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Research report

The function of dopaminergic neural signal transmission in auditory pulse perception: Evidence from dopaminergic treatment in Parkinson's patients

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ABSTRACT

Auditory pulse perception, which is the perception of relatively salient and regularly appearing events in an acoustic sequence, is a necessary function in humans and has been suggested to rely on basal ganglia function. Our study investigated the effect dopamine depletion has on the auditory pulse perception in Parkinson's disease (PD). We examined PD patients and healthy seniors in this study, and all participants performed a pulse perception task and a motor control task. The pulse perception task consisted of a two alternative forced choice task in which subjects had to identify stimuli as metrical or non-metrical. We tested PD patients before and after the administration of L-3,4-dihydroxyphenylalanin (L-DOPA). The healthy control group performed the same tasks twice. PD patients that were dopamine depleted performed the pulse perception task equally well and as fast as did the healthy control group. However, after the administration of L-DOPA, PD patients performed the pulse perception task significantly faster than they did before the pharmacological intervention, which showed that pulse perception can be modulated by dopaminergic stimulation. These findings indicate that pulse perception relies on dopaminergic mechanisms but is not affected by dopamine depletion in the early stages of PD.

1. Introduction

Timing perception is necessary for any form of sensory perception and is, therefore, important to structure and accurately perceive our environment. Most humans are able to tap to or dance to music, which is an ability that relies on the perception of periodicity, also called auditory pulse or beat perception. Pulse perception refers to the perception of relatively salient and regularly occurring tones in an acoustic sequence [1–3]. Developmental research has shown that pulse perception is one of the earliest timing abilities present in humans. For example, newborns are sensitive to deviations from pulse as evidenced by electrophysiological measures [4]. Pulse perception has been investigated by psychologists for more than half a century [5–9], evidencing listeners' preference for sequences containing a pulse over sequences containing no pulse [10–14]. It has also been shown that sequences containing a pulse provide perceptual benefits in discriminating tones and rhythms [15–18], and that they facilitate reproduction of and synchronization with rhythms [14,19,20]. Several neuroimaging studies have reported the involvement of cortico-striatal activity in pulse perception [21]. Specifically, increased hemodynamic responses in the putamen has been observed when listeners processed tone sequences containing a pulse as compared to sequences containing no pulse [22,23]. Whereas functional localization using functional magnetic resonance imaging can help identify target brain regions involved in a perceptual mechanism, it does not reveal the physiological mechanisms, e.g., transmitter systems that are involved in the perceptive process. The purpose of this study was to investigate the potential physiological mechanisms underlying the involvement of the striatum in pulse perception. Several potential neurotransmitter systems could underly activity in the striatum, including dopaminergic, cholinergic, or GABA-ergic systems [24]. Based on previous literature, however, the dopaminergic system is the most likely to be associated with pulse perception. A large body of evidence suggests a role of the dopamine system in timing perception at various time scales [25–27]. For example, some dopamine receptor antagonists have shown to affect interval timing [28,29], which led to the suggestion that dopamine modulates the speed of our internal clock [30,31]. Moreover, internal clock processes are suggested to take place in the cortico-striatal circuitry [32,33], a claim that is corroborated by various studies showing dorso-striatal involvement in timing perception [34–36]. Thus, the dopaminergic system is the most prone to be investigated in relation to pulse perception.

Investigating Parkinson's disease (PD) patients allows researchers to monitor behavioral performance in relation to dopaminergic treatment. Early stage PD patients suffer from a dopamine deficiency as a consequence of progressive neurodegeneration of the substantia nigra pars compacta [37–39]. The

