Cognitive effects of a single dose of methylphenidate in Parkinson's disease patients using electrophysiological measures.

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Abstract

Background: Recent studies have suggested that methylphenidate (MPD) may have therapeutic effects in Parkinson's disease (PD) patients, primarily on gait and apathy. However, the effects of MPD on attention or cognition, in PD, have not been investigated to date.

Objectives: To examine the cognitive effects of a single 20 mg dose of MPD in non-demented PD patients, using behavioural and electrophysiological measures, in a randomized, double-blind, placebo-controlled, single-dose, cross-over clinical trial study.

Methods: To this end, we recorded EEG in PD patients during the performance of an extended version of a visual oddball task. We compared the processing of predictive versus random targets, and the extent to which predictive sequences are utilized. Two recording sessions (20 mg of MPD or placebo) were performed in each patient, 7-14 days apart, in a double-blinded, randomized, counterbalanced manner.

Results: We found that a single-dose of MPD induced an event-related facilitation of target detection of predicted stimuli, compared to placebo, in the PD patients. This cognitive facilitation was indicated by shorter P3b latencies for predicted targets in the MPD compared to the placebo session.

Conclusions: Our findings suggest that MPD is safe and may have beneficial cognitive effects in normotensive patients with PD, by enhancing top-down endogenous control processes, which are altered in PD.

Key words: methylphenidate; EEG; P3b; Parkinson's disease.

1. Introduction

Methylphenidate (MPD) is a stimulant that has an inhibitory action on dopamine and norepinephrine reuptake, particularly in the prefrontal cortex [1–5]. There is evidence to suggest that the fronto-striatal networks are the major targets for the modulating effects of catecholamines on cognitive performance and sustained attention [6,7]. Thus, MPD may facilitate cognitive performance in clinical populations who are compromised in catecholaminergic neurotransmission such as attention deficit disorder [8,9]. MPD has also been shown to improve executive functioning in patients with vascular cognitive impairment [10], attenuate apathy in dementia, and improve cognitive functions in patients with brain injury, neurodegenerative disorders and fatigue [11–13]. In addition, MPD has been shown to be associated with decreased risk of parkinsonism [14].

In healthy adults MPD has been shown to have inverted- U- dose-dependent effects on prefrontal cortex (PFC) working memory functions [1–3]. Thus, lower doses of MPD may improve PFC dependent cognitive functions and facilitate working memory by modulating the neural activity in fronto-parietal regions [5,15]. There are only a few studies examining the cognitive effects of MPD in elderly adults. The findings of these studies suggest that MPD effects are attenuated in elderly subjects compared to younger adults, showing no working memory improvements and only limited effects on attention [16,17], while others observed MPD induced improvements of executive functions and enhanced attention in older adults [18]. Studies reporting improved working memory performance typically utilized more demanding tasks and working memory load [16].

Recently several studies have examined the therapeutic effects of MPD in Parkinson's disease (PD) patients, primarily on gait and apathy[19–22]. Other studies have suggested that MPD may enhance Levo-dopa effects in PD patients [23], although motor improvements were small and variable [24]. However, most of these studies have not incorporated measures of attention or cognition. To date the studies that have been conducted to examine cognitive effects of MPD in patients with PD have been mainly open-label studies, using a small sample size. Two open-label MPD studies showed enhanced attention using a single 20 mg dose [25], or a 50-80 mg daily dose for three months [26]. Another single dose study in five PD patients showed faster reaction times but no change in attention or executive function [27]. A double-blind study in naïve PD patients showed a positive effect of a single 10 mg MPD dose on anhedonia and vigor [28]. Few double-blind studies have examined the effects of a three-month course of MPD in PD patients. These studies evaluated primarily measures of gait and freezing episodes, showing gait improvements in advanced PD patients [22,26], while others did not observe significant gait improvements [20,21].

