuli, and has been considered a neurophysiological index of novelty detection and frontal lobe preservation (Deouell and Knight, 2009; Friedman et al., 2001; Polich, 2007; Schröger and Wolff, 1998). Novelty detection has been related to fronto-striatal functioning (Zink et al., 2006), and the role of nigral dopaminergic neurons for this process has been demonstrated in these patients (Mikell et al., 2014). Recently, our group described a strong association between PD and the P3a. This ERP was not only diminished since early and mid stages of PD (Solís-Vivanco et al., 2011), but the disease duration predicted inversely its amplitude, regardless of demographic, clinical and pharmacological variables across patients (Solís-Vivanco et al., 2015). This result allowed us to propose the P3a as a potential biomarker for PD progression.

Nevertheless, the underlying neurophysiological mechanisms of impaired novelty detection in PD are far from being completely understood. ERPs represent phase- and time-locked brain electrical activity respecting sensory, motor, or cognitive processes, and can inform about these with an optimal temporal resolution (Luck, 2014). Unfortunately, ERPs fail to represent neural dynamics that are not necessarily phase-locked to the event (i.e. induced activity). Also, it is difficult to identify the underlying oscillatory activity (in terms of frequency) that give rise to ERPs when using traditional (time-domain) estimation. Such difficulties can be overcome using time-frequency based analyses, which are intended to describe EEG dynamics with frequency as a prominent dimension and keeping a good temporal resolution (Tallon-Baudry et al., 1996). Additionally, time-frequency analyses may help quantifying amplitude changes and phase alignment in response or in anticipation to the onset of a stimulus, both processes being directly related to ERPs elicitation (Makeig et al., 2002). Moreover, time-frequency analyses allow to interpret results in terms of underlying neural oscillations (Cohen, 2014), which have been strongly linked to cognitive functions in the last years (Bonnefond et al., 2017; Buzsaki and Draguhn, 2004; Fries, 2005; Singer, 1999).

Neural oscillations represent rhythmic fluctuations in the excitability of single neurons, local neuronal populations, or multiple neuronal assemblies across far regions (Mathalon and Sohal, 2015). As temporal constriction is a major feature of neuronal excitability, the emergence of complex behavioral and cognitive processes must be dynamically organized by transient but robust synchronization across local and distributed neuronal populations (Buzsaki and Watson, 2012). Neurodegeneration may give rise to aberrant or reduced synchronization across neuronal populations, resulting in behavioral and cognitive impairment. Since each neurodegenerative disorder implies specific genetic, molecular, neurochemical, and neuroanatomical patterns for neural damage and loss across time, underlying “oscillopathies” for these disorders may represent important targets for early disease identification, progress monitoring, and pharmacological design (Nimmrich et al., 2015).

While there is substantial research regarding brain oscillations related to abnormal movement in PD (Brown, 2006; Hammond et al., 2007; Krawinkel et al., 2015; Nimmrich et al., 2015), there is, surprisingly, much less evidence about the brain rhythms underlying cognitive impairment in this “oscillopathy” (Schnitzler and Gross, 2005). Specifically, new knowledge about the neural dynamics and behavioral features related to P3a and novelty detection in PD is mandatory for this ERP to be considered a potential hallmark of disease evolution. Thus, our aim for this study was to explore for the first time whether impaired novelty detection could be observed through phase- and time-locked brain oscillatory activity since early PD.

2. Materials and methods

2.1. Participants

We included 27 patients with idiopathic PD diagnosis established by a movement disorders specialist and fulfilling the United Kingdom Parkinson's Brain Bank criteria (Hughes et al., 1992; Gibb and Lees, 1988). In all patients, < 5 years had passed from the time of motor symptoms onset, and their Hoehn and Yahr score was < 3. None of the patients showed dyskinesia or were taking other psychoactive drugs. Clinical recruitment was carried out at the Movement Disorders Clinic from the National Institute of Neurology and Neurosurgery (INNN) in Mexico City. Twenty-four healthy participants with no history of neurological or neuropsychiatric disorders were included as a control group. Healthy controls were family or friends of the members of the Department. Also, healthy persons that accompanied patients (but not family members) were invited and recruited at the waiting room of the Movement Disorders Clinic from the INNN. None of the participants were compensated for their participation. Demographic and clinical characteristics of the participants were obtained through an interview, or from medical files. All participants were right-handed and reported normal auditory function. Exclusion criteria for both groups included cognitive decline (Minimental State Examination (MMSE) < 24, (Folstein et al., 1975; Reyes et al., 2004)) and mild depressive symptomatology (Beck Depression Inventory (BDI) > 16 (Beck, 1978; Jurado et al., 1998)).

The local Institutional Review Board and Ethics Committee approved the study in accordance with the declaration of Helsinki (WMA, 2011). All participants gave written informed consent before the evaluation.

