PERTURBATION-EVOKED CORTICAL RESPONSES ARE ASSOCIATED WITH BALANCE ABILITY IN HEALTHY YOUNG ADULTS AND IN OLDER ADULTS WITH PARKINSON'S DISEASE

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PERTURBATION-EVOKED CORTICAL RESPONSES ARE ASSOCIATED WITH BALANCE ABILITY IN HEALTHY YOUNG ADULTS AND IN OLDER ADULTS WITH PARKINSON'S DISEASE

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LIST OF SYMBOLS AND ABBREVIATIONS

ACC	Anterior cingulate cortex
cm	centimeters
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ERN	Error-related negativity
ERP	Event related (brain) potential
g	(units of) gravity
HYA	Healthy young adult
MG	Medial gastrocnemius
MiniBESTest	Mini Balance Evaluation Systems Test
MoCA	Montreal Cognitive Assessment
ms	milliseconds
N1	The first negative peak in perturbation-evoked cortical responses
noPD	The control group of healthy older adults
PD	Parkinson's disease
s	seconds
SAS	Statistical Analysis Software (registered trademark)
SC	Sternocleidomastoid muscle
SMA	Supplementary motor area
TA	Tibialis anterior muscle
μV	microvolts

SUMMARY

Balance and cognitive impairments negatively impact quality of life in old age and in Parkinson's disease (PD) and are associated through unknown mechanisms. Measuring brain activity during reactive balance recovery may yield insight into the relationship between balance and cognitive function, facilitating the development of better treatment strategies. Electroencephalography (EEG) recordings show that sudden perturbations to standing balance reliably evoke a cortical N1 response localized to the supplementary motor area. The cortical N1 response is known to be influenced by cognitive processes because it is smaller when perturbations are predictable and enhanced when people are afraid or paying more attention to balance. Because the cortical N1 response is evoked by balance perturbations and influenced by cognition, it has the potential to reflect a site of interaction between balance and cognitive function. Despite knowledge of these cognitive influences on the cortical N1 response, there are no existing theories of how the cortical N1 response might influence subsequent balance recovery behavior. Through a series of studies, I present a novel hypothesis that perturbation-evoked cortical responses reflect cortical contributions to balance recovery, which are greater in people with lower balance ability. First, I show in healthy young adults (HYA) that a very small proportion of the cortical N1 response amplitude can be explained by the magnitude of sensory inputs, and that cortical N1 responses differ to a much larger extent between individuals. Then, I demonstrate that cortical N1 responses are larger for HYA who have lower balance ability, and that the cortical N1 response is larger when people take compensatory steps, suggesting that the cortical N1 response may reflect the need for cortically-mediated compensatory

motor outputs. Then, I show that perturbation-evoked cortical responses in older adults with and without PD contain two component peaks, with smaller amplitudes of the second peak reflecting balance impairment in PD. Finally, I show that perturbation-evoked cortical responses are impacted by PD in a different manner than a related cortical response called the error-related negativity, which occurs when mistakes are made in computer-based cognitive tasks. The basic science work presented in this thesis may inform future studies into the relationship between balance and cognitive impairments, thereby facilitating the development of better rehabilitation strategies for balance impairments in Parkinson's disease.

CHAPTER 1. INTRODUCTION

Balance and cognitive impairments negatively impact quality of life in old age and in Parkinson's disease (PD) and are associated through unknown mechanisms. Falls due to loss of balance are the leading cause of unintentional injury death in adults over 65 (CDC 2013), and those with PD fall at 5 times the rate of age-matched adults (Dimitrova et al. 2004), with 70% of PD patients falling at least once a year (Grimbergen et al. 2004). Balance problems are particularly disabling in PD (Bloem 1992; Grimbergen et al. 2009), respond poorly to antiparkinsonian medication (Bloem 1992; Grimbergen et al. 2009; Grimbergen et al. 2004), and contribute to falls (Grimbergen et al. 2004), which increase healthcare costs (Grimbergen et al. 2004) and reduce health-related quality of life (Grimbergen et al. 2004; Grimbergen et al. 2013). Balance impairment is associated with cognitive impairment, but the mechanisms underlying this association are unknown (Bolton 2015; Sollinger et al. 2010). Specifically, executive dysfunction predicts new (Herman et al. 2010) and recurrent (Mak et al. 2014) falls in PD, and postural instability predicts the development of dementia (Alves et al. 2006). Further, cognitively engaging balance rehabilitation improves balance in PD (McKay et al. 2016; Petzinger et al. 2013) and healthy aging (Kraft 2012; Wu et al. 2016). A better understanding of the mechanisms underlying the relationship between balance and cognition would enable the development of more targeted rehabilitation strategies.

Measuring brain activity during reactive balance recovery may yield insight into cortical contributions to balance recovery. The primary experimental model in this thesis is reactive balance recovery evoked by sudden sliding perturbations of the floor beneath

standing human subjects. A sudden balance perturbation evokes an involuntary balance-correcting motor response 100 ms later (Carpenter et al. 1999; Welch and Ting 2009; 2008), which can be followed by increasingly voluntary behaviors at longer latencies (Jacobs and Horak 2007a). A cortical N1 response localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015) occurs simultaneous to the involuntary balance-correcting motor response, but it is unclear whether the cortical N1 response has any functional role in balance recovery. This cortical response is thought to reflect sensory processing of a balance disturbance (Dietz et al. 1985b; 1984b; 1984a; Dietz et al. 1985a; Staines et al. 2001), but it is also affected by cognitive processes including attention (Little and Woollacott 2015; Quant et al. 2004b), perceived threat (Adkin et al. 2008; Adkin et al. 2006; Mochizuki et al. 2010; Sibley et al. 2010), and predictability (Adkin et al. 2008; Adkin et al. 2006; Mochizuki et al. 2010; Mochizuki et al. 2008), suggesting that this response my reflect activation of a brain area with a cognitively-dependent role in balance correction.

Measuring brain activity in cognitive tasks yields quantitative and temporally precise information about executive cognitive functions. While relatively little is known about the perturbation-evoked cortical N1 response, an immense literature exists relating cortical responses in other contexts to cognitive function. Computer-based cognitive tasks evoke cortical markers of executive function that provide quantitative and temporally precise information about attention, action and response monitoring, reward processing, visuospatial working memory, and other cognitive functions (Downes et al. 2017). The perturbation-evoked cortical response appears to resemble a particular cognitive marker called the error-related negativity (ERN), which reflects recognition of a self-committed

error, and relates to action correction (Falkenstein et al. 1990; Gehring et al. 2018; 1993). The following chapter reviews the relevant literature to highlight the similarities between the ERN and the perturbation-evoked cortical N1 response in terms of similar dependencies on motivation, perceived consequences, perceptual salience, expectation, development, and aging. Although the cortical N1 response is an order of magnitude larger than the ERN, and has a slightly posterior scalp localization, the similar influence of all of these factors suggests that their underlying circuits may be largely similar or overlapping. On the basis of these parallels, we propose that the ERN and the cortical N1 might rely on shared underlying mechanisms, which may provide insight into the relationship between balance and cognitive impairments in old age and in PD. One well-replicated result of the ERN is that it is reduced in amplitude in people with PD, however the cortical N1 response has never been investigated in people with PD.

Before investigating the perturbation-evoked cortical response in people with PD, I performed multiple studies to investigate relationships between the cortical N1 response and sensory inputs and motor outputs in healthy young adults to investigate the possibility that the cortical N1 response could be involved in a longer sensorimotor control circuit contributing to balance recovery after the brainstem-mediated automatic balance corrections. In Chapter 3, I investigate the relationship between the perturbation-evoked cortical N1 response and sensory information in healthy young adults, finding that the effect of sensory input was very limited. Unexpectedly, I found that cortical N1 responses were vastly different between subjects, and were larger in shorter subjects who had greater difficulty resisting compensatory stepping responses. In Chapter 4, by controlling for height-related differences in perturbation difficulty between subjects, I found that cortical

N1 responses were larger in people who had greater difficulty recovering balance due to lower intrinsic balance ability, supporting the possibility that the cortical N1 response may be involved in compensating for the limitations of automatic balance control. In Chapter 5, I show that cortical response amplitudes are larger with the execution of compensatory stepping responses to difficult balance perturbations in healthy young adults, which may be one example of the cortical N1 response being involved in compensatory control after automatic balance corrections.

After findings in healthy young adults suggested that cortical N1 responses may be related to compensatory balance control, I assessed perturbation-evoked cortical responses in older adults with and without PD, hoping to gain insight into the relationship between balance and cognitive impairments through changes in cortical activity. In Chapter 6, I report preliminary results showing that perturbation-evoked cortical responses contain two distinct component peaks in older adults with and without PD, and that reductions in the amplitude of the second component peak are associated with balance impairments in PD. Finally, in Chapter 7, I show that perturbation-evoked cortical responses and the ERN are not impacted in the same way by PD, suggesting a difference in their underlying mechanisms.

CHAPTER 2. DO SENSORIMOTOR PERTURBATIONS TO STANDING BALANCE ELICIT AN ERROR-RELATED NEGATIVITY?

2.1 Attribution of efforts

The following chapter was published in Psychophysiology with co-authors Greg Hajcak and Lena H. Ting.

2.2 Abstract

Detecting and correcting errors is essential to successful action. Studies on response monitoring have examined scalp event-related potentials (ERPs) following the commission of motor slips in speeded-response tasks, focusing on a frontocentral negativity (i.e., error-related negativity or ERN). Sensorimotor neurophysiologists investigating cortical monitoring of reactive balance recovery behavior observe a strikingly similar pattern of scalp ERPs following externally imposed postural errors, including a brief frontocentral negativity that has been referred to as the balance N1. We integrate and review relevant literature from these discrepant fields to suggest shared underlying mechanisms and potential benefits of collaboration across fields. Unlike the cognitive tasks leveraged to study the ERN, balance perturbations afford precise experimental control of postural errors to elicit balance N1s that are an order of magnitude larger than the ERN and drive robust and well-characterized adaptation of behavior within an experimental session. Many factors that modulate the ERN, including motivation, perceived consequences, perceptual salience, expectation, development, and aging are likewise known to modulate the balance

N1. We propose that the ERN and balance N1 reflect common neural activity for detecting errors. Collaboration across fields could help clarify the functional significance of the ERN, and poorly understood interactions between motor and cognitive impairments.

2.3 Error-related negativity

For nearly three decades, psychophysiologists have studied a specific neural response to error commission, referred to as the error-related negativity (ERN or Ne; (Falkenstein et al. 1990; Gehring et al. 2018; 1993)). The ERN is elicited when participants make errors (i.e., motor slips) in forced-choice speeded-response tasks. The most common tasks that have been used to elicit and study the ERN are variations on the Flankers task, Stroop task, and Go/No-go tasks (Meyer et al. 2013), which involve basic stimulus-response pairs that are verbally explained at the beginning of the task, e.g. "when you see stimulus A, press response button 1." Although the tasks are relatively simple, participants make mistakes on a small percentage of trials. By having participants perform hundreds of trials while recording electroencephalographic (EEG) activity, it is possible to evaluate event-related brain potentials (ERPs) time-locked to errors compared to correct responses. The ERN is observed as a sharp negative peak within the first 100ms of the ERP following incorrect response commission at frontocentral EEG electrodes (Fz, FCz, or Cz) (Gehring et al. 1993). Figure 2-1A shows the ERN evoked by errors in a Flankers task from Marlin et al. (Marlin et al. 2014).

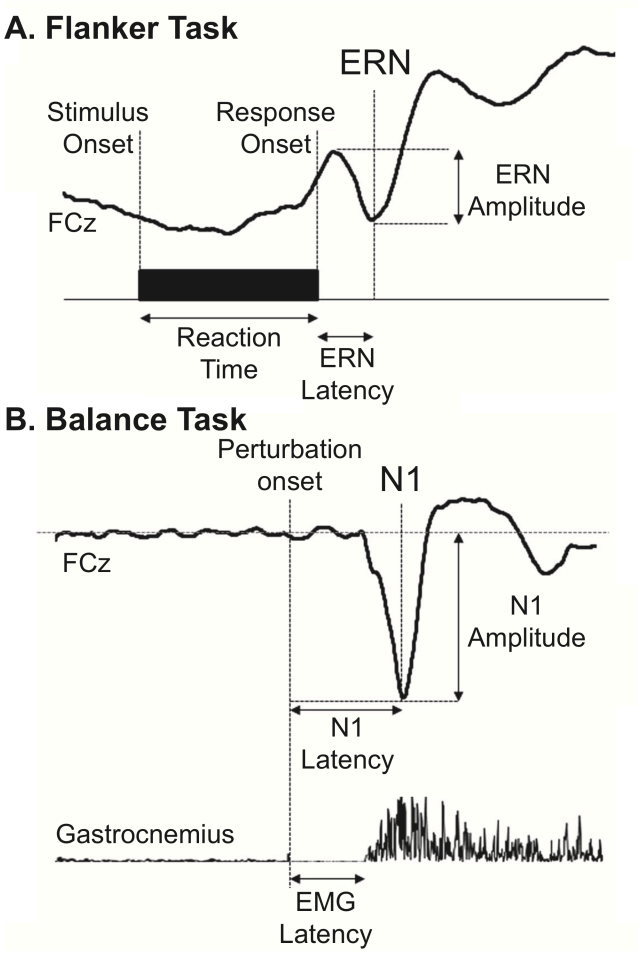


Figure 2-1. Comparison of the error-related negativity (ERN) and balance N1, collected in the same recording session in N=11 healthy young adults (8 female) from Marlin et al. 2014. (A) ERN evoked by errors in an arrow Flankers Task. (B) N1 evoked by sudden release of a cable supporting a portion of body weight from an upright posture. This figure is republished from Marlin et al. 2014 with permission from the Journal of Neurophysiology.

The ERN appears to reflect activation of the anterior cingulate cortex and/or the supplementary motor area based on extracranial EEG (Dehaene et al. 1994; Gentsch et al. 2009; Marlin et al. 2014; Miltner et al. 1997), intracranial EEG (Bonini et al. 2014), functional magnetic resonance imaging (Badgaiyan and Posner 1998; Carter et al. 1998; Hauser et al. 2014) and magnetoencephalography studies (Miltner et al. 2003). The ERN is thought to represent the activation of a generic neural system for error detection because

it is relatively consistent across different tasks (Meyer et al. 2013; Riesel et al. 2013) and responding limbs (Holroyd et al. 1998). Theoretical and computational models suggest that the ERN reflects detection of errors, situations conducive to errors (Carter et al. 1998; Kerns et al. 2004; Ullsperger and von Cramon 2001; van Veen et al. 2001; Yeung et al. 2004), or unexpected events (Alexander and Brown 2011) to recruit cognitive control to improve behavior (Holroyd and Coles 2002b; Ridderinkhof et al. 2004; Shackman et al. 2011; Ullsperger et al. 2014). That is, theories of the ERN generally suggest it is functionally linked to post-error adaptation. However, observable changes in behavior accompanying errors in the tasks most commonly used to study ERN are limited to less forceful entry of errors compared to correct responses, subsequent entry of the correct response on the same trial, slower reaction time on subsequent trials, and increased probability of responding correctly on the next trial (Dutilh et al. 2012; Gehring et al. 1993). Thus, behavioral changes include differences in error-related responses or post-error performance measures.

Although the amplitude of the ERN has been correlated with changes in behavior after errors (Gehring et al. 1993; Ullsperger et al. 2014), a number of experimental factors limit the ability to rigorously test adaptive hypotheses of the ERN. Primarily, reliance on subjects to sporadically commit errors limits experimental control over error frequency, timing, and sequencing. Additionally, discrete classification of responses as either overtly correct or erroneous limits the ability to observe continuous behavioral adaptation within subjects. Although some groups have begun to assess partial errors in the form of muscle activation in the nonresponding limb in trials with an overtly correct response (Spieser et al. 2015), adaptation in these tasks is typically estimated as an increasing probability of an

overtly correct response on subsequent trials (Gehring et al. 1993), rather than being directly measured in terms of incremental progress (e.g., skill acquisition toward the development of expertise within individuals (Shadmehr et al. 2010)). Given that accuracy often exceeds 90% in these simple tasks, the odds of a correct response following an error would be quite high even in the absence of behavioral adaptation. While it is possible to observe incremental changes in response latency across trials within individuals, it is unclear if behavioral changes such as post-error slowing after errors in speeded-response tasks actually reflect control-related processes, or rather, orienting responses to infrequent events (Dutilh et al. 2012; Notebaert et al. 2009; Wessel 2018; Wessel and Aron 2017). Further, whether such orienting responses increase (Houtman and Notebaert 2013) or decrease (Botvinick et al. 2001) the likelihood of errors on subsequent trials depends on, and is thus confounded by, the duration of inter-trial-intervals (Jentzsch and Dudschig 2009; Wessel 2018). A more complex behavioral task providing better experimental control and the presence of robust behavioral adaptation could overcome these limitations to facilitate a more mechanistic investigation of the ERN in relation to post-error changes in behavior.

2.4 Balance perturbations and the balance N1

Reactive balance recovery following externally imposed balance errors provides greater experimental control over errors than tasks typically used to elicit the ERN. Reactive balance recovery can be evoked by a variety of physical perturbations imposing errors on whole body posture, including shove (Adkin et al. 2006) or release (Mochizuki et al. 2010) perturbations of the upper torso, as well as tilts (Ackermann et al. 1986) or translations of the floor during standing (Welch and Ting 2009), walking (Dietz et al.

1985b), or sitting (Mochizuki et al. 2009a; Staines et al. 2001). In contrast to cognitive paradigms that rely on subjects to sporadically commit errors, perturbation devices can be used to precisely control the type, frequency, extent, and sequencing of balance perturbations, which can be repeated across subjects (Adkin et al. 2006; Welch and Ting 2009; 2008; 2014). In each case, a rapid and highly motivated motor reaction is necessary to prevent a fall or possible bodily harm. The earliest balance-correcting muscle activity, called the automatic postural response, is an involuntary behavior mediated by brainstem sensorimotor circuits (Carpenter et al. 1999; Jacobs and Horak 2007a), which can be predicted in fine detail from movement-based error trajectories, i.e. the deviation of the body from the upright, standing position (Welch and Ting 2009; 2008). In this way, balance recovery is an ecologically relevant error-correcting behavior that evokes error-related and error-correcting muscle activity. And most importantly, balance perturbations evoke an error-related scalp ERP resembling the ERN, that has been referred to as the balance N1. Figure 2-1B shows the balance N1 evoked by sudden release of a cable supporting a portion of body weight from an upright leading posture from Marlin et al. (Marlin et al. 2014).

Motor reactions to balance perturbations have been well-characterized as rapidly adapting error-driven responses. Balance performance error can be measured by the position, velocity, and acceleration of the body's center of mass relative to the feet, which serve as three error signals that simultaneously evoke balance-correcting muscle activations (Figure 2-2A; (Lockhart and Ting 2007; Welch and Ting 2009; 2008)). Sensitivities to each of these error signals can vary independently and substantially within a range of solutions that are sufficient to generate forces to correct balance errors, and differences in these sensitivities can parsimoniously explain apparently complex

differences in balance-correcting motor responses between individuals (Figure 2-2ABC; (Welch and Ting 2009; 2008)). These error sensitivities can adapt on a trial-by-trial basis within an experimental session toward optimal solutions that can be predicted through physics (Welch and Ting 2014). Such adaptation can also occur over motor rehabilitation, as demonstrated by an increase in sensitivity to velocity and position errors in cats when the sensory afferents encoding acceleration error were damaged by pyridoxine overdose (Lockhart and Ting 2007). The mechanisms underlying such changes in error-sensitivities remain unclear, but a better understanding could facilitate rehabilitation of balance disorders.

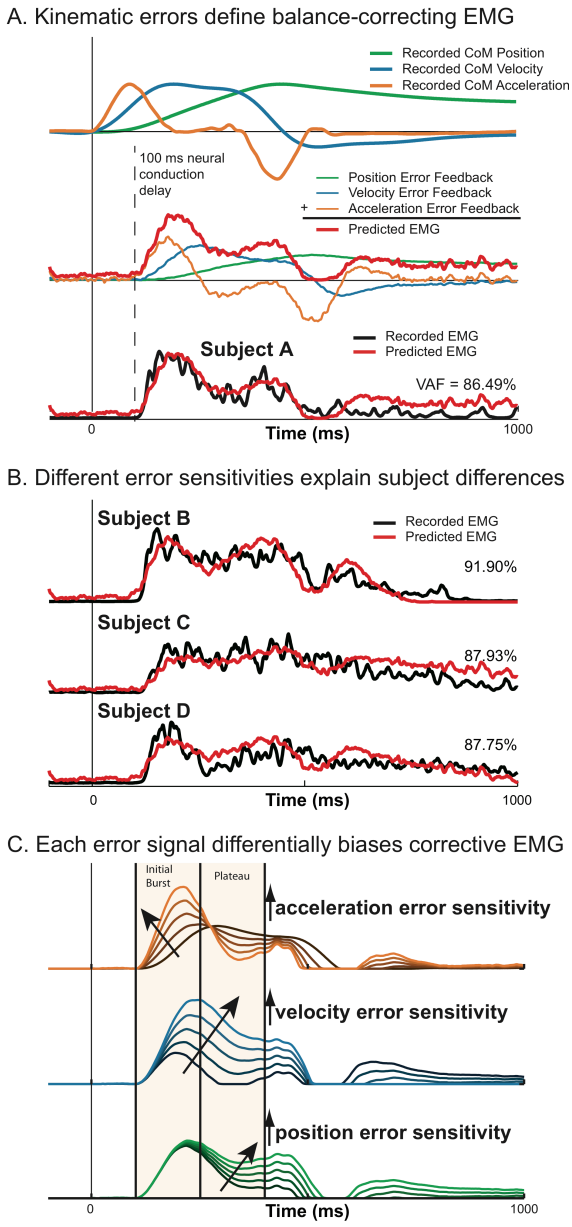


Figure 2-2. Kinematic error signals define the balance-correcting motor response to perturbation. (A) Recorded center of mass kinematics (top) are multiplied by subject- and muscle-specific error sensitivities, added together, clipped below zero, and delayed 100ms (middle) to reconstruct recorded balance-correcting EMG response (bottom). (B) Different kinematic error sensitivities can explain differences in balance-correcting EMG between subjects responding to the same perturbation. (C) changes in sensitivity to acceleration error (top) primarily influences the initial burst of balance-correcting response, whereas changes in sensitivity to velocity (middle) or position errors (bottom) influence later portions of the response due to the relative peak timings of the error signals. Data in this figure is republished from Welch and Ting 2008 with permission from the Journal of Neurophysiology.

In addition to error-related and error-correcting muscle activity, balance perturbations elicit error-related cortical activity resembling the ERN (Figure 2-1). Specifically, a frontocentral negativity called the balance N1 is evoked simultaneous to the balance-correcting muscle activity (Payne et al. 2018). The balance N1 is a negative peak of cortical activity occurring between 100-200ms after balance perturbation at frontal and central midline EEG electrodes (Fz, FCz, Cz) (Marlin et al. 2014; Mierau et al. 2015), with amplitudes large enough to observe on single trials (Mierau et al. 2015; Payne et al. 2018). The balance N1 has been localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015), but theories of its function are extremely limited. The balance N1 was initially thought to reflect sensory activity from balance perturbations (Dietz et al. 1985b; 1984b; Dietz et al. 1985a). However, the absence of the balance N1 when perturbations are predictable (Adkin et al. 2006) suggests that the balance N1 may represent an error-signal similar to the ERN. In fact, many factors known to modulate the ERN, including motivation, perceived consequence, perceptual salience, expectation, development, and aging are likewise known to modulate the balance N1 (Section 3). If the balance N1 and ERN are manifestations of a common neural system for error detection, sensorimotor perturbations may present a more controllable experimental paradigm to study the relationship between errors, the action monitoring system, and subsequent changes in behavior (Section 4).

2.5 Parallels between the balance N1 and ERN

The previous sections defined the ERN and balance N1 as frontocentral negativities time-locked to an error event, which have largely overlapping scalp distributions (Figure 2-3) and sources localized to the medial frontal cortex (Marlin et al. 2014). In this section,

we describe parallel outcomes of investigations of the balance N1 and the ERN to support the argument that these brain responses reflect similar functions of the action monitoring system, and in the following section we conclude with the suggestion that collaboration across fields could overcome barriers to progress in both fields. One apparent contrast is that the ERN is typically quantified within the first 100ms of the response-locked ERP waveform whereas the balance N1 is typically quantified in the second 100ms of the stimulus-locked ERP waveform. However, in tasks that elicit the ERN, the onset of muscle activity associated with the erroneous response entry can be observed 100ms before the response button is pressed (Spieser et al. 2015). Thus, if the ERN were quantified relative to the onset of the error event rather than completion of the error event, its timing would be more aligned with the timing of the balance N1 relative to the onset of perturbation acceleration. In other words, both the balance N1 and ERN could be equivalently quantified within the second 100ms relative to the onset of an error, whether the error is internally generated, as in the case of the ERN, or externally applied, as in the case of the balance N1. Much like the ERN, which displays a similar scalp distribution whether responses are entered by the hand or foot (Holroyd et al. 1998), or even by the eyes (Endrass et al. 2007; Nieuwenhuis et al. 2001; Van't Ent and Apkarian 1999), the balance N1 displays a similar scalp distribution regardless of whether perturbations are delivered during standing or sitting (Mochizuki et al. 2009a), consistent with a generic system for error detection.

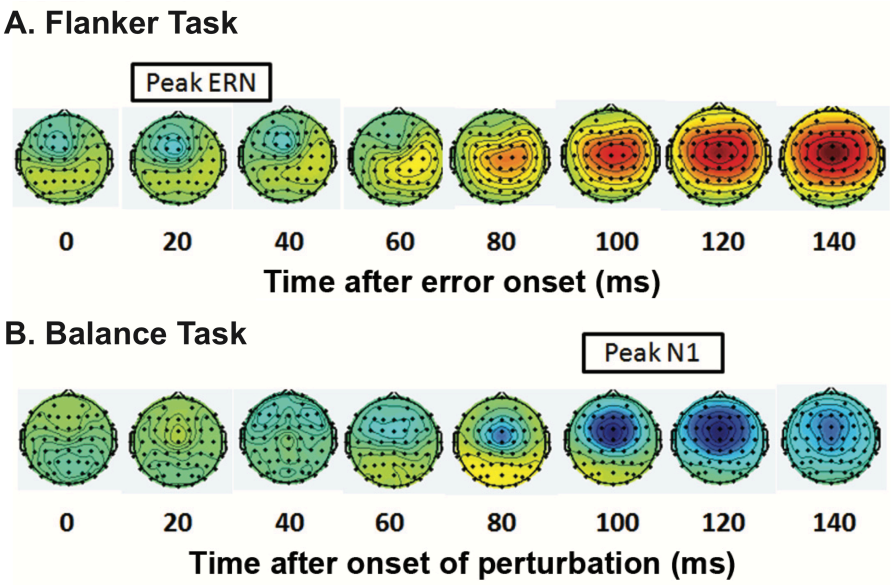


Figure 2-3. Scalp distributions of the error-related negativity (ERN) and balance N1, collected in the same recording session in N=11 healthy young adults (8 female) from Marlin et al. 2014. (A) Scalp distribution of the ERN evoked by errors in an arrow Flankers Task. (B) Scalp distribution of the N1 evoked by sudden release of a cable supporting a portion of body weight from an upright leaning posture. This figure is republished from Marlin et al. 2014 with permission from the Journal of Neurophysiology.

Larger and more intense balance perturbations elicit a larger balance N1 response (Mochizuki et al. 2010; Payne et al. 2018; Staines et al. 2001). Likewise, the ERN increases in amplitude with the extent of an error, such as when an error is committed with both the wrong finger and the wrong hand compared to errors committed with either the wrong finger or the wrong hand (Bernstein et al. 1995). The balance N1 also decreases in amplitude when sensory input is partially blocked by tendon vibration (Staines et al. 2001), or when sensory input is naturally suppressed during walking (Dietz et al. 1985b). These data are similar to observed reductions in the amplitude of the ERN in a visual two-choice reaction task under degraded stimulus conditions (Scheffers and Coles 2000). In contrast to the balance N1 studies that directly altered the sensory experience of the error, the

degraded visual stimulus condition in Scheffers and Coles (2000) altered the representation of the error by making subjects more uncertain about the identity of the appropriate response. In either case the error-related cortical response was influenced by altering the perceptual intensity of the information necessary to compare the actual and desired events, thereby implicating some dependency on the sensory manifestation of the error-related stimulus.

The balance N1 and the ERN both scale in amplitude with the perceived consequence of an error. The balance N1 is increased in amplitude when a balance failure would be more significant, such as when the participant is perturbed at an elevated height (Adkin et al. 2008; Sibley et al. 2010). In this case, the externally applied force of the perturbation is the same, but the change in context from standing at ground level to standing at the edge of an elevated platform increases the perceived consequences of a possible balance failure and increases the amplitude of the balance N1. The ERN likewise increases when an error is perceived as more significant, e.g. when an error incurs a higher monetary loss (Hajcak et al. 2005a; Pailing and Segalowitz 2004a) or when the participant is informed that their performance is being evaluated and judged (Hajcak et al. 2005a; Kim et al. 2005). Interestingly, the elevated height perturbation context also increased self-reported level of anxiety and worry about falling (Adkin et al. 2008), which aligns with findings of higher ERN amplitudes in individuals with greater general anxiety and worry (Hajcak et al. 2003), which may modulate the perceived consequences of errors. These studies suggest that the balance N1 and ERN depend not only on the sensory phenomena of errors, but also on the cognitive valuation of the perceived consequences of balance perturbations and errors, respectively.

The balance N1 is reduced in amplitude when a participant's attention is diverted from a balance task by performing a simultaneous visuomotor tracking task (Quant et al. 2004b) or visual working memory task (Little and Woollacott 2015). Likewise, ERN amplitude is reduced when a participant's attention is diverted from the primary speeded-response task by simultaneous performance of an interleaved visual working memory task (Klawohn et al. 2016; Maier and Steinhauser 2017) or while simultaneously listening to a series of numbers for a particular sequence (Pailing and Segalowitz 2004b). These studies suggest that the amplitude of both the balance N1 and the ERN are modulated by the availability of cognitive resources.

When a balance perturbation is predictable in timing, magnitude, and direction, the balance N1 amplitude is substantially reduced (Mochizuki et al. 2010) or even absent (Adkin et al. 2008; Adkin et al. 2006). Along similar lines, an unexpected balance perturbation in a different direction following a series of predictable perturbations elicits a large balance N1 (Adkin et al. 2008; Adkin et al. 2006). Additionally, self-initiated balance perturbations elicit smaller balance N1s than those initiated by an experimenter (Dietz et al. 1985a; Mochizuki et al. 2009b; Mochizuki et al. 2008). These data suggest that the balance N1 scales with predictability and are consistent with observations that ERN amplitude is larger when errors are less frequent and therefore more unexpected (Holroyd and Coles 2002b; Santesso et al. 2005). Collectively, these studies suggest a parallel potentiation of ERN when errors are more infrequent and unexpected and balance N1 when perturbations are unexpected.

The balance N1 evoked by whole body perturbations increases in amplitude from early childhood (Berger et al. 1987) and declines in amplitude with old age (Duckrow et

al. 1999). This developmental trajectory is similar to that of the ERN, which has also been observed to increase in amplitude from childhood to adolescence, plateauing in adulthood (Ladouceur et al. 2007; Santesso and Segalowitz 2008; Tamnes et al. 2013; Wiersema et al. 2007) and declining with old age (Beste et al. 2009; Nieuwenhuis et al. 2002). However, increases in ERN amplitude from childhood to adulthood are often confounded by a reduction in error frequency (Ladouceur et al. 2007; Santesso and Segalowitz 2008; Wiersema et al. 2007), making it unclear whether the increase in ERN amplitude from childhood to adulthood is due to age or increased unexpectedness of errors due to performance improvement. However, when comparing younger adults to older adults, errors continue to become less frequent while the ERN amplitude declines (Beste et al. 2009; Nieuwenhuis et al. 2002), suggesting there are indeed changes in ERN amplitude with age that do not depend on changes in error rate.

