Neurophysiological investigation of auditory intensity dependence in patients with Parkinson's disease

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ABSTRACT

There is accumulating evidence for auditory dysfunctions in patients with Parkinson's disease (PD). Moreover, a possible relationship has been suggested between altered auditory intensity processing and the hypophonic speech characteristics in PD. Nonetheless, further insight into the neurophysiological correlates of auditory intensity processing in patients with PD is needed primarily.

In the present study, high-density EEG recordings were used to investigate intensity dependence of auditory evoked potentials (IDAEPs) in 14 patients with PD and 14 age- and gender-matched healthy control participants (HCs). Patients with PD were evaluated in both the on- and off-medication states. HCs were also evaluated twice.

Significantly increased IDAEP of the N1/P2 was demonstrated in patients with PD evaluated in the on-medication state compared to HCs. Distinctive results were found for the N1 and P2 component. Regarding the N1 component, no differences in latency or amplitude were shown between patients with PD and HCs regardless of the medication state. In contrast, increased P2 amplitude was demonstrated in patients with PD evaluated in the on-medication state compared to the off-medication state and HCs.

In addition to a dopaminergic deficiency, deficits in serotonergic neurotransmission in PD were shown based on increased IDAEP. Due to specific alterations of the N1-P2 complex, the current results suggest deficiencies in early-attentive inhibitory processing of auditory input in PD. This interpretation is consistent with the involvement of the basal ganglia and the role of dopaminergic and serotonergic neurotransmission in auditory gating.

KEYWORDS

Parkinson's disease, auditory processing, auditory event-related potentials, intensity dependence of auditory evoked potentials, P1-N1-P2 complex, auditory gating

DECLARATIONS

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Conflicts of interest

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The study was performed in accordance with the Declaration of Helsinki. All participants signed a written informed consent approved by the Ethics Committee of the Ghent University Hospital.

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Data is considered confidential.

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Code availability: not applicable.

Author's contributions

Conceptualization: Kim De Keyser, Miet De Letter, Patrick Santens, Durk Talsma, Dick Botteldooren, Annelies Bockstael; Method: Kim De Keyser, Miet De Letter, Patrick Santens, Durk Talsma, Dick Botteldooren, Annelies Bockstael; Formal analysis and investigation: Kim De Keyser; Data

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1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by an alpha-synuclein pathology and the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). The neurodegeneration causes a dopamine deficiency in the striatum and leads to a dysfunction of the basal ganglia (BG) circuitry (Bartels and Leenders 2009; Rietdijk et al. 2017). Whereas dysfunctions of the cortico-BG-thalamo-cortical circuitry give rise to the motor symptoms characteristic of PD, the presence of non-motor symptoms, such as autonomic dysfunctions, cognitive deficits, depression, sleep disorders, and sensory-perceptual alterations, has been increasingly recognized (Chaudhuri et al. 2006; Jankovic 2008; Park and Stacy 2009). Accordingly, recent research has drawn attention to auditory dysfunctions in patients with PD (De Groote et al. 2020; Jafari et al. 2020).

In addition to an age-related decline affecting peripheral and central auditory processes, as well as general cognitive abilities (Alain et al. 2004; Getzmann et al. 2014), altered auditory processing has been demonstrated in patients with PD compared to age-matched healthy control participants (HCs) along the various stages of the auditory pathway (De Groote et al. 2020; Jafari et al. 2020). Moreover, the importance of investigating auditory processing in patients with PD has been emphasized based on the suggestion that dysfunctions in auditory perception could be a possible factor contributing to the motor speech disorder in PD (Kwan and Whitehill 2011; Sapir 2014). The hypothesis seems in line with a central role of the BG in sensorimotor integration (Dubbioso et al. 2019). Hereby, the gating of sensory input for motor control has been considered a key concept (Boecker et al. 1999; Dubbioso et al. 2019; Kaji et al. 2005; Lidsky et al. 1985).

Auditory gating refers to the neurophysiological process by which repetitive incoming auditory information is filtered and stimulus overload of higher-order cognitive functioning can be avoided (Freedman et al. 1991; Lijffijt et al. 2009; Thwaites et al. 2013; Venables 1964). Whereas auditory gating has been predominantly regarded as a bottom-up filter mechanism, the involvement of top-down

attentive modulations has also been suggested, making the process a multi-component and multi-stage concept (Boutros et al. 1999; Golubic et al. 2019; Lijffijt et al. 2009).

