Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Reduced mind wandering in patients with Parkinson's disease

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ARTICLE INFO

Article history:
Received 26 March 2017
Received in revised form
26 August 2017
Accepted 30 August 2017

Keywords:
Mind wandering
Parkinson's disease

ABSTRACT

Background: Mind Wandering (MW) refers to the process of disengaging from the immediate external environment and participating in internally driven mentation. This process has been suggested to be supported by a distributed set of brain regions, collectively referred to as the Default Mode Network (DMN). Recently, reduced recruitment and connectivity of the DMN has been described in Parkinson's disease (PD) patients compared to healthy controls. We thus aimed to explore whether PD patients with normal cognitive test scores show differential MW capabilities compared to healthy controls.
Methods: Thirty PD patients and thirty age-matched controls, all with a Montreal cognitive assessment (MoCA) score of 26 or above, performed a novel yet validated thought-sampling paradigm used to assess the frequency and extent of MW irrespective of cognitive load in which participants were asked to observe a series of geometric shapes and describe their thoughts after watching them. Shapes were presented one at a time for varying durations across nine trials.
Results: PD patients showed significantly less MW compared to the control. ANCOVA revealed a significant interaction indicating that the difference in MW scores was driven by trials with short stimulus presentation times.
Conclusions: These findings provide evidence for decreased MW in PD patients. We propose that this is due to difficulties in performing MW within short time frames.

1. Introduction

The term Mind Wandering (MW) refers to the process of internally driven mentation that often takes place when awake individuals disengage from their immediate external environment [1] and do not participate in a cognitively demanding task [2]. Moreover, if MW persists during task performance its extent predicts slower and less accurate responses to task demands [3].

The content of MW is self-generated [4] and can relate to autobiographical memory [5], self-referential thinking, personal prospective planning [6], social cognition [7] and more. Thus, MW comprising up to 47% of total mental functioning and seems to be a basic and relevant quality of the healthy human brain [8]. The high prevalence MW naturally invokes curiosity regarding its goal, with controversial answers found in current literature. Its comprehensive, autonomous, and continuous nature has led the majority of scientists to suggest that rather than being an undesired lapse of attention to the external world, MW must have an adaptive role in healthy cognition [4,9]. Relatedly, findings suggest that MW can promote future planning [10,11] and increase creative faculties [12]. Other studies support the notion that MW plays an important functional role in planning everyday life [13]. However, such benefits might come at a cost of negative mood, as during and

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http://dx.doi.org/10.1016/j.parkreldis.2017.08.030
1353-8020/

immediately following MW people have been shown to be less happy compared to when they did not engage in MW [8,14].

Neurobiologically, MW has been suggested to be supported by a distributed set of brain regions. Those regions include the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), bilateral inferior parietal lobes (IPL), and the medial temporal lobe (MTL) [15,16], regions that collectively constitute what has been termed the brain's Default Mode Network (DMN) [17]. The association between DMN activity and the psychological process of MW is supported by numerous studies that established a strong connection between MW and DMN activation. For example, from a functional perspective, the DMN remains active during non-task periods and is also active in times of low cognitive demands, similar to MW [1]. In addition, activation of the medial prefrontal and parietal areas was demonstrated during self-related tasks [18]. This can relate to the evidence that personal information from memory might form the content of MW episodes [2]. In addition, damage to parts of the DMN (e.g., mPFC) is associated with "mental emptiness" as well as lack of thought and spontaneous speech [19]. Together, accumulating evidence seems to suggest that the DMN serves as the neural basis for MW. Such findings support the assumption that MW is a behavioral manifestation of DMN activation.

The clinical diagnosis of Parkinson's disease (PD) is based on its motor symptoms of bradykinesia, rigidity, resting tremor and postural instability [20]. However, non-motor symptoms are abundant in PD patients even before the appearance of motor symptoms [21]. Recently, studies have documented reduced functionality of the DMN among PD patients compared to age-matched controls, even in cognitively preserved individuals [22]. However, whether such changes affect MW in PD patients has not yet been assessed. We, therefore, examined the frequency of MW in PD patients with normal MoCA test scores and their age-matched healthy controls using a validated MW behavioral assessment paradigm [23]. We hypothesized, in light of the described DMN abnormality, that even PD patients with normal MoCA test scores would demonstrate reduced frequency of MW compared to controls.