There is growing evidence linking gait to higher cognitive functions[29,30] and it has been proposed that gait disorders are influenced by attention disorders [19]. Importantly, mild cognitive impairment is a common feature observed in 30-40% of PD patients at the time of diagnosis [31,32]. The cognitive deficits observed in Parkinson's disease patients include executive dysfunction and deficits in working memory and attention [33–40]. Recent EEG studies in PD patients have demonstrated deficits in processing predictive goal directed information within working[41,42], showing an impaired ability to translate this predictive

information into a self-guided internal cue, to facilitate detection of target events. Thus, it is of importance to further investigate the effect of MPD on attention and cognition in patients with PD. In addition, cognitive impairment in PD, specifically executive dysfunction, has a significant impact on the quality of life of the patients as well as intensifying the burden of caregivers.

Several EEG studies have examined the effects of MPD in healthy adults, showing improved response readiness [43], or increased rates of target detection and P3b amplitudes, while showing no effects on primary perceptual processing [44]. EEG studies examining MPD effects in subjects with attention deficit disorder also showed increased P3 amplitudes[45,46] after administration of MPD. However, there were no MPD effects on earlier ERPs such as P1, N1, P2 or N2 [46]. Collectively these studies suggest that MPD seems to act selectively on top-down endogenous mechanisms associated with target detection and sustained attention, with no significant effects on bottom-up exogenous processes such as early visual processing.

The objective of the current study was to determine whether MPD has beneficial effects on cognition and attention in non-demented patients with PD. Our study was a randomized, double-blind, placebo-controlled, single-dose, cross-over study. To examine the cognitive effects of a single dose of MPD in PD patients, we utilized a paradigm and electrophysiological measures that were shown to be associated with the processing of predictive information, and to be deficient in PD patients [41,42,47,48]. To this end, we recorded EEG, during the performance of the task, in PD patients after the administration of MPD and placebo. We hypothesized that MPD will modulate electrophysiological measures associated with later top-down cognitive processes such as the P3b, and that these alterations will be specific to task-relevant and predictive stimuli.

Thus, our hypothesis was that MPD will enhance the processing of predictive task-dependent stimuli. To our knowledge this is the first placebo controlled double-blind study to examine the cognitive effects of MPD in patients with PD, in contrast to studies to date that have mainly evaluated these effects on gait.

2. Materials and Methods

2.1. Participants

Patients were diagnosed with idiopathic Parkinson´s disease, with the Hoehn and Yahr [49] score ranging from 1- 3. Inclusion criteria for the study included patients with PD who were 30-78 years old, up to 8 years of diagnosis of PD, having a good response to levodopa. Patients with the following criteria were excluded from the study: dementia, as indicated by a score of less than 25/26 on the Montreal Cognitive Assessment (MOCA) [50], clinically significant depression, patients who have suffered from hallucinations, delusions or psychosis, severe motor fluctuations and prominent ON dyskinesia, unbalanced arterial hypertension of more than 140/80 during siting on the day of the study, uncontrolled hypertension, hepatic or renal failure, uncontrolled malignancy, or untreated glaucoma, and patients treated with Monoamine Oxidase Inhibitors. Forty patients diagnosed with PD fit the inclusion criteria and were contacted to participate in the study. Fourteen patients refused to participate, and four patients were unable to perform at least one of the recording sessions due to high blood pressure measurements on the day of the experiment. One adverse event was reported by a patient who experienced dizziness after completing the recording session, where MPD was administered. In total 22 patients completed both recording sessions. All the subjects were right-handed and had normal or corrected-to-normal visual acuity. Subjects were asked to take their regular medication on the

day of the experiment. The local ethics committee of Hospital Universitario Fundación Alcorcon approved the study. The study was registered as a clinical trial in the European Union Drug Regulating Authorities Clinical Trials Database.

