Clinical Neurophysiology 130 (2019) 224–230

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Changes in event-related potentials during dual task walking in aging and Parkinson's disease

Inbal Maidan [a,b,c,d,e,*], Firas Fahoum [c,d], Shiran Shustak [a,b], Eran Gazit [b], Dmitry Patashov [f,g], Dmitry Tchertov [g], Nir Giladi [a,b,c,d,e,h], Jeffrey M Hausdorff [b,c,e,i,j], Anat Mirelman [a,b,c,d,e]

[a] Laboratory of Early Markers of Neurodegeneration, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[b] Center for the Study of Movement, Cognition, and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[c] Neurological Institute, Tel Aviv Medical Center, Tel-Aviv, Israel
[d] Department of Neurology, Sackler School of Medicine, Tel Aviv University, Israel
[e] Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
[f] Faculty of Science, Holon Institute of Technology, Holon, Israel
[g] Faculty of Engineering, Holon Institute of Technology, Holon, Israel
[h] Sieratzki Chair in Neurology Tel Aviv University, Israel
[i] Department of Physical Therapy, Sackler Faculty of Medicine, Tel Aviv University, Israel
[j] Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

ARTICLE INFO

Article history:
Accepted 10 November 2018
Available online 8 December 2018

Keywords:
Parkinson's disease
Electroencephalographic
P300
Gait
Dual-task

HIGHLIGHTS

- Prolonged P300 latency during walking is pronounced in aging and Parkinson's disease (PD).
- Prolonged P300 latency is correlated with reduced cognitive and motor function.
- Reduced P300 amplitude during walking is found only in patients with PD.

ABSTRACT

Objective: To investigate EEG changes during an auditory odd-ball task while walking (dual-task) in young adults, older adults, and patients with Parkinson's disease.
Methods: 11 young adults, 10 older adults, and 10 patients with Parkinson's disease (PD) performed an auditory oddball task during standing and walking on a treadmill, while wearing a wireless EEG cap. The amplitude and latency of P300 were compared between groups and within conditions using linear mix model analysis. Gait was evaluated using wearable sensors and cognition was assessed using the Color Trail Test.
Results: P300 latency became longer during walking in all groups ($p = 0.005$). During walking, older adults ($p = 0.005$) and patients with PD ($p = 0.001$) showed prolonged P300 latency compared to young adults. Significant task by group interaction was found in P300 amplitude ($p = 0.008$). Patients with PD demonstrated reduced P300 amplitude during walking compared to standing ($p = 0.023$). Among all subjects, better motor and cognitive performance correlated with shorter P300 latency ($r = 0.457$, $p = 0.014$ and $r = 0.431$, $p = 0.040$, respectively).
Conclusions: These findings provide direct evidence of the physiological recruitment of attentional networks during walking and their impact by ageing and disease.
Significance: This study is the first to report on changes in P300 latency and amplitude during dual-task oddball walking in older adults and patients with PD.

1. Introduction

It has been theorized that walking in everyday life conditions requires higher cognitive processes that utilizes a complex neural network that incorporates cognitive and motor information

* Corresponding author at: Center for the study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
E-mail addresses: inbalm@tlvmc.gov.il (I. Maidan), firasf@tlvmc.gov.il (F. Fahoum), shiransh@tlvmc.gov.il (S. Shustak), erang@tlvmc.gov.il (E. Gazit), DmitryP@hit.ac.il (D. Patashov), dimach13@gmail.com (D. Tchertov), nirg@tlvmc.gov.il (N. Giladi), jhausdor@tlvmc.gov.il (J.M Hausdorff), anatmi@tlvmc.gov.il (A. Mirelman).

https://doi.org/10.1016/j.clinph.2018.11.019
1388-2457/

(Woollacott and Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). Most evidence supporting this notion relies on behavioral studies stemming from dual-task paradigms during walking to increase cognitive demands. These studies show that adding a simultaneous task to walking taxes executive function and attention and leads to changes in gait performance (Hausdorff et al., 2008; Yogev-Seligmann et al., 2008). This effect is exacerbated with ageing and neurodegenerative diseases such as Parkinson's disease (PD) (Segev-Jacubovski et al., 2011; Woollacott and Shumway-Cook, 2002; Yogev-Seligmann et al., 2008) and is related to falls (Segev-Jacubovski et al., 2011) providing indirect evidence of the importance of the interconnection between motor and cognitive functions during walking. In recent years, various neuroimaging techniques were used to study the role of cognitive resources during walking. fMRI studies used motor imagery (Maidan et al., 2016b; Peterson et al., 2014) and alternating movements of feet (Nieuwhof et al., 2017; Shine et al., 2013) to mimic gait in the scanner. These studies reported increased activation in various frontal regions related to the attentional networks (Maidan et al., 2016b; Peterson et al., 2014; Shine et al., 2013), however these findings are limited as they do not directly capture actual gait.

