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Neural Preparation For Step Initiation In Unpredictable Conditions With Age And Parkinson's Disease

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NEURAL PREPARATION FOR STEP INITIATION IN UNPREDICTABLE CONDITIONS WITH AGE AND PARKINSON'S DISEASE

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ABSTRACT

Mobility is essential for the independent lifestyle. However, as the US population ages, challenges to mobility start to arise, among them just the aging itself which leads to decreased postural stability, falls and the second most common neurodegenerative disease, that is Parkinson's disease (PD). We decided to investigate step initiation as it is crucial to mobility: walking is not possible without the first step.

Step initiation is impaired in PD. However, the impact of PD on the neural mechanisms of step initiation when some of the step parameters are unpredictable remains unexplored. Cortical preparation for step initiation can be assessed by beta event-related desynchronization (ERD) derived from electroencephalography (EEG) recordings. We hypothesized that subjects with PD would exhibit less cortical modulation between conditions of forward step initiation with and without prior knowledge of limb choice. Further, we hypothesized that decreased cortical modulation in PD would associate with a higher impairment of motor performance. Results identified that the group with PD exhibited decreased beta ERD amplitudes that were similar regardless of condition, whereas control subjects modulated beta ERD amplitudes between conditions, particularly in early stages of pre-movement processing in areas overlying sensory cortex. Subjects with PD presented with delayed and reduced postural preparation with increased step target error across both conditions and exhibited a greater incidence of multiple anticipatory postural adjustments (APAs) in the predictable relative to the unpredictable condition. Delayed postural preparation significantly correlated with lower amplitudes of beta ERD. We concluded that diminished early pre-movement processing over sensory cortex was concomitant with poor pre-selection of the stepping limb in predictable conditions and that a generally diminished amplitude of cortical pre-movement processing relates to delayed step initiation in people with PD.

Furthermore, impaired mobility accompanies healthy aging, but there is a need for deeper understanding of how aging changes central control of motor behavior. Using previous study's method, we compared cortical preparation for step initiation using beta ERD in young and older healthy subjects performing forward steps with and without prior knowledge of limb choice. Our results show that older subjects exhibited increased beta ERD amplitudes before the step regardless of whether they were informed of limb choice or not. Moreover, older subjects exhibited early increases in beta ERD in the "sensory" cluster of electrodes, but only when full limb-choice information was available. Behaviorally, the older subjects also exhibited shortened and increased anticipatory postural adjustments which led to earlier step initiation and similar swing-foot velocities but was also accompanied by greater target step placement errors and decreased postural stability. For the older group, condition-related increases in beta ERD amplitudes and stability correlated with condition-related prolongation of APA durations. We conclude that older subjects exhibited a spectrum across two strategies: (1) a "fast" strategy associated with decreased neural preparation that trades shortened step preparation and higher swing-foot velocity for target step errors and lowered postural stability; and (2) an "accurate" strategy associated with greater neural preparation, longer step-preparation time, and higher stability during step execution.

In conclusion, this thesis provides more support for beta ERD as a useful tool for studying cortical preparation non-invasively. We have also established the importance of the signals recorded by "sensory" clusters: in subjects with PD the absence of beta ERD similar to the control group was associated with impaired motor behavior even when conditions were predictable. Similarly, a part of the older group seemed to pre-potentiate its cortex lying beneath the cluster of "sensory" electrodes which was associated with more safe and accurate steps. Further investigations should focus on the importance of sensorimotor integration and its' changes due to PD or healthy aging and beta ERD may be an excellent tool for this task.

CITATIONS

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CHAPTER 1: COMPREHENSIVE LITERATURE REVIEW

1.1. Epidemiology of Aging and Parkinson's Disease

The population of the most developed countries is in the process of becoming older due to several factors. First, the marriage of contemporary science and medicine had a significantly prolonged life expectancy in the past century but also opened a Pandora's box of impairments that come with age. The number of people aged 65 years and older grew from 3 million in 1900 to 46 million in 2014 ("Federal Interagency Forum on Aging-Related Statistics: Older Americans 2016: Key Indicators of Well-Being. https://www.karger.com/Article/PDF/109998. (accessed June 24, 2018).", 2016). An even more drastic change was observed for the population aged 85 years: there were just over 100,000 of them in 1900 and now their population is 6 million in 2014. This is a great achievement but with a caveat: life expectancy and quality of life do not always go hand in hand. Even discarding neurodegenerative diseases for a moment now, healthy aging itself is associated with significant differences taking place in the central motor system. For example, aging is associated with an increased incidence of falls and fall-related mortality (Alamgir, Muazzam, & Nasrullah, 2012). Transitions between motor states (e.g., step initiation) increase the risk of falling due to the complex coordination required of the central motor and musculoskeletal systems (Topper, Maki, & Holliday, 1993), which often degrade with age (Polcyn, Lipsitz, Kerrigan, & Collins, 1998). To prevent falls in older adults, a deeper understanding of age-related changes in the neural

control of transition movements is necessary. To date, most of the studies on the effects of age on mobility and postural stability involve self-initiated movements (Azizah Mbourou, Lajoie, & Teasdale, 2002; Couillandre, Brenière, & Maton, 2000; Maki, 1997) or simple-reaction-time tasks (Brunt, Santos, Kim, Light, & Levy, 2005; Halliday, Winter, Frank, Patla, & Prince, 1998; Hass, Waddell, Wolf, Juncos, & Gregor, 2008; Henriksson & Hirschfeld, 2005; Rogers, Johnson, Martinez, Mille, & Hedman, 2003; Varghese, Merino, Beyer, & McIlroy, 2016). Studying deficits that healthy aging bring is crucial to improving mobility and quality of life of the older population. Even more, the everyday environment necessitates rapid and dynamic adaptation of movement parameters, a process that may rely on appropriate cortical modulation of the central motor system, more research must focus on determining the changes in cortical preparation and step initiation of older adults when movement parameters were unpredictable.

Unfortunately, aging also opens avenues for neurodegenerative diseases with Alzheimer's and Parkinson's disease (PD) being the most common (De Lau & Breteler, 2006). PD is associated with numerous motor impairments, among them hypometria (lower movement amplitude), bradykinesia (slowness of movements), tremors, rigidity, altered postural alignment, postural instability, freezing of gait, as well as autonomic and cognitive dysfunctions (Jankovic, 2008). The disease onset may be as early as 40 years old with the incidence growing with age and peaking in the 70-79 age group. Initially close between males and females (3.26 for females and 3.57 for males per 100,000 person-years in 40-49 years old group), incidence grows faster in males than in females for reasons yet to be discovered (103.48 for females and 258.47 for males per 100,000

person-years at age 80+) (Hirsch, van Wegen, Newman, & Heyn, 2018). Approximately, there are between 630,000 to 1,000,000 people with PD in the United States as of 2013 and these numbers are projected to roughly double by 2040 (Kowal, Dall, Chakrabarti, Storm, & Jain, 2013). The economic burden of PD through direct and indirect costs was estimated to be $ 15.5 billion per year (Kowal, et al., 2013). PD is a progressive, irreversible disease attributed to a number of cellular changes among which the most notable is the death of dopaminergic neurons in the basal ganglia (BG) of the brain and the following deficiency of dopamine in the BG. However, the disease is also associated with other changes in cellular mechanisms: a) an accumulation of α-synuclein protein, also known as Lewy bodies, b) mitochondrial malfunction, c) oxidative stress, d) calcium homeostasis, e) axonal transport and f) neuroinflammation (Poewe, et al., 2017). Although there has been significant progress in the understanding of cellular and molecular changes accompanying it, it is still unclear what causes PD. Its progression is assessed clinically using Hoen and Yahr's scale (along with others, e.g. MDS-UPDRS scale (Goetz, et al., 2008)) that assigns scores from one to four with four associated with the most severe manifestation of PD, including but not limited to: lack of movement and bed-ridden condition that requires significant care (Hoehn & Yahr, 1998). Together, healthy aging and PD represent a decrease in quality of life, limited mobility, as well as a significant economic burden for society.

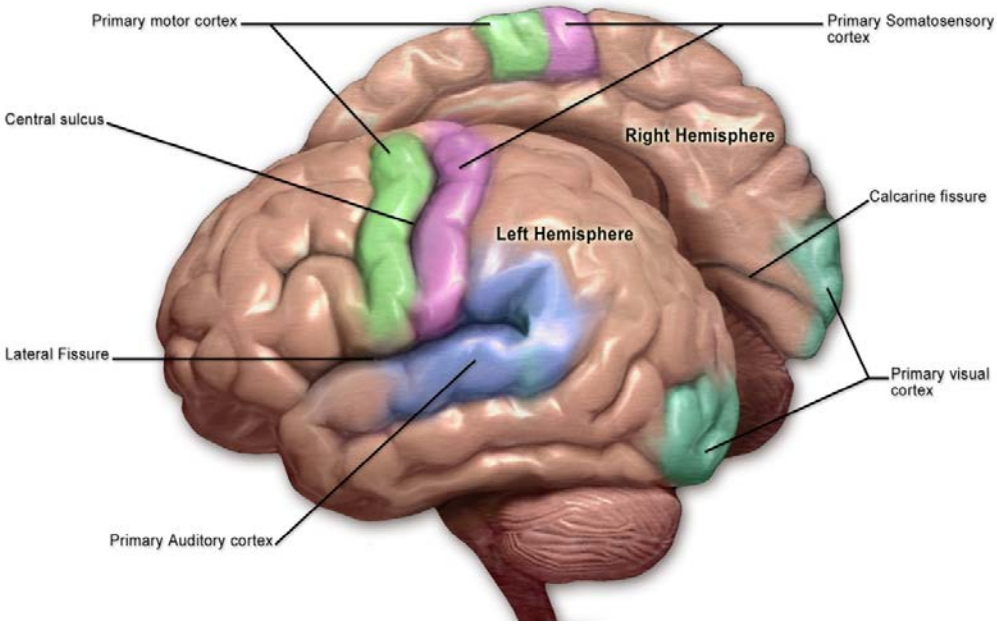

Figure 1. Primary Motor and Somatosensory Cortices. Source: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. (https://commons.wikimedia.org/wiki/File:Blausen_0103_Brain_Sensory&Motor.png), „Blausen 0103 Brain Sensory&Motor“, https://creativecommons.org/licenses/by/3.0/legalcode

Given these facts, it is important to understand the workings of the human central motor system using data from populations with impairments, as comparisons between healthy young and older and/or affected by a disease often give insights into how neural systems work. This knowledge can then be translated into clinical applications that will alleviate the suffering and increase the quality of life of a large portion of humanity.

1.2 The Anatomy of the Human Motor System

1.2.1. Primary Motor Cortex

It has been long thought that the primary motor cortex (M1) lies within the precentral gyrus of the human brain (shown in green in Figure 1). Similar to other regions of CNS, M1 adheres to the somatotopic organization (Figure 2) with lateral efferents projecting to the brainstem and spinal cord regions that operate facial, neck,

and upper limb musculature. Conversely, neurons closer to the vertex and on the midline, next to interhemispheric fissure supply information to lower trunk and limbs as well as genitalia. To aid in understanding the principle of somatotopy, body parts controlled by the respective regions of M1 are overlayed by a drawing, a so-called "homunculus" (a little man in Latin). Of note, because studies presented in this thesis focused on neural preparation for movement of lower limbs and thus topologically excluded lateral M1 as a region of interest. As for afferent connections to M1, recent tracing studies have shown that M1 receives very dense input from several premotor areas, as well as the basal ganglia, and cerebellum via the thalamus (Dum & Strick, 2002). It also must be noted that the motor function depends on the trinity of vision, proprioception and vestibular information (or, more precisely, on congruency between sensory modalities).

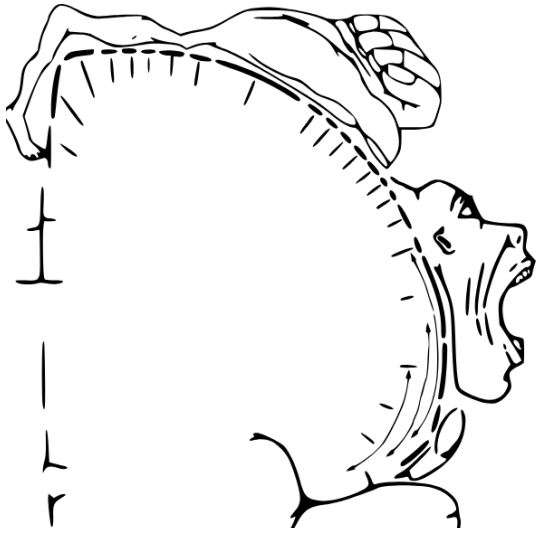

Figure 2. Motor Homunculus. Source: mailto:ralf@ark.in-berlin.de (https://commons.wikimedia.org/wiki/File:Motor_homunculus.svg), https://creativecommons.org/licenses/by-sa/4.0/legalcode

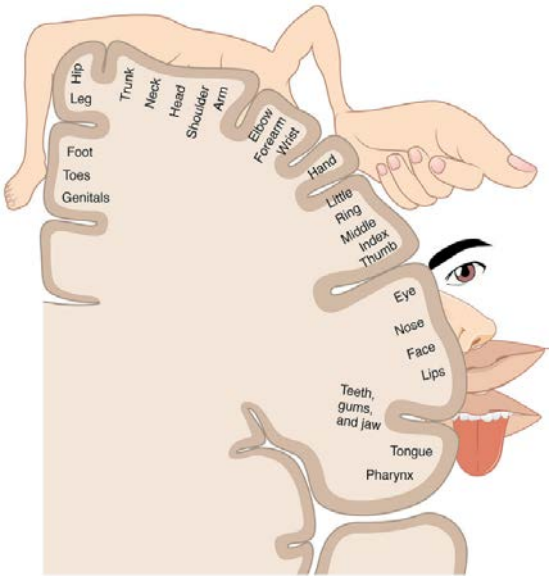

Figure 3. Somatosensory homunculus. (https://commons.wikimedia.org/wiki/File:1421_Sensory_Homunculus.jpg), „1421 Sensory Homunculus ", https://creativecommons.org/licenses/by/3.0/legalcode)

Anatomically, visual, vestibular, and somatosensory information is integrated into the cortical region called multimodal association area which is located primarily within the inferior parietal lobule. In healthy subjects, postural sway was induced in an eyes-closed condition and was retained for a short while even after they open their eyes (Peterka & Loughlin, 2004). In PD, it's been shown that subjects with PD have a deficit in the reorganization of sensory modalities after their vision had been blocked for several seconds (Brown et al., 2006). In healthy aging, sensorimotor integration also becomes impaired: older subjects had longer reaction times after a movable platform moved than the control subjects. Moreover, when the older group was presented with conflicting sensory inputs, half of the group lost balance (Woollacott, Shumway-Cook, & Nashner, 1986). Therefore, all three sensory modalities are important for error detection and adaptation of movements (with vision seeming to be the most important of three) and the dependence on congruent multisensory input increases with age and PD.

Functionally, it has been long thought that M1 was the lowest in the hierarchy of the central motor system and had a major function of activating musculature associated with a specific M1 region through projections to respective spinal cord targets. However, there is mounting evidence that M1 neurons accomplished more than just activation of a muscle unit but rather are involved in the intricate processing of movement parameters such as the force, speed, and direction of movement (Moran & Schwartz, 1999a, 1999b; Sergio, Hamel-Pâquet, & Kalaska, 2005). Others reported that they detected subsets of M1 neurons that regulated muscular synergies required for a complex task, like reaching out an arm and pressing a specific button (Holdefer & Miller, 2002). Therefore, one may

contend that these new findings make previous hierarchical model outdated and update it by one where each region of the central motor system is employed in different kinds of processing of movement-related information.

1.2.2. Primary Somatosensory Cortex

Primary somatosensory cortex (S1) is located on the postcentral gyrus, posteriorly to M1 (highlighted by cyan color on Figure 1). Its homunculus differs slightly from the motor one particularly visible in the areas corresponding to lips and tongue. This slight mismatch exhibits how much of neural tissue is dedicated to the processing of the information from the corresponding regions: the larger a cortical region – the more detailed information is gleaned.

Somatosensation is a general term for a number of sensory modalities each conveying a different type of information (e.g., crude or fine touch, vibration, pressure) Of interest for studying the central motor system are the fibers Ia, Ib, and II types. Ia fibers come from muscle spindles and convey the rate of change of muscle length as well as a change in velocity of this change. Conversely, II type fibers are active when a muscle is still. Finally, Ib-type fibers are comings from Golgi tendon organs located where muscle tendons are attached to the skeletal structures and convey how much tension is created by a muscle. Sensory cells are pseudounipolar with one part of an axonal process extending towards the sensor and the other enter the spinal cord. Targets are cerebellum and a number if cerebral structures via the thalamus. Altogether these sensory modalities form a sense named proprioception which is important for monitoring the motor state that the body has a moment to moment.

1.2.3. Premotor Cortical Regions

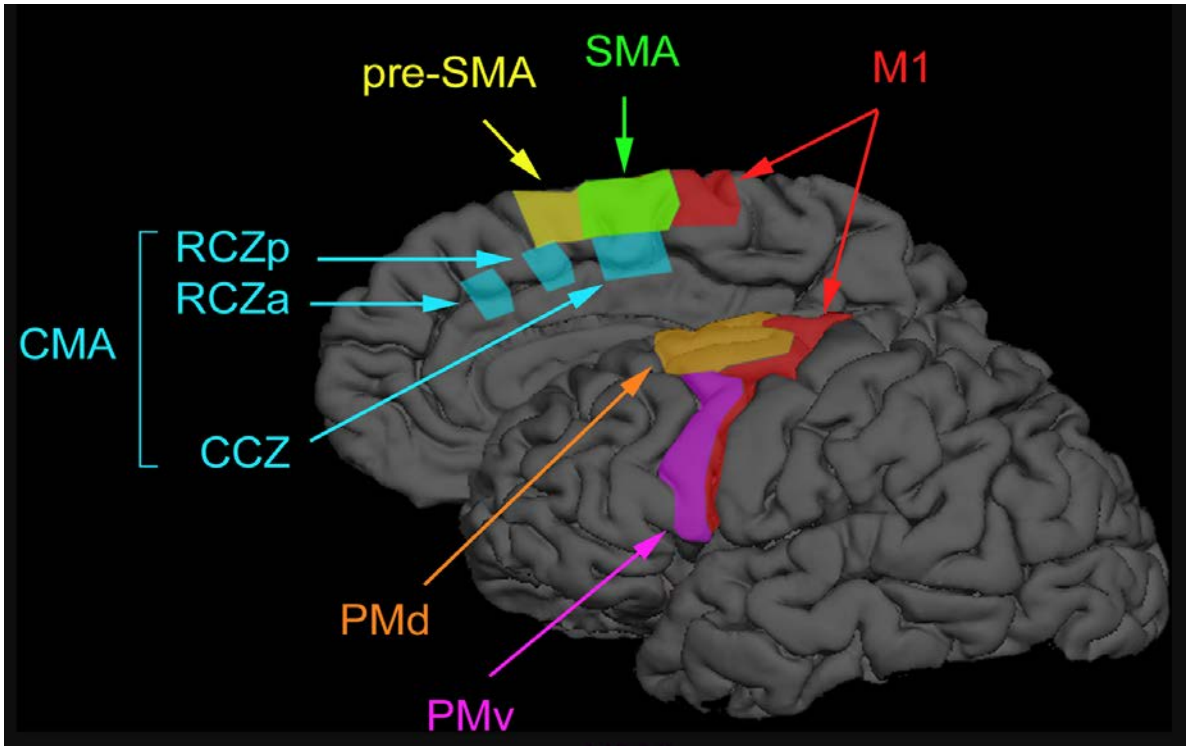

Figure 4. Premotor Regions. Source: (Chouinard & Paus, 2010). (https://commons.wikimedia.org/wiki/File:Motor_areas_in_the_frontal_lobe.jpg), „Motor areas in the frontal lobe“, ttps://creativecommons.org/licenses/by/3.0/legalcode

Most premotor regions of the cortex are located most caudally in the frontal lobes and immediately anteriorly to precentral gyrus (Figure 4). Supplementary motor area (SMA) is found on the medial surface as well as the most caudal part of the superior frontal gyrus. To greatly simplify, the function of the SMA is a generation of complex, sequential voluntary movements. For example, electric stimulation of an SMA region elicits activation of muscle groups as opposed to M1, where higher precision can be achieved (Fried, et al., 1991). The SMA has dense reciprocal connections with the M1 and contributes to corticospinal tracts (~10% of corticospinal cells originate from the SMA) with axons terminating similarly to M1 axons on lower motor neurons (Dum & Strick, 1991, 1996)

Pre-SMA is located rostrally to SMA and has less understood function. It is connected to the SMA and send dorsolateral efferents but is thought to be lacking the same input into M1 as SMA has. Some evidence suggests that pre-SMA is involved in registering remaining movements in the sequence, the number of the movement in the sequence, as well as in learning new movement sequences (Nachev, Kennard, & Husain, 2008; Nakamura, Sakai, & Hikosaka, 1999). Moreover, Pre-SMA is located closer to the frontal lobe that contains regions involved in higher cognition. Such a bridge-like position might be the reason why pre-SMA is more active during experiments where there is switching between the rules (Crone, Wendelken, Donohue, & Bunge, 2005; Nachev, et al., 2008; Rushworth, Hadland, Paus, & Sipila, 2002; Simmonds, Pekar, & Mostofsky, 2008). Finally, both pre-SMA and SMA itself send projections to the BG (caudate and putamen to be more specific).