2.2. Experiment

The experimental task has been widely described in studies of P3a (Hölig and Berti, 2010; Schröger et al., 2000; Schröger and Wolff, 1998) and has been previously used by our group (Solís-Vivanco et al., 2011; Solís-Vivanco et al., 2015). Briefly, it consisted in the administration of pure frequent tones (90%, 1000 Hz) and pure deviant tones (10%, 900 and 1100 Hz) delivered binaurally through earphones, with an intensity of 80 dB. The tones were presented in a pseudo-random order, in such a way that in between two deviant tones there was at least one frequent tone. All tones had two durations with the same probability of presentation: 200 and 400 ms. The inter-stimulus interval was 2000 ms.

While sitting on a chair in an acoustically attenuated room, participants were asked to distinguish short (200 ms) from long (400 ms) tones and to respond as quickly as they could regardless of the tone frequency, by selectively pressing one of two buttons of a response panel. A total of 640 tones were delivered (576 frequent, 32 low deviants (900 Hz) and 32 high deviants (1100 Hz)). Before performing the task, all the participants were trained with one block of 30 frequent tones. In order to be included in the study, they had to respond correctly on 60% of the training block. Patients responded with the hand that was less affected by PD. Twelve participants (50%) from the control group responded with the left hand and the other 12 with the right hand. All participants responded to the task with closed eyes. Reaction times (RT) and hit rates (HR) were estimated for all participants.

2.3. EEG recording and analysis

A digital EEG was continuously recorded from 19 tin electrodes (10–20 International System (Jasper, 1958)) attached to an elastic cap (ElectroCap Inc.) and using linked ear lobes as a reference. We used SCAN 4.3.1 software (Neuroscan Inc.), with a bandwidth of 0.1 to 30 Hz and a sampling rate of 1000 Hz, using a NuAmps amplifier (Neuroscan Inc.). Eye movements were recorded with two electrodes in the external and sub-orbital canthus of the right eye, respectively. The electrodes

impedance was kept below 5 KΩ. All EEG were recorded between 9 am and 1 pm. This schedule before afternoon coincided with usual patients' appointments at the INNN and allowed us to reduce excessive fatigue in our participants. Patients undergoing dopaminergic treatment were recorded and neuropsychologically assessed during ON state.

All data analyses were done using Matlab custom scripts and the Fieldtrip toolbox (Oostenveld et al., 2011). After preprocessing EEG segments (−1 to 1.5 s respecting stimuli onset) and resampling to 256 Hz, those associated with incorrect responses or responses given 200 ms before or 1100 ms after tone onset were excluded, as well as those corresponding to frequent tones present after a deviant tone. Remaining epochs underwent visual inspection to exclude those with eye movement, blinks, or muscle artifacts.

Time-frequency representations (TFR) of power in all channels were performed. We used a fast Fourier transformation (FFT) with an adaptive sliding time window of two cycles long (ΔT = 2/f; e.g. ΔT = 200 ms for 10 Hz) in steps of 10 ms from 1 to 30 Hz. As the frequency sample we used was 256 Hz (maximum detectable frequency = 128 Hz), the number of points for each frequency was 2*256/f (e.g. 51 pts. for 10 Hz). A Hanning taper (ΔT long) was multiplied by the data prior to the FFT. The power of the individual trials was averaged over stimuli type (frequent and deviants) and log-transformed.

In order to explore the phase locking after stimuli onset across trials, phase data were used to estimate the phase locking factor (PLF) or inter-trial phase clustering (Tallon-Baudry et al., 1996). The PLF over N trials is defined as:

$$PLF(f_o, t) = \frac{1}{N}\left|\sum_{k=1}^{N} e^{i\varphi^k(f_0,t)}\right|$$

where $\varphi^k(f_o, t)$ corresponds to the estimated phase at frequency f_o and time t resulting from the time-frequency analysis. The PLF represents the extent to which distribution of phase angles at each time-frequency-sensor point across trials is non-uniformly distributed. A PLF close to 0 reflects a strong phase variability, whereas a PLF = 1 indicates that all trials exhibit the same phase at a given frequency and time point. As for the TFR analysis of power, the PLF was calculated with respect to a sliding time window 2 cycles long to which we applied a Hanning taper. Obtained PLF values were normalized by transforming them to Rayleigh Z values ($Z = n \cdot PLF^2$, where n is the number of trials (Cohen, 2014)).

Additionally, the P3a was estimated for the same trials. EEG epochs were demeaned, linearly detrended and baseline corrected (−100 to 0 ms). Averages in the time domain were obtained separately for frequent and deviant tones. The differential wave was estimated by subtracting the grand average of the frequent tones from the grand average of the deviant tones in each participant. The P3a was considered as the maximum voltage peak between 300 and 550 ms in the difference wave. In order to guarantee similar signal to noise ratios between stimuli types, the same number of trials for each one was used within participants for all of the analyses (TFR, PLF, and ERPs). We chose to do this according to experimental recommendations (Cohen, 2014; Luck, 2014), and also because the PLF is sensitive to the number of observations (Cohen, 2014). The mean number of included trials across participants was 74 ± 8, with no significant differences between groups (t(49) = 0.43, p = 0.68).

