Title: Distinct features of the cortical N1 response to balance perturbation are associated with balance and cognitive impairments in Parkinson's disease

Running Title: Balance N1 in Parkinson's disease

Authors: Aiden M. Payne[1], J. Lucas McKay[2,3], and Lena H. Ting[1,4]

Affiliations:
[1]Wallace H. Coulter Department of Biomedical Engineering, Emory University and Georgia Tech, Atlanta, Georgia, United States of America
[2]Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, Georgia, United States of America
[3]Jean & Paul Amos Parkinson's Disease & Movement Disorders Program, Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, United States of America
[4]Division of Physical Therapy, Department of Rehabilitation Medicine, Emory University, Atlanta, GA, United States

Correspondence:
Lena H. Ting, lting@emory.edu

ABSTRACT

Mechanisms underlying associations between balance and cognitive impairments in older adults with and without Parkinson's disease (PD) are poorly understood. Balance disturbances evoke a cortical N1 response that is associated with both balance and cognitive abilities in unimpaired populations. We hypothesized that the N1 response reflects a neural mechanism that is shared between balance and cognitive function, and would therefore be associated with both balance and cognitive impairments in PD. Although N1 responses did not differ at the group level they showed distinct associations with balance and cognitive function in the PD vs. control (noPD) groups. In noPD, higher N1 amplitudes were correlated with lower cognitive set shifting ability and lower balance confidence. However, in PD, higher N1 amplitudes were correlated with lower overall cognitive function, while earlier and narrower N1 peaks were correlated with more severe PD and balance impairments. Our results show that balance and cognitive impairments are dissociable and associated with distinct features of the N1 response, suggesting that the N1 response reflects coordination of distinct mechanisms for balance and cognitive function. Identifying coordinated but dissociable mechanisms underlying balance and cognitive processes may reveal potential targets for rehabilitation of comorbid balance and cognitive impairments.

Key Words: aging, EEG, cognitive-motor interactions, posture, set shifting

INTRODUCTION

Assessing cortical activation during balance recovery behavior may provide insight into the relationships between balance and cognitive impairments with aging and Parkinson's disease. Cognitive decline predicts new and recurrent falls in otherwise healthy older adults (Gleason et al. 2009; Herman et al. 2010; Mirelman et al. 2012) and people with Parkinson's disease (Allcock et al. 2009; Camicioli and Majumdar 2010; Mak et al. 2014). Although balance recovery behavior is largely automatic and mediated by brainstem sensorimotor circuits in healthy young adults (Jacobs and Horak 2007a), cognitive engagement in balance control becomes more evident with aging (Rankin et al. 2000), fall history (Shumway-Cook et al. 1997), fall risk (Lundin-Olsson et al. 1997), and Parkinson's disease (Kelly et al. 2012). Older adults, and particularly people with Parkinson's disease, show increased cortical activation for walking and balance tasks, which may reflect cognitive engagement to compensate for reduced automaticity of behavior (Petzinger et al. 2013; Wu et al. 2015a), providing an opportunity for cognitive impairment to influence balance control. However, most studies of cortical activation during walking and balance tasks in older adults have relied on relatively slow measures, such as changes in prefrontal blood oxygenation (functional near infrared spectroscopy) or changes in oscillatory power (electroencephalography, EEG), with studies investigating time-domain EEG activity largely focused on pre-movement preparatory periods (Stuart et al. 2018). Measuring rapid brain responses to a balance disturbance could provide insight into changes in balance control in balance impaired populations.

A balance disturbance evokes a fast cortical response that has been associated with both balance ability and cognitive processing, and may therefore provide insight into relationships between balance and cognitive function. A sudden balance disturbance evokes an automatic balance-correcting muscle response from the brainstem at ~100 ms, with the potential for cortical involvement in balance recovery behavior at longer latencies (>150 ms) (Jacobs and Horak 2007a). A cortical "N1" response peak evoked in the EEG activity ~150 ms after a balance disturbance has been localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015; Payne et al. 2019a), which has the potential to mediate interactions between neighboring prefrontal and motor cortical areas (Goldberg 1985). In young adults the cortical N1 is larger in individuals with lower balance ability (Payne and Ting 2020a) and on trials that include compensatory stepping behaviors (Payne and Ting 2020c; Solis-Escalante et al. 2020), and may therefore reflect compensatory cortical engagement in balance recovery behavior. The cortical N1 is also influenced by cognitive processing in young adults, becoming smaller when attention is directed away from balance recovery by a dual task paradigm (Little and Woollacott 2015; Quant et al. 2004b), and larger when perturbations are perceived to be more threatening (Adkin et al. 2008; Mochizuki et al. 2010) or less predictable (Adkin et al. 2008; Mochizuki et al. 2010). While studies in older populations have been limited, older adults generally have smaller and later cortical N1s (Duckrow et al. 1999; Ozdemir et al. 2018), with changes in temporal characteristics including the appearance of multiple component peaks in some individuals with reduced mobility (Duckrow et al. 1999). We recently reported associations between larger N1 amplitudes, lower cognitive set shifting ability, stiffer balance recovery behavior, and increased antagonist muscle activity in older adults (Payne et al. 2021), further implicating the cortical N1 in the relationship between balance and cognitive problems with aging. We now investigate the cortical N1 responses in a population of older adults with Parkinson's disease, who have both balance and cognitive impairments.

Parkinson's disease affects several factors known to influence the cortical N1, but it is unknown whether the N1 is altered in Parkinson's disease. The N1 depends on attention to balance control (Little and Woollacott 2015; Quant et al. 2004b), which is increased Parkinson's

disease (Petzinger et al. 2013; Wu et al. 2015a). N1 amplitude also depends on the perceived threat of a balance disturbance (Adkin et al. 2008; Mochizuki et al. 2010), and fear of falling is common in Parkinson's disease (Grimbergen et al. 2013). Additionally, N1 amplitude in younger adults is associated with lower balance ability (Payne and Ting 2020a), a hallmark of Parkinson's disease (Bloem 1992; Grimbergen et al. 2004; Koller et al. 1989). Further, in older adults N1 amplitude is associated with lower cognitive set shifting ability and greater antagonist muscle activity (Payne et al. 2021), both of which are associated with balance impairment in Parkinson's disease (Lang et al. 2019; McKay et al. 2018). All of these associations in unimpaired populations suggest the N1 would be larger in Parkinson's disease, related to greater cortical engagement to compensate for balance impairments, but there are also reasons to suspect the N1 might be reduced in Parkinson's disease. The N1 is localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015), which is the cortical node of the basal ganglia thalamocortical "motor circuit" that is impaired in Parkinson's disease (Albin et al. 1989; Alexander and Crutcher 1990; Alexander et al. 1991; Alexander et al. 1986). Further, the N1 resembles the more widely studied error-related negativity (Payne et al. 2019b), which is reduced in amplitude in Parkinson's disease (Seer et al. 2016). The error-related negativity is evoked by mistakes in cognitive tasks, depends on dopamine (de Bruijn et al. 2004; de Bruijn et al. 2006; Zirnheld et al. 2004) and connections to the basal ganglia (Ullsperger et al. 2014). A brief report on balance N1s in mild Parkinson's disease showed multiple component peaks (Dimitrov and Gatev 2001) resembling N1s in older adults without Parkinson's disease (Duckrow et al. 1999), but did not include a control group or measures of balance or cognitive function. Here we compare cortical N1s between people with and without Parkinson's disease, and test for associations with various measures of balance and cognitive function.