Recent studies using functional Near Infrared Spectroscopy (fNIRS), a neuroimaging technique measuring blood oxygenation levels from the brain convexity during actual walking, showed increased activation of the prefrontal cortex (PFC) in healthy young and older adults during dual task walking, as compared to usual walking (Holtzer et al., 2015; Metzger et al., 2017; Mirelman et al., 2017). Patients with PD presented similar findings but also showed increased activation already during usual walking (Maidan et al., 2016a) suggesting a reliance on cognitive resources already during simple tasks. However, similar to fMRI, the temporal resolution of the fNIRS is low and it measures hemodynamic responses only in specific superficial areas of interest, unable to distinguish isolated effects from network function (Ferrari and Quaresima, 2012).

Spontaneous electroencephalographic (EEG) recording as well as event-related potentials (ERPs) are direct measurements of neuronal activity, with high temporal resolution, that can be applied during walking. Variations in ERP responses including amplitude, polarity, distribution, and latency have been associated with various cognitive measures (Duncan et al., 2009; Picton et al., 2000; Woodman, 2010). Changes were mainly observed in P300, the most studied ERP related to attention and cognitive decline, elicited using the "oddball" task. Task in which a random sequence of stimuli is presented and subjects are required to mentally count the rare target events (Polich, 2004). Accumulating evidence from EEG and fMRI studies show that P300 generation stems from the connection between frontal lobe and hippocampal/temporal-parietal function (Huang et al., 2015; Kiehl et al., 2001; Knight, 1996). It has been suggested that frontal areas account for the attention mechanism that directs neural responsivity to a new stimulus (Daffner et al., 2000a; Daffner et al., 2000b), whereas the tempo-parietal regions correspond to the attentional resources used to maintain memory entries (Berti et al., 2004; Huang et al., 2015). Patients with PD have decreased P300 amplitude and increased peak latency during sitting tasks as compared to healthy older adults and as the severity of cognitive dysfunction increases (Yilmaz et al., 2017). Although these changes in P300 were highly sensitive to cognitive decline and attentional impairments (Batterink et al., 2012), they were also observed in other pathologies such as Alzheimer's disease (Benz et al., 2014) showing low specificity.

As demonstrated previously (Yogev-Seligmann et al., 2008), PD involves deficits in motor and cognitive functions that are often exacerbated during dual-task in which motor and cognitive tasks are performed simultaneously. In this study, we combined the oddball task with walking to evaluate the dual-task effect of an attentional demanding task while walking in healthy young adults, healthy older adults and patients with PD. Using this approach, we aimed to reveal specific changes in P300 while walking and dual-tasking in older adults and patients with PD. We hypothesized that P300 latency will increase and amplitude will decrease during dual-task walking because of the additional attentional load, and that these changes will be more pronounced with aging and disease.

2. Methods

2.1. Participants

Thirty-one subjects, i.e., 11 healthy young adults, 10 healthy older adults, and 10 patients with PD, participated in this study. Recruitment was performed by reaching out to the geriatric and neurology outpatient clinics in Tel Aviv Medical Center. Participants were excluded if they had: MOCA $\leq$ 21, a history of neurological disorder other than PD that could affect their performance, inability to walk at least 5 minutes, unstable medical condition including cardio-vascular instability, hearing problems or significant psychiatric co-morbidity. The study was approved by local ethical committee and was performed according to the principles of the Declaration of Helsinki. All participants gave their informed written consent prior to participation.

2.2. Protocol

All participants performed the auditory oddball tasks during standing and walking on a treadmill (TM), while wireless EEG was recorded via a 20-channel EEG cap (Enobio 20 Neuroelectrics, Barcelona). Subjects were secured by a harness attached to the ceiling. The auditory stimuli consisted of 600 Hz pure tone bursts as standard stimuli and 1200 Hz pure tone bursts as target stimuli. The tones were presented in a randomized order, with a stimulus interval raging between 2.8 and 3.2 seconds. Each of the oddball tasks lasted 2 minutes consisting of 40 stimuli tones; 30 standard tones and 10 odd high tones considered the target stimuli (25% of total tones). The subjects were instructed to count the target tones silently, reporting the total odd tones at the end of the session. Three oddball tasks were performed during quite standing on the TM and three oddball tasks while walking on TM at the subjects' comfortable speed (a total of 90 standard tones and 30 odd tones in each position). The order of the conditions was randomized. After completing the oddball tasks participants performed the Montreal cognitive assessment (MOCA) to assess global cognitive function and the color trail test (CTT) (D'Elia et al., 1996) for a more refined measure of attention and executive function. Patients with PD also underwent the Unified Parkinson's Disease Rating Scale (UPDRS) to assess disease severity (Goetz et al., 2008).