Time-frequency analyses of the ERN (Luu et al. 2004) and balance N1 (Peterson and Ferris 2018; Varghese et al. 2014) have been used to suggest that both of these ERPs may reflect a transient synchronization of theta frequency (4-7 Hz) brain activity. However, in simulated datasets, such analyses are unable to distinguish synchronization of oscillatory components from discrete component peaks (Yeung et al. 2007). The extent to which these ERPs relate to theta frequency brain activity observed in other contexts remains unclear. Although theta power and ERN amplitudes are similarly modulated by novelty, conflict, and error within subjects (Cavanagh et al. 2012), theta power and ERN amplitude can be relatively independent individual difference measures (Cavanagh et al. 2017). Whether the balance N1 evoked by postural perturbations is mechanistically related to continuous theta frequency brain activity observed in continuous balance tasks (Hulsdunker et al. 2015; Sipp

et al. 2013) remains unclear, but presents another interesting area of future investigation and integration.

On the basis of these parallels, we propose that the balance N1 and the ERN reflect similar functions of the action monitoring system and suggest that balance and other sensorimotor perturbation paradigms could be leveraged to probe neural mechanisms of error detection and behavioral adaptation. While anatomical studies have suggested that the ERN reflects activity within a cortical node of cortico-basal ganglia-thalamocortical circuits (Ullsperger and von Cramon 2006), the balance N1 may likewise reflect activity within a cortical node of parallel or overlapping cortico-basal ganglia-thalamocortical circuits, which are known to be highly parallel in nature and are suspected to perform similar functions based on detailed anatomical studies in animals (Alexander et al. 1986). In particular, the possible differences in localization of the ERN to the anterior cingulate cortex and the balance N1 to the supplementary motor area (Marlin et al. 2014) provides further support for the possibility that these ERPs may arise from the aforementioned parallel circuits, as the anterior cingulate cortex represents the cortical node of the so called "cognitive loop" of the cortico-basal ganglia-thalamocortical circuit and the supplementary motor area represents the cortical node of the so called "motor loop" of the cortico-basal ganglia-thalamocortical circuit (Alexander et al. 1986). However, these differences in localization may also be influenced by differences in overlap between the ERN or balance N1 and associated stimulus-locked visual or proprioceptive and vestibular ERPs respectively (Hajcak et al. 2004). If the balance N1 is a perturbation-elicited ERN, the experimental control and robust adaptation within balance paradigms could be leveraged to test adaptive hypotheses of the ERN, and theoretical and computational models of the

ERN could be leveraged to design mechanistic investigations of the balance N1. Further, collaboration across fields could reveal interactions between motor and cognitive impairments, as well as cross-modal and synergistic benefits seen in combined motor and cognitive rehabilitation interventions.

2.6 Summary and future directions

Detecting and correcting errors is essential to successful behavior. By error, we refer to any deviation from a desired or expected goal or bodily state, which can be recognized by the nervous system as the impetus to modify behavior to achieve the desired state or goal. Although a perturbation does not reflect commission of a motor error, it produces a deviation from the desired upright posture that must be rapidly detected and corrected to prevent bodily harm. In this way, we believe that balance perturbations recruit many of the same control processes that are recruited by commission of motor errors, which is supported by a range of parallel influences on scalp ERPs described in the preceding section. Because of the similarities between error-correcting motor responses to balance perturbations and error-correcting motor responses in perturbations to the arms during voluntary movement (Crevecoeur and Kurtzer 2018), it is possible that these cortical responses would generalize more broadly across sensorimotor control paradigms.

In contrast to cognitive paradigms that rely on subjects to sporadically commit errors, perturbation devices can be used to precisely control the type, frequency, extent, and sequencing of errors, which can be repeated both within and across subjects (Adkin et al. 2006; Welch and Ting 2009; 2008; 2014) across a wide range of ages (Berger et al. 1987; Duckrow et al. 1999). Prediction or expectation errors can also be controlled in

sensorimotor paradigms by altering verbal instructions or sequencing of perturbations, e.g. by providing a series of perturbations that are predictable in timing, direction, and magnitude, and manipulating any of these dimensions on selected "catch" trials (Adkin et al. 2006; Welch and Ting 2014). In addition, it is also possible to examine outcome errors, e.g. by instructing a subject to recover balance without stepping in perturbations large enough to guarantee stepping reactions (Chvatal and Ting 2012; McIlroy and Maki 1993b). It is therefore possible to leverage precise control over sensorimotor errors to experimentally isolate factors for a more detailed understanding of how each aspect of errors influences cortical activity. In turn, leveraging knowledge of the ERN to design sensorimotor perturbation experiments could be a major step toward identifying the functional role of cortical action monitoring on adaptation of sensorimotor behaviors.

Given the parallel outcomes of investigations of the ERN and the balance N1, several questions arise from the ERN literature that have yet to be tested of the balance N1. First, if the balance N1 and ERN share neural circuitry, then drugs that influence the ERN should also influence the balance N1. In particular, do dopamine agonists and antagonists, which increase (de Bruijn et al. 2004) and decrease (de Bruijn et al. 2006; Zirnheld et al. 2004) the amplitude of the ERN in healthy young adults, likewise influence the amplitude of the balance N1? Second, if the balance N1 and ERN share neural circuitry, then disorders that influence the ERN should also influence the balance N1. In particular, do individuals with Parkinson's disease who present with reduced ERN amplitudes (Seer et al. 2016), likewise show reduced balance N1s? And could this relate to balance impairment in Parkinson's disease? Do individuals with obsessive-compulsive disorder who present with larger ERN amplitudes (Endrass et al. 2010; Klawohn et al. 2014) also display larger

balance N1s? And could this relate to reduced postural sway in obsessive-compulsive disorder (Kemoun et al. 2008)? Further, can reward and punishment, which can cause a lasting increase in ERN amplitude (Riesel et al. 2012), likewise cause lasting changes in the balance N1 amplitude? Or, if the balance N1 and ERN share underlying circuitry, can the effect of punishment on ERN amplitude cross domains to increase the balance N1 in the absence of punishment in balance tasks? While such correlational investigations are interesting and may provide insight into the neural underpinnings of performance monitoring, a much greater challenge will be leveraging such insight to benefit people with altered performance monitoring.

ERN amplitude is characteristically altered in multiple patient populations that seek rehabilitation from persistent pathological behaviors and thought processes, including those with obsessive-compulsive disorder (Gehring et al. 2000; Klawohn et al. 2014), generalized anxiety disorder (Weinberg et al. 2012; Weinberg et al. 2010), substance abuse (Franken et al. 2007; Schellekens et al. 2010), old age, Parkinson's disease (Seer et al. 2016), and Huntington's disease (Beste et al. 2009). While such between-population differences can be leveraged as a risk factor to predict the development of certain neuropsychiatric disorders (Meyer et al. 2015), attempts to leverage knowledge about altered cortical action monitoring and error processing to devise treatment strategies are just beginning. Potential rehabilitation strategies targeting the action monitoring system include, but are not limited to, strategic reorienting of attention from overvalued errors in individuals with obsessive-compulsive disorder (Klawohn et al. 2016) or anxiety (Waters et al. 2018) or toward undervalued or unrecognized errors in individuals with PD; habituation of maladaptive error responses or training of alternative behavioral responses

to compete with pathological behaviors (Jacoby and Abramowitz 2016); or targeted noninvasive electrical stimulation of the action monitoring system (Bellaiche et al. 2013; Reinhart and Woodman 2014). A better understanding of the action monitoring system could therefore be advantageous for treating a range of neuropsychiatric disorders, and could even extend into balance rehabilitation if action monitoring spans behavior more broadly. Although the brainstem-mediated involuntary balance-correcting motor responses can adapt rapidly within a single experimental session in healthy young adults (Horak and Nashner 1986; Welch and Ting 2014), understanding brain involvement is critical for rehabilitation of balance recovery behavior in individuals with balance impairments due to Parkinson's disease (Grimbergen et al. 2004), cerebellar dysfunction (Horak and Diener 1994), or cognitive impairment (Herman et al. 2010). Further, the rapid behavioral adaptation observable in balance paradigms could provide an experimental model in which to test hypotheses about error-driven changes in behavior more broadly and may prove particularly helpful in the context of comorbidities between motor and psychiatric disorders.

Finally, we suggest that collaboration across fields could clarify poorly understood interactions between motor, cognitive, and psychiatric disorders, leading to more integrated models of the ERN and balance N1, as well as potential treatment strategies. Many populations with altered error responses also display differences in balance behavior, including frequent comorbidities between anxiety disorders and balance disorders (Balaban 2002; Balaban and Thayer 2001; Bolmont et al. 2002; Yardley and Redfern 2001), and substantially reduced postural sway in individuals with obsessive-compulsive disorder (Kemoun et al. 2008). Further, balance impairment is strongly associated with

cognitive impairment in older adults with (Allcock et al. 2009; Mak et al. 2014) and without (Camicioli and Majumdar 2010; Gleason et al. 2009; Herman et al. 2010; Mirelman et al. 2012) Parkinson's disease, and rehabilitation interventions that simultaneously target cognitive engagement show greater improvement in motor function in healthy aging (Kraft 2012; Wu et al. 2016) and in Parkinson's disease (Petzinger et al. 2013) than interventions that target motor function alone. Collaboration across fields could provide new insight into these synergistic benefits of combined interventions, and may help explain counterintuitive findings that balance training can ameliorate anxiety disorders (Bart et al. 2009) or that cognitive training can improve balance and gait (Smith-Ray et al. 2015), leading to the development of more integrated treatment strategies for comorbid motor, cognitive, and psychiatric disorders.

CHAPTER 3. DISSOCIATION OF MUSCLE AND CORTICAL RESPONSE SCALING TO BALANCE PERTURBATION ACCELERATION

3.1 Attribution of efforts

The following chapter was published in the Journal of Neurophysiology with co-authors Greg Hajcak and Lena H. Ting.

3.2 Abstract

The role of cortical activity in standing balance is unclear. Here we tested whether perturbation-evoked cortical responses share sensory input with simultaneous balance-correcting muscle responses. We hypothesized that the acceleration-dependent somatosensory signals that drive the initial burst of the muscle automatic postural response also drive the simultaneous perturbation-evoked cortical N1 response. We measured in healthy young adults (N=16) the initial burst of the muscle automatic postural response (100-200ms), startle-related muscle responses (100-200ms), and the perturbation-evoked cortical N1 potential, i.e. a negative peak in cortical EEG activity (100-200ms) over the supplementary motor area. Forward and backward translational support-surface balance perturbations were applied at four levels of acceleration, and were unpredictable in timing, direction, and acceleration. Our results from averaged and single-trial analyses suggest that although cortical and muscle responses are evoked by the same perturbation stimulus, their amplitudes are independently modulated. While both muscle and cortical responses increase with acceleration, correlations between single-trial muscle and cortical responses

were very weak. Further, across subjects, the scaling of muscle responses to acceleration did not correspond to scaling of cortical responses to acceleration. Moreover, we observed a reduction in cortical response amplitude across trials that was related to a reduction in startle-related, but not balance-correcting, muscle activity. Therefore, cortical response attenuation may be related to a reduction in perceived threat rather than motor adaptation or changes in sensory inflow. We conclude that the cortical N1 reflects integrated sensory inputs simultaneously related to brainstem-mediated balance-correcting muscle responses and startle-reflexes.

3.3 Introduction

It is unclear how cortical activity is related to balance-correcting behavior. The earliest muscle activation after a balance disturbance is a monosynaptic spinal stretch reflex, followed by a larger burst of balance-correcting muscle activity, called the automatic postural response (APR), mediated by brainstem sensorimotor circuits (Carpenter et al. 1999; Jacobs and Horak 2007a). While the initial stretch reflex response is quite small, the much larger balance-correcting APR muscle activity is initiated at ~100 ms latency (Carpenter et al. 1999), with its initial burst of activity scaling with perturbation acceleration (Welch and Ting 2009; 2008) due to proprioceptive sensory inputs (Lockhart and Ting 2007). Unpredictable balance disturbances can also serve as a startling stimulus (Campbell et al. 2013; Oude Nijhuis et al. 2010), evoking brainstem-mediated startle reflex muscle activity (Brown et al. 1991), simultaneous to the balance-correcting APR, particularly during the first few trials (Nonnekes et al. 2015; Siegmund et al. 2008). Similarly, the earliest cortical event-related potentials (ERPs) after a balance disturbance include a small and variable positive peak (P1) followed by a large and robust negative peak (N1). The cortical balance N1 peak occurs between 100-200 ms after perturbation

onset, with the largest amplitude at central and fronto-central midline scalp electrodes, and has been localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015). Recent advances in technology have made it possible to directly measure cortical electrical activity during reactive balance recovery (Bolton 2015) and to perform trial-by-trial analyses (Mierau et al. 2015). Here, we focus on the possible relationship between the cortical balance N1 and the initial burst of the muscle APR. Based on the similarity of their latencies, the cortical balance N1 cannot directly cause the initial burst of the muscle APR or startle-related muscle activity, rather, these phenomena are triggered by the same event and may be modulated common sensory inputs.

Prior studies examining averaged responses have suggested that the amplitude of cortical and muscle responses to balance perturbations are modulated by shared somatosensory inputs. The earliest studies of cortical responses to balance perturbations compared treadmill perturbations applied during walking and standing. Both the cortical balance N1 and the initial burst of the muscle APR were smaller and later when evoked during walking compared to standing (Dietz et al. 1984b). The inhibition of group I somatosensory afferents during walking was posed as a possible explanation for the observation of a shared delay and attenuation of cortical and muscle responses to perturbations during walking versus standing. Consistent with this hypothesis, ischemic block of group I somatosensory afferents was shown to attenuate both cortical and muscle responses to perturbations during standing, as well as somatosensory cortical potentials (SEPs) evoked by electrical stimulation of the tibial nerve (Dietz et al. 1985b). Moreover, these amplitude and latency differences in cortical and muscle responses during perturbations to walking are not apparent prior to age six, and develop with the suppression of stretch reflexes during walking (Berger et al. 1987). Further support of a common peripheral site of origin was the demonstration that both cortical and muscle responses to balance perturbation were delayed by approximately 30 ms in a patient with slow

peripheral conduction velocities (Dietz et al. 1985a). More recently, in a lean and release balance perturbation paradigm, the cortical balance N1 and initial burst of the muscle APR scaled to perturbation amplitude (Mochizuki et al. 2010).

Trial-by-trial variations of the cortical balance N1 and the initial burst of the muscle APR could arise from dynamic processes over the course of an experiment such as habituation, adaptation, and learning. All of the studies above relied on averaging across multiple trials (~100 trials in Dietz, 30-60 trials in Mochizuki), which would mask any time- or history-dependence of cortical and muscle responses. Recently, using single-trial analysis, a gradual reduction of cortical balance N1 amplitude was shown across a series of ten identical perturbations that were unpredictable in timing (Mierau et al. 2015). Such a systematic reduction in the cortical balance N1 across identical, consecutive trials suggests that the processes underlying the cortical balance N1 are dynamic across trials and suggests a need to conduct single-trial analysis to examine its potential function and relationship to muscle responses. Our prior work demonstrated that non-random sources of trial-by-trial variation in the initial burst of the muscle APR include trial-by-trial variation in postural response strategy (Torres-Oviedo and Ting 2010), center of mass kinematics , i.e. the acceleration, velocity, and displacement of the body relative to the base of support (Safavynia and Ting 2012; Welch and Ting 2009), and adaptation of the underlying sensorimotor transformation (Horak and Nashner 1986; Welch and Ting 2014). If the cortical balance N1 shares the ascending sensory input with the brainstem sensorimotor circuit underlying the initial burst of the muscle APR, then the cortical balance N1 could also share these sources of trial-by-trial variation, leading to the prediction that cortical and muscle response amplitudes would be correlated across single trials. Indeed, Mierau and colleagues found a weak correlation between single-trial cortical and muscle responses despite the fact that muscle responses did not also decrease systematically across trials (Mierau et al. 2015). However, the experimental paradigm used did not explicitly alter

sensory inputs across trials, so the question of whether changes in sensory inflow cause correlated changes in the cortical balance N1 and the initial burst of the muscle APR remains unanswered.

We previously demonstrated that the initial burst of the muscle APR scales with perturbation acceleration and is encoded by somatosensory inputs, but it is not known whether the cortical balance N1 shares this acceleration dependency. Using a series of unpredictable translational support surface perturbations with randomized peak acceleration amplitude, a simple delayed feedback model of kinematic errors explained the balance-correcting muscle response in humans (Welch and Ting 2009; 2008) and cats (He et al. 1991; Lockhart and Ting 2007). The initial burst of the muscle APR was explained by center of mass acceleration error, which depends on the imposed level of perturbation acceleration. We further showed in cats that this acceleration-dependent initial burst of the muscle APR was absent or reduced after loss of group I somatosensory afferents from pyridoxine-induced peripheral neuropathy (Lockhart and Ting 2007; Stapley et al. 2002). Acceleration-dependence of the cortical N1 has only been tested in three subjects perturbed while seated, two of which showed acceleration-dependent scaling of the cortical N1 (Staines et al. 2001). We are not aware of any prior studies demonstrating dependence of the cortical N1 on perturbation acceleration during standing.

We hypothesized that if the cortical balance N1 shares group I somatosensory afferent inputs with the initial burst of the muscle APR, then its amplitude would scale with peak perturbation acceleration in standing balance on a trial-by-trial basis. To test whether cortical and muscle responses are similarly scaled to sensory information, we compared single-trial amplitudes of muscle and cortical responses to balance perturbations that varied in peak acceleration magnitude. Healthy young adults were tested in a series of randomized support-surface balance perturbations that varied in perturbation acceleration in forward and backward directions. We predicted that the cortical balance N1 would increase with

perturbation acceleration and would be correlated with the initial burst of the muscle APR across trials due to shared sensory inputs. Due to the possibility for motor responses following the APR to involve a transcortical sensorimotor response (Jacobs and Horak 2007a), we also performed exploratory analyses relating the cortical balance N1 to longer latency muscle activity. Our results suggest that muscle and cortical responses to translational support-surface perturbations share sensory inputs but have independent scaling mechanisms.

3.4 Methods

3.4.1 Participants

Seventeen healthy young adults were recruited from Emory University and the surrounding population to participate in an experiment that was approved by the Emory University Institutional Review Board. All subjects signed written informed consent before participating. One subject was excluded from analysis for deviation from the experimental protocol. The remaining sixteen subjects (9 female, 7 male) used in our analyses were 26 years old (SD 5), 171 cm (SD 13) tall, and 72 kg (SD 11).

3.4.2 Experimental Protocol

To test the effect of varying perturbation acceleration on evoked cortical and muscle activity, we presented subjects with a series of ramp-and-hold perturbations in which the floor was displaced during quiet standing across a range of perturbation accelerations. Perturbations were delivered using a custom-designed perturbation platform (Factory Automation Systems, Atlanta, GA). Sixty-four perturbations were delivered to each subject, divided evenly between four levels of peak acceleration (0.23-0.66 g), and

between forward and backward directions. All perturbations reached a peak velocity of 40 cm/s and a total displacement of 10 cm (Figure 3-1).

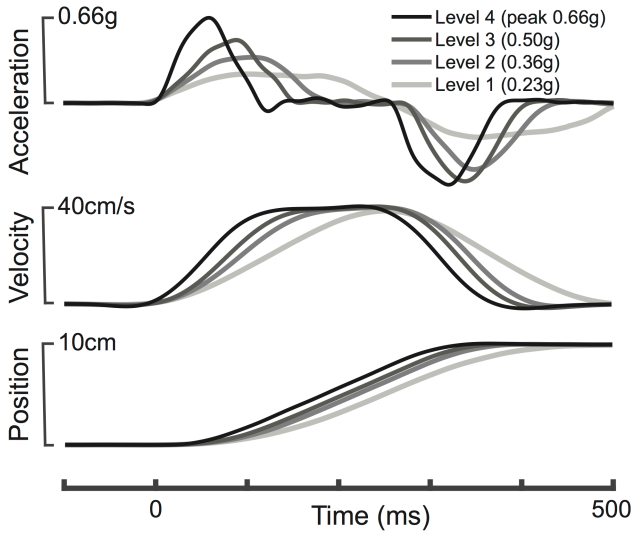


Figure 3-1. Perturbation kinematics. Peak accelerations varied between 0.23, 0.36, 0.50, and 0.66g, with a peak velocity of 40cm/s, and a total displacement of 10cm. Larger accelerations are indicated with darker lines.

Perturbations were unpredictable in timing, direction, and acceleration magnitude. Perturbations were presented in eight blocks, with each block containing one replicate of each of the eight distinct perturbations (2 directions x 4 accelerations) in random order. The blocks were also randomized into three different block orders across subjects. The total duration of the sixty-four perturbation series was 16.8 minutes (SD 4.4), with a 5-minute rest enforced for durations longer than 15 minutes to prevent fatigue. Inter-trial-intervals (as measured from perturbation onset to perturbation onset) were 16 s (SD 4, range 7 s-1.7 minutes, not counting the 5-minute rest period when present).

To minimize recording artifacts, perturbations were initiated only when electroencephalography (EEG) activity was relatively quiescent, based on visual inspection

of a monitor displaying the online EEG recording. Subjects were instructed to cross their arms across their chest, and to try to maintain balance without taking a step while staring at a central location in a 73x106 cm poster of a mountain landscape on a wall 4.5 m in front of them. Subjects were verbally reminded to relax and look forward when electromyography (EMG) activity or large eye movements were visually apparent in ongoing EEG recording. Subjects were asked if they would like to take a break if alpha oscillations became visually apparent in the ongoing EEG recording. Subjects were allowed to blink freely.

Reflective markers placed on the head, neck (C7), hips (left and right anterior and superior iliac crest), knees, ankles, and foot were sampled at 100 Hz by a 10-camera Vicon 3D motion analysis system to track body motion in three dimensions. Stepping responses were noted during collection and manually confirmed by checking motion data. To assess the potential for movement artifacts during the window in which cortical data were quantified, we assessed absolute motion of the head and heel markers in the anterior-posterior plane at 100 ms and 200 ms after perturbation onset relative to the moment of perturbation onset. One subject was excluded from kinematic analyses (N=15) due to data miscalibration.

3.4.3 Electroencephalography (EEG) collection

Thirty-two active EEG electrodes (ActiCAP, Brain Products, Germany) were placed on the scalp according to the International 10-20 system of EEG electrode placement, with the exception of electrodes TP9 and TP10, which were placed directly on the mastoid bones beneath the EEG cap for offline re-referencing. ActiCAP active

electrodes improve signal quality by performing impedance conversion using powered circuits integrated into the electrodes which transform high input resistance due to the scalp into a lower output resistance to reduce the impact of external sources of interference as the signals travel from the electrodes to the amplifier. Active electrode sites were prepared by rubbing the scalp with a blunt-tipped needle, which was subsequently used to apply conductive electrode gel (SuperVisc 100 gr. HighViscosity Electrolyte-Gel for active electrodes, Brain Products). Mastoid electrode sites were additionally prepared by scrubbing the skin with an alcohol pad. Impedances at primary electrode sites (i.e., Cz and mastoids) were below 10 kOhm before the start of data collection. All other active electrode sites were similarly prepared, but impedance values were not generally below 10 kOhm before the start of data collection due to time limitations and were in many cases out of range of the impedance measurement.

To enable subtraction of blink and eye movement artifacts, electrooculography (EOG) data were collected using bipolar pairs of passive electrodes (E220x, Brain Products); a ground electrode was placed in the center of the forehead. Electrodes were prepared with high-chloride abrasive gel (ABRALYT HiCl 250 gr., High-chloride-10% abrasive electrolyte gel, Brain Products), and electrode sites were prepared by scrubbing the skin with an alcohol pad. Vertical EOG was measured between a pair of electrodes that vertically bisected the pupil of the right eye.

EEG and EOG data were amplified on a BrainAmp DC amplifier (Brain Products) sampling at 1000 Hz, with a 16-bit A/D converter. Online filtering consisted of a first-order low-pass filter with a cut-off (-12 dB point) of 0.016 Hz with a 6 dB/octave slope, and a fifth-order Butterworth low-pass filter with a cut-off of 1000 Hz with a 30 dB/octave slope.

3.4.4 EEG data preprocessing

The raw (non-segmented) EEG data were high-pass filtered offline using a third-order zero-lag Butterworth filter with a cut-off frequency (-3 dB point) of 0.05 Hz, with a slope of 18 dB/octave. EEG data were then centered on zero by subtracting the mean value from each channel for each subject before applying a similarly designed low-pass filter with a cut-off frequency of 25 Hz. EEG data from electrode Cz was then re-referenced to the average of the two mastoid electrodes, and epoched into segments of 2.4 seconds, beginning 400 ms before perturbation onset. The 2.4 second duration of the epochs was selected as the longest time window for which both EEG and EEG data existed across all trials, ensuring that edge effects of filtering and artifact detection and correction (described below) would not overlap with the primary time windows of interest. Vertical EOG electrode voltages were filtered and segmented identically to EEG but were not re-referenced.

Blinks and vertical eye movement artifacts were subtracted using the Gratton and Coles algorithm (Gratton et al. 1983), which uses sequential linear regressions and subtractions to remove non-event-related correlations between vertical EOG activity and EEG activity at the Cz electrode due to blinks and eye movement. Segmented data were then baseline corrected by subtracting the mean value of a 100 ms time window ending 50 ms prior to the onset of platform acceleration.

3.4.5 Electromyography (EMG) data collection

Surface EMGs (Konigsberg Instruments, Pasadena, CA) were collected from tibialis anterior (TA), medial gastrocnemius (MG), and sternocleidomastoid (SC) muscles

bilaterally. TA and MG were selected because of their roles as primary agonist muscles responding to forward and backward perturbations, and SC was selected as a primary indicator of startle responses (Brown et al. 1991; Campbell et al. 2013; Nonnekes et al. 2015). EMG signals were analog filtered with a 500 Hz low-pass anti-alias filter and sampled at 1000 Hz. Skin was scrubbed with an alcohol pad and shaved if necessary prior to electrode placement. Silver silver-chloride disc electrode pairs were placed with 2 cm inter-electrode distance.

3.4.6 EMG data preprocessing

Raw EMG signals were segmented into epochs of 2.4 seconds, beginning 400 ms before perturbation onset. Segmented EMG signals were high-pass filtered offline using a third-order zero-lag Butterworth filter with a cut-off frequency (-3 dB point) of 35 Hz, with a slope of 18 dB/octave. EMG signals were then centered on zero by subtracting the mean from each epoch, and were subsequently half-wave rectified. Rectified EMG signals were then low-pass filtered using a similarly designed Butterworth filter with a cut-off of 40 Hz. Bilateral EMG signals were then averaged across left and right sides.

3.4.7 Justification of time window of analysis for EEG and EMG data

The time window for primary analyses for both EEG and EMG data was defined a priori as 100 ms to 200 ms after the onset of perturbation acceleration. This time window begins at 100 ms because the onset of TA activity occurs approximately 100 ms after the onset of perturbation, with the initial burst of TA activity reflecting perturbation acceleration at a 100 ms delay (Welch and Ting 2009). Accordingly, perturbations were designed to reach peak perturbation acceleration within the first 100 ms after perturbation

onset. This same time bin is also ideal for analysis of the cortical balance N1, which occurs approximately 150 ms after the onset of platform acceleration (Marlin et al. 2014; Mierau et al. 2015). A later 200-300 ms time bin used in secondary analyses was not defined a priori.

3.4.8 Quantification of EEG

Subject-averaged cortical ERPs were created by averaging cortical activity across all trials within subjects at electrode Cz time-locked to perturbation onset. Likewise, condition-averaged cortical ERPs were created for each subject by averaging cortical activity across the 8 trial replicates within each of the 4 levels of perturbation acceleration in each direction at electrode Cz. The N1 peak was defined and quantified as the absolute peak amplitude in μV (of a negative peak) in a time window from 100 ms to 200 ms after the onset of platform motion for subject- and condition-averaged ERPs as well as on single-trial data. N1 peak latency was also quantified as the time between perturbation onset and N1 peak in subject- and condition-averaged ERPs.

3.4.9 Quantification of EMG

Muscle responses to perturbation were likewise quantified as the peak amplitude of EMG activity in the same time bin from 100 ms to 200 ms after the onset of platform motion, on both single trials and condition averages. On single trials and condition averages, peak measures of the muscle responses were normalized to have a maximum value of 1 within each subject.

3.4.10 Quantification of signal-to-noise ratios (SNRs)

On single trials and on condition averages, we quantified the peak value between 100-200 ms (as described above) and the standard deviation of the baseline period (-150 to -50 ms). These single-trial values were then averaged within subjects and then each subject's average peak measure was then divided by the subject's average baseline standard deviation as a measure of single-trial SNR for each subject. These measurements were also repeated on condition averages. We report these SNR values as the mean and standard deviation across subjects for single trials and condition averages.

3.4.11 Statistical Analyses

Step frequency. To examine the effect of perturbation acceleration and direction on the frequency of stepping responses, we performed an ANOVA on the number of trials in which subjects took steps at each level of perturbation acceleration in each direction. Post-hoc Tukey tests were used for all multiple comparisons. ANOVAs were performed in SAS statistical software.

Differences in cortical response amplitudes and latencies between subjects. We used a paired t-test to compare subject-averaged cortical response amplitudes and latencies between forward and backward perturbation directions to justify combining cortical responses across forward and backward perturbations in subject averages. We then used univariate linear regressions to assess correlations between the subject-averaged N1 amplitude or latency and between-subjects measures, including height, weight, age, and number of trials on which steps were taken. Given four comparisons, we apply a Bonferroni correction to obtain a significance threshold of $\alpha=0.05/4=0.0125$ for regressions on subject-averaged cortical responses. All linear regressions were performed in SAS, and all R^2

values are reported as adjusted R^2 values. Based on apparent relationships between cortical response amplitude, subject height, and frequency of stepping, we also used a univariate linear regression to assess correlation between subject height and frequency of stepping responses.

Effect of acceleration on cortical response amplitudes in condition averages and single trials. To examine the effect of perturbation acceleration and direction on cortical response amplitudes, we performed a balanced, mixed model ANOVA (with acceleration and direction as within-subject factors, including possible acceleration*direction interaction, accounting for subject as a random effect) on cortical response amplitudes on condition averages. We further quantified the effect of acceleration by using a univariate linear regression to assess the correlation between z-transformed single-trial cortical response amplitudes and peak acceleration measured on single trials across subjects, both within and across perturbation directions. The z-transformation was performed prior to this regression to remove between-subjects variance, in order to quantify the within-subjects effect of acceleration. Unlike the ANOVA, which used integer values to code for the four acceleration conditions, linear regressions used the maximum acceleration recorded in the first 100 ms of perturbations on single trials. To account for the combination of multiple subjects in the univariate linear regression, we report the p-value from a corresponding generalized linear model including subject and subject by acceleration interaction terms (p-values were identical within the precision reported). To further assess the distribution of the acceleration effect across subjects, we additionally performed linear regressions between single-trial cortical response amplitudes and perturbation acceleration within each subject individually. We report the number of subjects showing a significant correlation

between cortical response amplitude and perturbation acceleration (at α=0.05), and the mean and standard deviation of the significant R^2 values. The regressions between cortical response amplitude and perturbation acceleration within individuals used data without prior z-transformation so that slopes of the regressions could be compared across subjects. Based on apparent relationships between acceleration scaling relationships and subject-averaged cortical response amplitudes, we additionally performed a univariate linear regression to assess the correlation between subject-averaged cortical response amplitudes and the slopes from the cortical response amplitude vs. perturbation acceleration regressions.