Lateral premotor cortex (PMC, Figure 4; here it has been separated by authors into dorsal and ventral subparts that they abbreviated as PMd and PMc, respectively) is located within the caudal aspects of middle and inferior frontal gyri. Unlike SMA, it has connections with parietal association areas, prefrontal cortex, and cerebellum. If the SMA region has been associated with initiation of voluntary movements, PMC is thought to process externally-guided movements (thus the connections to the parietal, prefrontal, somatosensory regions of the brain). Some evidence suggests that the ventral PMC (PMv in Figure 4) is involved in interpreting the environmental information such as position, orientation or the shape of the external object into data understandable by the rest of the motor system, PMd specifically. The role of PMd is then to translate this information into movement instructions (Hoshi & Tanji, 2007).

Located within the interhemispheric fissure on the medial surfaces of cerebral hemispheres, there are parts of cingulate gyrus that similarly project to other motor cortical regions and are named collectively cingulate motor area (CMA, Figure 4). Although, as the figure suggests there is a number of functional subdivisions of the CMA, in essence, it is associated with emotional or attentionally important movements as well as with reward resulting from the movements (Isomura & Takada, 2004).

This overview of some important cortical regions that process planning, selection, anticipation, and execution of movements is by no means exhaustive and has the aim to provide the basic relationship of the central motor system subparts.

1.2.4. Basal Ganglia

The basal ganglia (BG) is a collection of deep brain nuclei that include the caudate, putamen, globus pallidus externum (GPe) and internum (GPi), substantia nigra pars compacta (SNc) and pars reticulata (SNr), subthalamic nucleus (STN), and in some literature nucleus accumbens (Figure 5). Collectively, caudate nucleus and putamen are called corpus striatum and at cellular level contains the same type of cells. Anatomically, the striatum is split into two seemingly separate structures by cortical axonal bundles called the internal capsule. Corpus striatum is located anterior and superior to the thalamus and partially create the walls of the anterior horn of the lateral ventricles. Tails of the caudate recede in size and curl past trigone into the inferior horn of the lateral ventricles. Like many other brain structures, corpus striatum is somatotopically arranged and is also the primary input location for cortical projections targeting the BG (Alexander

& Crutcher, 1990). However, more recently there has been discovered a pathway from cortex to the BG (STN specifically) that bypasses the corpus striatum (Nambu, Tokuno, & Takada, 2002). It was named as a “hyperdirect” pathway due to shorter signal propagation time compared to the corticostriatal route. The interplay of these pathways has been a hot topic of an ongoing debate and will be touched upon below.

Similarly to the corpus striatum being a combination of two basal ganglia, putamen and globus pallidus at times is referred to as lentiform nucleus (due to the lens-like shape in the coronal cross-section, Figure 5). Unlike corpus striatum, lentiform nucleus does not have similar cellular makeup and borrows the name solely due to anatomical appearance.

Finally, the last two nuclei that complete the BG are located ventral to the thalamus (STN, a part of diencephalon) and SNr/SNc, which are located within the ventral midbrain posterior to cerebral peduncles. The substantia nigra is composed of two parts: SNc is mainly projecting up to the striatum, supplying it with dopamine and SNr serves as the output

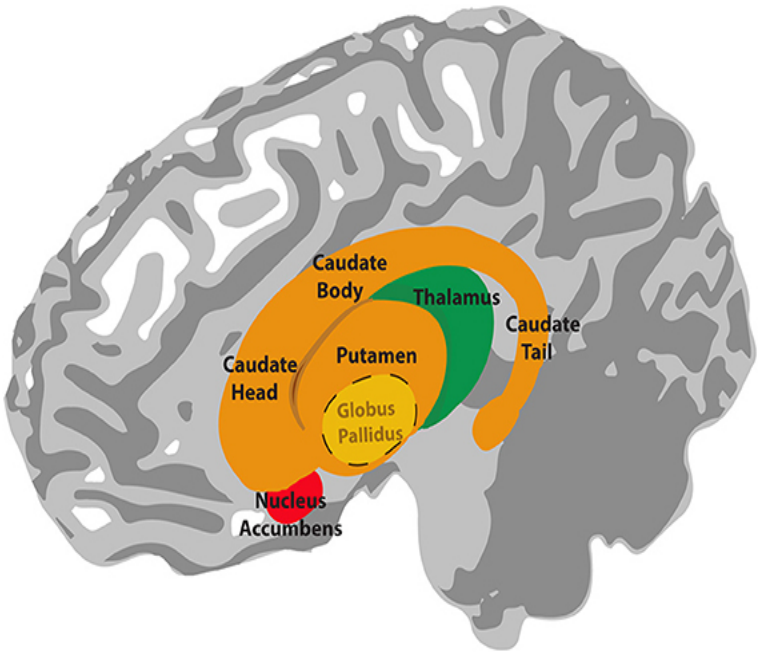

Figure 5. Anatomy of the Basal Ganglia. Lim S-J, Fiez JA and Holt LL (https://commons.wikimedia.org/wiki/File:Anatomy_of_the_basal_ganglia.jpg), „Anatomy of the basal ganglia“, https://creativecommons.org/licenses/by/3.0/legalcode

region that, along with GPi, sends inhibitory projections to the thalamus (Figure 6). Commonly, SNr/GPi is called the “output of the BG”. The structure of the BG shown in Figure 6 is omitting many connections, however, they are omitted to provide the reader at least an approximated model of the BG.

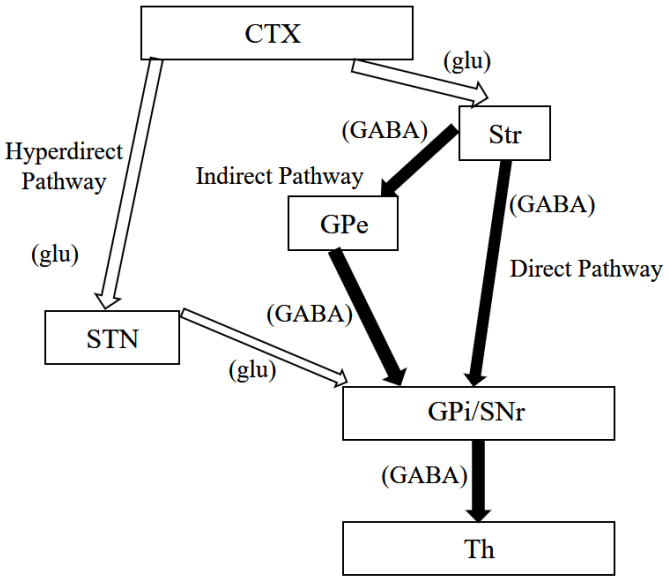

Figure 6. Diagram of the Basal Ganglia Pathways. Open arrows – excitatory glutamatergic (glu), filled arrows - inhibitory GABAergic (GABA) projections. Cx – cerebral cortex; GPe - globus pallidus externus; GPi - globus pallidus internus; SNr - substantia nigra pars reticulata; STN - subthalamic nucleus; Str - striatum; Th – thalamus. Figure is redrawn with minor omission **from Nambu et al. (2002).**

The function of the BG is very complex as is its circuitry. It has at least five cortico-basal-ganglia-thalamic loops that originate in the motor, oculomotor, associative, lateral orbitofrontal, and anterior cingulate cortical areas, each having multiple parallel loops (Tisch, Silberstein, Limousin-Dowsey, & Jahanshahi, 2004). These rich associations between BG circuits and cortical areas underline the importance of the BG in the normal function of the brain.

For the purposes of this thesis, the focus will remain on the motor loop. It has sophisticated circuitry, which function is still a topic of debate but for the sake of simplicity, a model proposed by (Nambu, et al., 2002) will be considered the most up to date. However, it must be noted that it omits a number of pathways that may in future prove to be too important to omit. Nevertheless, according to (Alexander & Crutcher,

1990; Nambu, et al., 2002) cortical excitatory input is received by corpus striatum and then may travel through a shorter "direct" pathway that through double inhibition disinhibits the thalamus (Figure 6). The thalamus then closes the loop projecting back to the cortex via excitatory connections (not shown). The "indirect" pathway takes an additional step: cortically activated striatum inhibits the activity of the GPe which results in disinhibition of the STN. In turn, disinhibited STN stimulates GPi/SNr, which both suppress thalamic activity, thereby limiting its ability to excite the cortex. Aside from these two pathways, there is also the "hyperdirect" pathway that connects cortical regions straight to STN bypassing the corpus striatum (the usual input nucleus of the BG).

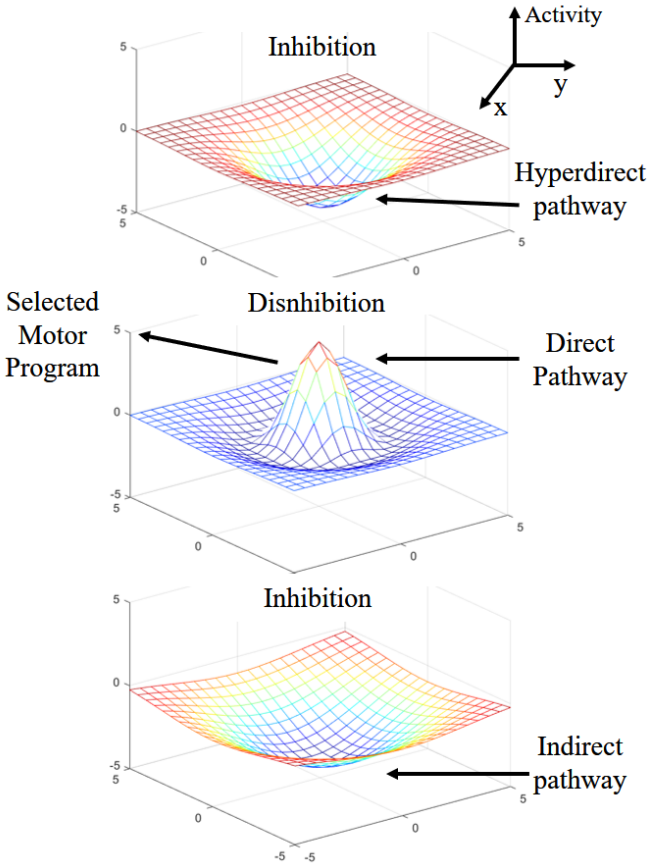

Figure 7. Proposed Mechanism of Action Selection in the Basal Ganglia. This figure was redrawn using a combination of Gaussian distributions to display the idea illustrated in Nambu et al. (2002).

Current understanding of the BG's contribution to the motor function (excluding its involvement in learning) is that it helps cortex choose and allow an appropriate motor action from a number of actions arriving through parallel channels. The putative mechanism of action selection is shown in Figure 7. First, when cortical mechanisms of

movement initiation are activated, a signal through “hyperdirect” pathway first inhibits both large thalamic and cortical areas associated with desired and competing motor programs. This is followed by a targeted release of the selected motor program via the “direct” pathway. Finally, the inhibition provided by the “indirect” pathway suppresses cortical areas pertaining to competing motor programs helping to reduce ambiguity. As this process unfolds in time, a sequence of different motor programs may be selected and executed without one interrupting the other.

The dopamine produced in SNc is released both tonic and phasic modes in the corpus striatum (Jenkinson & Brown, 2011). Here, it may act on two families of dopaminergic receptors that collectively had been divided into D1- and D2-types. Activation of D1-type receptors leads to excitation of the postsynaptic targets. Conversely, D2-type receptors, when activated by dopamine, produce post-synaptic inhibitory potentials. Moreover, D1-type dopaminergic receptors are found exclusively within the parts of the corpus striatum that begin the “direct” pathways and D2-type dopaminergic receptors are located in the parts of the corpus striatum that produce belong to the “indirect” pathway. If one traces what the simultaneous release of dopamine on both pathways would do, one would quickly find an overall increase in thalamic and thus cortical activity. Conversely, if the dopamine would drop below the baseline levels, it would produce an inhibitory effect in both pathways leading to suppression of the cortical activity. In fact, this is thought to be the main reason for some of the most pronounced symptoms in Parkinson’s disease. For example, this is associated with the slowness of movement (bradykinesia), decreased step length (hypometria). However, it must be noted that not all of the key PD impairments (e.g., tremors) can be explained by this model.

Recently, there has been an exploration of other neurotransmitters' potential involvement in PD (e.g., acetylcholine) in hopes to find what is causing spasticity, postural instability (which are not fully understood by the dopamine deficiency model) (Calabresi, Picconi, Parnetti, & Di Filippo, 2006; Picciotto & Zoli, 2008; Yarnall, Rochester, & Burn, 2011).

1.2.5. Brainstem and other regions

There are additional central regions that help regulate the motor function. In experiments using cats (which have shown to be tentatively translatable to humans despite cats being quadrupeds), it's been established that muscle tone is upregulated by mesencephalic and cerebellar locomotor regions that project to the ventromedial medullary reticular formation (v-MRF). These regions also activate so-called central pattern generators (CPGs) cells in the spinal cord. CPGs generate a rhythm used in locomotion by activating the flexor and extensor muscles in antiphase (Takakusaki, 2013). Further, subthalamic (receives inputs from the limbic system) and cerebellar locomotor regions also evoke CPG activity. Another important region called pedunculopontine tegmental nucleus (PPN) that receives inputs from both the BG and the limbic system conveys muscle tone inhibitory signals via its cholinergic projections down to the pontine reticular formation (PRF) and the dorsomedial medullary reticular formation (d-MRF). This is a simplified overview of midbrain and brainstem regions pertaining to the central motor system but this already conveys the complexity involved in generating fluid and fine movements.

1.3. Methods of Recording the Activity of the Human Motor System

1.3.1. Electroencephalography (EEG)

The technique of electroencephalography (EEG) has a long history with first attempts to record the neural activity of mammals going back to the early twentieth century (Pravdich-Neminsky, 1912). However, the first human EEG recordings were performed by Hans Berger in 1924 (Haas, 2003). EEG is not a direct measure of neural spiking, which happens on the order of several to tens milliseconds, but rather is scalp electrical currents that are caused by the collective signal of changes in the extracellular electric field due to post-synaptic potentials. Post-synaptic potentials last longer than the action potentials that caused them, thus producing electrical field changes that can be detected with EEG. Additionally, EEG is afforded by the collective parallel alignment of pyramidal cortical neurons that cause the changes in extracellular ion concentrations after spiking (Figure 8). If pyramidal neurons were not aligned roughly perpendicular to the cortical surface, individual electrical fields produced by collective activity would have canceled each other out. It has to be taken into

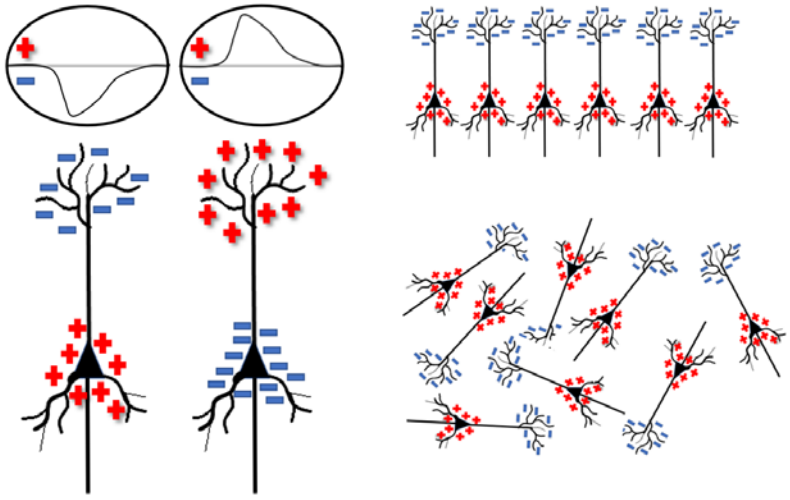

Figure 8. How EEG Signal is formed. On the left, it is shown how signals arriving to the soma or to the dendritic arbor may produce the same recording. On the right side, it shown show only aligned pyramidal neurons on top can produce detectable recording unlike the lower arrangement.

consideration that the signal obtained through EEG has come through several layers of dielectrics (e.g., meninges, cranial bones) that serve as low-pass filters (i.e., favoring lower frequency changes over the higher frequencies) and its quality depends on the conductivity of the scalp. Typically, subjects that are invited to EEG sessions are asked not to apply any hair conditioner, creams, or any cosmetical substances that are lipid-rich as these will render skin much less conductive. Before the experiment, subjects wear a head cap with electrodes similar to the one shown in Figure 9. To establish a high-fidelity contact with the skin of the scalp, experimenter either fills each suction cup (which itself has an electrode inside) with a conductive gel or, in case of dry systems, the cap is worn tightly and each electrode is slight screwed until a robust contact is established.

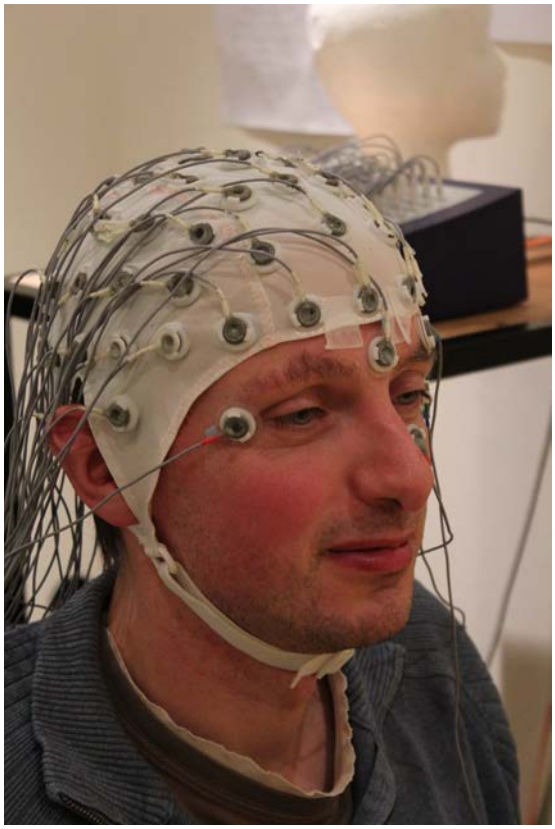

Figure 9. A typical EEG cap setup on a human subject. Photo by Chris Hope. Permission to republish granted to Tim Sheerman-Chase. (https://commons.wikimedia.org/wiki/File:Three_quarter_view_of_EEG_subject.jpg, „Three quarter view of EEG subject“, https://creativecommons.org/licenses/by/2.0/legalcode

The EEG signal can be transformed from the time domain into a spectral domain using a mathematical tool called Fourier transform. Resulting in a periodogram, Fourier transforms shows approximately how much of a certain frequency does the signal contain. If one stacks a series of periodograms taken through repeating time intervals, a spectrogram is obtained, which

shows power changes in selected frequencies. This technique is useful when EEG-derived outcome measures are time-locked to behaviors that humans perform during the experiment as it allows to draw associations between neural dynamics and behavioral outcomes.

Since the dawn of the EEG research on humans, the spectrum was roughly split into several frequency bands that often were associated with specific behaviors (Van Albada & Robinson, 2013). Exact boundaries are still a topic for debate but roughly human EEG spectrum can be split into several bands:

a. 4 Hz or lower waves are called delta waves and are found in babies and adults that are in slow-wave sleep;

b. 4-7 Hz waves are called theta waves and typically are found in young children, drowsy adults, and teenagers;

c. 8-15 Hz waves (with some literature limiting this band to 8 to 12 Hz (Klostermann, et al., 2007)) are called alpha waves and are typically found posteriorly (especially, if a human subject closes his/her eyes). Its function is still under investigation but some evidence points to alpha waves are being associated with sensory integration (Smith, Jacobs, & Horak, 2012);

d. 16-31 Hz waves (with some sources quoting 13-30 Hz (Jenkinson & Brown, 2011)) are called beta waves are typically associated with the function of the central motor system;

e. 32 Hz and above are collectively called gamma waves and are thought to represent higher cognitive processes that require a high concentration of cortical resources.

These associations between frequency bands and human behavior open a window of opportunity for studying certain processes (e.g. sleep, speech, mobility) without any invasive procedures since electrodes are simply placed on subject's head and with comparatively simple and mobile equipment.