2. Methods

2.1. Participants

Seventy-seven subjects, of which 38 were PD patients diagnosed by a movement disorders specialist (A.T, J.Z), participated in this study, which was approved by Institutional Review Board of the Tel Aviv Sourasky Medical Center. All subjects signed an informed consent before participation. All participants were screened for cognitive dysfunction using the Montreal Cognitive Assessment scale (MoCA) with a cutoff of 26 [24]. Exclusion criteria included chronic movement disorders other than PD, other known neuropsychiatric illness, alcohol or illicit drug abuse, prior use of dopamine depleting medications and head trauma. PD patients were assessed in the ON condition, while using their usual medications, and were asked not to change their medical treatment before the experiment.

2.2. Behavioral and clinical assessment

Prior to performing the MW task, participants underwent a comprehensive assessment battery which included the ***Unified Parkinson's Disease Rating Scale (MDS-UPDRS)*** [25], daily drug intake was converted to the ***Levodopa Equivalent Daily Dose (LEDD)*** as customary [26] and depression was assessed using the ***Beck Depression Inventory (BDI- II)*** [27].

2.3. Shape expectations task

This task was developed by O'Callaghan and colleagues [23] to assess MW capabilities during realistic conditions known to contribute to MW – that is, minimal external stimulation without the constraints of performing a concurrent cognitive task. Crucially, this task, unlike other MW sampling tasks, does not rely on any cognitive load. Participants were instructed to focus on stimuli presented on a computer screen with the only objective of watching the screen and relaxing. The stimuli consisted of nine different two-dimensional colored geometric shapes presented on a white background (see Supplementary Information). These nine static shapes were presented one at a time for varying durations ranging from 5 s to 120 s. Each shape had only one specific time interval. This created nine different trials. Immediately after viewing each shape, participants were instructed to report the thoughts they experienced during viewing ("what were you thinking about just now?"). No time limitations were imposed during this phase, and participants were encouraged to provide as many details as possible. All responses were subsequently transcribed verbatim by the experimenter before moving to the next trial. A practice trial was conducted before the beginning of the task. The entire task lasted approximately 15 min.

The scoring system of this task was developed to provide information about the level of MW in each trial based on the reported content of thoughts [23]. MW levels ranged from 1 to 4: 1- an absence of internally generated thoughts (e.g., "Orange circle"); 2- responses that are heavily dependent on stimulus attributes (e.g., "Blue is my favorite color"; "This one was very short").; 3- stimulus-related extrapolation responses that characterize an intermediate zone between stimulus-bound thinking and instances of "pure" MW (e.g., "It reminds me of the moon"); 4- MW thoughts unrelated to task and stimuli (e.g., "I thought about the sunny day I had on my trip to Japan last year"). The final score given for each trial reflected the highest level of MW achieved on that specific trial. Three independent raters (N.S, H.S, and E.B.S) blinded to participants' group (PD/healthy control (HC)) were trained in the scoring system and subsequently scored all transcripts. An average of the raters' scores was given as a final verdict on trial score. Later, we discarded the scores for the cross shape out of the analyses since it was associated with the Christian cross by the majority of the participants (72%) and could not be regarded as a neutral stimulus for a Jewish study group, unlike in the original task. Therefore, there were eight trials of varying lengths and shape per participant.

In line with O'Callaghan and colleagues [23], we examined three measures of MW performance as follows: Overall MW performance was calculated as the sum of each trial's MW level score (maximum score of 32). The responses rated at each MW level during the entire paradigm were also calculated as a proportion score reflecting the frequency over the entire number of trials (e.g. total instances of 4's/8*100). Finally, to measure the effect of trial duration, the eight trials were divided into two categories based on the trial's duration: short stimulus presentation (four trials that lasted between 5 and 30 s) and long stimulus presentation (four trials that lasted between 45 and 120 s). We then calculated the average MW performance for each of these categories (ranging 1 to 4).