2.3. Gait assessment

Two 3D-accelerometers attached to the right and left ankles (Opal™, APDM) were used to determine spatiotemporal gait characteristics while walking on the TM. Gait measurements included gait speed and stride and step regularity, a measure of the consistency of the stride-to-stride or step-to-step pattern. These measures were calculated by an unbiased autocorrelation procedure that analyzed the pattern of acceleration in the vertical, mediolateral and anteroposterior directions (Barden et al., 2016). Dual task (DT) cost, a measure that reflects the effect of the second task on gait ability, as compared with baseline single task walking was cal-

culated as, DT cost = 100 × (single-task step/stride regularity − DT step/stride regularity)/single-task step/stride regularity.

2.4. EEG analysis

Data processing was performed to clean artifacts. This was done for both conditions; standing and walking, and included: (1) band pass FIR filter 1–40 Hz to reduce motion artifacts (2) rejection of channels with prominent artifact based on visual inspection, (3) adaptive independent component analysis mixture model algorithm (AMICA) using the default extended-mode training parameters, (4) rejection of artifactual components based on manually inspection and SASICA toolbox (Gramann et al., 2010). Matlab EEGLAB toolbox was used for the analysis. The analyzed signals were divided into 3 seconds epochs, 1 second pre-stimulus and 2 seconds post-stimulus. Epochs with probability of occurrence >3 SD from the mean across all epochs were rejected from further analysis to reduce noise (Gwin et al., 2010). For ERP analysis, we randomly chose the same number of standard trials as the odd trails and averaged 20 different combinations to represent the ERP of standard trials. This was performed due to the different frequency of odd and standard trials (ratio of 1:4). P300 was identified from the maximum positive deflection peak between 250 and 650 ms from the stimulus. Amplitude and latency of the signal were evaluated at a 100 ms time window (50 ms before and after the P300 detected event) and compered to pre-stimulus (at 200 ms). P300 was measured from channel Pz as P300 scalp distribution is defined as the amplitude change over the midline electrodes (Fz, Cz, Pz), which typically increases in magnitude from the frontal to parietal electrode sites (Polich, 2007).

2.5. Statistical analyses

Means and standard errors were calculated for all dependent variables. In order to account for variability and gain symmetry we transformed P300 latency into Log latency and P300 amplitude into square amplitude based on Box cox variance stability methods (Sakia, 1992). Liner mixed model analysis was used to examine the effect of condition (standing vs. walking), group (healthy young, healthy older adults, and patients with PD), and condition × group interaction on P300 amplitude and latency, while controlling for age, gender, and gait speed. Univariate ANOVA was performed to compare between groups during each one of the condition (standing and walking) including measures of gait and cognition. The associations between P300 measurements and motor and cognitive performance were explored using Pearson correlation coefficients. Statistical significance was set to $p = 0.05$. Statistical analysis was performed using SPSS for Windows version 22.

3. Results

3.1. Participants

Participant characteristics are presented in Table 1. Healthy older adults and patients with PD were similar in age ($p = 0.227$). MOCA, gait speed, and CTT scores were significantly lower in patients with PD, compared to healthy young (Table 1).

3.2. Oddball task performance and P300 evaluation

All participants were engaged in the oddball task and demonstrated high accuracy of performance during standing (healthy young 100 ± 0.0%, healthy older adults 98 ± 1.7%, and patients with PD 97.4 ± 1.1%) and during walking (healthy young 99.2 ± 0.4%, healthy older adults 99.4 ± 0.4%, and patients with PD 99.4 ± 0.4%). The P300 potentials of 1 healthy older adult and two patients with PD could not be achieved. Therefore, the data of these three subjects were not included in the analysis. Table 2 summarizes the P300 latency and amplitude during standing and walking.

3.3. P300 latencies and amplitudes

Analysis of differences between conditions (i.e., standing and walking) showed prolonged P300 latency during walking compared to standing in all groups ($p = 0.005$, Fig. 1A), while P300 amplitude was similar between conditions ($p = 0.528$). Similar results were observed after controlling for LEDD (latency: $p = 0.014$, amplitude: $p = 0.687$) or MOCA (latency: $p = 0.012$, amplitude: $p = 0.687$).

P300 latency during walking was significantly shorter in the healthy young subjects compared to the healthy older adults ($p = 0.032$) and to the patients with PD ($p = 0.005$). No differences were observed between the healthy older adults and the patients with PD in this condition ($p = 0.976$). Between group differences in P300 latency during standing were only observed between healthy young and patients with PD ($p = 0.041$).

A significant condition × group interaction was found for P300 amplitude ($p = 0.008$) (Fig. 1B). Similar amplitude between standing and walking was shown in healthy individuals (both healthy young and healthy older adults) and a smaller P300 amplitude during walking (compared to standing) was demonstrated in patients with PD ($p = 0.023$, Fig. 2).