One research technique that may be of specific interest to investigate this specialized aspect of central auditory processing in patients with PD, is the recording of auditory event-related potentials (ERPs) (Alain and Tremblay 2007; Duncan et al. 2009; Fritz et al. 2007; Luck 2014; Picton et al. 1971; Shinn-Cunningham 2017). Auditory ERPs represent voltage fluctuations in the ongoing electroencephalogram (EEG) that are time-locked to an auditory event with a millisecond temporal resolution (Kappenman and Luck 2012). More specifically, the auditory P1-N1-P2 complex has been considered an ERP correlate of sound detection (Alain and Tremblay 2007; Lightfoot 2016). Its waveform consists of three deflections, namely P1, N1, and P2 that reach their maximal amplitude at around 50, 100, and 160 ms respectively, each component representing at least partially independent auditory processes (Arnott et al. 2011; Crowley and Colrain 2004; Paiva et al. 2016). Although the P1-N1-P2 complex has been acknowledged an 'obligatory' exogenous response (Alain and Tremblay 2007; Arnott et al. 2011), its neurophysiology may be influenced in a top-down manner by the level of arousal, alertness, and attention of the participant (Lightfoot 2016; Woldorff et al. 1993). In this regard, investigation of the P1-N1-P2 complex could help us to understand auditory gating as an interface between the bottom-up and top-down aspects of auditory processing in patients with PD.

A paired-click paradigm in which the suppression of the response to the second stimulus is measured, has been widely used to evaluate pre-attentive auditory gating of the P1 component (Adler et al. 1982; Mayer et al. 2009). Following this method, decreased auditory gating was found in patients with PD evaluated in the on-medication state compared to HCs (Teo et al. 1997; Teo et al. 1998). However, significant differences between groups were only evident for patients with PD at the higher disease stages (Hoehn and Yahr stage IV - V), suggesting that alterations in pre-attentive bottom-up auditory gating are evident further in disease progression. Nonetheless, since auditory gating has been considered a multi-stage concept, gating mechanisms in PD have also been investigated at the later

stages of information processing based on the auditory N1 and P2 components (Rosburg et al. 2009). Using a variety of methodological approaches, decreased auditory gating of the P1/N1 complex, N1 component, and N1/P2 complex was reported in the studies of Gulberti et al. (2015), Annanmaki et al. (2017), and Lukhanina et al. (2009) respectively. Nevertheless, further research is needed as a limited number of studies have investigated auditory gating in PD and neurophysiological mechanisms are far from clear.

Since a reduced speech intensity or hypophonia has been considered a prominent feature of the motor speech disorder in PD (Darley et al. 1969; Duffy 2005) and behavioral evidence has been found for altered speech intensity perception (Clark et al. 2014; De Keyser et al. 2016; Ho et al. 2000; Kwan and Whitehill 2011), intensity dependence of auditory evoked potentials (IDAEP) may be of specific interest to study in patients with PD. Considering IDAEP, an increased auditory stimulus intensity generally results in an increased N1/P2 amplitude (Mulert et al. 2005; Paiva et al. 2016). Accordingly, IDAEP represents a linear N1/P2 amplitude change in response to different stimulus intensities measured as a slope function at the fronto-central and central scalp electrodes (Hegerl and Juckel 1993; Hensch et al. 2008; Juckel et al. 2008). The IDAEP amplitude stimulus intensity function has been specifically related to serotonergic neurotransmission as increased IDAEP has been associated with reduced serotonin functioning and vice versa (Beauducel et al. 2000; Beucke et al. 2010; Hegerl et al. 2001; Hegerl and Juckel 1993; Juckel et al. 2003; Juckel et al. 1999; O'Neill et al. 2006).

To our knowledge, only two studies have investigated IDAEP in patients with PD. In the study of Beucke et al. (2010), altered IDAEP was found in nine early stage unmedicated patients with PD. Patients with PD demonstrated a significantly increased IDAEP of the N1/P2 amplitude compared to HCs (p = 0.05). After 12 weeks of dopaminergic treatment, IDAEP values did no longer differ between patients with PD and HCs (Beucke et al. 2010). Likewise, the effect of 12 weeks of dopaminergic medication on IDAEP was investigated in 30 initially unmedicated patients with PD in the study of Park

et al. (2020). The main finding of their study was related to a decreased IDAEP of the N1 component in the post- compared to the pre-treatment condition. Although the pilot study of Beucke et al. (2010) and the study of Park et al. (2020), yield interesting results regarding altered IDAEP in de-novo PD, no study has investigated the intensity dependence of the P1-N1-P2 complex in long-term L-dopa treated patients with PD.