The advantages of EEG make it a choice method for various experiments. Firstly, it is non-invasive making most of the population potential subjects (if they qualify for inclusion criteria, of course). Secondly, the whole EEG system is much cheaper than its competitors (fMRI, MEG) and is portable to some extent. The recent advances in the EEG industry introduced wireless dry EEG caps that don't need to use conductive gel, essentially allowing greatly cut the set up time and perform experiments with greater degrees of freedom as long as a stable contact with a patch of scalp skin can be maintained (e.g., where a subject freely walks, steps, does physical activity (Guger, Krausz, & Edlinger, 2011)). This needs to be thoroughly checked but if the production companies' promises hold up, this would a great breakthrough from previous generations of EEG systems. Even though gel-based systems take longer to set up, they remain a staple in the EEG industry as the conductive gel can alleviate slight cap movements. Proprietary software is typically used to monitor conductances of all of the channels and any situation (e.g., gel drying out during longer experiments) may be taken care of immediately. From personal experience, dry caps still lack this advantage. Nevertheless, the dry cap industry is developing at a higher pace than ever for both scientific and customer purposes (e.g., simple dry-electrode systems for mobile phone control using your own EEG signatures translated into commands). Overall, it seems that at the moment gel-based EEG systems are more reliable for measuring cortical activity during

postural or stepping experiments due to the higher fidelity of the signals. Thirdly, EEG provides great temporal resolution with sampling rates (e.g., Advanced Neuro Technology from Enschede, the Netherlands provides a system that acquires a sample 1024 times per second).

However, EEG comes with its own limitations as well. Firstly, the currents that are recorded are three orders of magnitude lower than any current that activates any facial musculature (microvolts for EEG vs. millivolts for facial musculature). Even eye-blinking or changing one's facial expression introduces heavy distortion in the recordings. This is partially overcome by instructing participants not to blink during the most important moments, relax their face and neck. Still, EEG recordings need to undergo different artifact removal techniques, some of which are based on the independent component analysis (Lee, 1998), to weed out these artifacts. Some subjects forget the instructions or have problems with not blinking for the time required by the experimental protocol. Secondly, unless these new EEG systems (Guger, et al., 2011) become common, EEG will remain only well-suited for experiments where the head remains in roughly the same position as any tug on the cap will change the conductivity of some channels and will corrupt the data. Thirdly, while enjoying a decent temporal resolution, EEG is a poor technique for establishing the cortical source of the specific signal (although there are systems with up to 256 electrodes that cover the expanse of the scalp quite thoroughly and different mathematical algorithms for source estimation (Grech, et al., 2008)). Moreover, there will still be area inaccessible to EEG (e.g., cortical tissues lining the surface of the cortex in the interhemispheric tissue or deep cerebral

structures like the BG). Therefore, different methods are necessary to glean data that will revolutionize our understanding of the brain.

1.3.2. Magnetoencephalography (MEG)

Beginning with Maxwell's discovery in the latter half of the nineteenth century, it's a common knowledge that alternative electric currents give rise to magnetic fields. This is one of the reasons the magnetoencephalography could be employed in the first place. If electric potentials measured on the scalp were quite minuscule in amplitude and had to be isolated from any sort of bodily and external interference, the magnetic field produced by the brain is even smaller when compared with the environment (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). For example, the strength of the magnetic field produced by a human brain is approximately 50-500 fT or one part in 10^9 or 10^8 of the Earth's magnetic field. To pick

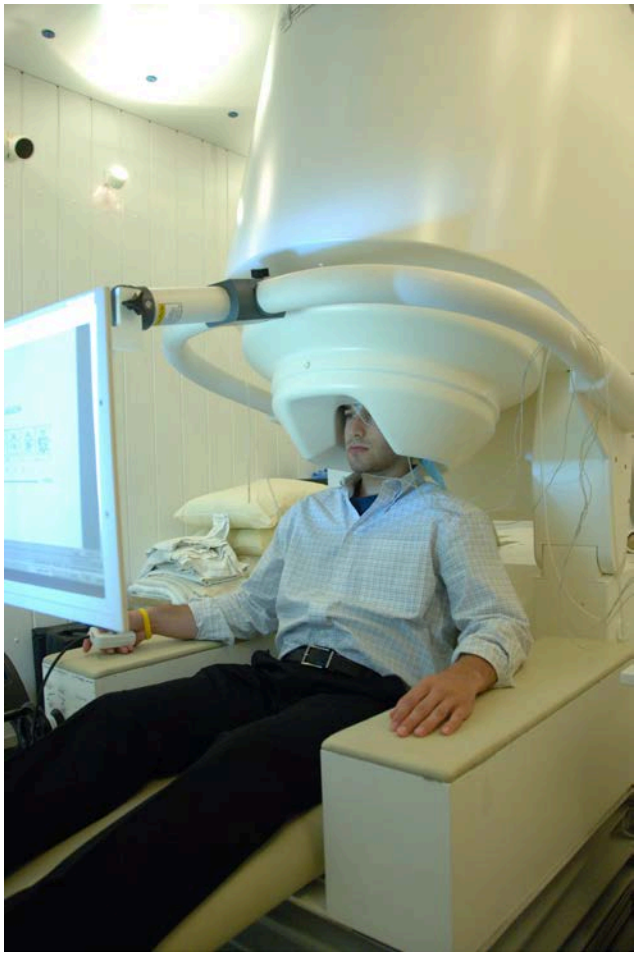

Figure 10. Magnetoencephalography device with a subject. Unknown NIMH author (https://commons.wikimedia.org/wiki/File:NIMH_MEG.jpg), „NIMH MEG", marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-US

up such minuscule changes in the magnetic field, specialized superconducting quantum interference device (SQUIDs) gradiometers were developed (Figure 10). They have induction coils floating in the liquid helium at almost absolute zero temperature thus becoming superconductive. This superconductive state then allows recording the changes in the magnetic field within a patient's cranium.

Advantages of using MEG devices include both better spatial and temporal resolution increasing the resolution of neural dynamics and thus elucidating more than EEG would (Mellinger, et al., 2007). As a result, MEG can localize the source of the signal with higher precision (Lal, et al., 2005). They are also very convenient to subject if compared to EEG: there is no the lengthy process of preparing the cap with a gel or constantly checking the quality of connection as gel tends to dry out or leak out of suction cups. From an experimenter point of view, it is also beneficial as one can easier to recruit subjects for a study and go through a larger sample size than in an EEG-based study.

Nevertheless, MEG does have its drawbacks as well. It's even more sensitive to electromagnetic noise and requires significant shielding from the outside influences. Since the MEG apparatus is bulky and stationary, it only allows movement experiments that are limited to lying or sitting and performing simple limb movements. One more aspect of MEG to consider is its cost. It is not affordable to many laboratories thereby limiting exploration through the means of MEG. To conclude, if money were not a part of the equation, a MEG apparatus could be a great addition to EEG research, helping to pinpoint the signal sources more precisely and with a very little toll on both subjects and experimenters.

1.3.3. Electrocorticography (ECoG)

Originally, electrocorticography (ECoG) technique was only used in a clinical setting to estimate the source of intractable epileptic seizures that could not be located otherwise. ECoG is an invasive method that requires craniotomy to get access to the subdural space (Nicolas-Alonso & Gomez-Gil, 2012a) and thus requires a high-risk operation with a chance of serious side effects. When the cranium is open, a small mat with electrodes (also called strips and grids) is placed on the region of interest (therefore, whole brain ECoG is yet impossible) and may stay there up to 14 days in a clinical setting (Vale, Pollock, Dionisio, Benbadis, & Tatum, 2013). Experiments carried out on animals concur this: their ECoG systems supplied reliable signals for several months (Chao & Nagasaka). Considering all of the limitations that ECoG has at the moment, it cannot be a reliable tool for studying neural dynamics but may occasionally provide a sharper view on it, if the medical situation necessitates craniotomy.

1.3.4. Functional Magnetic Resonance Imaging (fMRI)

Magnetic resonance imaging (MRI) and functional MRI (fMRI) are widespread methods of assessing the structure (MRI) and function (fMRI) of the brain. The method has one of the most diverse families of more specialized and niche variations that one could dedicate a series of books just to that purpose. Here, I am only mentioning the basics of the method to assess its suitability for testing hypotheses that will be stated later in this thesis.

fMRI is, unlike EEG/MEG/ECoG, an indirect method of measuring the neural activity (however, previously mentioned methods themselves could be labeled as such since they don't measure actual action potentials but their aftermath). fMRI records Blood Oxygen Level Dependent (BOLD) signal, which is not directly linked to neuronal activity. However, there is an established association between the two (Christopher deCharms, et al., 2004). Crudely speaking, fMRI machine first uses a strong magnetic field from 1.5 to 7 T (actually stronger than Earth's magnetic field which ranges from 25 to $65*10^{-6}$ (Finlay, et al., 2010)) to align nuclei within tissue along a single axis and when that magnet is turned off the observations are made how nuclei are relaxing back to their natural state.

Advantages of MRI devices are numerous: they allow to study neural tissues' structure and function without invasive procedures. They have a high spatial definition but due to the fact that for fMRI there is a 1-2 second lag between consecutive scans fMRI here loses to EEG's 0.05 s time resolution (Nicolas-Alonso & Gomez-Gil, 2012b). Nevertheless, fMRI can observe changes in deep cerebral structures, unlike EEG. Similar to MEG devices, the size of an MRI device and the necessity to put a subject quite deep inside the apparatus both restrict amount of movement studies that can be performed to finger movements (e.g., button presses) or leg movements (e.g., dorsi- or plantarflexion of the feet, flexion of the knees). While these movement paradigms are extremely useful for studying neural processes relating to simple movements, fMRI cannot be used for such tasks as step initiation, gait, etc. This makes it unsuitable for our experiments.

1.3.5. Kinesiology Recordings

Key to understanding the motor control is pairing neural events with observable behavioral events. Kinesiology is an umbrella term that includes the study of human motion (i.e., kinematics), forces developed during movement (i.e., kinetics), joint angle measurement (i.e., goniometry), as well as measuring biological parameters (e.g., blood pressure and oxygenation).

Human motion recording using passive markers typically employs infrared or near-infrared light captured by a set of cameras focused on the subject. One such motion capture system is installed in the University of Vermont (produced by Vicon, Denver, CO, USA). It includes a set of 9 cameras that track reflections from bead-like passive sensors attached by the experimenter to subject's key locations on the body. Increasing the number of cameras helps to more precisely record marker positions as they may become occluded during movement to some cameras. The proprietary software then analyzes each camera's data to estimate each marker's movement through space and time. Further, these data can be processed to calculate positions, velocities, and accelerations of the body's segments during the task.

Forces developed during human locomotion are recorded by so-called "force plates" (usually one for each foot). These force plates output data about force and moment vectors when a subject is in contact with them. Using a formula derived from (Henry, Fung, & Horak, 1998), an approximation of the center of pressure (CoP) can be made. CoP is an important outcome variable as it summarizes and displays how a human subject applied forces to the ground during different tasks and is frequently used in postural

studies (Collins & De Luca, 1993; Kavounoudias, Roll, & Roll, 1998; Maki, Holliday, & Topper, 1994; Maki & McIlroy, 1997, 1999).

For this thesis, both kinetic and kinematic recordings were key in establishing the resulting behavior between conditions and were, therefore, recorded and analyzed.

1.4. Assessing Motor Preparation Using Cortical Potentials

1.4.1. Amplitude-Based Potentials

The first attempts to quantify anticipation and motor preparation were done through EEG-derived Bereitschaftspotential (BP; also - readiness potential) and the contingent negative variation (CNV). The BP is a slow, negative drift in the (EEG) signal that is detected prior to self-initiated voluntary movements (Kornhuber & Deecke, 1965), whereas the CNV potential is a slow, negative drift observed in the EEG signal between warning and imperative cues when the inter-stimulus interval is known to the subject (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The two-stimulus paradigm associated with CNV allows modification of the experimental task from predictable to unpredictable (by withholding movement parameters until the second cue) and, therefore, CNV was a candidate for the studies presented in this thesis. BP was not considered as it pertains to only self-initiated voluntary movements.

CNV is considered to represent both non-motor processes related to the anticipation of the second stimulus and sensorimotor processes related to the preparation of movement (Brunia & Van Boxtel, 2001; Fischer, Langner, Diers, Brocke, & Birbaumer, 2010). Known generators of CNV motor components include the supplementary motor, lateral premotor and primary sensorimotor cortex (Bareš, Nestrašil,

& Rektor, 2007; Hamano, et al., 1997; Lamarche, Louvel, Buser, & Rektor, 1995). Previous studies suggest that the late CNV amplitude is related to motor preparation and anticipatory attention towards the second cue (Brunia & Van Boxtel, 2001; Rohrbaugh, Syndulko, & Lindsley, 1976), whereas the peak CNV amplitude represents maximal anticipatory attention and/or onset time of attentional shift towards sensory information and the execution of motor command (Fujiwara, Kiyota, & Maeda, 2011; Jacobs, et al., 2008; Macar & Vidal, 2002). Although subjects with PD usually exhibit decreased (Deecke, 2000) or even absent (Praamstra & Pope, 2007) CNV amplitudes, most studies examine simple upper-limb button-press or wrist movement tasks that do not test standing postural control (Amabile, et al., 1986; Ikeda, et al., 1997; Magnani, et al., 1998; Oishi, Mochizuki, Du, & Takasu, 1995; Pulvermüller, et al., 1996; Van Boxtel & Brunia, 1994).

1.4.2. Spectrum-Based Potentials

Beta event-related desynchronization (ERD) is a more recent way of assessing motor preparation (Heinrichs-Graham & Wilson, 2016; Labyt, et al., 2003; Leocani & Comi, 2006; Pfurtscheller, 2006; Pfurtscheller & Da Silva, 1999). Beta ERD has also been recently used to study cortical preparation for voluntary step initiation (Varghese, et al., 2016). Beta ERD is a spectral outcome measure because it's derived from raw EEG recordings that were band-pass-filtered in beta range (12 -30 Hz, although exact figures differ by studies) and then converted into the spectral domain using a number of approaches. Beta ERD is an interesting outcome measure because it associates with motor preparation, inhibition of tonic activation, and/or anticipation of an impending

need for movement, and ERD is thought to represent changes in synchronization of corticostriatal circuits involving the motor regions of cortex (Fogelson, et al., 2006; Jenkinson & Brown, 2011; Klostermann, et al., 2007; Wheaton, Carpenter, Mizelle, & Forrester, 2008).

In terms of functional relevance, oscillatory activity in the upper beta frequencies is hypothesized to be the idling rhythm of motor networks (Pfurtscheller, Stancak, & Neuper, 1996). This hypothesis is supported both by the desynchronization/resynchronization pattern observed in beta-band cortical oscillatory activity associated with voluntary movements, as well as by increased synchrony during steady muscle contractions (Baker, Olivier, & Lemon, 1997; Kilner, et al., 1999; Sanes & Donoghue, 1993). Interestingly, in the experiments with cued voluntary movements, beta ERD is only observed when the Go cue can reliably predict the need to perform a voluntary movement (Zaepffel, Trachel, Kilavik, & Brochier, 2013), which suggests that unpredictability might be associated with diminished and/or absent beta ERD. Furthermore, beta-band synchrony increased when healthy subjects suppressed or actively resisted a movement (Androulidakis, et al., 2007). Recently, this "idling rhythm" hypothesis has been updated to state that beta-band cortical oscillatory activity is not a mere passive process reflecting the lack of motor activity, but rather an active mechanism for maintaining current motor set and preventing new movements (Engel & Fries, 2010; Gilbertson, et al., 2005; Pogosyan, Gaynor, Eusebio, & Brown, 2009). These findings render beta ERD an interesting tool to study cortical processing of pre-movement motor changes, however, it is just starting to pick up momentum as the human movement community learns about it. For example, beta ERD in people with PD was used to

discover an association between beta ERD delayed onset time or decreased amplitude prior to a voluntary upper-limb task (Heinrichs-Graham, et al., 2013; Labyt, et al., 2005). When preparing to maintain standing posture in response to an externally induced loss of balance, modulation of beta ERD amplitudes correlated with the subjects' ability to modulate postural responses based on prior knowledge of perturbation magnitude (Smith, et al., 2012). During a choice response task involving the upper limb, subjects with PD exhibited severely diminished preparatory ERD, however, upon reaction stimulus subjects demonstrated a quick and high-amplitude ERD, which nevertheless was followed up by reduced or even absent resynchronization of cortical oscillatory activity in upper beta frequencies (Praamstra & Pope, 2007). Findings from these studies reveal an abnormal temporal and spatial profile of beta ERD in persons with PD, which remains to be confirmed for step initiation. As for the use of beta ERD in studies of motor control in aging populations, in a study involving upper-limb movements, beta ERD becomes increased and more widespread in older subjects (Sailer, Dichgans, & Gerloff, 2000). Increased beta ERD amplitudes observed in older subjects may reflect higher cognitive effort in response to weakened proprioceptive feedback (Toledo, Manzano, Barela, & Kohn, 2016) or impaired sensory integration (Labyt, et al., 2003; Toledo, et al., 2016).

Therefore, together, CNV and upper beta ERD provide unique measures of cerebrocortical activity prior to movement (Babiloni, et al., 1999; Bender, Oelkers-Ax, Resch, & Weisbrod, 2004; Filipović, Jahanshahi, & Rothwell, 2001) that are relevant neural correlates of step initiation. However, upper-beta ERD (20-29 Hz) is thought to offer a more focal sensory-motor localization than CNV or lower beta and alpha

frequency bands (Klostermann, et al., 2007; Pfurtscheller & Da Silva, 1999). Therefore, it was chosen as a neural correlate in the studies presented in this thesis.

The goal of this thesis was to evaluate the pre-movement measures of cortical preparation in order to gain insights into processes of motor preparation during step initiation under predictable and unpredictable conditions, with and without PD in the older population. We hypothesized that subjects with PD would exhibit less cortical modulation between conditions of forward step initiation with and without prior knowledge of limb choice. Further, we hypothesized that decreased cortical modulation in PD would associate with a higher impairment of motor performance.

As for effects of age, we hypothesized that older subjects would exhibit increased cortical preparation, but also decreased and prolonged postural preparation as well as delayed and less stable step execution. Further, we hypothesized that unpredictability would decrease cortical preparation and further impair step initiation. To the best of our knowledge, there are no published works that explore step initiation in unpredictable conditions using beta ERD.

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CHAPTER 2: EFFECTS OF PARKINSON'S DISEASE ON NEURAL PREPARATION AND STEP INITIATION IN UNPREDICTABLE CONDITIONS

2.1 Abstract

Step initiation is impaired in Parkinson's disease (PD). However, the impact of PD on the neural mechanisms of step initiation when some of the step parameters are unpredictable remains unexplored. Cortical preparation for step initiation can be assessed by beta event-related desynchronization (ERD) derived from electroencephalography (EEG) recordings. We hypothesized that subjects with PD would exhibit less cortical modulation between conditions of forward step initiation with and without prior knowledge of limb choice. Further, we hypothesized that decreased cortical modulation in PD would associate with a higher impairment of motor performance. Results identified that the group with PD exhibited decreased beta ERD amplitudes that were similar regardless of condition, whereas control subjects modulated beta ERD amplitudes between conditions, particularly in early stages of pre-movement processing in areas overlying sensory cortex. Subjects with PD presented with delayed and reduced postural preparation with increased step target error across both conditions and exhibited a greater incidence of multiple APAs in the predictable relative to the unpredictable condition. Delayed postural preparation significantly correlated with lower amplitudes of beta ERD. We concluded that diminished early pre-movement processing over sensory cortex was concomitant with poor pre-selection of the stepping limb in predictable conditions and that a generally diminished amplitude of cortical pre-movement processing relates to delayed step initiation in people with PD.

Keywords: Parkinson’s disease, cortical preparation, step initiation, Beta ERD, choice reaction time

2.2 Introduction

Despite the relentless effort of both scientific and medical communities, Parkinson's disease (PD) remains the second most common neurodegenerative disease in older adults after Alzheimer's disease (De Lau & Breteler, 2006). PD is associated with numerous motor impairments, among them hypometria, bradykinesia, tremors, rigidity, altered postural alignment, postural instability, freezing of gait, as well as autonomic and cognitive dysfunctions (Jankovic, 2008).

Start hesitation, freezing of gait, as well as bradykinetic gait (Rahman, Griffin, Quinn, & Jahanshahi, 2008) are important contributors to the decreased quality of life for those with PD. Step initiation − the interval of changing one's mechanical condition between standing at rest and the moment when the toe of the stance limb is lifted off the ground (Nissan & Whittle, 1990) − is, therefore, an important element of functional independence and must be understood in great detail. Step initiation in the context of PD has generally been studied with subjects performing self-initiated steps (Crenna, Frigo, Giovannini, & Piccolo, 1990; Jacobs, Lou, Kraakevik, & Horak, 2009; Rocchi, et al., 2006; Shoushtarian, Murphy, & Iansek, 2011; Vidailhet, et al., 1993) or using a simple-reaction-time paradigm (Burleigh-Jacobs, Horak, Nutt, & Obeso, 1997; Gantchev, Viallet, Aurenty, & Massion, 1996) under predictable conditions. However, everyday activities often require initiation of gait in dynamic environments with far less predictability than what is usually tested by simple-reaction-time experiments. Therefore, this study sought to determine the effects of PD on step initiation and the cortical preparation for step initiation when step parameters are difficult to predict.

