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Repetitive Finger Movement, Buttoning and Purdue Pegboard Tasks in People with Parkinson’s Disease

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Repetitive finger movement, buttoning and Purdue pegboard tasks in people with Parkinson’s disease

by

Jennifer Uzochukwu

A thesis submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Kinesiology

Program of Study Committee:
Elizabeth Stegemöller, Major Professor
Ann Smiley-Oyen
Daniel Russell

Iowa State University
Ames, Iowa
2016

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I would like to thank my committee chair, Dr. Elizabeth Stegemöller, and my committee members, Dr. Ann Smiley-Oyen, and Dr. David Russell, for their guidance and support throughout the course of this research.

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Studies have shown repetitive finger movement performance in people with Parkinson’s disease (PD) may be rate dependent. When performing acoustically cued repetitive finger movements at rates near to and above 2 Hz, they exhibit increased movement rate, reduced movement amplitude, and loss of phase accompanied by frequent hesitations. The relationship between this movement deficit and functional fine motor tasks in people with PD is unknown. The purpose of this study was to examine if people with PD who demonstrate repetitive finger movement impairment at rates near to and above 2 Hz perform worse on a buttoning task and a Purdue pegboard task compared to those who do not demonstrate repetitive finger movement impairment at rates near to and above 2 Hz. Forty-eight participants with PD completed an acoustically cued repetitive finger movement task, incrementing from a rate of 1 Hz to 3 Hz in 0.25 Hz. Movement rate and movement amplitude were compared to participants’ performance at 1 Hz and 1.25 Hz, respectively. Participants with PD were divided into groups based upon changes in movement rate and movement amplitude at rates near to and above 2 Hz. Participants also completed a buttoning and Purdue pegboard assembly task. Buttoning and Purdue pegboard performance was compared between groups.

For movement rate, there were no significant differences between the fast rate group (moved faster than the tone at rates near to and above 2 Hz) and the normal group (those that were within 2 SD of the tone rate) on the buttoning and Purdue Pegboard tasks. Similarly, there were no significant differences between subgroups for movement amplitude alone on the functional tasks. This study demonstrated that changes in movement rate and movement
amplitude during the performance of repetitive finger movement at rates near to and above 2 Hz have differential relationships to performance of functional fine motor tasks in persons with PD. Consideration and evaluation of both movement rate and movement amplitude, separately, may have clinical applications in the treatment of people with PD.
CHAPTER I
INTRODUCTION

Overview

Across the globe, seven million people are diagnosed with a progressive neurodegenerative disorder known as Parkinson’s disease (PD) (Foley, Kaschel, & Della Sala, 2013). It is characterized by the degeneration of nigrostriatal neurons in the basal ganglia that result in decreased dopamine transmission. The disease comprises both motor and non-motor symptoms. The motor phenotypes include bradykinesia - slowness of movement, hypokinesia – reduced movement amplitude, dysrhythmia – abnormality in physiologic rhythm, akinesia – lack of or paucity of movement, rigidity and tremor (Teo, Rodrigues, Mastaglia, & Thickbroom, 2013; Taylor Tavares et al., 2005). The non-motor phenotypes that are frequently presented include cognitive impairment or dementia, sleep disorders, psychiatric symptoms, and autonomic dysregulation (Zhang, Liu, Ye, Cohen & Zhang, 2015). Although the cause of the disease is unknown, the pathological process is linked to the development and spread of alpha synuclein protein in the form of Lew bodies or Lewy neurites in various brain regions (Shulman, De Jager, Feany, 2011; Braak et al., 2003, Halliday & McCann, 2010). The accumulation and advancement of these bodies manifest correlative presentation and decline of both motor and non-motor symptoms.

The motor symptoms of the disease typically respond well to a treatment of dopamine replacement therapy; however, disease progression eventually renders some of motor symptoms unresponsive to treatment (Fahn, 2003). Additionally, with continued progression of the disease, modulation of the basal ganglia (the subthalamic nucleus or globus pallidus
internal activity aids in the management of the motor symptoms. Other alternative treatment therapies such as physical therapy and music therapy that target individualized motor and non-motor symptoms concurrently aid in delaying disabilities and prolonging the life expectancy of those affected by the disease.

One of the cardinal motor symptoms in particular, bradykinesia, is clinically assessed with the finger tapping task (item 3.4) in the Movement Disorder Society-Sponsored Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), the most widely used assessment tool of the longitudinal course of the disease (Okuno, Yokoe, Akazawa, Abe, & Sakoda, 2006). This task involves repetitively tapping the index finger to the thumb as rapidly and wide as possible so as to measure movement amplitude, velocity and rhythm. Because it provides useful information about upper-extremity fine motor skills and changes with the individual’s ability and symptoms, it is a good measure of motor performance in people with PD (Ozen Barut, Emre, Korucu, & Barut, 2011). It is also useful in diagnosing, evaluating disease severity and monitoring medication response in patients with the disease.

The literature has shown that performance of this finger tapping task is more impaired in people with PD compared to healthy controls. During repetitive self-paced finger tapping, the movement is initially slow with subsequent movements progressively exhibiting detriment in movement rate and amplitude until cessation (Marsden, 1989). Addition of levodopa treatment helps to normalize movement amplitude and speed (Espay et al., 2009). However, with the introduction of auditory cues ranging from 0.5 to 6 Hz with which participants are instructed to synchronize, some patients with PD exhibit a hastening phenomenon at the critical rate of 2 Hz in which they tap faster than the intended rate (Nakamura, Nagasaki, & Narabayashi, 1978; Freeman, Cody, & Schady, 1993; Stegemöller,
Simuni, & MacKinnon, 2009; Muir, Jones, Andreae, & Donaldson, 2009; Yahalom, Simon, Thorne, Peretz, & Giladi, 2004). This impairment is interestingly unaffected by dopamine therapy or fatigue (Stegemöller, Allen, Simuni, & MacKinnon, 2010). The hastening is present in both healthy controls and people with PD; nonetheless, those with PD show this transition at a much earlier tone rate (near to and above 2 Hz) compared to controls. The appearance of this motor impairment is contradictory to the typically expected symptom of bradykinesia that results from alteration of the nigrostriatal activity. It therefore incites the inquiry of what pathway(s) may be involved to produce such a phenomenon and how it affects performance of tasks requiring fine motor control in people with PD, if at all.

Although research is beginning to provide possible explanations of neural activity associated with the impairments observed with auditory cued and uncued finger tapping, research is quite limited on how the 2 Hz hastening impairment is related to functional tasks in people with PD.

In view of this, the aim of this research project is to answer this question by investigating the presence of hastening in participants with Parkinson’s disease (PD) and how it relates to their performance of tasks of fine manual dexterity. These dexterous tasks will include both buttoning a vest and an assembly task on a Purdue Pegboard. Buttoning clothing is a functional, dexterous task reported to be difficult to accomplish in people with PD (Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995) whereas the Purdue pegboard assembly task is a dexterous task reported to be significantly correlated to tapping performance (Müller, Schäffer, Kuhn, & Przuntek, 2000). Both tasks act as good measures of the 2 Hz hastening phenomenon. The proceeding text will explore and present previous literature on repetitive finger movement as it relates to PD, neurological findings regarding the disease and
correlates of the impairment in repetitive finger movement, relationship of bradykinesia and dexterity to finger tapping, and the research study to address the question of how the 2 Hz impairment relates to functional tasks of manual dexterity in people with PD.
References


CHAPTER II

PARKINSON’S DISEASE: LITERATURE REVIEW

Symptoms and Causes of Parkinson’s Disease

Parkinson’s disease (PD) is a progressive movement disorder attributed to the loss of dopaminergic neurons in the substantia nigra pars compacta (SNC). Next to Alzheimer’s disease, it is the second most common neurodegenerative disorder with a risk of 1 in 40-50 (Schapira, 2006) and affecting 7 million people worldwide (Foley, Kaschel, & Della Sala, 2013). It is characterized by four cardinal symptoms, which include tremor, bradykinesia (slowness initiating voluntary movement or gradual loss of spontaneous movement), rigidity, and postural instability (Samli, Nutt, & Ransom, 2004; Foley et al., 2013). Other motor symptoms of PD include freezing of gait, micrographia (progressively smaller handwriting), mask-like expression, hypophonia (soft speech or a weak voice), sialorrhea (excessive drooling), and dysphagia (difficulty swallowing). Non-motor symptoms that frequently occur include cognitive disorders such as depression and hallucinations, autonomic dysfunction such as urinary bladder retention, sleep disturbances, and fatigue. The disease is typically asymmetrical and diagnosis ranges from clinically possible, probable, to definite. The diagnostic criteria for clinical diagnosis must include the asymmetric presence of resting tremor (3-6 Hz), rigidity, and bradykinesia, as well as responsiveness to dopaminergic treatment.