In order to gain further insight into stimulus-related central auditory intensity processing in PD, the goal of the present study is to compare IDAEP between L-dopa treated patients with PD and matched HCs, differentiating the P1, N1 and P2 component, and the IDAEP slope function. In addition, the effect of dopaminergic medication on IDAEP in PD will be investigated by evaluating patients with PD in both the on- and off-medication states. As serotonergic dysfunctions have been demonstrated in PD, increased IDAEP could be hypothesized in patients with PD compared to HCs, possibly affecting the partially independent subcomponents differently. Considering the opponent interactions between the serotonergic and dopaminergic neurotransmitter systems (Daw et al. 2002; Kapur and Remington 1996; Seo et al. 2008), altered IDAEP could be most evident based on additional serotonergic suppression when patients with PD are evaluated in the on-medication state. Taken together, this will be the first study that addresses IDAEP in patients with PD to further explore the neurophysiological mechanisms that could be involved in altered auditory intensity processing in PD. The findings may provide future directions into research on the possible relationship between speech perception and production deficits in patients with PD in both a fundamental and a clinically relevant way.

2. METHOD

2.1 Participants

Fourteen non-demented patients with idiopathic PD participated in the study. The PD group included 11 men and 3 women, mean age 63.0 years (*SD* = 7.78; range 51-73 years) and mean disease duration 8.7 years (*SD* = 3.22; range 3-14 years). PD severity was evaluated with the commonly used Hoehn and Yahr (H&Y) scale. Patients with a H&Y scale ≤ 3 were included whereas patients with deep brain stimulation were excluded. The HC group was matched for age and gender, and included 11 men and 3 women, mean age 62.9 years (*SD* = 7.64; range 49-73 years). All participants were right-handed (except for 1 HC). Table 1 represents the demographic and clinical data of the patients with PD and HCs.

Table 1 Demographic and clinical data of the patients with PD and HCs.

	PD		*HC*		
Participant characteristics	*M*	*SD*	*M*	*SD*	*P*
Age (y)	63.0	7.78	62.9	7.64	*0.961*
Education (y)	13.3	3.24	13.4	3.37	*0.910*
MoCA	28.4	1.45	27.6	1.50	*0.137*
BDI - II	12.0	6.86	3.3	3.65	*< 0.001*
PTA (dB HL)	17.9	8.86	18.5	9.15	*0.866*
Disease duration (y)	8.7	3.22	NA		NA
LEDD (mg)	816.1	359.26	NA		NA
UPDRS-III (on)	22.9	11.70	NA		NA
H&Y (on)	1.9	0.79	NA		NA

Note. PD, patients with Parkinson's disease evaluated in the on-medication state; HC, healthy control participants; *P*, *p*-value based on the independent Student's *t*-test between PD and HC; *M*, mean; *SD*, standard deviation; y, years; MoCA, Montreal Cognitive Assessment; BDI - II, Beck Depression Inventory - II; PTA, pure tone average; LEDD, levodopa equivalent daily dose (Tomlinson et al. 2010);

UPDRS-III, Unified Parkinson's Disease Rating Scale – Part III; H&Y, Hoehn and Yahr stage; NA, not applicable.

2.2 Procedure

Almost all participants took part in a previous study (De Keyser et al. 2019), in which they underwent an audiological screening, cognitive screening and a self-scored depression inventory. More specifically, participants were screened for age-related normal hearing. Pure-tone hearing thresholds were measured at conventional octave frequencies under headphone (TDH39 headphones, Interacoustics, Assens, Denmark) using a AA222 audiometer (AA222 Audio Traveller, Interacoustics, Assens, Denmark). The pure-tone average (PTA) threshold was calculated as the average air conduction hearing thresholds at 0.5, 1.0, 2.0, and 4.0 kHz. In addition, the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) was used for cognitive screening. Symptoms of depression and related severity were measured with the Beck Depression Inventory - II (BDI - II; Beck et al. 1961, 1996; Smarr 2003). Finally, patients with PD underwent a clinical and neurological evaluation that included part III of the Unified Parkinson's Disease Rating Scale (UPDRS - III; Goetz et al. 2007) and H&Y staging scale (Goetz et al. 2004; Hoehn and Yahr 1967) in both medication states.