3.4. Gait performance

Young healthy adults showed higher stride ($p = 0.037$) and step regularity ($p = 0.050$) compared to patients with PD during oddball

Table 1
Participants characteristics.

Parameter	Healthy young N = 11	Older adults N = 10	PD N = 10	*p*-values
Age (years)	32.3 ± 1.8	67.1 ± 1.7*	60.5 ± 3.6**	<0.001
Gender (M/F)	7/6	4/6	6/4	0.853
TM Gait speed (m/s)	0.8 ± 0.02	0.6 ± 0.03	0.6 ± 0.02**	0.015
MOCA	28.2 ± 0.4	27.7 ± 0.5	25.2 ± 0.8** #	0.003
CTT (s)	32.2 ± 4.2	51.8 ± 3.4	67.9 ± 14.7**	0.014
Disease duration (years)	na	na	2.9 ± 0.5	na
UPDRS motor	na	na	20.2 ± 3.4	na
LEDD (mg)	na	na	303 ± 114	na

PD = Parkinson's disease, M = Male, F = Female, MOCA = Montreal cognitive assessment, CTT = Color trail test, UPDRS = Unified Parkinson Disease Rating Scale, LEDD = Levodopa equivalent daily dose.
* Significant difference between healthy older adults and young.
** Significant difference between PD and young.
# Significant difference between PD and older adults.

Table 2
P300 latency and amplitude during each condition in each group.

Condition Standing					Walking			
Variable	Subject (n)	Latency (ms)	Amplitude (mamp)	Achieved P300 (%)	Subjects (n)	Latency (ms)	Amplitude (mamp)	Achieved P300 (%)
Young	11	396 ± 29	7.1 ± 1.6	91.7	11	415 ± 23	7.7 ± 1.0	75
Older adults	9	456 ± 32	6.9 ± 0.9	80	9	526 ± 27	7.3 ± 0.7	70
PD	8	478 ± 13	6.2 ± 0.9	70	8	558 ± 33	3.8 ± 0.6	50

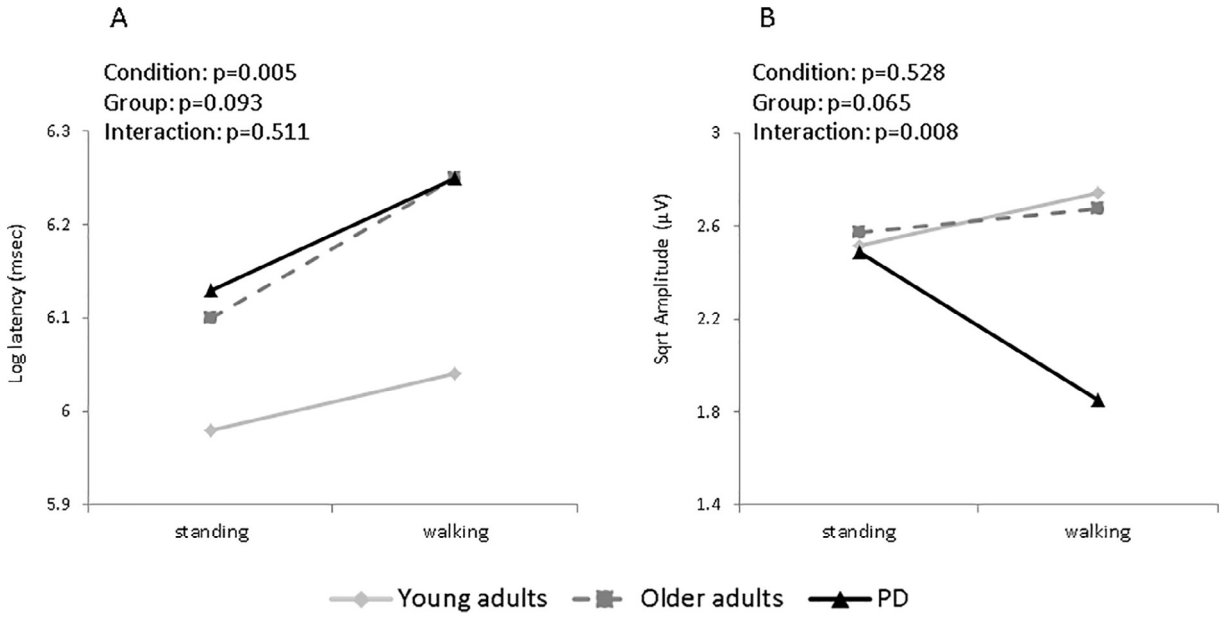

Fig. 1. Changes in P300 (A) log latency and (B) square root amplitude between standing oddball and walking oddball in young adults, older adults, and patients with PD. P300 latency during walking is significantly longer than during standing in all groups ($p = 0.005$), while P300 amplitude during walking is significantly lower than during standing only in patients with PD ($p = 0.008$).