Although PD is not hereditary, there are genetic and environmental risk factors. The etiology of the disease is still uncertain, but there is the accumulation of the alpha synuclein protein in certain sites of the brain as either Lewy bodies or Lewy neurites (Halliday &
McCann, 2010). According to Braak and colleagues (2003) who proposed a staging scheme for the progression of alpha synuclein in PD, there is the presence of Lewy neurites and Lewy bodies in the olfactory regions and lower brain stem in Stages I and II. In Stage III and IV the protein aggregation extends to the midbrain, particularly the substantia nigra pars compacta. Lastly, Stages V and VI involve the extension of the protein aggregates to higher order cortical association areas such as the anterior cingulate area and neocortex. The advancement of these stages of alpha synuclein pathology in brain regions correlates with the presentation and decline of motor and non-motor symptoms of PD. For instance, stage IV correlates with observable motor symptoms, and the end stages with cognitive decline.

Conversely, this staging scheme is not always unified with clinical utility considering the variability in PD pathological phenotypes (Halliday & McCann, 2010). There are also cases in which the disease is linked to family history, known as familial cases. The genes linked to these familial cases include mutations in the PARK1 (SNCA) gene (codes for alpha synuclein protein), PARK2 (codes for Parkin protein), PARK5 (codes for ubiquitin C-terminal hydrolase L1), PARK7 (linked to early onset form of PD), PARK6, and other gene loci that include PARK3, PARK4, PARK8, and PARK10 (Samli et al., 2004; Nolden et al., 2014). These familial cases occur in about 15% of patients with PD. Although genetic and alpha synuclein pathology may explain pathological underpinnings, the exact cause is as of yet still unclear.

Neural Underpinnings of Parkinson’s Disease

Irrespective of the cause being genetic or due to protein mutations, the primary structure affected in PD are the basal ganglia, a group of interconnected subcortical nuclei
that include but are not limited to the dorsal striatum (caudate and putamen), globus pallidus, subthalamic nucleus, and substantia nigra. The symptoms observed in PD are a result of the loss of dopaminergic neurons in the substantia nigra pars compacta that in turn lead to a deficiency of the neurotransmitter dopamine in the striatum. At the presentation of the motor symptoms in PD, approximately 70-80% of these dopamine-producing neurons may already be lost (Nolden et al., 2014).

To better understand the pathology of PD, it is critical to delve into the normal connections of the basal ganglia and how this is altered with PD. The major input structure of basal ganglia is the striatum while the globus pallidus interna (GPI) and substantia nigra pars reticulata (SNr) act as the major output structures. The basal ganglia motor circuit comprises of a direct and indirect pathway that begins from subpopulations of neurons in the putamen and terminates in the output structures. The direct pathway (Figure 1, highlighted in yellow) functions to reduce the inhibition of the thalamus in order to produce intended movements (Albin, Young, and Penney, 1989; DeLong, 1990). This begins with input to the putamen from cortical motor structures such as the motor cortex,
supplementary motor area, and premotor area. The putamen forms an inhibitory projection to the GPi and SNr suppressing their inhibitory activity and in turn lessening the inhibition of ventrolateral thalamus thus exciting the motor cortex and producing movement. Additionally, the SNc releases dopamine to the D₁ dopamine receptors in the striatum, which excites the GABAergic inhibitory neurons in the putamen that inhibit the GPi leading to excitation of the thalamus and motor cortex. Both of these input pathways to the striatum (cortical motor regions to putamen, and SNc to putamen) work together to initiate movement.

On the other hand, the indirect pathway (Figure 2, highlighted in yellow) functions to prevent unintended movements by increasing the inhibitory output to the ventrolateral thalamus. This begins with the globus pallidus externa (GPe) receiving inhibitory input from the putamen. It projects to the subthalamic nucleus (STN) and because the inhibitory output of the GPe is suppressed, the STN, which contains glutamatergic neurons (excitatory), excites the GPi that, subsequently inhibits the thalamus decreasing the excitatory output to the motor cortex. In addition, the SNc projects to the D₂ dopamine receptors in the striatum that transiently inhibit the GABAergic neurons in the
putamen, which decrease inhibition of the GPe thus inhibiting the STN. Decreased excitatory output from the STN results in less inhibition of the VA/VL thalamus and motor cortex. As such, this works in accord with the direct pathway to increase motor activity while decreasing competing movements. It is of note that this is merely a simplified view of the connections between the BG and the cortical motor regions.

From this model of direct and indirect pathways, a theory for how PD affects basal ganglia circuitry has been proposed. In PD, the loss of the dopamine-producing neurons in the nigrostriatal pathway results in reduced amplification of the direct pathway at the level of the GPi thus increasing inhibition of the thalamocortical circuit and producing decreased movement output (DeLong, 1990). In the indirect pathway, there is a decrease in the tonic discharge of the GPe that allows for excitation of the STN and successively the GPi, which tightens the output from the thalamus yielding decreased movement. Overall, there is an increase in transmission of the indirect pathway and decreased transmission in the direct pathway. In this manner, slow movement or movement initiation, also known as bradykinesia, and rigidity is observed in people with PD. However, the aforementioned alteration in normal output circuitry of the BG does not explain the symptom of akinesia, a lack or paucity of movement, in people with PD. Moreover, the basal ganglia are not the only regions that contributes to the symptoms observed in PD as will be later expanded upon.

Accordingly, as there is a decrease in the output of the direct pathway and increase in that of the indirect pathway with Parkinson’s disease (PD), there are also simultaneous changes in the neuronal firing patterns of basal ganglia neurons. The globus pallidus interna (GPi) and globus pallidus externa (GPe) are known to provide the major GABAergic inputs to the subthalamic nucleus (STN) while motorcortical areas (primary motor cortex, premotor
and supplementary motor area) provide majority of the glutamatergic input. The STN is capable of firing independently of these GABAergic and glutamatergic synaptic inputs (Bevan, Hallworth, & Baufreton, 2007). Chronic depletion of dopamine as seen in Parkinson’s disease affects the STN neurons such that there is a reduction in the frequency of spontaneous activity. The STN neurons also show increased bursting in parkinsonian animals and likely in patients as well (Bergman, Wichmann, Karmon, & DeLong, 1994; Steigerwald et al., 2008) and have a strong correlation to the severity of the disease (Sharott et al., 2014; Remple et al., 2011). The increased firing of STN neurons and the decreased firing of GPe neurons, result in increased firing of neurons in the GPi and substantia nigra reticulata with dopamine depletion. This effect leads to some of the motor symptoms observed in people with PD, and as such the STN is prime target for deep brain stimulation, a form of treatment for patients with the disease used to help alleviate some of the symptoms.

However, the manifestation of motor symptoms is not restricted to the impairments in the basal ganglia. Neurophysiologic and imaging techniques have shown that there is generally an underactivation of the medial cortical motor areas that include the supplementary motor area (SMA) and nearby areas that may be coupled with increased activation of lateral premotor areas (Berardelli et al., 2001). The underactivation of the SMA may explain difficulties in formulating internally generated movement whereas the increase in activity of premotor areas may be a compensation for the impairment in the basal ganglia and SMA. Moreover, as previously mentioned, there is an accumulation of Lewy bodies and neurites that extends to the olfactory region, midbrain, cortex, amygdala, peripheral autonomic nervous system, locus ceruleus, and vagal nucleus (Halliday & McCann, 2009;
Braak et al., 2003). Impairments in these areas may also lead to the decline of motor and non-motor symptoms in people with PD.

Treatment Options

Due to the variety of motor and non-motor symptoms that arise with the disease, dopaminergic replacement therapies are the primary treatment strategies for the management of PD motor symptoms. The most effective treatment is a combination of carbidopa/levodopa (Sinemet). Other treatments include dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, catechol O-methyltransferase (COMT) inhibitors, injectable dopamine agonist, N-methyl-D-aspartate receptor (NMDA) inhibitor, and anticholinergics (Gazewood, Richards, & Clebak, 2013). Antiparkinson medications help to restore some of the movement speed by altering the output of GPi in the basal ganglia; however, it does not completely normalize the movement speed as with a healthy individual (Robichaud, Pfann, Comella, & Corcos, 2002). Early and prolonged administration of carbidopa/levodopa and dopamine agonists may result in dyskinesia (involuntary stiff and jerky movements of the face and body). An alternative treatment option is deep brain stimulation (DBS), which targets the subthalamic nucleus or globus pallidus interna in the basal ganglia. This treatment option aids in the management of dyskinesia and freezing of gait; however, it does not slow the pathological progression of the disease. Additional allied therapies to aid in the management of motor and non-motor symptoms include exercise interventions, physical therapy, occupational therapy, speech therapy, and music therapy. These therapies also help to improve the quality of life of the patients affected by PD.
Bradykinesia and Finger Tapping

Of the four cardinal symptoms (tremor, bradykinesia, rigidity, postural instability), bradykinesia is the most debilitating in early PD, affecting fine motor skills and making it difficult to perform activities of daily living such as buttoning up clothing, handwriting, and cutting food (Samli et al., 2004; Nolden, Tartavoulle, & Porche, 2014). With bradykinesia being a prominent symptom of PD, it is routinely examined through rapid sequential limb movements in the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS-III). For the upper limbs, these tests include finger tapping (item 3.4), hand opening and closing (item 3.5), and hand pronation and supination (item 3.6) (Goetz et al., 2008). Finger tapping entails having the arm slightly raised, the thumb abducted, index finger extended with other fingers flexed and repetitively tapping the index to the thumb. Hand opening and closing requires the patient to alternately open and close the hand as much as instructed while the performance of forearm pronation and supination entails that the forearm rests on the thigh in a pronated position with the fingers fully extended. The patient alternately pronates and supinates the forearm and rests it on thigh after each submovement. For these movements, patients are always instructed to perform them as big and fast as possible for each hand. The Movement Disorder Society revised UPDRS (MDS-UPDRS) rates these items on a scale of 0-4 where 0 indicates normal functioning, 1 = slight referring to low frequency/intensity of signs/symptoms with no effect on function, 2 = mild indicating frequency or intensity of signs/symptoms causing modest impact on function, 3 = moderate indicating frequency or intensity of signs/symptoms that considerably impact function but not prevent it, and lastly 4 = severe, which refers to sign/symptoms that prevent function. Thus in the subjective assessment, speed, amplitude, hesitations, halts and decrementing
amplitude are evaluated. In addition to the subjective evaluation, quantitative assessment further analyzes these measures which cannot be wholly captured subjectively.