In the current study, all participants participated in two EEG-sessions in which both exogenous (i.e. IDAEP) and endogenous (i.e. mismatch negativity and P3) auditory ERPs were investigated. In patients with PD, one session was performed in the on- and one in the off-medication state with the order of medication states counterbalanced across participants. To induce a practically defined off-medication state, patients with PD were tested at least 12 hours after not taking their regular anti-parkinson medication (CAPSIT-protocol, Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease protocol; Defer et al. 1999). HCs performed the same procedure twice. The results of the exogenous auditory ERP components are discussed in the present article.

The study was performed in accordance with the Declaration of Helsinki. All participants signed a written informed consent approved by the Ethics Committee of the Ghent University Hospital.

2.3 IDAEP paradigm

Stimulus presentation was generated by E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA) and delivered binaurally by ER1 insert earphones (Etymotic Research). Stimuli were calibrated using a Brüel & Kjaer head and torso simulator (Type 4128C – Brüel & Kjaer, Naerum, Denmark) and PULSE LabShop software (Version 15.1.0 – Brüel & Kjaer, Naerum, Denmark). The IDAEP paradigm consisted of 500 pure tones (1000 Hz, 80 ms stimulus duration, 10 ms rise/fall time) presented at five intensity levels of 60, 70, 80, 90, and 100 dB SPL in a randomized order. A variable stimulus-onset-interval of 1200-1800 ms was used. Stimulus presentation was divided into four blocks of 125 stimuli each, offering participants the possibility to take a break between blocks. During stimulus presentation, participants watched a silent video.

Fig. 1 Paradigm for recording of the intensity dependence of auditory evoked potentials. Participants watched a silent video during stimulus presentation.

2.4 EEG recording

The EEG was recorded from 126 electrode sites using an EasyCap electrode cap (Brain Products, Munich, Germany). The online reference electrode was FCz. Ground electrode impedance was maintained below 10 kOhm. Data were collected with a BrainVision BrainAmp amplifier (Brain Products, Munich, Germany) and were continuously digitized with a sampling frequency of 500 Hz. BrainVision Recorder was used as recording software (Brain Products, Munich, Germany).

2.5 ERP data-analysis

BrainVision Analyzer 2 (Brain Products, Munich, Germany) was used for off-line data analysis. First, raw data inspection was performed followed by IIR filtering (low cut-off 0.3 Hz, high cut-off 30 Hz, slope 12 dB/oct). A notch filter was enabled at 50 Hz. Artifacts related to eye blinks and eye movements were removed based on independent component analysis (ICA). Topographic interpolation was used to replace electrode channels that were disabled based on raw data inspection followed by re-referencing the data to the average of P9-P10 electrode positions. Subsequently, the

EEG was segmented into epochs of -100 to 500 ms relative to stimulus onset. Baseline correction was applied using the pre-stimulus window of -100 ms. It should be noted that in this study, all markers were corrected based on a 50 ms mismatch between stimulus onset and trigger. This correction factor was justified based on a flat baseline of the grand average across all conditions, and a flat baseline of the grand average of the conditions separately. After artifact rejection (gradient 75 µV, amplitude -100 µV – 100 µV, max-min 150 µV/200 ms, low activity 0.5 µV/100 ms), segments were averaged for each stimulus intensity. At least 2/3 of the segments had to remain to be included for further data-analysis. Measurement windows were determined based on a grand average across all conditions and its topographical distribution at all electrode positions. Finally, 50% peak latency and mean amplitude values were derived for each stimulus intensity at the FCz electrode positions for P1 in an 30 – 60 ms window, N1 in a 70 – 140 ms window, and P2 in a 150 – 290 ms window. Mean-to-mean amplitudes were then calculated for the N1/P2 slope function. Mapping of the current source density (CSD) or surface Laplacian was used to represent the topographical pattern of the ERP activity based on a spherical spline algorithm (Kamarajan et al. 2015; Perrin et al. 1989).