Step initiation is preceded by an anticipatory postural adjustment (APA) that serves to attenuate postural instability when transitioning from stance to gait and aids in the generation of forward momentum (Dietrich, Breniere, & Do, 1994; Dyson, Miron, & Drew, 2014; Elble, Moody, Leffler, & Sinha, 1994) by displacing the body's center of gravity (CoG) forward and maintaining its position near the initial stance limb (Elble, et al., 1994). People with PD exhibit small-amplitude APAs that are often of prolonged duration and are concomitant with decreased initial step velocity and shorter initial step length (Burleigh-Jacobs, et al., 1997; Crenna, et al., 1990; Gantchev, et al., 1996; Jacobs, Lou, et al., 2009; Rocchi, et al., 2006). Environmental effects on the APA in the context of PD had been studied less, but reports have demonstrated that persons with PD fail to scale APA amplitudes after changing stance width from narrow to wide (Rocchi, et al., 2006), highlighting decreased adaptability often observed in PD. In contrast, step initiation guided by external cues was associated with increased APA amplitudes and shorter APA duration (Burleigh-Jacobs, et al., 1997; Rochester, et al., 2005). However, when dual-tasking during step initiation with an n-back working memory task, subjects with PD exhibited a dual-task cost on the accuracy, which was not evident in a control group (Roemmich & Elrod, 2013). This PD-specific cost to cognitive performance suggests that subjects with PD require prioritized attention to movement in order to maintain motor performance at the cost of cognitive performance. Furthermore, the behavioral improvements associated with cueing may come at a cost of compensation by increased cortical resources, which has been demonstrated during continuous gait rather than step initiation (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999). Step initiation within the context of limited predictability may potentially present a sudden

cognitive load, similar to dual-tasking, due to the necessity to choose the appropriate movement strategy within a limited time frame and, thus, result in worsened motor performance.

Regarding neural control, the APA is a centrally pre-programmed set of motor instructions when anticipating destabilization due to voluntary movement, rather than a feedback-driven, reactive process. Both the APA and the goal-directed prime movements are thought to be generated as partially separate, parallel, but integrated circuits that include the primary motor cortex, supplementary motor area (SMA), basal ganglia and postural centers of the brainstem (Jacobs, Lou, et al., 2009; MacKinnon, et al., 2007; Massion, 1992; Schepens, Stapley, & Drew, 2008; Yakovenko & Drew, 2009).

PD is known to have direct influence on the dynamics of a number of the central nervous system's regions, including the basal ganglia, SMA, primary motor cortex, and thalamus, which are commonly referred to as a cortico-striatal loop (Albin, Young, & Penney, 1989; DeLong & Wichmann, 2007). Therefore, PD associates with impaired APAs and affects similar cortical networks as those used to generate APAs, but in order to advance treatment strategies, a deeper understanding of altered cortical processing pertaining to anticipation, planning, and execution of step initiation is crucial.

To assess neural correlates of anticipation and motor preparation, we analyzed beta event-related desynchronization (ERD), which has only recently been used to study cortical preparation for voluntary step initiation (Varghese, Merino, Beyer, & McIlroy, 2016). Beta ERD is a band-specific (12.5-30 Hz) change in power associated with an event such as movement (Pfurtscheller & Da Silva, 1999). Beta ERD is localized at mesial central electrodes overlying the SMA and is thought to represent changes in

synchronization of cortico-striatal circuits involving the motor regions of cortex (Fogelson, et al., 2006; N. Jenkinson & Brown, 2011; Klostermann, et al., 2007; Wheaton, Carpenter, Mizelle, & Forrester, 2008). Functionally, beta ERD associates with motor preparation, inhibition of tonic activation, and/or anticipation of an impending need for movement (Pfurtscheller, 2000).

Thus, beta ERD represents an interesting measure to study cortical processing of motor changes observed in PD, however, only a few studies have examined the effects of PD on movement-related beta ERD; to the best of our knowledge, none of them have yet evaluated beta ERD during step initiation under unpredictable conditions. For example, people with PD exhibit beta ERD with a delayed onset time or decreased amplitude prior to a voluntary upper-limb task (Heinrichs-Graham, et al., 2013; Labyt, et al., 2005). When preparing to maintain standing posture in response to an externally induced loss of balance, modulation of beta ERD amplitudes correlated with the subjects' ability to modulate postural responses based on prior knowledge of perturbation magnitude (Smith, Jacobs, & Horak, 2012). During a choice-response task involving the upper limb, subjects with PD exhibited severely diminished preparatory ERD, however, upon reaction stimulus subjects demonstrated a quick and high-amplitude ERD (Praamstra & Pope, 2007). Findings from these studies reveal an abnormal temporal and spatial profile of ERD in persons with PD, which remains to be confirmed for step initiation.

Therefore, upper beta ERD provides a unique measure of cerebrocortical activity prior to movement (Babiloni, et al., 1999; Filipović, Jahanshahi, & Rothwell, 2001) that is affected by PD and relevant to neural correlates of step initiation. We evaluated this pre-movement measure in order to gain insights into processes of motor preparation

during step initiation under predictable and unpredictable conditions, with and without PD. We hypothesized that subjects with PD would exhibit less cortical modulation between conditions of forward step initiation with and without prior knowledge of limb choice. Further, we hypothesized that decreased cortical modulation in PD would associate with a higher impairment of motor performance.

2.3 Methods

A total of 22 subjects, 10 with PD and 12 control subjects without PD, participated in the study. Inclusion criteria for the subjects without PD included the absence of neurological or musculoskeletal disorders such as diabetes, peripheral neuropathy, uncorrected visual problems, hearing problems, disabling joint pain, arthritis, fracture, stroke, seizure, dementia, and PD. In addition, potential control subjects taking medications known to alter motor or musculoskeletal function were excluded from the study. For the subjects with PD, criteria included: (1) diagnosis of idiopathic PD (2) presentation of rigidity, impaired gait, or bradykinesia, and (3) modified Hoehn & Yahr stage of 1.5-3 in the OFF state. All of the subjects with PD stopped taking antiparkinsonian medications at least 12 hours before the experiment.

Subjects with PD were recruited from the neurology department and a center for movement disorders at a university medical center. A neurologist, board certified in neurology and clinical neurophysiology, determined whether subjects met inclusion criteria. The protocol was approved by the Institutional Review Board, and all of the subjects provided written informed consent before the experiment.

Procedures

Members of both experimental groups filled out a demographics and health history questionnaire that included reporting of fall history, and the Physical Activity Scale for the Elderly Questionnaire – PASE (Washburn, Smith, Jette, & Janney, 1993). Subjects with PD completed additional questionnaires: (1) Section II of the Movement Disorder Society-sponsored revision of the Unified PD Rating Scale – MDS-UPDRS (Goetz, et al., 2008), (2) the self-administered freezing of gait questionnaire - FOGQsa (Nilsson, et al., 2010), and (3) the 8-item Parkinson's Disease Questionnaire – PDQ-8 (C. Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997). In addition, the ambulatory capacity measure (ACM) calculated as the sum of items 13 (falling), 14 (freezing), 15 (walking), 29 (gait), and 30 (postural stability) of the UPDRS (Parashos, et al., 2015) as well as Section III of the MDS-UPDRS were executed by the experimenter. The questionnaires and physical exam were used to identify the functional relevance of impairments in the experimental task by correlating the impairments of step initiation with clinical symptoms, falls, activity limitation, and quality of life.

Subjects were then prepared for EEG and kinematic recordings. For EEG recordings, subjects wore an Advanced Neuro Technology (ANT; Enschede, the Netherlands) Waveguard 128-electrode EEG cap (sintered silver / silver-chloride electrodes; standard 10/5 system placement (Oostenveld and Praamstra 2001)). Each electrode was filled with a conductive gel (Electro-gel; Electro-Cap International; Eaton, OH, USA) to obtain impedances below 10 kΩ. For kinematic recording, passive reflective markers were placed bilaterally with two-sided tape on the following landmarks in order to record the subjects' motion during testing with a 9-camera motion

capture system (Vicon, Denver, CO, USA): the tuberosity of the fifth metatarsals, the distal phalange of the first toe, the calcaneus, lateral maleoli, lateral femoral condyles, greater trochanters, acromia, lateral humeral epicondyles, ulnar styloid processes, as well as the lateral supraorbital processes, the preauricular notches, and on the force platforms.

During experimental trials, the subjects were attached to an overhead harness that did not provide support during upright stance, but which prevented falls to the ground in order to minimize the risk of injury. Subjects stood on a pair of force plates (AMTI, Watertown, MA, USA) with the feet in a standard stance width of 11% of their body height (McIlroy and Maki 1997). This position was marked with tape to ensure consistent foot placement across trials.

At the beginning of the experiment, subjects performed three trials of self-initiated stepping in order to calculate an average preferred step length. Specifically, the task was to take one step with an identified limb followed by a step of matching length with the trail limb. This preferred step length was then used to calculate the target position of 125% step length, and targets were placed at that distance anterior to the initial starting position of the first toe for use in subsequent trials. The extended step length served to increase requirements on the APA as well as to require non-preferred step placement as might be required of stepping in unpredictable conditions.

Subjects then performed 4 conditions of 30 trials each: (1) predictable steps with the right foot, (2) predictable steps with the left foot, (3) unpredictable steps with the left foot, and (4) unpredictable steps with the right foot. The order of conditions (first both predictable and then both unpredictable) was chosen to minimize effects of central set switching, which is impaired in PD (R. Brown & Marsden, 1988; Richards, Cote, &

Stern, 1993; Robertson & Flowers, 1990; Smith, et al., 2012). Unpredictable trials of the left and right foot were pooled together and were presented in random order. Subjects were instructed to step with the left or right foot for the predictable conditions, such that they were aware of the chosen stepping limb before each trial, or to step with the foot indicted by the cue to step for the unpredictable conditions, such that they were uncertain about which stepping limb to select until the presentation of each trial's step cue. For all conditions, subjects were instructed to stand with their vision focused on a computer screen positioned approximately two meters ahead of them at eye level, to maintain an even weight under both feet (the vertical weight loading on the force plate under each foot was monitored online by the experimenter), to minimize eye blinks prior to stepping for 5-10 seconds, and to relax the muscles of the neck and face. These instructions served to (a) decrease the risk of pre-weighting the stance limb, which negates the need for an APA and alters pre-movement cortical activity (Varghese, et al., 2016) and (b) minimize artifacts in the EEG signal. Two large images were presented on the computer screen with an inter-stimulus interval of 2 seconds, which was known to the subjects. The first image was a plus sign (+) and represented a warning cue, to which subjects were instructed not to respond, and the second image contained either the word "LEFT" or "RIGHT". The subjects were instructed to step as quickly as possible and as accurately as possible with the indicated limb to the target located on the same side, and then to take a matching step with the trail limb to bring the feet parallel.

Data Processing

The EEG signals were recorded by an ANT high-density ASA direct-current amplifier system. Data from each electrode were referenced to the mastoids and sampled

with a 22-bit resolution at 1024 Hz. Recording and pre-processing were performed in ASA software version 4.7.3 (Advanced Neuro Technology, Enschede, Netherlands). The ASA software's artifact detection/correction feature was used to remove ocular artifacts by selecting the two components that most represented the artifacts' characteristics. The data were then high-pass filtered at 0.01 Hz using the whole length of the recording. The cue signals provided synchronization with the other systems, and 6-second epochs were spliced for each trial from 3 seconds before the step cue to 3 seconds after the cue. We analyzed, on average, 25 trials out of 30 recorded per each of the four conditions (range = 16-29 trials per condition). Artifacts related to unstable electrode-scalp interaction, a lack of established baseline signal prior to trial onset due to direct-current amplifier signal displacements, or electromyographic activity were identified by visual analysis of each trial and confirmed by independent agreement between two of the investigators. In order to increase the number of trials averaged for analysis, the two predictable conditions of left and right steps were pooled, as were the two unpredictable conditions of left and right steps. ERD amplitudes were thus derived from 32-59 trials per subject, per predictable or unpredictable condition; the number of trials available in the unpredictable versus predictable conditions was not significantly different $t(20) = 1.97, p = 0.063$). To establish the minimal number of trials necessary for calculating a stable value of beta ERD, we recalculated beta ERD amplitudes using only first 5, 7, 10, 12, and 15 trials. The t-tests and Spearman's correlations of values from truncated data and all available data demonstrated significant correlations and no significant differences when compared to all available trials, with the exception of the early-phase motor cluster in the unpredictable condition, which required 15 trials to achieve a significant correlation. Therefore, the

available artifact-free trials appear to provide a consistent and representative assessment of beta ERD amplitudes for comparison across groups and conditions. All further analysis was performed using lab-generated scripts in MATLAB (Mathworks, Natick, MA, USA).

For quantifying upper beta ERD, the EEG signals from each trial were digitally re-referenced to a common average reference that included every cephalic electrode in order to obtain a reference-free analysis and improve the focal spatial pattern of ERD (Pfurtscheller & Da Silva, 1999). Continuous Morlet wavelet transforms were executed within the upper beta frequencies of 20-29 Hz for each trial. The upper beta frequency range was chosen due to more focused sensory-motor localization, unlike lower beta and alpha frequency bands (Fogelson, et al., 2006; Pfurtscheller & Da Silva, 1999). These Morlet coefficients were then rectified, low-pass filtered at 5 Hz, then averaged by condition and participant, and, lastly, averaged across the upper beta frequency band. Data from left- and right-limb trials were pooled together and averaged to create two final sets of Morlet coefficients, one for the predictable condition and one for the unpredictable condition. After that, the time-varying beta coefficients were normalized to a baseline calculated from 500 ms before the warning cue. Our a priori analysis was to evaluate the effects of group and condition at the electrode of maximal ERD. Upon inspection of the grand averaged topographic plots (Figure 1), however, it became apparent that the beta ERD was primarily evident over specific clusters that exhibited a caudal to rostral development across the inter-stimulus interval prior to the cue to step. To better illustrate this observation, we have recorded two movies (one per condition) exhibiting grand average topographies for both groups, side by side, during the last 1000 ms before the

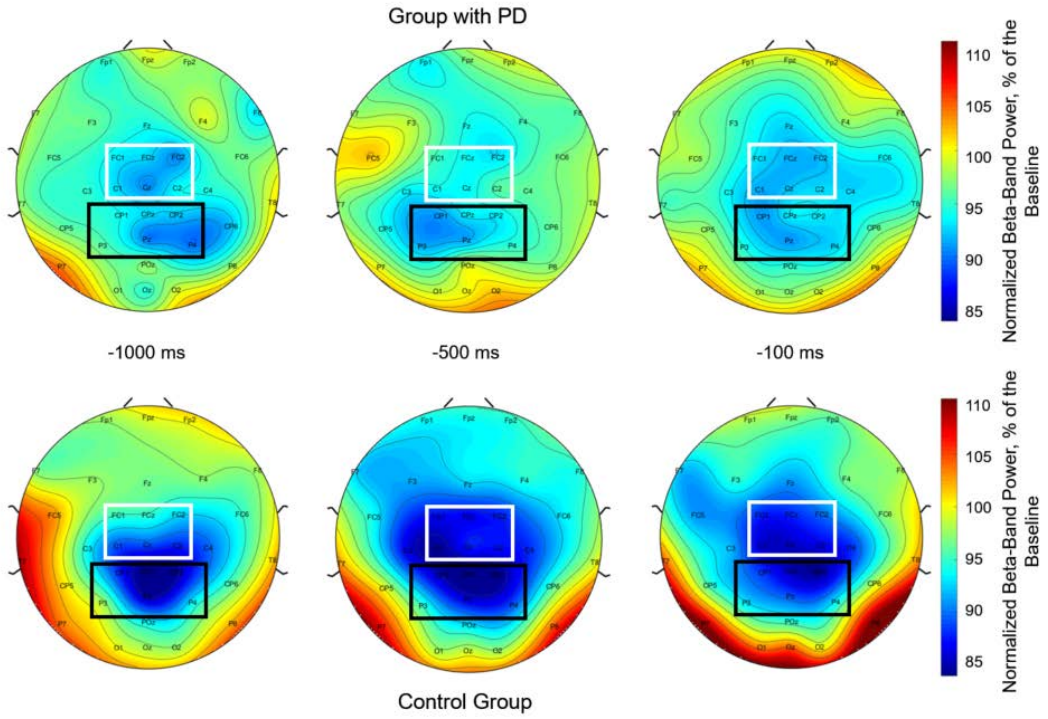

Figure 1. Grand mean upper beta-band (20-29 Hz) event-related desynchronization (ERD), identifying sensory and motor electrode clusters. Black box outlines electrodes chosen for analysis of beta ERD that overlie sensory areas of cortex (i.e., sensory cluster); white box outlines electrodes that overlie motor and pre-motor areas of cortex (i.e., motor cluster). Time points are with respect to the onset time of the step cue. Power displayed was normalized with respect to the 500 ms average before the onset of the warning cue**.**

step cue. These videos are available online as supplementary materials. We, therefore, report on an analysis of beta ERD from a cluster consisting of the FC1, FCz, FC2, C1, Cz, C2 electrodes and a cluster consisting of the CP1, CPz, CP2, P3, Pz, P4 electrodes during the time bin from -1000 ms to -500 ms relative to the step cue as well as from -500 ms to 0 ms relative to the step cue. Please note that the planned analysis from a single, maximum-amplitude electrode was still undertaken with similar-between group outcomes as our reported analysis, but such an analysis offered less insight than the cluster analysis.

To estimate the temporal properties of the APA (i.e., onset time, duration, and time-to-peak amplitude), we calculated the normalized weight distribution between each foot (W_{distr}) using vertical forces recorded from the force plates under the subjects' feet, as previously reported (Jacobs, Nutt, Carlson-Kuhta, Stephens, & Horak, 2009). Force signals were amplified by 1000 and sampled with 12-bit resolution at 1000 Hz. The force-plate signals were recorded by Nexus software and then exported for processing in MATLAB. The W_{distr} traces were low-pass filtered to 10 Hz and baseline subtracted from the average of the 100 ms just prior to the step cue. Outcomes included identifying (a) the APA onset time, defined as the time after the step cue when the W_{distr} trace deflected towards a limb, (b) the foot-lift onset time, defined as the time when the W_{distr} trace reached ±100% for the stance limb (negative for the right foot, positive for the left foot), (c) the APA duration, defined as the time from APA onset to the onset of the foot-lift, and (d) whether the trial had one or multiple APAs (the majority of trials with multiple APAs had only two APAs), which was decided based on observing the oppositely-directed APA (i.e., towards the stance limb) preceding the correct APA (i.e., directed towards the swing limb). The oppositely-directed APA had to be at least 10% of normalized weight to be considered (Figure 2, A).

To disentangle the anteroposterior from mediolateral APA amplitude, each directional component of the whole-body center of pressure (CoP) was calculated from the triaxial forces and moments recorded from the force plates under the subjects' feet (Henry, Fung, & Horak, 1998). The CoP signals were low-pass filtered to 10 Hz, baseline subtracted based on the average of the 100 ms before step cue onset, and then the mediolateral and anteroposterior CoP components were normalized to stance width and

foot length, respectively. Peak backward and swing-limb-directed lateral displacements were then determined prior to foot lift (Figure 2, B).

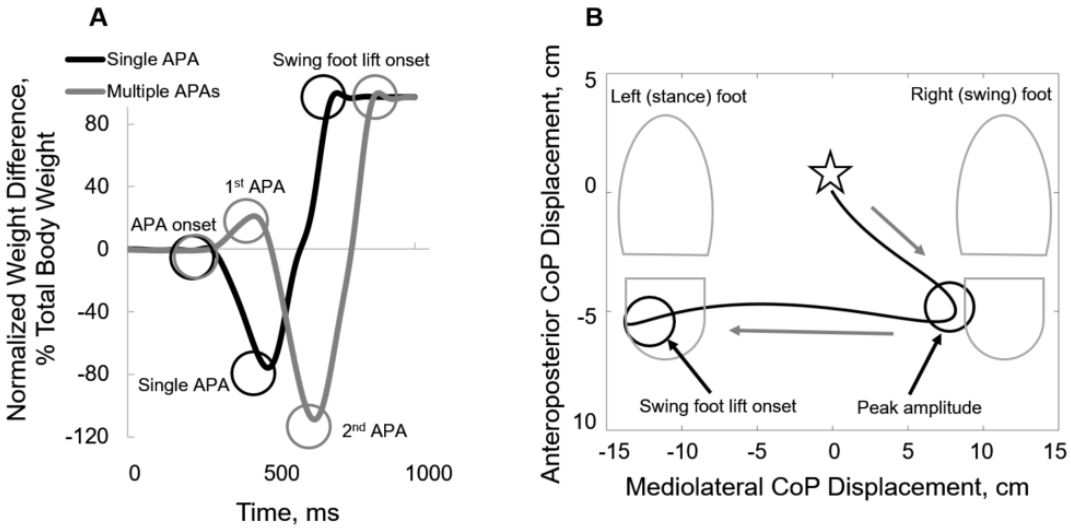

Figure 2. Calculation of the anticipatory postural adjustment (APA) parameters. A: Normalized weight difference (two trials from one representative subject) was used to detect the APA onset time and duration as well as the presence of multiple APAs; B: Center of pressure (CoP) displacement was used to detect mediolateral (x-axis) and anteroposterior (y-axis) APA amplitudes. Star marks the location of CoP in the beginning of the trial. Data were selected from one representative subject performing right-foot steps in the predictable condition.