In an example of quantitative assessment of bradykinesia, Agostino and colleagues (1998) tested repetitive finger, hand, and wrist movements in people with PD off medication. Participants were instructed to move as widely and fast as possible. Results revealed that patients indeed have difficulty performing each movement task, however, performance of finger tapping was significantly ($p < 0.05$) more impaired than the other repetitive movement tasks. This was followed up with investigation of individual (index-thumb oppositions) versus non-individual (all four fingers against the thumb pad) finger movements in order to determine if individual movements were predominantly impaired in people with PD. This was also conducted in the off state (Agostino et al., 2003). Results showed the presence of bradykinesia and hypometria, the reduction of movement amplitude, with motor performance deterioration easier in the individual than non-individual finger movements. This may indicate that bradykinesia is worse with isolated finger movements compared to gross hand movements. Another study (Espay et al., 2009) found that comparison of this isolated finger tapping task to that of healthy controls given the same instruction to tap as rapidly and widely as possible produced more affected movement amplitude in the off state. The addition of levodopa treatment during this self-cued tapping task normalized the movement amplitude and movement speed. However, these studies examined self-paced repetitive movements, and rate of movement was not controlled.

To control for movement rate, previous studies have provided auditory cues at rates from as low as 0.5 Hz to as high as 6 Hz. Collectively, these studies have shown that when patients with PD are required to synchronize with an external auditory cue at high movement
rates, studies show at tone rates near to and above 2 Hz, patients reveal a hastening phenomenon in which they tap faster than the intended tone rate at frequencies up to 5-6 Hz with a decrease in tempo when approaching tones rates of 5 Hz or higher (Nakamura, Nagasaki, & Narabayashi, 1978; Freeman, Cody, & Schady, 1993; Stegemöller, Simuni, & MacKinnon, 2009). Removing the auditory cue and having the patients pace themselves to the same rhythm results in greater prominence of the hastening and faltering phenomena observed and increase in movement variability (Freeman et al., 1993; Yahalom, Simon, Thorne, Peretz, & Giladi, 2004). According to Muir and colleagues (1995), when compared to healthy controls, this hastening phenomenon is not confined to only patients with PD but normal subjects as well. Additionally, patients with PD lose synchrony while tapping at a considerably lower frequency than controls. There is also a fixed hastening frequency in which patients can no longer surpass irrespective of the cued frequency.

The finger tapping hastening phenomenon near to and above 2 Hz is accompanied by a decrease in movement amplitude also observed in Espay et al., (2009) along with hesitations (Stegemöller et al., 2009, see review Vercruysse et al., 2014). Yahalom and colleagues (2004) demonstrated the presence of hastening in tremor-predominant (TP) and freezing-predominant patients (FP) with PD. Hastening was more provoked in TP patients when performing the tapping task with an abrupt shift in tone frequency (switch from 1 to 2.5 Hz) compared to a stepwise increase in frequencies. These participants were also off anti-Parkinson medication. In contrast, the participants with PD involved in the Stegemöller et al (2009) study had a maximum score of 2 (mild) for resting and action tremor and 60% demonstrated hastening above 2 Hz tone frequencies, which occurred in a stepwise manner. Participants were also tested after a 12-hr withdrawal from anti-Parkinson medication and 1-
hr post optimal medication ingestion. Medication appeared not to affect the hesitations or movement arrest that accompanied the movement hastening. Further study on this rate-dependent impairment revealed that it was not a contribution of peripheral fatigue in maximal force production during the repetitive finger movement (Stegemöller, Allen, Simuni, & MacKinnon, 2010). These studies suggest that tremor, fatigue, and dopamine therapy are inconsequential factors affecting the hastening appearance near to and above 2 Hz and as a result must be due to a different factor or mechanism.

Based on this supporting behavioral evidence, timing may be impaired in people with PD that contributes to disrupted performance of repetitive movements. Freeman and colleagues (1993) demonstrated that patients with PD were dependent on external timing cues to regulate the tempo of their finger tapping, suggesting a disturbance in the internal timekeeper. Wing and Kristofferson (1973) proposed a model for analyzing repetitive movement that involves an internal timekeeper and an implementation system. The internal timekeeper is responsible for triggering and determining when a response should be made whereas the implementation system is involved in executing the motor command. This process would not require feedback as the movement is performed in an open look fashion in accordance with the model. The inter-response interval is a sum of the internal timekeeper and motor implementation system calculated as the sum of the timekeeper and the difference in a response and a preceding one. Variability in the inter-response interval will also account for variability in the model. Using this model, Pastor et al. (1992) showed that levodopa medication improved rhythmic accuracy (lower mean IRI) of auditory cued repetitive movement at higher movement frequency compared to the off state. Again, significant group differences between PD patients and controls were observed at the higher frequencies (2 and
2.25 Hz) and non-significant and lower movement frequencies (0.5 – 1.5 Hz) supporting a rate-dependent impairment of repetitive movement. The Wing and Kristofferson (1973) model assumes that repetitive movement will only be performed in an open loop manner. It does not consider repetitive movement at low rates such as from 0.5 Hz to 1.5 Hz that can and will be performed in a closed loop fashion due to having enough time for feedback to the timekeeper. Taken together, these studies suggest that there is differential impairment of repetitive finger movements at low and high rates. Differences in the underlying neural control of this movements may provide further insight.

Neural Correlates of Impaired Timing and the Relationship to Impairments in Repetitive Finger Movement

The basal ganglia have been purported to have possible involvement in regulation of motor timing considering impairment of motor timing with withdrawal of dopamine medication and substantial improvement with reintroduction of medication (Pastor et al., 1992; O’Boyle, 1996). Further investigation of the basal ganglia in motor timing processes was done by Harrington et al. (1998) who studied its involvement in time perception and motor timing. Participants with PD in the on state performed a paced repetitive finger-tapping task in which they were to synchronize with a series of tones (induction phase), continue to tap at the same pace with the cessation of the tone (continuation phase) and with reappearance of the tone (resynchronization phase) in two randomly presented conditions whereby the tones were separated by a 300-ms interval or a 600-ms interval. The participants also performed a duration perception task where they were to judge the duration of two tone pairs separated by 300 or 600-ms. Results revealed that duration perception was impaired in the PD group for both intervals compared to the controls and there was greater total
variability (clock variability and motor delay variability) in the PD group for the finger tapping task (p < 0.025) compared to the controls irrespective of interval, which also increased with duration in both groups. The results of this study indicate the involvement of the basal ganglia in mediating internal timing processes.

However, the cerebellum has also been purported to be involved in movement timing. Ivry et al. (2002) classified two types of timing: emergent and event timing. Emergent timing occurs without explicit temporal representation in which anticipating a moment may not be due to an internal timer and may be highly influenced by varying degrees of attention and arousal. Event timing, on the other hand, is subject to explicit temporal representation. This was explained by comparing a finger tapping task to a continuous circle drawing and intermittent circle drawing task in which the circle was divided into a movement phase (complete circle) and pause phase (remain at one position) in association with a pacing signal (Zelaznik, Spencer, & Ivry, 2002). Results of this experiment revealed high correlation (.50) between the tapping and intermittent circle drawing tasks compared to low correlation (.30) between the continuous circle drawing and the other two tasks. A second experiment within the same study revealed significant correlations for temporal variability in both the tapping and intermittent circle drawing tasks with neither correlating with the continuous circle drawing task. This is indicative of a similar timing process involved in the tapping and intermittent circling tasks. This may then explain the difference observed in performance of the finger tapping task at low rates (below 2 Hz) considering that each tap is a discrete movement and may involve more cerebellar control (event timing) as opposed to tapping at high movement rates (2 Hz and above) being more continuous and involving emergent timing, a different timing process.
Considering the involvement of the basal ganglia and cerebellum in temporal processing and the demarcation of movement performance at the critical rate of 2 Hz, examining motor cortical activity may provide more information. One method is to investigate the effect of movement rate on the activation and coupling of motor cortical areas in alpha (8-12 Hz) and beta (16-20 Hz) bands. This is done by looking at changes in electroencephalography (EEG) band-power and event-related EEG correlation, which are representative of regional motor cortical activation and interregional functional coupling respectively. Alpha band activity may be representative of sensory function whereas beta band activity is correlated with motor activity (Salmelin, Hämäläinen, Kajola, & Hari, 1995). A decrease in EEG band power is known as event-related desynchronization (ERD) while a subsequent rebound of the power band above baseline is known as event-related synchronization (ERS) (Pfurtscheller, Stancák, & Edlinger, 1997). The ERD is associated with cortical activation whereas ERS is associated with cortical idling or resetting.