2.4. Time-frequency windows of interest

In order to identify time-frequency windows of interest, we followed two main steps: 1) As temporal dynamics of novelty detection were the main objective of this study, we averaged the TFR of total power of all participants (regardless of group), computed the difference between tones (log(deviant/frequent)), and focused on the time-frequency range and topographic distribution usually described for the P3a in elder subjects (Polich, 2007; Solís-Vivanco et al., 2015), i.e. from 300 to 550 ms after tone onset in the delta-theta range (3–7 Hz) at frontal regions (Fig. 1). This time-frequency window, driven by previous research, revealed increased frontal power for deviant compared to frequent tones. Averaged values from Fz in this time-frequency window were used for subsequent comparisons between groups. 2) A data-driven time-frequency window was selected as well: The differential TFR across participants also revealed reduced power of alpha-beta activity (8–25 Hz) from 400 to 650 ms with maximal decrease at parieto-occipital regions (Fig. 1). In order to identify the time- but not phase-locked (induced) oscillations, we subtracted the ERP from each trial in each condition and repeated the TFR process. Only the alpha-beta activity survived this step (see Inline Supplementary Figure). Thus, averaged values from Pz in this time-frequency window were used for subsequent comparisons between groups. In the case of TFR of PLF, we used the same channel-time-frequency window of slow activity selected for total power (Fz, 300–550 ms, 3–7 Hz). As expected, no changes of alpha-beta activity were observed in the TFR of PLF. For P3a, mean voltage amplitudes (± 50 ms) of the difference wave were measured with respect to the highest peak between 300 and 550 ms at Fz.

2.5. Neuropsychological assessment

Additional to the EEG and task, a brief neuropsychological battery focused on executive functioning was administered to all participants. We included tests for attention and working memory (Digit Span forward and backwards and the Letter-Number Sequencing Test (Wechsler, 1997a, 1997b)), cognitive flexibility (Wisconsin Card Sorting Test (WCST, (Berg, 1948)), and inhibitory control (Stroop Test (Jensen and Rohwer Jr, 1966)). We chose this battery based on international recommendations for neuropsychological assessment in PD (Litvan et al., 2012). All of the clinical, neuropsychological and electrophysiological assessments were done in the same day. The order of neuropsychological and electrophysiological procedures was counterbalanced across participants.

2.6. Statistics

Descriptive analysis was performed in terms of mean, standard deviation and percentages. Demographic, clinical, and neuropsychological variables were compared by *t*-tests or χ^2 test as required.

The behavioral variables (RT and HR) were analyzed with repeated measures ANOVA (RM-ANOVA), with type of tone (frequent/deviant) as within-subject factor, and group (PD/Control) as between-subject factor.

For power and PLF, averaged data points from each tone type per

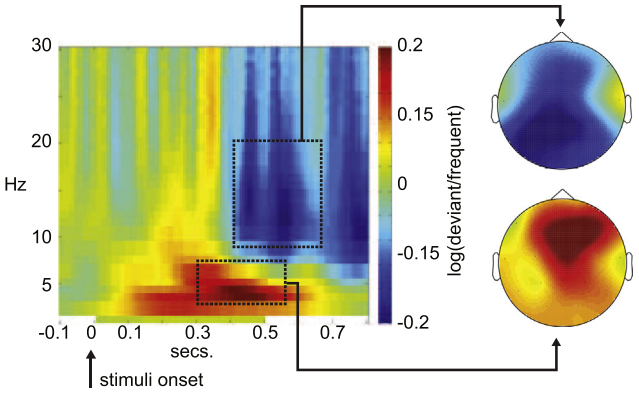

Fig. 1. Time-frequency representation (TFR) of differential power between deviant and frequent tones across participants. A frontal increase at 300–550 ms in the delta-theta range and a posterior reduction at 400–650 ms in the alpha-beta range were considered as windows of interest (see dashed rectangles).

Table 1
Demographic and clinical characteristics of the groups.

	Parkinson's disease	Control	p
	Mean ± SD	Mean ± SD	
Gender (men, n(%))	19(70)	12(50)	0.11
Age (years)	58 ± 8	52 ± 8	0.008
Education (years)	13 ± 5	14 ± 4	0.35
PD duration (years)	2 ± 1	–	–
Hoehn and Yahr 1, n(%)	20(74)	–	–
Onset side right, n(%)	16(59)	–	–
Tremor dominant, n(%)	20(74)	–	–
Medication			
Levodopa/carbidopa, n(%)	6(22)	–	–
Other antiparkinsonian agents, n (%)	7(26)	–	–
Non medicated, n(%)	14(52)	–	–

participant were analyzed with a RM-ANOVA for each frequency range independently (delta-theta and alpha-beta), with tone type as within-subject factor and group as between-subject factor. Post hoc comparisons were made using the Bonferroni test. Since time-frequency windows were selected based on differences between tone type, we ignored tone type effects and focused on group effects or on the tone type*group interactions. P3a amplitudes from Fz channel were compared between groups with a t-test.