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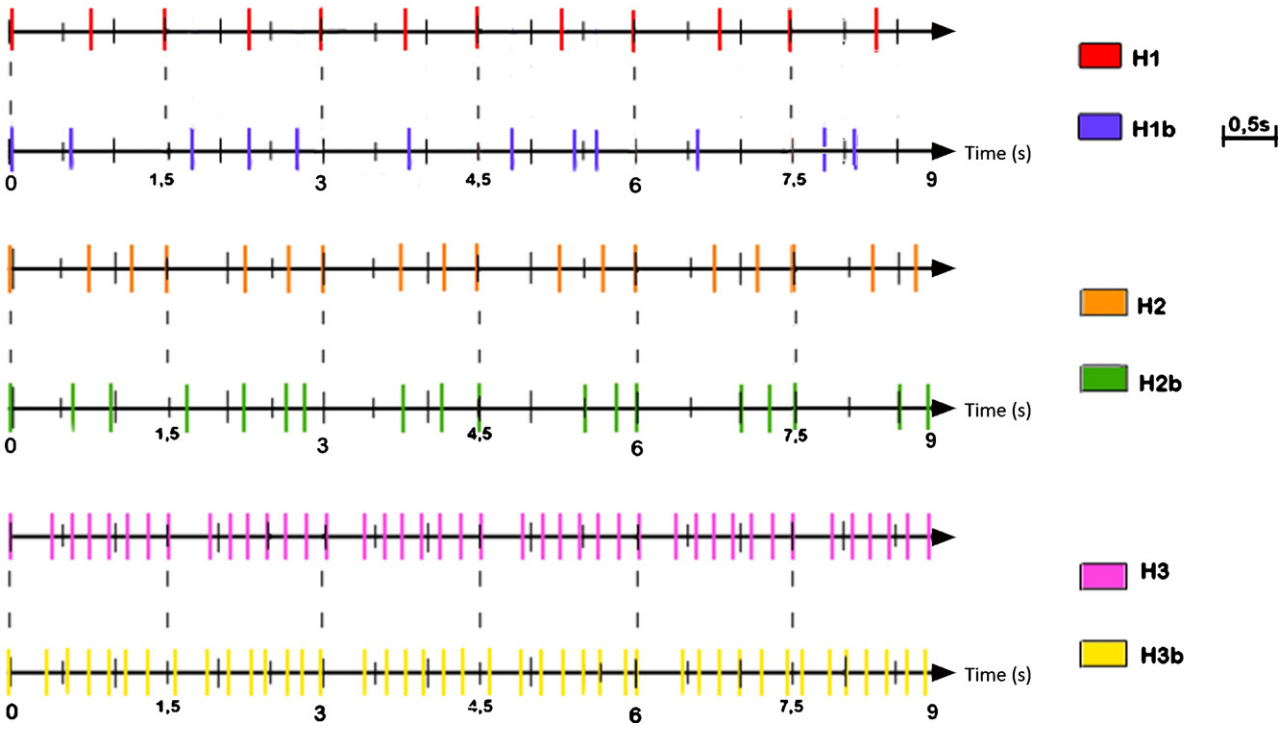

Fig. 1. Stimulus material for the meter detection task. Vertical lines indicate the beginning of each tone in time. Dashed vertical lines (- - -) represents the location of the pulse. Metrical stimuli (H1, H2, H3) contain a pulse. Stimuli with an increasing number of metrical hierarchies are indicated by H1, H2, and H3 respectively. Non-metrical stimuli (H1b, H2b, H3b) contain no pulse and match their metrical counterpart in average tone frequency.

subsequent loss of dopaminergic innervations in the striatum, starting in the posterolateral region, results in the classic symptoms referred to as the "motor triad": rigor, tremor, and akinesis. While several studies have reported interval timing deficits in PD patients [40–44], few have examined pulse perception in PD patients. Experiments including pulse-like acoustic cues have investigated the ability of Parkinson's patients to perform motor synchronization. PD patients were generally able to perform motor synchronization tasks, such as walking to an external cue [45–47] or tapping to an external cue [48,49]. Only two studies have investigated pulse perception in a purely perceptive paradigm. It was reported that PD patients impaired in duration perception performed as well as healthy control subjects in a duration perception task when the critical duration was embedded in the context of an isochronous click-train [44]. In contrast, it has been reported that Parkinson's patients are not able to profit from auditory pulse perception when performing a rhythm discrimination task. While healthy subjects discriminated rhythms containing a pulse better than rhythms containing no pulse, this performance difference was not observed in early PD patients [18]. Thus, additional evidence is needed to clarify whether PD patients display impaired pulse perception. The specific pathophysiology of PD allows testing of how both dopamine depletion and its therapeutic substitution impact pulse perception, while reducing variance in a typical heterogeneous group of patients. We used two experimental paradigms to examine pulse perception in Parkinson's patients: a pulse detection task and a motor reaction time task. We hypothesized that the dopaminergic system is involved in pulse perception and thus expected that the performance of the pulse perception task in PD patients would benefit from the administration of a dopamine substitute (L-3,4-dihydroxyphenylalanin) in that patients would show increased hit-rate and decreased reaction time after the administration of the dopamine substitute as compared to before the administration of the drug.