Toma et al. (2002) used this EEG method to investigate alpha and beta band activity as a result of movement rate in a group of healthy middle-aged participants. Participants were asked to perform repetitive abduction of the right thumb and synchronize to an auditory cue ranging from 0.5–4 Hz. Results of the study revealed a transition from synchronization to syncopation between tone rates of 1-3 Hz with 2 Hz being the critical transition point; there was also approximately a half-cycle lag at tone rates of 3 and 4 Hz suggesting that participants lacked time for upcoming movement preparation due to the rapidly presented cue. It was also shown that for slow repetitive movement, activation (ERD) of motor cortical areas measured (left and right sensorimotor areas and medial frontal cortex) was immediately followed by transient deactivation (ERS). In the same manner there was functional coupling
and immediate transient decoupling between the motor cortical areas. This was not the case during the fast-repetitive movements, which demonstrated continuous activation of motor cortical areas without deactivation and likewise sustained coupling of motor cortical areas particularly the contralateral primary sensory motor area and medial frontal cortex. The EEG activity observed for fast repetitive movements may indicate the brain’s inability to separately control each individual movement and as such may have separate time-keeping systems for preferred movements rate (slow versus fast).

Because beta oscillations are a part of normal motor functioning, it is also present in patients with PD. However, it has been recorded at lower levels in people without PD (Sochurkova and Rektor, 2003). Considering the constant maintenance of desynchronous beta band activity during fast finger tapping in healthy individuals (Toma et al., 2002; Muthukumaraswamy, 2010) it is interesting to determine if the same is present or otherwise in people with PD. As such, local field potentials (LFP) were measured in the subthalamic nucleus of patients with PD who underwent deep brain stimulation implantation and were on PD medication (Joundi et al., 2013). Participants also similarly performed a synchronized index finger tapping task in which auditory stimulus were at rates of 0.5, 1, and 2 Hz and respectively categorized as low, medium, and high rates. In support of the findings presented in Toma et al. (2002), results revealed persistent beta band desynchronization across all tone rates with rebound synchronization for the low and medium tapping rates that coincided with the inter-tap interval. At the high movement rate (2 Hz), taps also preceded the auditory cues by about 25 ms with persistent beta band suppression indicating an anticipatory nature of the tapping. These results further suggest a shift from discrete to continuous movement occurring at around 2 Hz (Huys, Studenka, Rheaume, Zelaznik, Jirsa., 2008). It is also possible that the
constant desynchronization observed at the fast/high movement rate may be due to cancellation of synchronous activity due to desynchronization of the proceeding tap thus maintaining a state of continuous tapping.

Further evidence of this hypothesis comes from Stegemöller and colleagues (2015) with report of alpha and beta band movement related oscillation (MRO) showing increased desynchronization with reduced modulation in the contralateral sensorimotor cortex in patients with PD at particularly high movement rates (around 2 Hz and above). This finding was not significantly altered with levodopa therapy indicating the mediation of this motor impairment by a non-dopaminergic pathway. Characteristic of the 2 Hz transition was also the emergence of hypokinesia and hastening contrasting performance of healthy subjects who predominantly exhibited a spontaneous transition in phase. Although the persistent desynchronization of alpha and beta band oscillation was present in both healthy and PD participants, it was markedly increased in the PD group with beta oscillations being approximately doubly suppressed in comparison to the control group (~40% vs. ~20% respectively) when tested in the ON and OFF states. Based on these findings, it appears that there is increased activation of the motor circuity that bypasses dopaminergic input at high movement rates independent of the basal ganglia motor circuit.

It has been hypothesized that both the cerebellum and basal ganglia are involved in temporal processing of discrete tasks with the cerebellum being more active in intervals spanning less than a second and the basal ganglia being more active in intervals spanning seconds (Ivry, 1996). However, a contrasting view from a more recent study provided evidence for both the cerebellum and basal ganglia involvement in intervals within the millisecond range (Wiener, Turkeltaub, & Coslett, 2010). If the latter is the case, then it is in
contradiction of the studies that posit a lack of influence of dopamine therapy towards the hastening phenomenon at and above 2 Hz. If the former hypothesis is the case, the basal ganglia may be predominantly active in the ‘seconds’ interstimulus range as suggested by Ivry (1996) and thus unaffected by medication at medium to high rates. Timing of movement at high movement frequencies may therefore be controlled by other (sub)cortical regions and mechanisms.

Dexterity and Finger Tapping

While there is growing evidence regarding the neural activity associated with impairments in repetitive finger movements in persons with PD, there is limited evidence in how this impairment relates to more functional skills, such as buttoning and manual dexterity. Given that the quantitative assessment of repetitive finger movement as a measure of bradykinesia, it is surmised that people with PD have difficulty controlling individual finger movements. This can lead to difficulties performing activities of daily living that involve fine motor skills in addition to practiced skills such as hand writing. Indeed, patients with PD frequently report more difficulty with dexterity (Nijkrake et al., 2009). Specifically, 72% of patients tested report difficulty with manipulating an object. Regarding, fine motor skills, Teulings and colleagues (1997) studied handwriting in PD patients and found that patients had problems coordinating their fingers and wrist and exhibited decreased control of wrist flexion. Considering that handwriting is a skill that occurs at high movement frequencies of approximately 4-8 Hz (Toma et al., 2002), there may be a relationship between the impairment observed and movement rates near to and above 2 Hz during
repetitive finger movements and other fine motor tasks of high movement rates in people with PD.

The primary focus of the repetitive finger tapping task is to assess bradykinesia. However, with manual dexterity being an issue for people with PD, studies have used the coin rotation task to assess both finger dexterity and speed (Gebhardt, Vanbellingen, Baronti, Kersten, & Bohlhalter, 2008; Lee et al., 2010; Hill, Barkemeyer, Jones, Santa Maria, & Browndyke, 2010). Gebhardt et al. (2008) argues that impaired finger dexterity being is independent of a dopaminergic deficit. Using the coin rotation task (CR), which entails rotating a coin approximately the size of nickel between the thumb, index and middle fingers, and a finger tapping task participants performed both while on and off PD medication. The study demonstrated the improvement of finger tapping scores by about 40% when participants were tested on medication in contrast to little improvement on coin rotation scores indicating a higher dopaminergic effect on finger tapping than coin rotation. The authors posit that the problems observed with finger dexterity is a result of limb kinetic apraxia, loss of elementary fine control inexplicable by simple motor dysfunction such as weakness, circumventing a dopaminergic deficit as opposed to bradykinesia. This concept was also supported by a previous study of nine PD patients performing both the finger tapping and coin rotation tasks while on medication (Quencer et al., 2007). There were no group differences in performance of the finger tapping task but patients exhibited worse performance on the coin rotation task.

Further investigation of finger dexterity impairment in PD patients by comparison of the finger tapping and coin rotation tasks has shown that coin rotation scores have shown no correlation with the clinical measures of finger bradykinesia (as measured by the Unified
Parkinson’s Disease Rating Scale (UPDRS)) or finger tapping scores (Lee et al., 2010). Rather, it is negatively correlated with somesthetic temporal discrimination threshold, a measure of discriminative cutaneous sensory dysfunction. On the other hand, finger tapping scores correlated with clinical finger bradykinesia scores. Contradicting the stance of impaired manual dexterity in PD as a contribution of limb kinetic apraxia, the authors suggested that neither limb kinetic apraxia nor bradykinesia explained the result, but an effect of higher-order sensory dysfunction and impaired sensorimotor integration at the basal ganglia. In the case of these three aforementioned studies arguing against bradykinesia in relationship to finger dexterity, the finger tapping task involved in those studies did not use quantitative assessment to isolate individual components of the taps such as amplitude or movement rate. Moreover, movement rate was not controlled. Patients were instead instructed to move as fast as possible. For this reason, it is of interest to consider whether the presence of movement impairments such as hastening and decreased amplitude that have been reported at rates of 2 Hz and higher in auditory cued tapping have a relationship to impairments in finger dexterity in PD.