Associations between power, PLF, P3a (from the difference wave), and behavior (including neuropsychological performance) were explored with Pearson correlations across all participants. Statistical significance was set at $p < 0.05$. IBM SPSS 20 software (IBM Corp.) was used for all statistical analyses.

3. Results

3.1. Demographic and clinical results

Table 1 shows the demographic and clinical characteristics of the sample. There were no significant differences between groups for most of the demographic variable, though a lower age was found for the control group. Derived from this, age was included in all RM-ANOVA as a covariable. Most of the patients were at very initial stages of PD (Hoehn and Yahr scale = 1) with a predominant tremor profile. The PD group showed significant reduced performance in mainly all neuropsychological tests (Table 2).

3.2. Behavior

RM-ANOVA of RT revealed a significant effect for tone type ($F(1,48) = 6.18$, $p = 0.016$), with longer RT for the deviant compared to the frequent tones (Mean difference (MD) = 40.22, $p < 0.001$; Fig. 2a). No group effect was found ($F(1,48) = 2.07$, $p = 0.16$), nor an interaction of tone type*group ($F_{(1,48)} = 1.25$, $p = 0.27$). HR analysis did not show any significant effect for intra or inter-subject factors ($p > 0.16$ in all cases; Fig. 2b).

3.3. Time-frequency analysis of total and induced power

Table 3 shows descriptive data for power, PLF, and P3a results, and Fig. 3 shows the TFR and time-domain representation (in the case of P3a) of the three of them. The RM-ANOVA of power at 300–550 ms in delta-theta range revealed a group effect ($F_{(1,48)} = 5.31$, $p = 0.03$), with higher power in the PD group compared to controls (MD = 0.40, $p = 0.03$). Nevertheless, a significant interaction of tone type*group was found ($F_{(1,48)} = 5.33$, $p = 0.025$). Post hoc comparisons revealed increased power for the deviant compared to frequent tones in the

Table 2
Neuropsychological scores and behavioral results in each group.

	Parkinson's disease	Control	p
	Mean ± SD	Mean ± SD	
MMSE	27 ± 2	28 ± 2	0.1
Digit span			
Forward	5 ± 1	5 ± 1	0.49
Backward	3 ± 1	4 ± 1	0.03
Number and letter sequencing[a]	9 ± 2	6 ± 3	< 0.001
WCST			
Number of trials administered	124 ± 13	117 ± 19	0.15
Correct responses	62 ± 15	74 ± 12	0.003
Errors	62 ± 22	43 ± 20	0.003
Perseverative responses	46 ± 28	27 ± 21	0.008
Perseverative errors	38 ± 21	23 ± 16	0.003
Nonperseverative errors	21 ± 12	18 ± 14	0.40
Conceptual level responses	42 ± 19	60 ± 14	< 0.001
Number of categories completed	3 ± 2	4 ± 2	0.002
Stroop			
Interference errors	9 ± 13	1 ± 1	0.004
Correct responses	25 ± 12	37 ± 9	< 0.001
Beck Depression Inventory	8 ± 5	6 ± 5	0.38
HR			0.86[b]
Frequent	0.89 ± 0.05	0.89 ± 0.08	
Deviant	0.82 ± 0.10	0.81 ± 0.14	
RT			0.39[b]
Frequent	811 ± 93	762 ± 90	
Deviant	875 ± 101	839 ± 119	

[a] Scoring represents the sum of all correct items, rather than the maximal span given by the participant (Wechsler, 1997a, 1997b).
[b] P-value of the interaction group × tone type.

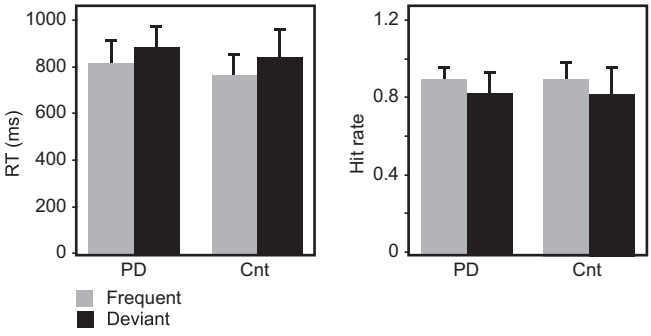

Fig. 2. Task-related behavior in each group. (A) Reaction time. (B) Hit rate. Cnt: Control group; PD: Parkinson's disease group.

Table 3
Mean ± SD for total power, PLF and P3a for each group.