2.6 Statistical analysis

Statistical analysis was performed using SPSS Statistics (Version 26 – IBM). Regarding the demographic and clinical data of the patients with PD and HCs, the normal distribution of data and equality of variances were evaluated with the Shapiro-Wilk test and Levene's test respectively. The parametric independent Student's *t* test was used to compare the demographic data and the results of the MoCA, BDI - II, and PTA between patients with PD and HCs. In addition, the paired Student's *t* test was addressed to estimate the effect of dopaminergic medication on the UPDRS-III motor score and the H&Y stage. Regarding the IDAEP data, multiple linear mixed models (LMMs) were applied for the P1, N1, P2, and N1/P2 respectively. The N1/P2 amplitude was calculated as the absolute amplitude difference between N1 and P2. 50% peak latency and/or mean amplitude values were addressed as dependent variables. Condition (PD ON, PD OFF, HC), test moment (evaluation 1, evaluation 2), and gender, age, BDI - II score were considered as independent variables and possible confounding

variables inherent to IDAEP respectively. Independent variables and confounding variables were added as fixed factors by default. Participants, intercepts and stimulus intensity (60, 70, 80, 90, and 100 dB SPL) were considered as random factors. In addition, post hoc pairwise comparisons were computed using Bonferroni correction. Any p values < 0.05 were considered statistically significant.

3. RESULTS

Participants were screened for age-related normal hearing, cognitive impairment and depression. All participants had a mean PTA ≤ 35 dB HL and no significant differences were found for hearing thresholds between patients with PD and HCs, independent Student's t test, $t(26) = -0.170$, $p = 0.866$ and $t(26) = -0.036$, $p = 0.971$, in the on- and off-medication state respectively. The score on the cognitive assessment was ≥ 25 for all participants and did not differ between patients with PD and HCs, $t(26) = 1.534$, $p = 0.137$. Regarding depression, a significantly higher score, $t(26) = 4.196$, $p < 0.001$, was found in the PD group compared to the HC group, indicating minimal depression in the patient group. In patients with PD, statistical analysis also demonstrated a significantly higher UPDRS-III motor score, paired Student's t test, $t(13) = 2.547$, $p = 0.024$, and significantly higher H&Y stage, $t(13) = 3.373$, $p = 0.005$, in the off-medication state compared to the on-medication state.

3.1 P1 component

Based on the LMMs for P1 latency and amplitude, no significant main effect of condition was found, $F(2, 69) = 1.758$, $p = 0.180$, and $F(2, 88) = 1.747$, $p = 0.180$ respectively.

3.2 N1 component

Based on the LMM for N1 latency, a significant main effect of condition, $F(2, 41) = 4.355$, $p = 0.019$ was found. Post-hoc pair-wise comparisons demonstrated a shorter N1 latency in the off-medication state compared to the on-medication state with a mean difference of -1.925 ms, 95% CI [-3.807, -0.042], $p = 0.043$. Based on the LMM for N1 amplitude, also a significant main effect of condition was found $F(2, 39) = 7.006$, $p = 0.002$. Post-hoc pairwise comparisons demonstrated a higher

N1 amplitude in the off-medication state compared to the on-medication state with a mean difference of -0.612 µV, 95% CI [-1.016, -0.208], p = 0.001.

3.3 P2 component

Based on the LMM for P2 latency, no significant main effect of condition was found, $F(2, 41)$ = 0.042, p = 0.959. Based on the LMM for P2 amplitude, a significant interaction of condition*intensity was found $F(2, 42)$ = 7.204, p = 0.002. Post-hoc pairwise comparisons demonstrated a significant effect of condition for stimulus intensities of 80, 90 and 100 dB SPL ($p \leq 0.002$). A higher P2 amplitude was found in patients with PD evaluated in the on-medication state compared to the off-medication state at 80, 90, and 100 dB SPL and compared to HCs at 90 and 100 dB SPL (Table 2).

Table 2 Mean amplitude values of the P2 component per stimulus intensity level in patients with PD and HCs.

P2 mean amplitude	*PD ON*		*PD OFF*		*HC*		
	M	*95% CI*	*M*	*95% CI*	*M*	*95% CI*	*P-value*
60 dB	2.302	[1.277, 3.327]	2.107	[1.090, 3.123]	1.653	[0.700, 2.605]	0.577
70 dB	3.226	[2.228, 4.225]	2.863	[1.870, 3.856]	2.030	[1.083, 2.978]	0.083
80 dB	4.151	[3.130, 5.171]	3.619	[2.603, 4.635]	2.408	[1.433, 3.384]	0.002
90 dB	5.075	[3.987, 6.163]	4.376	[3.293, 5.458]	2.786	[1.753, 3.820]	0.001
100 dB	5.999	[4.804, 7.194]	5.132	[3.946, 6.317]	3.164	[2.046, 4.283]	0.001

Note. PD ON, patients with Parkinson's disease evaluated in the on-medication state (IDAEP average: n = 12); PD OFF, patients with Parkinson's disease evaluated in the off-medication state (IDAEP average: n = 13); HC, healthy control participants (IDAEP average: n = 2 x 14); *M*, mean; *95% CI*, 95% confidence interval.