Effect of acceleration on condition-averaged cortical response latencies. To examine the effect of perturbation acceleration and direction on cortical response latency, we performed a balanced, mixed model ANOVA (with acceleration and direction as within-subject factors, including possible acceleration*direction interaction, accounting for subject as a random effect) on cortical response latencies on condition averages. For comparison, we also perform the same ANOVA on the latency of peak perturbation acceleration in condition-averaged data. To assess the relationship between the peak latency of cortical responses and the peak latency of perturbation acceleration, we performed a univariate linear regression to assess the correlation between cortical response peak latency and perturbation acceleration peak latency.

Effect of trial number on cortical response amplitudes. To assess effects of trial number on cortical response amplitude, we performed a balanced, repeated measures, mixed model ANOVA (with within-subject factors direction and acceleration repeated across trial blocks, including possible acceleration*trial block interaction, accounting for

subject as a random effect) on single-trial cortical response amplitudes. We further quantified the effect of trial number by using a univariate linear regression to assess the correlation between z-transformed single-trial cortical response amplitudes and trial number across subjects, both within and across perturbation directions. This linear regression used trial numbers (1-64) instead of block numbers (1-8), which were used in the ANOVA. To account for the combination of multiple subjects in the univariate linear regression, we report the p-value from a corresponding generalized linear model including subject and subject by trial number interaction terms (p-values were identical within the precision reported). To further assess the distribution of the effect of trial number across subjects, we additionally performed linear regressions between single-trial cortical response amplitudes and trial number within each subject individually. We report the number of subjects showing a significant correlation between cortical response amplitude and trial number (at α=0.05), and the mean and standard deviation of the significant R^2 values. The regressions between cortical response amplitude and trial number within individuals used data without prior z-transformation so that slopes of the regressions could be compared across subjects. Based on apparent relationships between changes in cortical response amplitudes across trials and subject-averaged cortical response amplitudes, we additionally performed a univariate linear regression to assess the correlation between subject-averaged cortical response amplitudes and the slopes from the cortical response amplitude vs. trial number regressions. Because not all subjects showed significant dependencies of cortical response amplitudes with trial number or perturbation acceleration, we performed Fisher's exact test of independence to test for association

between dependence of cortical response amplitudes on perturbation acceleration and dependence of cortical response amplitudes on trial number.

Effect of acceleration on muscle response amplitudes. To examine the effect of perturbation acceleration and direction on muscle response amplitudes, we performed a balanced, mixed model ANOVAs (with acceleration and direction as within-subject factors, including possible acceleration*direction interaction, accounting for subject as a random effect) on muscle response amplitudes (independently for TA-EMG, MG-EMG, and SC-EMG) on condition averages. We further quantified the effects of acceleration by using univariate linear regressions to assess correlations between z-transformed single-trial muscle response amplitudes and peak acceleration measured on single trials across subjects, both within and across perturbation directions for each muscle. Again, the z-transformation was performed prior to these regressions to remove between-subjects variance, in order to quantify the within-subjects effects of acceleration. To account for the combination of multiple subjects in the univariate linear regression, we report the p-value from a corresponding generalized linear model including subject and subject by acceleration interaction terms (p-values were identical within the precision reported). To further assess the distributions of the acceleration effects across subjects, we additionally performed linear regressions between single-trial muscle response amplitudes and perturbation acceleration within each subject and each muscle individually. We report the number of subjects showing significant correlations between muscle response amplitudes and perturbation acceleration (at α=0.05), and the mean and standard deviation of the significant R^2 values.

Effect of trial number on muscle response amplitudes. To assess effects of trial number on muscle response amplitudes, we performed balanced, repeated measures, mixed model ANOVAs (with within-subject factors direction and acceleration repeated across trial blocks, including possible acceleration*trial block interaction, accounting for subject as a random effect) on single-trial muscle response amplitudes. We further quantified the effects of trial number by using univariate linear regressions to assess the correlations between z-transformed single-trial muscle response amplitudes and trial number across subjects, both within and across perturbation directions for each muscle. To account for the combination of multiple subjects in the univariate linear regression, we report the p-value from a corresponding generalized linear model including subject and subject by trial number interaction terms (no adjustments to p-values crossed the significance threshold of α=0.05). To further assess the distribution of the effects of trial number across subjects, we additionally performed linear regressions between single-trial muscle response amplitudes and trial number within each subject and each muscle individually. We report the number of subjects showing significant correlations between muscle response amplitudes and trial number (at α=0.05), and the mean and standard deviation of the significant R^2 values. Because not all subjects showed significant dependencies of muscle response amplitudes with trial number or perturbation acceleration for each muscle, we additionally performed Fisher's exact test of independence to test for association between dependence of response amplitudes for each muscle on perturbation acceleration and dependence of response amplitudes for the same muscle on trial number.

Associations between cortical and muscle response amplitudes. We used univariate linear regressions to assess correlations between z-transformed cortical response

amplitudes and z-transformed simultaneous (100-200ms) or subsequent (200-300ms) muscle response amplitudes across all subjects, both within and across perturbation directions, for each muscle and each time bin independently. To account for the combination of multiple subjects in the univariate linear regression, we report the p-value from a corresponding generalized linear model including subject and subject by response amplitude interaction terms (no adjustments to p-values crossed the significance threshold of α=0.05). To further assess the distribution of correlations between muscle and cortical response amplitudes across subjects, we additionally repeated these linear regressions within each subject individually. We report the number of subjects showing significant correlations between muscle and cortical response amplitudes (at α=0.05), and the mean and standard deviation of the significant R^2 values. To assess whether acceleration-dependence of cortical response amplitudes was associated with acceleration-dependence of simultaneous muscle response amplitudes, we performed Fisher's exact test of independence to test for association between acceleration-dependence of cortical response amplitudes and acceleration-dependence of simultaneous response amplitudes for each muscle. To assess whether dependence of cortical response amplitudes on trial number was associated with dependence of simultaneous muscle response amplitudes on trial number, we additionally performed Fisher's exact test of Independence to test for association between dependence of cortical response amplitudes on trial number and dependence of simultaneous response amplitudes for each muscle on trial number.

3.5 Results

3.5.1 Summary

Overall, our results revealed that cortical and muscle responses increased weakly in amplitude with increasing perturbation acceleration in condition-averaged and single-trial data. Cortical and muscle responses also decreased weakly in amplitude throughout the duration of the experiment across single-trial data. Muscle and cortical responses were only weakly correlated with each other across single trials. Further, increasing cortical response amplitudes with perturbation acceleration within an individual did not predict whether or not the individual would also show larger balance-correcting muscle responses or startle-related muscle responses with acceleration. In contrast, reduction in cortical response amplitude throughout the duration of the experiment was significantly associated with a reduction in startle-related muscle activity across subjects, but was not associated with a reduction in balance-correcting muscle activity.

3.5.2 Behavioral responses and body motion

All participants were able to recover balance without assistance but were not always able to resist stepping responses to perturbations. Despite instructions to recover balance without taking a step, subjects stepped on 243 of 1024 perturbations (24% of trials), with individuals ranging from 0-56 steps out of 64 perturbations. Stepping trials were not excluded from analysis because steps occurred later than the window of analysis, consistent with prior findings (Chvatal et al. 2011). Accordingly, by the end of our primary window of analysis (100 ms-200 ms) we observed foot displacements due to platform translation to be larger than 5 cm, while head displacements were much less than 0.5 cm (Figure 3-2). For these time windows analyzed, signal-to-noise ratios of cortical and muscle responses on single trials were about half that of condition averages (Figure 3-3) and were sufficient for single-trial analyses.

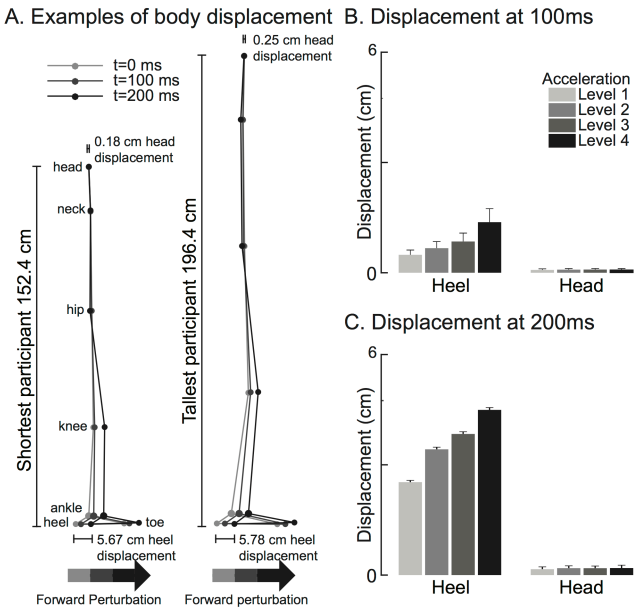


Figure 3-2. Subject kinematics during primary window of analysis. (A) Examples of body displacement are shown for the shortest (152.4cm, female, left) and tallest (196.4cm, male, right) participants in the first exposure to the largest forward perturbation at perturbation onset (light gray), 100ms (dark gray), and 200ms (black) after perturbation onset. The average absolute head and heel displacements for these individuals across perturbations at the highest acceleration at 200ms are indicated in text by the head and heel markers. (B) Bar plot shows the mean and standard deviation of heel and head displacements at 100ms after perturbation onset across subjects (N=15, 9 female, 6 male, 1 subject was excluded due to miscalibration), with the same measures at 200ms shown in (C).

Stepping responses were more frequent in forward perturbations and at higher accelerations. ANOVA revealed significant effects of perturbation direction ($F(1,108)=76.5$, $p<0.0001$) and acceleration level ($F(3,108)=5.3$, $p=0.002$) on step frequency. Post-hoc Tukey tests revealed stepping responses were more frequent in forward perturbations (36% of trials, SD 31) compared to backward perturbations (12%, SD 19, $p<0.05$). Stepping responses were more frequent at the highest acceleration level compared to all other levels ($p<0.05$), with no other significant differences in step frequency between acceleration levels. Additionally, the number of stepping responses

across subjects was inversely correlated with subject height (p=0.01, R^2=0.34), with shorter subjects taking compensatory steps more frequently.

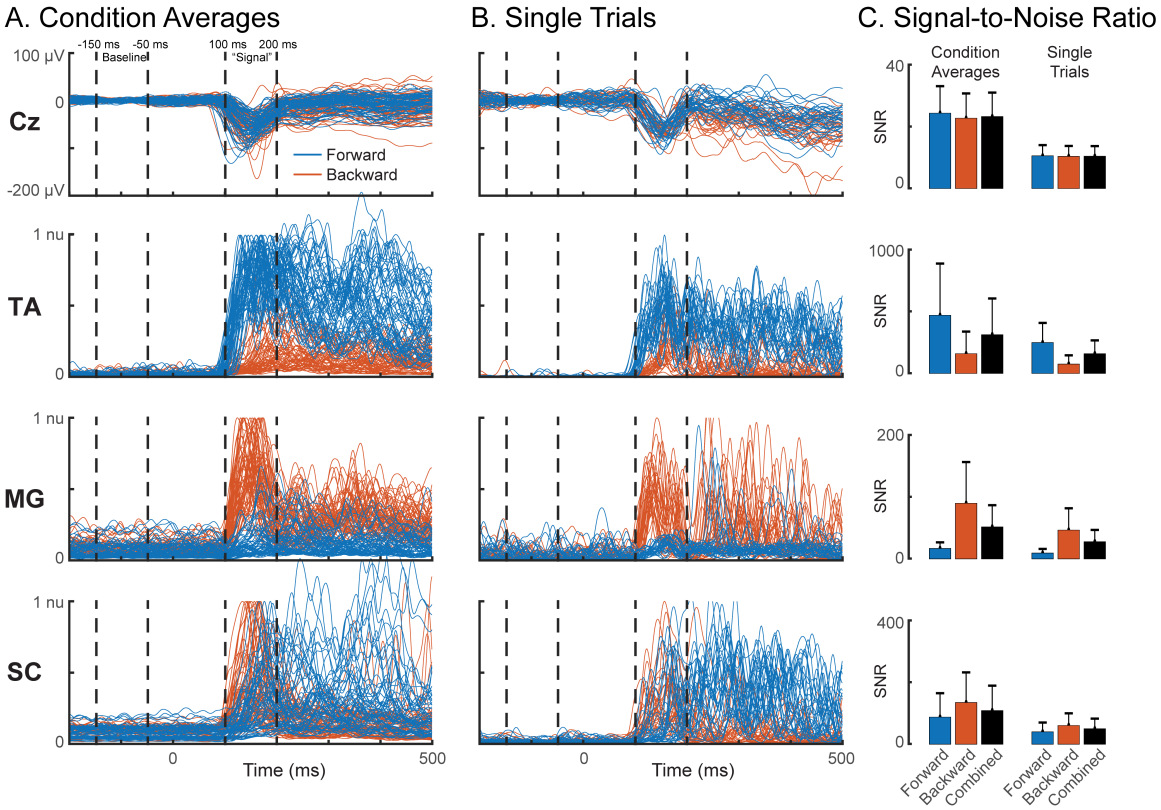


Figure 3-3. Signal-to-noise ratio (SNR) of condition-averaged and single-trial data. (A) Condition-averaged responses are shown for all conditions (4 accelerations x 2 directions) and all subjects (N=16, 9 female, 7 male). Responses to forward perturbations are in blue and responses to backward perturbations are in red. (B) Single-trial responses are shown in a representative subject (female) across all (64) trials. (C) SNR is shown for condition averages (left) and single trials (right) for forward perturbations (blue), backward perturbations (red), and both directions combined (black, N=16, 9 female, 7 male).

3.5.3 Cortical response amplitudes varied with subject height

Subject height was the only factor explaining large differences in cortical balance N1 amplitude between subjects (Figure 3-4). Subject-averaged cortical responses were combined across directions because cortical balance N1 (Figure 3-4AB; 56 µV, SD 23, 153

ms, SD 9) did not differ between forward (57 μV, SD 24, 153 ms, SD 10) and backward (56 μV, SD 23, 153 ms, SD 11) directions in peak amplitude (p=0.6, paired t-test) or latency (p=0.8). N1 amplitudes were inversely correlated with subject height, with larger amplitudes in shorter subjects (Figure 3-4C; p=0.002). The difference in N1 amplitude between subjects could not be explained by differences in weight (Figure 3-4D; p=0.3) or differences in actual (recorded) perturbation acceleration (p=0.4). N1 amplitude was not significantly correlated with age (Figure 3-4E; p=0.5) or number of steps taken (Figure 3-4F; p=0.04) at significance level α=0.0125. N1 latency did not show significant correlation with any of these measures (all p>0.0125).

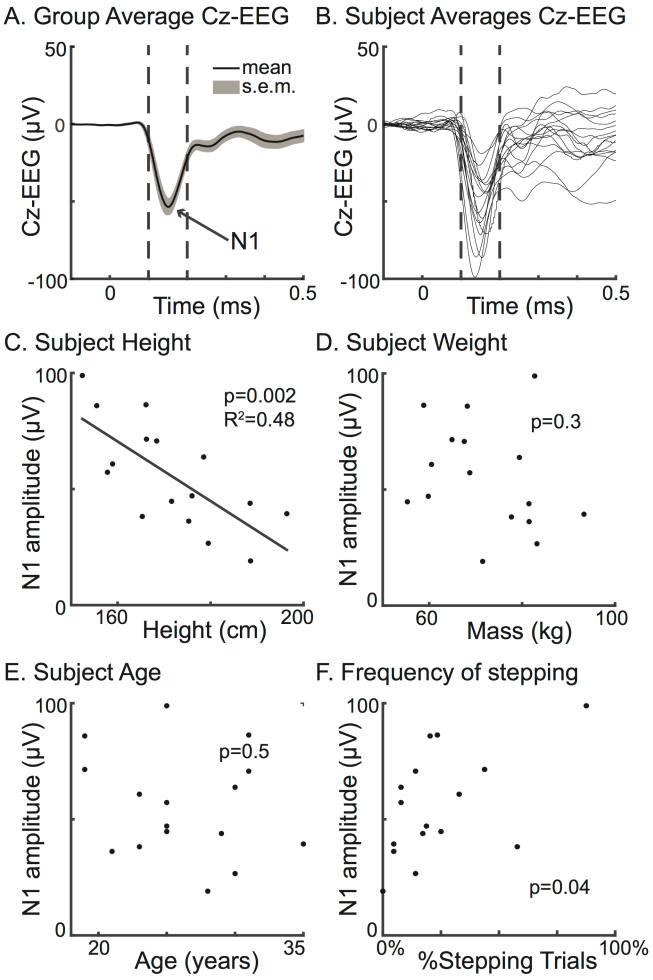


Figure 3-4. N1 amplitude across subjects is related to subject height. (A) In the grand average of Cz-EEG across all subjects, an N1 peak of 54μV occurred 152ms after perturbation onset. The standard error of the mean (s.e.m.) is shown in gray. (B) In Cz-EEG averages within subjects, cortical balance N1 peaks of 56μV (SD 23) occurred 153ms (SD 9) after perturbation onset. (C) N1 amplitude was inversely correlated with subject height (p=0.0002), but did not show significant associations with subject weight (D, p=0.3), subject age (E, p=0.5), or the proportion of trials on which subjects were unable to resist stepping responses (F, p=0.04) at significance level α=0.0125. In all panels, N=16 (9 female, 7 male).

3.5.4 Cortical response amplitudes increased with perturbation acceleration in condition averages and single trials

Cortical responses increased in amplitude with perturbation acceleration in condition averages (Figure 3-5) and on single trials (Figure 3-6A) and did not differ

between perturbation directions (Figure 3-5). ANOVA revealed a significant effect of acceleration ($F(3,105)=19.7$, $p<0.0001$) but not direction ($p=0.7$) on the cortical balance N1 peak amplitude in condition averages. Acceleration by direction interaction effects were not significant ($p=0.5$). A post-hoc Tukey test revealed a significant increase in cortical balance N1 peak amplitude in all comparisons with increasing acceleration (Figure 3-5D; $p<0.05$), except for the comparison between acceleration levels 1 and 2. Single-trial *z*-scored N1 amplitudes were positively correlated with peak perturbation acceleration recorded on single trials (Figure 3-6A; $p<0.0001$). Combining data across directions within individuals, 12 of 16 individuals showed significant positive correlations between single-trial N1 amplitudes and peak acceleration ($p<0.05$), with $R^2=0.14$ (SD 0.06) across directions (forward: $R^2=0.19$, SD 0.13; backward: $R^2=0.20$, SD 0.09). The slopes of significant acceleration scaling relationships were positively correlated with subject-averaged N1 amplitudes (N=12, $p=0.04$, $R^2=0.30$), such that stronger acceleration scaling relationships were observed in subjects with larger N1 amplitudes. A similar correlation is obtained when including the slopes from non-significant acceleration scaling relationships (N=16, $p=0.002$, $R^2=0.48$).

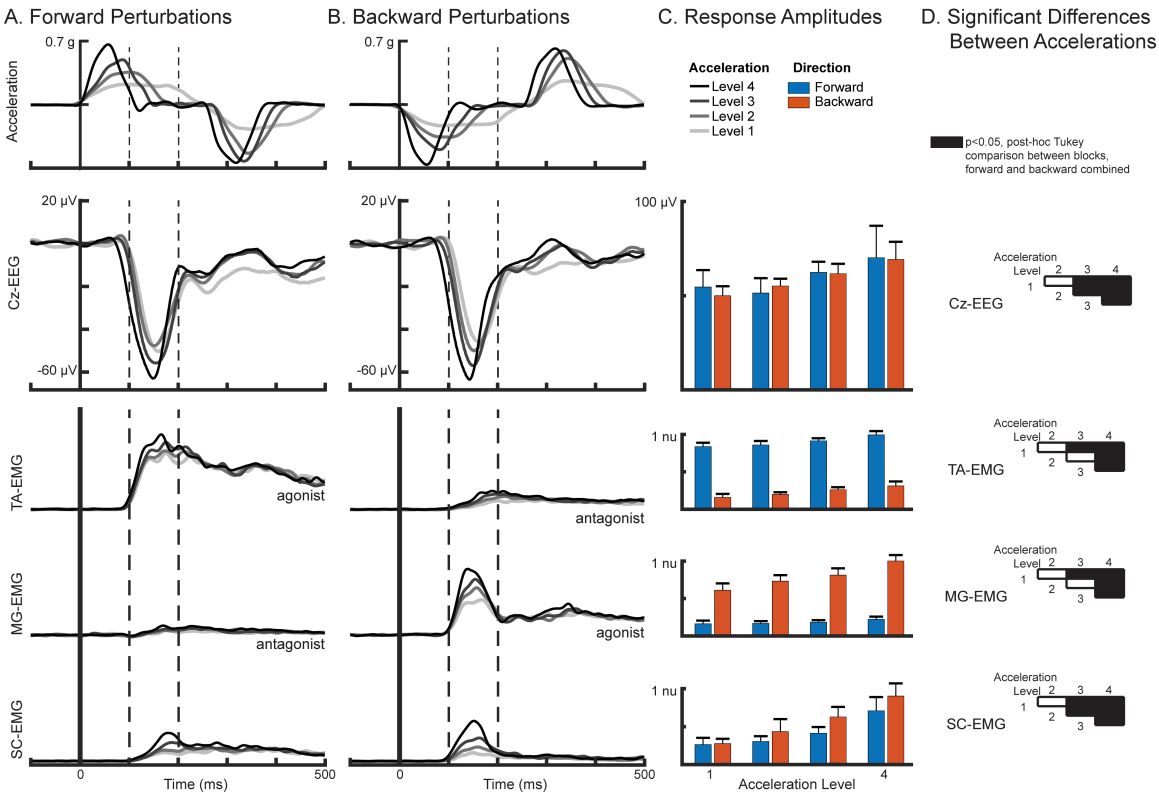


Figure 3-5. Grand averages of cortical and muscle responses by acceleration. (A) Averaged responses to forward perturbations are plotted by acceleration level. Darker lines indicate larger accelerations. Peak platform acceleration is reached in the first 100ms, and response amplitudes are quantified in the following 100ms (indicated by dashed vertical lines). (B) Averaged responses to backward perturbations are plotted by acceleration level. (C) Bar plots show mean and standard deviation of response amplitudes on condition averages by direction and by acceleration level. Subject-averages were subtracted before calculating standard deviations for error bars to more closely match ANOVA analyses. Responses to forward perturbations are in blue and responses to backward perturbations are in red. (D) Significant post-hoc comparisons (Tukey, p<0.05) between acceleration levels are indicated by black spaces on the comparison grid. In all panels, N=16 (9 female, 7male).

3.5.5 Cortical response latencies were shorter for larger perturbations

Cortical response latency on condition averages decreased with increasing perturbation acceleration and did not differ between perturbation directions. ANOVA revealed a significant effect of acceleration ($F(3,105)=34.4$, $p<0.0001$) but not direction

(p=0.8) on cortical balance N1 peak latency in condition averages. Acceleration by direction interaction effects were not significant (p=0.3). A post-hoc Tukey test revealed a significant decrease in peak latency with each comparison of increasing acceleration (p<0.05) except for the comparison between acceleration levels 2 and 3. We also note that the perturbations in the different acceleration conditions also varied in acceleration peak latency (Figure 3-1; $F(3,105)=636.7$, p<0.0001), with significant differences in acceleration peak latency between all comparisons of acceleration levels (p<0.05). The highest acceleration (level 4) had the shortest peak latency, followed by acceleration level 3, then level 1, with the longest latency at acceleration level 2. Accordingly, cortical balance N1 peak latency was positively correlated with the latency of peak perturbation acceleration in condition-averaged data (p<0.0001, R^2=0.19), with greater variation in acceleration peak latency than cortical balance N1 peak latency.

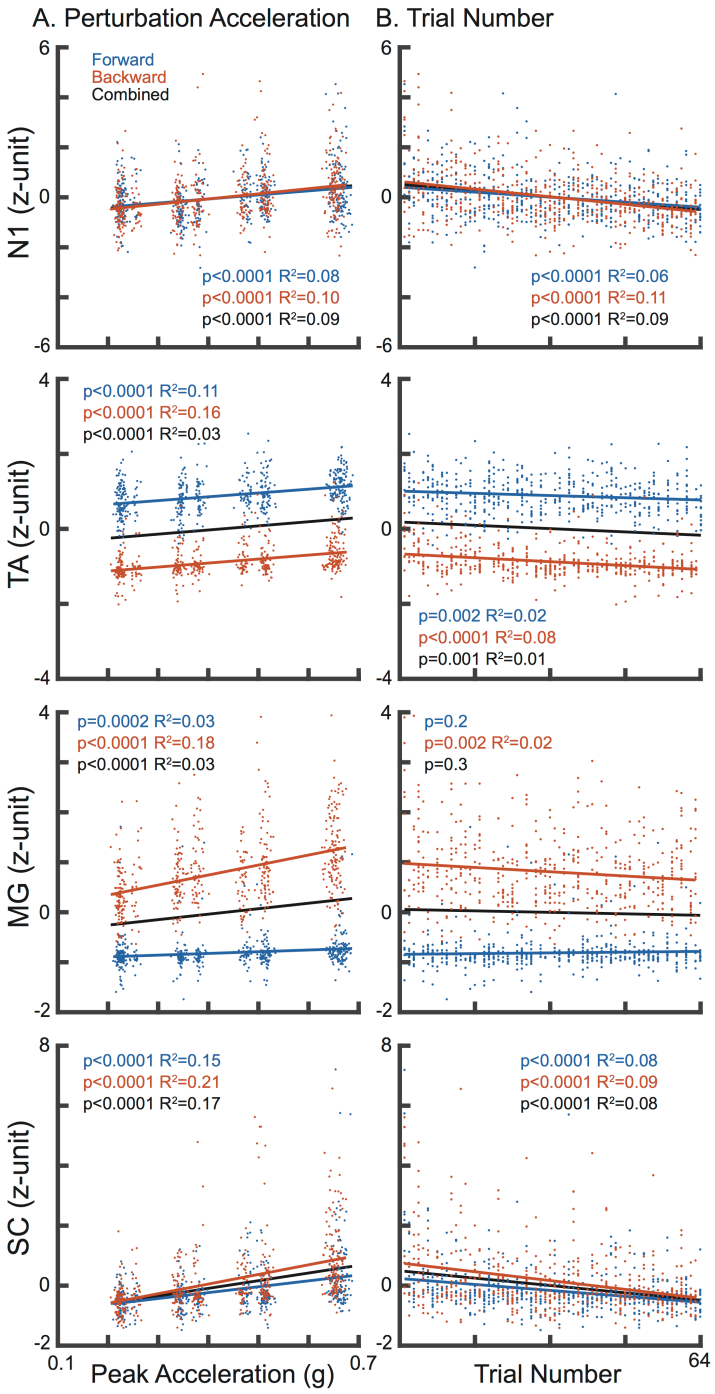


Figure 3-6. (A) Z-scored single-trial response amplitudes are plotted against peak acceleration measured on single trials. Data and regression lines from forward perturbations are in blue and data and regression lines from backward perturbations are in red. Regression lines including data across both perturbation directions are in black. P-values and adjusted R^2-values of the regression lines follow the same color coding. (B) *Z*-scored single-trial response amplitudes are plotted against trial number. In all panels, N=16 (9 female, 7 male).

3.5.6 Cortical response amplitudes decreased across trials

Single-trial cortical responses decreased in amplitude across trial blocks in both directions (Figure 3-6B and Figure 3-7). ANOVA revealed a significant effect of trial block ($F(7,105)=14.1$, $p<0.0001$) on the cortical balance N1 peak amplitude on single trials. Post-hoc Tukey tests revealed that the cortical balance N1 was significantly larger in the first trial block compared to blocks 3-8 ($p<0.05$). Other significant comparisons are indicated in Figure 3-7D. Effects of acceleration were consistent with those reported for condition averages above. Acceleration by block interaction effects were not significant ($p=0.6$). Single-trial *z*-scored N1 amplitudes were inversely correlated with trial number (Figure 3-6B; $p<0.0001$). Combining data across directions within individuals, 10 of 16 individuals showed significant negative correlations between single-trial N1 amplitudes and trial number ($p<0.05$), with $R^2=0.18$ (SD 0.10) across directions (forward: $R^2=0.19$, SD 0.07; backward: $R^2=0.28$, SD 0.13). The slopes of significant reductions in N1 amplitude across single trials were inversely correlated with subject-averaged N1 amplitudes (N=10, $p=0.03$, $R^2=0.64$), such that individuals with larger subject-averaged N1 amplitudes showed greater reductions in single-trial N1 amplitude across trials. A similar correlation is obtained when including the slopes from non-significant reduction in N1 amplitude across trials (N=16, $p=0.03$, $R^2=0.25$). The individuals who showed significant correlations between N1 amplitude and trial number were statistically independent of those who showed significant correlations between N1 amplitude and perturbation acceleration (Fisher's exact test of independence, $p=0.1$).

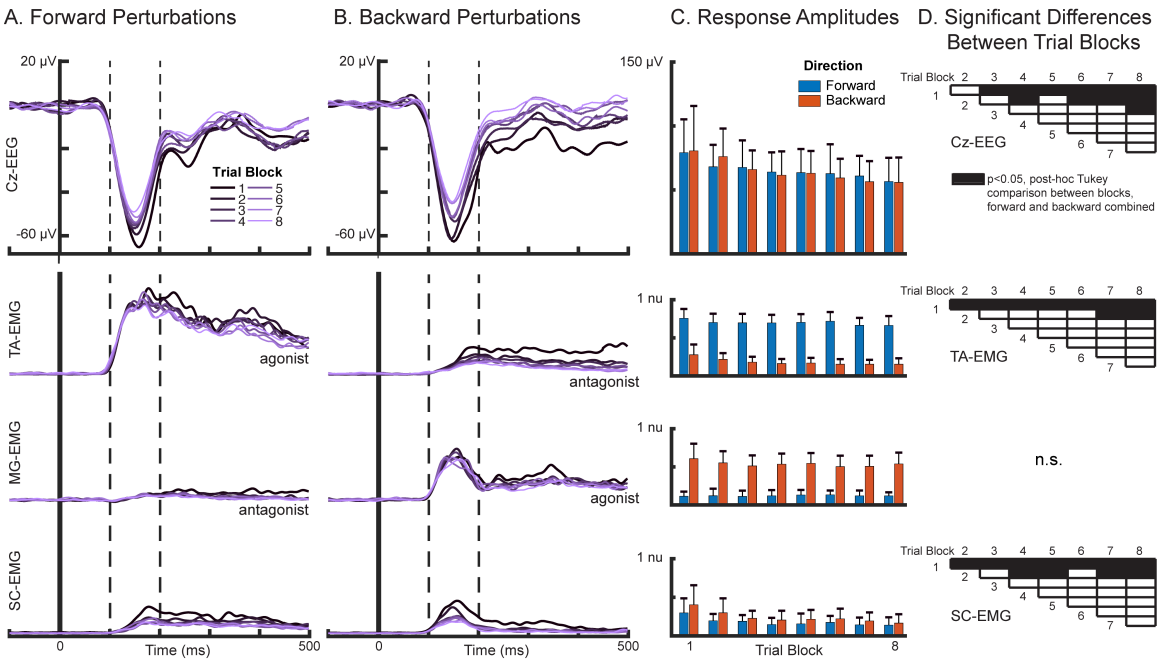


Figure 3-7. Grand averages of cortical and muscle responses by trial block. (A) Averaged responses to forward perturbations are plotted by trial block. Darker shades of purple indicate earlier trial blocks. (B) Averaged responses to backward perturbations are plotted by trial block. (C) Bar plots show mean and standard deviation of response amplitudes on single trials by direction and by trial block. Subject-averages were subtracted before calculating standard deviations for error bars to more closely match ANOVA analyses. Responses to forward perturbations are in blue and responses to backward perturbations are in red. (D) Significant post-hoc comparisons (Tukey, $p<0.05$) between trial blocks are indicated by black spaces on the comparison grid. In all panels, N=16 (9 female, 7 male).