	Parkinson's disease		Control	
	Frequent	Deviant	Frequent	Deviant
Power (log)				
Total delta-theta (3–7 Hz, 300–550 ms)	2.84 ± 0.7	2.85 ± 0.7	2.42 ± 0.4	2.54 ± 0.5
Induced alpha-beta (8–25 Hz, 400–650 ms)	2.67 ± 0.5	2.62 ± 0.5	2.42 ± 0.7	2.21 ± 0.6
PLF (Rayleigh Z)				
Delta-theta (3–7 Hz, 300–550 ms)	2.79 ± 2.2	4.50 ± 2.9	3.43 ± 2.3	7.63 ± 6.5
P3a (μV)	Deviant-frequent		Deviant-frequent	
	2.66 ± 1.9		3.38 ± 2.2	

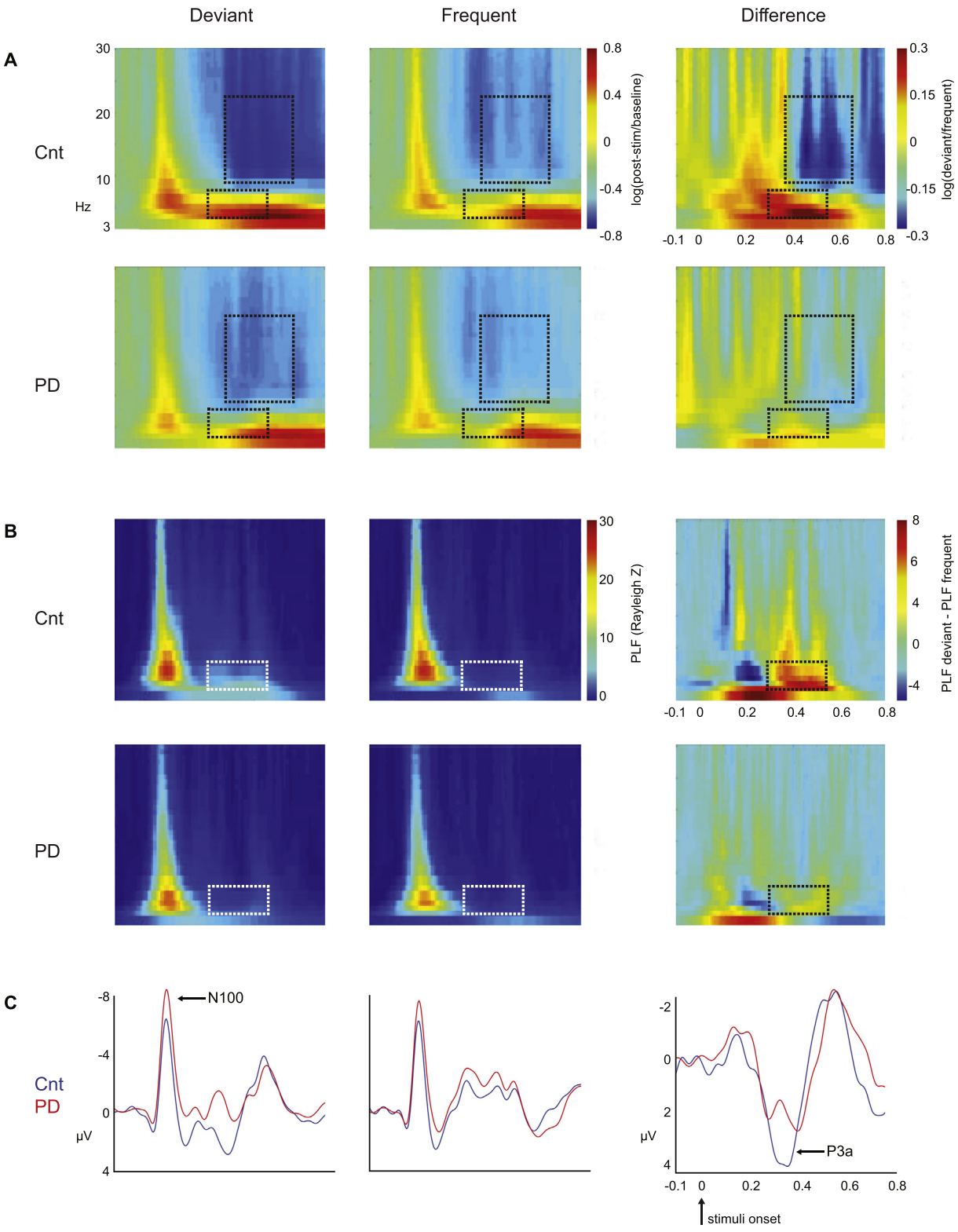

Fig. 3. Time-frequency representations (TFR) for deviant and frequent tones in each group for (A) Power and (B) Phase-locking factor. Time-frequency windows of interest are marked in each TFR with dashed rectangles. (C) ERP for each type of tone at Fz channel. The P3a is marked in the difference wave. Cnt: Control group; PD: Parkinson's disease group.

control group (MD = 0.14, p = 0.003), but this was not observed in the PD group (MD = 0.006, p = 0.89; Fig. 3a). Also, we found that power for frequent tones was significantly higher in the PD compared to the control group (MD = 0.47, p = 0.01), while deviant tones showed no significant differences between them (MD = 0.33, p = 0.07).