2.2. Experimental procedure

Each subject performed a total of two recording sessions, one after the administration of 20 mg of MPD and another after the administration of a placebo saccharine pill. Each session was performed on a different day, 7 to 14 days apart, using the same procedures. EEG recordings were performed 90 mins after the administration of either the MPD or placebo pill. The order of administration of MPD versus placebo was randomized and counterbalanced across the subjects. All the sessions were recorded in the morning hours to control for environmental effects on attention, while the patients were in ON state.

During the EEG recording subjects performed a cognitive task. See [41,42,47,48] for a detailed description of the paradigm. In brief, stimuli consisted of 15% targets (downward facing triangle) and 85% of equal amounts of three types of standards (triangles facing left, upwards and right, at 90-degree increments). Recording blocks consisted of targets preceded by either randomized sequences of standards or by sequences including a three-standard predictive sequence (see Figure 1). Subjects were asked to detect and press a button for target events and to pay attention to the predictive sequence when it appears. press a button for target events. Presentation of the stimuli and response recordings were controlled using E-prime (Psychology Software Tools, Inc., Pittsburgh, USA).

2.3. EEG recordings

EEG was recorded from a 64 Ag-AgCl electrode array using the ActiveTwo system (Biosemi, The Netherlands). Signals were amplified and digitized at 512 Hz. Post processing and ERP analysis of the data was performed using Brain Vision Analyzer (Brain Products GmbH, Germany). All channels were re-referenced to averaged linked earlobes.

2.4. Behavioural analysis

Accuracy was defined as the percentage of targets for which a button press was detected. Reaction times were calculated by averaging correct trials for predicted and random targets in each subject for each session. Misses (no button press 150-1150 ms post-stimulus onset) were excluded from reaction time analysis. Premature responses were not taken into consideration in the analysis of reaction time.

2.5. ERP Analysis

Epochs containing premature responses, misses (no button press 150-1150 ms post-stimulus onset) and eye saccades were excluded from further analysis. EEG signals were filtered at 0.1-30 Hz and were sorted and averaged relative to the stimulus onset, with epochs set from -200 to 1000 ms relative to stimulus onset. EEG epochs with amplitude of more than 75 μV at any electrode were excluded. ERP analysis included evaluation of the following components: N1 (early visual processing), N2 (early attention), and P3b (detection of task-relevant stimuli). The ERP components N1, N2 and P3b were evaluated for the two target conditions (predicted and random). P3b was also evaluated for randomized standards and the three stimuli consisting of the predictive sequence.

2.6. N1 and N2

Peak N1 amplitudes (measured in μV) were determined at PO7 and PO8 for both predicted and random targets. N1 was determined as the most negative peak in the latency range of 50-200 msec. N2 was defined as the largest negative peak, at electrode site CPz, in the time window starting with the P2 peak and ending 350 ms after target onset.

2.7. P3b

P3b was determined as the most positive point in the latency range of 300-500 ms. Peak P3b amplitudes (measured in μV) were evaluated at electrode sites AFz, Fz, FCz, Cz, CPz, and Pz for six different conditions in each session (MPD and placebo): targets after predictive sequences (predicted, P), targets after non predictive random sequences (random, R), random preceding standards (standards excluding those comprising the predicting sequence, S) and the three standards consisting of the predictive sequence: the last most-informative standard (n-1), the middle standard (n-2) and the first least-informative standard (n-3) of the predicting sequence. Peak P3b latencies (measured in ms) were evaluated for predicted and random targets at the electrode site with the largest P3b amplitude (CPz).

2.8. Statistical analysis

Comparisons of the reaction time and the ERP variables were performed using analysis of variance (ANOVA) with the Greenhouse-Geisser correction, followed by post-hoc parametric paired t-tests, Sidak corrected for multiple comparisons unless otherwise stated. Mean values with ± standard error of the mean (SEM) are used throughout the text. Since the distributions of

the accuracy values were not Gaussian, non-parametric analysis was performed for the comparisons, using Wilcoxon test to evaluate differences between the sessions for predicted and random targets. Correlations were calculated using Pearson´s Product Moment correlation coefficient.