2.4. Statistics

Data was analyzed using SPSS19.0 (SPSS, Chicago, IL). Clinical measures, overall MW scores and demographic variables were normally distributed for both PD group and control group, as assessed by the Kolmogorf-Smirnof test, and by visual inspection of normal Q-Q plots (see Supplementary Information). In both groups, Pearson correlations were used to analyze the relationship

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between overall MW scores to demographic and clinical variables. In the PD group, Pearson correlations were assessed between MW total score and disease duration, LEDD, UPDRS total score, and MoCA scores.

A first mixed-model ANCOVA was used to test the effect of group (PD/HC) on MW levels as measured by the proportion of the four MW levels (1/2/3/4). T-test was used for post hoc simple effects. A second mixed-model ANCOVA was used to test the effect of trial duration (short/long) on average MW score in the two groups (PD/HC). T-test was used for post hoc simple effects. All tests were two-sided, and a significance level of $\alpha < 0.05$ was used to detect effects. All the following analyses were adjusted for age and BDI score, in view of the significant differences between-group differences.

3. Results

3.1. Participants

Out of the 77 participants screened for this study 17 were excluded (seven from the HC group and ten from the PD group), due to MoCA scores below 26. Groups were well matched for MoCA scores, years of education, gender, and age. However, PD patients rated higher on the BDI ($p = 0.001$), the MDS-UPDRS ($p < 0.001$), and were slightly older ($p = 0.038$). LEDD and disease duration were calculated for 29 PD patients; for one additional patient, this data was unavailable. Clinical, demographical and behavioral findings are presented in Table 1.

3.2. MW scores

To test whether these factors described in the previous paragraph were associated with the performance in the MW task, we calculated the Pearson correlation coefficient between these two variables and the overall MW score. A significant negative correlation was found between BDI and MW for the entire study sample ($r = -0.386$, $p = 0.002$, $n = 60$). No correlations were found between the overall MW score to other variables in the entire study sample or in each separate group of subjects (all p value > 0.211, $n = 60$, all p values > 0.820, $n = 30$, respectively). No correlation between age and MW and clinical variables were found in the PD group (all p values > 0.391, $n = 30$).

3.3. Proportion of responses across the four levels

We performed a mixed-model ANCOVA with MW level (1/2/3/4) as a within-subject factor and group (PD, HC) as a between-subject factor. Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated (X^2 (5) = 31.317, $p < 0.001$), so the Greenhouse–Geisser correction was applied. A significant main effect of MW level was found [$F(2.230,124.896) = 3.349$, $p = 0.033$; Fig. 1]. Simple effects revealed that the percentage of level 3 was significantly higher than all the other levels (all p values < 0.0001, Sidak corrected). When assessing each group separately, simple-effects tests display that the percentage of level 3 responses was significantly higher (56.250 ± 27.415) than all other levels (levels 1/2/4 respectively: 10.417 ± 13.164, 19.167 ± 23.381, 14.167 + 13.823; all p values < 0.001, Sidak corrected) among the PD group. In the HC group level 3 responses were also significantly higher (55 ± 19.309) than all the other levels (levels 1/2/4 respectively: 5.833 ± 9.701, 12.083 ± 10.109, 27.083 ± 18.301; all p values < 0.002, Sidak corrected). In the HC group, there was a significantly higher grade of level 4 responses compared to levels 1 and 2 (all p values < 0.020, Sidak corrected). In the PD group, no significant differences were found between level 4 responses to those of level 2 and 1 (all p values > 0.876, Sidak corrected). Though a similar pattern of MW score per level was apparent for each group (all p values > 0.351, Sidak corrected), a significant difference in the percentage of the 4th level was found between PD patients (14.167 ± 13.823) and HC (27.083 ± 18.301; $p = 0.003$, Sidak corrected), demonstrating lower 4th level (MW episode) scores in PD patients. No other significant interactions between MW level and other covariates were found (all p values > 0.145, Sidak corrected).