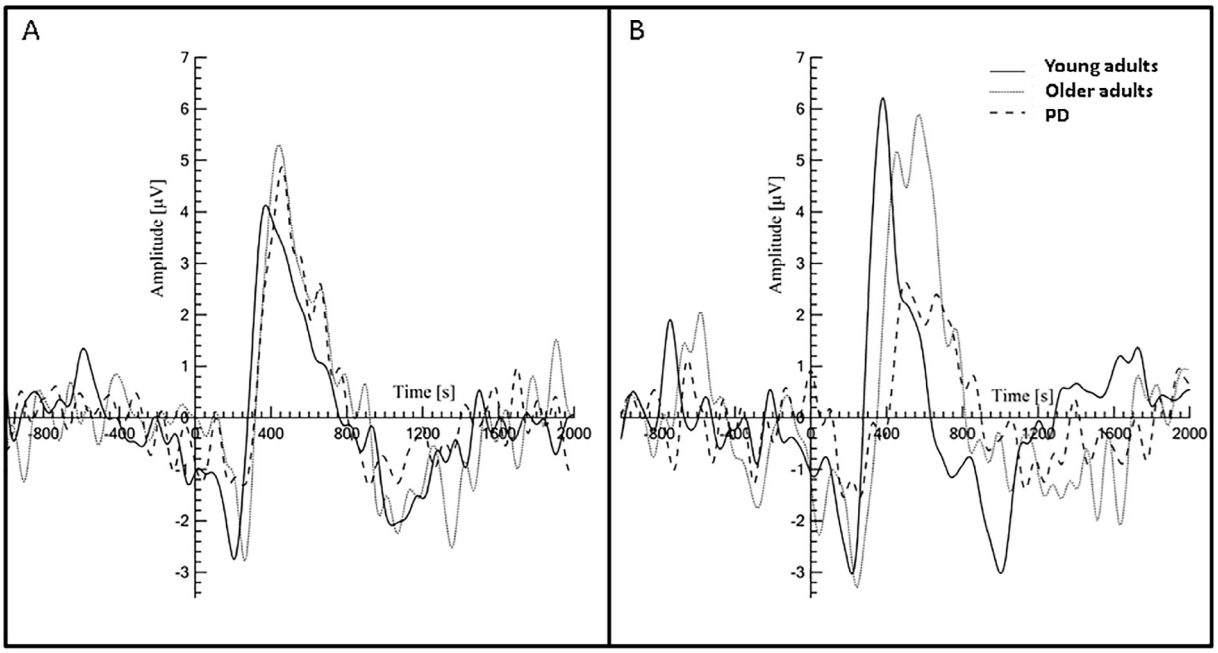

Fig. 2. P300 during (A) standing and (B) walking in young adults, older adults, and patients with PD. No differences in P300 latency and amplitude are observed between the groups during standing. In contrast, P300 amplitude is significantly lower in patients with PD (dash line) compared to young and older adults during walking ($p = 0.023$).

walking. Trend toward significant was observed during usual walking (stride regularity $p = 0.072$, step regularity ($p = 0.071$). No differences in dual task cost between the groups were observed (dual task cost stride time $p = 0.616$, DT-cost stride regularity $p = 0.971$, DT-cost step regularity $p = 0.295$). Gait speed was significantly lower in patients with PD ($p = 0.018$) (Table 1).

3.5. Correlations between P300 and gait

P300 latency was inversely correlated to gait speed ($r = -0.457$, $p = 0.014$) in all participants indicating that lower gait speed (worse motor ability) was associated with prolongation of P300 (Fig. 3A). In addition, a significant correlation was found between CTT and P300 latency (Fig. 3B). P300 amplitude was not associated with cognitive or gait measures.

4. Discussion

P300 is an index of stimulus processing which has been considered a motor free measure of cognitive function (Magliero et al., 1984; Polich, 2004). In this study, we aimed to elucidate specific changes in P300 associated with dual tasking in older adults and patients with PD using EEG. Our findings demonstrate (1) prolonged P300 latency during walking is more pronounced in aging and PD, (2) there is an association between P300 latency and reduced cognitive function as measured by CTT and motor function as measured by gait speed, and (3) reduced P300 amplitude during walking was found only in patients with PD. These findings provide direct evidence of specific changes in electrical brain activity during dual task walking.