Posterior induced alpha-beta activity was shown to be increased in the PD compared to the control group ($F_{(1,48)}$ = 5.42, p = 0.02). Again, a significant tone type*group interaction ($F_{(1,48)}$ = 10.87, p = 0.002), revealed that control participants reduced alpha-beta power after deviant compared to frequent tones (MD = −0.21, p < 0.001), but this

was not observed in the PD group (MD = 0.04, p = 0.20; Supplementary Figure). Also, while power for frequent tones was not significantly different between groups (MD = 0.32, p = 0.09), deviant tones showed reduced power in the control compared to the PD group (MD = −0.49, p = 0.005). In conclusion, analysis of power revealed reduced modulation of slow and fast oscillations by deviant tones in the PD group.

3.4. Phase locked activity

PLF comparisons in the delta-theta range revealed stronger phase alignment for the control participants in general (group effect: $F_{(1,48)} = 5.48$, p = 0.02) and a significant interaction tone type*group was observed ($F_{(1,48)} = 4.67$, p = 0.04). Post hoc comparisons revealed that control participants increased phase alignment after deviant tones compared to frequent (MD = 4.61, p < 0.001), contrary to the PD group (MD = 1.35, p = 0.18). Also, while PLF values did not differ between groups after frequent tones onset (MD = 0.37, p = 0.58), they were significantly higher for deviant tones in the control group compared to PD (MD = 3.62, p = 0.02; Fig. 3b). In sum, PD patients showed reduced phase alignment of slow oscillations across trials exclusively after deviant stimuli onset, compared to controls.

Both power and phase-locked analyses were repeated comparing medicated (N = 14) vs. non-medicated patients (N = 13). Though medicated patients showed higher total delta-theta power compared to non-medicated patients ($F_{(1,24)} = 4.66$, p = 0.04; MD = 0.54), there were no significant interactions with tone type. No significant differences or interactions were observed for induced alpha-beta power or PLF.

3.5. P3a event related potential

Fig. 3c shows the ERPs for both types of tone and the difference between them (P3a). Though there were not significant differences for the P3a between the groups (t(49) = −1.23, p = 0.22), we found a significant correlation between this ERP and PLF in the delta-theta range (r = 0.49, p < 0.001). Also, the P3a amplitude was inversely associated with the years passed since motor symptoms onset in the PD group (r = −0.45, p = 0.018; Fig. 4a). This association remained significant after controlling by age (r = −0.51, p = 0.008). P3a was not significantly different between medicated and non-medicated patients (t(25) = 0.13, p = 0.89). In summary, phase alignment of slow oscillations accounted for the amplitude of the P3a and this ERP was inversely associated with years of evolution of the disease.

In order to rule out that power or phase locking decrease in the PD group was not exclusive of the P3a time range, we performed similar analyses for the frequency and time range of the preceding N100 ERP (50–200 ms, 4–10 Hz, see Fig. 3c). RM-ANOVA of total power revealed an effect of condition ($F_{(1,48)} = 4.06$, p = 0.05) but not of group ($F_{(1,48)} = 0.68$, p = 0.41), nor an interaction between factors ($F_{(1,48)} = 1.45$, p = 0.23). No significant effects were observed for PLF or ERPs analyses (p > 0.1 in all cases).

3.6. Association between oscillations, P3a and behavior

Across all participants, both higher PLF values for deviant respecting frequent tones (PLF modulation) and higher P3a amplitudes were associated with stronger distraction effects (deviant RT – frequent RT; r = 0.45, p = 0.001 and r = 0.35, p = 0.01, respectively; Fig. 4b and c). Also, within the control group stronger induced alpha-beta power modulation (deviant respecting frequent tones) was associated with a better performance in the WCST (total errors: r = 0.41, p = 0.04, and conceptual level responses: r = −0.54, p = 0.007, see Inline Supplementary table).

4. Discussion

This study aimed to explore the brain oscillations associated with auditory novelty detection at early PD. Our main finding was a diminished power and phase alignment of slow oscillations (delta-theta) after the onset of deviant stimuli in PD patients with < 5 years of evolution and mild severity. An additional reduced late induced desynchronization in the alpha-beta range was found in this group. Also, changes in both slow and alpha-beta oscillations were associated with attentional and executive performance.

In general, research about neural oscillations in PD has focused on their association with abnormal movement. For motor symptomatology, the most frequently associated rhythm has been the beta band (Chen et al., 2011; Chen et al., 2007; Heinrichs-Graham et al., 2014a; Heinrichs-Graham et al., 2014b; Kuhn et al., 2008). Basal ganglia activity recorded both in animal models of PD and patients undergoing deep-brain stimulation (DBS) has shown a consistent oscillatory pattern of ~20 Hz (Bergmann et al., 2012; Herz et al., 2014; Krawinkel et al., 2015; Kuhn et al., 2009). Beta activity is also hypersynchronous in motor regions of unmedicated PD patients (Marceglia et al., 2006; Priori et al., 2004; Weinberger et al., 2006). Also, local field potential activity recorded in subthalamic nucleus (STN) and globus pallidus of PD patients has shown decreased beta power prior to and during paced voluntary movements (Cassidy et al., 2002), and after informative cues in reaction time tasks (Williams et al., 2005). In the same line, increased