3. Results

Twenty-two patients with PD (mean age ± standard error of mean = 68.5 ± 1.7 years, 10 females) were included in the study (Table 1). The mean duration since the PD diagnosis was 3.8 ± .8 years, prior to participating in the study. Patients had a mean score of 21.7 ± 1.6 on the Unified Parkinson's Disease Rating Scale [51] and a mean Hoehn and Yahr score of 1.9 ± .1. Seventeen patients were taking Parkinsonian medication, while five patients who were recently diagnosed were not undergoing treatment (see Table 1). Nine patients had the most pronounced symptoms on the right side, twelve- on the left side and 1 patient had symmetric motor presentation. 11 had tremor predominant disease and 11 had postural instability-rigidity form.

3.1. Behavioural results

We found no significant accuracy differences between the MPD and placebo sessions across the target conditions (mean accuracies = 96 ± 1.2% and 97 ± .9% for the MPD and placebo sessions, respectively, $p = .637$).

To compare the reaction times (RT) for the targets, and to test whether there is a behavioural facilitation in the sessions, we performed an ANOVA with condition (predicted, random targets) and session (MPDs, placebo) as the repeated measures factors. There was a significant main

effect for condition (F (1,21) = 18.54, p< .0001). However, there was no significant main effect for session (F (1,21) = .99, p= .329), nor a significant condition x session interaction. Across both sessions, patients showed faster RTs for predicted (mean RT = 396 ± 13 ms) compared to random targets (mean RT = 425 ± 12 ms, p≤ .001).

3.2. N1 and N2

Peak N1 and N2 amplitudes showed no significant main effects for condition (predicted, random targets), or session (MPD, placebo).

3.3. P3b amplitude

The main P3b findings are displayed in figure 2, illustrating the waveforms of the grand-averaged ERPs in each of the sessions.

Peak P3b amplitudes were compared by performing an ANOVA with session (MPD, placebo), condition (P, R, n-1, n-2, n-3, and S), and electrode site (AFz, Fz, FCz, Cz, CPz, and Pz) as the repeated measures factors. There were significant main effects for condition (F(5,105) = 10.86, p=.001), and electrode site (F(5,105) = 24.88, p< .0001), but no significant main effect for session (F(1,21) = .07, p=.792). Across the sessions, post-hoc tests corrected for multiple comparisons, showed that peak P3b amplitudes were larger for conditions P, R and n-1 compared with condition n-3 and standards (p≤0.022). Post-hoc tests corrected for multiple comparisons, showed maximal and minimum peak P3b amplitudes at electrode sites CPz (12.38 ± .1.10 μV) and AFz (9.38 ± .86 μV), respectively, across conditions and sessions (p≤0.007).

3.4. P3b latency

To test whether processing speed of the two target conditions was modulated across the sessions, peak P3b latencies were compared at electrode site CPz, and an ANOVA was performed with condition (predicted, random targets) and session (MPD, placebo) as the repeated measures factors. There was a significant main effect for condition ($F(1,21) = 10.71$, $p = .004$), and a significant condition x session interaction ($F(1,21) = 12.64$, $p = .002$). Post hoc tests showed that in the MPD session, peak P3b latencies were shorter for predicted targets (mean P3b latency = 401 ± 11 ms) compared with random targets (mean P3b latency = 455 ± 9 ms, $t(21) = 6.43$, $p < .0001$). On the other hand, in the placebo session, there were no significant peak P3b latency differences between the two target conditions (mean P3b latency = 432 ± 12 ms and 440 ± 10 ms for predicted and random targets, respectively, $t(21) = .534$, $p = .599$). These comparisons are displayed in figure 3. In addition, peak P3b latencies for predicted targets were significantly prolonged in the placebo compared to the MPD session ($t(21) = 3.07$, $p = .006$).