3.5.7 Muscle response amplitudes increased with acceleration and varied by perturbation direction in condition averages and single trials

Muscle responses increased in amplitude with perturbation acceleration in condition averages (Figure 3-5) and on single trials (Figure 3-6B). ANOVA revealed significant effects of acceleration on the initial burst of muscle activity in TA-EMG ($F(3,105)=17.4$, $p<0.0001$), MG-EMG ($F(3,105)=28.4$, $p<0.0001$), and SC-EMG ($F(3,105)=58.6$, $p<0.0001$) in condition averages. Post-hoc Tukey tests revealed TA-EMG and MG-EMG were significantly larger at the highest acceleration compared to all other

levels and higher at acceleration level 3 compared to level 2 (Figure 3-5D; $p<0.05$), and SC-EMG was significantly larger for all comparisons of increasing acceleration ($p<0.05$) except for the comparison between acceleration levels 1 and 2. Single-trial *z*-scored muscle response amplitudes were positively correlated with recorded peak acceleration in both directions for TA-EMG (Figure 3-6A; $p<0.0001$), MG-EMG (forward: $p=0.0002$; backward: $p<0.0001$; combined: $p<0.0001$), and SC-EMG ($p<0.0001$).

Muscle responses also varied by direction. ANOVA revealed significant effects of perturbation direction on TA-EMG ($F(1,105)=1670.2$, $p<0.0001$), MG-EMG ($F(1,105)=1139.8$, $p<0.0001$) and SC-EMG ($F(1,105)=20.4$, $p<0.0001$). Post-hoc Tukey tests revealed TA-EMG was larger in forward perturbations ($p<0.05$), while MG-EMG and SC-EMG were larger in backward perturbations ($p<0.05$). An acceleration by direction interaction effect was found for MG-EMG ($F(3,105)=14.9$, $p<0.0001$), but not TA-EMG ($p=0.9$) or SC-EMG ($p=0.09$). The acceleration by direction interaction for MG-EMG was characterized by stronger acceleration scaling in backward perturbations (Figure 3-6A).

Acceleration scaling of single-trial muscle response amplitudes was observed within most individuals. 12 of 16 individuals showed significant positive correlations between single-trial *z*-scored TA-EMG amplitudes and peak acceleration in at least one direction ($p<0.05$), with $R^2=0.24$ (SD 0.12) in forward perturbations and $R^2=0.29$ (SD 0.12) in backward perturbations. 13 of 16 individuals showed significant positive correlations between single-trial *z*-scored MG-EMG amplitudes and peak acceleration in at least one direction ($p<0.05$), with $R^2=0.28$ (SD 0.15) in forward perturbations and $R^2=0.27$ (SD 0.15) in backward perturbations. Combining data across directions within individuals, 15 of 16 individuals showed significant positive correlations between single-trial *z*-scored SC-EMG

amplitudes and peak acceleration (p<0.05), with R^2=0.18 (SD 0.12) across directions (forward: R^2=0.33, SD 0.13; backward: R^2=0.27, SD 0.11).

3.5.8 Muscle response amplitudes decreased across trials

Single-trial TA-EMG and SC-EMG muscle responses decreased in amplitude across trial blocks in both directions, while MG-EMG only decreased across forward perturbations (Figure 3-7). ANOVA revealed a significant effect of trial block on TA-EMG (F(7,105)=10.2, p<0.0001) and SC-EMG (F(7,105)=22.0, p<0.0001), but not MG-EMG (p=0.1). Post-hoc Tukey tests revealed that both TA-EMG and SC-EMG were larger in the first trial block compared to all other blocks (p<0.05). Other significant post-hoc comparisons are indicated in Figure 3-7D. Effects of acceleration and direction were consistent with those reported for condition averages above. Acceleration by block interaction effects were not significant for TA-EMG (p=0.99), MG-EMG (p=0.2), or SC-EMG (p=0.06). Single-trial z-scored muscle response amplitudes were inversely correlated with trial number in both directions for TA-EMG (Figure 3-6B; forward: p=0.002; backward: p<0.0001; combined: p=0.001) and SC-EMG (p<0.0001). MG-EMG amplitudes were inversely correlated with trial number only across perturbations in the backward direction (forward: p=0.2; backward: p=0.002; combined: p=0.3).

Reduction in single-trial muscle response amplitude on a trial-by-trial basis within individuals was most apparent for non-balance-correcting muscle activity. 11 of 16 individuals showed significant inverse correlations between single-trial z-scored SC-EMG amplitudes and trial number (p<0.05), with R^2=0.11 (SD 0.09) across directions (forward: R^2=0.17, SD 0.07; backward: R^2=0.21, SD 0.10). 10 of 16 individuals showed reductions

of single-trial *z*-scored antagonist TA-EMG amplitudes with trial number across backward perturbations ($p<0.05$, $R^2=0.26$, SD 0.09), whereas only 3 of 16 individuals showed reductions of single-trial *z*-scored agonist TA-EMG amplitudes with trial number across forward perturbations ($p<0.05$, $R^2=0.18$, SD 0.06). Single-trial *z*-scored MG-EMG amplitudes reduced with trial number in 4 of 16 individuals in backward perturbations ($p<0.05$, $R^2=0.22$, SD 0.10) and 3 of 16 individuals in forward perturbations ($p<0.05$, $R^2=0.25$, SD 0.19). No significant associations were found between individuals who showed correlations between muscle response amplitudes and perturbation acceleration and individuals who showed correlations between muscle response amplitudes and trial number in either direction (Fisher's exact test of independence, all $p>0.05$).

3.5.9 Associations between cortical and muscle response amplitudes were very weak

Single-trial cortical response amplitudes were weakly correlated to simultaneous muscle response amplitudes (Figure 3-8A) but showed relatively stronger correlations with startle-related muscle responses than with balance-correcting muscle responses. Single-trial *z*-transformed cortical balance N1 amplitudes were weakly correlated to simultaneous *z*-transformed EMG activity in both directions in TA-EMG (Figure 3-8A; forward: $p=0.0002$; backward: $p<0.0001$; combined: $p=0.001$) and SC-EMG ($p<0.0001$), but were only correlated to simultaneous *z*-transformed MG-EMG in backward perturbations (forward: $p=0.2$; backward: $p<0.0001$; combined: $p<0.0001$). Combining single-trial data across perturbation directions within individuals, 11 of 16 individuals showed significant correlations between single-trial cortical balance N1 amplitude and simultaneous SC-EMG ($p<0.05$) with $R^2=0.40$ (SD 0.15) (forward: $R^2=0.36$, SD 0.21; backward: $R^2=0.50$, SD 0.20). 9 of 16 individuals showed significant correlations between single-trial cortical

balance N1 amplitude and simultaneous antagonist TA-EMG in backward perturbations (p<0.05, R^2=0.36, SD 0.18), whereas only 3 of 16 individuals showed significant correlations between single-trial N1 amplitude and simultaneous agonist TA-EMG in forward perturbations (p<0.05, R^2=0.17, SD 0.10). Only 3 of 16 individuals showed significant correlations between single-trial cortical balance N1 amplitude and simultaneous agonist MG-EMG in backward perturbations (p<0.05, R^2=0.26, SD 0.16), whereas 7 of 16 individuals showed significant correlations between single-trial N1 amplitude and simultaneous antagonist MG-EMG in forward perturbations (p<0.05, R^2=0.14, SD 0.04).

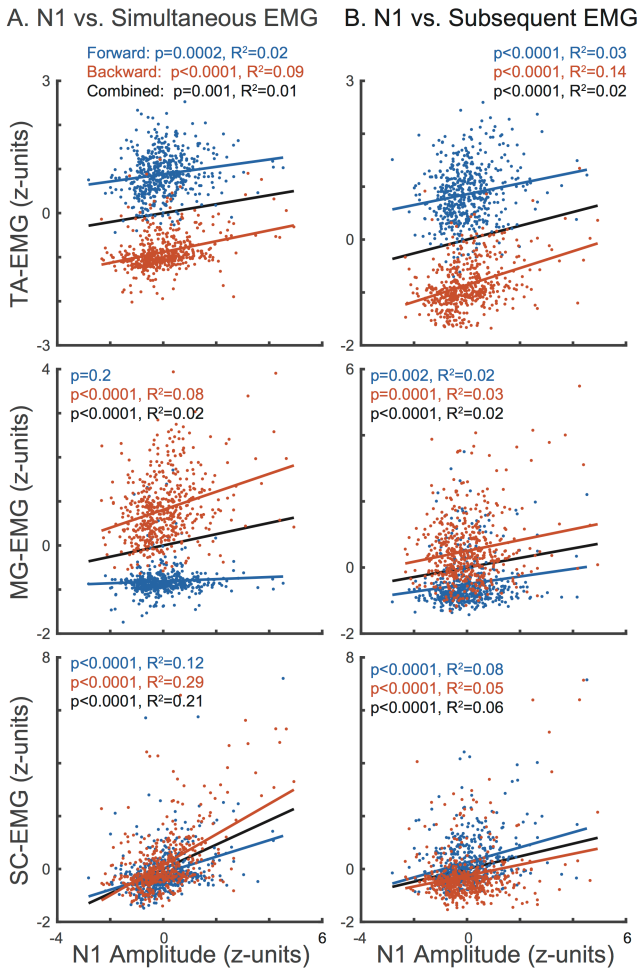


Figure 3-8. Correlations between cortical and muscle response amplitudes were weak. Linear regressions between z-transformed cortical balance N1 amplitudes and (A) simultaneous (100-200ms) and (B) subsequent (200-300ms) z-transformed muscle response amplitudes. Data and regression lines from forward perturbations are in blue and data and regression lines from backward perturbations are in red. Regression lines including data across both perturbation directions are in black. *P*-values and adjusted R^2-values of the regression lines follow the same color coding. In all panels, N=16 (9 female, 7 male).

Correlations between single-trial cortical response amplitude and perturbation acceleration were not predictive of correlations between muscle response amplitude and perturbation acceleration. Individuals who showed significant correlations between perturbation acceleration and single-trial cortical balance N1 amplitude were statistically independent of individuals who showed significant correlations between perturbation

acceleration and simultaneous single-trial TA-EMG (Fisher's exact test of independence, forward: p=0.2; backward: p=0.4), MG-EMG (forward: p=0.3; backward: p=0.1), and SC-EMG (p=0.3 across directions).

Reduction in single-trial cortical response amplitude with trial number was associated with a reduction in startle-related muscle activity but was not associated with a reduction in balance-correcting muscle activity. There was a significant association between individuals who showed significant correlations between trial number and cortical balance N1 and individuals who showed significant correlations between trial number and SC-EMG (Fisher's exact test of independence, p=0.03 across directions). Specifically, individuals who showed a reduction (or lack of reduction) in cortical response amplitude across trials were more likely to show a similar reduction (or lack of reduction) in SC-EMG amplitude across trials. In contrast, individuals who showed significant correlations between trial number and single-trial cortical balance N1 amplitude were statistically independent of individuals who showed significant correlations between trial number and simultaneous TA-EMG (forward: p=0.5; backward: p=0.3) or MG-EMG (forward: p=0.3; backward: p=0.4).

Single-trial cortical response amplitudes were also weakly correlated to subsequent muscle response amplitudes (Figure 3-8B). Single-trial z-transformed cortical balance N1 amplitudes were weakly correlated to subsequent (200-300 ms) z-transformed EMG activity in both directions in TA-EMG (Figure 3-8B; p<0.0001), MG-EMG (forward: p=0.002; backward: p=0.0001; combined: p<0.0001), and SC-EMG (p<0.0001). Combining single-trial data across perturbation directions within individuals, 7 of 16 individuals showed significant correlations between cortical balance N1 amplitude and

subsequent (200-300 ms) SC-EMG (p<0.05) with R^2=0.23 (SD 0.10) across directions (forward: R^2=0.25, SD 0.15; backward: R^2=0.25, SD 0.16). 9 of 16 individuals showed significant correlations between single-trial cortical balance N1 amplitude and subsequent antagonist TA-EMG in backward perturbations (p<0.05, R^2=0.35, SD 0.18), whereas only 4 of 16 individuals showed significant correlations between N1 amplitude and subsequent agonist TA-EMG in forward perturbations (p<0.05, R^2=0.14, SD 0.04). Only 4 of 16 individuals showed significant correlations between cortical balance N1 amplitude and subsequent agonist MG-EMG in backward perturbations (p<0.05, R^2=0.15, SD 0.04), and only 2 of 16 individuals showed significant correlations between N1 amplitude and subsequent antagonist MG-EMG in forward perturbations (p<0.05, R^2=0.32, SD 0.20).

3.6 Discussion

Our results suggest that cortical and muscle responses to balance perturbation are elicited by common sensory inputs, but their amplitudes are modulated by independent mechanisms. Although both cortical and muscle responses each scaled weakly with perturbation acceleration, consistent with prior studies concluding shared sensory drive (Berger et al. 1987; Dietz et al. 1985b; 1984b; Dietz et al. 1985a; Staines et al. 2001), acceleration scaling was not apparent in all individuals. Moreover, scaling of cortical response amplitude to sensory input, and attenuation of cortical responses across trials were dissociated from the amplitude of balance-correcting muscle responses on a trial-by-trial basis within subjects. In contrast, attenuation of cortical responses was associated with attenuation of startle responses, consistent with a reduction in perceived threat (Adkin et al. 2008). Moreover, individuals with larger N1 amplitudes had greater attenuation across trials, suggesting that these individuals initially perceived perturbations as more

threatening. Dissociations in modulation of cortical and balance-correcting muscle response amplitudes are likely due to differences between spinal and supraspinal sensory gating (Berger et al. 1990; Staines et al. 2000). Accordingly, cortical responses in balance have been shown to be influenced by perceived threat (Adkin et al. 2008; Mochizuki et al. 2010), attention (Little and Woollacott 2015; Quant et al. 2004b), and predictability (Adkin et al. 2008; Adkin et al. 2006; Mochizuki et al. 2010; Mochizuki et al. 2008), which may vary between subjects and across trials.

Our averaged data were in agreement with prior studies showing cortical response scaling with perturbation amplitude (Mochizuki et al. 2010) and suggesting shared sensory inputs to cortical and muscle responses (Berger et al. 1987; Dietz et al. 1985b; 1984b; Dietz et al. 1985a; Staines et al. 2001). However we demonstrated a trial-by-trial dissociation between cortical and muscle response scaling to sensory input within subjects. Studies in the 1980s relied on averaging as many as 100 trials (Dietz et al. 1985b; 1984b; Dietz et al. 1985a), which may have been necessary due to motor artifacts in perturbed walking, as well as the lower signal-to-noise ratio of older EEG technology. Recent studies using postural perturbations average across 15-60 trials per condition (Adkin et al. 2008; Adkin et al. 2006; Mochizuki et al. 2010; Mochizuki et al. 2009a; Mochizuki et al. 2008; Quant et al. 2004b; Quant et al. 2004a). However, Quintern and colleagues (1985) and Mierau and colleagues (2015) both used single-trial analyses to demonstrate a dissociation between cortical and balance-correcting muscle responses as we do here. The feasibility of single-trial analysis depends in part on advances in EEG technology, including the use of active electrodes, but may also depend on details of the experimental design. In particular, applying perturbations at the feet induces smaller and later motion of the head compared

to the rest of the body (Figure 3-2). Additionally, we only delivered perturbations during periods of low background EEG activity, which we monitored during the experiment.

Our results reinforce the idea that the cortical balance N1 is not yoked in amplitude to the initial brainstem-mediated corrective muscle activity (Mierau et al. 2015; Quintern et al. 1985) that arises from sensory inputs from perturbation (Lockhart and Ting 2007; Welch and Ting 2009; 2008). This was particularly evident in individuals who exhibited scaling to acceleration in only muscle or cortical responses, but not both, and was supported by the very weak correlations between single-trial muscle and cortical response amplitudes. Nevertheless, the N1 response is time-locked to the perturbation and likely triggered by the sensory input that modulates balance-correcting muscle responses. This is supported by the comparable time delay for both muscle and cortical responses in a patient with slow peripheral conduction velocities (Dietz et al. 1985a). Our perturbation effects on the balance N1 are in line with, but smaller than those reported by Mochizuki et al. (2010) who used larger differences in perturbation amplitudes, but could not dissociate the effects of perturbation acceleration, peak velocity, total displacement, or perturbation duration. While we did not previously define individuals as either "scalers" or "non-scalers" in terms of their muscle responses due to perturbation acceleration, we did observe a range of sensitivities to perturbation acceleration across individuals (Welch and Ting 2009; 2008). Similarly, a prior study using seated perturbations also showed cortical response scaling with acceleration in two of three subjects (Staines et al. 2001), where the lack of scaling in one subject was suggested to be due to a ceiling effect in response amplitude. However, our study shows greater acceleration scaling of cortical responses in individuals with larger cortical response amplitudes. Therefore, rather than disappearing due to saturation,

acceleration scaling may be an additional component of the cortical responses that can be reduced or absent in some individuals. Although we cannot rule out the possibility that a wider range of accelerations might have revealed scaling in more individuals, some subjects could intrinsically be non-responders, or the lack of scaling in some individuals could be due to more transient factors, such as differences in attention or threat assessment.

Attenuation of cortical responses was associated with attenuation of startle responses rather than attenuation of balance-correcting muscle responses. Attenuation of cortical balance N1 amplitude has previously been dissociated from balance-correcting muscle responses across perturbations that were predictable in direction and amplitude (Mierau et al. 2015; Quintern et al. 1985). Because our perturbation directions and amplitudes were randomized, we did not expect muscle or cortical responses to decrease across trials (Horak and Diener 1994; Horak and Nashner 1986; Welch and Ting 2009; 2008; 2014). However, replicating the dissociation between attenuations of cortical balance N1 and balance-correcting muscle responses, suggests that the decrease in cortical response amplitude is not related to changes in sensory activation nor adaptation of the corrective muscle responses. Instead, we found the attenuation of cortical responses was associated with attenuation of sternocleidomastoid muscle activity, representative of the startle reflex (Nonnekes et al. 2015), suggesting attenuation of cortical responses was related to a reduction in perceived threat with experience (Adkin et al. 2008; Mochizuki et al. 2010). Although the sternocleidomastoid muscle may also be activated as part of the balance-correcting motor response, both startling acoustic stimuli and postural perturbations activate the sternocleidomastoid muscle in coordination with the masseter muscle of the jaw, which does not contribute to postural correction. These neck and jaw muscles

habituate on similar time-scales, both faster and to a greater extent than habituation of primary agonist muscle activations in the leg (Oude Nijhuis et al. 2010). Thus, contributions of balance-correcting activations of the sternocleidomastoid muscle are likely smaller than contributions of startle-reflex activity. Although our perturbations were unpredictable in timing, amplitude, and direction, we cannot exclude the possibility that other features of the perturbation became more predictable with experience, which could have further influenced cortical response amplitudes across trials (Adkin et al. 2006).

Our data suggest that differences in cortical responses amplitudes between subjects were related to differences in subject height and perceived threat, but there are likely other factors that we did not measure. The effect of subject height reflects our failure to match perturbation magnitudes to body size, but height only explains half of the variation between subjects. Specifically, taller subjects experienced proportionally smaller perturbations relative to their body size, consistent with their smaller cortical responses. Perturbations were relatively more difficult for shorter subjects, who had higher rates of stepping responses. The effect of height could not be attributed to differences in subject weight or perturbation acceleration, as the same variability in peak perturbation acceleration was observed in all individuals and in both perturbation directions. Although age has been previously shown to influence the cortical balance N1 amplitude (Duckrow et al. 1999), we did not find a relationship between N1 amplitude and age, likely due to our relatively narrow age distribution (26, SD 5, range 19-35). Individuals showing greater attenuation of cortical responses across trials also displayed larger cortical response amplitudes overall, suggesting they initially perceived greater threat. Although larger cortical responses were also associated with higher rates of stepping and greater increases in amplitude with

perturbation acceleration, the lack of a relationship between increasing cortical responses with acceleration and decreasing cortical responses across trials, and the lack of a relationship between either of these effects and the rate of stepping suggests that these were independent factors contributing to differences in cortical response amplitudes between subjects. Additionally, some subjects may intrinsically produce larger cortical responses to perturbation. Indeed, evoked cortical responses in cognitive tasks have a strong genetic component. One example is the influence of dopamine-related genetic polymorphisms on the cortical error-related and feedback-related negativities in cognitive assessments (Ullsperger 2010). Although we are not aware of any genetic variants on the cortical balance N1, it is possible that such influences exist.

It is also possible that differences in cortical response amplitudes and modulation between subjects and across trials reflect more transient factors, such as attention. Although we did not directly measure attention in the present study, subjects anecdotally reported being more nervous and alert at the beginning of the experiment, becoming more comfortable and less attentive as they realized they were not likely to fall, which is consistent with previously reported reductions in electrodermal responses to repeated perturbations (Sibley et al. 2008). As such, previously reported decreases in the cortical balance N1 amplitude with reduced attention (Little and Woollacott 2015; Quant et al. 2004b) may contribute to the reduction in cortical response amplitudes observed across trials in the present study, and could explain why individuals who scaled cortical responses with perturbation acceleration showed larger amplitude cortical responses. Additionally, it is possible that the specific focus of attention could have influenced whether an individual's cortical responses tracked perturbation acceleration. Indeed, asking subjects to pay

attention to either perturbation velocity or perturbation magnitude in order to rank successive perturbations with respect to either feature influenced afferent activity in a manner that enhanced discrimination of the task-relevant feature at the expense of task-irrelevant information (Ribot-Ciscar et al. 2009). Further, focusing attention toward cutaneous or proprioceptive stimuli based on task goals has been demonstrated to selectively facilitate somatosensory evoked cortical potentials (SEPs) to task-relevant information while suppressing task-irrelevant information (Staines et al. 2000) via attentional mechanisms in a brain network involving prefrontal cortex (Staines et al. 2002). Although SEPs are distinct from the cortical balance N1, occurring over somatosensory cortex in response to stimulation of somatosensory nerves, this example demonstrates a more complex influence of attention on ascending sensory information to the cortex, which could possibly extend to the cortical balance N1.

CHAPTER 4. BETTER BALANCE ABILITY IS ASSOCIATED WITH SMALLER PERTURBATION-EVOKED CORTICAL RESPONSES IN HEALTHY YOUNG ADULTS

4.1 Abstract

Background: Reactive balance recovery evokes a negative peak of cortical activity (N1) that is simultaneous to brainstem-mediated involuntary balance-correcting muscle activity and can be recorded using scalp electroencephalography (EEG). While the processes underlying the cortical N1 response during reactive balance are unclear, we recently observed larger N1 responses in individuals who had greater difficulty resisting compensatory steps in response to balance perturbations (Payne et al. 2018). **Research Question:** We hypothesized that people with lower balance ability engage more cortical processes during balance recovery. We predicted that people with lower balance ability would exhibit larger cortical N1 responses during balance perturbations. **Methods:** In 20 healthy young adults (11 female, ages 19-38) we measured the amplitude of the cortical N1 response evoked by 48 backward translational support-surface perturbations of unpredictable timing and amplitude. Perturbations included an easy (8 cm) perturbation that was identical across all subjects, as well as moderate (13-15 cm) and difficult (18-22 cm) perturbations scaled to subject height to control for height-related differences in perturbation difficulty (Payne et al. 2018). To assess balance ability, we measured the distance traversed on a narrow (0.5-inch wide) 12-foot beam. Correlations between N1 response amplitude and balance ability were assessed across subjects. **Results:** Cortical N1 response amplitudes (54 μV, SD 18) were inversely correlated with performance on the

beam-walking task (R^2=0.20, p=0.029). **Significance:** Our results show that individuals who have greater difficulty maintaining balance in the challenging-beam-walking task have greater cortical activation during balance recovery, which may reflect greater perceived threat or attention to balance related to lower balance ability. It is also possible that this increased cortical activity is related to compensatory cortical contributions to balance control, or that this increased cortical activation interferes with automatic balance control.

4.2 Introduction

Reactive balance recovery invokes hierarchical sensorimotor control mechanisms, but the nature and role of cortical activity in balance recovery are unclear. Reactive balance recovery behavior begins with an involuntary brainstem-mediated balance-correcting muscle response at ~100 ms latency (Carpenter et al. 1999); voluntary influences can additionally affect muscle activity at longer latencies (Jacobs and Horak 2007a). During the involuntary phase of balance recovery, electroencephalography (EEG) recordings have revealed a robust negative peak of activity (N1) localized to the supplementary motor area, peaking ~150 ms after perturbation (Dietz et al. 1984b; 1984a; Marlin et al. 2014; Mierau et al. 2015). Scaling of the cortical N1 response to perturbation magnitude is inconsistent across individuals (Mochizuki et al. 2010; Payne et al. 2018; Staines et al. 2001). In our recent work we demonstrated that shorter subjects had larger cortical N1 responses and greater difficulty resisting compensatory steps in response to support-surface translation perturbations that were not matched to body size (Payne et al. 2018). Because perturbation difficulty depends on both perturbation size and balance ability, we controlled for height-related differences in perturbation difficulty by scaling perturbations to subject height. We

then tested whether differences in cortical N1 response amplitudes reflect differences in balance ability across subjects when perturbations were controlled for subject height.

Balance ability in healthy individuals is difficult to assess objectively, referring generally to the ability to maintain balance in a challenging context through a combination of automatic and volitional mechanisms. We use a challenging beam-walking task as a validated and sensitive measure of balance ability in healthy individuals (Sawers and Ting 2015). The beam-walking task requires balance corrections engaging both automatic and volitional mechanisms. Balance corrections are highly variable when walking on a beam and the associated cortical activity is not easily interpreted or time-locked to an event (Sipp et al. 2013). Conversely, using controlled balance perturbations allows for the evoked motor and cortical activity to be time-locked to the onset of the perturbation, but body kinematics and rates of compensatory stepping are not sensitive measures of balance ability. In both experimental paradigms, we hypothesize that greater difficulty recovering balance requires more cortical control to compensate for limitations of involuntary, automatic balance control mechanisms.

Cortical processing can influence balance recovery behaviors following the initial involuntary balance-correcting reactions, and these influences seem to be greater in those with balance problems. Older adults are thought to engage in more cortically-mediated balance control, based on greater dual-task interference on muscle responses to perturbations (Rankin et al. 2000) and center-of-pressure variation during quiet stance (Shumway-Cook et al. 1997). Dual-task interference occurs to an even greater extent in older adults with a history of falls (Shumway-Cook et al. 1997), suggesting that people with lower balance ability may be more reliant on cortically-mediated control. Further,

dual-task performance of a cognitive task during balance perturbations does not influence initial balance-correcting motor responses, but can influence muscle activity beyond 150 ms, and this effect is greater for older adults compared to younger adults (Rankin et al. 2000). Moreover, among older adults, cortical N1 amplitude is larger for those with less mobility (Duckrow et al. 1999), suggesting that cortical N1 responses may reflect more cortically-mediated control to compensate for motor impairments. Given that the N1 amplitude decreases during dual-task performance in healthy young adults (Little and Woollacott 2015; Quant et al. 2004b), the N1 may reflect use of the same compensatory cortical mechanisms that balance-impaired older adults rely on.

We hypothesized that people with lower balance ability use more cortical processes during balance recovery. We predicted that healthy young adults with worse performance on the beam-walking task would have larger cortical N1 responses to translation perturbations. To control for height-related differences in perturbation difficulty, we scaled perturbation magnitudes to subject height. We measured cortical N1 response amplitudes across three perturbation difficulty levels, keeping only the easiest perturbation identical across subjects to differentiate height-related and ability-related differences in perturbation difficulty. We assessed balance ability in a challenging beam-walking task (Sawers and Ting 2015).

4.3 Methods

Participants. We recruited 20 healthy young adults (11 female, ages 19-38) to participate in a research study approved by the Institutional Review Board of Emory

University. All participants signed written informed consent prior to participation. Subjects were 26 years old (SD 5), 168 cm tall (SD 8, range 156-185 cm), and 70 kg (SD 14).

Perturbations. Subjects were exposed to 48 backward translational support-surface perturbations of unpredictable timing and amplitude while barefoot (Figure 4-1A). Perturbations were delivered using a custom perturbation platform (Factory Automation Systems, Atlanta, GA). Perturbations were evenly divided between easy, moderate, and difficult perturbation magnitudes to vary perturbation difficulty and to maintain unpredictability of perturbation magnitude. The easy perturbation (7.7 cm, 16.0 cm/s, 0.23 g) was identical across all subjects. To control for height-related differences in perturbation difficulty (Payne et al. 2018), the moderate (12.6-15.0 cm, 26.6-31.5 cm/s, 0.38-0.45 g) and difficult perturbations (18.4-21.9 cm, 38.7-42.3 cm/s, 0.54-0.64 g) were linearly scaled down from an upper bound of 15.8 cm, 34.1 cm/s, and 0.49 g for moderate perturbations and 23.7 cm, 45.8 cm/s, and 0.69 g for difficult perturbations, by multiplying by a scaling factor equal to the height of the subject divided by 200 cm. Across all perturbation magnitudes used, the timing and duration of acceleration, velocity, and displacements were identical for the first 500 ms of perturbation (Figure 4-2). Subjects were asked to execute a stepping response on half of perturbations and to resist stepping on the other half. In this chapter, stepping and nonstepping responses will be combined for comparisons between subjects (except for kinematic analyses, where stated). Comparisons between stepping and nonstepping responses are presented in the following chapter.

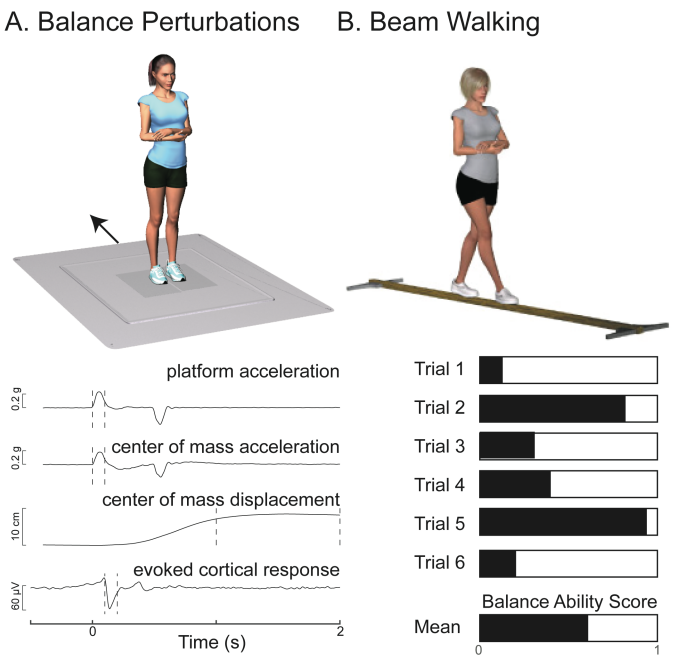


Figure 4-1. Balance tasks. (A) Support-surface perturbations were used to evoke cortical N1 responses. The time window of interest is indicated by vertical grey bars for platform and center of mass acceleration (0-100 ms), center of mass displacement (1-2 s), and evoked cortical response (100-200 ms) in data from a single example subject, averaged across multiple nonstepping responses to easy perturbations. (B) A narrow balance beam was used to assess balance ability. Balance ability score was calculated as the normalized average distance travelled across six trials. Shoes are depicted in both panels, but shoes were only worn during the beam-walking task. CoM: Center of Mass.