2. Materials and methods

2.1. Participants

Twenty-eight volunteers participated in the study. Patients were recruited from a cohort of patients who came to the Movement Disorders Center of the University hospital of Bern, Switzerland, for a diagnostic L-DOPA test. All patients were off dopaminergic medication for at least 12 h. The inclusion criteria required patients to score at least 30 on the motor part of the Parkinson's disease rating scale (UPDRS-III) and to have a diagnosis of Parkinson's disease according to the UK Brain Bank criteria with at least a partial improvement in their motor score after L-DOPA administration according to the UPDRS III (>10%) [50]. They were all in a early stage of the disease (Hoehn and Yahr <3). Furthermore, all patients had to score at least 28 (94%) on the Mini Mental State Examination [51] and to be right-handed [52]. Nine patients met those criteria (mean age 65.9 ± 10.6, 5 men and 4 women). Nine volunteers were part of the age- and gender-matched control group (mean age 59.8 ± 11.7, 4 men 5 women) measured at the Massachusetts Institute of Technology (USA). The control subjects had no history of neurological or psychiatric illness. All procedures were approved by the local ethics committee and were carried out in accordance with the code of Ethics of the World Medical Association, Declaration of Helsinki. Before the test, all patients provided their written informed consent to participate in a research study during their diagnostic session.

2.2. Experimental tasks

We applied two different experimental tests: a pulse perception test and a reaction time test that served as a control measure for motor reaction time. The stimuli for the *pulse perception test* consisted of 9 s lasting sequences of tones. Three metrical and three non-metrical stimulus conditions were constructed. The relative tone-onsets of the metrical and non-metrical sequences are indicated in Fig. 1. The basis for the stimulus material consisted of auditory 6-bar 4/4 rhythms with a pulse duration (from the beginning of one bar to the beginning of the next bar) of 1.5 s. The metrical stimuli (H1, H2, H3) contained a pulse [14], while in the non-metrical stimuli (H1b, H2b, H3b) all temporal regularity was removed resulting in a sequence of non-integer temporal intervals. The temporal distinctiveness between the two experimental conditions was assessed in pilot testing. Both, the metrical and non-metrical condition included three sub-conditions containing different frequencies of tones per time. That is, stimuli of condition H1, H2, and H3 comprised increasing numbers of metrical hierarchies in accordance with the model of Povel and Essens [19,53]. The first level consisted of two 1/2 tones per bar (H1). The second level consisted of one 1/2 tone followed by two 1/4 tones (H2), and the third

level consisted of one 1/2 tone and six 1/8 tones (H3). The stimuli consisted of piano tones with a rise time of 1.5 ms and 790 ms, respectively. The tone duration varied depending on the onset of the following tone. Pitch manipulations on the pulse level were included in the stimulus material, which additionally underlined metricality. That is, tones at the pulse level were lower or higher in pitch (277.4 Hz and 415.7 Hz) than the rest of the tones (329.5 Hz). The stimuli were constructed using the open-source LilyPond software (http://lilypond.org/web/) and exported as midi-files. Then the sound stimuli were synthesized using a piano sound on one note (g′) using "fruity-loop" software (http://www.flstudio.com/) and exported as wav-files at a sampling rate of 44.1 kHz. Metrical stimuli and non-metrical stimuli did not differ in volume as measured on a root-mean-square based measure (m: 0.0677 ± 0.0121, nm: 0.0680 ± 0.0123, $t_{16} = 0.06$, $p = 0.953$). In total, the experiment consisted of 18 pseudo-randomly presented experimental trials and the same number of trials after the administration of L-DOPA. The inter-trial intervals were each 12 s. Subjects were instructed to press the left button with the right index finger when they perceived a metrical stimulus and the right button with their right middle finger when they perceived a non-metrical stimulus.

The second test presented to the subjects was a *reaction time test*, which aimed to control for possible motor reaction time changes after L-DOPA administration in patients. Subjects heard either a piano tone (277 Hz) or white noise, both presented at a sampling rate of 44.1 kHz for a duration of 800 ms. Subjects were instructed to respond as quickly as possible to the stimuli by pressing the left button with the right index finger when they perceived a tone and the right button with their right middle finger when they perceived a white noise. The reaction time test consisted of 30 experimental trials presented with inter-trial intervals of 3 s.