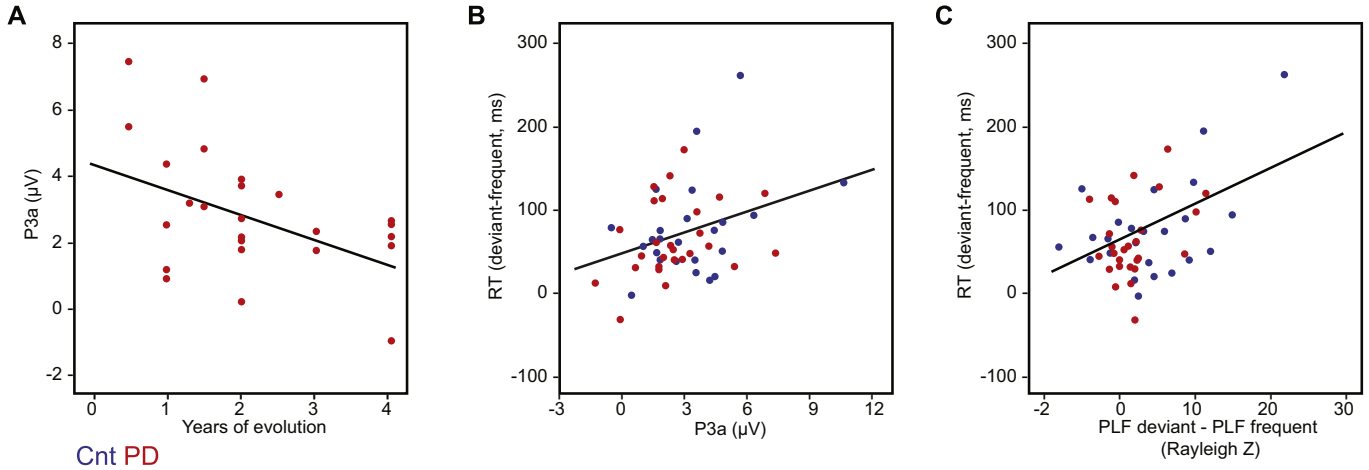

Fig. 4. (A) Association between P3a and years of evolution of Parkinson's disease. P3a (B) and delta-theta Phase-locking factor (C) modulation (deviant-frequent) predicted distraction effects as measured by reaction time (deviant-frequent).

beta power of STN has been observed before movement cancellation (Kuhn et al., 2004). Moreover, beta-band activity is reduced after dopamine replacement therapy and DBS (Brown et al., 2001; Kuhn et al., 2008), and this modulation is consistently associated with reduction of bradykinesia and rigidity (Kuhn et al., 2009), which complements the finding that STN stimulation in the beta range (20 Hz) affects grip force in PD (Chen et al., 2011).

Consequently, the beta band has been proposed to be essentially akinetic and relevant for bradykinesia. Brown (2006) has suggested that suppression of beta activity at basal ganglia following behaviorally relevant stimuli might trigger the processing of novel events and renewed movement. In the same line, Engel and Fries (2010) have proposed that the beta band may represent an active process that promotes the maintenance of existing motor or cognitive sets at the expense of neuronal processing of new movements or flexible cognition. On the other hand, alpha oscillations have been shown to index neural inhibition both in reactive and top-down modalities (Foxe and Snyder, 2011; Jensen and Mazaheri, 2010; Klimesch et al., 2007). Accordingly, reduction of its power at posterior cortical sites has been reported after the onset of target or relevant stimuli compared to non-target (Yordanova and Kolev, 1998). Also, unexpected sounds can promote alpha power decrease in occipital regions and improve visual perception (Feng et al., 2017), indicating that novelty detection in one sensory domain may enhance the processing of potential relevant information in another one. In this study, we found a reduction of both induced beta and alpha activity after the onset of deviant stimuli at parieto-occipital sites in controls, but not in the PD group. It is important to note that the differences in these frequency bands between groups was exclusive for the deviant tones, showing that the impairment in PD relied in the processing of novel stimuli, and not in a more general perceptual inability. Interestingly, alpha-beta reduction after novel stimuli was associated with cognitive flexibility. From these results, alpha-beta band suppression might allow not only the interruption and resetting of ongoing behavior, but an effective instauration of neural pathways for cognitive and behavioral adjustment after novelty processing. Nevertheless, this last hypothesis should be taken with caution in the case of PD, as this association was found exclusively in the healthy participants. Future studies might explore deeper the role of alpha-beta desynchronization on executive functioning, both under normal and neurodegenerative conditions.