Beam-walking task. After the perturbation series, subjects were asked to traverse a narrow balance beam to assess balance ability as described by Sawers and Ting (Sawers and Ting 2015) (Figure 4-1B). The beam was 12 feet long, 0.5-inch wide, and 1 inch above the floor. Subjects were given standardized shoes and asked to make 6 attempts to cross the narrow beam with their arms crossed. Subjects were not given instructions regarding speed or step length. Each trial ended when the participant (1) reached the end of the beam, (2) stepped off the beam, or (3) uncrossed their arms. For trials in which participants traversed the full length of the beam, beam distance was recorded as 144 inches. Otherwise,

beam distance was measured as the parallel distance from the start of the beam to the back of the heel on the forward foot. Balance ability was then scored as the normalized distance traveled, with a maximum possible score of 1 if the full length of the beam was traversed on all 6 trials.

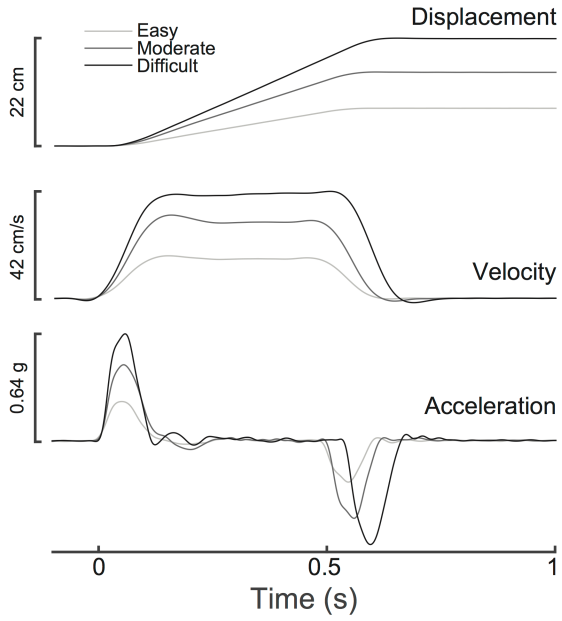


Figure 4-2. Perturbation kinematics are shown for the upper bound of perturbation magnitudes delivered based on subject height. The lightest gray lines correspond to the easy perturbation magnitude, which was identical across subjects (7.7 cm, 16.0 cm/s, 0.23 g). The darker two colors correspond to the moderate (12.6-15.0 cm, 26.6-31.5 cm/s, 0.38-0.45 g) and difficult (18.4-21.9 cm, 38.7-42.3 cm/s, 0.54-0.64 g) perturbation magnitudes, which were scaled by subject height.

Electroencephalography (EEG) collection. EEG data was collected during the perturbation series, and recording equipment was removed from participants prior to the beam-walking task. Thirty-two active EEG electrodes (ActiCAP, Brain Products, Germany) were placed on the scalp according to the international 10-20 system of electrode placement. Electrodes TP9 and TP10 were removed from the standard locations and placed directly on the skin over the mastoid bones behind the ears for offline re-referencing. After

the wired electrode cap was placed on the subject, the active electrode sites were prepared by applying conductive electrode gel (SuperVisc 100 gr. HighViscosity Electrolyte-Gel for active electrodes, Brain Products) using a blunt tipped needle, which was simultaneously used to rub the scalp to improve electrode impedance. Mastoid sites were additionally scrubbed with an alcohol swab prior to placement. Impedances below 10 kOhm were obtained for Cz and mastoid electrodes before the start of data collection.

To enable subtraction of eye movement and blink artifacts, electrooculography (EOG) data were collected using a bipolar pair of passive electrodes (E220x, Brain Products) that vertically bisected the pupil of the right eye with a reference electrode on the forehead. Prior to electrode placement, the skin was scrubbed with an alcohol swab, and electrodes were prepared with high-chloride abrasive gel (ABRALYT HiCl 250 gr., High-chloride-10% abrasive electrolyte gel, Brain Products). EEG and EOG data were amplified on an ActiCHamp amplifier (Brain Products) sampling at 1000 Hz, with a 24-bit A/D converter and an online 20 kHz anti-aliasing low-pass filter.

EEG data preprocessing. Raw EEG data were high-pass filtered offline at 1 Hz with a third-order zero-lag Butterworth filter, mean-subtracted within each channel, and then low-pass filtered at 25 Hz. Cz data was then re-referenced to the mastoids and epoched into 2.4 s segments beginning 400 ms before perturbation onset. Vertical EOG data was filtered and segmented following the same steps without re-referencing. Blinks and vertical eye movement artifacts were subtracted from the epoched data at Cz using the algorithm developed by Gratton and Coles (Gratton et al. 1983), as described in Payne et al. (Payne et al. 2018). Single-trial epochs of Cz data were then baseline-corrected by subtracting the mean voltage between 50-150 ms prior to perturbation onset.

EEG quantification. Epoched cortical responses were averaged within each subject across all trials, both within and across perturbation magnitudes. Cortical N1 peak response amplitudes (μV) and latencies (ms) were then measured between 100-200 ms after perturbation onset in the averaged cortical response waveforms.

Center of mass position and trunk angle. A 10-camera Vicon Nexus 2 motion capture system was used to record body motion at 100 Hz during perturbations. Subjects were prepared using a reflective 25-marker set that enabled Vicon's Plug-in Gait model to calculate positions and masses of the following body segments: head-arms-trunk, and bilateral thigh and shank-foot. Center of mass position was then calculated as a weighted sum of body segment positions and masses. Center of mass position was then baseline-subtracted by subtracting the mean position between 50-150 ms prior to perturbation onset to obtain a measure of center of mass displacement. Trunk angles were calculated relative to the vertical using a vector created from the average position of the hip markers to the average position of the shoulder markers. One subject was excluded from center of mass position and trunk angle calculations due to a missing marker that prevented calculation of one of the body segments (N=19).

Center of mass acceleration. Ground reaction forces were collected using AMTI OR6-6 force plates mounted in the platform under each foot. Ground reaction forces were anti-alias filtered with a 500 Hz low-pass filter and sampled at 1000 Hz. Acceleration of the body center of mass was calculated by dividing the ground reaction forces by the mass of each participant. One subject was excluded from acceleration calculations due to miscalibration of ground reaction forces (N=19, not the same subject excluded from position measurement). Platform acceleration was also recorded directly.

Quantification of center of mass displacement and acceleration. Kinematics were only assessed along the axis of platform motion for nonstepping responses in the easy perturbation that was identical across subjects. Displacement and acceleration data were averaged across the appropriate trials within each subject. Center of mass peak displacement was then quantified as the maximum displacement between 1-2 s after perturbation onset for each subject. Center of mass and platform accelerations were quantified as the peak amplitude in the first 100 ms after perturbation onset for each subject.

Quantification of trunk angle. Trunk angles were only considered in nonstepping responses to difficult perturbations, because these perturbations were proportional to body height, and because these perturbations were generally large enough to cause many subjects to bend at the hips. Trunk angle measurements were averaged across the appropriate trials within each subject, and then quantified as the maximum angle observed between 0.5-1 s after perturbation onset.

Statistical analyses. We used univariate linear regressions to assess correlations between normalized beam distance and cortical N1 response amplitudes and latencies within and across perturbation magnitudes. As controls, we additionally assessed correlations between normalized beam distance or cortical N1 response amplitudes and subject height, weight, age, and kinematic measures. We used mixed model ANOVAs to assess the fixed effect of perturbation magnitude on cortical N1 response amplitudes and latencies, accounting for subject as a random effect. All analyses were performed in SAS statistical software.

4.4 Results

Center of mass acceleration but not displacement was correlated with subject height and weight. Center of mass peak acceleration was positively correlated with subject height (R^2=0.39, p=0.0025) and weight (R^2=0.85, p<0.0001), with larger peak accelerations for taller and heavier subjects. Center of mass peak displacement was not correlated with subject height or weight (p>0.05). Center of mass displacements and accelerations were not correlated with subject age (p>0.05). Platform acceleration was not correlated with subject height, weight, or age (all p>0.05).

Subject-averaged cortical N1 response amplitudes of 54 μV (SD 18) were observed at 141 ms (SD 14) across subjects (Figure 4-3A). No correlations were observed between subject height, weight, age, center of mass acceleration or displacement, trunk angle, or platform acceleration and cortical N1 response amplitudes (all p>0.05, within and across perturbation magnitudes).

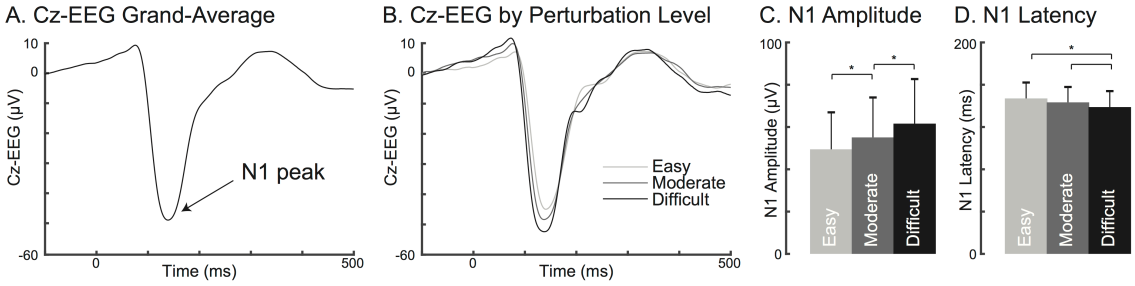


Figure 4-3. Cortical responses varied with perturbation difficulty. (A) The grand-average cortical response at Cz is shown with a peak N1 response of 54 μV (SD 18) occurring 141 ms (SD 14) after perturbation onset. (B) Averaged cortical responses are shown by perturbation difficulty, with darker lines for increasing perturbation difficulty. Bar plots display cortical N1 response peak amplitude (C) and latency (D) as the mean and SD across subjects. Asterisks (*) indicate significant differences identified in post-hoc Tukey comparisons (p<0.05). In all panels, N=20 (11 female).

Cortical N1 responses were larger and earlier for more difficult perturbations. Within subjects, cortical N1 response amplitudes increased (F(2,38)=20.0, p<0.0001) and latencies

decreased ($F(2,38)=10.7$, $p=0.0002$) as perturbation difficulty increased (Figure 4-3B). Cortical N1 response amplitudes increased by 5 or 6 μV with each increase in perturbation difficulty (Figure 4-3C, all $p<0.05$), and cortical N1 response latencies were shorter in difficult perturbations compared to moderate (~4 ms) and easy (~8 ms) perturbations (Figure 4-3D, $p<0.05$).

Most subjects were unable to travel the full length of the beam. The average normalized beam distance travelled was 0.40 (SD 0.21), which ranged from 0.15 to 0.84 across subjects. Four subjects (20%) were able to walk the full length of the beam on any trial, for a total of 10 trials where a subject reached the end of the beam across all trials and subjects (8%). Performance on the beam-walking task was not correlated with subject height, age, weight, displacement of the body center of mass in perturbations, or trunk angle in perturbations (all $p>0.05$).

Better performance on the beam-walking task was associated with smaller cortical N1 response amplitudes. Distance travelled on the beam was inversely correlated with the cortical N1 response amplitude across perturbation difficulties ($R^2=0.20$, $p=0.029$). Correlation between beam performance and cortical N1 response amplitudes was strongest in difficult perturbations (Figure 4-4A, $R^2=0.24$, $p=0.016$), but was also observed in moderate perturbations (Figure 4-4B, $R^2=0.21$, $p=0.025$). Cortical N1 response amplitudes in easy perturbations were not correlated with beam performance (Figure 4-4C, $p=0.09$). Performance on the beam-walking task was not correlated to cortical N1 response latency, within or across perturbation magnitudes (all $p>0.05$).

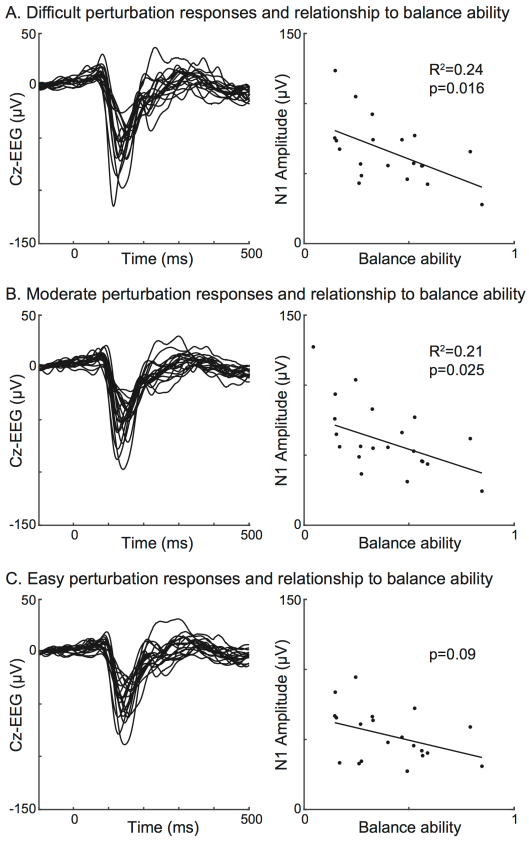


Figure 4-4. Cortical response amplitudes were inversely correlated with balance ability. (A) Subject-averaged cortical responses to difficult perturbations are shown on the left. On the right, cortical N1 response peak amplitudes from difficult perturbations are plotted on the vertical axis against the normalized distance travelled in the narrow beam-walking task on the horizontal axis. The same are shown for moderate perturbations in (B) and easy perturbations in (C). In all panels, N=20 (11 female).

4.5 Discussion

Our results support the hypothesis that people with lower balance ability engage more cortical processes during balance recovery. Cortical N1 responses were larger when people had greater difficulty recovering balance, either due to more difficult perturbations, or due to lower intrinsic balance ability. Increases in cortical N1 responses are consistent with prior work (Mochizuki et al. 2010; Payne et al. 2018; Staines et al. 2001). Scaling perturbations to subject height eliminated previously-observed height-related differences

in cortical N1 response amplitudes between subjects (Payne et al. 2018). Remaining differences in N1 amplitudes across subjects were inversely correlated with distance traversed in a difficult beam-walking task, suggesting a relationship between cortical activity and intrinsic balance ability. Larger cortical N1 responses in individuals with lower balance ability may reflect greater perceived threat (Adkin et al. 2008; Mochizuki et al. 2010; Sibley et al. 2010) or attention to balance (Little and Woollacott 2015; Quant et al. 2004b) related to lower balance ability. It is also possible that this increased cortical activity is related to compensatory cortical contributions to balance control, or that this increased cortical activation interferes with automatic balance control.

Cortical N1 amplitude may reflect individual differences in difficulty recovering balance related to balance ability. Consistent with the hypothesis that people with lower balance ability engage more cortical processes during balance recovery, subjects who performed worse on the beam-walking task had larger perturbation-evoked cortical N1 responses. Similarly, our prior work showed that that subjects who had a harder time resisting compensatory steps also had larger cortical N1 responses (Payne et al. 2018). Although reactive balance recovery behavior is initially brainstem-mediated and involuntary (Carpenter et al. 1999), voluntary contributions can be incorporated at longer latencies (Jacobs and Horak 2007a). Greater cortical activation in subjects with lower balance ability may reflect a greater need for cortical compensation for less effective automatic balance control, as suggested by greater dual-task interference in older adults with a history of falls (Shumway-Cook et al. 1997). However, we cannot rule out the possibility that greater cortical involvement impairs balance by interfering with automatic balance control.

Cortical N1 amplitude also reflects variation in perturbation difficulty within individuals. Consistent with the larger cortical N1 responses in those individuals who had greater difficulty recovering balance due to lower balance ability, cortical N1 responses were also increased within individuals when balance recovery was more difficult due to more difficult perturbations. Prior work may have observed inconsistent increases in N1 responses with perturbation magnitude across subjects because individual differences in balance ability were not accounted for (Payne et al. 2018; Staines et al. 2001). The cortical N1 response amplitude may relate more to subjective perturbation difficulty rather than direct changes in sensory and motor activity across perturbation magnitudes. That is, those who showed increasing N1 response amplitudes with perturbation magnitude in prior studies (Payne et al. 2018; Staines et al. 2001) may have found the larger perturbations more difficult. The possibility that the cortical N1 response amplitude indexes more subjective aspects of a perturbation is supported by observations of larger N1 response amplitudes in the context of greater perceived threat (Adkin et al. 2008; Sibley et al. 2010).

Increasing cortical N1 responses with perturbation difficulty is consistent with increasing theta frequency (4-7 Hz) brain activity in more difficult continuous balance tasks. Time-frequency analyses have been used to suggest that the cortical N1 response to perturbations reflects a transient synchronization of theta frequency brain activity (Peterson and Ferris 2018; Varghese et al. 2014). Such observations must be interpreted cautiously, as such analyses are unable to distinguish synchronization of oscillatory components from individual component peaks (Yeung et al. 2007). However, continuous balancing tasks elicit oscillatory activity in the theta frequency range that is greater for more challenging balance tasks (Hulsdunker et al. 2015; Sipp et al. 2013). The similar increase in cortical N1

responses within and across subjects as balance difficulty increased is consistent with the previously-suggested relationship to theta brain activity.

While we show increases in balance N1 with balance difficulty, such changes might reflect cognitive resource allocation, such as increased vigilance or perceived threat. For example, cortical N1 responses are larger when subjects stand at the edge of an elevated platform (Adkin et al. 2008), where healthy young adults report a shift to more conscious control of posture (Huffman et al. 2009). Reduction in cortical N1 response amplitude when subjects are distracted by a simultaneous cognitive dual-task (Little and Woollacott 2015; Quant et al. 2004b) is also consistent with the hypothesis that cortical N1 response amplitude reflects the degree of conscious control or attention to balance. Further study of perturbation-evoked cortical N1 responses may provide insight into the greater reliance on conscious balance control and greater dual-task interference in older adults with a history of falls (Shumway-Cook et al. 1997). Balance perturbation-evoked cortical N1 responses may eventually prove useful as a biomarker or potential therapeutic target (Jacobs et al. 2009) for rehabilitation in individuals who have difficulty maintaining balance.

CHAPTER 5. CORTICAL N1 RESPONSE TO DIFFICULT BALANCE PERTURBATION IS LARGER WHEN EXECUTING PLANNED COMPENSATORY STEPS

5.1 Abstract

Reactive balance recovery evokes a cortical N1 response that is simultaneous to brainstem-mediated involuntary balance-correcting muscle activity. While the processes underlying the cortical N1 response are unclear, we recently observed larger cortical responses in individuals who had greater difficulty resisting unplanned compensatory steps, suggesting a possible role for the cortical N1 response in the preparation or execution of compensatory steps for balance recovery. Here, we compare stepping to nonstepping reactions, as well as planned to unplanned stepping reactions to investigate the potential relationship of the balance N1 to the execution or planning of compensatory stepping responses. We hypothesized that unplanned stepping reactions would be associated with larger cortical N1 responses. In 20 healthy young adults (11 female, ages 19-38) we measured the amplitude of the cortical N1 response evoked by 48 backward translational support-surface perturbations of unpredictable timing and amplitude. Subjects were asked to plan a compensatory stepping reaction for half of perturbations, and to resist stepping on the other half of perturbations. Perturbations included an easy (8 cm) perturbation that was identical across subjects and did not naturally elicit compensatory steps, and a height-adjusted difficult (18-22 cm) perturbation that often elicited compensatory steps despite instructions

to resist stepping. In contrast to our hypothesis, cortical N1 response amplitudes did not differ between planned and unplanned stepping reactions, but cortical responses were larger with the execution of planned compensatory steps in response to difficult perturbations. These results suggest a possible role for the cortical N1 in the execution of compensatory stepping reactions for balance recovery, and this role is not influenced by whether the compensatory step was planned before the perturbation.

5.2 Introduction

Subcortically mediated involuntary balance-correcting motor reactions are affected by intention, expectation, and arousal in ways that may depend on descending influences from cortical processes. Reactive balance recovery behavior begins with a brainstem-mediated automatic postural response (Carpenter et al. 1999) that can be followed by voluntary corrections at longer latencies (Jacobs and Horak 2007a). The earliest involuntary reactions can be influenced by instructed motor goals, such as whether to resist or give in to perturbations (Weerdesteyn et al. 2008), or whether or not to take a step in response to perturbations (Burleigh and Horak 1996; Burleigh et al. 1994; McIlroy and Maki 1993b). These involuntary reactions are also reduced in amplitude with experience (Horak et al. 1989; Maki and Whitelaw 1993; Welch and Ting 2014) and predictability (Horak et al. 1989), and enhanced with perceived threat (Carpenter et al. 2004). Such changes in involuntary balance recovery reactions are often attributed to changes in "central set" (Prochazka 1989), referring to the ability of the central nervous system to pre-select the gain of stimulus-evoked responses in consideration of motor goals, environmental context, prior experience, and arousal. While is unclear how such changes

in central set occur, the influence of motor goals suggests involvement of higher cortical areas in modulation of the automatic motor responses mediated by subcortical circuits.

Cortical N1 responses evoked by balance perturbations are also influenced by expectation and arousal, but the extent to which they are affected by motor intention remains unclear. The cortical N1 response has been localized to the supplementary motor area (SMA) (Marlin et al. 2014; Mierau et al. 2015) and is simultaneous to the involuntary balance-correcting motor response (Payne et al. 2018). While the function of the cortical N1 response is unknown, it is reduced in amplitude with prior experience (Mierau et al. 2015; Payne et al. 2018) and predictability of perturbations (Dietz et al. 1985a; Mochizuki et al. 2009b; Mochizuki et al. 2008) and enhanced with perceived threat (Adkin et al. 2008; Adkin et al. 2006), much like the evoked motor responses. When perturbations are entirely predictable the cortical N1 response is absent (Adkin et al. 2008; Adkin et al. 2006), but a slow and sustained negativity can be observed leading up to perturbation onset (Jacobs and Horak 2007b; Mochizuki et al. 2010; Mochizuki et al. 2009b; Mochizuki et al. 2008). These observations seem to suggest that the changes in central set that influence the evoked motor reactions may similarly influence the cortical N1 response. We recently observed larger cortical N1 responses in subjects who had greater difficulty resisting compensatory steps (Payne et al. 2018), suggesting a possible relationship to online changes in response strategy or execution of compensatory steps. Whereas prior studies have suggested that the cortical N1 depends on the extent that a perturbation differs from expectations, it is also possible that the cortical N1 response depends on the extent that the motor response differs from expectations. As such the cortical N1 response could be involved in incorporating unexpected information during the perturbation into the upcoming motor reaction. Indeed,

the SMA has been widely implicated in the transformation of intention into action through a variety of direct pathways to cortical areas and spinal motor neurons, as well as indirect pathways via basal ganglia-thalamocortical loops (see (Goldberg 1985) for an extensive review).

We hypothesized that prior planning of a compensatory stepping reaction would reduce the amplitude of the cortical N1 response to unpredictable balance perturbations. Healthy young adults performed a series of translational support-surface balance perturbations that were unpredictable in timing and amplitude but predictable in direction. To differentiate the effects of motor planning versus motor execution on cortical N1 responses, we compared the effect of planning on N1 amplitudes between planned and unplanned stepping reactions and the effect of execution between planned stepping and nonstepping reactions. Subjects were asked to recover balance without taking a compensatory step on half of trials, and on the other half of trials subjects were asked to plan and prepare to take a single compensatory step to recover balance in response to the upcoming perturbation. Perturbations varied in magnitude, including a very easy low magnitude perturbation that did not naturally elicit stepping reactions, and a very difficult high magnitude perturbation that often elicited stepping reactions despite instructions to resist stepping. We predicted that the cortical N1 response would be larger in amplitude on trials in which unplanned steps were elicited compared to trials in which stepping responses were planned prior to the onset of perturbations. We predicted that the cortical N1 response would not differ in amplitude between nonstepping reactions and trials in which stepping responses were planned prior to the onset of perturbations.

5.3 Methods

5.3.1 Participants

20 healthy young adults (11 female, ages 19-38 years) were recruited from Emory University and the surrounding population to participate in an experiment that was approved by the Emory University Institutional Review Board. All subjects signed written informed consent before participation. Different analyses from these same subjects were reported in the previous chapter. Subjects were 26 years old (standard deviation, SD 5), 168 cm tall (SD 8), and 70 kg (SD 14).

5.3.2 Experimental Protocol

The experimental protocol was adapted from McIlroy and Maki (1993b). To test the effects of execution and planning of compensatory steps, we presented subjects with a series of ramp-and-hold perturbations in which the floor was displaced backward during quiet standing while subjects were instructed whether or not to step (Figure 5-1). When instructed to step, subjects were told, "When the platform moves, recover your balance by taking a single step forward with your right [or left] leg." When instructed not to step, subjects were told, "Do your best to recover balance without taking a step. If you must take a step, please try to do so with your right [or left] leg." Stepping leg was pre-determined based on "the leg used to kick a ball."

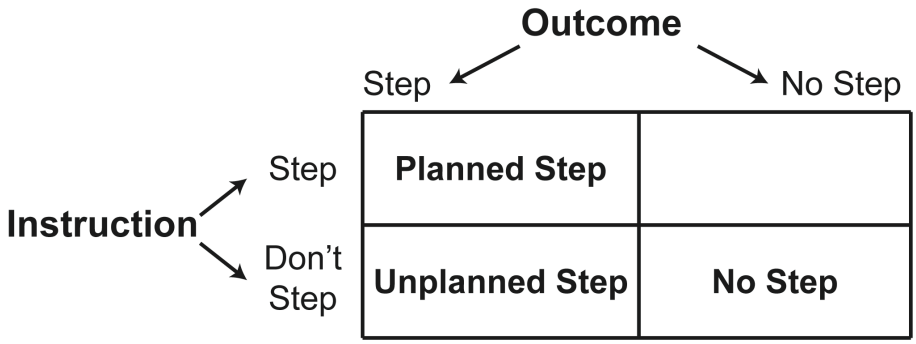


Figure 5-1. Experimental design. Subjects were instructed whether or not to plan to step in response to upcoming perturbations. In some cases, subjects failed to resist taking a compensatory step, resulting in an unplanned step that was not intended prior to perturbation. We test the effect of stepping by comparing planned steps to nonstepping reactions, and we test the effect of planning by comparing planned steps to unplanned steps.

Each subject was exposed to 3 levels of perturbation, which will be referred to as easy, moderate, and difficult. The easy perturbation (7.7 cm, 16.0 cm/s, 0.23 g) was the same across subjects and could be easily resisted without stepping. To account for the previously observed effect of subject height on evoked cortical responses (Payne et al. 2018), the moderate (12.6-15.0 cm, 26.6-31.5 cm/s, 0.38-0.45 g) and difficult (18.4-21.9 cm, 38.7-42.3 cm/s, 0.54-0.64 g) perturbations were scaled linearly with subject height. The difficult perturbation was large enough to force most subjects to occasionally take unplanned steps despite instructions not to step.

Forty-eight perturbations were delivered to each subject, divided evenly between the three perturbation magnitudes and divided evenly between the two instructed conditions. Perturbations were randomized into eight blocks each containing two replicates of each perturbation magnitude in random order. Each block was randomly assigned to instruction on whether or not to step. Two different block randomizations were used across subjects, and each of the block randomizations were presented in two different versions in

which the instructions were reversed within each block to control for any effect of instruction order. Perturbations were unpredictable in timing and amplitude, but subjects were told that all perturbations would be in the backward direction. Perturbations were delivered using a custom perturbation platform (Factory Automation Systems, Atlanta, GA).

To prevent fatigue, a 5-minute break was enforced during the perturbation series when the total duration was expected to take longer than 16 minutes. Not counting these breaks, the total duration of the perturbation series was 17 minutes 30 seconds (SD 1 minute 40 seconds). Inter-trial-intervals, measured from perturbation onset to perturbation onset, excluding the 5-minute rest break, was 22 seconds (SD 13 seconds).

As described in Payne (2018), to reduce the potential for recording artifacts, perturbations were only initiated when electroencephalography (EEG) activity was relatively quiescent, based on visual inspection of a live monitor displaying the online EEG data. Regardless of stepping instructions, subjects were asked to cross their arms and to stare at a central location in a poster of a mountain landscape on a wall 4.5 m in front of them. Subjects were reminded to relax and look forward whenever electromyography (EMG) activity or eye movements were apparent in the live EEG data. Subjects were allowed to blink freely.

5.3.3 Data collection and quantification

Ground reaction forces. Platform-mounted force plates (AMTI OR6-6) collected ground reaction forces under each foot during perturbations. Ground reaction forces were sampled at 1000 Hz after a 500 Hz low-pass analog anti-alias filter.

Quantification of foot-off latency. Single trial recordings of left and right vertical ground reaction forces were relabeled in association with the stance or swing limb based on based on the instructed stepping leg for each subject. The presence and timing of a stepping reaction was defined as a reduction in the vertical load force under either limb to a value below 5 Newtons within the first 1000 ms after perturbation. Based on these events, stance and swing labels were corrected for any trial in which subjects stepped with the opposite leg. Latencies to foot-off were then averaged across trial replicates in each condition of interest for each subject.

Quantification of anticipatory postural adjustments. To assess whether the instruction to plan a compensatory step was associated with an anticipatory lateral weight shift prior to perturbation onset, vertical load forces under the stance and swing limbs were averaged across all trials for each subject within each instruction condition. Specifically, vertical load forces were averaged across all trials in which a subject was instructed to (1) plan a compensatory step, or (2) plan a feet-in-place reaction, regardless of the upcoming perturbation magnitude or stepping outcome. The averaged vertical load force data were then quantified as the mean amplitude between 50-150 ms before perturbation onset for each instruction condition within each subject under the stance and swing limbs.

Electroencephalography (EEG) collection. Thirty-two active EEG electrodes (ActiCAP, Brain Products, Germany) were placed on the scalp according to the international 10-20 system of electrode placement, with the exception of electrodes TP9 and TP10, which were placed on the mastoid bones for offline re-referencing. Active electrode sites were prepared by applying a conductive electrode gel (SuperVisc 100 gr. HighViscosity Electrolyte-Gel for active electrodes, Brain Products) using a blunt-tipped

needle, which was simultaneously used to rub the scalp to improve electrode impedance. Mastoid sites were additionally prepared with an alcohol swab before electrode placement. Impedances for Cz and mastoid electrodes were below 10 kOhm before the start of data collection.

Electrooculography (EOG) data were collected using a bipolar pair of passive electrodes (E220x, Brain Products) that vertically bisected the pupil of the right eye. An EOG reference was placed on the forehead. Before electrode placement, skin was prepared with an alcohol swab, and electrodes were filled with high-chloride abrasive gel (ABRALYT HiCl 250 gr., High-chloride-10% abrasive electrolyte gel, Brain Products). EEG and EOG data were amplified on an ActiCHamp amplifier (Brain Products) sampling at 1000 Hz, with a 24-bit A/D converter and an online 20 kHz low-pass filter.

EEG data preprocessing. As described in Payne et al. (2018), raw EEG data were high-pass filtered offline at 0.05 Hz with a third-order zero-lag Butterworth filter, mean-subtracted within each channel, and then low-pass filtered at 25 Hz. Cz data were re-referenced to linked mastoids and epoched into 2.4s segments beginning 400 ms before perturbation onset. Vertical EOG data was filtered and segmented following the same steps without re-referencing. Blinks and vertical eye movement artifacts were subtracted from the epoched data at Cz using the algorithm developed by Gratton and Coles (Gratton et al. 1983), as described in Payne et al. (2018). Single-trial epochs of Cz data were then baseline-corrected by subtracting the mean voltage between 50-150 ms prior to perturbation onset.

Quantification of EEG. Cortical event-related potentials (ERPs) were created by averaging EEG data at the Cz electrode across like trials within each subject. The cortical N1 response was then quantified as the peak amplitude and peak latency between 100-200 ms after perturbation onset within the ERPs.