3.4 N1/P2 slope

Regarding N1/P2 slope in patients with PD, an average slope of 1.34 µV/10 dB, 95% CI [1.076, 1.613] and an average slope of 1.14 µV/10 dB, 95% CI [0.877, 1.401] were found in the on- and off-medication states respectively. No significant difference was evident for the N1/P2 slope values in

patients with PD evaluated in the on-medication state compared to the off-medication state. In contrast, N1/P2 slope was significantly increased ($p < 0.05$) in patients with PD in the on-medication state compared to the average N1/P2 slope of 0.96 µV/10 dB, 95% CI [0.733, 1.182] found in HCs (Fig. 1).

Fig. 2 IDAEP of the P1-N1-P2 complex in patients with Parkinson's disease evaluated in the on- (PD ON) and off-medication states (PD OFF) and healthy control participants (HCs). Intensity dependence of the P1-N1-P2 complex is shown for five stimulus intensities at the FCz electrode position. CSD mapping was used for the topographical distribution of the N1 sink and P2 source – *Please print in color online only*

4. DISCUSSION

The aim of the current study was to gain insight into the different aspects of stimulus-related central auditory intensity processing in patients with PD based on the intensity dependence of the P1-N1-P2 complex. The findings are discussed following the early and late auditory ERP subcomponents and the IDAEP slope function.

4.1 Early components of auditory stimulus intensity processing

The auditory P1 and N1 subcomponents are considered to reflect the early stages of stimulus-related auditory processing (Getzmann et al. 2014). In this regard, the P1 component has been related to auditory pre-attentive arousal, whereas the N1 component has been recognized to reflect the detection of and orientation to auditory changes (Arnott et al. 2011; Hari et al. 1987; Paiva et al. 2016). In the present study, no differences in latency or amplitude of the auditory P1 component were found between patients with PD and HCs. In addition, no effect of dopaminergic medication on the auditory P1 was shown when patients with PD were evaluated in the on- and off-medication states. The result may imply comparable levels of auditory pre-attentive arousal between patients with PD regardless of the medication state and HCs (Arnott et al. 2011; Hari et al. 1987).

In addition, no differences in latency or amplitude of the N1 component were shown between patients with PD and HCs. This finding suggests that sound intensity detection in patients with PD seems not considerably altered compared to HCs (Arnott et al. 2011; Paiva et al. 2016). Nevertheless, latency of the N1 component slightly decreased and amplitude increased when patients with PD were assessed in the off- compared to the on-medication state. This result could be interpreted as a slightly increased auditory signal detection when patients with PD are evaluated without their dopaminergic medication.

4.2 Late components of auditory stimulus intensity processing

Remarkably, increased P2 amplitude values were clearly demonstrated in patients with PD evaluated in the on-medication state compared to the off-medication state and HCs. Primary processes of attentional allocation, perceptual learning, and memory have been related to the P2 component (Arnott et al. 2011; Paiva et al. 2016). Moreover, it has been suggested that the P2 component may be related to inhibitory processing and gating mechanisms regulating sensory input (Paiva et al. 2016). Increased P2 amplitudes have been interpreted to represent an age-related decline in inhibitory control (Amenedo and Diaz 1998; Anderer et al. 1996; Harris et al. 2007). As such, the current findings may suggest a dysfunctional inhibition at specific stages of auditory input processing in patients with PD.

Although sensory gating has generally been considered as a bottom-up filter mechanism, the involvement of top-down early-attentive modulations has also been hypothesized, making the process a multi-component and multi-stage concept (Boutros et al. 1999; Golubic et al. 2019; Lijffijt et al. 2009). In previous studies, decreased auditory gating in PD has been shown based on the subcomponents of the auditory P1-N1-P2 complex (Annanmaki et al. 2017; De Groote et al. 2020; Gulberti et al. 2015; Lukhanina et al. 2009). The present study broadens the view of multi-stage gating alterations in PD by demonstrating increased P2 amplitude values based on the IDAEP of the P1-N1-P2 complex in L-dopa treated patients with PD. In HCs, the configuration of the P1-N1-P2 complex corresponds to a