In addition to alpha-beta oscillations, we found a reduced modulation of phase-locked delta-theta activity after the onset of deviant stimuli. This activity was observed in the P3a range, and since both (delta-theta and P3a) showed a strong association and predicted distraction effects as measured by RT, it can be assumed that this oscillatory activity underlies P3a. Though the origin of ERPs remains under debate, it is generally accepted that slow phase-locked oscillations may account for the elicitation of different ERPs (Cohen, 2014; Makeig et al., 2002; Mazaheri and Jensen, 2008). It could be argued that P3a and slow phase-locked oscillations represent mainly the same phenomenon. We agree with that possibility, though it must be noted that each measure provided differential information (i.e. association with disease duration and decreased phase alignment after novel stimuli from early stages of PD, respectively).

As in the case of alpha-beta oscillations, the reduced phase-locked slow activity in the PD group was exclusive of the deviant stimuli. In the same line, a preceding sensory or perceptual impairment in the PD group could not be concluded, since no differences were found between groups for the N100 ERP. Interestingly, though no differences in P3a amplitudes were observed between groups, underlying oscillations revealed reduced phase alignment in PD after deviant tones. These results indicate that decreased novelty detection in PD can be observed from early stages in neurophysiological terms, even when the ERP is not significantly reduced at this point, and there are no behavioral differences either. In addition, P3a was already associated with PD evolution in patients with < 5 years since motor symptoms started, even after controlling by age. This replicates our previous reports (Solís-Vivanco et al., 2011; Solís-Vivanco et al., 2015) and coincides with recent results by Lange et al. (2016a), who explored the P3a in a visual task resembling the WCST and showed that this ERP is reduced in PD regardless of the sensory modality under which it is evoked.

The origin of the observed diminishment in phase alignment after novelty detection in PD remains to be explained. Loss of nigral dopaminergic neurons disrupts not only nigro-striatal connections, but the functional dynamics of fronto-striatal communication as well, giving rise to the classic motor features of the disease (Nimmrich et al., 2015). This neurodegenerative pattern has been associated with pathological oscillatory changes in basal ganglia (Brown and Williams, 2005; Hammond et al., 2007). Nevertheless, such changes have been mainly related to motor symptoms and dopaminergic medication. On the other hand, the role of basal ganglia for detection of salient stimuli has been widely reported (Cools, 2006; Delgado et al., 2003; Marco-Pallarés et al., 2010; Schultz, 1994; Zink et al., 2006). From a neurophysiological perspective, phasic input from basal ganglia into cortex after detection of salient stimuli may exert an alerting action, promoting a neural reorganization at frontal areas for adaptive cognition and behavior (Nieoullon, 2002). This reorganization might include a phase resetting of slow oscillations (P3a) at frontal regions to create a rapid neural inhibition of ongoing activity that can promote the processing of deviant stimuli and attentional reallocation, as suggested by Polich (2007). In general, phase resetting has been associated with enhanced attentional behavior and cognitive control (Helfrich and Knight, 2016; Voloh et al., 2015).

It must be noted that while dopamine has been widely related to salience and novelty detection (Nieoullon, 2002; Ungless, 2004), we found no differences in P3a nor phase alignment between medicated and non-medicated patients. Whether diminished emergence of P3a and reduced phase alignment in PD is a consequence of deplenishment in other neurotransmitters like norepinephrine or acetylcholine remains to be explored (Brown et al., 2015; Nieuwenhuis et al., 2005; Ranganath and Rainer, 2003).

Though we did not find any association between P3a or phase alignment and neuropsychological performance, other authors have reported consistent associations between this ERP and executive and memory impairment in PD. While cognitive flexibility (WCST) has been related to P3a in this disease (Lange et al., 2016a; Tsuchiya et al., 2000), recently Schomaker et al. (2014) found that decreased novelty detection affected negatively memory encoding in PD. The differences between studies could be due to years of evolution or severity stages in the mentioned studies (a mean of 8 years in the case of Lange and colleagues and Hoehn and Yahr (HY) scores of 2–3 in Schomaker et al. study vs. 2 years and HY < 3 in this study).

Our study has many limitations. For instance, to our knowledge this is the first report exploring underlying brain oscillations related to novelty detection in PD, so no studies can be used to compare our results. Brain sources of oscillation changes and P3a reductions in our sample were not analyzed. Fast oscillations (> 30 Hz) were not explored either, and we were not able to explore the association between the P3a reduction and motor and non-motor symptoms in our sample. Also, implications of decreased novelty detection for everyday life in PD should be explored.

In order to further explore novelty detection and its neurophysiological correlates (P3a and underlying oscillations) as potential biomarkers for PD duration and severity, specificity of this measures compared to other movement disorders (see for example, Lange et al. (2016b)) must be assessed, and at-risk populations (i.e. REM sleep behavior disorder) should be studied. Also, longitudinal studies are warranted in order to explore the evolution of P3a and underlying brain oscillations in the same patients.

In conclusion, our results show that novelty detection impairment can be identified in neurophysiological terms from very early stages of PD, and this impairment evolves linearly with illness duration. In

addition, induced alpha-beta oscillations underlying novelty detection are related to executive functioning.

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