We hypothesized that the N1 response reflects neural processing related to both balance and cognitive function, and would therefore be altered in Parkinson's disease in association with balance and cognitive impairments. We evoked the cortical N1 response using unpredictable forward and backward translations of the support surface. We assessed the amplitude and temporal characteristics of the cortical N1, including the peak amplitude, latency, and width of the evoked component peak. We used multiple measures of balance and mobility, including the clinical miniBESTest (Leddy et al. 2011), the Timed Up and Go test (Beauchet et al. 2011), and measures of cognitive function, including the Montreal Cognitive Assessment (Nasreddine et al. 2005) and the Trail Making Test (McKay et al. 2018; Sanchez-Cubillo et al. 2009). Although we did not find differences in the cortical N1 responses between groups, within groups different features of the cortical N1 response were associated with balance and cognition in people with versus without Parkinson's disease.

MATERIALS AND METHODS

Study populations

Participants. Sixteen older adults with Parkinson's disease (PD, N=16, age 69±7, 4 female) and nineteen older adults without Parkinson's disease (noPD, N=19, age 71±6, 6 female) are included in analyses after exclusion of four participants detailed below. Written consent was obtained from all participants after a detailed explanation of the protocol according to procedures approved by the Emory University Institutional Review Board. Different analyses have been previously reported in the noPD control group (Payne et al. 2021).

OFF-medications. Individuals with PD participated in the experiment OFF their dopamine medications, practically defined as a minimum of 12 hours after their last dose of dopaminergic medication for PD. Each participant's neurologist was consulted and signed an OFF-medication clearance form before they were asked to withhold their medications for the purpose of this experiment. All clinical and behavioral measures were collected during the same OFF-medication session, with disease duration and compatibility with inclusion/exclusion criteria additionally verified in patient clinical records when available.

Participant recruitment. Participants were recruited from the community surrounding Emory University and the Emory Movement Disorders clinic through flyers, outreach events, word of mouth, and databases of prior participants from collaborating groups. Adults over age 55 were screened for the following inclusion criteria: vision can be corrected to at least 20/40 with glasses, no history of stroke or other neurological condition (except for PD), no musculoskeletal conditions or procedures that cause pain or limit mobility of the legs, ability to stand unassisted for at least 15 minutes, and cognitive ability to consent. Potential participants were excluded for prior experience on the perturbation platform, present cholinergic medications, or lack of neurologist's approval to withhold dopaminergic medications. Participants with PD were recruited first, and then the older adult control participants were recruited to maintain similar age and sex distributions between groups.

Four participants with PD were excluded after partial or complete participation in the study, resulting in the reported N=16 after an initial recruitment of N=20. Two were excluded due to a brain tumor or severe peripheral neuropathy of the legs noted in their clinical record. One was excluded due to failure to save the EEG data. One was unable to tolerate being OFF-medication and opted to leave prior to the balance perturbations.

Experimental protocol and data collection

Parkinson's disease motor symptom severity. The motor subscale of the International Parkinson and Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) was used to assess the severity of motor impairment in participants with PD (Goetz et al. 2007). The test was administered by AMP, who is certified by the Movement Disorders Society, and filmed for subsequent scoring by a practicing neurologist. Postural instability/gait difficulty subscores were determined from the items of the MDS-UPDRS III (Stebbins et al. 2013) and included in analyses. Hoehn & Yahr (H&Y) stage (Goetz et al. 2004), a 5 point rating scale of PD severity focused on postural instability, was determined by a neurologist from the recorded videos and included in analyses.

Parkinson's disease duration. Participants with PD were asked to report the number of years since PD diagnosis at the time of participating in the study, and this was verified in the clinical record when possible.

Balance ability. The miniBESTest (www.bestest.us) was used as a measure of balance ability (Leddy et al. 2011; Lofgren et al. 2017; Magnani et al. 2020) which assesses anticipatory postural control, reactive postural control, sensory orientation, and dynamic gait. For items that scored the left and right sides separately, only the lower of the two scores was considered for a maximum possible score of 28 (Lofgren et al. 2017).

Balance Confidence. The Activities-Specific Balance Confidence (ABC) Scale (Powell and Myers 1995) was used to assess balance confidence. This survey consists of sixteen items describing different situations that might lead to a loss of balance. For each item, participants are asked to indicate their confidence that they would not lose their balance in a particular setting by answering with a percentage between 0-100%. The average score across the 16 items is reported as the total score.

Mobility. The Timed Up and Go (TUG) test (Beauchet et al. 2011) was administered within the miniBESTest, and additionally scored in more detail than considered within the miniBESTest. Participants begin seated in a chair with arms in their lap, and when told to "Go," must get up, walk at their comfortable speed across the lab, around a cone, and come back to a seat in the starting chair. This test is timed, and then repeated with a dual task of counting backward by 3s out loud. While the miniBESTest only scores this item categorically, based on whether participants were able to complete the dual task condition, and if so, whether it resulted in more or less than a 10% reduction in speed, we included additional continuous measures in our analyses. Specifically, we included the TUG single task time (TUG-ST), dual task time (TUG-DT), and dual task interference (DTI) calculated as the difference between the single and dual task times divided by the single task time and multiplied by 100 (Kelly et al. 2010; Palmer et al. 2021). A more negative value for DTI indicates a greater reduction in speed during the dual task condition. Two individuals with Parkinson's disease were unable to complete the TUG-ST or TUG-DT due to mobility impairments including freezing of gait, and an additional two individuals were able to complete TUG-ST but not TUG-DT. These individuals are therefore excluded from the corresponding continuous measures, but could be appropriately scored on the miniBESTest.

Overall cognition. The Montreal Cognitive Assessment (MoCA, www.mocatest.org) was used to measure overall cognitive ability, including executive function, attention, and memory (Hoops et al. 2009; Nasreddine et al. 2005). Years of education was self-reported.