Furthermore, we evaluated the P3b latency shift for each subject between the two target conditions (subtraction of the peak P3b latency of random targets from that of predicted targets) and compared the P3b latency shift between the two sessions. We observed larger P3b latency shifts in the MPD compared to the placebo session (mean P3b latency shift = 54 ± 8 ms and 7 ± 13 ms, respectively, $t(21) = 3.556$, $p = .002$).

3.5. Correlations

To determine the association between the main electrophysiological findings and the symptom severity in the PD patients, we correlated the UPDRS scores with the peak P3b latencies for predicted and random targets, and the P3b latency shift, and found no significant correlations.

4. Discussion

Our findings demonstrated that in patients with PD, MPD modulated P3b latencies of task-relevant predicted targets. Specifically, P3b latencies for predicted targets were faster after the administration of a single dose of MPD compared to placebo. Thus, MPD facilitated task-relevant stimulus evaluation of predictable targets in PD.

4.1. Behavioural facilitation across the sessions

Patients with PD demonstrated, shorter reaction times for predicted versus random targets in both the MPD and placebo sessions, suggesting that the patients were able to perform the task adequately. These results are in line with earlier findings [41,42,47,48] showing a behavioural facilitation in the detection of predicted versus random targets in both PD and control subjects. However, we did not demonstrate MPD modulation of behaviour in the current study, possibly due to the use of a relatively low, single dose of MPD and of behavioural ceiling effects of the task. In addition, reaction times may not be a sensitive measure to assess behavioural modulation in PD, especially in target and choice reaction tasks, such as the one employed here.

4.2. MPD induced effects on ERPs in PD

We observed significant differences between the MPD and placebo sessions, in the processing speed of predicted targets. Thus, we found that the P3b latency shift (between predicted and

random targets) was significantly larger, and that the peak P3b latencies for predicted targets, were significantly faster, in the MPD compared to the placebo session. These findings suggest that in PD patients, a single dose of MPD induced an electrophysiological facilitation of the evaluation time of predicted targets [41,52,53], replicating results in healthy elderly controls[41,47]. However, in the placebo session this electrophysiological facilitation was not observed, which is in line with earlier studies showing deficits in the differential processing of predicted versus target conditions in PD [41,42,54]. These findings are of importance since MPD specifically enhanced an electrophysiological correlate that was attenuated in PD patients compared with control subjects [41,42,47]. These earlier studies showed that PD patients were able to detect the predictive sequence but were limited in their ability to translate this information into a self-guided internal cue.

In the current study, we found no significant modulatory effects of MPD on the peak amplitudes of N1, N2 or P3b. Across both sessions, significantly larger P3b amplitudes were generated by task-relevant stimuli (targets and n-1) compared with randomized standards. Thus, in both sessions, task relevant targets induced maximal P3b amplitudes, with the predictive sequence becoming a secondary target for the subjects [41,55].

The MPD induced modulations may be associated with changes within top-down attentional networks, so that increased attentional allocation facilitated the processing and utilization of predictive contextual information [42,47,48]. Our findings demonstrate that the MPD induced effects were specific to predictive, task-relevant stimuli and to later cognitive ERPs such as the P3b, that may have required a higher degree of cognitive control, rather than having a

generalized effect in PD. These findings are in line with MPD effects in healthy adults, showing increased rates of target detection, while showing no effects on primary perceptual processing [44], or on earlier ERPs such as N1 and N2 [46]. Our findings thus support the proposition that MPD seems to act selectively on top-down endogenous mechanisms associated with target detection and sustained attention, with no significant effects on bottom-up exogenous processes such as early visual processing, and extend these findings to patients with PD.

4.3. Potential therapeutic effects of MPD in PD

Our findings suggest that MPD may have potential therapeutic benefits for cognitive performance in non-demented patients with PD. In the current study we utilized a task that relies on the processing and utilization of goal-directed information in working memory. This is of clinical importance since the cognitive deficits observed in Parkinson's disease patients include executive dysfunction and deficits in working memory and attention [33,36]. It has been proposed that MPD may improve prefrontal cognitive functions and facilitate working memory by modulating the neural activity specifically within frontal networks [5,15]. Furthermore, a recent study suggested that MPD may suppress the abnormal synchronization of the beta frequency in the subthalamic nucleus in PD [56].