The correlation between better performances in CTT, a cognitive processing speed test, and shorter P300 latency suggests that P300 latency reflects a stimulus process and not solely response generation. In line with the literature, we found shorter latencies in young adults compared to older adults and patients with PD (Polich, 2004; Yilmaz et al., 2017). These results suggest an ageing or neurodegeneration effect corresponding to slower speed processing, exacerbated during a more demanding task such as walking. No changes in the findings of P300 latency after controlling for LEDD suggest a minimal effect of dopaminergic drugs on cognitive processing speed (Rektorova et al., 2005). Moreover, the basal ganglia, specifically the striatum, have been shown to play an integrative role in cognitive information processing, in motor and non-motor tasks (Rektor et al., 2005). Providing an additional explanation to the prolonged latency we found in patients with PD.

P300 amplitude is a sum of all the extracelluar currents that are time-locked to the task. Therefore, it has been related to the amount of attention resources engaged during task (Katsarou et al., 2004; Yilmaz et al., 2017) and considered an indicator of the amount of neurons, that were activated during the processing of incoming information (Johnson, 1993). One explanation is that detection of odd stimuli invokes additional attentional processes to update the neural representation of the stimulus, therefore higher P300 amplitude reflects a better recruitment of additional attention resources (Polich, 2007). Alternatively, it has been proposed that higher P300 amplitude reflects long-lasting global activation of workspace neurons, found throughout a distributed attention network of cortical association areas, indicating a better attention (Dehaene et al., 2003; Sergent et al., 2005).

The similar P300 amplitude in young, older adults, and patients with PD during oddball while standing indicates that the recruitment of attentional resources during relatively simple tasks is preserved throughout life. In contrast, when greater attentional demands are present, such as during walking, then changes related to ageing and disease are revealed. The lack of differences in the performance accuracy of the oddball task indicates that it was a simple task and the lack of differences in dual task cost may be due to the constant external pace of the TM alleviating the effects of dual task and improving gait performance (Thumm et al., 2018). Altogether, the similar performance of the groups suggests good utilization of attention. However the lower P300 amplitude seen in patients with PD suggests that less neurons were active reflecting impaired neuronal recruitment in terms of timing and coordination.

Recent studies using fNIRS to measure prefrontal cortex activation (PFC) showed increased PFC activation during usual walking in patients with PD compared to older adults. These results suggest a potential compensatory mechanism that involves recruitment of attentional networks in PD (Holtzer et al., 2011; Maidan et al., 2016a; Mirelman et al., 2017). This activation was further

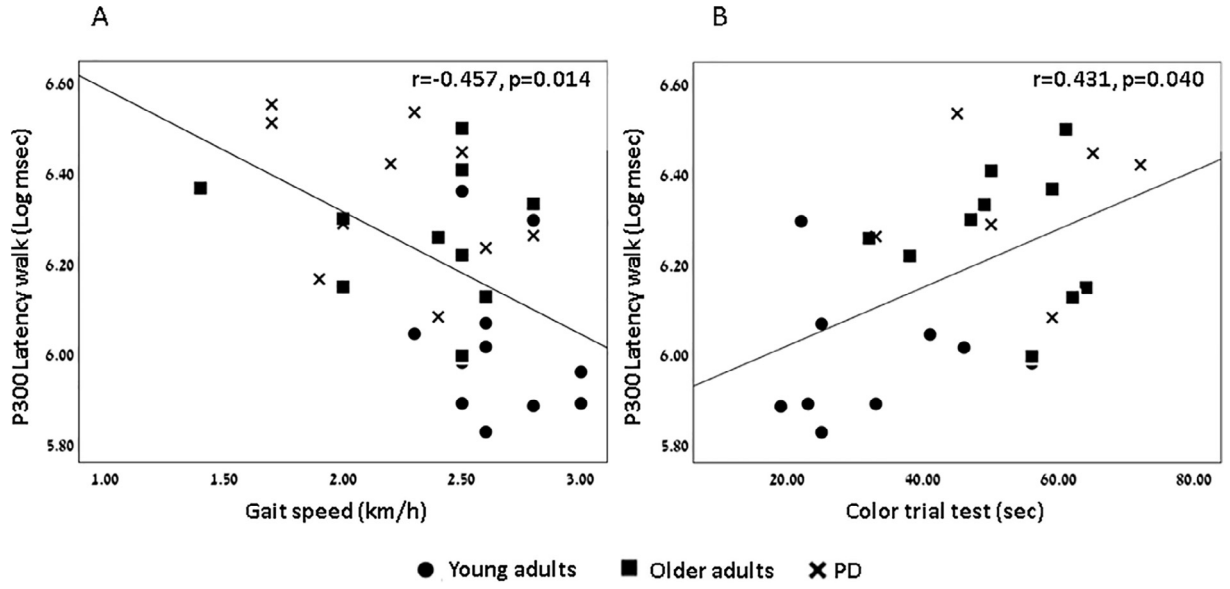

Fig. 3. Correlation between P300 latency during walking and (A) gait speed, (B) color trial test in all subjects. Subjects with shorter P300 latency walked faster and completed the color trial test faster.