Cognitive set shifting ability. The set shifting ability score was measured as the difference in time to complete Part B minus Part A of the Trail Making Test (McKay et al. 2018; Payne et al. 2021; Sanchez-Cubillo et al. 2009), where a longer time to complete Part B compared to Part A indicates lower cognitive set shifting ability.

Perturbations. A series of 48 translational support-surface perturbations of unpredictable timing, direction, and magnitude were delivered during quiet standing (Payne et al. 2021). Perturbations consisted of forward and backward perturbation directions and three magnitudes. The low magnitude (0.15 g, 11.1 cm/s, 5.1 cm) was identical across participants, while the medium (0.21-0.22 g, 15.2-16.1 cm/s, 7.0-7.4 cm) and high (0.26-0.29 g, 19.1-21.0 cm/s, 8.9-9.8 cm) magnitudes were adjusted according to participant height as previously described (Payne et al. 2021) to account for the effect of height on the cortical responses (Payne et al. 2019a) and to ensure that the more challenging perturbations were more mechanically similar across different body sizes. Perturbation characteristics for an example participant are shown in Figure 1.

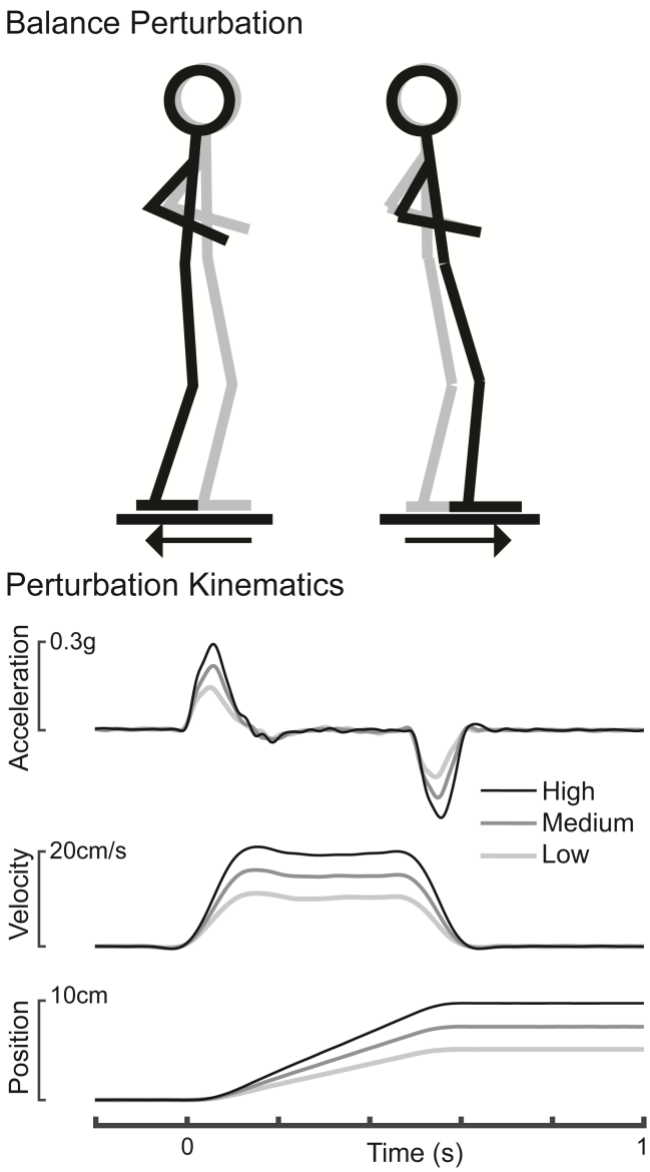

Figure 1. Balance perturbations. A schematic shows the support-surface perturbation along with perturbation kinematics for an example participant (194 cm in height).

To minimize effects of fatigue, a 5-minute break was enforced halfway through the perturbation series, or more frequently without limitations if requested. Excluding rest breaks, the duration of the perturbation series was 21±2 minutes (PD: 20±1 minutes; noPD: 21±2 minutes). Inter-trial-intervals, measured between perturbation onsets, excluding rest breaks longer than a minute, were 23±12 seconds (PD: 23±13 s; noPD: 23±12 s).

Recording artifacts were minimized by ensuring that perturbations were only initiated during a relatively quiescent baseline in the live electroencephalography (EEG) data based on visual inspection. Participants were instructed maintain their arms crossed across their chest, focus their vision on a poster of a mountain landscape 4.5 m ahead, and to do their best to recover balance without taking a step. Trials in which steps were taken (8% of all trials; PD: 9%; noPD: 8%) were excluded from analysis.

Cortical activity. EEG data were collected during the perturbation series as previously described (Payne et al. 2021). Thirty-two active electrodes (ActiCAP, Brain Products, Germany) were placed according to the international 10-20 system, except for two reference electrodes placed on the mastoid bones behind the ears. Electrodes were prepared with conductive gel (SuperVisc 100 gr. HighViscosity Electrolyte-Gel for active electrodes, Brain Products) using a blunt-tipped syringe that was also used to abrade the skin to reduce impedances. Impedances at Cz and mastoid electrodes were generally below 10 kOhm prior to data collection.

Electrooculography (EOG) data were collected to enable subtraction of eye-related artifacts. Bipolar passive electrodes (E220x, Brain Products) were prepared with abrasive gel (ABRALYT HiCl 250 gr., High-chloride-10% abrasive electrolyte gel, Brain Products) and placed above and below the right eye and referenced to a similar electrode on the forehead. EEG and EOG data were sampled at 1000 Hz on an ActiCHamp amplifier (Brain Products) with a 24-bit A/D converter and an online 20 kHz anti-aliasing low-pass filter.

EEG and EOG data were filtered between 1 Hz and 25 Hz using sixth-order zero-lag Butterworth filters. Cz data were then re-referenced to the mastoids and epoched between 400 ms before to 2000 ms after perturbation onset (defined based on recorded platform acceleration, Figure 1). Blink and vertical eye movements were subtracted using a serial regression and subtraction approach (Gratton et al. 1983) as previously described (Payne et al. 2019a). Cz epochs were then averaged across non-stepping trials within each individual and baseline subtracted using a baseline of 50-150 ms before perturbation onset.

Cortical N1 response amplitudes and latencies were quantified as amplitude and latency of the most negative point between 100-200 ms after perturbation onset in the subject-averaged EEG waveform at Cz. Because the waveform shape differed to a large extent between individuals, often containing multiple peaks, but not consistently enough to enable measurement of a distinctly identifiable additional peak across individuals (Figure 2 CD), cortical N1 width was assessed using the full-width half-maximum. Specifically, the duration that the N1 response continuously maintained at least half of its most negative amplitude was measured for each individual.