Electromyography (EMG) collection. Surface EMGs (Motion Analysis Systems) were collected from tibialis anterior (TA), medial gastrocnemius (MG), and sternocleidomastoid (SC) muscles bilaterally. EMG signals were anti-alias filtered with a 500 Hz low pass filter and sampled at 1000 Hz. MG and TA were selected based on their roles as primary agonist and antagonist muscles in response to backward translations, and SC was selected as an indicator of startle-related muscle activity (Brown et al. 1991; Campbell et al. 2013; Nonnekes et al. 2015). Skin was shaved and scrubbed with an alcohol pad before electrode placement. Bipolar silver silver-chloride electrodes were used (Nortrode 20, Myotonics, INC, Kent, WA).

EMG data preprocessing. Raw EMG signals were segmented into 2.4 s epochs starting 400 ms before the onset of platform motion. Segmented EMG signals were high-pass filtered at 35 Hz offline with a third-order zero-lag Butterworth filter. EMG signals were then mean-subtracted and half-wave rectified. Rectified EMG signals were then low-pass filtered at 40 Hz with a similar Butterworth filter.

Quantification of EMG. Single-trial EMG recordings were normalized so that each muscle had a maximum value of 1 between 100-200 ms after perturbation onset across all trials within each subject. Because all perturbations were in the backward direction, i.e. the direction in which the TA is an antagonist, this normalization may make TA-EMG

antagonist activity appear unusually large in figures, but this does not impact the within-subjects comparisons across conditions. Left and right MG-EMG and TA-EMG were relabeled in association with the stance or swing limb as described for the ground reaction forces. Bilateral SC-EMG, and stance and swing limb MG-EMG and TA-EMG were then averaged across replicates of like trials within each subject. SC-EMG was averaged across left and right sides. EMG data were then quantified as the peak amplitudes observed in early (100-200 ms) and late (200-300 ms) time windows, and as the mean during a baseline (-150 to -50 ms) time window. EMG onsets were manually identified from averaged responses across like trials.

Electrodermal response (EDR) collection. EDRs were collected as a measure of arousal (Sibley et al. 2008; Sibley et al. 2010) to assess whether the surprise of an unplanned step increases autonomic responsivity, which would influence the interpretation of any changes in N1 amplitude. EDRs were collected from the thenar and hypothenar eminences of the right hand using a galvanic skin conductance sensor (Brain Vision). Electrodermal responses were amplified on the actiCHamp amplifier and sampled at 1000 Hz with a 24-bit A/D converter and an online 20 kHz low-pass filter.

Quantification of EDRs. EDRs were averaged across like trials within subjects, baseline-subtracted between 50-150 ms before perturbation, and quantified as the peak amplitude and peak latency between 2-6 s after perturbation.

5.3.4 Statistical Analyses

Anticipatory postural adjustments. Paired two-way t-tests were used to test for differences in vertical load forces under the stance or swing limb before perturbation onset between the two instruction conditions.

Latencies to foot-off. Paired two-way t-tests were used to test for differences in latency to foot-off between planned compensatory steps in easy and difficult perturbations, and between planned and unplanned compensatory steps in difficult perturbations. All statistical analyses were performed in SAS statistical software, with a significance threshold of $\alpha=0.05$.

Effect of executing a compensatory step. Paired two-way t-tests were used to test for differences in muscle, cortical, and electrodermal response amplitudes between (planned) stepping and (planned) nonstepping reactions to easy and difficult perturbations. This compares the stepping and nonstepping reactions when both reactions are congruent with the behavior subjects were explicitly asked to execute in response to the perturbation.

Effect of planning a compensatory step. Paired two-way t-tests were used to test for differences in muscle, cortical, and electrodermal response amplitudes between planned stepping and unplanned stepping reactions in difficult perturbations.

Relationship between effects across subjects. Regardless of main group effects, we also tested for correlations between the effect of step planning or step execution on pairs of variables across subjects. That is, whether or not there is a group effect of e.g. step planning on cortical N1 response amplitude or anticipatory postural adjustments, could some subjects who displayed more or less anticipatory postural adjustments with step planning have had more or less of an effect of step planning on their cortical N1 response

amplitudes? New variables were created by subtracting response amplitudes for each variable (i.e. lateral weight shift, N1, early and late EMG, electrodermal response) across conditions (i.e. planned stepping reactions minus nonstepping reactions and planned minus unplanned stepping reactions). Univariate linear regressions were then used to assess correlations between changes in N1 amplitude, anticipatory postural adjustments, and all other variables across subjects between conditions.

5.4 Results

5.4.1 Behavior and biomechanics

No subjects took unplanned steps in response to easy perturbations, and only three subjects (15%) were able to resist unplanned steps in response to all difficult perturbations. Due to misunderstanding the instructions, the first 14 trials were discarded from a single subject (~30% of trials for this individual). In easy perturbations, subjects had an average of 7.8 (SD 0.5) trials with nonstepping reactions and 7.6 (SD 0.9) trials with planned stepping reactions. In difficult perturbations, subjects had 3.1 (SD 2.3) trials with unplanned stepping reactions, 7.9 (SD 0.5) trials with planned stepping reactions, and 5.0 (SD 2.5) trials with nonstepping reactions. Three subjects who took no unplanned steps were excluded from comparisons between unplanned and planned stepping reactions in difficult perturbations (i.e. N=17 in comparisons that include unplanned stepping reactions), but these subjects were included in comparisons within easy perturbations. Additionally, one subject who had no nonstepping reactions to difficult perturbations is excluded from corresponding comparisons (i.e. N=19 in comparisons that include nonstepping reactions to difficult perturbations).

Instructions to plan a stepping reaction resulted in an anticipatory postural adjustment toward the stance leg (Figure 5-2A). When instructed to plan stepping reactions, subjects slightly unloaded the swing leg by <10 N, or <1 kg-force (p=0.024).

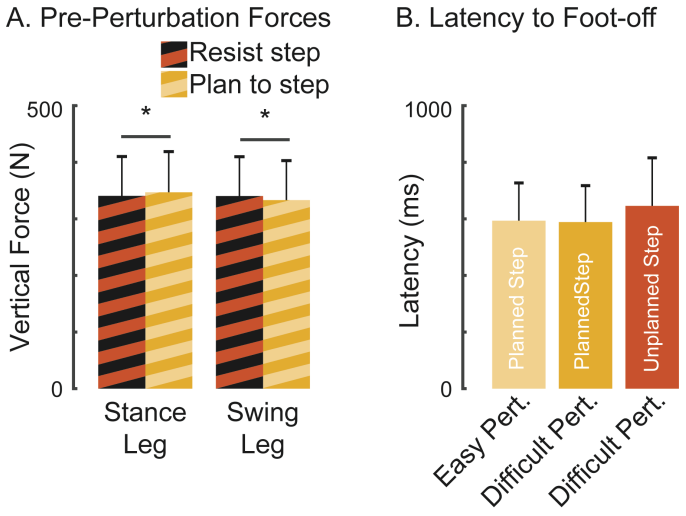


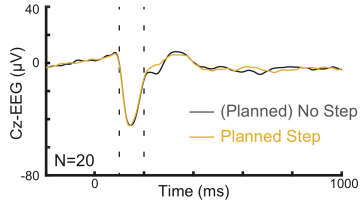
Figure 5-2. Instruction to step induced a lateral weight shift but did not influence step latency. (A) Bar plots show pre-perturbation (50-150ms before perturbation onset) vertical load forces under the stance and swing legs. Forces are shown for trials in which subjects were asked to step in shades of yellow, and for trials in which subjects were asked to resist stepping in black and red. Asterisks indicate significant differences at α=0.05. (B) Latency to foot-off is shown for planned steps to easy perturbations in light yellow and planned steps to difficult perturbations in dark yellow. Latency to foot-off is shown for unplanned steps to difficult perturbations in red. Latencies to foot-off did not differ between conditions at α=0.05. There is no black bar corresponding to the nonstepping condition in panel B because there was no foot-off in this condition, but this nonstepping condition is included in panel A because this represents the bulk of the trials in which subjects were asked not to step.

Perturbation magnitude and instruction to step did not alter the latency to step (Figure 5-2B). The latency of foot-off did not differ between planned stepping reactions to easy perturbations (593 ms, SD 134 ms) and planned stepping reactions to difficult perturbations (589 ms, SD 129, p=0.86), or between planned and unplanned stepping reactions (646 ms, SD 170, p=0.33) to difficult perturbations.

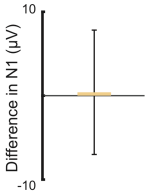
5.4.2 Step execution

Cortical responses were larger with the execution of a compensatory step only in difficult perturbations, whereas muscle responses were altered with step execution in easy and difficult perturbations. In easy perturbations, the execution of a planned step was accompanied by a reduction in early and late stance-MG (Figure 5-3B, N=20, early, $p=0.0002$; late, $p<0.0001$), and increases in early and late swing-MG (early, $p=0.0059$; late, $p<0.0001$), stance-TA (early, $p=0.0034$; late, $p=0.0001$), and swing-TA (early, $p=0.0087$; late, $p=0.0055$). In difficult perturbations, the execution of a planned step was accompanied with increases in early and late swing-MG (Figure 5-4B, N=19, early, $p=0.0013$; late, $p=0.0006$), as well as a reduction in baseline stance-TA ($p=0.047$) and an increase in early stance-TA ($p=0.0083$). Cortical N1 responses increased by 6.6 μV with the execution of a compensatory step in difficult perturbations (Figure 5-4A, N=19, $p=0.020$), but did not differ with the execution of a compensatory step in easy perturbations (Figure 5-3A, N=20, $p>0.05$). Electrodermal response amplitudes were larger with the execution of a planned step only in easy perturbations (Figure 5-3C, N=20, $p=0.038$). SC activity did not differ with the execution of planned stepping reactions in easy or difficult perturbations ($p>0.05$).

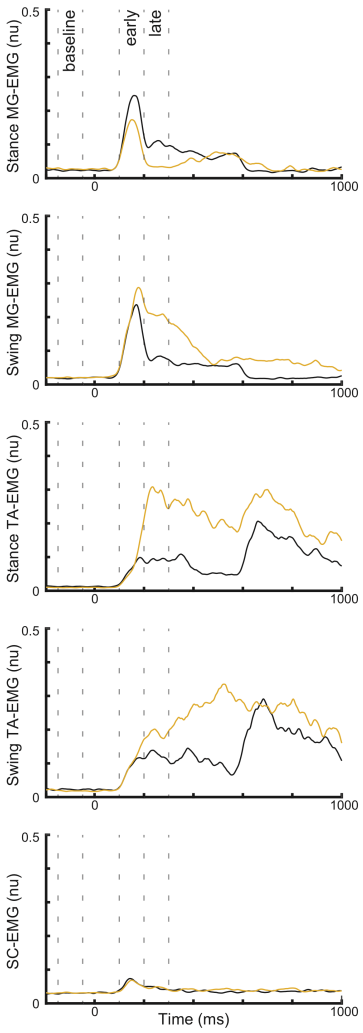
A. Cortical Responses - Step Execution in Easy Perturbations



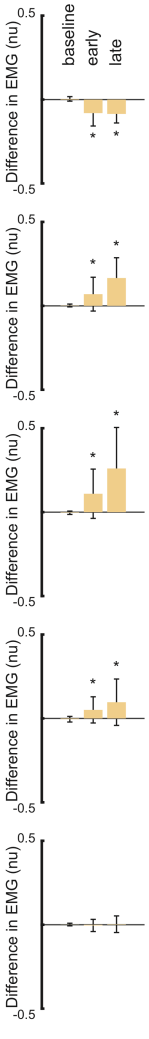
B. Effect of Step on N1 Amplitude



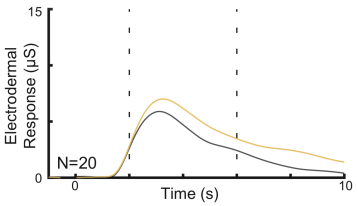
C. Muscle Responses - Step Execution in Easy Perturbations



D. Effect of Step on EMG Amplitude



E. Electrodermal Responses (EDR) - Step Execution in Easy Perturbations



F. Effect of Step on EDR Amplitude

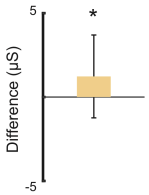


Figure 5-3. Effect of step execution in easy perturbations. (A) Group-averaged cortical responses are shown for nonstepping (black) and planned stepping reactions (yellow) in easy perturbations. Vertical dashed bars indicate the time window of 100-200 ms. (B) The bar plot shows the mean and standard deviation of the difference in N1 response amplitude between conditions across subjects. (C) Group-averaged EMG responses are shown for each muscle for the same conditions shown in A. Vertical dashed bars indicate the baseline (-150 to -50 ms), early (100-200 ms) and late (200-300 ms) time windows. (D) Bar plots show the mean and standard deviation of the difference in EMG activity between conditions in each time window across subjects. (E) Group-averaged electrodermal responses are shown for the same conditions shown in A. Vertical dashed bars indicate the time window of 2-6 s. (F) The bar plot shows the mean and standard deviation of the difference in electrodermal response amplitude between conditions.

The only difference in response latencies with the execution of planned steps was in the stance-TA. Stance-TA onset was ~8 ms earlier with the execution of a planned step compared to nonstepping reactions ($N=19$, $p=0.010$) in difficult perturbations. No other changes in muscle onset latency, or peak latency of cortical or electrodermal responses were observed with the execution of planned steps in easy or difficult perturbations (all $p>0.05$).

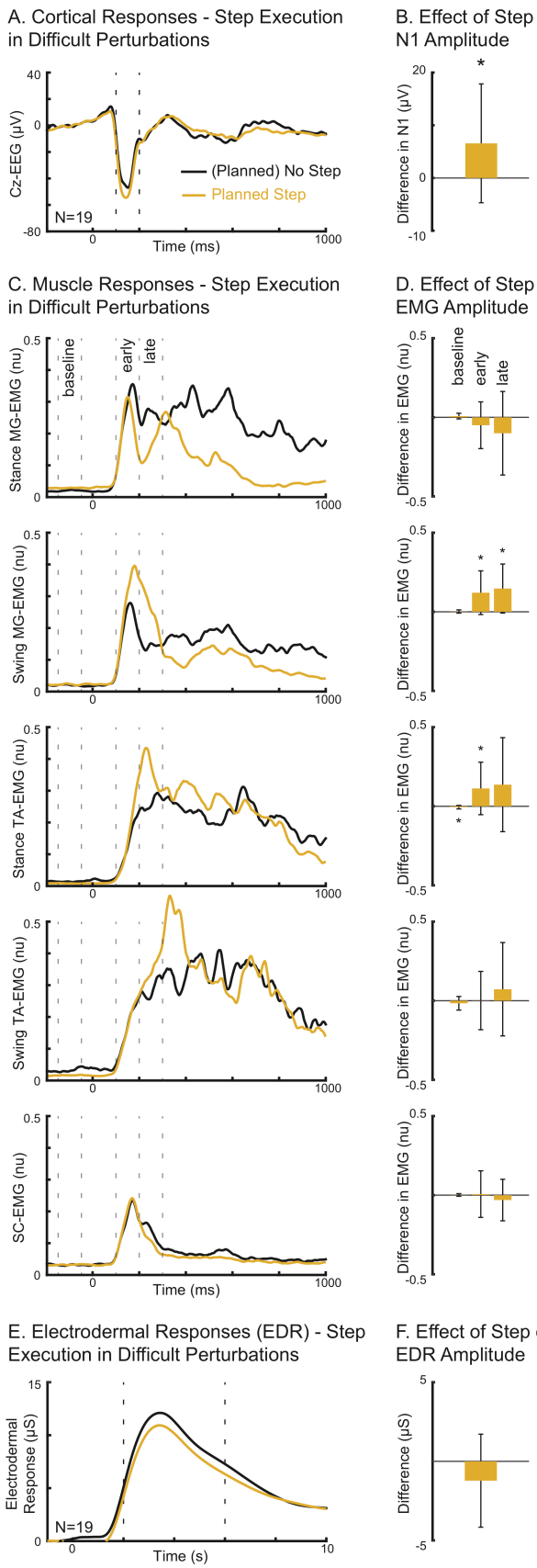

A. Cortical Responses - Step Execution in Difficult Perturbations
B. Effect of Step on N1 Amplitude
Cz-EEG (μV)
(Planned) No Step
Planned Step
N=19
Time (ms)
Difference in N1 (μV)
C. Muscle Responses - Step Execution in Difficult Perturbations
D. Effect of Step on EMG Amplitude
baseline
early
late
Stance MG-EMG (nu)
Swing MG-EMG (nu)
Stance TA-EMG (nu)
Swing TA-EMG (nu)
SC-EMG (nu)
Difference in EMG (nu)
E. Electrodermal Responses (EDR) - Step Execution in Difficult Perturbations
F. Effect of Step on EDR Amplitude
Electrodermal Response (μS)
Time (s)
Difference (μS)

Figure 5-4. Effect of step execution in difficult perturbations. (A) Group-averaged cortical responses are shown for nonstepping (black) and planned stepping reactions (yellow) in difficult perturbations. Vertical dashed bars indicate the time window of 100-200 ms. (B) The bar plot shows the mean and standard deviation of the difference in N1 response amplitude between conditions across subjects. (C) Group-averaged EMG responses are shown for each muscle for the same conditions shown in A. Vertical dashed bars indicate the baseline (-150 to -50 ms), early (100-200 ms) and late (200-300 ms) time windows. (D) Bar plots show the mean and standard deviation of the difference in EMG activity between conditions in each time window across subjects. (E) Group-averaged electrodermal responses are shown for the same conditions shown in A. Vertical dashed bars indicate the time window of 2-6 s. (F) The bar plot shows the mean and standard deviation of the difference in electrodermal response amplitude between conditions.

5.4.3 Step planning

Cortical responses did not differ between planned and unplanned stepping reactions, despite differences in early stance-TA and late reactions in other muscles. Unplanned steps were associated with decreases in early stance-TA (Figure 5-5B, N=17, $p=0.0077$), late swing-MG ($p=0.0021$), and late SC activity ($p=0.0022$), and an increase in late stance-MG ($p=0.017$). Cortical N1 responses did not differ between planned and unplanned steps (Figure 5-5A, N=17, $p>0.05$). Electrodermal response amplitudes did not differ between planned and unplanned steps (Figure 5-5C, N=17, $p>0.05$). No differences were observed in peak or onset latencies for muscle, cortical, or electrodermal responses with the execution of unplanned steps (all $p>0.05$).

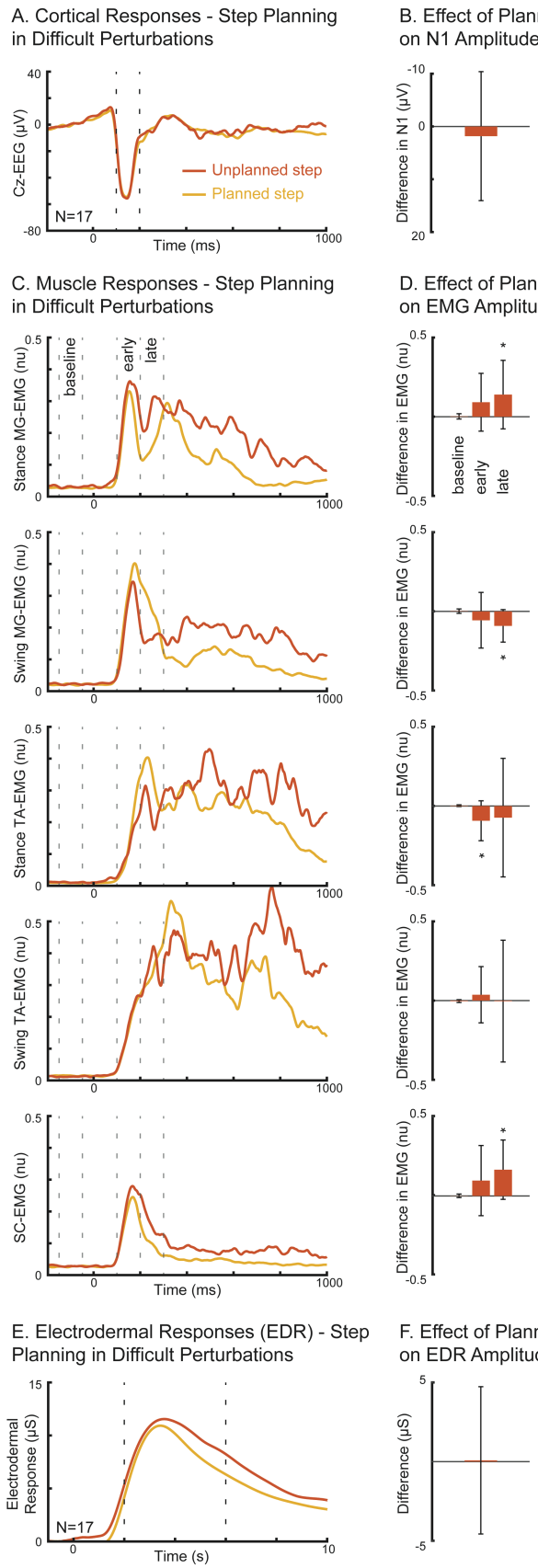

A. Cortical Responses - Step Planning in Difficult Perturbations
B. Effect of Planning on N1 Amplitude
Cz-EEG (μV)
Unplanned step
Planned step
N=17
Time (ms)
Difference in N1 (μV)
C. Muscle Responses - Step Planning in Difficult Perturbations
D. Effect of Planning on EMG Amplitude
Stance MG-EMG (nu)
Swing MG-EMG (nu)
Stance TA-EMG (nu)
Swing TA-EMG (nu)
SC-EMG (nu)
baseline
early
late
Difference in EMG (nu)
E. Electrodermal Responses (EDR) - Step Planning in Difficult Perturbations
F. Effect of Planning on EDR Amplitude
Electrodermal Response (μS)
Time (s)
Difference (μS)

Figure 5-5. Effect of step planning in difficult perturbations. (A) Group-averaged cortical responses are shown for planned steps (yellow) and unplanned steps (red) in difficult perturbations. Vertical dashed bars indicate the time window of 100-200 ms. (B) The bar plot shows the mean and standard deviation of the difference in N1 response amplitude between conditions across subjects. (C) Group-averaged EMG responses are shown for each muscle for the same conditions shown in A. Vertical dashed bars indicate the baseline (-150 to -50 ms), early (100-200 ms) and late (200-300 ms) time windows. (D) Bar plots show the mean and standard deviation of the difference in EMG activity between conditions in each time window across subjects. (E) Group-averaged electrodermal responses are shown for the same conditions shown in A. Vertical dashed bars indicate the time window of 2-6 s. (F) The bar plot shows the mean and standard deviation of the difference in electrodermal response amplitude between conditions.

5.4.4 Relationships between effects across subjects

Across subjects, differences in anticipatory postural adjustments could not explain differences in effects of step planning or step execution on any response variable. Lateral weight shifts were not associated with changes in cortical N1 response amplitude, early or late EMG response amplitudes, or electrodermal responses between stepping and nonstepping reactions to easy or difficult perturbations or between planned and unplanned stepping reactions to difficult perturbations (all $p>0.05$).

Across subjects, increases or decreases in cortical N1 response amplitudes with planned stepping in response to easy perturbations were positively associated with similar changes early stance-TA (Figure 5-6A, $R^2=0.28$, $p=0.01$). Changes in cortical N1 response amplitudes with stepping in response to easy perturbations were not associated with changes in electrodermal responses or any other early or late EMG response amplitude (all $p>0.05$).

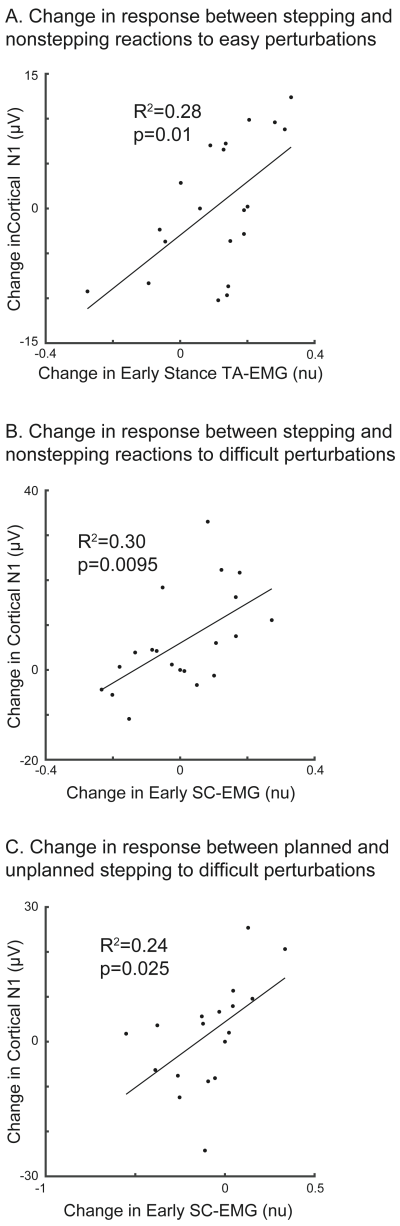


Figure 5-6. Associations between changes in muscle and cortical responses between conditions across subjects. (A) Across subjects, increases or decreases in cortical N1 response amplitude between stepping and nonstepping reactions to easy perturbations were positively correlated with similar changes in stance-TA activity. (B) Increases or decreases in cortical N1 response amplitude between stepping and nonstepping reactions to difficult perturbations were positively correlated with similar changes in early SC-EMG activity across subjects. (C). Increases or decreases in cortical N1 response amplitude between planned and unplanned stepping reactions to difficult perturbations were positively correlated with similar changes in early SC-EMG activity across subjects.

Across subjects, increases or decreases in cortical response amplitudes in difficult perturbations were positively correlated with similar changes in SC-EMG activity. Increases or decreases in cortical N1 response amplitude between stepping and nonstepping reactions to difficult perturbations were positively correlated with similar changes in SC-EMG in the same comparison (Figure 5-6B, $p=0.0095$, $R^2=0.30$). Increases or decreases in cortical N1 response amplitude between planned and unplanned stepping reactions to difficult perturbations were positively correlated with similar changes in SC-EMG in the same comparison (Figure 5-6C, $p=0.025$, $R^2=0.24$). Changes in cortical N1 response amplitudes between stepping and nonstepping reactions or between planned and unplanned stepping reactions to difficult perturbations were not associated with changes in any other response variable (all $p>0.05$).

5.5 Discussion

Our results suggest a possible role for the cortical N1 response in the execution but not planning of a compensatory stepping reaction. The influence of prior planning on the earliest involuntary balance-correcting motor responses is consistent with prior work (Burleigh and Horak 1996; Burleigh et al. 1994; McIlroy and Maki 1993b), and cannot be explained by anticipatory postural adjustments, and thus likely reflects a planning-related change in central set (Prochazka 1989). In contrast to our hypothesis, cortical N1 responses did not differ between planned and unplanned compensatory stepping reactions, suggesting that the cortical response is not influenced by the planning-related changes in central set that influence the evoked motor reactions. Instead, cortical responses were larger when

executing a planned compensatory stepping reaction compared to nonstepping reactions in challenging perturbations, suggesting a possible role for the cortical N1 in the execution of compensatory steps for balance recovery, and that this role is not influenced by whether the compensatory step was planned before the perturbation. Across subjects, changes in evoked cortical responses were not associated with the extent of preceding lateral weight shifts or subsequent later motor reactions, suggesting that any role of the cortical responses in the execution of compensatory steps is not due to changes in sensory input resulting from anticipatory postural adjustments and is not directly expressed in the agonist or antagonist muscles crossing the ankle joint.

Consistent with prior studies, the intention to step altered the early automatic motor responses, likely through planning-related changes in central set. Consistent with Burleigh et al. (1994), we observed a reduction in early stance-MG when planning a step, but unlike Burleigh et al. (1996), this reduction did not require predictability of perturbation magnitude. Although it is possible that the lateral weight shift prior to planned stepping reactions contributed to asymmetric changes in early MG-EMG, these changes in MG-EMG were not associated with the magnitude of anticipatory postural adjustments across subjects in any comparison. Further, these anticipatory postural adjustments cannot explain the bilateral increase in early TA-EMG when planning a step, which we interpret to reflect a change in central set, consistent with Mcilroy and Maki (1993b). Particularly, the consistency of the increase in early stance-TA across all comparisons with planned stepping is consistent with a planning-related change that appears to be independent of changes related to the execution of a compensatory step. Thus, we conclude that the

intention to respond to perturbations by taking a step resulted in a modification of central set, altering the sensitivity of the motor responses to the subsequent perturbations.

In contrast to our hypothesis, cortical N1 response amplitude was altered with the execution, rather than the planning, of a compensatory stepping reaction. We previously observed larger cortical N1 responses in subjects who more frequently failed to resist compensatory steps, particularly in larger perturbations (Payne et al. 2018). While prior studies have suggested that the cortical N1 response amplitude reflects the error of a perturbation stimulus from expectations (Adkin et al. 2008; Adkin et al. 2006; Dietz et al. 1985a; Mochizuki et al. 2009b; Mochizuki et al. 2008), we hypothesized that an error of the evoked motor reaction from expectations would likewise be associated with larger cortical responses. However, lack of variation in cortical N1 response amplitude between planned and unplanned compensatory stepping reactions suggests the cortical N1 response does not reflect an online change in the motor response strategy. Because evoked motor reactions showed planning-related changes in central set between conditions without similar planning-related changes in cortical N1 responses, we conclude that the cortical N1 response is not influenced by the mechanisms that alter the sensitivity of the involuntary motor reactions with changes in motor goal. In contrast, in difficult perturbations we found an increase in cortical N1 responses when a planned step was executed in comparison to a successful nonstepping responses, suggesting a possible relationship between the cortical N1 response and the execution of compensatory steps for balance recovery. This increase in cortical responses with step execution was only observed in difficult perturbations where steps were helpful and was not observed in easy perturbations where steps were not needed for balance recovery. Given these results, we propose a new hypothesis that the cortical N1

response may be involved longer latency compensatory behaviors, such as stepping, which occur after the automatic postural response when the automatic postural response is insufficient for balance recovery.

Across subjects, increases or decreases in cortical responses were associated with similar changes in early stance-TA and startle-related muscle activity, and were not associated with changes in arousal or anticipatory postural adjustments. In difficult perturbations, increases or decreases in cortical N1 responses with planning and execution of compensatory steps were associated with similar changes in early SC-EMG activity across subjects, which is representative of the startle reflex (Brown et al. 1991; Campbell et al. 2013; Nonnekes et al. 2015). This association between evoked cortical responses and startle responses is consistent with prior observations (Payne et al. 2018), and suggests that the different changes in cortical N1 responses across subjects may be related to how startled they were by each condition. In contrast, changes in cortical responses were not associated with changes in electrodermal responses in any comparison, consistent with prior suggestions that the cortical N1 response is not related to physiological arousal or autonomic reactivity more broadly (Sibley et al. 2008; Sibley et al. 2010). In easy perturbations, increases or decreases in cortical responses between stepping and nonstepping reactions were associated with similar changes in early stance-TA activity across subjects, but the lack of such an association across other comparisons with planned stepping reactions fails to support a relationship between planning-related changes in muscle and cortical responses. Additionally, changes in evoked cortical responses were not associated with the extent of preceding lateral weight shift or subsequent motor reactions, suggesting that any role of the cortical responses in the execution of compensatory steps is

not due to changes in sensory input due to anticipatory postural adjustments and is not directly expressed in the agonist or antagonist muscles crossing the ankle joint.