Trials of each of the two tests were preceded by a fixation cross on the screen and subjects were instructed to indicate their answer as quickly as possible and not wait until the sequence had finished. Visual feedback communicating whether the response was correct or wrong was given after each trial. After the instruction, all subjects performed 2–4 practice trials, which were repeated when necessary.

2.3. Procedure and data analysis

Parkinson syndrome patients were recruited during a diagnostic pharmacological test (see above) by orally administering the dopamine precursor L-DOPA with a decarboxylase inhibitor benserazid (Madopar®). After somatic testing required for the diagnostic session (blood pressure, clinical testing), patients received instructions for the task and were familiarized with the stimuli in a practice test. Patients then performed the first set of tasks. Approximately 1 h after intake of the drug (125–375 mg L-DOPA), patients performed the second set of tasks in addition to the second clinical testing (UPDRS III). During the behavioral test, subjects were seated comfortably in front of a screen. Stimuli were presented through headphones (Sennheiser, HD 25-1-70 μ) using E-prime software (Version 2.0) with a loudness level adjusted to each subjects preference. All subjects performed each experimental task twice, once before the application of L-DOPA and once after the application of L-DOPA. One behavioral testing session lasted 25 min on average. Control subjects performed the first set of tasks after providing written informed consent to participate in the research study. The second set of tasks was performed after a break of 1 h.

In both behavioral tests, the percent of correctly identified trials per subject and condition was calculated. The analysis of reaction times was performed on correctly identified trials only and computed from the onset of the stimulus. As behavioral data are naturally skewed, no correction for individual outliers was performed. Instead, statistical analysis was performed on median-reaction times for each condition and subject. One missing value (the second reaction time test of one patient) was replaced by the mean value of the group. To test the effect of L-DOPA in Parkinson's patients as well as the effect of test-repetition among control subjects on behavioral performance, a repeated-measured ANOVA for independent variables with the within subjects factors "test" (two levels; before and after L-Dopa and first and second test respectively), "meter" (two levels), and "hierarchy" (three levels) and the between-subject factor "group" (Patient, Controls) was performed. Subsequently, repeated-measured ANOVAs were performed for each group. The descriptive statistic is given as mean and standard deviation.

3. Results

No differences between the patients and controls were found in the performance rate ($F_{1,16} = 0.004$ $p = 0.948$) or reaction time ($F_{1,16} = 0.004$, $p < 0.952$). There was a tendency for an interaction between group and meter ($F_{1,16} = 3.251$, $p = 0.09$), however, with controls showing higher percent of correct answers in metrical as compared to non-metrical stimuli (Fig. 2).

All subjects' performance rates were better in conditions with lower hierarchies ($F_{2,32} = 16.861$, $p < 0.001$), specifically in the non-metrical conditions as indicated by an interaction effect of meter × hierarchy ($F_{2,32} = 6.788$, $p < 0.01$), shown in Fig. 4. Furthermore, all subjects responded faster to non-metrical as compared to metrical stimuli ($F_{1,16} = 6.353$, $p < 0.05$), specifically in the middle metrical hierarchy, as indicated by an interaction effect of meter × hierarchy ($F_{2,32} = 4.576$, $p < 0.05$). We will now describe the performance rate and the reaction time analyses, which were performed separately for each group.

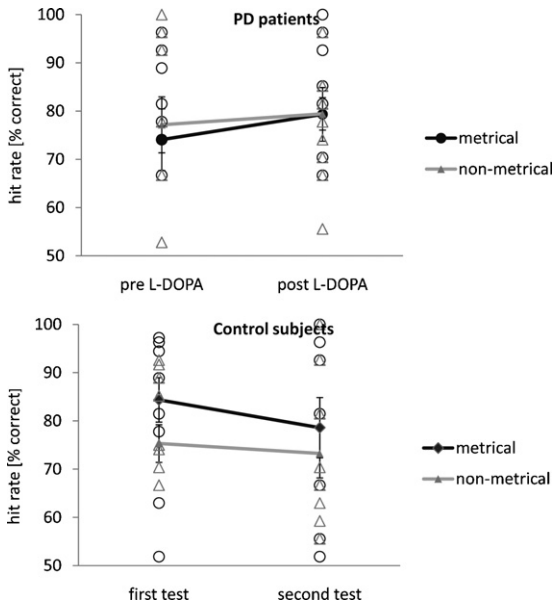

Fig. 2. Average hit-rate in the pulse perception test for PD patients (above) and control subjects (below) plotted separately for metrical and non-metrical stimuli. Results are collapsed over subconditions (H1–H3 and H1b–H3b) and plotted for the first test (before L-DOPA resp.) on the left and for the second test (after L-DOPA resp.) on the right. Error bars indicate standard errors. No significant differences were observed.