neurophysiological response of auditory input processing during a task that implies automaticity, i.e. auditory stimulus processing while watching a silent video (Arnott et al. 2011). In contrast, the increased P2 amplitude shown in patients with PD may suggest a dysfunction in withdrawing attentional allocation towards the stimuli and seems comparable with an enhanced P2 component for non-target stimuli in an attentive oddball paradigm (Crowley and Colrain 2004; Garcia-Larrea et al. 1992). Therefore, the results of this study specifically suggest alterations of auditory input processing that may be related to top-down early-attentive inhibitory processing. Although no evidence was found for differences in the early components of auditory input processing between patients with PD and HCs in the present study, early stage input alterations in PD have been suggested based on other methodological approaches (De Groote et al. 2020). Therefore, an increased allocation of attention could also be interpreted as a compensatory mechanism for changes along the auditory pathway inducing a PD-specific approach of auditory input processing (Alain et al. 2004; Boecker et al. 1999; Getzmann et al. 2014; Keesom and Hurley 2020).

4.3 IDAEP slope function

Whilst the pathological hallmark of PD consists of a dopamine deficiency in the striatum due to dopaminergic neurodegeneration in the substantia nigra, neurodegeneration in PD also affects other brainstem nuclei, thereby affecting multiple neurotransmitter systems (Barone 2010). More specifically, neurodegeneration of the locus coeruleus and raphe nuclei may cause noradrenergic and serotonergic deficits in PD respectively (Braak et al. 2003). Since a close reciprocal relationship exists between the noradrenergic, serotonergic and dopaminergic neurotransmitter systems (Beucke et al. 2010; Guiard et al. 2008; Millan et al. 1998), altered central auditory processing needs to be investigated and interpreted taking into account the multiple neurotransmitter systems involved in PD.

In the present study, increased IDAEP of the N1/P2 was found in patients with PD suggesting low levels of serotonergic neurotransmission (Beauducel et al. 2000; Beucke et al. 2010; Hegerl et al.

2001; Hegerl and Juckel 1993; Juckel et al. 2003; Juckel et al. 1999; O'Neill et al. 2006). This interpretation seems consistent with the significantly higher scores on the BDI - II that were found in patients with PD compared to HCs. Moreover, the present research findings could suggest an involvement of serotonin in auditory dysfunctions in patients with PD as serotonin has been considered to modulate auditory processing based on inhibitory mechanisms (Gopal et al. 2000; Hall et al. 2011; Hurley and Hall 2011; Jastreboff and Jastreboff 2015). More specifically, a low serotonergic neurotransmission might be related to a reduced inhibition of auditory input in PD.

Furthermore, a close reciprocal neurophysiological interaction has been recognized between the serotonergic and dopaminergic neurotransmitter systems (Beucke et al. 2010; Daw et al. 2002; Guiard et al. 2008; Kapur and Remington 1996; Millan et al. 1998). Serotonergic neurons from the dorsal raphe nuclei are known to provide a major input to the ventral tegmental area (VTA) in the brainstem (Li et al. 2019; Wang et al. 2019; Watabe-Uchida et al. 2012). In turn, dopamine is transmitted from the VTA toward the ventral striatum and prefrontal cortex (PFC) through the mesocorticolimbic projections. Compared to the profound loss of dopaminergic neurons in the SNc from which dopamine is transmitted through the nigrostriatal projections toward the dorsal striatum, a relatively spared ventral striatum has been considered in PD (Al Jaja et al. 2020; Cools 2006; MacDonald and Monchi 2011). Since opponent interactions between serotonin and dopamine have been hypothesized, low serotonergic function may imply disinhibition of dopaminergic activity in the ventral striatum and PFC (Daw et al. 2002; Kapur and Remington 1996; Seo et al. 2008). This hypothesis may be in line with a decreased inhibitory control associated with dopamine overflow in the ventral striatum (Georgiev et al. 2015). Alternatively, the BG might be in a central position to serve dynamic gating mechanisms for updating stable cognitive representations in the PFC (Cools 2006; Gulberti et al. 2015). As such, alterations in top-down modulations indexing early-attentive processes have also been related to the hypothesis of a decreased intracortical inhibition in patients with PD (Lukhanina et al. 2009; Lukhanina et al. 2010). In the present study, a distinct frontal topographical distribution in the PD compared to the HC group was demonstrated.