Another method of testing bradykinesia involves the pegboard dexterity test. Performance on the test correlates well to the severity of motor and nigrostriatal dopaminergic deficit, and has good test-retest reliability (Tiffin, 1948; Vingerhoets, Schulzer, Calne, & Snow, 1997; Brown & Jahanshahi, 1998). The pegboard test consists of both unimanual and bimanual tasks. Müller and colleagues (2000) studied the correlation between tapping and insertion of pegs in the Purdue pegboard in people with PD. Patients were required to individually transfer 25 pegs from a rack on the board to a hole (2.8 mm in diameter) as fast as they could. They also performed a tapping task on a contact board for 32
seconds as quickly as possible. The study results revealed that there was a significant
correlation of peg insertion to tapping in the PD participants but was stronger for the left than
the right hand. Despite the correlation, it has been argued that the Purdue pegboard is not a
good measure of finger dexterity due to influence by speed of arm and hand movement (Lee
et al, 2010). Proud et al., (2010), nevertheless, supported the finding of Müller et al. (2000)
by showing strong correlations between the Purdue pegboard test and UPDRS motor scores
as well as UPDRS total scores in PD indicating decreased dexterity with increased disease
severity. This study also entailed the unimanual placement of 25 pegs on the board in 30
seconds. Previous literature has used the Pegboard test to assess dexterity in medication trials
(Tan, Ratnagopal, Han, Wong, Piribedil, 2003) and neurosurgery (Pal, Samli, & Kishore,
2000) in patients with PD as well as dexterity in healthy individuals (Fleishman & Gaylord,
1962). As such, the Purdue pegboard test appears to be a good representative measure of
dexterity in healthy individuals as well as those with Parkinson’s disease considering its
correlation to the motor section of the UPDRS.

Another task that has posed as a good measure of dexterity is timed buttoning
(Teixera, & Alouche, 2007). Buttoning clothing is among the tasks that require fine motor
dexterity, which has been reported to present difficulty for people with PD (Peto, Jenkinson,
Fitzpatrick, & Greenhall, 1995). The extent of fine motor impairment also extends to dual
tasking. When dual-tasking, performance on timed-dexterity tasks had greater reduction as
measured by the Purdue pegboard and concurrent verbal-cognitive task in patients with PD
on medication compared to controls (Proud et al., 2010). This entailed placing as many pegs
as possible down the pegboard for 30 seconds while counting backwards from seven
beginning with a random number from 290 to 310. Participants with PD placed less pegs in
the board compared to unimpaired controls indicative of greater dual-task interference. It appears that people with PD may need greater reliance on visual input or require more attentional resources to properly perform complex dexterity tasks. This can affect their multitasking ability in their daily life. Additionally, they have also exhibited greater dual-task reduction as measured by a timed buttoning task while also saying the first names of females (Teixera, & Alouche, 2007). Exclusion of this dual task, showed decreased performance compared to the controls when done in people with PD. Taking into consideration that testing for dexterity is a measure of bradykinesia, the results of these studies, particularly timed buttoning is also an indicator of the basal ganglia’s involvement in controlling the speed of voluntary movement. Because the Purdue pegboard and buttoning tasks also consist of sequential movements as in finger tapping, and normally occur at high movement rates, they deem to be good functional measures of the 2 Hz hastening phenomenon. It is of interest to examine whether the phenomenon is completely independent of the bradykinetic pathway, and if this is the case, determining how it affects functional tasks of dexterity.

Based on the literature presented, the movement impairment in repetitive finger tapping, characterized by hastening, reduced amplitude, and loss of phase, is observed with externally cued finger tapping at the critical rate of 2 Hz in people with Parkinson’s disease (PD). This impairment does not occur in all patients with PD and is not exemplary of the expected bradykinetic effect associated with the loss of dopaminergic neurons in the nigrostriatal pathway. Because people with PD also have problems with manual dexterity, it is of interest to know whether the movement impairment observed near to 2 Hz and above during repetitive finger movement possibly affects the performance of tasks involving finger dexterity, particularly tasks that occur at higher movement frequencies. Buttoning clothing
has been reported to be difficult for patients with PD. This is a learned sequential task that can occur at movement rates of 4 Hz or higher and involves finger dexterity. As such, it presents as a good correlative measure of finger tapping to functional tasks in addition to the Purdue pegboard. Thus, the purpose of this project is to determine the relationship, if any, of the repetitive finger movement impairment present near to and above 2 Hz to functional tasks of manual dexterity that include buttoning clothing and the Purdue pegboard task.
References


CHAPTER III

THESIS RESEARCH PROJECT: REPETITIVE FINGER MOVEMENT, BUTTONING AND PURDUE PEGBOARD TASKS IN PEOPLE WITH PARKINSON’S DISEASE

Introduction

Patients with Parkinson’s disease (PD) frequently report difficulties with manual dexterity such as buttoning clothing, handwriting, tying shoelaces, and typing on a keyboard (Nijkrake et al., 2009). This impairment is traditionally ascribed as a consequence of bradykinesia, which is typically assessed through clinical evaluation of repetitive movements. Among the clinical evaluation of repetitive movement using the Unified Parkinson’s Disease Rating Scale (UPDRS-III), finger tapping was considered the most difficult (Agostino, Berardelli, Currà, Accornero, & Manfredi, 1998; Agostino et al., 2003). Hence, repetitive finger movement is often used as a clinical tool to evaluate disease severity, progression, and treatment efficacy in PD. However, little is known regarding how repetitive movement performance, specifically repetitive finger movement, impacts functional fine motor tasks in persons with PD.

One of the most frequently reported problems of activities of daily living in patients with PD is dexterity, including object manipulation, (Nijkrake et al., 2009). The Purdue pegboard has been used to examine manual dexterity and movement speed (Proud & Morris, 2010; Tan, Ratnagopal, Han, & Wong, 2003). Both bimanual and unimanual tests for gross hand, and arm movements as well as fine fingertip dexterity can be examined with the Purdue pegboard. Performance on the test correlates well to the severity of motor and nigrostriatal dopaminergic deficit, and has good test-retest reliability (Tiffin, 1948; Vingerhoets, Schulzer, Calne, & Snow, 1997; Brown & Jahanshahi, 1998). Müller and
colleagues (2000) studied the correlation between finger tapping as fast as possible and insertion of pegs in the Purdue pegboard in people with PD, and revealed a significant correlation between task performances. However, the movement rate of the tapping task was not controlled. In addition, because buttoning clothing involves sequential action and fine motor control, this task has also been used as a measure of functional tasks of daily living (Ikeguchi et al., 2003; Aaron & Jansen, 2003; Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995). However, only one study has examined buttoning performance in persons with PD during a dual task condition (Teixera, & Alouche, 2007). It remains unknown if repetitive finger movement performance impacts buttoning in persons with PD.

Interestingly, dexterity tasks involve high movement rates over 2 Hz (Kunesch, Binkofski, & Freund, 1989), which is the same rate at which impairments in repetitive finger movements emerge (Freeman, Cody, & Schady, 1993; Nakamura, Nagasaki, & Narabayashi, 1978; Yahalom, Simon, Thorne, Peretz, & Giladi, 2004; Stegemöller, Simuni, & MacKinnon, 2009; Stegemöller, Allen, Simuni, & MacKinnon, 2010;). Yet, this impairment does not emerge in all patients with PD. This would suggest that there is a need to control for movement rate and variable task performance when comparing repetitive finger movement tasks with functional fine motor tasks. Moreover, research has shown that some participants with PD exhibit an increase in movement rate, a decline in movement amplitude, frequent hesitations, and the loss of phase, while others demonstrated a decrease in movement rate and increase in movement amplitude at rates near to and above 2 Hz (Stegemöller et al., 2009; Stegemöller et al., 2010; Espay et al., 2011). This may further suggest that movement amplitude and movement rate are differentially controlled and this should be taken into
consideration when examining functional fine motor tasks (Teo, Rodrigues, Mastaglia, & Thickbroom, 2013; Rodrigues, Mastaglia, & Thickbroom, 2009).

The purpose of this study was to determine if performance of fine motor tasks differs between those participants with PD that demonstrate impairments in the performance of repetitive finger movement at rates near to and above 2 Hz and those that do not. All participants completed an acoustically cued repetitive finger movement task from 1-3 Hz, a timed buttoning task, and a timed assembly Purdue pegboard task. Changes in movement rate and movement amplitude were analyzed independently. We hypothesized that participants with impairments in repetitive finger movements (either movement rate or movement amplitude) at rates near to and above 2 Hz would 1) demonstrate longer times for buttoning and 2) assemble fewer pieces for the Purdue pegboard task compared to those who did not present this performance impairment.

Methods

Participants

Data were collected from 48 participants PD (mean age = 70 ± 10; 23 male, 25 female) diagnosed with idiopathic PD (mild to moderate). Participants were tested on antiparkinson medication. Previous research has demonstrated that impairments in repetitive finger movements at rates near to and above 2 Hz are not improved with medication (Stegemöller et al., 2009). The most affected side was determined from participant report. All participants gave their written informed consent prior to inclusion into the study, and the Iowa State University Institutional Review Board approved the procedures.
Data Collection

Repetitive finger movement

Participants used the most affected side for the repetitive finger movement task. Participants were seated comfortably in a chair with elbow flexed at 90° and forearm of most affected side supported in an arm brace with palm facing downward. Movement was restricted to the index finger by securing the remaining fingers and thumb. Participants completed three trials of an unconstrained index finger flexion-extension (finger tap) movement in synchrony with acoustic tones (50ms 500 Hz, 80dB) presented at a starting rate of 1 Hz with a gradual increase to 3 Hz in increments of 0.25 Hz. Fifteen tones at each rate were presented. Each trial lasted for approximately 90 seconds and comprised a total of 135 finger taps. Three trials were collected. Participants were allowed a practice trial and rest between trials as needed. This task has been used previously (Stegemöller et al., 2009; Stegemöller, Allen, et al., 2010; Stegemöller, Uzochukwu, et al., 2015).