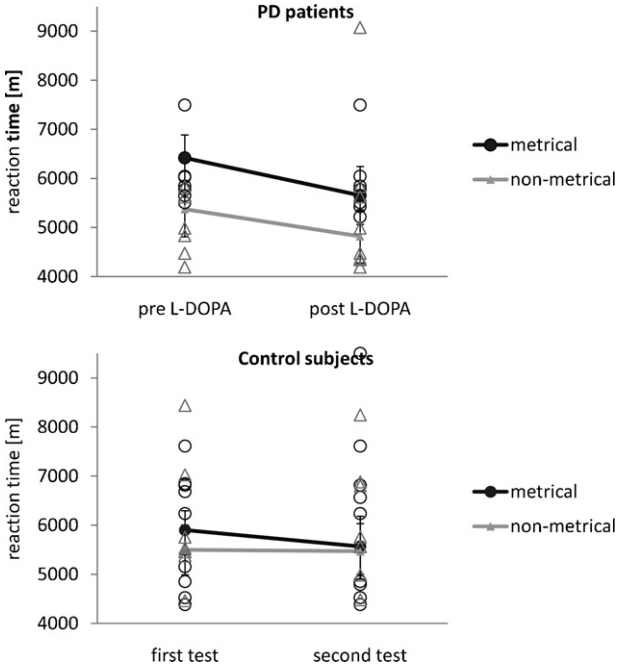

Fig. 3. Average reaction time in the pulse perception test for PD patients (above) and control subjects (below) plotted separately for metrical and non-metrical stimuli. Results are collapsed over subconditions (H1–H3 and H1b–H3b) and plotted for the first test (before L-DOPA resp.) on the left and for the second test (after L-DOPA resp.) on the right. Error bars indicate standard errors. The difference in reaction time between the pre L-DOPA and the post L-DOPA test in patients was significant ($p < 0.01$).

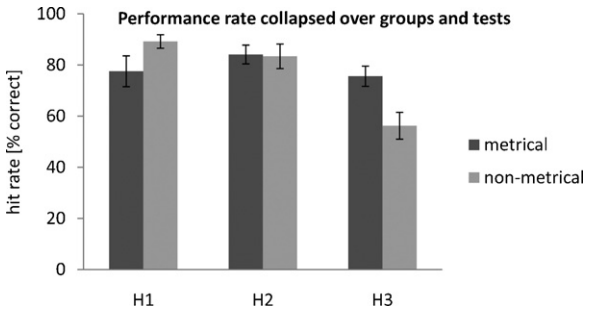

Fig. 4. Performance rate in the pulse perception test of all subjects collapsed over both tests plotted separately for metrical (dark) and non-metrical (light) stimuli of each metrical hierarchy. The interaction between metricity and hierarchy ($p < 0.01$) and the main effect of hierarchy ($p < 0.001$) was significant.

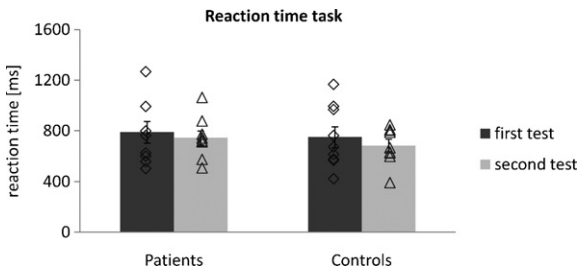

Fig. 5. Average reaction time in the reaction time test for PD patients and control subjects plotted separately for the first test (before L-DOPA resp.) and for the second test (after L-DOPA resp.). Error bars indicate standard errors. No significant effects were observed.