The findings of the current study are limited to modulatory effects of P3b latencies of predicted targets and show no correlation with the clinical features of the patients. There may be a few explanations for these results. First, the MPD dose of 20 mg may have been too small to observe more extensive modulatory effects. Second, we evaluated non-demented PD patients and thus any cognitive improvement may have been limited. Third, the utilized task may have been

insufficiently demanding. Nonetheless, the current study is the first double-blind study in patients with PD to show an electrophysiological cognitive facilitation induced by MPD. To date, the studies that have examined the therapeutic effects of MPD in PD, focused primarily on gait and apathy [19–22] or have been mainly open-label studies, with variable results on attentional processing [25–27]. Our study may be of clinical relevance for patients with PD, since cognitive impairment in PD, specifically executive dysfunction, has a significant impact on the quality of life of the patients as well as intensifying the burden of caregivers.

Finally, we would like to point out the limitations of our experimental approach in the current study. First, the sample size and medication dose used in the current study were relatively small and findings need to be replicated in a larger sample, with administration of MPD for longer durations. Second, the effect of medication needs to be addressed since seventeen out of the twenty-two patients were taking parkinsonian medication. However, we found electrophysiological changes that were task-specific and that were not significantly correlated with the clinical features of the patients and their treatment pattern. In addition, accuracy values were comparable across subjects, suggesting that the patients performed the task adequately.

In conclusion, our findings demonstrated that in non-demented, normotensive patients with PD, the administration of a single 20 mg dose of MPD was safe and facilitated task-relevant stimulus evaluation of predictable targets, as indicated by faster P3b latencies, compared with placebo. Our findings suggest that MPD may have therapeutic cognitive benefits in patients with PD. Furthermore, our study identified electrophysiological indices that were specially modulated by

MPD, thus contributing in establishing objective mechanism-based markers for the assessment of cognitive therapies in PD.

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Author contributions

N.F. design, collection of behavioral and EEG data, analysis, writing and editing of manuscript. E.M.L: recruiting patients, collection of clinical data. M.R.G: recruiting patients, collection of clinical data. M.F.d.O. collection of behavioral and EEG data. T.G. design and editing of manuscript. L.V.D: design, recruiting patients, collection of clinical data, editing of manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

The authors have no financial disclosures or conflict of interest to report.

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Figure. 1. Task timeline. Sequences of standards S1, S2 and S3 with a predicted sequence (top) and in randomized order (bottom) preceding the target (T). The predictive sequence is always S1 (n-3), followed by S2 (n-2), and then S3 (n-1). Stimuli are presented to the left or right visual field. Inter-trial intervals (1000 msec), including duration of stimulus presentation (150 ms) are displayed. Each block consisted of 6 different randomized sequences of standards (3-8 standards long) preceding the target; and 6 sequences of standards (3-8 standards long) with the predictive sequence preceding the target in each.

Figure 2. Grand average at CPz for the 4 conditions: targets after random (Random) and predictive sequences (Predicted), the last most informative standard comprising the predicting sequence (n-1) and random preceding standards (Standard); for the placebo (**A**) and methylphenidate (**B**) sessions in PD patients. Vertical dotted lines (0 msec) indicate time of stimulus presentation onset (note that the grand averages for n-2 and n-3 have overlap with the signal of the grand average for random standards, and are thus not displayed, for the purpose of clarity of the figure).

Figure 3. Peak P3b latencies at electrode site CPz, for predicted and random targets, in the placebo and methylphenidate (MPD) sessions in the PD patients. Significant differences ($p < .05$) are highlighted with a star. Bars = SEM.