Finger movement was measured with a goniometer collected using a data acquisition board (Micro 1401, Cambridge Electronic Design, UK) and software (Spike2, CED). Signals were digitized at a sampling rate of 100 Hz.

Buttoning

For the buttoning task, participants wore a vest with three medium sized buttons (1.2 cm). Participants started from a neutral position (a Velcro button closure at the top the vest) and buttoned down the vest as fast as possible. At the closure of the last button, both hands were placed facing downward on thighs to signal the stop time. Total time from the neutral
start position to hand placement on thighs was recorded with a stopwatch. Participants completed three trials.

Purdue Pegboard

Participants completed three trials of an assembly task on the Purdue pegboard. Beginning with the dominant hand and then utilizing both hands interchangeably, participants assembled four pieces in the following order: pin - washer – collar – washer. Demonstration of this procedure was provided prior to the beginning of data collection, and participants were allowed to practice before beginning. Participants were allotted one minute to complete as many assemblies as possible. Each piece assembled (pin, washer, or collar) yielded the score of one, with a complete assembly yielding a score of four.

Data Analyses

For the repetitive finger tapping task, movement rate was calculated based on the timing between each peak displacement and averaged across each tone rate. Peak-to-peak amplitude was calculated for each movement and averaged across movements at each tone rate. To allow for comparison between participants, movement amplitude was normalized to data at 1 Hz. As a measure of hesitation, the coefficient of variation (CV) was also determined for both movement rate and movement amplitude by dividing the standard deviation by the mean across three trials for each tone rate.

Based on movement rate performance, participants were divided into groups contingent on exceeding the 2 Hz pacing tone, FAST (n = 13) and NORMAL (n = 35). They were also categorized by movement amplitude. Movement rate difference (MRΔ) data for all participants (n = 48) from tone rates of 1.25 and above on the most affected side were
compared to the standard deviation of MRA at 1 Hz (SD = ± 0.20). If participants moved faster than this value by two standard deviations for three or more consecutive tone rates at 2 Hz or above, they were assigned to the FAST group. Those who were within two standard deviations for three or more consecutive tone rates were assigned to the NORMAL group. Likewise, participants were categorized by movement amplitude, SMALL (n = 13) and NORMAL (n = 35). The normalized peak-to-peak amplitude data for all participants from tone rates of 1.5 Hz to 3 Hz on the most affected side were compared to the standard deviation of normalized movement amplitude at 1.25 Hz (SD = ± 0.22). If participants had low movement amplitude of two standard deviations from this value, they were grouped as SMALL. Those within two standard deviations were grouped as having NORMAL amplitude. No participants demonstrated MRA that was slower by two standard deviations or movement amplitude that was larger by two standard deviations for three or more consecutive tone rates above 2 Hz.

**Statistical Analysis**

Statistical analysis was first completed to establish if differences existed among the groups after stratification. An independent samples t-test was used to compare age and disease duration between groups stratified by movement rate and movement amplitude. Alpha level of significance was set at 0.05. To compare movement rate and movement amplitude between groups, a repeated measures ANOVA was used to determine differences in movement rate, normalized peak-to-peak movement amplitude, and CV across tone rates. The between-group factor was fast vs. normal for movement rate, small vs. normal for movement amplitude, and the within-subjects factor was tone rate. Alpha level of
significance was set at 0.05. Post hoc comparisons were completed with Bonferroni correction with alpha level of significance set at 0.006. Independent samples t-test was also conducted to test the main hypotheses (comparing differences between groups), in order to determine differences between groups for each dependent measure (buttoning and Purdue pegboard tasks) with an alpha level of significance at 0.05.

Results

Grouped by rate on the finger-tapping task, 13 participants (mean age 67±10) had increased movement rate (fast), and 35 participants (mean age 71±8) had no change in movement rate (normal) compared to movement rate difference (MRAΔ) at 1 Hz. When grouped by movement amplitude, 13 participants (mean age 70±9) had small movement amplitude, and 35 participants (68±10) had no change (normal) in amplitude compared to normalized peak-to-peak amplitude at 1.25 Hz. There were no significant differences in age or disease duration between both movement rate and movement amplitude groups (Table 1).

Table 1. Demographic information of groups stratified by movement rate and movement amplitude

<table>
<thead>
<tr>
<th>Movement Rate</th>
<th>Movement Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>Normal</td>
</tr>
<tr>
<td>n = 13</td>
<td>n = 35</td>
</tr>
<tr>
<td></td>
<td>Small</td>
</tr>
<tr>
<td></td>
<td>n = 13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (Mean±SD)</th>
<th>67±10</th>
<th>71±8</th>
<th>70±9</th>
<th>68±10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handedness (%R)</td>
<td>92</td>
<td>86</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>Hand Tested (%R)</td>
<td>38</td>
<td>69</td>
<td>38</td>
<td>63</td>
</tr>
<tr>
<td>Gender (%M)</td>
<td>46</td>
<td>49</td>
<td>46</td>
<td>49</td>
</tr>
<tr>
<td>Disease Duration (Mean±SD)</td>
<td>9±5</td>
<td>8±6</td>
<td>8±4</td>
<td>8±6</td>
</tr>
</tbody>
</table>
Figure 3A shows movement rate for each group (fast and normal) across all tone rates. Statistical comparison for movement rate revealed significant main effect of tone rate ($F(8) = 30.62, p < 0.001$), significant group effect ($F(1) = 121.27, p < 0.001$), and a significant interaction effect ($F(8) = 3.30, p < 0.001$). Post hoc comparisons revealed significant differences ($p < 0.001$) in MRA between groups at tone rates of 2 Hz to 3 Hz. For the CV of MRA (Figure 3B), there was a significant main effect of tone rate ($F(8) = 4.06, p < 0.001$), significant group effect ($F(1) = 6.85, p < 0.05$), and a significant interaction effect ($F(8) = 2.48, p < 0.05$). Post hoc analysis revealed that the fast group demonstrated significantly ($p < 0.006$) increased variation of movement compared to the normal group, particularly at rates of 1.75 Hz, 2 Hz and 2.5 Hz (Figure 2B).

**Figure 3A. Movement rate difference (MRA).** Mean and standard error for MRA across all tone rates for fast and normal movement rate groups. Significance set at $\alpha = 0.006$. Asterisk (**) designate significant differences between groups at $p < 0.001$.
Figure 4 shows the normalized peak-to-peak amplitude and CV across all tone rates for each group (small and normal). There was a significant main effect of tone rate (F(8) = 11.11, p < 0.001), a significant group effect (F(1) = 27.14, p < 0.001), and a significant interaction effect (F(8) = 9.69, p < 0.001) for normalized movement amplitude. Post hoc comparisons of normalized movement amplitude between groups revealed significant differences (p<0.006) across tone frequencies of 1.5 Hz to 3 Hz (Figure 4A), particularly at tone rates of 2.25 Hz to 3 Hz (p<0.001). There was no main effect of tone rate, group, or interaction effect for CV of normalized movement amplitude (Figure 4B).
**Figure 4A.** Normalized movement amplitude. Mean and standard error for normalized movement amplitude across all tone rates for small and normal amplitude groups. Significance set at $\alpha = 0.006$. Asterisk (*) designate significant differences between groups. (***) designate significant differences at $p<0.001$

**Figure 4B.** Normalized movement amplitude coefficient of variation (CV). Mean and standard error for normalized movement amplitude CV across all tone rates for small and normal amplitude groups.
Table 2 shows performance on buttoning and Purdue pegboard tasks based on the stratification by MRΔ and movement amplitude. Independent t-test results for stratification by MRΔ revealed a lack of main group effect for buttoning (t(46) = -1.37, p = 0.18) and Purdue pegboard (t(46) = -0.44, p = 0.66) performance. Participants in the fast and normal groups had nearly similar pegboard scores. However, those in the normal group appeared to perform the buttoning task faster (35.4±29.6 s) than those in the fast group (24.6±22.2 s).

Stratification by movement amplitude revealed the observation that there were no significant effects of group for either buttoning (t(46) = -1.89, p = 0.06) or the Purdue pegboard (t(46) = 1.48, p = 0.15) task. The small (amplitude reduced at rates near to and above 2 Hz) and normal amplitude groups demonstrated close scores for the pegboard assembly task. Similar to the performance observed in the group stratification by MRΔ, participants in the normal group tended to have shorter time (23.5±21.1 s) for completion of the buttoning task compared to those with small movement amplitude (38.2±30.6 s).