Variables of the step phase were derived from the motion capture system and included peak swing-foot velocities as well as anteroposterior and mediolateral error distances of step placement (error measures were normalized to the distance between each subject's starting swing foot position and its target). Data from the motion capture system were recorded at 100 Hz and then exported to MATLAB for processing. The peak velocity of a subject's swing foot was determined from the derivative of the toe marker's anterior-posterior displacement during the swing phase of the step (i.e., between foot-lift and the moment when the toe subsequently reached the ground). Anteroposterior errors were calculated as the distance between the step target marker location and the toe marker's location at the end of the step along the anteroposterior axis. Similarly,

mediolateral step errors were calculated using the same approach along the mediolateral axis. All of the outcome variables, unless noted otherwise, were averaged across left- and right-step trials by the predictable and unpredictable condition for each subject.

Statistical analysis

Given the mixed-factorial design of this study, the main effects of unpredictability and PD, as well as group-by-condition interactions were tested using generalized linear mixed models. Group was specified as a between-subjects factor, and condition (predictable or unpredictable), as well as the cluster (sensory or motor; so named based on the areas of cortex underlying the electrodes of the clusters (Koessler et al. 2009)), were specified as repeated-measures factors, with the subject identified as a random effect. The model assumed a normal distribution, identity link, and diagonal covariance matrix structure. This choice of the model structure was based on the Akaike-corrected information criterion. These analyses were undertaken for two time bins: a) from -1000 to -500 ms before the step cue (1^{st} time bin) and b) from -500 to 0 ms before the step cue (2^{nd} time bin). Spearman's rho correlation coefficients were used to verify the relevance of cortical findings to the behavioral and clinical measures of impairment; i.e., we sought to determine correlations of beta ERD amplitude to measures of step initiation that were found to be significantly affected by PD or to the clinical measures assessed by the questionnaires and the MDS-UPDRS exam. Original, not transformed, data are reported. Statistical analysis was performed in SPSS Statistics for Windows, version 23.0 (IBM corp., Armonk, NY). Statistical significance was set at 0.05; when post-hoc pairwise comparisons were warranted, significance was evaluated using the Least Significant Difference (LSD) method.

2.4 Results

Groups were not significantly different in body mass index, height, age, gender or dominant leg (Table 1). The final group with PD was comprised of subjects with Hoehn and Yahr stage $1.5\ (n = 3)$, $2\ (n = 4)$, $3\ (n = 3)$.

Table 1. Group Demographics. Mean (95% CI)

	Group with PD	Control Group	Significance
Height (cm)	170.5 ± 5.6	169.1 ± 4.7	$t(20) = 0.39, p = 0.7^{\dagger}$
Body Mass Index	25.2 ± 2.6	24.6 ± 2.5	$t(20) = 0.37, p = 0.72^{\dagger}$
Age (yrs)	67.6 ± 5.3	65.8 ± 4.8	$t(20) = 0.52, p = 0.61^{\dagger}$
Sex	$6 - M, 4 - F$	$7 - M, 5 - F$	$p = 1.0^{\ddagger}$
Dominant Leg	$3 - L, 7 - R$	$5 - L, 7 - R$	$p = 0.68^{\ddagger}$
PASE score	173.7 ± 58.3	193.4 ± 54.4	$t(20) = -0.52, p = 0.6^{\dagger}$

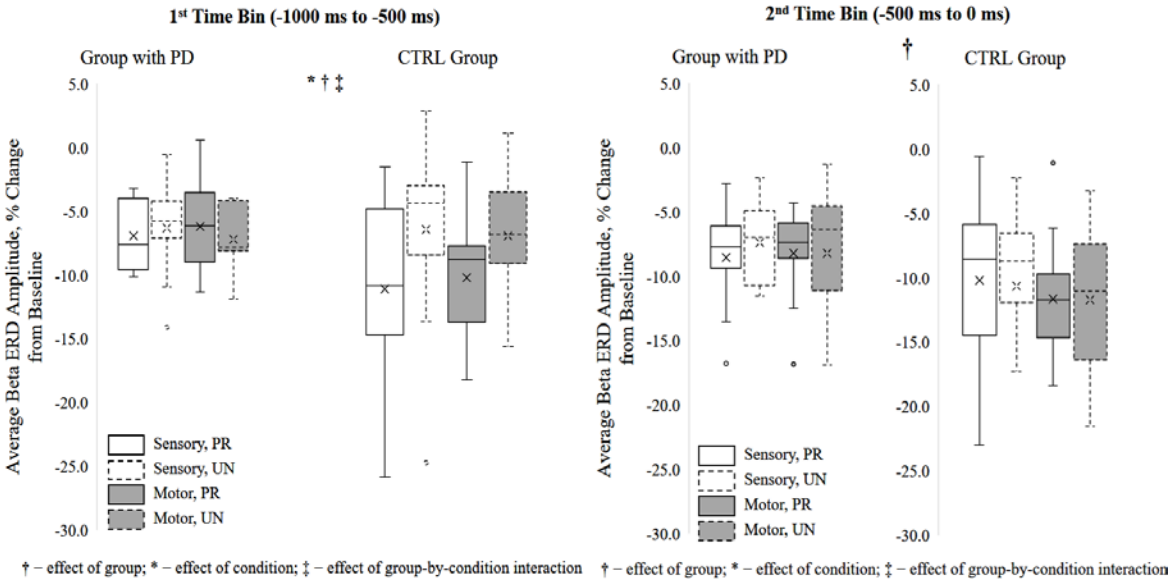

Figure 3: Measures of beta event-related desynchronization (ERD) derived from sensory and motor clusters. Left: Mean beta ERD amplitudes derived from the sensory cluster (consisting of CP1, CPz, CP2, P3, Pz, P4 electrodes) and motor cluster (consisting of FC1, FCz, FC2, C1, Cz, C2 electrodes) during the first time bin (-1000 ms to -500 ms before the step cue). Right: Mean beta ERD amplitudes derived from the same clusters during the second time bin (-500 ms to 0 ms before the step cue). Empty boxes represent the data from the group with Parkinson's disease, filled boxes represent the data from the control group. Solid lines represent the predictable (PR) condition and dotted lines represent the unpredictable (UN) condition. Larger beta ERD amplitudes are more negative. "X" represents the mean and the line within the box represents the median.

Cortical preparation

Figure 3 illustrates the results of the cluster analysis of beta ERD amplitudes during the 1st and 2nd time bins (panels A and B respectively). For the 1st time bin (from -1000 to -500 ms before the step cue), the group with PD had a significantly decreased beta ERD amplitude compared to the control group ($F(1,83) = 9.2, p = 0.003$). In addition, unpredictability decreased beta ERD amplitudes ($F(1,40) = 7.8, p = 0.006$). Interestingly, both motor and sensory clusters were not significantly different ($F(1,83) = 0.02, p = 0.9$). Finally, there was a significant group-by-condition interaction ($F(1,83) = 8.7, p = 0.004$). Further, post-hoc contrasts identified that the control group's beta ERD amplitudes of the sensory and motor clusters were diminished (less negative) in the unpredictable compared to the predictable condition (sensory cluster: $-4.5 \pm 2.2\%$ ($t(11) = -4.4,\ p = 0.001$; motor cluster: $-3.2 \pm 2.5\%$ ($t(11) = -2.8,\ p = 0.018$). Contrary to the cortical behavior of the control group, the group with PD exhibited similar beta ERD amplitudes across conditions within both clusters (sensory cluster: $-0.62 \pm 2.94, t(9) = -0.48, p = 0.65$; motor cluster: $-0.99 \pm 3.57, t(9) = 0.63, p = 0.55$).

During the second time bin (from -500 to 0 ms before the step cue), mean beta ERD amplitudes were significantly decreased (less negative) in the group with PD compared to the control group ($F(1,83) = 44.5, p < 0.001$). Otherwise, there were no significant main effects of the cluster ($F(1,83) = 1.1, p = 0.31$) or condition ($F(1,83) = 0.004, p = 0.95$), nor a significant group-by-condition interaction ($F(1,83) = 0.09, p = 0.76$).

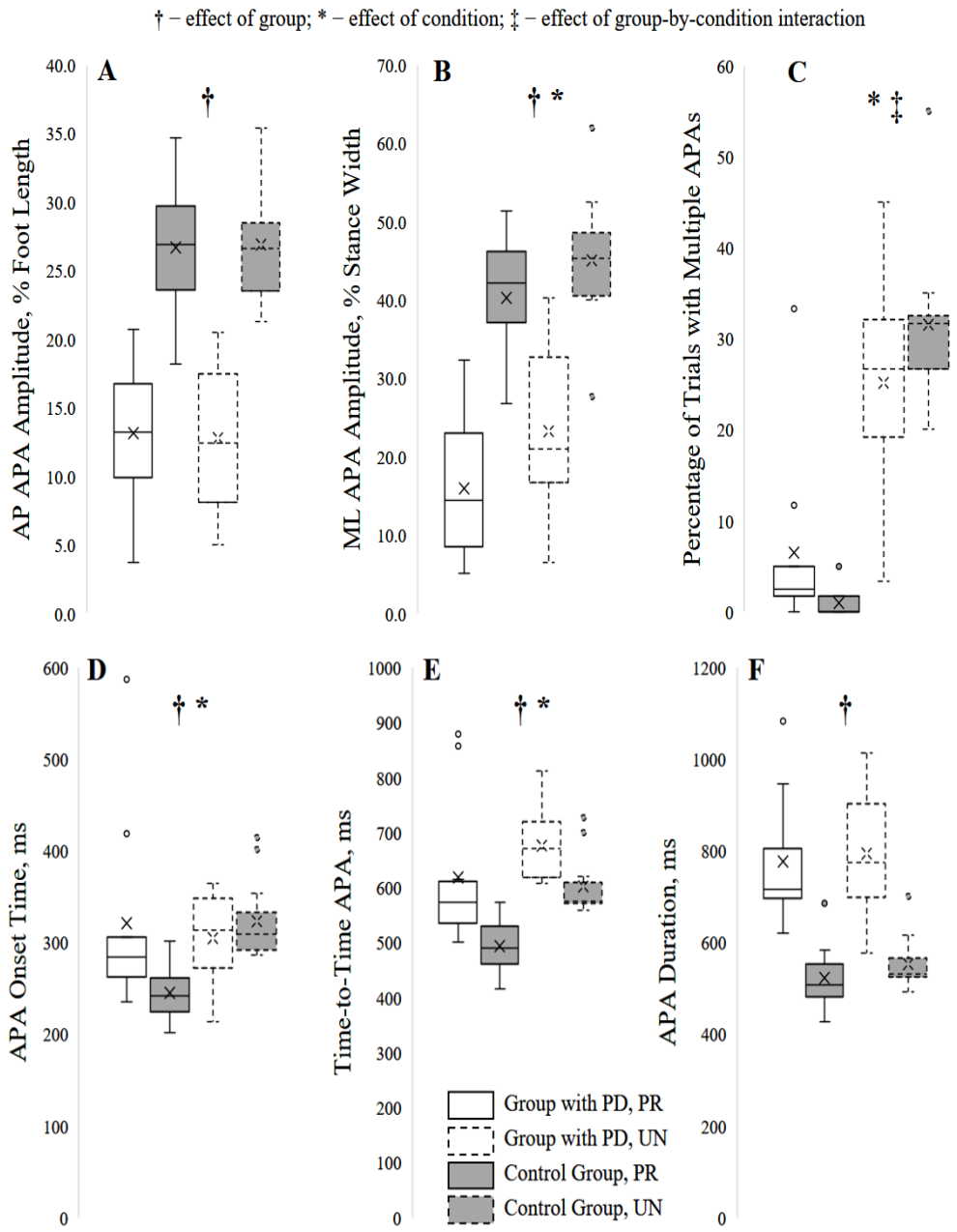

Figure 4. Measures of step preparation. A, B: Anteroposterior (AP) and mediolateral (ML) amplitudes of anticipatory postural adjustment (APA) normalized to the foot length and the stance width, respectively; C: The incidence of trials with multiple APAs; D: APA onset time; E: Time-to-peak APA; F: APA duration. Empty boxes represent the data from the group with Parkinson's disease, filled boxes represent the data from the control group. Solid lines represent the predictable (PR) condition and dotted lines represent the unpredictable (UN) condition. Larger beta ERD amplitudes are more negative. "X" represents the mean and the line within the box represents the median.

Step preparation

Anteroposterior APA amplitudes (Figure 4, A) were significantly diminished in the group with PD compared to the control group ($F(1,36) = 496.8, p < 0.001$). There were no significant effects of condition ($F(1,36) = 0.004, p = 0.95$) nor a significant group-by-condition interaction ($F(1,36) = 0.29, p = 0.6$). Further, mediolateral APA amplitudes (Figure 4, B) were diminished in the group with PD compared to the control group ($F(1,36) = 523, p < 0.001$). During the unpredictable trials, mediolateral APA amplitudes were increased compared to the predictable trials ($F(1,36) = 30.5, p < 0.001$). There was no significant group-by-condition interaction ($F(1,36) = 1.4, p = 0.242$).

The number of trials with multiple APAs (Figure 4, C) significantly increased in the unpredictable compared to the predictable condition ($F(1,38) = 87.6, p < 0.001$). Interestingly, subjects with PD exhibited a significantly lesser increase in the number of trials with multiple APAs from the predictable to the unpredictable condition than subjects in the control group (significant group-by-condition interaction, $F(1,38) = 5.1, p = 0.03$). Post-hoc contrasts showed significant between-group differences in both conditions: in the predictable condition the group with PD had $5.6\% \pm 5.8\%$ higher incidence of multiple-APA trials ($t(38) = 4523.4, p < 0.001$), and in the unpredictable condition, the group with PD had $6.3\% \pm 1.6\%$ lower incidence of trials with multiple APAs ($t(38) = -2.36, p = 0.023$).

Subjects with PD exhibited APA onset times that were significantly delayed (Figure 4, D) compared to the control group ($F(1,38) = 5.3, p = 0.027$). Similarly, unpredictability significantly delayed the APA onset time compared to the predictable

condition ($F(1,38) = 7.6, p = 0.009$). There was no significant group-by-condition interaction ($F(1,36) = 2.1, p = 0.15$).

Time-to-peak APA amplitude (Figure 4, E) was significantly delayed in the group with PD compared to the control group ($F(1,38) = 16.3, p < 0.001$), as well as in the unpredictable compared to the predictable condition ($F(1,38) = 15.9, p < 0.001$). There was no significant group-by-condition interaction ($F(1,38) = 1.4, p = 0.24$). Subjects with PD exhibited significantly longer APA durations (Figure 4, F) compared to the control group ($F(1,38) = 95.9, p < 0.001$), but unpredictability had no significant effect on the APA duration ($F(1,38) = 1.9, p = 0.18$). There was no significant group-by-condition interaction ($F(1,36) = 0.14, p = 0.71$).

Step execution

Subjects with PD lifted the swing foot off the ground significantly later compared to the control group ($F(1,38) = 47.0, p < 0.001$), and foot-lift onset times were delayed in

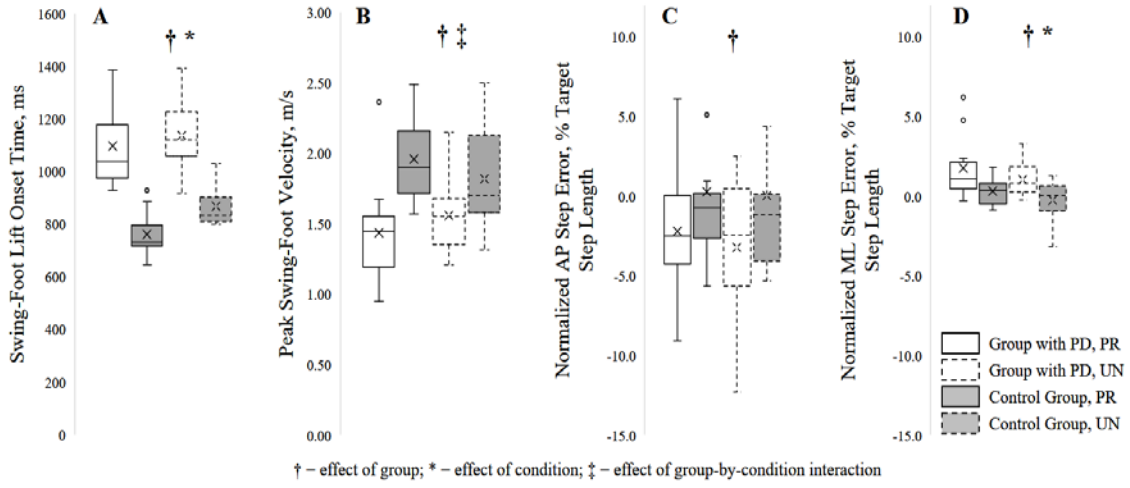

Figure 5. Measures of step execution. A: Foot-lift onset time; B: Peak foot-swing velocity; C: Anteroposterior (AP) step error; D: Mediolateral (ML) step error. Empty boxes represent the data from the group with Parkinson's disease, filled boxes represent the data from the control group. Solid lines represent the predictable (PR) condition and dotted lines represent the unpredictable (UN) condition. Larger beta ERD amplitudes are more negative. "X" represents the mean and the line within the box represents the median.

the unpredictable compared to the predictable condition ($F(1,38) = 8.1, p = 0.013$) (Figure 5, A). There was no significant group-by-condition interaction ($F(1,36) = 1.7, p = 0.197$). Subjects with PD exhibited significantly slower peak foot-swing velocity (Figure 5, B) compared to the control group ($F(1,40) = 8.7, p = 0.005$). Interestingly, while the control group, as expected, exhibited decreased peak foot-swing velocity in the unpredictable compared to the predictable condition, subjects with PD showed a reverse trend by increasing their peak foot-swing velocity in the unpredictable compared to the predictable conditions (significant group-by-condition interaction: $F(1,40) = 6.2, p = 0.017$). Post-hoc contrasts identified that the group with PD had 0.36 ± 0.16 m/s lower peak foot-swing velocity ($t(40) = -4.5, p < 0.001$) in the predictable condition, with no statistically significant difference between groups in the unpredictable condition ($t(40) = -1.2, p = 0.23$). Normalized anteroposterior step errors (Figure 5, C) were more negative in the group with PD (i.e., subjects with PD exhibited steps that failed to reach the step target) than in the control group ($F(1,40) = 19.5, p < 0.001$), but there was no significant main effect of condition or group-by-condition interaction (condition: $F(1,40) = 0.75, p = 0.39$; group-by-condition interaction: $F(1,40) = 0.32, p = 0.58$). Further, normalized mediolateral step errors (Figure 5, D) were significantly more positive (i.e., had overall rightward bias) in the group with PD compared to the control group ($F(1,40) = 12.1, p = 0.001$). In addition, in the unpredictable compared to the predictable condition, normalized lateral step errors significantly decreased ($F(1,40) = 8.9, p = 0.005$). There was no significant group-by-condition interaction ($F(1,40) = 0.05, p = 0.82$).