Statistical Analyses

Between-group comparisons. Two-tailed t-tests were used to test for differences between PD and noPD groups for the following variables: age, height, weight, balance ability (miniBESTest), balance confidence (ABC Scale), overall cognition (MoCA), years of education, N1 peak amplitudes, N1 peak latencies, and N1 peak widths. PROC TTEST in SAS was used for t-tests, including the Satterthwaite correction in cases of unequal variances. Fisher's exact test of independence was used to test for sex differences between groups using the two-sided table probability in PROC FREQ in SAS.

Within-group associations. Simple linear regressions were used to test for correlations between pairs of study variables (listed below) within the PD and noPD groups separately. Parameter estimates for the regression slopes were compared against the hypothesized value 0 with two-tailed t-tests using PROC GLM in SAS. Variables that violated the assumption of normality (Shapiro-Wilk test p-values<0.05) were transformed to a normal distribution prior to regression using boxcox.m in MATLAB. Figures display original, untransformed data points with p-values and R^2 values from the adjusted variables when appropriate. All R^2 values are adjusted R^2 values. Tables include Cohen's F^2 measure of effect size (Cohen 1992) for all simple linear regressions.

Within the noPD group, linear regressions were used to test for correlations between cortical response variables (N1 peak amplitude, latency, and width) and age, balance ability,

balance confidence, TUG single task time, TUG dual task time, TUG dual task interference, years of education, overall cognition, and cognitive set shifting ability.

Within the PD group, linear regressions were used to test for correlations for all of the variables listed above, as well as PD duration, MDS-UPDRS-III motor symptom severity, and postural instability/gait difficulty scores. Fisher's exact test of independence was used to test for associations between dichotomized cortical response variables (median split) and Hoehn & Yahr stage (split between N=10 at stage 2 and N=6 at stages more severe than 2). Additionally, because postural instability/gait difficulty scores were distributed approximately as a negative binomial distribution, tests of association between cortical responses and postural instability/gait difficulty scores were repeated with a negative binomial regression using PROC GENMOD on the untransformed score in SAS (McKay et al. 2021).

Principal components analysis. Because cortical responses were correlated with multiple measures of balance and cognitive function in the PD group (Figure 4), and because many of these variables were correlated with one another (Supplemental Information), we performed a probabilistic principal components analysis (probabilistic PCA, using ppca.m in MATLAB) to reduce the dimensionality of the covariate space. Probabilistic PCA is an established extension of PCA that is able to accommodate small numbers of missing values (i.e., two missing values for TUG-ST and four missing values for both TUG-DT and DTI from individuals unable to complete the tasks). The following variables were centered and scaled and entered into the probabilistic PCA: age, MDS-UPDRS-III motor symptom severity, Hoehn & Yahr stage, balance ability, balance confidence, TUG single task time, TUG dual task time, TUG dual task interference, years of education, overall cognition, and cognitive set shifting ability. The first two principal components accounted for 44% (PC1) and 19% (PC2) of the total variance of the regression variables. We refer to these PCs as balance and cognitive constructs, respectively, based on the fact that balance-related variables were represented strongly in PC1 and cognitive-related variables were represented strongly in PC2 (Figure 5).

Construct multiple linear regression. Each cortical response variable (N1 peak amplitude, latency and width) was entered into a separate multivariate regression including the balance construct, the cognitive construct, and PD duration as simultaneous predictors using PROC GLM in SAS. PD duration was otherwise excluded from the principal component analysis so it could be used as a measure of PD status independent of the cognitive or motor presentation of the disease. Figures display simple linear regressions between cortical response variables and the balance and cognitive construct variables with p-values from the multivariate regression. No outcomes differed between univariate and multivariate regressions. The corresponding table displays Cohen's F^2 value for the association between each cortical response variable and each predictor using a modified formula that considers the R^2 value from the full model relative to the model that leaves out the variable of interest (Selya et al. 2012).

RESULTS

The group with Parkinson's disease had lower balance ability and balance confidence

Table 1. Group characteristics.

	noPD (N=19)	PD (N=16)
Age (years)	71 ± 6	69 ± 7
Gender (male/female, % female)	13 / 6, 32%	12 / 4, 25%
Height (cm)	175 ± 10	171 ± 11
Weight (kg)	79 ± 16	85 ± 25
miniBESTest (/28)	**25 ± 2**	**21 ± 6**
Balance Confidence	**94 ± 4**	**75 ± 25**
Montreal Cognitive Assessment	26 ± 3	25 ± 3
Education (years)	17 ± 2	17 ± 2
MDS-UPDRS-III		31 ± 15
PD Duration		6 ± 3

Note: Bold text indicates significant group differences at $p<0.05$.

Participant groups (Table 1) did not differ in age ($p=0.44$), gender distribution ($p=0.72$), height ($p=0.30$), or weight ($p=0.39$). The PD group had lower balance ability ($p=0.027$, Cohen's $d=0.81$) and balance confidence ($p=0.008$, $d=0.98$) than the noPD control group, but did not differ in overall cognition ($p=0.41$) or years of education ($p=0.84$).

Cortical N1 responses were similar between groups

Cortical N1 responses were similar between groups (Figure 2). There was a nonsignificant trend for earlier N1 peak latencies in the PD group (PD: 170±19 ms, noPD: 182±18 ms, $p=0.062$, $d=0.63$). N1 peak amplitudes (PD: 28±16 μV, noPD: 30±15 μV, $p=0.66$, $d=0.15$) and widths (full-width half-maximum, PD: 69±29 ms, noPD: 85±39 ms, $p=0.17$, $d=0.47$) were similar between groups.