3.1. Performance rate

Fig. 2 indicates the performance rate measured by the percentage of correct answers in the pulse perception test for each group of subjects. *Patients* performance rate before ($75.6 \pm 5.7\%$) and after ($79.4 \pm 4.3\%$) the administration of L-DOPA was not significantly different ($F_{1,8} = 0.85$, $p = 0.384$). There was no effect of meter found in patients (m: $76.7 \pm 5.4\%$, nm: $78.3 \pm 4.3\%$, $F_{1,8} = 0.294$, $p = 0.603$). In *controls* there was a tendency to perform better given the metrical ($81.5 \pm 4.8\%$) as compared to the non-metrical ($74.3 \pm 3.6\%$) stimuli ($F_{1,8} = 2.56$, $p = 0.148$). The performance rate of control subjects did not differ between the first ($79.8 \pm 2.6\%$) and the second ($75.9 \pm 4.7\%$) test either ($F_{1,8} = 1.63$, $p < .238$).

Both, patients and controls, performed better on the lower hierarchies as compared to the higher hierarchies (Fig. 4). Patients' performance rate was $81.8 \pm 5.8\%$ (H1), $83.6 \pm 5.9\%$ (H2), and $67.1 \pm 3.8\%$ (H3) ($F_{2,16} = 9.382$, $p < 01$, corrected). The performance rate of control subjects was $84.9 \pm 5.4\%$ (H1), $83.9 \pm 5.3\%$ (H2), and $64.8 \pm 3.5\%$ (H3) ($F_{1,16} = 8.112$ $p < 01$, corrected).

3.2. Reaction time

Fig. 3 indicates the reaction time in the pulse perception task for each group of subjects. *Patients* performed the pulse perception task significantly faster after the administration of L-DOPA compared to the pre-administration of L-DOPA ($F_{1,8} = 17.58$, $p < 01$). The mean reaction time before the administration of L-DOPA was 5896 ± 504 ms, and the mean reaction time after the administration of L-DOPA was 5237 ± 547 ms. To ensure that the reaction time performance of the patient group after L-DOPA was an effect of pulse perception and not of decreased motor reaction time only, we analyzed the reaction time test (Fig. 5). We did not find any difference in reaction time between the measurements taken before (789 ± 84 ms) and after (744 ± 53 ms) the administration of L-DOPA ($F_{1,8} = 0.79$, $p = 0.4$) in the reaction time test. Furthermore, patients responded faster to the non-metrical stimuli (5097 ± 539 ms) as compared with the metrical stimuli (6037 ± 511 ms) ($F_{1,8} = 45.3$, $p < 0.001$). Interestingly, the *control group* did not show different reaction times on the pulse perception test for the second test (5698 ± 412 ms) compared with the first test (5518 ± 512 ms) ($F_{1,8} = 0.31$, $p = 0.238$). Controls did not show an effect of meter ($F_{1,8} = 0.31$, $p = 0.238$).

4. Discussion

Our study provides evidence that pulse perception is preserved in PD patients during the early stages of the disease. PD patients "off" medication performed the pulse perception task equally well and as fast as the control group and were thus able to perceive a pulse in acoustic cues (Figs. 2 and 3). Separate analysis of patients and controls revealed, however, that PD patients displayed shorter reaction times after the administration of L-DOPA as compared with before the administration of L-DOPA. This indicates that the administration of L-DOPA facilitates pulse perception in early stage PD patients.

The aim of our study was to investigate the effect that clinically effective dopamine substitution has on pulse perception in PD patients. All patients in our study showed an improvement in their clinical symptoms after the administration of L-DOPA as measured by the UPDRS III. The comparison of PD patients with healthy controls in the pulse perception task showed no differences in reaction times or percentage of correct responses. This indicates that pulse perception is preserved in early PD patients with reference to the measure of pulse perception applied in our study. It further suggests that pulse perception might not exclusively rely on dopaminergic parts of the cortico-striatal pathway. Although this finding does not confirm our original hypothesis, it is consistent with two lines of previous evidence. First, it conforms to the findings of a seminal study on duration perception in PD patients compared to healthy control subjects [44]. In that study, patients displayed increased duration perception thresholds when isolated temporal intervals were presented on one hand, but no increased duration perception thresholds when the duration was presented in a series of isochronous tones. Since a series of isochronous tones is the most simple acoustic sequence conveying a pulse, this study might indicate that pulse perception is unimpaired in the investigated patient group. The authors of that study suggested that a deficit in memory processing affects duration perception thresholds but is not detrimental when duration is perceived in the context of isochrony, a condition that provides repetitive durational information. Several other studies have also reported that effects of click-trains on duration perception are similar in PD patients and controls [54,55]. Secondly, our finding of unimpaired pulse perception fits clinical evidence regarding motor timing in PD patients. One of the most prevalent motor symptoms in PD is disturbed velocity of self-paced voluntary movement [56,57], a feature clinically quantified in the UPDRS III. Synchronizing motor behavior to an external auditory cue is not impaired in these patients, however [48,49,58–60]. Thus, motor impairment is reported solely in situations in which movements require self-pacing, whereas an external regular signal ameliorates these symptoms. We can only speculate that self-paced voluntary movement requires the internal generation of a regular temporal grid. Although both the perception and the production of the pulse have been shown to rely on shared 'motor' brain areas [18,61], there is also evidence that synchronization to a pulse and the internal representation of the pulse might rely on distinct brain mechanisms when tested in the context of a tapping task [62,63]. The observation that PD patients can perceive temporally regular cues such as an auditory pulse, allow for the hypothesis that