Following the spatio-temporal progression of dopamine depletion, dopaminergic medication may improve motor and cognitive function associated with the dorsal striatum, whereas relatively intact brain areas such as the ventral striatum and PFC could be overdosed (Cools 2006; MacDonald and Monchi 2011). In the present study, differences in mean between the PD and HC group further increased when patients with PD were evaluated with their regular dopaminergic medication suggesting additional dopaminergic dysregulation and serotonergic suppression. In addition, the effects of dopamine overdose could still be present when patients with PD are evaluated in the off-medication state. Long-term effects of dopamine on the VTA have been suggested (MacDonald and Monchi 2011) which may imply that a washout period as proposed by the CAPSIT protocol might be too short to distinctively alter specific aspects of cognitive functioning in patients with PD chronically treated with dopaminergic medication. Furthermore, the effect of dopaminergic medication might explain why the results in long-term L-dopa treated patients with PD differ from the research findings reported in the studies of Beucke et al. (2010) and Park et al. (2020). In their studies, beneficial effects of dopaminergic medication on IDAEP have been reported in de-novo patients with PD (Beucke et al. 2010; Park et al. 2020).

As in the present study IDAEP was investigated in patients with PD, the current discussion specifically focused on the involvement of serotonin and its relationship with dopaminergic neurotransmission in auditory processing in PD. Nonetheless, other neurotransmitter systems and various interactions could also be involved (Keesom and Hurley 2020). More specifically, dopamine, glutamate, gamma-aminobutyric acid, and acetylcholine are common neurotransmitters of the auditory system and BG circuitry (Jafari et al. 2020; Lee and Godfrey 2014; Oestreicher et al. 2002; Ruel et al. 2007). In this way, possible neurophysiological interaction mechanisms between peripheral and central auditory processing, and non-auditory systems must be considered in PD (Keesom and Hurley 2020). Finally, dopamine and dopaminergic medication exert their influence on the various neurotransmitters and their interactions involved (Jafari et al. 2020), making understanding of the neurophysiological mechanisms of auditory input processing in PD challenging.

4.4 Limitations and future directions

Although this study provided evidence for alterations in auditory intensity processing in PD, certain limitations and suggestions for further research need to be considered. First, sample size could be considered relatively small. This aspect could threat the statistical power of the present study and may hamper the generalization of the research findings. Nevertheless, few studies have investigated auditory processing in PD by evaluating the same patients with PD in both the on- and off-medication states. Furthermore, a balanced study design was provided by also evaluating the HCs twice. Second, alterations of auditory input processing in PD were found at the late components of auditory stimulus intensity processing. No evidence was found for differences in the early components of auditory input processing between patients with PD and HCs in the present study. However, it can be hypothesized that an increase in auditory processing load, for example by using a high stimulus rate, complex signals such as speech, or noise-added conditions could result in other insights (De Groote et al., 2020; Schwent et al. 1976a, Schwent et al. 1976b; Talsma et al. 2010). Third, research into sensory and cognitive processing in PD has been characterized by dysfunctions in various oscillatory networks (Dushanova et al. 2009, Dushanova et al. 2010; Dushanova 2011; Güdücü et al. 2019; Güntekin et al. 2018; Solís-Vivanco et al. 2018). Frequency or joint time-frequency analysis (Zhang 2019) may provide valuable insights into the spectral power changes that are associated with auditory processing in patients with PD. Finally, the present research findings underline important clinical implications of the possible involvement of serotonin in auditory processing in PD. In the review article by Keesom and Hurley (2020), alterations in peripheral and central auditory processing, cognitive functioning, and social interaction have all been interrelated by possible deficiencies of the serotonergic neurotransmission system. The authors provide a conceptual diagram that may be considered highly valuable to support both the fundamental and clinical relevance of further research into altered auditory processing within the communication deficits in PD.

5. CONCLUSION

In the present study, deficits in serotonergic neurotransmission in PD were shown based on increased IDAEP. More specifically, a significantly increased P2 amplitude was demonstrated in patients with PD evaluated in the on-medication state compared to the off-medication state and HCs. Due to these specific alterations of the N1-P2 complex, the current results may suggest a disturbed gating of auditory input at an early-attentive stage of auditory processing in PD. The findings are consistent with the involvement of the basal ganglia and the role of dopaminergic and serotonergic neurotransmission in auditory gating. Accordingly, further insights into how the pathophysiology of PD could imply distinct alterations in auditory intensity processing have been provided. However, future research is needed to unravel both the fundamental and clinical implications of the present findings.

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