increased with dual task but performance did not improve suggesting inefficient activation (Maidan et al., 2016a). While fNIRS studies were focused on the PFC, higher activation measured by the BOLD signal reflected higher recruitment of specific attentional resources and cognitive networks, suggesting a possible compensatory mechanism. At first glance, the previously reported fNIRS results are in contradiction to our EEG findings which are consistent with lower neuronal recruitment during dual task. However, it is important to note that fNIRS and fMRI have lower temporal resolution. Therefore it is hard to conclude whether the increased activations are the cause or the effect or if they are a result of compensatory activation stemming from network function. In contrast, EEG signals have low spatial resolution and higher temporal resolution. This may imply that the lower P300 amplitude reflects unsynchronized activation of various resources (lower timing and coordination between different brain regions) that led to activation of less neurons during dual task walking in patients with PD. To this end, perhaps, fNIRS and EEG methods represent complimentary aspects of brain recruitment during task performance. In the future, simultaneous study of both modalities could help to further study this question.

The study has several limitations that need to be acknowledged. It included a small sample size limiting generalizability of the results. Patients with PD had lower cognitive function than our older adults as measured by the MoCA test. In addition, the walking test was conducted while walking on a treadmill which provides an external cue that directly affects walking patterns and perhaps brain responses. Thus, forthcoming studies should also explore changes in P300 during over ground walking to minimize the effects of the external cueing on gait. Future studies should also include a larger cohort of patients with PD, in different stages of the disease including naïve patients that are cognitively intact, to investigate whether these findings can be used as a marker of prodromal cognitive decline in PD. Additional groups of patients with neurodegenerative diseases should be included to investigate the specificity of our findings. Moreover, future studies should include differentiation of P300 to its components P300a and P300b to better specify the attentional and memory deficits associated with PD.

5. Conclusions

To our knowledge, this study is the first to report on alterations in neuronal activity using EEG during dual task oddball walking in patients with PD. These high temporal resolution EEG findings provide an additional layer to our knowledge regarding executive function deficits in aging and PD demonstrating new direct evidence of the physiological recruitment of attentional networks during walking and their impact by ageing and disease.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

References

Barden JM, Clermont CA, Kobsar D, Beauchet O. Accelerometer-based step regularity is lower in older adults with bilateral knee osteoarthritis. Front Hum Neurosci 2016;10:625.

Batterink L, Karns CM, Neville H. Dissociable mechanisms supporting awareness: the P300 and gamma in a linguistic attentional blink task. Cereb Cortex 2012;22:2733–44.

Benz N, Hatz F, Bousleiman H, Ehrensperger MM, Gschwandtner U, Hardmeier M, Ruegg S, Schindler C, Zimmermann R, Monsch AU, Fuhr P. Slowing of EEG background activity in Parkinson's and Alzheimer's disease with early cognitive dysfunction. Front Aging Neurosci 2014;6:314.

Berti S, Roeber U, Schroger E. Bottom-up influences on working memory: behavioral and electrophysiological distraction varies with distractor strength. Exp Psychol 2004;51:249–57.

D'Elia LF, Satz P, Uchiyama CL, White T. Color Trails Test. Professional manual. Odessa, FL: Psychological Assessment Resources; 1996.

Daffner KR, Mesulam MM, Holcomb PJ, Calvo V, Acar D, Chabrerie A, Kikinis R, Jolesz FA, Rentz DM, Scinto LF. Disruption of attention to novel events after frontal lobe injury in humans. J Neurol Neurosurg Psychiatry 2000a;68:18–24.

Daffner KR, Mesulam MM, Scinto LF, Acar D, Calvo V, Faust R, Chabrerie A, Kennedy B, Holcomb P. The central role of the prefrontal cortex in directing attention to novel events. Brain 2000b;123(Pt 5):927–39.

Dehaene S, Sergent C, Changeux JP. A neuronal network model linking subjective reports and objective physiological data during conscious perception. PNAS 2003;100:8520–5.

Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Naatanen R, Polich J, Reinvang I, Van PC. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin Neurophysiol 2009;120:1883–908.

Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage 2012;63:921–35.

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129–70.

Gramann K, Gwin JT, Bigdely-Shamlo N, Ferris DP, Makeig S. Visual evoked responses during standing and walking. Front Hum Neurosci 2010;4:202.

Gwin JT, Gramann K, Makeig S, Ferris DP. Removal of movement artifact from high-density EEG recorded during walking and running. J Neurophysiol 2010;103:3526–34.

Hausdorff JM, Schweiger A, Herman T, Yogev-Seligmann G, Giladi N. Dual-task decrements in gait: contributing factors among healthy older adults. J Gerontol A Biol Sci Med Sci 2008;63:1335–43.

Holtzer R, Mahoney JR, Izzetoglu M, Izzetoglu K, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. J Gerontol A Biol Sci Med Sci 2011;66:879–87.