Correlation analyses

Non-parametric correlation analyses using two-tailed Spearman's ρ were employed to assess the relationship between clinical symptoms and disability scores with the measures of cortical preparation and step initiation. For this analysis, we have used outcome measures obtained from the group with PD and averaged between conditions

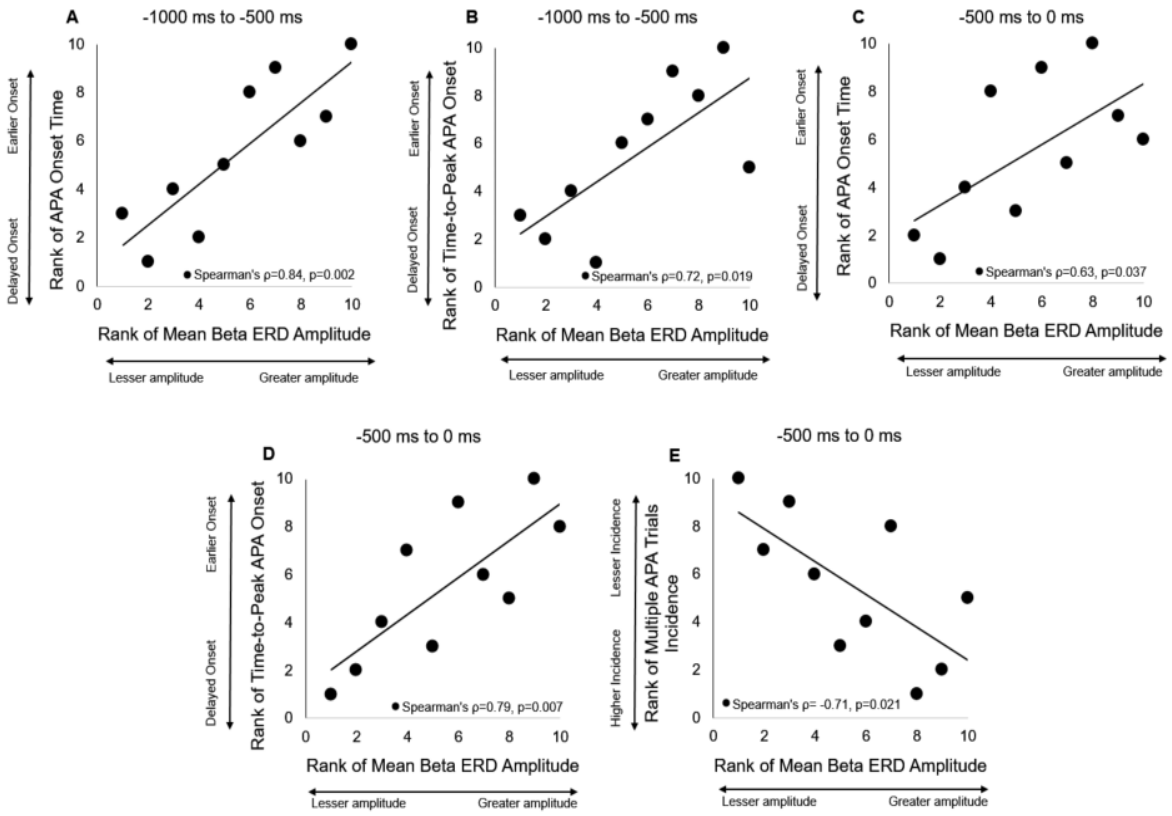

Figure 6. Correlation analysis using mean beta ERD amplitudes of the group with PD. All correlations were performed on beta ERD amplitudes averaged across conditions and clusters, as these factors were not significantly different in the group with PD. These mean beta ERD amplitudes were correlated with behavioral outcome variables, which were found significantly different from the control group and clinical questionnaires. Spearman's ρ coefficients and ranks of values are reported (maximum positive values received a rank of 1). Time bin used in each significant correlation is reported above each panel.

and clusters due to the lack of between-condition and between-cluster differences. Outcome measures that were significantly different between groups were used in these analyses and included (a) mean beta ERD amplitudes, (b) peak and time-to-peak APA amplitude, APA onset time and duration, and (c) foot-lift onset times, peak foot-swing velocity, and step errors. Because the non-parametric correlation analysis is based on rank rather than the actual value, ranks of outcome measure values are displayed in the figures, with a higher rank (i.e., rank = 1) representing the largest, positive value.

Mean beta ERD amplitudes exhibited by the group with PD significantly correlated with temporal parameters of step preparation (Figure 6). Specifically, greater (more negative) mean beta ERD amplitudes during the first time bin (from -1000 ms to -500 ms before the step cue) correlated with earlier onset times and time-to-peak APA amplitude (APA onset: $\rho = 0.84, p = 0.002$; time-to-peak APA: $\rho = 0.72, p = 0.019$; Figure 6, A and B, respectively). Further, greater (more negative) mean beta ERD amplitudes during the second time bin (from -500 ms to 0 ms before the step cue) correlated with earlier onset times and times-to-peak APA amplitudes (Figure 10, C; $\rho = 0.63, p = 0.037$; time-to-peak APA: $\rho = 0.79, p = 0.007$; Figure 6, C and D, respectively). Interestingly, greater (more negative) mean beta ERD amplitudes during the second time bin correlated with greater incidence of trials with multiple APAs ($\rho = -0.71, p = 0.021$; Figure 6, E). There were no significant correlations of the cortical measures to the clinical measures.

2.5 Discussion

We hypothesized that subjects with PD would exhibit less cortical modulation between conditions of forward step initiation with and without prior knowledge of limb

choice. Further, we hypothesized that decreased cortical modulation in PD would associate with a higher impairment of motor performance. Supporting our hypothesis, subjects with PD exhibited beta ERD amplitudes that were similar between conditions and were diminished compared to those generated by the control group and diminished beta ERD amplitudes correlated with delayed postural preparation. These observations are similar to previous studies that reported reduced or delayed beta ERD in subjects with PD prior to other voluntary upper-limb movement tasks (Engel & Fries, 2010; Heinrichs-Graham, et al., 2013; Labyt, et al., 2005; Nelson, et al., 2017). What could be the source of such a "ceiling" effect? A recent review of the dopaminergic effects on beta oscillations and motor function in PD (Jenkinson & Brown, 2011) had conjectured that out of two modes of dopamine release (i.e., tonic and phasic), the tonic suffered most. As a result, lowered tonic extracellular dopamine levels and associated higher power of beta oscillations result in a lower likelihood of the anticipation and preparation for a change of motor states. When the time for the movement comes, it takes longer to accumulate enough dopamine for a phasic release and it crosses a threshold to a point lower than in healthy individuals. This delayed accumulation to threshold results in hypometric movements that are initiated slower than in control subjects. Moveover, Jenkinson and Brown (2011) state that relative lengthening of reaction times should be most prominent when subjects with PD should benefit from prospective information, i.e. warning cues and known length of the interstimulus interval (Berardelli, Rothwell, Thompson, & Hallett, 2001; Jurkowski, Stepp, & Hackley, 2005). Similar to their prediction, our study shows an unexpectedly higher incidence of trials with multiple APAs when conditions were predictable. In addition, unpredictability seemed to have decreased postural

preparation and step execution for the PD group less than it did for the control group. We argue that these slightly unexpected findings could support the model proposed by Jenkinson and Brown (2011). To summarize, our data highlight that persons with PD have limited cortical resources available for motor preparation, and this limitation affects their ability to perform even simple movements; when environmental conditions necessitate a more rapid response, persons with PD fail to modulate their cortical responses (as they already function at full capacity) and as a result exhibit worsened movement behavior.

The analysis of electrode clusters overlying sensory cortex identified that the beta ERD amplitudes of the sensory cluster in the group with PD were unchanged between conditions and diminished (less negative) compared to the control group in the predictable condition. The control group's cortical modulation between conditions might reflect the nature of the choice-reaction task: the unpredictable trials inhibited the ability to pre-select the stepping limb, which potentially delayed the onset of sensorimotor processing until complete information about the stepping task was released, as was observed in a study of healthy subjects presented with tasks that had differential amount of information about the task withheld until the step cue onset (Tzagarakis, Ince, Leuthold, & Pellizzer, 2010). As for the lack of modulation of beta ERD in the sensory cluster of the group with PD, it might reflect central impairment of sensory integration reported earlier in a number of studies (Contreras-Vidal & Gold, 2004; Demirci, Grill, McShane, & Hallett, 1997; Lyoo, Ryu, Lee, & Lee, 2012). Interestingly, these studies point out that abnormal central integration of sensory information in PD is associated with hypometria (abnormally short movements), which was observed in our study via

diminished APA amplitudes and step lengths that failed to reach the stepping target. Although the diminished beta ERD and hypometric step initiation were concomitantly evident in the group with PD, the correlation analysis revealed a tighter relationship between the diminished ERD amplitudes and delays in postural preparation, suggesting that desynchronized beta activity as part of cortical pre-movement processing may additionally facilitate faster motor response times. Such a speculation on a correlation analysis, however, will require further study to clarify the causative role of beta ERD to postural preparation during step initiation in people with PD.

Mentioned earlier, subjects with PD exhibited a smaller increase in trials with multiple APAs in the unpredictable condition than the control group, which was partly explained by the subjects with PD exhibiting a higher initial incidence of trials with multiple APAs in the predictable condition. This high rate of multiple APAs in the predictable condition is unusual given that limb selection errors should be minimized by prior knowledge of the stepping limb. The concomitantly high number of multiple APAs in the predictable condition with a diminished early beta ERD processing over sensory cortex in the predictable condition suggests that impaired early-phase beta desynchronization over sensory cortex may represent a neurophysiologic mechanism that contributes to multiple APAs, which has been linked to freezing during step initiation (Jacobs, Nutt, et al., 2009). Further, the correlational analysis showed that greater beta ERD amplitudes were associated with the higher incidence of trials with multiple APAs in the group with PD (Figure 6, E). These paradoxical errors in postural preparation when information about the stepping behavior is fully known, in addition to the correlation to early-phase processing over sensory cortex, seem to suggest that the source of errors may

be an inability to accurately integrate the appropriate APA to the intended step due to impaired sensory processing. However, this interpretation represents a combined speculation of two correlative observations and must be tested further.

Delayed APAs with diminished amplitudes, delayed foot-lift onset times and decreased peak foot-swing velocities were observed in the group with PD performing the predictable task, as was hypothesized at the beginning of the study. However, when performing unpredictable trials, subjects with PD exhibited increased peak foot-swing velocity in opposition to the decreased velocity evident in the control group. This seemingly worsened behavior during the predictable condition could be attributed to an order effect because all of the subjects performed all 60 predictable trials first, and then 60 unpredictable trials. It is also known that subjects with PD demonstrate improved motor performance with repetition (Fisher, et al., 2008; Mille, et al., 2009; Stebbings, Brown-Toms, & Goetz, 1994). Therefore, it is likely that subjects with PD improved their peak foot-swing velocity as well as decreased mediolateral step errors due to accommodation to the stepping task throughout the course of the experiment. The fixed order was originally chosen because people with PD exhibit an impaired ability to rapidly switch central set between conditions (R. Brown & Marsden, 1988; Richards, et al., 1993; Robertson & Flowers, 1990; Smith, et al., 2012), and we sought to ensure the protocol would be sensitive to differences in predictability without being confounded by switching of central set between trials. Although trading the order effect to control for confounding sources of impairment, this potential order effect represents a limitation to this study that will require further study to disentangle it from central-set mediated impairment.

The following methodological considerations must be addressed. First, our study evaluated individuals with relatively mild PD in an “off” medication state that may limit generalizability to the broader population with PD and to the medicated state. Second, although we’ve indicated the rationale for our order of conditions within the experiment, an order effect may exist and may have differentially affected the groups with and without PD. Third, our task protocol required visual and attentional re-orientation between the computer screen and its displayed cues to a marked target on the floor at a non-preferred step location. Although we contend that such a situation likely parallels a scenario in which a sudden, unpredictable environmental event occurs, results are likely affected by these conditions in a manner that increases sensitivity to differences due to PD. Nevertheless, this study demonstrates that diminished early pre-movement processing over sensory cortex was concomitant with poor pre-selection of the stepping limb in predictable conditions and that a generally diminished amplitude of cortical pre-movement processing relates to delayed step initiation in people with PD. This study, therefore, offers new mechanistic insights into impaired step initiation, which is known to represent a clinically significant function to mobility and disability in people with PD.

Conflict of interests: The authors declare that they have no conflict of interest.

2.6 Acknowledgements

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CHAPTER 3: EFFECTS OF AGE ON NEURAL PREPARATION AND STEP INITIATION IN UNPREDICTABLE CONDITIONS

3.1 Abstract

Impaired mobility accompanies healthy aging, but there is a need for deeper understanding of how aging changes central control of motor behavior. Initiating a new movement is preceded by cortical preparation and can be assessed by beta event-related desynchronization (ERD) derived from electroencephalography (EEG). We compared cortical preparation and resulting step initiation in young (21-29 years old) and older (56-80 years old) healthy subjects performing forward steps either being informed of the limb choice before the trial (predictable trials) or learning which limb to step with concurrently with seeing the step cue (unpredictable trials). We used EEG, kinematic, and kinetic recordings to analyze subjects' step preparation and execution. Our results show that older subjects exhibited increased beta ERD amplitudes before the step regardless of whether they were informed of limb choice or not. Moreover, older subjects exhibited early increases in beta ERD in the "sensory" cluster of electrodes, but only when full limb-choice information was available. Behaviorally, the older subjects also exhibited shortened and increased anticipatory postural adjustments which led to earlier step initiation and similar swing-foot velocities but was also accompanied by greater target step placement errors and decreased postural stability. For the older group, condition-related increases in beta ERD amplitudes and stability correlated with condition-related prolongation of APA durations. We conclude that older subjects exhibited a spectrum across two strategies: (1) a "fast" strategy associated with decreased cortical preparation that trades shortened step preparation and higher swing-foot velocity for target step errors

and lowered postural stability; and (2) an “accurate” strategy associated with greater cortical preparation, longer step-preparation time, and higher stability during step execution.

Keywords: Aging, Cortex, Step Initiation, Beta ERD, Choice Reaction Time

3.2 Introduction

Aging associates with an increased incidence of falls and fall-related mortality (Alamgir et al. 2012). Transitions between motor states (e.g., step initiation) increase the risk of falling due to the complex coordination required of the central motor and musculoskeletal systems (Topper et al. 1993), which often degrade with age (Polcyn et al. 1998). To prevent falls in older adults, a deeper understanding of age-related changes in the neural control of transition movements is necessary. To date, most of the studies on the effects of age on mobility and postural stability involve self-initiated movements (Azizah Mbourou et al. 2002; Couillandre et al. 2000; Maki 1997) or simple-reaction-time tasks (Brunt et al. 2005; Halliday et al. 1998; Hass et al. 2008; Henriksson and Hirschfeld 2005; Rogers et al. 2003b; Varghese et al. 2016). Because the everyday environment necessitates rapid and dynamic adaptation of movement parameters, we sought to determine the changes in cortical preparation and step initiation of older adults when movement parameters were unpredictable.

Step initiation is an important component of healthy mobility (Topper et al. 1993). To mitigate instability and facilitate forward movement during step initiation, anticipatory postural adjustments (APAs) are generated, such that the center of gravity (CoG) is shifted forward and laterally towards the stance limb prior to foot-lift (Dietrich et al. 1994; Elble et al. 1994; Halliday et al. 1998; Maki and McIlroy 1997; Massion 1992; McIlroy and Maki 1999). The effects of age on the APA and step initiation include decreased amplitudes of the momentum-generating anterior-posterior component of the APA, prolonged lateral APAs, multiple erroneous APAs, decreased peak swing-foot velocity, and decreased step length (Chang and Krebs 1999; Cohen, Nutt, & Horak, 2011; Halliday et al. 1998; Khanmohammadi, Talebian, Hadian, Olyaei, & Bagheri, 2017;

Rogers, Kukulka, Brunt, Cain, & Hanke, 2001; Sparto, et al., 2015). The neural mechanisms of step preparation that contribute to these age-related changes in the APA and step initiation, however, remain uncertain.

Both APA-related and step-related movements are thought to be generated by partially separate but parallel, integrated circuits that include the primary motor cortex, the supplementary motor area, the basal ganglia, and postural centers of the brainstem (Jacobs et al. 2009; MacKinnon et al. 2007; Massion 1992; Schepens et al. 2008; Yakovenko and Drew 2009). Several neurodegenerative processes associated with normal aging affect this circuitry (de Laat et al. 2012; Rosano et al. 2010; Rosano et al. 2012; Ryberg et al. 2011; Sparto et al. 2008), suggesting that mechanisms of central impairment likely contribute to age-related changes in step initiation. During simple limb movements, older subjects express higher activation levels of some central nervous areas and additional recruitment of other areas that were not active in control subjects (Heuninckx et al. 2008; Mattay et al. 2002; Vallesi et al. 2011; Ward and Frackowiak 2003). These changes in neural activation are thought to be compensatory to negate the neurodegenerative effects of age on the generation of volitional movements. However, these changes in central neural control remain to be observed in more complex tasks, such as step initiation, and in the unpredictable environments that better represent the daily challenges of older subjects.

Human anticipation and motor preparation during step initiation have been noninvasively assessed by electroencephalography (EEG) via the measure of beta event-related desynchronization (ERD) (Varghese et al. 2016). Beta ERD is a band-specific (12.5-30 Hz) change in power associated with an event such as movement (Pfurtscheller

and Da Silva 1999). Topologically, beta ERD is localized at mesial central electrodes overlying the supplementary motor area (SMA) and thought to represent changes in synchronization of corticostriatal circuits involving the motor regions of cortex (Fogelson et al. 2006; Jenkinson and Brown 2011; Klostermann et al. 2007; Wheaton et al. 2008). During upper-limb movements, aging associates with increased and more widespread beta ERD (Sailer, Dichgans, & Gerloff, 2000). The increased beta ERD amplitudes observed in older subjects is consistent with a compensation hypothesis and may reflect higher cognitive effort or neural recruitment in response to neurodegeneration of motor circuits or, perhaps, to impaired sensory feedback and integration processes (Labyt, et al., 2003; Toledo, et al., 2016). Therefore, beta ERD is an informative tool for studying human anticipation and motor preparation during step initiation that is sensitive to age-related changes during other motor tasks.

The purpose of this study was to investigate how age affects cortical preparatory activity before initiating a step in predictable and unpredictable conditions regarding the choice of stepping limb. Reflecting the literature reviewed above, we hypothesized that older subjects would exhibit increased cortical preparation, but also decreased and prolonged postural preparation as well as delayed and less stable step execution. Further, we hypothesized that unpredictability would decrease cortical preparation and further impair step initiation. To the best of our knowledge, there are no published works that explore step initiation in unpredictable conditions using beta ERD.

3.3. Methods

A total of 24 subjects, 12 healthy young (the control group) and 12 healthy older adults (the older group), participated in the study. Groups were not significantly different in body mass index, gender or dominant leg, but did significantly differ in height (Table 1). Inclusion criteria for both groups included the absence of neurological or musculoskeletal disorders and no use of medications known to alter motor or musculoskeletal function. The protocol was approved by the Institutional Review Board, and all of the subjects provided written informed consent before the experiment.

Procedures

The subjects completed a demographics and health history questionnaire, as well as the Physical Activity Scale for the Elderly - PASE (Washburn et al. 1993). Subjects were then prepared for EEG and kinematic recordings. Subjects wore an Advanced Neuro Technology (ANT; Enschede, the Netherlands) Waveguard 128-electrode EEG cap (sintered silver / silver-chloride electrodes; standard 10/5 system placement (Oostenveld and Praamstra 2001)). Each electrode was filled with a conductive gel (Electro-gel; Electro-Cap International; Eaton, OH, USA) to obtain impedances below 10 kΩ. Passive reflective markers were then placed bilaterally with two-sided tape on the following landmarks in order to record the subjects' motion during testing with a 9-camera motion capture system (Vicon, Denver, CO, USA): the tuberosity of the fifth metatarsal, distal phalange of the first toe, calcaneus, lateral malleolus, lateral femoral condyle, greater trochanter, acromion, lateral humeral epicondyle, ulnar styloid process,

as well as the lateral supraorbital process, the preauricular notch, and on the force platforms of the support surface.

During experimental trials, the subjects were attached to an overhead harness that did not provide support during upright stance, but which prevented falls to the ground in order to minimize the risk of injury. Subjects stood on a pair of force plates (AMTI, Watertown, MA, USA) with the feet in a standard stance width of 11% of their body height (McIlroy and Maki 1997). This position was marked with tape to ensure consistent foot placement across trials.

At the beginning of the experiment, subjects performed three trials of self-initiated stepping in order to calculate an average preferred step length. Specifically, the task was to take one step with an identified limb followed by a step of matching length with the trail limb. This preferred step length was then used to calculate the target position of 125% step length, and targets were placed at that distance anterior to the initial starting position of the first toe for use in subsequent trials. The extended step length served to increase requirements on the APA as well as to require non-preferred step placement as might be required of stepping in unpredictable conditions.

During the experiment, subjects performed 4 conditions of 30 trials each: (1) predictable steps with the right foot, (2) predictable steps with the left foot, (3) unpredictable steps with the left foot, and (4) unpredictable steps with the right foot. Unpredictable trials of the left and right foot were pooled together and were presented in random order. For the predictable condition, subjects were instructed to step with the left or right foot prior to the trials, such that they were aware of the chosen stepping limb before each trial. For the unpredictable condition, the subjects were instructed to step

with the foot indicted by the cue to step, such that they were uncertain about which stepping limb to select until the presentation of each trial's step cue. For all conditions, subjects were instructed to stand with their vision focused on a computer screen positioned approximately two meters ahead of them at eye level, to maintain an even weight under both feet (the vertical weight loading on the force plate under each foot was monitored online by the experimenter), to minimize eye blinks prior to stepping for 5-10 seconds, and to relax the muscles of the neck and face. These instructions served to (a) decrease the risk of pre-weighting the stance limb, which negates the need for an APA and alters pre-movement cortical activity (Varghese et al. 2016), and (b) minimize artifacts in the EEG signal. Two large images were presented on the computer screen with an inter-stimulus interval of 2 seconds, which was known to the subjects. The first image was a plus sign (+) and represented a warning cue, to which subjects were instructed not to respond, and the second image contained either the word "LEFT" or "RIGHT". The subjects were instructed to step as quickly and as accurately as possible with the indicated limb to the target located on the same side, and then to take a matching step with the trail limb to bring the feet parallel.