3.4. Effect of trial duration on MW

We performed a mixed model ANCOVA with trial duration (short/long) as a within factor and group (PD/HC) as a between subject factor. A significant main effect of group was found [$F(1,56) = 4.100$, $p = 0.048$; Fig. 2]. This effect was qualified by significant trial duration by group interaction [$F(1,56) = 4.313$, $p = 0.042$]. Follow up simple effect analysis indicated that PD patients' average MW scores during the short trials were significantly lower (2.587 ± 0.477) than HC patients' MW scores during the same type of trials (2.963 ± 0.393; $p = 0.001$, Sidak corrected). There was also a significant difference between the short and long trials among PD patients (2.984 ± 0.522; $p = 0.005$, Sidak corrected). No other significant differences in average MW performance were found among HC between long and short trials and between PD patients and HC during long trials (all p-values>0.304, Sidak corrected). In addition, no other significant interaction was found between trial duration to other covariates. Additionally, we found a significant main effect of BDI score [$F(1,56) = 4.384$, $p = 0.041$], reflecting the above mentioned negative correlation found between BDI and MW.

Finally, we used a receiver operating characteristic (ROC) curve in order to investigate whether the mean MW scores of the short trials have the sensitivity and specificity to distinguish PD status from MW status. The ROC curve analysis showed an area under the ROC curve of 0.747 [$p = 0.001$; 95% CI(0.624, 0.869), Fig. 3], which consider as a fair ability to differentiate between the groups. As the threshold increases with a higher MW score, the sensitivity increases as more sessions were correctly categorized as PD, but the specificity decreases (or bias increases) as more sessions were incorrectly categorized as PD.

Table 1
Demographics and clinical information: Medians (Interquartile range) of demographic variables and questionnaires scores for Parkinson's disease (PD) patients and healthy control (HC) groups, as well as the p-value of an independent *t*-test or Mann Withney *U* test (for years of education) comparing group differences. Beck Depression Inventory (BDI), Montreal Cognitive Assessment (MoCA), Levodopa Equivalent Daily Dose (LEDD), Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

	HC	PD	*P value*
N	30	30	
Gender (M:F)	13:17	17:13	0.310
Age	62 (6)	67 (12)	0.040
Years of Education	15 (2)	15 (3)	0.220
BDI	5(6)	10 (6)	0.001
MoCA	28(1)	27(2)	0.530
LEDD	–	512.5 (451)	–
Disease duration	–	10 (8)	–
MDS- UPDRS	2 (14)	46.5 (39)	0.000

4. Discussion

Applying a novel MW paradigm designed to be independent of cognitive resources [23], we detected reduced levels of MW among PD patients compared to healthy controls. Moreover, results remain significant after controlling for depression and age. Therefore, MW deficits in PD seem to be specifically related to the disease process

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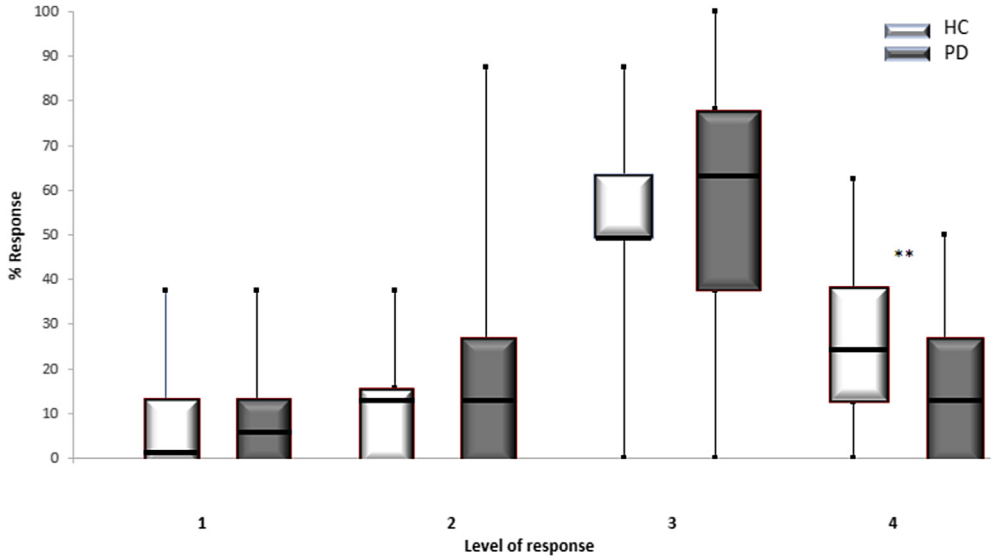

Fig. 1. Overall performance in the shape expectation task across the two groups. Based on proportions of response for each response level; MW is equal to level 4. The box plots indicate medians and interquartile range (for each group N = 30).
**p < 0.005.