Holtzer R, Mahoney JR, Izzetoglu M, Wang C, England S, Verghese J. Online fronto-cortical control of simple and attention-demanding locomotion in humans. Neuroimage 2015;112:152–9.

Huang WJ, Chen WW, Zhang X. The neurophysiology of P 300–an integrated review. Eur Rev Med Pharmacol Sci 2015;19:1480–8.

Johnson Jr R. On the neural generators of the P300 component of the event-related potential. Psychophysiology 1993;30:90–7.

Katsarou Z, Bostantjopoulou S, Kimiskidis V, Rossopoulos E, Kazis A. Auditory event-related potentials in Parkinson's disease in relation to cognitive ability. Percept Mot Skills 2004;98:1441–8.

Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. Psychophysiology 2001;38:133–42.

Knight R. Contribution of human hippocampal region to novelty detection. Nature 1996;383:256–9.

Magliero A, Bashore TR, Coles MG, Donchin E. On the dependence of P300 latency on stimulus evaluation processes. Psychophysiology 1984;21:171–86.

Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N, Deutsch JE, Hausdorff JM, Claassen JA, Mirelman A. The role of the frontal lobe in complex walking among patients with Parkinson's disease and healthy older adults: an fNIRS study. Neurorehabil Neural Repair 2016a;30:963–71.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, Hausdorff JM, Mirelman A. Altered brain activation in complex walking conditions in patients with Parkinson's disease. Parkinsonism Relat Disord 2016b;25:91–6.

Metzger FG, Ehlis AC, Haeussinger FB, Schneeweiss P, Hudak J, Fallgatter AJ, Schneider S. Functional brain imaging of walking while talking - An fNIRS study. Neuroscience 2017;343:85–93.

Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. Brain Cogn 2017;115:41–6.

Nieuwhof F, Bloem BR, Reelick MF, Aarts E, Maidan I, Mirelman A, Hausdorff JM, Toni I, Helmich RC. Impaired dual tasking in Parkinson's disease is associated with reduced focusing of cortico-striatal activity. Brain 2017;140:1384–98.

Peterson DS, Pickett KA, Duncan RP, Perlmutter JS, Earhart GM. Brain activity during complex imagined gait tasks in Parkinson disease. Clin Neurophysiol 2014;125:995–1005.

Picton TW, Bentin S, Berg P, Donchin E, Hillyard SA, Johnson Jr R, Miller GA, Ritter W, Ruchkin DS, Rugg MD, Taylor MJ. Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. Psychophysiology 2000;37:127–52.

Polich J. Clinical application of the P300 event-related brain potential. Phys Med Rehabil Clin N Am 2004;15:133–61.

Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 2007;118:2128–48.

Rektor I, Bares M, Brazdil M, Kanovsky P, Rektorova I, Sochurkova D, Kubova D, Kuba R, Daniel P. Cognitive- and movement-related potentials recorded in the human basal ganglia. Mov Disord 2005;20:562–8.

Rektorova I, Rektor I, Bares M, Dostal V, Ehler E, Fanfrdlova Z, Fiedler J, Klajblova H, Kulist'ak P, Ressner P, Svatova J, Urbanek K, Veliskova J. Cognitive performance in people with Parkinson's disease and mild or moderate depression: effects of dopamine agonists in an add-on to L-dopa therapy. Eur J Neurol 2005;12:9–15.

Sakia RM. The Box-Cox Transformation Technique: A Review. J Roy Statist Soc, Series D (The Statistician) 1992:169–78.

Segev-Jacubovski O, Herman T, Yogev-Seligmann G, Mirelman A, Giladi N, Hausdorff JM. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? Expert Rev Neurother 2011;11:1057–75.

Sergent C, Baillet S, Dehaene S. Timing of the brain events underlying access to consciousness during the attentional blink. Nat Neurosci 2005;8:1391–400.

Shine JM, Matar E, Ward PB, Frank MJ, Moustafa AA, Pearson M, Naismith SL, Lewis SJ. Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia. Brain 2013;136:3671–81.

Thumm PC, Maidan I, Brozgol M, Shustak S, Gazit E, Shema SS, Bernad-Elazari H, Beck Y, Giladi N, Hausdorff JM, Mirelman A. Treadmill walking reduces pre-frontal activation in patients with Parkinson's disease. Gait Posture 2018;62:384–7.

Woodman GF. A brief introduction to the use of event-related potentials in studies of perception and attention. Atten Percept Psychophys 2010;72:2031–46.

Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. Gait Posture 2002;16:1–14.

Yilmaz FT, Ozkaynak SS, Barcin E. Contribution of auditory P300 test to the diagnosis of mild cognitive impairment in Parkinson's disease. Neurol Sci 2017;38:2103–9.

Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. Mov Disord 2008;23:329–42.