CHAPTER 6. SMALLER PERTURBATION-EVOKED CORTICAL RESPONSES ARE ASSOCIATED WITH BALANCE IMPAIRMENT IN PARKINSON'S DISEASE

6.1 Abstract

Indirect evidence from dual-task studies suggests that impairment of automatic balance control in Parkinson's disease (PD) requires increased reliance on attention-dependent compensatory control. Measurement of brain activity has the potential to provide a more direct measure of attention-dependent compensatory control. Electroencephalography (EEG) recordings during reactive balance recovery reveal a cortical N1 response localized to the supplementary motor area occurring 100-200 ms after perturbation. The cortical N1 response is smaller when young adults direct attention away from balance control during dual-task performance, and the cortical N1 response is larger in young adults who have lower balance ability and on trials where compensatory steps are taken. I hypothesized that smaller amplitudes of the cortical N1 response in PD would reflect failure of cognitively-dependent cortical compensation for impaired balance in PD. I predicted that the cortical N1 response amplitude would be smaller in people with PD and simultaneously associated with lower balance and cognitive scores. In this chapter I report preliminary results in 13 people with PD (OFF dopamine medications) and 10 control subjects. The cortical N1 response was elicited by unpredictable translational perturbations of the floor during quiet standing. Balance ability was measured with the MiniBESTest. Cognitive ability was measured using the Montreal Cognitive Assessment. In contrast to perturbation-evoked cortical responses in young adults, cortical responses in older adults both with and without

PD contained two negative peaks. In contrast to our hypothesis, the cortical N1 response did not differ between groups or relate to balance or cognitive scores. However, the unexpected later negativity following the cortical N1 was smaller in PD, and smaller amplitudes of the later negativity were associated with lower balance ability scores (R^2=0.35, p=0.03) in the PD group. These preliminary results suggest that perturbation-evoked cortical responses may be related to balance impairment in PD and warrant further study.

6.2 Introduction

An association between balance and cognitive impairments has been widely observed but remains yet unexplained. In otherwise healthy older adults, subtle cognitive impairments in domains of executive function, attention, and memory are associated with greater variation in center of pressure during stance (Deschamps et al. 2014), lower scores on the MiniBESTest of balance ability (Tangen et al. 2014), and serve as significant predictors of new (Herman et al. 2010) and recurrent falls (Gleason et al. 2009; Mirelman et al. 2012). Further, greater interference of a cognitive task on simultaneous balance performance is observed with increasing age (Rankin et al. 2000), fall history (Shumway-Cook et al. 1997), and impairment in executive function (Mirelman et al. 2012; Montero-Odasso et al. 2012), and can predict future falls (Lundin-Olsson et al. 1997). Although it is possible that the associated decline in balance and cognitive abilities is due to parallel age-related decline in both domains, evidence that combined cognitive and motor training provide synergistic benefits to balance ability (Kraft 2012; Wu et al. 2016) suggests the existence of a therapeutic target at the intersection of balance and cognitive dysfunction.

People with Parkinson's disease (PD) are particularly vulnerable to balance and cognitive impairments, and show similar associations between balance and cognitive impairments as those observed in people without PD. People with PD have a substantially increased risk of cognitive impairment (Dirnberger and Jahanshahi 2013) and a six times greater risk of falls (Bloem et al. 2001; Grimbergen et al. 2004; Paul et al. 2013) compared to those without PD. In people with PD, subtle cognitive impairments in domains of executive function, attention, and memory are associated with greater center of pressure variation during stance (Nocera et al. 2010) and balance problems including greater disturbances of posture and gait (Dirnberger and Jahanshahi 2013; Sollinger et al. 2010) and freezing of gait (Shine et al. 2013a). People with PD show greater interference of a cognitive task on simultaneous balance performance, and this interference is even greater in those with a history of falls (Plotnik et al. 2011). As in those without PD, subtle cognitive impairments can predict new (Allcock et al. 2009) and recurrent falls in PD (Camicioli and Majumdar 2010; Mak et al. 2014). Further, combination cognitively engaging and goal-oriented motor training benefits motor function in PD (Ellis et al. 2008; Monticone et al. 2015; Petzinger et al. 2013). These observations suggest that individuals with PD display similar, but more severe, interactions between motor and cognitive dysfunction, which may yield insight that is also relevant to those without PD.

Measuring brain activity during behavior may yield insight into the association between balance and cognitive decline in older adults with and without PD. Cognitive impairment in PD has been associated with a reduction in functional magnetic resonance imaging (fMRI) activity (Lewis et al. 2003; Shine et al. 2013c) and connectivity (Shine et al. 2013b) between frontal cortex and the striatum of the basal ganglia. Similarly, changes

in functional connectivity between frontal cortex and locomotor centers in the brainstem have been associated with gait disturbances in PD (Fling et al. 2014; Fling et al. 2013; Fling et al. 2018). Although fMRI is not possible during assessment of whole-body balance recovery, other tools, such as electroencephalography (EEG) are capable of measuring cortical brain activity during reactive balance recovery. EEG recordings during balance perturbations reveal a cortical N1 response occurring 100-200 ms after perturbation onset that is localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015), which is the cortical node of the so-called basal ganglia-thalamocortical "motor circuit" (Alexander et al. 1986). We showed in Chapter 4 that this cortical N1 response to perturbations is larger in healthy young adults who performed worse in a challenging dynamic balance task, suggesting that the cortical N1 may be related to compensatory balance control when the automatic balance corrections are insufficient. This cortical N1 response is reduced in amplitude by the performance of a simultaneous cognitive dual-task during balance perturbations in healthy young adults (Little and Woollacott 2015; Quant et al. 2004b), suggesting that this cortical N1 may reflect use of the attention-dependent compensatory mechanisms that are diverted by dual-tasking in older adults with balance problems. Further, the amplitude of the cortical N1 response is smaller in older adults compared to younger adults (Duckrow et al. 1999), suggesting that the underlying mechanisms are susceptible to age-related decline with healthy aging. However, among older adults, the cortical N1 response is larger in those with less mobility (Duckrow et al. 1999), similar to the larger amplitudes in healthy young adults with lower balance ability, suggesting that the underlying mechanisms may still be engaged as an attempt to compensate for motor problems despite the age-related decline.

I hypothesized that smaller amplitudes of the cortical N1 response in PD would reflect failure of cognitively-dependent cortical compensation for impaired balance in PD. I predicted that the cortical N1 response amplitude would be smaller in people with PD and simultaneously associated with lower balance and cognitive scores. In this chapter, I report preliminary results in an incomplete sample of 13 people with PD (OFF dopamine medications) and 10 people without PD. Unpredictable forward and backward translational perturbations of the floor during quiet standing were used to elicit the cortical N1 response. The MiniBESTest was used as a measure of balance ability (Leddy et al. 2011), which assesses anticipatory postural control, reactive postural control, sensory orientation, and dynamic gait. The Montreal Cognitive Assessment was used as a rapid screening tool for mild cognitive dysfunction, which assesses cognitive domains including executive function, attention, and memory (Hoops et al. 2009; Nasreddine 2004). We found not one but two negative peaks of cortical activity evoked by balance perturbations, with smaller amplitudes of the later negativity related to balance impairment in the PD group.

6.3 Methods

6.3.1 Participants

Projected Sample Size. Sample size for this study was determined based on reported differences between amplitudes of the error-related negativity during a Flankers task in OFF-medication state PD patients (ERN peak-to-peak amplitude of -9±4 μV) and matched control subjects (-5±4 μV) (Beste et al. 2009). This difference corresponds to an effect size ≈ 1.0 when expressed as Cohen's d (Cohen 1992). With N=20 per group, an unpaired-sample t-test will be able to detect effect sizes of ≥0.90 with 80% power.

Current Sample Size. This chapter reports preliminary results on the incomplete sample of N=13 people with Parkinson's disease (PD group) and N=10 people without Parkinson's disease (noPD group). All participants signed written informed consent before participation. The N=13 participants with PD does not include two individuals who were excluded; one for the use of different perturbations during piloting, and another for atypical presentation of parkinsonism. The N=10 participants in the noPD group does not include one individual who was excluded for blepharospasms.

Subject Recruitment. Participants with and without PD were recruited through flyers posted around Emory University and the Emory Movement Disorders Clinic, local outreach events, word of mouth, and databases of prior participants from collaborating research labs. Adults over 55 years old were screened for the following inclusion criteria: vision can be corrected to 20/40 or better with glasses, no history of stroke or other neurologic condition (except for PD), no musculoskeletal conditions or procedures that cause pain or limit mobility of the legs, and ability to stand unassisted for at least 15 minutes. Potential participants were excluded for prior experience on the perturbation platform. Participants with PD were recruited first, and then participants in the noPD group were recruited in attempt to maintain similar ages between groups.

OFF-medications. Participants with PD were asked to arrive to the lab OFF their dopamine medications, practically defined as following a minimum 12-hour period of withholding all dopaminergic medications for PD. The neurologist of each participant with PD signed an OFF-medication clearance form before each participant was asked to withhold their medications for the purpose of this experiment.

6.3.2 Experimental protocol and data collection

PD motor severity. The severity of motor impairments was assessed in participants with PD during the experimental session in the OFF-medication state using the motor subscale of the Movement Disorders Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) (Fahn and Elton 1987). The test was administered by A.M.P, who is certified by the Movement Disorders Society, and filmed for subsequent scoring by a trained neurologist. For one participant whose video was accidentally deleted, scores were obtained from a separate administration of the MDS-UPDRS III to the participant in the OFF-medication state less than two months later, by another certified scientist and scored by the same neurologist.

Balance ability. The MiniBESTest (www.bestest.us) was used as a measure of balance ability (Leddy et al. 2011) which assesses anticipatory postural control, reactive postural control, sensory orientation, and dynamic gait.

Cognitive ability. The Montreal Cognitive Assessment (MoCA, www.mocatest.org) was given as a rapid screening tool for mild cognitive dysfunction that assesses cognitive domains including executive function, attention, and memory (Hoops et al. 2009; Nasreddine 2004).

Perturbations. To test the effect of PD on the cortical response to balance perturbations, all subjects were exposed to 48 translational support-surface perturbations (Factory Automation Systems, Atlanta, GA) of unpredictable timing, direction, and magnitude. Perturbations were evenly divided between forward and backward directions, and three perturbation magnitudes, which will be referred to as low, medium, and high.

The low perturbation was (0.15 g, 11.1 cm/s, 5.1 cm) and was identical across participants. 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) perturbations were linearly scaled down from reference perturbations (medium: 0.22 g, 16.7 cm/s, 7.7 cm; high: 0.30 g, 21.8 cm/s, 10.2 cm) by multiplying perturbation acceleration, velocity, and displacement characteristics by the scaling factor shown in the equation below. The 48 perturbation series was divided into 8 blocks, each containing one replicate of each unique perturbation. Three different block-randomized perturbation orders were used across participants. The perturbations used for the tallest subject are shown in Figure 6-1.

$$Perturbation\ Scaling\ Factor = \frac{Height + 80cm}{280cm}$$

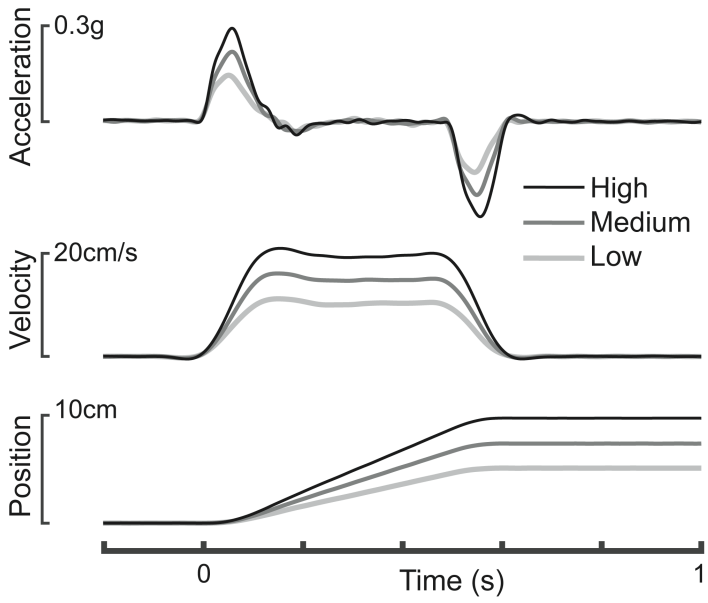


Figure 6-1. Example perturbation kinematics are shown for the tallest subject (194.2 cm), who was given perturbations up to 0.29 g, 21 cm/s, and 9.8 cm. Larger perturbations are indicated by darker lines.

To prevent fatigue, a 5-minute break was enforced halfway through the perturbation series unless the participant requested breaks more frequently. Participants were allowed to request sitting breaks as frequently as desired. Not counting these breaks, the total duration of the perturbation series was 20±1 minutes. Inter-trial-intervals measured from perturbation onset to perturbation onset, excluding the 5-minute rest break, was 23±13 seconds.

As described in the preceding chapters, to reduce the potential for recording artifacts, perturbations were only initiated when electroencephalography (EEG) activity was relatively quiescent, based on visual inspection of a live monitor displaying the online EEG data. During all trials, participants were asked to cross their arms and to stare at a central location in a poster of a mountain landscape on a wall 4.5 m away.

Electroencephalography (EEG) collection and pre-processing. EEG collection and pre-processing are as described in the preceding chapter (Data collection and quantification).

Evoked cortical response quantification. Cortical event-related potentials (ERPs) were created by averaging EEG data across all trials within each participant at the Cz electrode. Cortical N1 responses were quantified as the peak amplitude between 100-200 ms after perturbation onset in ERPs. An unexpected subsequent negative peak following the cortical N1 response was additionally quantified as the peak amplitude between 200-300 ms after perturbation onset in ERPs (Figure 6-2) and will be referred to as the late or later negativity.

6.3.3 Statistical Analyses

Comparisons across groups. Unpaired t-tests were used to compare subject characteristics (age, height, weight), ability scores (MoCA, MiniBESTest), and evoked cortical responses (cortical N1 and the later negativity) between PD and noPD groups. Fisher's exact test of independence was used to compare gender distribution between groups. In cases where the folded F statistic identified unequal variances between groups, the degrees of freedom of the t-test were adjusted by the Satterthwaite approximation. All statistical analyses were performed in SAS.

Correlations between cortical response amplitudes and subject characteristics. Univariate linear regressions were used to test for correlations between evoked cortical response amplitudes and subject characteristics or ability scores within PD and noPD groups. Shapiro-Wilk tests were performed to ensure that no variables going into linear

regressions displayed a significant deviation from a normal distribution. All R^2 values are reported as adjusted R^2 values.

6.4 Results

Table 6-1. Participant characteristics did not differ between groups. P-values are from comparisons between groups using unpaired two-way t-tests. *Comparison of gender distribution between groups was based on Fisher's exact test of independence.

	noPD (N=10)	PD (N=13)	p
Age	72.9 ± 6.4 years	70.5 ± 5.1 years	0.34
Gender	20.0% female	30.8% female	0.66*
Height	175.1 ± 9.5 cm	170.4 ± 12.0 cm	0.36
Weight	78.3 ± 12.3 kg	81.5 ± 20.4 kg	0.66
MiniBESTest	24.5 ± 2.6	21.9 ± 4.8	0.14
MoCA	25.4 ± 4.4	25.5 ± 2.8	0.97
MDS-UPDRS-III		28.5 ± 14.2	
PD Duration		4.6 ± 3.2	

6.4.1 Participant characteristics

Participant characteristics did not differ across groups (Table 6-1). PD and noPD groups did not differ in age (p=0.34), gender (p=0.66), height (p=0.36), or weight (p=0.66).

Groups also did not differ in balance (p=0.14) or cognitive (p=0.97) scores. Participants with PD had been diagnosed 4.6±3.2 years before participation and had scores of 28.5±14.2 on the motor subsection of the MDS-UPDRS.

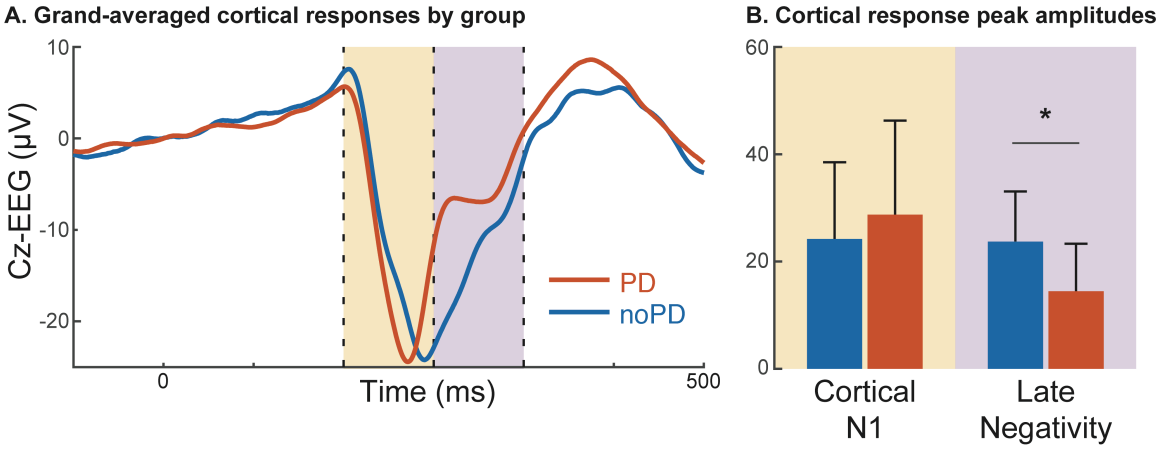


Figure 6-2. Grand-averages of evoked cortical responses. (A) Group-averaged cortical responses are shown in red for PD and blue for noPD groups. The time window of the cortical N1 response is shaded in yellow and the time window of the later negativity is shaded in purple. (B) The bar plot displays the mean and standard deviation of the subject-averaged cortical N1 response (over yellow shading) and the later negativity (over purple shading). Asterisk (*) indicates a significant difference in response amplitudes between groups at α=0.05 (unpaired, two-way t-test). PD: Parkinson's Disease. noPD: Control Subjects.

6.4.2 The amplitude of the later cortical negativity, but not the cortical N1 response, was smaller in PD

The later cortical negativity, but not the cortical N1 response, was smaller in the PD group (Figure 6-2). The cortical N1 response did not differ between groups (p=0.89), but the later negativity was 10.4 μV (41.8%) smaller in the PD group (Figure 6-2B, p=0.018). Variation in cortical responses within each group is illustrated in Figure 6-3, which shows cortical responses from two very different subjects in each subject group.

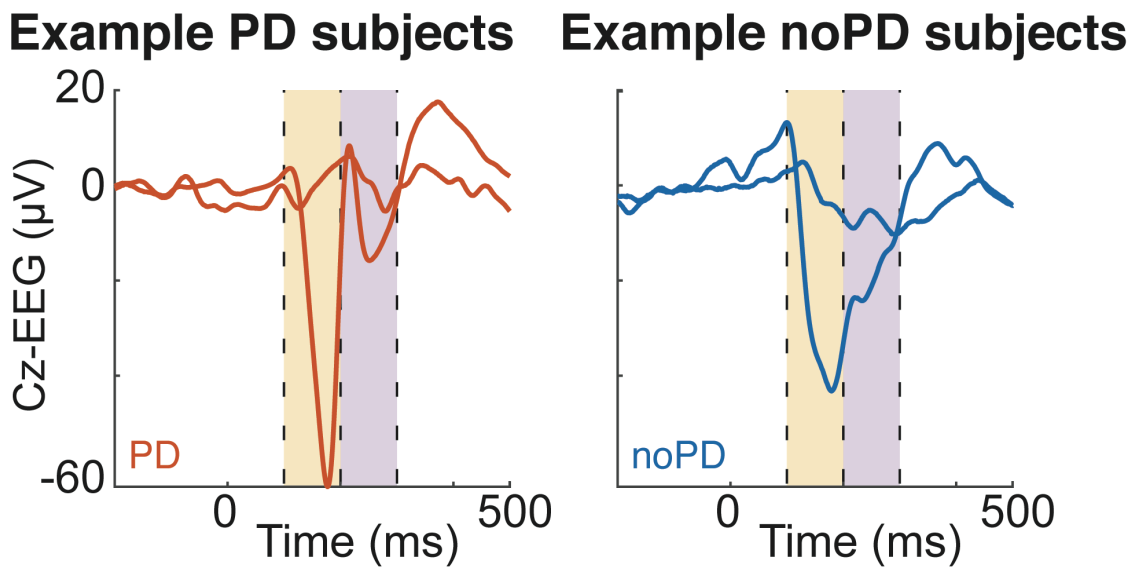


Figure 6-3. Perturbation-evoked cortical responses from very different example subjects in each group. The left plot shows subject-averaged cortical responses from two PD subjects with very different evoked responses. The plot on the right shows subject-averaged cortical responses from two noPD subjects with very different evoked responses. The time window of the cortical N1 response (100-200ms) is shaded in yellow and the time window of the later negativity is shaded in purple (200-300ms). PD: Parkinson's Disease. noPD: Control Subjects.

6.4.3 The evoked cortical responses were not associated with age or body size

The amplitudes of the cortical N1 response and the late negativity were not associated with participant characteristics (Figure 6-4). The amplitude of the cortical N1 response was not associated age (Figure 6-4A; PD: p=0.059, noPD: p=0.78), height (Figure 6-4B; PD: p=0.59, noPD: p=0.27), or weight (Figure 6-4C; PD: p=0.93, noPD: p=0.92). Likewise, the amplitude of the late negativity was not associated age (PD: p=0.15, noPD: p=0.66), height (PD: p=0.73, noPD: p=0.15), or weight (PD: p=0.82, noPD: p=0.41).

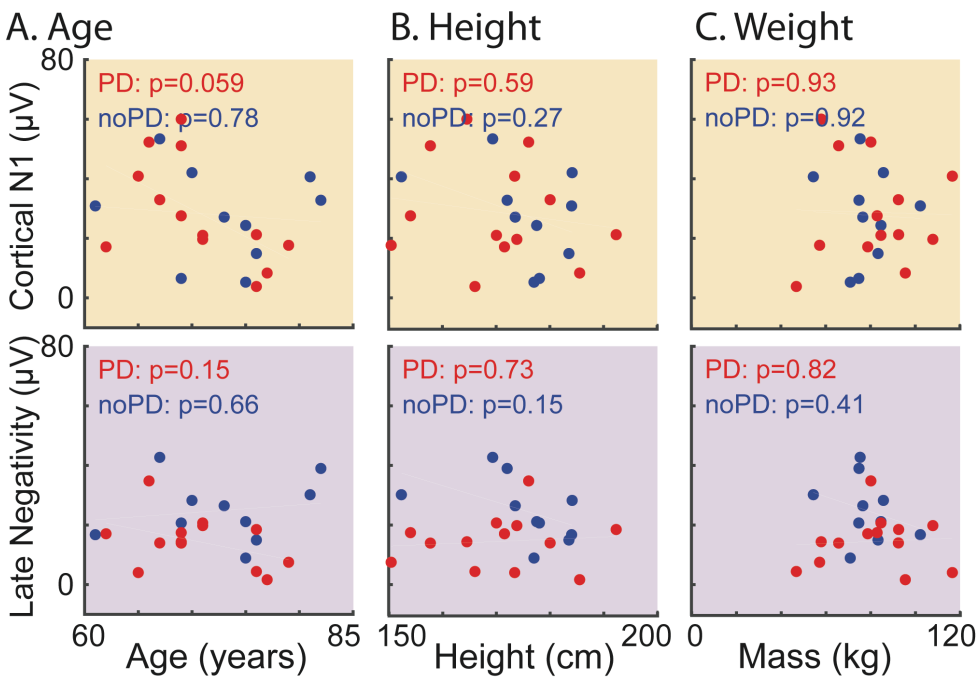


Figure 6-4. Perturbation-evoked cortical responses were not associated with participant characteristics. Vertical axes plot amplitudes of cortical N1 responses in the top row and amplitudes of the later negativity in the bottom row. Cortical response amplitudes are plotted against each participant's (A) age, (B) height, and (C) weight. Data from the PD group is shown in red and data from the noPD group is shown in blue. PD: Parkinson's Disease. noPD: Control Subjects.

6.4.4 Smaller amplitudes of the later negativity were associated with balance impairment in PD

The amplitude of the later negativity, but not the cortical N1 response, was associated with balance ability only in the PD group (Figure 6-5). The amplitude of the cortical N1 response was not associated with scores on the MiniBESTest in either group (Figure 6-5A; PD: p=0.95, noPD: p=0.90). Larger amplitudes of the late negativity were associated with better scores on the MiniBESTest in the PD group (Figure 6-5A; R^2=0.35, p=0.032) but not in the noPD group (p=0.92).

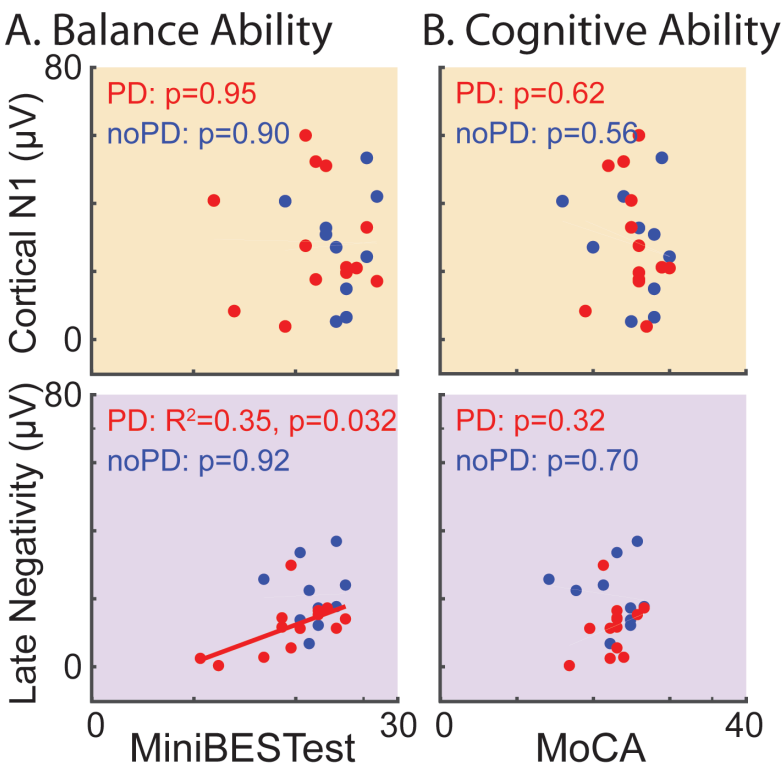


Figure 6-5. The late negativity was associated with balance ability only in the PD group. Vertical axes plot amplitudes of cortical N1 responses in the top row and amplitudes of the later negativity in the bottom row. Cortical response amplitudes are plotted against each participant's (A) MiniBESTest score of balance ability and (B) Montreal Cognitive Assessment score. Data from the PD group is shown in red and data from the noPD group is shown in blue. Lines are drawn where correlations are significant at α=0.05. PD: Parkinson's Disease. noPD: Control Subjects.

6.4.5 The evoked cortical responses were not associated cognitive scores

Neither the cortical N1 response nor the late negativity were correlated with cognitive scores (Figure 6-5B). The cortical N1 response amplitudes were not associated with MoCA scores in either group (Figure 6-5B; PD: p=0.62, noPD: p=0.56). Likewise, amplitudes of the late negativity were not associated with MoCA scores in either group (Figure 6-5B; PD: p=0.32, noPD: p=0.70).

6.5 Discussion

In contrast to perturbation-evoked cortical responses in healthy young adults, cortical responses in older adults contained two negative peaks, similar to those described by Duckrow et al (1999), but to a larger extent in the present case. In contrast to our hypothesis, the cortical N1 response did not differ between groups or relate to balance or cognitive impairments. However, the unexpected later negativity following the cortical N1 response was smaller in PD, and smaller amplitudes of the late negativity were associated with lower balance ability scores in the PD group. These preliminary results suggest that smaller amplitudes of perturbation-evoked cortical responses may be related to balance impairment in PD, and warrant further study.

Is the second component peak unique to older adults, or rather uniquely delayed relative to the cortical N1? The cortical N1 response has been localized in healthy young adults to the supplementary motor area, just anterior to the leg region of the primary motor cortex, with a broad distribution that spans frontocentral cortical areas (Marlin et al. 2014; Mierau et al. 2015). Given the appearance of a later component peak, first described by Duckrow and colleagues (1999), and supported here, the question arises of whether the later component reflects a process that is not activated in healthy young adults, or if this process is instead simultaneous with the cortical N1 response in healthy young adults. Indeed, Duckrow and colleagues showed that longer latencies between the component peaks were associated with lower mobility, and thus it is possible that these peaks occur simultaneously in young adults without mobility problems. Because this second component peak was not observed in localization studies of the cortical N1 response (Marlin et al. 2014; Mierau et al. 2015), it is possible that this second component peak could arise from a different brain region than the supplementary motor area, and should be

interpreted cautiously. While a localization study with a higher density EEG array would be needed to localize the second component peak in older adults, simultaneous activation of these two components in healthy young adults could bias in the localization of the cortical N1 response in healthy young adults under the assumption that the cortical N1 response is a single component arising from a single brain area.

The lack of effects of PD, balance ability, and age on the cortical N1 response was in contrast to the hypothesis of the present study and inconsistent with prior studies. While the lack of significant differences in balance or cognitive scores between groups could explain the similar N1 amplitudes between groups, it is unclear why the cortical N1 response was not associated with balance or cognitive scores within either group, given the relationship the balance ability in healthy young adults described in Chapter 4. Group averages of balance ability scores for both groups were above a previously defined cutoff for identifying fall risk (Leddy et al. 2011), but both groups contained multiple people with balance scores below this cutoff for fall risk, so we cannot attribute the lack of a relationship between the cortical N1 response and balance ability scores to a lack of observations of balance impairment. Thus, it is possible that the cortical N1 response has a different relationship to balance ability in older adults with and without PD compared to healthy young adults. Further, group averages of cognitive ability scores for both groups were below a previously defined cutoff for identifying mild cognitive impairment (Nasreddine 2004), indicating that both groups were cognitively impaired on average. Although we did not observe any associations between cortical response amplitudes and cognitive scores, it is possible that a larger sample size with greater variation in cognitive abilities, or cognitive tests for specific subdomains of cognition could reveal a relationship,

if such a relationship exists. In this sample, we were unable to assess the relationship between the cortical N1 response and subdomains of the Montreal Cognitive Test because the subscores displayed significant deviations from normal distributions. However, based on prior observations that the cortical N1 depends on the availability of attention (Little and Woollacott 2015; Quant et al. 2004b), we would expect some effect of attention on the cortical N1 response in older adults. And finally, the lack of a reduction in cortical N1 response amplitude with age is inconsistent with the effect of age reported by Duckrow and colleagues (1999), and it is possible that we failed to observe this effect due to our smaller sample size or the narrower range of ages (61-82 years). Overall, these results seem to suggest that the cortical N1 response in older adults may differ from cortical N1 responses in healthy young adults.

The relationship between balance impairment in PD and smaller amplitudes of the later negativity may explain the lack of findings in the cortical N1 response, and indirectly support our initial hypothesis relating the cortical N1 response to balance impairment in PD. Given prior findings that the latency between the two component peaks of the perturbation-evoked cortical response in older adults is associated with mobility impairments (Duckrow et al. 1999), it is possible that the later negativity may occur simultaneous to the cortical N1 response in healthy young adults, presenting as a delayed subcomponent of the cortical N1 response in older adults. While this is an interesting possibility, it is not sufficient to explain the different directionality of the relationship to balance ability between healthy young adults and older adults with PD. Specifically, the cortical N1 response was larger with worse balance ability in healthy young adults while

the later negativity was larger for better balance in PD. This discrepancy may be better understood by considering the early and late negativities as distinct components.