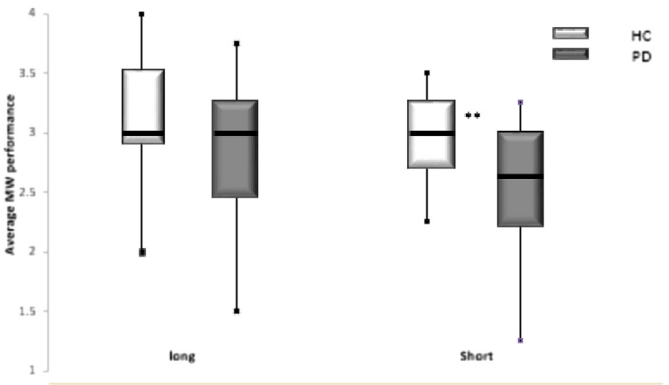

Fig. 2. MW across different trial times: The box plots indicate medians and interquartile range of the average overall MW performance score according to the length of measure among PD and control groups. (for each group N = 30).
**p < 0.005.

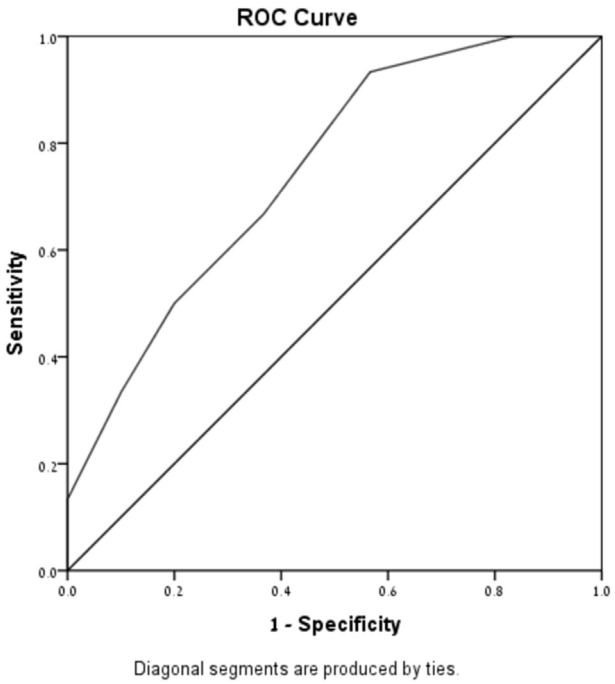

Fig. 3. Receiver operating characteristic (ROC) curves illustrate the sensitivity and specificity of the mean MW scores of the short trails in predicting PD. As the threshold increases, the sensitivity increases as more sessions were correctly categorized as PD, but the specificity decreases (or bias increases) as more sessions were incorrectly categorized as PD.

itself. In the trial duration based analysis (short and long measures), we found a significant interaction between group and trial duration. This indicated that the difference in MW rates between PD patients and healthy controls stems from differences in MW rates during shorter rather than longer trials.

Our findings support the postulation that stimulus independent thought is not an 'all or nothing' phenomenon, but one that follows a gradient pattern [23,28]. The rate of third level responses represents an intermediate zone between stimulus-bound thinking and instances of "pure" MW [23]. In our study, it was the most frequently observed among the two study groups with equal rates across groups. Crucially, MW rates among PD patients during the short trials were significantly lower compared to the HC group, with no significant between-group difference during long trials. This leads us to suggest that while PD patients can 'move away' from the original stimulus (i.e. reach levels 2–3) they demonstrate a more limited capability and have more difficulty in performing additional extrapolation toward the "pure" MW (i.e. level four responses) when viewing the stimulus for a short time. This group difference in MW rates during the short trials might provide a hint regarding the mechanism of the abnormal overall MW among the PD patients. We propose that among PD patients, MW will only occur when a surplus of time exists relative to healthy individuals, since PD patients might need to continuously draw on more cognitive sources in order to be attentive to their environment, allowing less time for MW to occur. For this reason, it will take them more time to reach higher levels of MW, while in a healthy population, this movement toward higher levels of MW is almost

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instantaneous.