Data Processing

The EEG signals were recorded by an ANT high-density ASA direct-current amplifier system. Data from each electrode were referenced to the mastoids and sampled with a 22-bit resolution at 1024 Hz. Recording and pre-processing were performed in ASA software version 4.7.3 (Advanced Neuro Technology, Enschede, Netherlands). The ASA software's artifact detection/correction feature was used to remove ocular artifacts

by selecting the two components that most represented the artifacts' characteristics. The data were then high-pass filtered at 0.01 Hz using the whole length of the recording. The cue signals provided synchronization with the other systems, and 6-second epochs were spliced for each trial from 3 seconds before the step cue to 3 seconds after the cue. We analyzed, on average, 21 trials out of 30 recorded per each of the four conditions due to artifacts. Artifacts related to unstable electrode-scalp interaction, a lack of established baseline signal prior to trial onset due to direct-current amplifier signal displacements, or electromyographic activity were identified by visual analysis of each trial and confirmed by independent agreement between two of the investigators. In order to increase the number of trials averaged for analysis, the two predictable conditions of left and right steps were pooled, as were the two unpredictable conditions of left and right steps. Beta ERD amplitudes were thus derived from 30-58 trials per subject, per predictable or unpredictable condition; the number of trials available in the unpredictable versus predictable conditions was not significantly different ($t(22) = -0.55, p = 0.59$), neither was the difference between the number of trials available from the control and older groups ($t(23) = 0.63, p = 0.54$). To establish the minimal number of trials necessary for calculating a stable value of beta ERD, we recalculated beta ERD amplitudes using only the first 5, 7, 10, 12, and 15 trials. The t-tests and Spearman's correlations of values from truncated data and all available data demonstrated significant correlations and no significant differences when compared to all available trials. Therefore, the available artifact-free trials appear to provide a consistent and representative assessment of beta ERD amplitudes for comparison across groups and conditions. All further analysis was performed using lab-generated scripts in MATLAB (Mathworks, Natick, MA, USA).

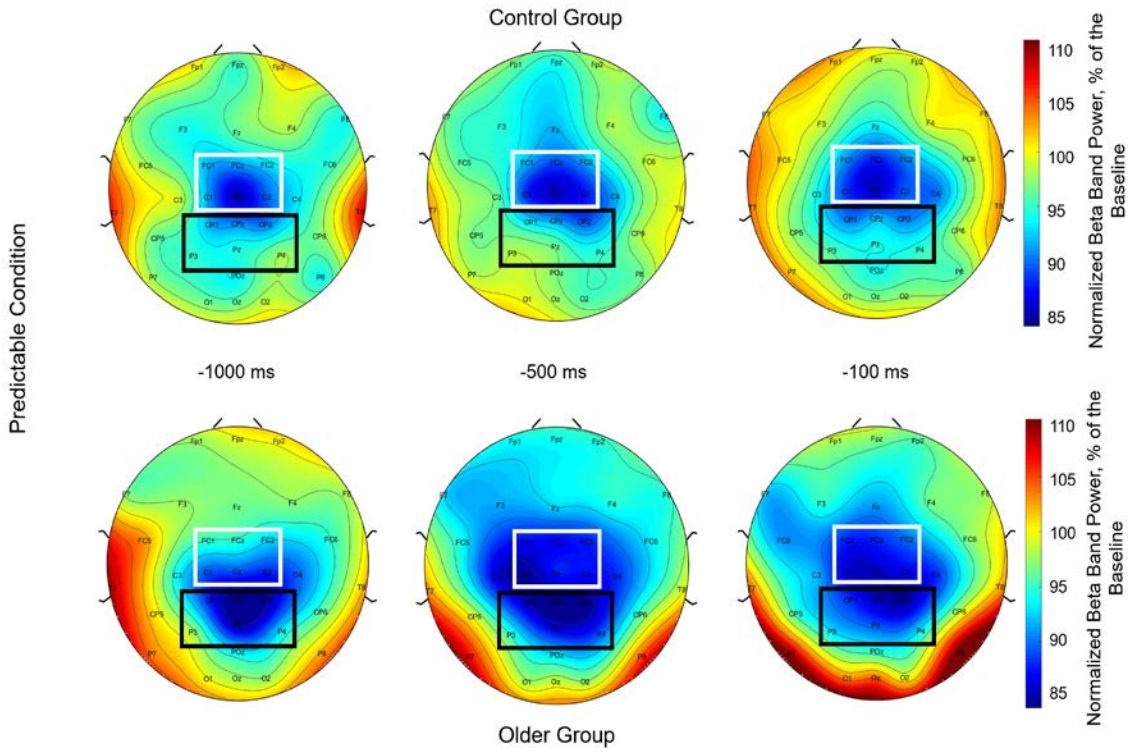

Figure 1. Grand mean upper beta-band (20-29 Hz) event-related desynchronization (ERD), identifying sensory and motor electrode clusters. Black box outlines electrodes chosen for analysis of beta ERD that overlie sensory areas of cortex (i.e., sensory cluster); white box outlines electrodes that overlie motor and pre-motor areas of cortex (i.e., motor cluster). Time points are with respect to the onset time of the step cue. Power displayed was normalized with respect to the 500 ms average before the onset of the warning cue. Data from the predictable condition only. Note the caudal-to-rostral progression of beta ERD in the older group (lower row).

For quantifying upper beta ERD, the EEG signals from each trial were digitally re-referenced to a common average reference that included every cephalic electrode in order to improve the focal spatial pattern of ERD (Pfurtscheller & Da Silva, 1999). Continuous Morlet wavelet transforms were executed within the upper beta frequencies of 20-29 Hz for each trial. The upper beta frequency range was chosen due to more focused sensory-motor localization, unlike lower beta and alpha frequency bands (Fogelson, et al., 2006; Pfurtscheller & Da Silva, 1999). These Morlet coefficients were then rectified, low-pass filtered at 5 Hz, then averaged by condition and participant, and, lastly, averaged across the upper beta frequency band. Data from left- and right-limb

trials were pooled together and averaged to create two final sets of Morlet coefficients, one for the predictable condition and one for the unpredictable condition. After that, the time-varying beta coefficients were normalized to a baseline calculated from 500 ms before the warning cue. Our a priori analysis was to evaluate the effects of group and condition at the electrode of maximal ERD. Upon inspection of the grand averaged topographic plots (Figure 1), however, it became apparent that the beta ERD may exhibit a caudal-to-rostral development for the older adults across the inter-stimulus interval prior to the cue to step. To better illustrate this observation, we have recorded two movies (one per condition) exhibiting grand average topographies for both groups during the last 1000 ms before the step cue (supplementary material). We, therefore, report on an analysis of beta ERD from a cluster consisting of the FC1, FCz, FC2, C1, Cz, C2 electrodes and a cluster consisting of the CP1, CPz, CP2, P3, Pz, P4 electrodes during the time bin from -1000 ms to -500 ms relative to the step cue as well as from -500 ms to 0 ms relative to the step cue. These time bins will be later referred to as the “early” (from -1000 ms to -500 ms before the step cue) and the “late” (from -500 ms to 0 ms before the step cue) time bins. Please note that the planned analysis from a single, maximum-amplitude electrode was still undertaken with similar-between group outcomes as our reported analysis, but such an analysis offered less insight than the cluster analysis.

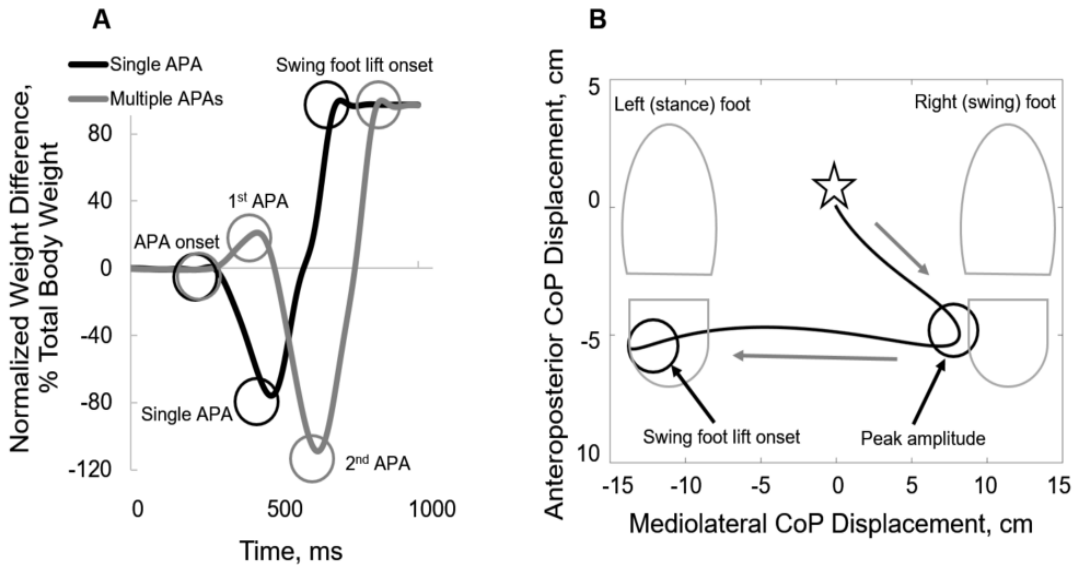

Figure 2. Calculation of the anticipatory postural adjustment (APA) parameters. *A*: Normalized weight difference (two trials from one representative subject) was used to detect the APA onset time and duration as well as the presence of multiple APAs; *B*: Center of pressure (CoP) displacement was used to detect mediolateral (x-axis) and anteroposterior (y-axis) APA amplitudes. Star marks the location of CoP at the beginning of the trial. Data were selected from one representative subject performing right-foot steps in the predictable condition.

To estimate the temporal properties of the APA (i.e., onset time, duration, and time-to-peak amplitude), we calculated the normalized weight distribution between each foot (W_{distr}) using vertical forces recorded from the force plates under the subjects' feet, as previously reported (Jacobs et al. 2009b). Force signals were amplified by 1000 and sampled with 12-bit resolution at 1000 Hz. The force-plate signals were recorded by Nexus software and then exported for processing in MATLAB. The W_{distr} traces were low-pass filtered to 10 Hz and baseline subtracted based on the average of the 100 ms just prior to the step cue. Outcomes included identifying (a) the APA onset time, defined as the time after the step cue when the W_{distr} trace deflected towards a limb, (b) the swing-foot lift onset time, defined as the time when the W_{distr} trace reached ±100% for the stance limb, (c) the APA duration, defined as the time from APA onset to the onset of the foot lift, and (d) whether the trial had one or multiple APAs (the majority of trials with

multiple APAs had only two APAs), which was decided based on observing the oppositely-directed APA (i.e., towards the stance limb) preceding the correct APA (i.e., directed towards the swing limb). The oppositely-directed APA had to be at least 10% of normalized weight to be considered (Figure 2, A).

To disentangle the anteroposterior from mediolateral APA amplitude, each directional component of the whole-body center of pressure (CoP) was calculated from the triaxial forces and moments recorded from the force plates under the subjects' feet (Henry et al. 1998). The CoP signals were low-pass filtered to 10 Hz, baseline subtracted based on the average of the 100 ms before step cue onset, and then the mediolateral and anteroposterior CoP components were normalized to stance width and foot length, respectively. Peak backward and swing-limb-directed lateral displacements were then determined prior to foot lift (Figure 2, B).

Variables of the step phase were derived from the motion capture system and included peak swing-foot velocities as well as step target errors calculated using the Euclidian formula for the distance between two points (error measures were also normalized to the distance between each subject's starting swing foot position and its target). Data from the motion capture system were recorded at 100 Hz and then exported to MATLAB for processing. The peak velocity of a subject's swing foot was determined from the derivative of the toe marker's anterior-posterior displacement during the swing phase of the step (i.e., between foot-lift and the moment when the toe subsequently reached the ground). Step lengths were also determined as the distances between when toe marker of the swing foot was at the beginning of a trial and when its height reached its initial value (i.e., when the swing foot was placed on the ground).

To determine the subjects' lateral stability during step initiation, the lateral time-to-contact (TtC) of the CoG to the base of support (BoS) was calculated according to the method described in (Haddad et al. 2006). In brief, CoG position was first estimated using regression coefficients and equations for Caucasian males and females from (Shan and Bohn 2003). Then, for each sample recorded between the step cue and the foot-lift onset times, each subject's overall CoG virtual trajectory was estimated based on instantaneous position, velocity, and acceleration. This virtual trajectory described the instantaneous CoG path relative to the outlined BoS if neither CoG velocity or acceleration were to change. The TtC was calculated as the time it would take the CoG to traverse the distance from its current position to the lateral boundary of the trapezoid outlined around a subject's feet.

All of the outcome variables, unless noted otherwise, were averaged by the predictable and unpredictable conditions for each subject.

Statistical analysis

Given the mixed-factorial design of this study, the main effects of unpredictability and age, as well as group-by-condition interactions were tested using generalized linear mixed models. Group was specified as a between-subjects factor, whereas condition (predictable or unpredictable) and cluster (sensory or motor; so named based on the areas of cortex underlying the electrodes of the clusters (Koessler et al. 2009)) were specified as repeated-measures factors, with the subject identified as a random effect. This choice of the model structure was based on the Akaike-corrected information criterion (AIC); for most outcome variables this was a normal distribution, identity link, and diagonal

covariance matrix structure with subjects and intercepts as random effects. However, two variables (peak step velocity and step length) had a better fit (i.e., lower AIC) with the AR1 covariance matrix. These analyses were undertaken for each of the early and late time bins. Seeking to understand the effects of unpredictability further, we used Spearman's rho correlation coefficients on between-condition differences in outcome measures to verify the relevance of cortical findings to the behavioral and self-reported measures; i.e., we sought to determine correlations of condition-related changes in beta ERD amplitude to condition-related changes in measures of step initiation that were found to be significantly affected by age as well as with PASE scores. Original, not transformed, data are reported. Statistical analysis was performed in SPSS Statistics for Windows, version 23.0 (IBM corp., Armonk, NY). Statistical significance was set at 0.05; when post-hoc pairwise comparisons were warranted, significance was evaluated using the Least Significant Difference (LSD) method.

Table 2. Group Demographics. Mean (95% CI)

	Control Group	**Older Group**	**Significance**
Height (cm)	177.8 ± 5.5	169.1 ± 4.7	$t(22) = 2.35, p = 0.028^{\dagger}$
Body Mass Index	25.4 ± 2.5	24.6 ± 2.7	$t(22) = 0.45, p = 0.65^{\dagger}$
Age (yrs)	25.2 ± 1.5	65.8 ± 4.0	$t(22) = -18.8, p < 0.001^{\dagger}$
Sex	$7 - M, 5 - F$	$7 - M, 5 - F$	$p = 1.0^{\ddagger}$
Dominant Leg	$4 - L, 8 - R$	$5 - L, 7 - R$	$p = 1.0^{\ddagger}$
PASE score	184.8 ± 44.6	193.5 ± 50.6	$t(22) = -0.25, p = 0.8^{\dagger}$

Values represent means ± 95% confidence intervals or counts. Legend: † - two-tailed independent samples t-test, ‡ - Fisher's exact test, 2-sided, F - female, M - male, L - left leg, R - right leg, PASE – the Physical Activity Scale for the Elderly Questionnaire (Washburn et al. 1993).

3.4. Results

Groups were not significantly different in body mass index, gender or dominant leg (Table 2). Control subjects were significantly taller than older subjects (Table 2).

Cortical preparation

During the early time bin, there was a main effect of condition (Figure 3, A; $F(1,87) = 9.18, p = 0.003$) as well as a group-by-condition interaction (Figure 3, A; $F(1,87) = 4.07, p = 0.047$), that were no longer observed in the late time bin (Figure 3, B; condition: $F(1,87) = 0.6, p = 0.44$); group-by-condition interaction: $F(1,87) = 1.19, p = 0.28$). Post-hoc contrasts showed that the older group exhibited $6.08\% \pm 5.31\%$ larger (more negative) beta ERD amplitudes in the sensory cluster than those produced by the control group $t(21) = 2.38, p = 0.027$); in the unpredictable condition, this group difference in early ERD amplitudes was no longer significant ($t(21) = 0.19, p = 0.85$). Beta ERD amplitudes derived from motor clusters did not differ significantly between groups (predictable: $t(21) = 1.19, p = 0.25$; unpredictable: $t(21) = 0.65, p = 0.52$).

During the late time bin, the older group exhibited significantly larger (more negative) beta ERD amplitudes (Figure 3, B; $F(1,87) = 4.45, p = 0.038$)) than the control group.

Although we observed a caudal-to-rostral development of beta ERD amplitude in the older group within the predictable condition, this development pattern was not any further evident, as there was no main effect of cluster on beta ERD amplitude during the

early (Figure 3, A; $F(1,87) = 0.21, p = 0.65$) or late (Figure 3, B; $F(1,87) = 2.31, p = 0.13$) time bins.

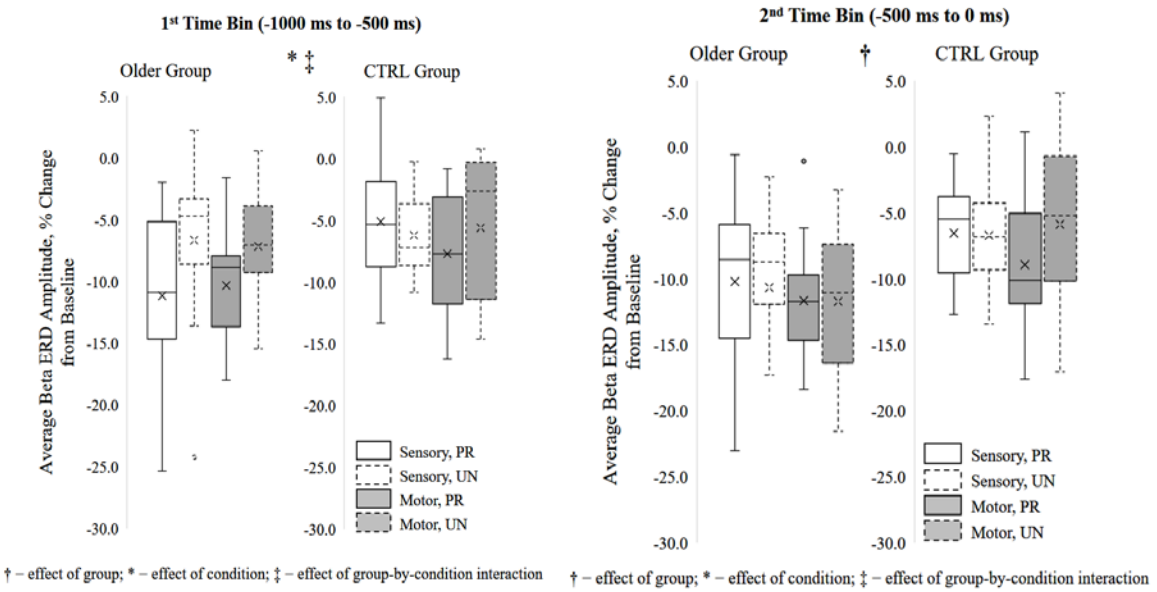

Figure 3: Measures of beta event-related desynchronization (ERD) derived from sensory and motor clusters. Left: Mean beta ERD amplitudes derived from the sensory cluster (consisting of CP1, CPz, CP2, P3, Pz, P4 electrodes) and motor cluster (consisting of FC1, FCz, FC2, C1, Cz, C2 electrodes) during the earlier time bin (-1000 ms to -500 ms before the step cue). Right: Mean beta ERD amplitudes derived from the same clusters during the later time bin (-500 ms to 0 ms before the step cue). Empty boxes represent the data from the older group, filled boxes represent the data from the control group. Solid lines represent the predictable (PR) condition and dotted lines represent the unpredictable (UN) condition. Larger beta ERD amplitudes are more negative. "X" represents the mean and the line within the box represents the median.

Step preparation

Both groups initiated step preparation (Figure 4, A) at similar times (APA onset time, the main effect of group: $F(1,42) = 1.43, p = 0.24$), which was significantly delayed by unpredictability (APA onset time, the main effect of condition: $F(1,42) = 60.56, p < 0.001$) in a similar fashion for both groups (APA onset time, group-by-condition interaction: $F(1,42) = 0.001, p = 0.97$). Similarly to APA onset time, only a significant condition effect was evident for time-to-peak APA amplitude

(Figure 4, B; group: $F(1,42) = 1.43, p = 0.24$; condition: $F(1,42) = 69.17, p < 0.001$; group-by-condition interaction: $F(1,42) = 0.56, p = 0.46$).