Given opposite relationships to balance ability between healthy young adults and older adults with PD, the cortical N1 response and the later negativity may reflect distinct processes. In healthy young adults, cortical N1 responses have been shown to be influenced by attention (Little and Woollacott 2015; Quant et al. 2004b), perceived threat (Adkin et al. 2008; Mochizuki et al. 2010), and predictability (Adkin et al. 2008; Adkin et al. 2006; Mochizuki et al. 2010; Mochizuki et al. 2008). All of these results could be mediated by changes in attention to balance, which would be larger when people are afraid (Huffman et al. 2009), and smaller when a perturbation is predictable. As such, the according modulations of the cortical N1 response amplitude in healthy young adults could be explained by attention-dependent facilitation of bottom up sensory information, which is known to influence the amplitude of somatosensory-evoked cortical potentials (Staines et al. 2000). While it is abnormal for healthy young adults to pay much attention to balance control, those with worse balance may have paid relatively more attention to the perturbations, potentially explaining the larger amplitudes of their cortical N1 responses. In contrast, older adults with balance impairments begin to rely on more attention-dependent compensatory control, as evidenced by larger effects of dual-task interference (Rankin et al. 2000; Shumway-Cook et al. 1997). If the cortical N1 response is related to bottom-up processing of sensory inputs, the later negativity could be related to top-down, potentially voluntary, compensation for impaired automatic balance control. In this case, those with smaller amplitudes of the later negativity may be those who are failing to

execute top-down compensatory control to overcome limitations of automatic balance control, leading to observably worse balance, as measured by the MiniBESTest.

While these preliminary results suggest that perturbation-evoked cortical responses may provide insight into balance impairments in PD, it remains unclear how to use this insight to improve the evaluation and treatment of balance impairments in PD. If the amplitude of the perturbation-evoked cortical responses presents a biomarker for balance ability, can this biomarker be used to track progress through rehabilitation, or to sort people into different interventions targeted to their specific needs? Could the cortical area or areas underlying these two component peaks serve as potential therapeutic targets for noninvasive cortical stimulation to enhance rehabilitation for balance impairments? Does the latency between the component peaks reflect the extent of impairment, as suggested by Duckrow and colleagues (1999), reflecting the extent of information loss in communication between the underlying brain areas? Do these two component peaks occur simultaneously in healthy young adults, and if so, would that bias attempts to localize the cortical N1 to a single brain area in young adults? Why is the late negativity larger for those with better balance in PD, when the cortical N1 response is smaller for those with better balance ability in healthy young adults? In any case, the possibility of a quantitative measure of cortical activity related to balance impairments in PD warrants further study of the perturbation-evoked cortical responses, and may eventually lead to better evaluation and treatment of balance impairments in PD.

CHAPTER 7. THE ERROR-RELATED NEGATIVITY AND PERTURBATION-EVOKED CORTICAL RESPONSES ARE INVERSELY CORRELATED IN PEOPLE WITH PARKINSON'S DISEASE

7.1 Abstract

The error-related negativity (ERN) is thought to reflect the recruitment of cognitive control to improve behavior after errors. In Chapter 2, we highlighted similarities between the ERN and the perturbation-evoked cortical N1 response in terms of similar dependencies on motivation, perceived consequences, perceptual salience, expectation, development, and aging, suggesting that the ERN and perturbation-evoked cortical responses share an underlying mechanism. While the ERN amplitude is generally smaller in people with Parkinson's disease (PD), it is unknown whether the ERN and perturbation-evoked cortical responses are impacted by PD in the same way. I hypothesized that some underlying mechanism shared between the ERN and perturbation-evoked cortical responses is impacted by PD. I predicted that ERN amplitudes and perturbation-evoked cortical response amplitudes would be positively correlated in people with PD. Subjects described in the preceding chapters additionally performed a computer-based task to elicit the ERN in the same recording session that their perturbation-evoked cortical responses were quantified. Here I report preliminary results comparing ERN amplitudes to perturbation-evoked cortical response amplitudes in healthy young adults (N=18), and older adults with (N=10) and without (N=10) PD. In contrast our hypothesis, we observed a negative association between the ERN and the perturbation-evoked cortical responses in PD.

Specifically, individuals with PD who had smaller ERNs had larger perturbation-evoked cortical responses, indicating that PD does not impact the ERN and perturbation-evoked cortical responses in the same way.

7.2 Introduction

The error-related negativity (ERN) is thought to reflect the recruitment of cognitive control to improve behavior after errors and is smaller in people with Parkinson's disease (PD). The ERN is a neural response elicited when a mistake is made in forced-choice speeded-response tasks (Falkenstein et al. 1990; Gehring et al. 2018; 1993). The ERN is typically studied in computer-based tasks where visual stimuli indicate responses that subjects are asked to enter as quickly as possible each time they appear during the task (Meyer et al. 2013). Despite the simplicity of the tasks, people make errors on a small percentage of trials. The ERN is obtained in the response-locked event-related brain potential (ERP) generated by subtracting the averaged EEG activity in all correct trials from the averaged EEG activity in all trials containing errors at frontocentral electrodes. In theory, this subtraction removes stimulus- and response-associated aspects of the brain activity, leaving behind only brain activity relating to the fact that an error was made. The ERN has been localized to the anterior cingulate cortex (Dehaene et al. 1994; Gentsch et al. 2009; Marlin et al. 2014; Miltner et al. 1997), and is generally thought to reflect recruitment of cognitive control to modify behavior to reduce the extent or likelihood of committing the same error again in the future (Holroyd and Coles 2002b; Ridderinkhof et al. 2004; Shackman et al. 2011; Ullsperger et al. 2014). The ERN appears to be a dopamine-dependent phenomenon, as its amplitude can be modified bidirectionally by giving dopamine agonists or antagonists to healthy young adults (de Bruijn et al. 2004; de Bruijn

et al. 2006; Zirnheld et al. 2004). Further, the ERN amplitude is smaller in people with PD (Beste et al. 2009; Seer et al. 2016; Stemmer et al. 2007; Willemssen et al. 2009; Willemssen et al. 2008), but it is unclear whether the smaller ERN amplitudes in PD are related to reductions in similar ERPs, like the perturbation-evoked cortical responses.

Similar outcomes of investigations of the ERN and perturbation-evoked cortical responses suggest these responses share an underlying mechanism. In Chapter 2, we highlighted similarities between the ERN and the perturbation-evoked cortical N1 response in terms of similar dependence on motivation, perceived consequences, perceptual salience, expectation, development, and aging. On the basis of these parallels, we proposed that the ERN and the cortical N1 might reflect similar functions of the action monitoring system. In this chapter, I ask whether PD impacts the ERN and perturbation-evoked cortical responses in a similar manner.

I hypothesized that some underlying mechanism shared between the ERN and perturbation-evoked cortical responses is impacted by PD. I predicted that ERN amplitudes and perturbation-evoked cortical response amplitudes would be positively correlated in people with PD. Specifically, I predicted that individuals with smaller ERN amplitudes would likewise have smaller perturbation-evoked cortical responses, due to a shared underlying mechanism that is impacted by PD. Subjects described in the preceding chapters additionally performed a computer-based task to elicit the ERN in the same recording session that their perturbation-evoked cortical responses were quantified. Here I report preliminary results comparing ERN amplitudes to perturbation-evoked cortical response amplitudes in healthy young adults, and older adults with and without PD. In contrast to the hypothesized positive association between the ERN and perturbation-evoked cortical

responses, we observed a negative association between the two responses in PD. Specifically, individuals with PD who had smaller ERNs had larger perturbation-evoked cortical responses, indicating that PD does not impact the ERN and perturbation-evoked cortical responses in the same way.

7.3 Methods

7.3.1 Participants

Healthy young adults (HYA). 18 of the HYA described in Chapters 3 and 4 additionally performed an arrow flanker task (described below) after the perturbation series.

Older adults without PD (noPD). All 10 participants in the noPD group whose perturbation-evoked cortical responses were described in the previous chapter additionally performed an arrow flanker task after the perturbation series. As described below, one of these participants was excluded from analysis due to an extremely large ERN amplitude that resulted in a significant deviation of the sample from a normal distribution.

Older adults with PD. 10 of the 13 participants with PD described in the preceding chapter are considered in the present chapter. One subject was excluded due to failure of the triggering system necessary to time-lock EEG activity to events in the flanker task. Two subjects were excluded due to inability to perform the flanker task because they were unable to detect the visual stimuli (due to short, 200 ms duration). PD participants performed all tasks in the OFF-medication state as described in the preceding chapter.

7.3.2 Experimental Tasks

Flankers tasks. Participants performed two versions of an arrowhead flanker task in counterbalanced order in Presentation software (Eriksen and Eriksen 1974). In a widely used hand version of the task, responses were entered by clicking the left or right mouse buttons using the pointer and middle fingers of the hand of their choice. In a novel foot version of the task, which was designed to facilitate transition to future studies comparing muscle activity between balance and cognitive tasks, responses were entered by briefly lifting the ball of the left or right foot off of foot pedals that otherwise remain pressed throughout the task. Only data from the previously validated hand version of the flanker task will be considered in this chapter.

ERNs elicited during a flanker task have better psychometric properties and test-retest reliability than alternative tasks (Meyer et al. 2014; Meyer et al. 2013; Riesel et al. 2013). During each trial, participants were shown five arrowheads, and instructed to responds as quickly and accurately as possible using the left or right mouse button depending on the direction of the central arrowhead. There were two "compatible" conditions ("<<<<<" and ">>>>>") and two "incompatible" conditions ("<<><<" and ">><>>"). The stimuli were presented randomly such that 50% were incompatible. Each stimulus was presented for 200 ms, and the interval between the offset of one stimulus and the onset of the subsequent stimulus varied randomly between 2300 to 2800 ms. Participants first completed a supervised practice block containing 11 trials during which they were instructed to be both accurate and as fast as possible. The practice block was repeated if subjects still did not understand the task by the end of the practice block. After the practice block, the task consisted of up to 11 blocks of 30 trials (up to 330 trials total) with each block initiated by the participant. The tasks were automatically terminated early

once enough errors had been entered to quantify the ERN (20 or 21 errors) (Meyer et al. 2013). To encourage both fast and accurate responding, participants received feedback based on their performance at the end of each block. If performance was below 75% correct, the message "Please try to be more accurate" was be displayed; performance above 90% correct was be followed by "Please try to respond faster"; otherwise the message "You're doing a great job" was displayed.

7.3.3 Data collection

Electroencephalography (EEG) collection. EEG collection is as described in the preceding chapter.

EEG pre-processing. Raw EEG data from the flanker task were high-pass filtered offline at 1 Hz with a third-order zero-lag Butterworth filter, mean-subtracted within each channel, and then low-pass filtered at 15 Hz. EEG data at the Fz electrode were then re-referenced to the mastoids and epoched into 1.5 s segments beginning 500 ms before response entry. Vertical electrooculography (EOG) data were filtered and segmented following the same steps without re-referencing. Blinks and vertical eye movement artifacts were subtracted from the epoched EEG data at using the algorithm developed by Gratton and Coles (Gratton et al. 1983), as described in Payne et al. (Payne et al. 2018). Single-trial epochs were then baseline-corrected by subtracting the mean voltage between 200-500 ms prior to response entry.

Quantification of ERNs. Cortical event-related potentials (ERPs) were created by averaging EEG data across all correct trials and averaging EEG data across all incorrect trials at Fz for each participant in each task. The ERN was generated by subtracting the

ERP in correct trials from the ERP in incorrect trials within each subject. The amplitude of the ERN was then quantified as the minimum amplitude between 0-100 ms after response entry, multiplied by negative 1. Multiplying by negative 1 means that higher numbers correspond to larger (more negative) ERNs and was performed instead of taking the absolute value because in some cases the minimum amplitude in this window was above zero. Such ERNs are reported as negative amplitudes.

7.3.4 Statistical Analyses

Testing for normality and exclusion of one noPD subject. The Shapiro-Wilk test was used to identify significant deviations of sample variables from normality (at α=0.05). A significant deviation from normality (p=0.047) in the ERN amplitudes of the noPD group was driven by a single extreme value (ERN amplitude of 19.4 μV in one individual, compared to 2.4±3.5 μV for the rest of the noPD group). This deviation from normality was addressed by removing this subject from further consideration (Shapiro-Wilk: p=0.46 after exclusion).

Comparisons across groups. ERN amplitudes were compared between populations with a general linearized model (ANOVA), with Tukey tests for post-hoc comparisons at α=0.05. All statistics were performed in SAS.

Correlations between ERN amplitude and amplitude of perturbation-evoked cortical responses. Within each group, univariate linear regressions were used to compare ERN amplitudes in the flanker task at Fz with perturbation-evoked cortical responses at Cz (the cortical N1 for all three populations and the later negativity in PD and noPD groups).

For experimental methods on the perturbation series or the collection and quantification of perturbation-evoked cortical responses, see the preceding chapters.

7.4 Results

7.4.1 ERN amplitudes were largest in HYA, but did not differ between PD and noPD groups

ERN amplitudes were largest in the HYA group (Figure 7-1A; 13.30 ± 7.6 μV, ANOVA: $p=0.0005$; Tukey: $p<0.05$), but ERN amplitudes were not significantly different between PD (Figure 7-1C; 6.0 ± 6.5 μV) and noPD (Figure 7-1B; 2.4 ± 3.5 μV) groups (Figure 7-1E; Tukey: $p<0.05$).

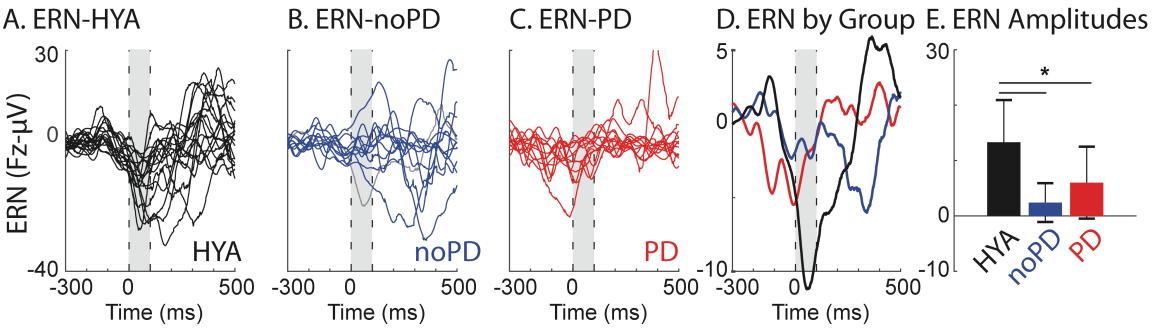


Figure 7-1. Error-related negativity (ERN) by subject and group. Subject ERNs are shown at Fz for the arrow flanker task for (A) HYA, (B) noPD, and (C) PD subjects. ERN from the excluded individual in the noPD group is shown with a gray line in panel (B). Group-averaged ERNs are shown in (D). The shaded gray area indicates the time window of quantification of the ERN (0-100ms after response entry). Bar plots show the mean and standard deviation of ERN amplitudes by group with the HYA group in black, the noPD group in blue, and the PD group in red. The asterisk indicates significant post-hoc comparisons (Tukey, α=0.05). ERN: Error-Related Negativity. HYA: Healthy Young Adults. noPD: Control Subjects. PD: Parkinson's Disease.

7.4.2 ERN amplitudes and perturbation-evoked cortical responses

ERN amplitudes were inversely correlated with perturbation-evoked cortical response amplitudes only in the PD group. The PD group showed inverse correlations between ERN amplitudes and cortical N1 response amplitudes (Figure 7-2; PD: R^2=0.40, p=0.030) and between ERN amplitudes and amplitudes of the later perturbation-evoked negativity (Figure 7-2; PD: R^2=0.41, p=0.030). ERN amplitudes in the noPD group were not correlated with cortical N1 response amplitudes (Figure 7-2; noPD: p=0.094) or amplitudes of the later perturbation-evoked negativity (Figure 7-2; noPD: p=0.52). Likewise, ERN amplitudes in the HYA group were not correlated with cortical N1 response amplitudes (Figure 7-2; HYA: p=0.87).

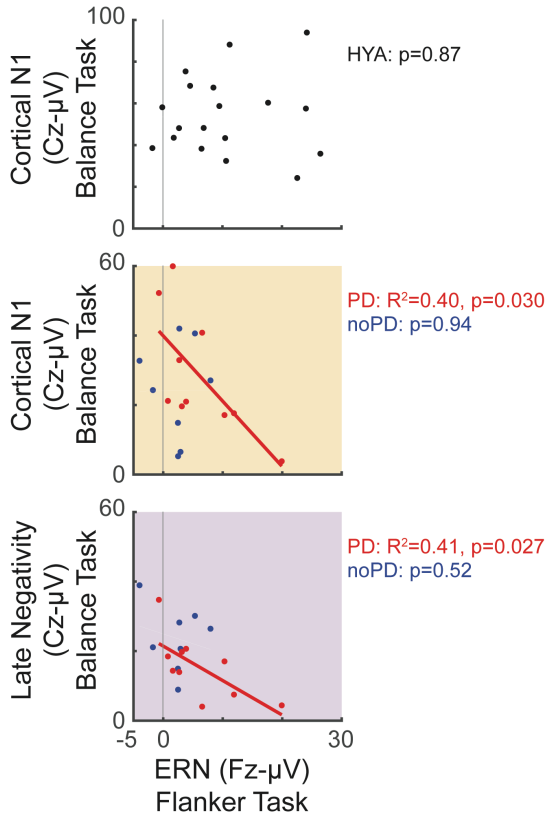


Figure 7-2. ERN amplitudes were inversely correlated with perturbation-evoked cortical responses in the PD group. Vertical axes plot cortical N1 response amplitudes for HYA in the top row, cortical N1 response amplitudes for PD and noPD groups in the middle row, and amplitudes of the later perturbation-evoked negativity in the PD

and noPD groups in the bottom row against ERN amplitudes on the horizontal axis. Data from the HYA group is in black, data from the PD group is in red, and data from the noPD group is in blue. Lines are drawn for correlations that are significant at α=0.05. ERN: Error-Related Negativity. HYA: Healthy Young Adults. noPD: Control Subjects. PD: Parkinson's Disease.

7.5 Discussion

Inverse correlations between ERN amplitudes and perturbation-evoked cortical response amplitudes in the PD group do not support the hypothesis that the ERN and perturbation-evoked cortical responses are similarly impacted by PD. Despite the many similarities between these ERPs described in Chapter 2, the inverse relationship between their amplitudes in the PD group suggests that these responses are not impacted by PD in the same way, and thus their underlying mechanisms must differ. These results are consistent with the difference in localization between the two ERPs, with the ERN localized to the anterior cingulate cortex and the cortical N1 response localized more posteriorly in the supplementary motor area (Marlin et al. 2014). The larger ERN amplitudes in the healthy young adult (HYA) group compared to both of the older adult groups is consistent with other reports of the effect of aging on ERN amplitudes (Beste et al. 2009). While the lack of a difference in ERN amplitudes between groups with and without PD is inconsistent with prior studies (Beste et al. 2009; Falkenstein et al. 2000; Ito and Kitagawa 2006; Rustamov et al. 2014; Seer et al. 2016; Stemmer et al. 2007; Willemssen et al. 2009; Willemssen et al. 2008), it is likely due to our smaller preliminary sample size (Holroyd et al. 2002a; Verleger et al. 2013), which will be doubled with the completion of this study. Overall, this study complements the large literature of similarities between the ERN and perturbation-evoked cortical responses as the second study to directly compare these ERPs and show a way in which they differ.

The ERN and perturbation-evoked cortical responses to not appear to be impacted by PD in the same way. Despite the similarities between the ERN and the cortical N1 response described in Chapter 2, the negative association between these evoked responses in the PD group does not support the hypothesis that ERNs and perturbation-evoked cortical responses are similarly impacted by PD. The different vulnerabilities of these responses to PD provides evidence of a difference in underlying mechanisms between these evoked responses and is consistent with the difference in their localization (Marlin et al. 2014). While it is possible that these responses could be similarly impacted by PD, but that one of the responses is more readily compensated for, such a difference in the ability to compensate for the effect of PD on these responses would still support a difference in the mechanisms underlying the ERN and perturbation-evoked cortical responses. For example, it is possible that performance monitoring, reflected by the ERN, could be increased as an attempt to compensate for degradation of bottom-up sensory processing and/or top-town behavioral control. It is also possible that the apparent difference between the two responses could be caused by the subtraction of stimulus- and response-associated components from the ERN. While it is not possible to subtract stimulus- and response-associated components from the perturbation-evoked cortical responses, it would be possible to compare the perturbation-evoked cortical responses to ERPs from error trials in the flanker task without subtracting the ERPs from correct trials. This and other alternative methods of analysis will be applied as we approach our intended sample size of 20 people per group.

The lack of differences in ERN amplitudes between older adults with and without PD is likely due to our small preliminary sample. Smaller ERN amplitudes in people with

PD is a widely replicated result (Beste et al. 2009; Falkenstein et al. 2000; Ito and Kitagawa 2006; Rustamov et al. 2014; Seer et al. 2016; Stemmer et al. 2007; Willemssen et al. 2009; Willemssen et al. 2008). Two other studies failing to observe smaller ERNs in PD (Holroyd et al. 2002a; Verleger et al. 2013) have in common with the present study a sample size smaller than 14 per group, whereas most studies reporting differences have at least 14 subjects per group. As we approach our expected sample of 20 people per group, it is very likely that differences will emerge. However, the larger ERN amplitudes in the HYA group compared to both older adult groups is consistent with a previously reported effect of aging on the ERN amplitude (Beste et al. 2009). Because much larger perturbations were used to evoke the cortical N1 response in HYA, cortical N1 response amplitudes could not be similarly compared between the HYA and other groups.

CHAPTER 8. DISCUSSION

I hope that the basic science work presented in this thesis will facilitate the development of better rehabilitation strategies for balance impairments in old age and in Parkinson's disease (PD). Balance and cognitive problems are associated through unknown mechanisms (Alves et al. 2006; Herman et al. 2010; Mak et al. 2014), and synergistic benefits of combined balance and cognitive rehabilitation interventions (Kraft 2012; Wu et al. 2016) suggest that a therapeutic target may exist at the intersection of balance and cognition. The brain processes underlying the cortical N1 response evoked by balance perturbations seems like a possible candidate for such a target due to its consistent activation during reactive balance recovery, and due to its influence by cognitive processes (Adkin et al. 2008; Adkin et al. 2006; Little and Woollacott 2015; Mochizuki et al. 2010; Mochizuki et al. 2008; Quant et al. 2004a). The cortical N1 response has been localized to the supplementary motor area (Marlin et al. 2014; Mierau et al. 2015), which is just anterior to the motor cortex, and posterior to the frontal lobe where executive functions are typically attributed (Alvarez and Emory 2006). The supplementary motor area is thought to be involved in the translation of intention into action by mediating interactions between motor cortex and areas in the frontal cortex (Goldberg 1985) and may therefore mediate interactions between cognitive and motor processes. Further, the supplementary motor area is the cortical focus of basal ganglia-thalamocortical motor circuits, which are impacted by Parkinson's disease (Alexander et al. 1986). By virtue of its cortical location, the supplementary motor area is accessible to noninvasive brain stimulation (Jacobs et al. 2009), which is used in motor rehabilitation in other contexts (Webster et al. 2006).

However, before we can design such rehabilitation strategies, we first need to better understand the role of the brain activity underlying the cortical N1 response in unimpaired balance control, and how it changes with balance impairment.

In Chapter 2 we motivated our interest in the cortical N1 response as it relates to the error-related negativity, which is thought to play a role in the correction of behavior following errors. Given many similarities between these evoked responses, we posed the question of whether the relationship between the perturbation-evoked cortical N1 response and the error-related negativity (ERN) could provide insight into the relationship between balance and cognitive impairments in old age and in PD. Before investigating these responses in PD, we investigated a few properties of the cortical N1 response in relation to unimpaired balance control in healthy young adults (HYA).

In Chapter 3 we became interested in the large differences in cortical N1 response amplitudes between individuals after finding that the effect of sensory input was very limited. Specifically, the perturbation-evoked cortical N1 response increased in amplitude with perturbation acceleration quite weakly in only a subset of the HYA group assessed, and the presence or absence of such amplitude scaling of the cortical N1 response was unrelated to the presence or absence of such amplitude scaling of the simultaneous balance-correcting motor response. This result was interpreted to mean that the majority of the cortical N1 response amplitude depends on something other than the magnitude of the perturbation stimulus. Additionally, we found that reductions in the cortical N1 response amplitude across trials was associated with a reduction in startle reflexes, suggesting that the cortical N1 response may be more related to cognitive or emotional evaluation of the perturbation stimulus. An unexpected finding of this study was that cortical N1 response

amplitudes varied to a much larger extent between individuals, and that the differences between individuals were associated with subject height. Specifically, shorter subjects had larger amplitude cortical N1 responses, and additionally had greater difficulty resisting compensatory steps to recover balance. Given multiple associations, it was unclear whether the larger cortical responses in these individuals were due to the fact that perturbations were proportionally larger for their body size, thus generating greater sensory activation and being relatively more difficult, or if the larger cortical responses were somehow related to the act of stepping, or the fact that such steps represented an error from the explicitly stated goal of recovering balance without taking a step. Chapters 3 and 4 set out to clarify these differences between subjects.

In Chapter 4 we found that HYA with worse balance exhibited larger cortical responses, possibly reflecting increased reliance on cortical control of balance. In this study, we eliminated the effect of subject height on cortical N1 responses by adjusting magnitudes of larger perturbations according to subject height and showed that remaining variation in cortical N1 response amplitudes between healthy young adults was related to balance ability. Specifically, individuals with larger perturbation-evoked cortical response amplitudes performed worse on a difficult beam-walking task that has been previously validated as a sensitive measure of balance ability in HYA (Sawers and Ting 2015). Further, by using an identical and trivially-easy smaller perturbation across subjects, we showed that height may matter less when a perturbation is not challenging, suggesting that the effect of height in the previous study may have been related to the greater difficulty that shorter subjects had maintaining balance in larger perturbations that were not adjusted according to their height. While it is unclear why cortical N1 responses are larger when

people have a harder time recovering balance, it is possible that the larger cortical N1 responses reflect greater cortical contributions to balance recovery to compensate for limitations of the involuntary balance-correcting motor response. However, it is also possible that greater cortical N1 responses might reflect greater perceived threat (Adkin et al. 2008; Adkin et al. 2006) related to lower balance ability. We also cannot rule out the possibility that the increased cortical activation interferes with automatic balance control.

In Chapter 5, larger cortical N1 response amplitudes with the execution of compensatory steps provided support for the suggestion that cortical N1 responses may be related to compensatory balance control. We compared cortical N1 response amplitudes between planned stepping reactions and nonstepping reactions to test the relationship between the cortical N1 response and the execution of compensatory steps. Additionally, we compared cortical N1 response amplitudes between planned and unplanned stepping reactions to test the relationship between the cortical N1 response and the failure of an explicitly stated goal of recovering balance without stepping. By comparison with the ERN, we hypothesized that a larger cortical N1 response would be associated with unplanned stepping reactions, which represent an error from the explicitly stated goal of recovering balance without stepping. In contrast to this hypothesis, the cortical N1 response amplitude was larger with the execution of stepping reactions, regardless of whether these stepping reactions were previously planned. These results suggest that the cortical N1 response may be involved in the execution of compensatory steps for balance recovery, which is one example of a longer latency compensatory behavior that occurs after the automatic balance-correcting motor response when the automatic response is insufficient for balance recovery.

In Chapter 6 I found that perturbation-evoked cortical responses were associated with balance impairment in PD, but that this relationship differed from that observed in healthy young adults. I set out to characterize the cortical N1 response in older adults with and without PD, and to assess whether this response was associated with balance or cognitive problems. Unexpectedly, I found that perturbation-evoked cortical responses in older adults with and without PD contained two distinct peaks, with a later negativity occurring in the 100 ms following the cortical N1 response. While the cortical N1 response did not differ between groups or relate to balance or cognitive abilities, the later negativity was smaller in people with PD, and smaller amplitudes of the later negativity were associated with balance impairment in PD. These preliminary results suggest that perturbation-evoked cortical responses may be related to balance impairment in PD and warrant further study.

In Chapter 7 I demonstrated that perturbation-evoked cortical responses are not impacted by PD in the same way as the ERN, suggesting a difference in the mechanisms underlying these event-related brain potentials (ERPs). Based on the similarities between the ERN and perturbation-evoked cortical responses described in Chapter 2, I hypothesized that these two ERPs would be similarly impacted by PD. However, a negative association between ERN amplitudes and perturbation-evoked cortical response amplitudes in PD was in conflict with this hypothesis, suggesting that their underlying mechanisms differ. This preliminary study complements the large literature of similarities between the ERN and perturbation-evoked cortical responses as the second study to directly compare these ERPs within subjects and show a way in which they differ.

From the insights gained through the work presented in this thesis, I present the novel hypothesis that perturbation-evoked cortical responses reflect the allocation of cortical resources, such as attention, to direct cortically-mediated balance control to compensate for the limitations of automatic balance corrections when needed. This work yields insight into a possible relationship between perturbation-evoked cortical responses and balance function and raises several new questions. Do larger cortical N1 responses in HYA reflect an attempt to compensate for limitations of automatic balance control mechanisms, or are these responses instead interfering with automatic balance control? Does the cortical N1 response in HYA simultaneously contain both of the component peaks observed in older adults, or is the later component peak unique to older adults? Why is the cortical N1 response associated with worse balance in HYA when the later component peak is associated with better balance in PD?

Although this work suggests perturbation-evoked cortical responses contain a biomarker for balance function, much more work is needed before we can translate these findings to better interventions for impaired balance. Could this biomarker be used to sort people into appropriate rehabilitation interventions that suit their specific needs and abilities? Are perturbation-evoked cortical responses impacted by rehabilitation interventions? Could the cortical areas underlying these two component peaks serve as potential therapeutic targets for noninvasive cortical stimulation to enhance rehabilitation for balance impairments? What is the brain area underlying the second component peak of the perturbation-evoked cortical response? If it arises from a different brain area that the first component peak, could the interaction between these two brain areas explain the relationship between balance and cognitive impairments in old age and in PD?

While this work presented in this thesis provides novel insight into a possible relationship between perturbation-evoked cortical activity and balance ability, there are many limitations to the experimental studies. Although the observed relationships between perturbation-evoked cortical responses and balance ability have been used to suggest the recruitment of cortical processes to compensate for balance impairments, causal manipulations in larger sample populations would be more convincing. The larger cortical responses in HYA could instead be interfering with balance recovery. Would simultaneous dual-task performance, which reduces the amplitude of the cortical N1 response in HYA (Little and Woollacott 2015; Quant et al. 2004b) make them more likely to fall by disrupting their compensatory control strategy? Or would dual-task performance make them less likely to fall by removing pathological performance monitoring, forcing them to rely on the faster automatic control mechanisms? Dual-task performance is known to disrupt compensatory control in balance-impaired older adults (Rankin et al. 2000; Shumway-Cook et al. 1997), but would dual-task performance affect both peaks of the perturbation-evoked cortical response in the same way? Further, would noninvasive electrical stimulation such as transcranial magnetic stimulation or transcranial direct current stimulation cause a transient or lasting effect on perturbation-evoked cortical responses? Would such a change impact balance recovery, or balance recovery interventions? Such intervention studies would be necessary to gain a more causal understanding of any potential relationship between perturbation-evoked cortical responses and reactive balance recovery.

In addition to causal study designs, there are more sophisticated analyses that could be applied to the data presented in this thesis. For example, a wavelet decomposition

(McKay et al. 2013) or independent components analysis (Delorme and Makeig 2004) may be better able to identify and separate the component peaks, rather than relying on peak amplitudes in pre-defined time-bins. Further, spectral analyses (Grosse et al. 2002) and cortico-muscular coherence analyses (Witham et al. 2011) may have greater power to detect relationships between cortical activity and muscle activity to demonstrate if and how perturbation-evoked cortical activity may influence muscle activity for balance recovery.

CHAPTER 9. REFERENCES

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