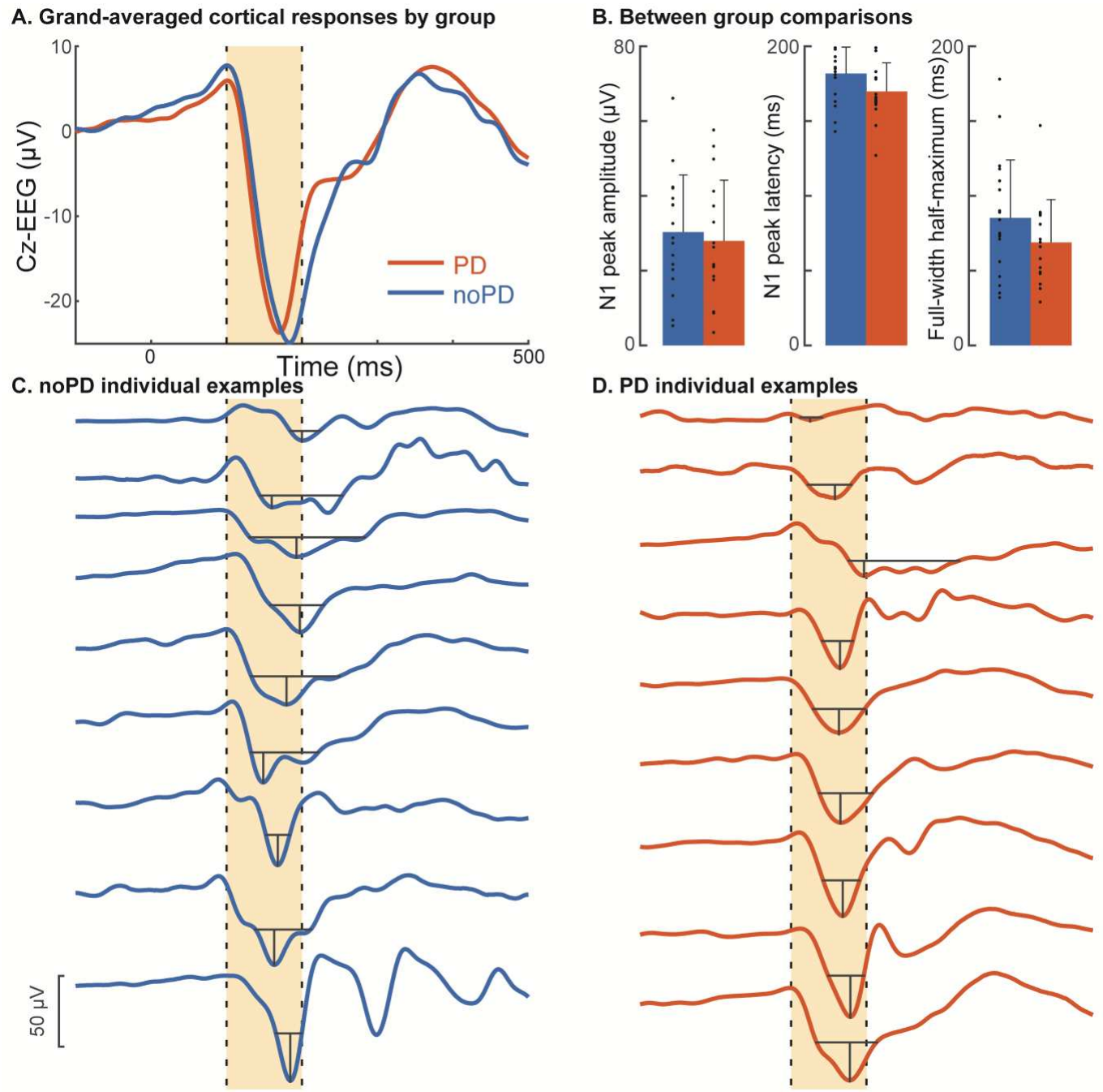

Figure 2. Differences in N1 responses between noPD and PD groups. (A) Grand-averaged cortical responses for each participant group. The yellow shaded region indicates the 100-200 ms window in which N1 peak amplitudes and latencies were quantified. (B) Bar plots show means and standard deviations of N1 peak amplitudes, latencies, and widths by group. Dots show individual data points. The lower panels show individual examples of subject-averaged cortical N1 responses at Cz in (C) the noPD control group and (D) the PD group. N1 peak amplitudes and latencies are indicated by vertical black lines and the duration of the full-width half maximum is indicated by horizontal black lines.

<u>In the control group, N1 amplitudes were associated with higher balance confidence and lower cognitive set shifting ability</u>

Table 2. Associations between cortical responses and other variables in the control group.

noPD group	N1 Amplitude		N1 Latency		N1 Width	
	F^2	p	F^2	p	F^2	p
Age	0.05	0.378	0.07	0.284	0.05	0.388
miniBESTest	0.00	0.928	0.02	0.551	0.05	0.379
Balance Confidence	**0.35**	**0.026**	0.01	0.753	0.09	0.226
TUG-Single Task	0.19	0.091	0.05	0.367	0.09	0.238
TUG-Dual Task	0.10	0.215	0.02	0.605	0.00	0.959
Dual Task Interference	0.04	0.448	0.04	0.419	0.01	0.676
Education	0.01	0.674	0.00	0.833	0.02	0.570
Montreal Cognitive Assessment	0.02	0.580	0.02	0.555	0.25	0.057
Cognitive Set Shifting	**0.57**	**0.006**	0.12	0.175	0.03	0.500

Note: Bold text indicates significant associations at $p<0.05$. Cohen's $F^2>0.35$ indicates a large effect and $F^2>0.15$ indicates a medium effect. TUG: Timed Up and Go

In the noPD group, larger N1 amplitudes were correlated with lower balance confidence (Figure 3A, p=0.026, R^2=0.26, F^2=0.35). As reported previously (Payne et al. 2021), larger N1 amplitudes were correlated with lower cognitive set shifting ability (p=0.006, R^2=0.37, F^2=0.57). Balance confidence was not associated cognitive set shifting ability (p=0.25). N1 amplitude, latency, and width were not associated with any other tested variables in the noPD group (Table 2). These associations were not observed in the PD group (Figure 3B and Table 3).

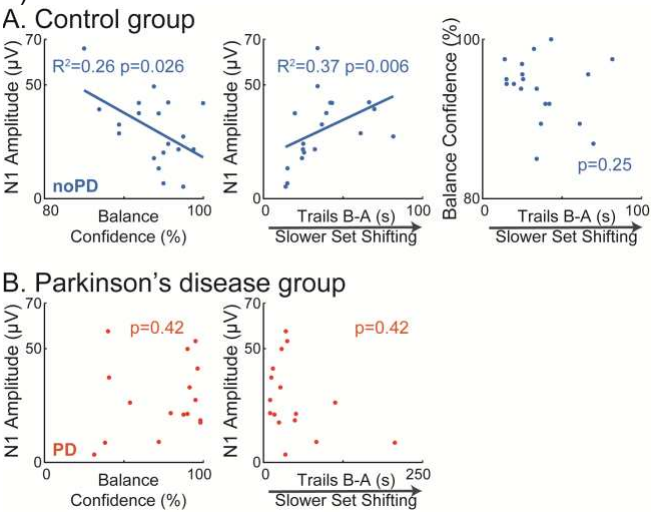

Figure 3. Relationships between cortical responses and clinical variables. (A) In the control group (noPD), N1 amplitudes were correlated with lower balance confidence and slower cognitive set shifting. Balance confidence and cognitive set shifting were not correlated with one another. (B) The group with Parkinson's disease (PD) did not share these associations between N1 amplitude and balance confidence or cognitive set shifting. Plots show original data with statistics obtained from transformed variables when appropriate.