this capacity might be a prerequisite for motor facilitation effects cited above. In sum, our data suggest that not all timing tasks are impaired in PD patients, as the ability to perceive pulse, at least, remains relatively intact in early stage of the disease.

We would like to mention, however, that there was a trend for an interaction between group and meter on the performance rate ($p = 0.09$). Although the hit-rate was above chance in all subjects and conditions, control subjects' percentage of correct answers was slightly higher in the metrical as compared with the non-metrical stimuli confirming earlier findings [14,18]. PD patients did not show this pattern in their performance. Significantly impaired use of auditory pulse in PD patients has been reported in a previous study [18]. This study applied a discrimination task that relied upon pulse perception; however, unlike our discrimination test, that task required additional rhythm discrimination. A comparison of the two findings suggests that perceptual benefits of pulse perception on rhythm discrimination deteriorate earlier in the disease, or possibly independent of simple pulse perception. While the former hypothesis could be tested in patients at later stages of the disease, our data suggest the latter.

Despite evidence of unimpaired pulse perception in PD patients based on the performance rate, our results evidence that L-DOPA nevertheless influences certain aspects of pulse perception. Patients showed significantly decreased reaction times in the pulse detection task after the administration of L-DOPA. To address the question whether the pharmacological stimulation decreased the reaction time by modulating the perceptive process or by modulating the motor reaction time only, we included a motor reaction time test in our experiment. The motor reaction time test did not show any effect of L-DOPA, which indicates that the performance difference in the pulse perception task must depend on an accelerated perception process rather than an accelerated motor response. Furthermore, patients could have been more familiar with the stimuli when tested for the second time and decreased reaction time could consequently be the result of a learning effect. However, control subjects did not display decreased reaction times when performing the pulse perception test for the second time. We can thus safely assume that the faster response of PD patients in their second test was due to an accelerated perception process as a result of the administration of L-DOPA. This result indicates that pulse perception is affected by dopaminergic manipulation. To interpret this finding one must consider that in the early stages of PD, the motor part of the striatum is primarily affected [39], whereas other parts of the basal ganglia remain relatively intact. However, the administration of L-DOPA is unspecific because it diffusely stimulates all sub-structures of the nigro-striatal dopaminergic system, including the associative, limbic, and motor parts of the striatum, as well as mesolimbic and mesocortical dopamine pathways in the brain [64–66]. The increased sensitivity to pulse perception after the administration of L-DOPA, therefore, could be the result of a hyper-stimulation in parts of the dopamine pathways that are unaffected by the disease. This interpretation cannot be clearly confirmed without testing healthy controls under a pharmacological test condition, however. Alternatively, the reduced reaction time could be the result of dopaminergic stimulation in the parts of the striatum which are affected by the disease. Most earlier studies on timing perception in PD patients have only analyzed performance rate measures [18,44,54,67,68] and reaction time are mostly reported in the context of motor timing tests [69,70]. Thus, additional evidence measuring perceptual reaction time will be needed to clarify the potential role of associative and limbic part of the striatum and frontal brain areas in pulse perception. Considering that performance rate was not significantly affected by L-DOPA in PD patients while the reaction time decreased, perceptual reaction time might be a very sensitive measure for fine grained modulation in timing perception in future studies.

In summary, our data show that dopamine depletion in early PD patients has no deteriorating effect on auditory pulse perception but can be modulated by administration of L-DOPA. This suggests that auditory pulse perception is thus regulated in part by dopaminergic pathways.

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