Table 2. Performance on buttoning and Purdue Pegboard tasks of groups based on movement rate and movement amplitude

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
<th>Buttoning Time (s)</th>
<th>Purdue Pegboard Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement Rate Difference</td>
<td>Fast</td>
<td>35.4±29.6</td>
<td>17±8</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>24.6±22.2</td>
<td>16±6</td>
</tr>
<tr>
<td>Movement Amplitude</td>
<td>Small</td>
<td>38.2±30.6</td>
<td>14±8</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>23.5±21.1</td>
<td>16±6</td>
</tr>
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Discussion

The principal finding of this study was that participants with PD that demonstrate increases in movement rate and decreases in movement amplitude at tone rates near to and above 2 Hz seemingly lack differential performance on fine motor tasks of manual dexterity. Stratified by movement rate difference, there were no significant differences between these groups for performance on either the Purdue pegboard task or the buttoning task. Stratifying participants by movement amplitude alone also revealed the lack of statistically significant differences in performance for buttoning or the Purdue pegboard tasks. These results suggest that further investigation on the evaluation of impairments in repetitive finger movement rate at tone rates near to and above 2 Hz, specifically hastening (movement faster than the auditory stimulus), may be needed. This is, after all, a simple method for determining the impact of Parkinson’s disease on fine motor movement tasks. It is possible that the small sample size allocated to the FAST movement rate and SMALL movement amplitude groups lacked the power to provide significant differences for both functional tasks. Although the study hypotheses were not supported, results of repetitive finger movement performance further support the presence of the hastening phenomenon at the critical rate of 2 Hz in some patients with PD. This hastening impairment has been demonstrated in both healthy participants and patients with PD (Muir, Jones, Andreae, & Donaldson, 1995, Nakamura et al., 1978; Espay, 2009). However, people with PD exhibit greater prominence than healthy controls at the 2 Hz critical frequency.

A study that measured finger tapping speed and amplitude in participants with idiopathic PD using an electromagnetic tracking device found that speed categories (slow, and very-slow) were more sensitive to improvement (“normalized”) with levodopa compared
to amplitude categories (low, and very-low) after levodopa therapy (Espay et al., 2009). That particular study did not evaluate the effect of levodopa on movement rates of high speed categories. However, our finding of participants presenting with hastening (FAST group) while on dopamine therapy further supports previous research showing lack of improvement of this movement performance impairment using the same paradigm while participants were on optimal medication (Stegemöller et al., 2009; Stegemöller et al., 2015). Contrary to the group divergence of movement rate difference at 1.75 Hz, normalized movement amplitude for the SLOW group began to significantly deviate at an early rate of 1.25 Hz and persisted to 3 Hz. This consequently indicates that movement amplitude was also not sensitive to medication corroborating the Espay et al. (2009) study. These findings suggest that impairment in repetitive finger movement may be mediated by a non-dopaminergic pathway.

Compared to the normal movement rate group, the hastening phenomenon (FAST group) was revealed at an earlier rate of 1.75 Hz and persisted to 3 Hz (Figure 1A). Movement amplitude but not hastening has been shown, however, to significantly improve at high externally paced rates with subthalamic nucleus deep brain stimulation (Stegemöller, Zadikoff, Rosenow, & MacKinnon, 2013). This improvement in movement amplitude but not rate suggests that separate neuronal pathways may independently modulate movement rate and amplitude. Thus, the lack of significant effect for movement amplitude groups on the buttoning and Purdue pegboard tasks may be due to the fact that participants were tested on medication. It can therefore be inferred that dopamine therapy may not significantly improve amplitude decrement during repetitive movement; however, performance of tasks involving fine manual dexterity in the daily lives of patients may not be significantly hindered.
Taking into consideration that participants for the present study were on medication, it is presumed that the nigrostriatal pathway within the basal ganglia was bypassed and other pathways that involve basal ganglia connectivity with cortical motor regions may potentially be involved in the 2 Hz motor impairment. One of these being the connectivity between the basal and the prefrontal cortex. The prefrontal cortex is thought to be involved in selectively attending to an action or monitoring movements (Durstewitz, Seamans, Sejnowski, 2000). Studies have shown abnormal interaction of the prefrontal cortex and motor areas during movement in people with PD (Jahanshahi et al., 2010; Wu, Wang, Hallett, Li, & Chan, 2010). However, this abnormal interaction is modified with the addition of dopaminergic medication (Jahanshahi et al., 2010; Rowe et al., 2002b; 2010). Using functional magnetic resonance imaging and electroencephalography techniques, Herz and colleagues (2014) found the reinstatement of the connectivity between the premotor and prefrontal cortex after the introduction of levodopa in patients with PD during externally paced movements. On the contrary, if this interaction is reinstated with dopamine therapy, it is possible that the basal ganglia-prefrontal circuity is impaired in participants that exhibit the hastening phenomenon with externally cued tapping despite being on medication. This is a possible explanation of the 2 Hz hastening phenomenon that is not quite understood and needs further exploration.

Additionally, the differing performance on the functional tasks compared to tapping (hastening) may be explained by internally versus externally generated movements. The repetitive tapping task is an auditory cued task and therefore externally generated whereas the functional tasks (buttoning and Purdue pegboard) engender internally generated movements. With self-initiated movements, there is greater medial activation of the rostral and caudal supplementary motor area (SMA), adjacent anterior cingulate cortex, bilateral
dorsolateral prefrontal cortex (DLPFC), and bilateral insular and premotor cortex (Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). These regions may be more active during the buttoning and Purdue pegboard tasks thus yielding similar performances for the movement rate and movement amplitude groups. In contrast, cued movements result in significantly less activation of medial premotor areas, and engages greater activation of the caudal cingulate motor area (Wessel, Zeffiro, Toro, & Hallett, 1997). In this manner, the repetitive finger tapping appears to differentially engage regions of the brain not highly involved in self-initiated movements expected to be involved with the buttoning and Purdue pegboard tasks. The dissimilarity of cortical activation for the tapping and functional tasks may hence not have truly characterized the effect of the hastening phenomenon on the functional tasks of manual dexterity selected for this study.

Furthermore, several studies have demonstrated the involvement of different cortical regions such as the supplementary motor area (SMA), premotor, cerebellum, and posterior parietal area in complex sequential movements, particularly the pre-SMA (rostral SMA) (Catalan, Honda, Weeks, Cohen, & Hallet, 1998; Samuel et al., 1997, Kawashima et al., 1999; Picard and Strick, 1996). The SMA is especially active when movement sequence is remembered and self-determined (Catalan et al., 1998). The buttoning task in itself is a skilled, bimanual task of fine motor control that is acquired from a young age and practiced throughout life, oftentimes without visual aid. The Purdue pegboard task, on the other hand, is a novel task that requires initial learning with practice. Based on this, it can be inferred that there may be greater activation of the pre-SMA with the buttoning task than on Purdue pegboard. Administration of dopamine therapy has been shown to increase activation of pre-SMA and SMA proper compared to non-treated patients (Haslinger, et al., 2001; Rascol et
al., 1992, 1994). The pre-SMA has been implicated in movement recognition and ideation, learning and performing movement sequences, switching between action sets, and is interconnected with the prefrontal cortex (see review Nachev, Wyndell, O’Neil, Husain, & Kennard, 2007). The SMA proper, on the other hand, has direct connections to the primary motor cortex and spinal cord, and is involved in motor execution. If activation of both these regions are increased with medication, it may be that medication somewhat balanced performance observed in both functional tasks irrespective of group assignment.

Is it then the case that dopamine medication has an effect on self-initiated tasks of manual dexterity and not repetitive movement at high movement rates? This is best answered by a study from MacKinnon and colleagues (1996). The authors investigated the simultaneous recordings of pre-movement potentials and positron emission tomography during simple repetitive finger tapping at a rapid rate of 2 Hz, and intermittently without cues. They found that the caudal SMA (SMA proper) was more activated with the rapid movements as opposed to the rostral SMA (pre-SMA) with the discrete intermittent movements. Participants in the present study were on dopamine therapy and still demonstrated differences in finger tapping as well as poor performance on the buttoning and Purdue pegboard tasks. This suggests that either medication may not fully restore SMA activity or that other non-dopaminergic mechanisms contribute to the differences between repetitive finger movement performance and functional fine motor tasks.