N1s were associated with multiple overlapping measures of balance and cognitive function in the group with Parkinson's disease

Table 3. Associations between cortical responses and other variables in the group with Parkinson's disease.

PD group	N1 Amplitude		N1 Latency		N1 Width	
	F^2	p	F^2	p	F^2	p
Age	**0.41**	**0.031**	0.02	0.590	0.00	0.805

PD Duration	0.02	0.626	0.00	0.812	0.01	0.698
PD Motor Severity (MDS-UPDRS-III)	0.00	0.882	0.03	0.507	0.29	0.062
PD Stage (Hoehn & Yahr)	-	1.000	-	0.119	**-**	**0.007**
Postural Instability/Gait Difficulty	0.01	0.719	0.10	0.255	**0.57**	**0.013**
miniBESTest	0.07	0.352	**0.39**	**0.035**	**0.35**	**0.044**
Balance Confidence	0.05	0.416	**0.42**	**0.029**	**0.76**	**0.006**
TUG-Single Task	0.00	0.919	0.14	0.216	**1.00**	**0.005**
TUG-Dual Task	0.03	0.599	0.02	0.649	0.27	0.132
Dual Task Interference	0.07	0.410	0.13	0.284	0.00	0.912
Education	**0.69**	**0.008**	0.00	0.907	0.10	0.253
Montreal Cognitive Assessment	0.03	0.500	0.11	0.240	**0.53**	**0.016**
Cognitive Set Shifting	0.05	0.422	0.16	0.157	0.19	0.130

Note: Bold text indicates significant associations at $p<0.05$. Cohen's $F^2>0.35$ indicates a large effect and $F^2>0.15$ indicates a medium effect. MDS-UPDRS: Movement Disorder Society's Unified Parkinson's Disease Rating Scale; TUG: Timed Up and Go

In the PD group, cortical N1 responses were associated with overlapping measures of balance and cognitive function (Table 3, Figure 4). Larger N1 amplitudes were correlated with younger age (p=0.031, R^2=0.29, F^2=0.41) and fewer years of education (p=0.008, R^2=0.41, F^2=0.69). Longer N1 latencies were correlated with higher clinical balance ability (p=0.035, R^2=0.28, F^2=0.39) and higher balance confidence (p=0.029, R^2=0.30, F^2=0.42). Narrower N1 peak widths were associated with more severe Hoehn & Yahr disease stages (Fisher's exact test, p=0.007), more severe postural instability/gait difficulty scores (linear regression p=0.013, R^2=0.36, F^2=0.57, negative binomial regression p=0.033), lower mobility (slower single task TUG, p=0.005, R^2=0.50, F^2=1.00), lower balance ability (p=0.044, R^2=0.26, F^2=0.35), lower balance confidence (p=0.006, R^2=0.43, F^2=0.76), and lower overall cognitive ability (Montreal Cognitive Assessment, p=0.016, R^2=0.35, F^2=0.53). The cortical N1 responses were not associated with the other tested variables in the PD group (Table 3).

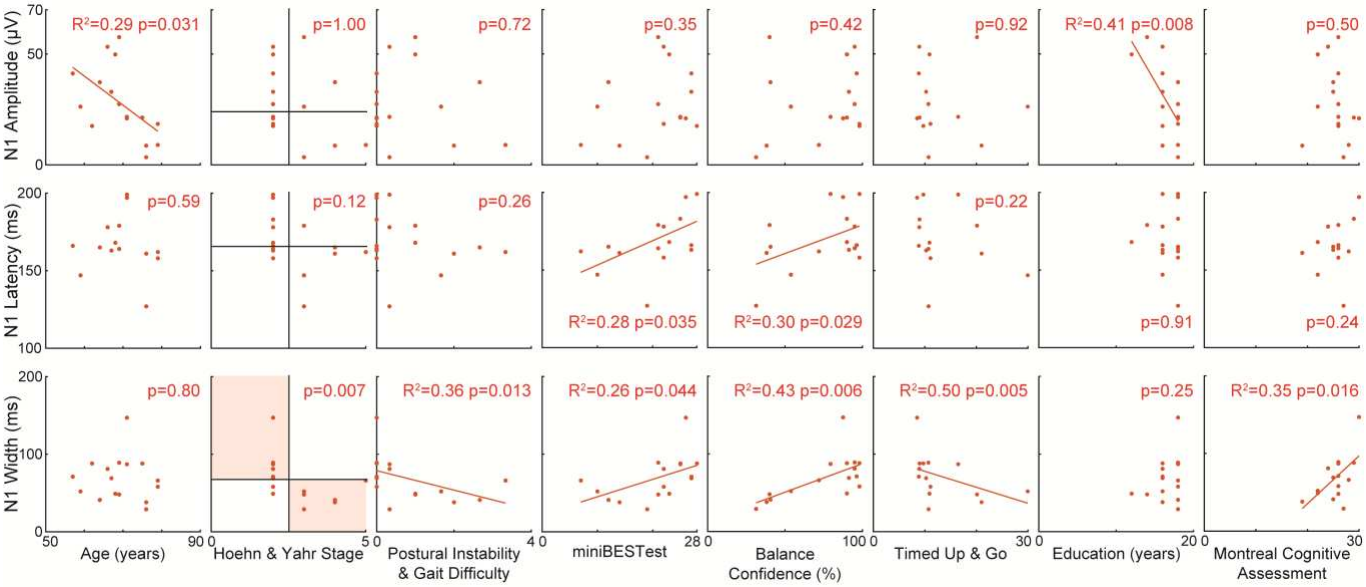

Figure 4. Associations between N1 measures and other variables in the PD group. Plots show original data with statistics obtained from transformed variables when appropriate.

Principal components analysis was applied to the dataset to reduce the number of comparisons and to account for covariation between the tested variables. Correlations between all pairs of tested variables are reported in Supplemental Information. The first two principal components accounted for 44% and 19% of the variance of the dataset and were labeled as the balance and cognitive constructs based on the variables most heavily represented in the components (Figure 5).