The incidence of trials with multiple APAs (Figure 4, C) was similar between groups ($F(1,42) = 1.88, p = 0.24$). Unpredictability, expectedly, increased the incidence of such trials ($F(1,42) = 177.43, p < 0.001$) but in a similar fashion for both groups, as the group-by-condition interaction was not significant ($F(1,42) = 3.36, p = 0.07$).

Unexpectedly, APA durations (Figure 4, D) were shorter in the older group compared to the control group ($F(1,42) = 4.44, p = 0.04$). Analogous to previous temporal outcome measures (APA onset time and time-to-peak APA amplitude), unpredictability prolonged APA durations ($F(1,42) = 6.23, p = 0.02$), and there was no significant group-by-condition interaction ($F(1,42) = 0.12, p = 0.74$).

Normalized peak amplitudes of anteroposterior (AP) and mediolateral (ML) APAs (Figure 4, E and F, respectively) were larger in the older group compared to the control group (AP: $F(1,40) = 4.6, p = 0.04$; ML: $F(1,40) = 10.78, p = 0.002$). Further, unpredictability increased mediolateral, but not anteroposterior, APA amplitudes (AP: $F(1,40) = 0.19, p = 0.64$; ML: $F(1,40) = 14{,}0, p = 0.001$). There were no significant group-by-condition interactions for AP or ML APA amplitudes (AP: $F(1,40) = 1.2, p = 0.28$; ML: $F(1,40) = 0.006, p = 0.94$).

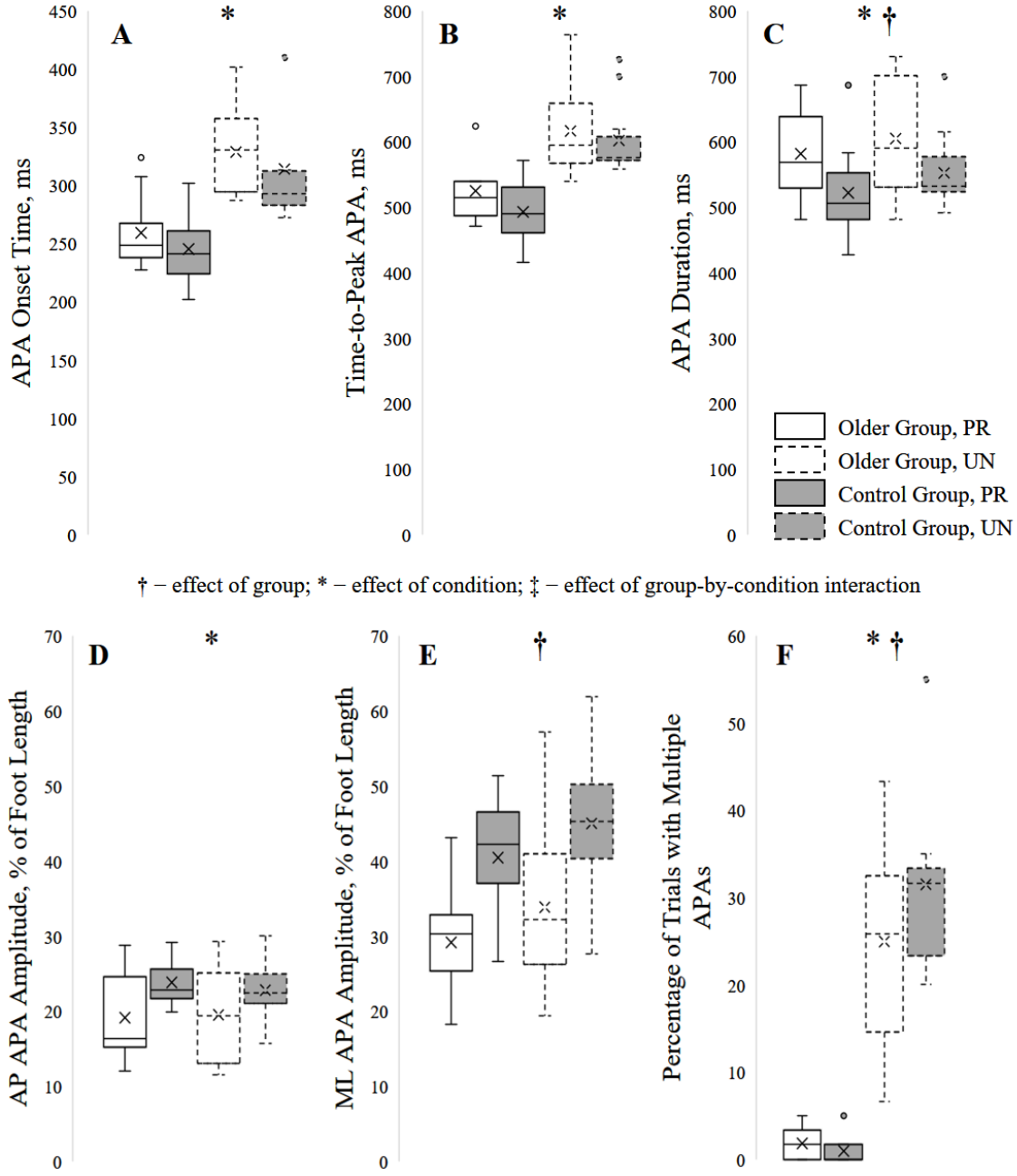

Figure 4. Measures of step preparation. *A*: APA onset time; *B*: Time-to-peak APA; *C*: The incidence of trials with multiple APAs; *D*: APA duration; *E, F*: Anteroposterior (AP) and mediolateral (ML) amplitudes of anticipatory postural adjustment (APA) normalized to the foot length and the stance width, respectively; Empty boxes represent the data from the older group, filled boxes represent the data from the control group. Solid lines represent the predictable (PR) condition and dotted lines represent the unpredictable (UN) condition. Larger beta ERD amplitudes are more negative. "X" represents the mean and the line within the box represents the median.

Step execution

Foot-lift onset times (Figure 5, A) were earlier in the older group compared to the control group ($F(1,42) = 4.90, p = 0.03$). Moreover, foot-lift onset times were delayed by unpredictability ($F(1,42) = 40.89, p < 0.001$). There was no significant group-by-condition interaction on foot-lift onset times ($F(1,42) = 0.17, p = 0.68$).

Peak swing-foot velocities (Figure 5, B) were not significantly different between the control and the older groups ($F(1,44) = 0.49, p = 0.49$). However, peak swing-foot velocities were diminished in the unpredictable compared to the predictable condition ($F(1,44) = 5.91, p = 0.019$). There was no significant group-by-condition interaction in peak swing-foot velocities ($F(1,44) = 2.1, p = 0.16$).

There was a significant main effect of group in step target errors (Figure 5, C; ($F(1,44) = 19.57, p < 0.001$). However, these errors remained similar between conditions ($F(1,44) = 2.08, p = 0.157$) and there was no group-by-condition interaction ($F(1,42) = 0.55, p = 0.463$).

TtC of the CoG to the BoS (Figure 5, D) was significantly shorter in the older group compared to the control group ($F(1,42) = 37.48, p < 001$) but was not different between conditions ($F(1,42) = 1.29, p = 0.262$). There was no significant group-by-condition interaction either ($F(1,42) = 0.77, p = 0.387$).

Self-reported PASE scores were not significantly different between the control and older groups ($t(22) = -0.25, p = 0.8$). The control group scores had a mean ($\pm$ 95% CI) score of 184.8 ± 50.1 compared to 193.5 ± 56.8 for the older group.

Because height was significantly different between groups, we tested whether this affected step lengths and found that height-normalized step lengths (data not shown) were

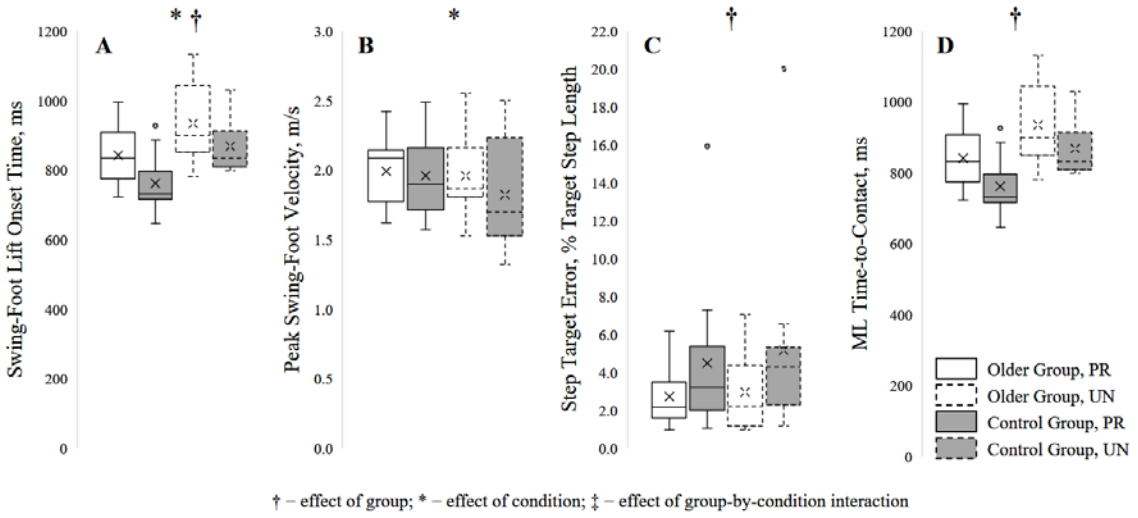

Figure 5. Measures of step execution. *A*: Foot-lift onset time; *B*: Peak swing-foot velocity; *C*: Step target error; *D*: Mediolateral (ML) time-to-contact of the center of gravity to the base of support. Empty boxes represent the data from the older group, filled boxes represent the data from the control group. Solid lines represent the predictable (PR) condition and dotted lines represent the unpredictable (UN) condition. Larger beta ERD amplitudes are more negative. "X" represents the mean and the line within the box represents the median.

not significantly different between groups ($F(1,44) = 0.54, p = 0.47$) or conditions ($F(1,44) = 0.12, p = 0.73$). There was no significant group-by-condition interaction either ($F(1,44) = 0.09, p = 0.77$).

Correlation analysis

In the older group, we found that the increase in the beta ERD amplitude (i.e., amplitude becoming more negative) from the predictable to the unpredictable condition during the earlier time bin correlated with prolonged APA durations (Figure 6, A; Spearman's $\rho = -0.63, p = 0.039$). Further, Prolonged APA durations correlated with increased ML TtC of the CoG to the BoS (i.e., increased postural stability) as shown in Figure 6, B (Spearman's $\rho = 0.61, p = 0.047$). Finally, we observed that higher PASE scores reported by the older group correlated with increased (or less decreased) peak swing-foot velocity between conditions (Figure 6, C; Spearman's $\rho = 0.67, p = 0.017$).

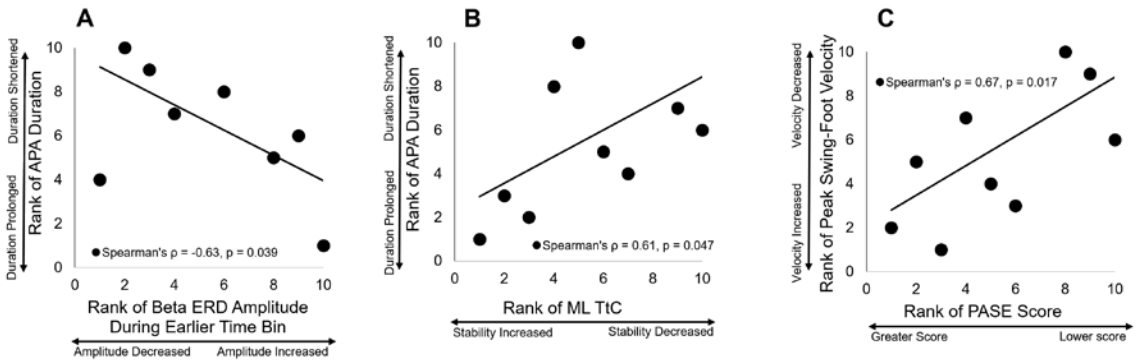

Figure 6. Correlation analysis using between-condition differences in the older group. *A*: Increased (more negative) early beta ERD amplitude correlated with prolonged APA durations; *B:* Prolonged APA durations correlated with increased mediolateral stability; *C:* Higher PASE scores (higher level of daily physical activity) correlated with greater peak swing-foot velocity. All correlations were performed on between-condition differences in outcome variables that were significantly different between groups. Spearman's ρ coefficients and ranks of values are reported (maximum positive values received a rank of 1). Abbreviations: APA – anticipatory postural adjustment, ERD – event-related desynchronization, ML TtC – mediolateral time-to-contact of the center of gravity to the base of support, PASE – the Physical Activity Scale for the Elderly Questionnaire (Washburn et al. 1993).

3.5. Discussion

We hypothesized that due to age-related changes, older subjects would exhibit increased, compensatory cortical preparation as measured by beta ERD amplitudes. We found that, during the early time bin in the predictable condition, older subjects exhibited greater beta ERD amplitude over the sensory region. This difference was lost when the condition became unpredictable. During the late time bin, older subjects had greater beta ERD amplitudes regardless of the cluster. These findings suggest that older subjects attempted to utilize available instructional information from the predictable condition with increased early processing over sensory regions to prepare for step initiation and then exhibited an enhanced level of sensory-motor processing regardless of condition in the late time bin just prior to the cue to step. This finding is consistent with previous reports of increased movement-related neural function in older subjects (Labyt, et al.,

2003; Sailer, et al., 2000; Toledo, et al., 2016) as well as observations of increased recruitment from other central neural regions that are not active in younger adults (Heuninckx et al. 2008; Mattay et al. 2002; Vallesi et al. 2011; Ward and Frackowiak 2003). We provide additional support to the hypothesis that older subjects may compensate for age-related deficits with increased and more wide-spread activation of sensorimotor cortical resources.

We also hypothesized decreased and prolonged postural preparation as well as delayed and less stable step execution in the older group (Halliday, Winter, Frank, Patla, & Prince, 1998; Rogers, Johnson, Martinez, Mille, & Hedman, 2003; Rogers, Kukulka, Brunt, Cain, & Hanke, 2001; Sparto, et al., 2015). Paradoxically, we observed similar APA onset times, time-to-peak APA amplitudes, and a similar increase in the incidence of trials with multiple APAs. To our surprise, older subjects spent less time during the APA phase, reached significantly greater AP and ML APA amplitudes, and initiated foot lift earlier than control subjects. The seemingly enhanced postural preparation in older subjects, however, appeared to result in a less controlled step marked by similar peak foot-swing velocities, increased step target placement errors, and reduced stability relative to the control group.

There are several potential reasons for our observations on postural preparation and step execution that may explain our differential findings from the literature. First, we instructed all subjects to react to the step cue as fast and as accurately as possible, and these competing objectives (among an implicit objective to maintain stability) may have caused older subjects to prioritize either objective. Indeed, older subjects that exhibited increased beta ERD amplitudes between conditions also spent more time during postural

preparation, and those that spent more time during postural preparation produced steps that were more stable. Second, although our inclusion criteria specified a sample of healthy older adults with no health conditions that affect balance and mobility, some sub-clinical impairment of sensory integration is possible (Labyt, et al., 2003; Toledo, et al., 2016), and older subjects may have misjudged the sensory feedback during postural preparation and engaged in a quickened and more forceful postural preparation that resulted in missing targets by larger distances and exposing themselves to a higher risk of losing postural stability. Third, the PASE scores of our subject sample indicate relatively high levels (or at least similar levels to the control group) of physical activity in the older group. Higher PASE scores obtained from older subjects correlated with higher peak-swing velocity, thus suggesting that the sample's physical activity status may have affected our outcomes for this task of step initiation.

We hypothesized that unpredictability would decrease cortical preparation and further impair step preparation and execution. Neural preparation appeared to diminish in the unpredictable condition during the early time bin, but this condition effect was primarily driven by an enhanced cortical preparation in the sensory cluster of the older subjects. Otherwise, neural preparation was generally similar in both conditions. Behaviorally, unpredictability did have a very similar effect on postural and stepping measures in both groups by delaying and prolonging different stages of the APA (onset time and time-to-peak amplitudes), prolonging durations of the APA, increasing the incidence of trials with multiple APAs, and increasing ML APA amplitudes. Further, unpredictability delayed foot-lift onset times and decreased peak swing-foot velocities. These effects are to be expected because the limb-choice information was retained from

the subjects up until the step cue and introduced delays in the central nervous system processing that further manifested as delays and prolongations in postural preparation and step execution. Unpredictability (i.e., choice reaction times relative to simple reaction times) is long known to increase reaction times of older persons (Deiber, Sallard, Ibañez, Ludwig, & Barral, 2014; Golob, Ovasapyan, & Starr, 2005; Khanmohammadi, Talebian, Hadian, Olyaei, & Bagheri, 2015; St George, Fitzpatrick, Rogers, & Lord, 2007; Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004). Our study supports that unpredictability delays and prolongs postural preparation and step execution.

We must take account of the methodological considerations associated with our study. First, our recruitment of healthy older adults did not enable a sub-group analysis of more granular age brackets (Golob, Ovasapyan, & Starr, 2005) or a comparison of older adults with and without balance impairment or fall history (Maki, Holliday, & Topper, 1994; Maki & McIlroy, 1997). Therefore, our results may not generalize to these other sub-groups of older adults. Second, our task protocol required visual and attentional re-orientation between the computer screen and its displayed cues to a marked target on the floor at a non-preferred step location. Although we argue that such a situation likely parallels a scenario in which a sudden, unpredictable environmental event occurs, results are likely confounded by these conditions. Nevertheless, we have shown that there is an increase in cortical activity over the sensory cluster during the earlier stage of cortical preparation that was only present in older subjects and only when conditions were predictable. Moreover, this study demonstrates that, on average, older subjects tend to increase later pre-movement cortical activity, achieve postural preparation that is shortened in duration and increased in amplitude, but suffer from loss of precision during

the step and jeopardize ML postural stability that, speculatively, may enhance fall risk. Finally, the correlation analysis suggests that there were two movement strategies exploited by the older subjects, one that utilized enhanced cortical preparation associated with prolonged postural preparation and enhanced postural stability, and another that prioritized timing over step accuracy or stability. This study, therefore, offers new mechanistic insights into how the aging brain achieves step initiation, related to healthy mobility.

Conflict of interests: The authors declare that they have no conflict of interest.

3.6 Acknowledgements

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CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTIONS

This thesis explored the utility of beta ERD as a measure of the neural preparation for step initiation when limb choice was unpredictable. It established that beta ERD is an informative tool for understanding the processes preceding a change in a motor state. Due to a higher degree of localization of upper-beta ERD, it, along with its derivatives (e.g., lateralization measures) will continue to be a mainstay in research of human motor control.

More specifically, in our studies beta ERD elucidated that: a) subjects with PD do not modulate their cortical preparation, even when conditions seem to demand it (perhaps due to already exerting maximal capacity), b) older subjects displayed greater cortical preparation (which may be a sign of compensation for degeneration of neural networks involved in the central motor control) but also split into two subgroups (i.e., "fast" or "accurate"). For those with PD, this means that their environment must be as predictable as possible as they have a quite diminished ability to handle unpredictability. As for older subjects, this thesis might underscore the benefits of the "accurate" strategy. Precisely, higher postural stability during the step diminished fall probability even in the unpredictable environment. Moreover, a greater beta ERD amplitude may be a reflection of subjects' lifestyle choices and this may hint that staying active and challenging oneself physically retains cortical function better than a passive lifestyle. Clinically, this may mean that an intervention physical therapy program may improve cortical preparation and, therefore, increase mobility and decrease fall-related injuries and mortality.

A serious limitation of this thesis is that it is built on assumption that beta ERD is a neural correlate of anticipation and motor preparation. However, even though that there

is evidence supporting this point of view, the debate on the exact meaning of the desynchronization and subsequent resynchronization (also termed ERS). Until there is a solid understanding of these processes, all of the work based on ERD/ERS is tentative. The work to understand these processes is severely limited by ethical considerations (e.g., most data recorded directly from the drain with electrodes of ECoG mat come from rare cases that involve a very risky craniotomy in those with epilepsy or PD) and the lack of a close animal model. Most neuroscience studies use rodents and very rarely non-human primates that lack the centers in their brains that are accountable for steady bipedal locomotion and proper posture present in the human brain (although there is some transferability of knowledge, see Takakusaki (2013)). Therefore, one interesting avenue for future research would be to create a computational model of ERD/ERS processes and hope that this model points to one of the current hypotheses about ERD/ERS thereby suggesting a most probable avenue for future research.

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