As all patients were tested during "ON" periods, we would expect them to be in good motor status. Nevertheless, bradyphrenia and bradykinesia may certainly still occur in these subjects. The cause of the between group differences was only speculated upon in this study and further research including both "ON" and "OFF" medication is needed in order to both validate these findings and understand their origin.

It is not clear why in the current study level three responses were the most common for both groups, while in the study by O'Callaghan et al. level four responses were found to be most common. One possible explanation for this difference is the removal of the cross shape from the current study. This shape is one of the longest presented shapes (90 s) and since there seems to be an association between length of stimulation and occurrence of MW, the removal of a long duration trial may have led to the observed change in different level proportions.

In this study, we found a negative correlation between MW tendencies and depression in patients. This is interesting, as previous studies have described a positive correlation of depression and dysphoria to MW rates [14,29], as well as increased activation of the DMN [30,31] However, this has recently been called into question. Konjedi et al. for example, show that MW does not necessarily have a positive correlation with negative mood in healthy individual or depression. They claim that negative mood as a consequence of MW may depend largely on other coexisting factors such as the existence of meta-awareness or the accompanying level of vigilance [32]. It is therefore possible that the commonly described positive link between mood, DMN and MW is altered in neurodegenerative disease as opposed to healthy controls and major depression.

Based on these findings, one can speculate that PD patients experience fewer episodes of MW compared to healthy age matched controls on a daily basis, as the need for longer time periods in order to move on the scale of attention-MW will create fewer MW opportunities. However, demonstrating such a tendency would require a study employing a more ecologcia thought sampling paradigm in order to demonstrate MW occurrence in real life. Furthermore, we cannot estimate what MW tendency in PD patients was before the onset of the disease, or whether this feature changed during the progression of the disease. Nevertheless, using ROC curve to plot MW measured during the short trials, we demonstrated a significant fair sensitivity in detecting PD patients rather than healthy controls, providing further support for reduced MW capabilities in PD as a potential non-motor diagnostic marker for PD.

Numerous studies have now established a strong connection between MW and DMN activation [1,2,18,19] and suggest that DMN serves as the neural basis for MW. Our hypothesis of reduced MW in PD patients was therefore formulated based on a recent study by Tessitore et al. who demonstrated decreased DMN connectivity among cognitively intact PD patients [22]. However, our study was only behavioral and did not include functional brain imaging. Therefore, future studies which include functional brain imaging would be needed in order to directly describe an association between the phenomenological occurrence of MW and DMN activity in PD patients, as well as its temporal dynamics. Another limitation is the sole use of the MoCA questionnaire as a screening tool for cognitive status, without in depth examination of specific cognitive domains. Future studies will need to use more elaborate cognitive evaluation tools to expand on these findings.

To conclude, our findings provide evidence for decreased MW in PD patients, possibly reflecting the previously described reduced functional connectivity of the DMN, which is apparent even in early PD. This might be a first stage in developing MW as a non-motor diagnostic, and follow-up tool that can be used independently of motor disease symptoms, i.e. even at the initial stages of the disease, or in at-risk populations.

Authors contribution

Geffen T. The conception and design of the study, acquisition of data. analysis and interpretation of data.

Thaler A. The conception and design of the study, acquisition of data, analysis and interpretation of data.

Gilam G. Analysis and interpretation of data.

Ben Simon E. The conception and design of the study.

Sarid N. Acquisition of data.

Gurevich T. Acquisition of data.

Giladi N. Acquisition of data.

Shabtai H. Acquisition of data.

Zitser J. Acquisition of data.

Schilman E. A. Analysis and interpretation of data.

Sharon H. The conception and design of the study, acquisition of data, analysis and interpretation of data.

All authors drafted the article or revised it, and all gave their final approval for the final version of the article.

Conflict of interest

There is no conflict of interest to declare.

Funding

The authors received no specific funding for this work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.08.030.

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Please cite this article in press as: T. Geffen, et al., Reduced mind wandering in patients with Parkinson's disease, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.08.030