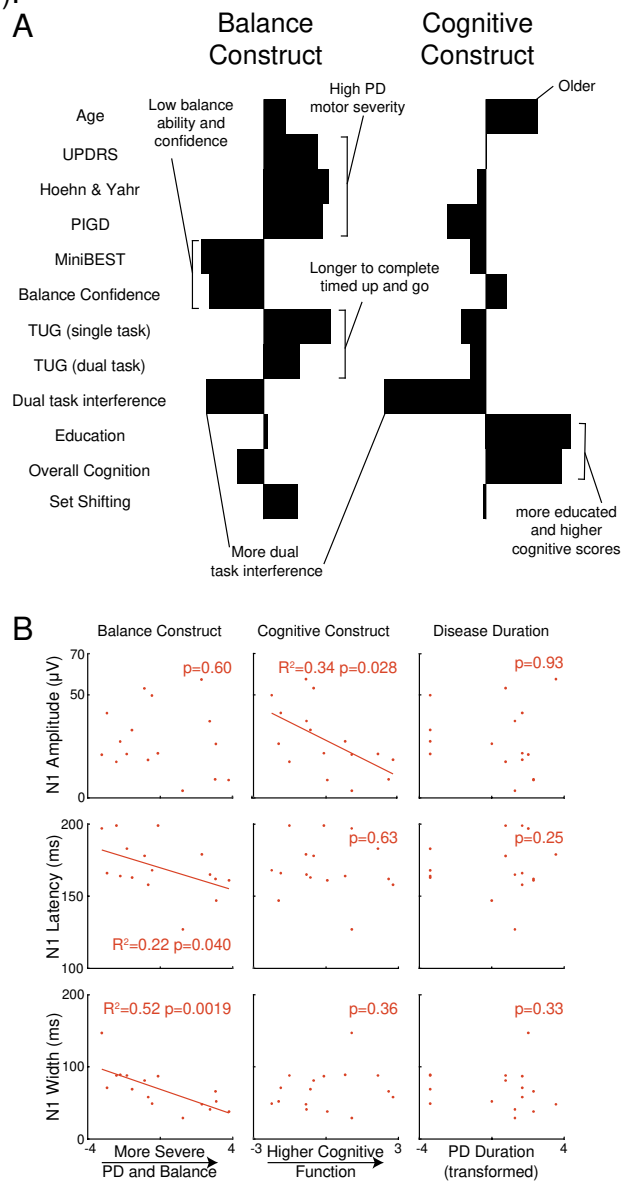

Figure 5. Principal component constructs and their correlations to features of the N1 response in Parkinson's disease. (A) The first two principal components were labeled the balance and cognitive constructs (44% and 19% of total variance, respectively) based on the variables represented. Note that cognitive set-shifting is more heavily represented in the balance rather than cognitive construct, and that cognitive-motor dual task interference is represented in both components. (B) Univariate regressions are displayed along with statistics derived from the multivariate regressions in which the balance and cognitive constructs and PD duration were entered as simultaneous predictors of each of N1 measures. No outcomes differed between univariate and multivariate models. UPDRS: Movement Disorder Society's Unified Parkinson's Disease Rating scale (part III, motor symptom severity); PIGD: Postural Instability/Gait Difficulty; TUG: Timed Up and Go

The N1 amplitudes were associated with the cognitive construct (Table 4, Figure 5), while the N1 peak latency and peak width were associated with the balance construct. In a multivariate regression, larger N1 amplitudes were correlated with the cognitive construct (lower cognitive function, $p=0.028$, $F^2=0.52$), but not the balance construct ($p=0.60$) or PD duration ($p=0.93$) included in the same model. Shorter N1 peak latencies were correlated with the balance construct (higher PD severity and lower balance function, $p=0.040$, $F^2=0.44$) but not the cognitive construct ($p=0.63$) or PD duration ($p=0.25$). Narrower N1 peak widths were also correlated with the balance construct (higher PD severity and lower balance function, $p=0.002$, $F^2=1.31$) but not the cognitive construct ($p=0.36$) or PD duration ($p=0.33$). Figure 5 displays univariate regressions between the N1 measures and balance and cognitive constructs with the statistics from the multivariate regressions. No outcomes differed between univariate and multivariate regressions.

Table 4. Associations between cortical responses and construct variables in the group with Parkinson's disease.

	N1 Amplitude		N1 Latency		N1 Width	
	F^2	p	F^2	p	F^2	p
Balance construct	0.02	0.601	**0.44**	**0.040**	**1.31**	**0.002**
Cognitive construct	**0.52**	**0.028**	0.02	0.628	0.07	0.363
PD Duration	0.00	0.929	0.12	0.245	0.08	0.334

Note: Statistics refer to multivariate regressions where the three row variables are entered as simultaneous predictors of the corresponding column variable. Bold text indicates significant associations at $p<0.05$. Cohen's $F^2>0.35$ indicates a large effect and $F^2>0.15$ indicates a medium effect.

DISCUSSION

This is the first paper to compare the balance perturbation-evoked cortical N1 response between people with and without Parkinson's disease. N1 responses were similar in amplitude, latency, and peak width between groups, but were associated with different aspects of balance and cognition in older adults with versus without Parkinson's disease. We previously reported that larger N1 responses were associated with lower cognitive set shifting ability in older adults (Payne et al. 2021), and we now add with the present study that the larger N1 responses are associated with lower balance confidence in the same group of older adults. However, N1 responses in the group with Parkinson's disease did not share these associations with cognitive set shifting or balance confidence, but rather were associated with multiple overlapping measures of balance and cognitive function. Within the Parkinson's disease group, balance and cognitive variables were statistically grouped into distinct constructs that were differentially associated with distinct features of the N1 responses. Larger N1 amplitudes in the group with Parkinson's disease were correlated with lower cognitive function, while earlier and narrower N1 peaks were correlated with balance impairments and greater parkinsonian motor symptom severity. Our results show that balance and cognitive impairments are dissociable and associated with distinct features of the N1 response, suggesting the N1 response reflects coordination of distinct mechanisms for balance and cognitive function. A better understanding of the neural mechanisms underlying the cortical N1 response may facilitate the development of more targeted rehabilitation for individuals with comorbid balance and cognitive impairments.