Although this study examined the effects of hastening near to and above 2 Hz in acoustically cued finger tapping, it was also of interest to examine the presence of hesitations during this motor impairment. Hastening was previously shown to be accompanied by decrement in movement amplitude and hesitations (Stegemöller et al., 2009). Movement
pattern involving an increase in movement rate and decline in movement amplitude accompanied by motor block (freezing or hesitations) may be recognized as festination (Nieuwboer, et al., 2001). This behavior is characteristic of festinating gait. Festination of gait is an involuntary, rapid increase in cadence accompanied by short step length and freezing (Giladi, Shabtai H., Rozenberg, & Shabtai E., 2001; Nieuwboer et al., 2001). This phenomenon is present in the off and on state in some people with PD (Iansek, Huxham, & McGinley, 2006; Nieuwboer et al., 2001) with the freezing more prominent in those on PD medication for an extensive period of time (Giladi et al., 2001). Although festination is usually associated with gait, results from acoustically cued finger tapping in participants with PD (Freeman et al., 1993; Nakamura et al., 1978; Yahalom et al., 2004, Stegemöller et al., 2009) suggest that finger tapping can also be used to assess finger festination. According to Nieuwboer et al. (2001), gait festination is likened to the hastening and motor blocks also observed during finger tapping in people with PD. As such, the coefficient of variation (CV) of movement rate difference was used to predict the presence of motor blocks (hesitations) in groups of movement rate (Figure 3B) and normalized movement amplitude (Figure 4B). Tone rate was shown to have statistically significant effect on movement rate CV with a trend of those in the fast group having greater variability than the normal group (Figure 3B) at rates near to and above 2 Hz. Although the presence of hesitations in the FAST group did not significantly impair performance on the functional tasks, its presence indicates that it is also not improved by medication. Consequently, repetitive finger movement may be used to evaluate the impact of non-dopaminergic pathways on functional tasks.
Limitations

Although the Purdue pegboard is not a cognitive task, participants had to remember the order of pieces for assembly even with practice. Some participants were guided on the assembly order and successive bimanual hand exchange for grasping assembly pieces during trials. This may also have contributed to the non-significant differences between groups on assembly task performance. A predetermined number of practice runs to ensure true comprehension of assembly sequence may have increased the differences observed between groups. Additionally, participants were tested on medication. Although medication state does not affect the impairment of repetitive finger movement at rates near to and above 2 Hz (Stegemöller et al., 2009), the effects of medication may have contributed to better motor performance on buttoning and Purdue pegboard tasks reducing differences between groups. There was also a lack of clinical data on participants such as the UPDRS score. Correlation of motor performance on the fine motor tasks to scores on the motor section of the UPDRS would be beneficial in understanding the relationship between subjective and quantitative evaluation of motor function in people with PD.

Conclusion

In conclusion, the movement rate of repetitive finger movement does not appear to be a determining factor in the control of finger movements when performing fine tasks of manual dexterity. It may therefore be that the hastening phenomenon does not significantly impact the performance of activities of daily living. The lack of significant effects observed between groups for both functional tasks may be due to the low number of participants assigned to the FAST and SLOW groups. Increasing the sample size may reveal contrasting
results. The results of the study may also be explained by differential pathways modulating externally generated movements and internally generated movements as seen with the cued finger tapping task and the functional tasks used herein, respectively. More studies need to be conducted to determine motor cortical oscillatory activity of hastening behavior in participants with PD at high externally paced cues. The use of quantitative analysis of repetitive finger movement in addition to current clinical assessments of patients with PD may be an advantageous tool in differentiating movements based on rate and amplitude and its impact on daily activities of people with PD.
References


Although some patients do develop symptoms that are not present in others, it is widely accepted that Parkinson’s disease (PD) presents the four cardinal symptoms of rigidity, tremor, bradykinesia, and postural instability. The degeneration of substantia nigra pars compacta dopaminergic neurons projecting to the striatum leads to several electrophysiological and chemical changes. These changes include the increased firing rate of neurons in the globus pallidus internal segment and subthalamic nucleus (Obeso et al., 2000). This consequently increases activation of the globus pallidus interna (output nuclei of the basal ganglia) thus inhibiting the thalamocortical motor system. As a result, the symptom of bradykinesia is often observed in patients with PD. This increase in activity of the basal ganglia output nuclei can be reversed with the administration of dopamine therapy. Clinical symptoms can also be improved with deep brain stimulation of the subthalamic nucleus or globus pallidus interna in addition to other forms of therapy. Of the four cardinal symptoms, bradykinesia was of interest for this research study as it pertains to repetitive finger movement due to its ability to affect fine motor skills and the performance of activities of daily living that include buttoning clothing.

Interestingly, bradykinesia can be improved with dopaminergic agents in people with PD. However, it is observed that during the performance of acoustically cued repetitive finger movement, some people with PD present with a hastening phenomenon at a critical rate of 2 Hz (Nakamura, Nagasaki, & Narabayashi, 1978; Freeman, Cody, & Schady, 1993) accompanied by a decrement in movement amplitude, hesitations and loss of phase.
(Stegemöller, Simuni, & MacKinnon, 2009). Although this hastening is also observed in healthy individuals, it is markedly increased in people with PD as demonstrated with beta band oscillatory activity (Stegemöller, Allen, Simuni, & MacKinnon, 2015; Joundi et al. 2013). This hastening phenomenon was of interest because it appeared to be negligible of a basal ganglia dopaminergic pathway as it has been shown to be unaffected by PD medication (Stegemöller et al., 2009; Stegemöller, Uzochukwu et al., 2015). As bradykinesia is known to affect performance of fine motor skills, it was of interest to investigate the effect of the 2 Hz hastening motor impairment on functional tasks of manual dexterity in people with PD. As such, this study used the assembly task on the Purdue pegboard and the buttoning task.

Results revealed non-significant differences between Purdue pegboard and buttoning tasks in groups stratified by movement rate and movement amplitude. This may be explained by internally generated versus externally generated movement. Both types of movements engage different cortical regions. Cued movements employ greater activation of the caudal cingulate motor area (Wessel, Zeffiro, Toro, & Hallett, 1997) and caudal SMA (SMA proper) for rapid movements (MacKinnon et al., 1996) as seen with tones of 2 Hz or more. Internally generated movements, on the other hand, involve greater activation of motor areas that include both caudal and rostral SMA (pre-SMA), insular and premotor cortex as well as the prefrontal cortex (Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). It is therefore possible that differential pathways affect the hastening phenomenon on the finger tapping task than the functional tasks selected for the study. However, considering that the pre-SMA and SMA proper are both involved in internally generated movements, they are expected to be activated when doing the Purdue pegboard and buttoning tasks. The pre-SMA has particularly been implicated in learning and performing movement sequences (Nachev,
Wyndell, O’Neil, Husain, & Kennard, 2007) and may be more involved in the Purdue pegboard task because it is a novel task therefore resulting in relatively equal scores on the task with groups in both stratified conditions of rate and amplitude. Because buttoning is a well-practiced task and practically second nature, the NORMAL groups in both stratifications produced slightly better time in completing the task.

It can be inferred that as the SMA is involved with performance of the functional tasks, the poor performance of both tasks may be due to medication not fully restoring SMA activity. Consequently, since the SMA proper is also involved in fast repetitive tapping, this explanation may partly account for the hastening effect. To account for the lack of significant differences between groups stratified by movement rate and amplitude on the functional task, it is beneficial to replicate the study with a larger sample size. Understanding the underlying mechanism of the 2 Hz hastening phenomenon will aid understanding of its effect in the daily lives of patients diagnosed with PD. It can therefore have clinical applications in the diagnosis and rehabilitation of people with PD.
References


APPENDIX. IRB APPROVAL

IOWA STATE UNIVERSITY
OF SCIENCE AND TECHNOLOGY

Date: 9/6/2015
To: Dr. Elizabeth L. Stegemoller
235 Forker

From: Office for Responsible Research

Title: Correlates of Repetitive Finger Tapping in Parkinson's Disease

IRB ID: 13-405

Approval Date: 9/6/2015
Date for Continuing Review: 9/16/2017
Submission Type: Continuing Review
Review Type: Expected

The project referenced above has received approval from the Institutional Review Board (IRB) at Iowa State University according to the dates shown above. Please refer to the IRB ID number shown above in all correspondence regarding this study.

To ensure compliance with federal regulations (45 CFR 46 & 21 CFR 50), please be sure to:

- Use only the approved study materials in your research, including the recruitment materials and informed consent documents that have the IRB approval stamp.
- Retain signed informed consent documents for 3 years after the close of the study, when documented consent is required.
- Obtain IRB approval prior to implementing any changes to the study by submitting a Modification Form for Non-Exempt Research or Amendment for Personnel Changes form, as necessary.
- Immediately inform the IRB of (1) all serious and/or unexpected adverse experiences involving risks to subjects or others, and (2) any other unanticipated problems involving risks to subjects or others.
- Stop all research activity if IRB approval lapses, unless continuation is necessary to prevent harm to research participants. Research activity can resume once IRB approval is reestablished.
- Complete a new continuing review form at least three to four weeks prior to the date for continuing review as noted above to provide sufficient time for the IRB to review and approve continuation of the study. We will send a courtesy reminder as this date approaches.

Please be aware that IRB approval means that you have met the requirements of federal regulations and ISU policies governing human subjects research. Approval from other entities may also be needed. For example, access to data from private records (e.g., student, medical, or employment records, etc.) that are protected by FERPA, HIPAA, or other confidentiality policies requires permission from the holder of those records. Similarly, for research conducted in institutions other than ISU (e.g., schools, other colleges or universities, medical facilities, companies, etc.), investigators must obtain permission from the institution(s) as required by their policies. IRB approval in no way implies or guarantees that permission from these other entities will be granted.

Upon completion of the project, please submit a Project Closure Form to the Office for Responsible Research, 1138 Pearson Hall, to officially close the project.

Please don't hesitate to contact us if you have questions or concerns at 515-294-4566 or IRB@iastate.edu.