The lack of differences in N1 peak amplitude, latency, or width at the group level suggests there is no specific effect of Parkinson's disease or dopamine depletion on the cortical N1 response. There were several reasons to suspect that the N1 amplitude would be either increased or decreased in people with Parkinson's disease, with the direction of the effect potentially shedding light on mechanisms underlying the cortical N1 response. For example, we would expect larger N1 amplitudes in people with Parkinson's disease based on prior findings of larger N1 amplitudes in young adults who have lower balance ability (Payne and Ting 2020a) and in older adults who have lower cognitive set shifting ability (Payne et al. 2021). However, comparison between the N1 and the error-related negativity would lead to the prediction of smaller N1 amplitudes in people with Parkinson's disease. The error-related negativity is a cortical response evoked by errors in cognitive tasks and is frequently compared to the N1 based on similar scalp distribution and dependencies on motivation, perceived consequences, perceptual salience, expectation, development, and aging (Payne et al. 2019b). Importantly, the error-related negativity is a dopamine-dependent phenomenon that is reduced in amplitude in people with Parkinson's disease (Seer et al. 2016) and bidirectionally modulated in amplitude by dopamine agonists or antagonists in young adults (de Bruijn et al. 2004; de Bruijn et al. 2006; Zirnheld et al. 2004). Thus, we would expect smaller N1 amplitudes in Parkinson's disease if the N1 shares the dopamine-dependent mechanism that underlies the error-related negativity. However, the N1 responses were similar between individuals with versus without Parkinson's disease, failing to support either of these possibilities. While we cannot rule out the possibility that an enhanced N1 due to lower balance and cognitive abilities is counteracted by an attenuation of the N1 response due to dopamine depletion in Parkinson's disease, the present data provide no evidence to suggest that the cortical N1 response depends on dopamine function or the basal ganglia and brainstem centers that are affected by Parkinson's disease.

In the older adult control group, N1 amplitudes were associated with cognitive function but not balance function. The present finding that N1 amplitudes are larger in older adults with lower balance confidence is consistent with prior findings that N1 amplitudes are larger in young adults under more threatening contexts (Adkin et al. 2008; Mochizuki et al. 2010). Although

there is not a direct parallel to the increased N1 amplitudes in older adults with lower cognitive set shifting ability, this finding adds another line of evidence connecting the N1 to cognitive processing, in addition to effects of surprise (Adkin et al. 2008; Mochizuki et al. 2010) and attention (Little and Woollacott 2015; Quant et al. 2004b) that have been shown to influence the N1 in young adults. The lack of association between N1 amplitudes and balance ability in the older adult group is in contrast to prior findings of larger N1 amplitudes in young adults with lower balance ability (Payne and Ting 2020a). However, balance ability was measured quite differently between these studies, using an extremely difficult continuous beam walking task in the young adults and an itemized clinical balance ability scale in the older adults. Unlike the continuous measure of balance ability used in young adults (Payne and Ting 2020a; Sawers and Ting 2015), the clinical balance test was designed to characterize balance disability in older adults upon arrival for balance rehabilitation (Franchignoni et al. 2010; Horak et al. 2009) and displayed a ceiling effect with scores clustered near the top of the range in our unimpaired older adult population (Payne et al. 2021). While it is possible that the N1 amplitudes would relate to a more challenging metric of balance ability in older adults, it is also possible that this reflects a difference in the N1 response between younger and older adult populations. This also suggests that the cortical N1 response may differ from other measures of brain activity during balance recovery, such as beta frequency (13-30 Hz) power, which is associated to both beam walking in young adults (Ghosn et al. 2020) and clinical balance ability in older adults (Palmer et al. 2021).

Distinct features of the N1 responses were associated with dissociable balance and cognitive constructs in Parkinson's disease, suggesting the N1 response may reflect a coordination of separable mechanisms related to balance and cognitive impairments. Based on associations between balance and cognitive decline in aging populations (Allcock et al. 2009; Camicioli and Majumdar 2010; Gleason et al. 2009; Herman et al. 2010; Mak et al. 2014; Mirelman et al. 2012), and prior associations between the N1 and balance (Payne and Ting 2020a) and cognitive (Payne et al. 2021) abilities, we hypothesized that the N1 response might reflect a single mechanism linking balance and cognition. Instead, our construct analysis, which resolved issues of multiple comparisons across covarying measures, revealed that our balance and cognitive measures were largely dissociable, and related to distinct features of the N1 response. Specifically, larger N1 amplitudes were associated with lower cognitive abilities, whereas earlier and narrower N1 peaks were associated with lower balance ability and greater parkinsonian motor symptom severity, suggesting the N1 relates to balance and cognitive function through distinct mechanisms. Although larger N1 amplitudes were associated with lower cognitive function in both groups, these associations differed in that cognitive set shifting, which was associated with N1 amplitudes in control group, was not represented in the cognitive construct that associated with N1 amplitudes in the group with Parkinson's disease. Instead, cognitive set shifting was represented in the balance construct, consistent with prior work linking cognitive set shifting ability to balance function in older adults (Payne et al. 2021) and to fall history in older adults with and without Parkinson's disease (McKay et al. 2018). Additionally, the cognitive construct represented an association between lower postural instability/gait difficulty scores and higher cognitive function, consistent with longitudinal work showing that postural instability/gait difficulty develops in tandem with accelerated cognitive decline in Parkinson's disease (Alves et al. 2006). The association between temporal features of the N1 response and balance ability in the group with Parkinson's disease is in contrast to the association between N1 amplitude and balance ability in young adults (Payne and Ting 2020a), but this is not the first study to link motor ability to temporal features of the N1 response (Duckrow et al. 1999). Despite different relationships across populations, the present results suggest that the N1 response reflects neural processes related to both balance and cognition, which could provide insight into the associations between balance and cognitive decline in aging populations.

We speculate that the N1 response reflects neural processes at the intersection of balance and cognitive function that could explain relationships between balance and cognitive impairments and their overlapping responses to treatment in aging populations. Although we are unable to separate and localize the underlying neural sources due to our limited electrode set, studies in young adults have shown that multiple neural sources synchronize during the N1 response (Peterson and Ferris 2018; 2019; Varghese et al. 2019). It is possible that the differences in N1 associations to balance and cognitive behaviors across populations reflect differences in the relative contributions of the multiple neural sources underlying the N1 response across populations. Additionally, the appearance of multiple component peaks in older populations (Dimitrov and Gatev 2001; Duckrow et al. 1999; Payne et al. 2021) could arise due to reduced synchronization or coordination between these underlying neural sources. It is possible that changes in the interactions between neural processes involved in balance and cognition could underlie associations between balance and cognitive declines in aging populations (Allcock et al. 2009; Camicioli and Majumdar 2010; Gleason et al. 2009; Herman et al. 2010; Mak et al. 2014; Mirelman et al. 2012), and might explain reciprocal crossover benefits between balance and cognitive rehabilitation (Hagovska and Olekszyova 2016; Kraft 2012; Manor et al. 2018; Smith-Ray et al. 2015). If the N1 response reflects neural processes at the intersection of balance and cognition, a deeper understanding of the underlying mechanisms could facilitate the development of more targeted rehabilitation for individuals with comorbid balance and cognitive impairments.

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