# On the Role of Attention in Finger Tapping and Towards Continuous, Objective, and Unobtrusive Measurement of Motor Speed

By

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CERTIFICATE OF APPROVAL

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To my daughter,
Who perhaps suffered the most during my schooling…
I love you

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# List of Abbreviations

| | |
|---|---|
| CDR | Clinical Dementia Rating |
| DD | Down Dwell |
| DT | Down Transition |
| FTT | (Halstead-Reitan) Finger Tapping Test |
| IKI | Inter-keystroke Interval |
| IRT | Initial Reaction Time |
| NP | Neuropsychological |
| QDG | Quantitative Digitography |
| SMS | Sensorimotor Synchronization |
| SMT | Spontaneous Motor Tempo |
| SD | Standard Deviation |
| ST | Single Task |
| UD | Up Dwell |
| UPDRS | Unified Parkinson’s Disease Rating Scale |
| UT | Up Transition |

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# Abstract

One of the great challenges facing modern science is the ability to measure cognitive function. This is important for making advances in brain research as well as for clinical practice involving diagnosis and treatment. Unfortunately, cognitive function cannot be measured directly and attempts to assess cognitive function through neuropsychological or other testing is based on comparing patient test scores to normative data to determine whether a patient is impaired. While successful for diagnosing disease and detecting brain damage, this methodology has been hampered in assessing cognitive deficits because the tests are not suitable for making inferences about the underlying cognitive processes involved in test performance. Advances in technology, monitoring and computational modeling generated an opportunity to link cognition directly to behavioral data. One very general approach is the use of computational models to build, fit, and test precise relationships that may link behavioral measurements to cognitive processes underlying the behavior, which we exploit to investigate the relationship between cognitive and motor function.

There has been increasing evidence that motor function is an important indicator of cognitive and physical function. For example, motor slowing precedes cognitive impairment and is diminished in neurodegenerative diseases. One of the most commonly used assessments of motor speed is the Halstead-Reitan finger tapping test (FTT). The FTT has been repeatedly linked to current levels of cognitive function and future cognitive decline, although it is considered to be a simple motor task with little cognitive involvement. In addition to the apparently disparate role of cognitive function in the task – it is perceived as a non-cognitive task despite other work showing cognition relates to

the FTT – the task administration suffers from several shortcomings common to many neuropsychological tests. Specifically, the test is administered infrequently, requires a trained assessor, outputs a final score that is aggregated across trials. These shortcomings make the test unable to distinguish between abrupt change and slower change over time and cause troubles with inter-rater reliability. Further, the test is not specific to different diseases and is not a naturally occurring task in everyday life (i.e., it lacks ecological validity).

In this thesis, we demonstrate that finger tapping does, in fact, recruit cognitive resources by explicitly characterizing the role attention plays in the task (as measured by a serial subtraction task known to also require elements of calculation and working memory). We first develop a novel finger tapping decomposition that allows us to statistically characterize the different physical components of the tapping task. Using this characterization, we are able to demonstrate that reduced attention and increased cognitive load both slows the speed and increases the variability in certain behavioral aspects of tapping (referred to as dwell phases). We also show that reduced attention does not modulate the other behavioral aspects of tapping (referred to as transition phases). Additionally, we demonstrate that monitoring typing at the keyboard during normal computer use can be used as a surrogate for the FTT, which overcomes all the normal limitations of finger tapping assessment outlined above. Specifically, this provides an objective and continuous assessment of motor function that not only has face validity to the FTT but also demonstrates the high correlation between tapping and typing speed, suggesting a high degree of overlap between the cognitive and motor function used in the two tasks.

Taken together, our results not only indicate that finger tapping is a cognitively demanding task but also provide the first steps toward characterizing the interplay of cognitive, motor and sensory function during the task by characterizing the role of attention in the task. We also provide a novel methodology for obtaining a continuous, unobtrusive, and objective assessment of motor function by means of everyday typing at the computer.

# Chapter 1: Introduction

One of the great challenges facing modern science is the ability to measure and make direct inferences about cognitive processes and individuals' cognitive function, which has many applications including improved health care, early detection of disease, and increased understanding of the organization and function of the human brain. To date, cognition cannot be measured directly, thus inference mechanisms must be developed to relate cognitive processes to observed measurements, such as different facets of observed behaviors. Neuropsychological and other clinical testing used currently have attempted to make inferences about cognitive function through various tests that attempt to measure different cognitive domains such as executive function or memory[1]. While successful for identifying various disease states such as Alzheimer's disease or detecting brain damage, these tests often lack specificity and do not measure the underlying mechanisms causing poorer test scores. Instead, they often use a wide body of normative data for similar patient groups (e.g., same age range or gender) to identify "normal" scores from which poor scores can be identified that are associated with poor cognitive function or adverse health outcomes. In order to overcome these limitations in the state-of-the-art of cognitive testing, new approaches are needed that can link cognition directly to something observable, such as behavior.

One of the most promising approaches towards solving this problem is the use of computational models. Within the last 10-20 years, the cost of computing has decreased enough to make feasible the collection of thousands of measurements a second (or more) while also providing the computing power to build, fit, and test precise models linking the large number of measurements from observed behavior to the cognitive processes underlying this behavior. At a high level, the focus of this thesis is on exploring the relationship between cognition and motor function while also addressing some of the problems with measuring cognitive and motor function, as will be described in detail below. However, the overarching theme of this thesis is that the investigations described below are only possible because we specialize the power of computational modeling to one of the most commonly used neuropsychological tests to model a direct and causal link between the important cognitive function of attention and the observed behavior of finger tapping. In particular, we find that if we reduce attention available to the tapping task by adding a concurrent cognitive task, we can measure a coincident change in tapping performance. Attention is a concept that describes one's ability to allocate cognitive processing resources, and our ability to measure attentional capacity depend on the the effects of the cognitive load(s) used to recruit attentional resources. Here and throughout this thesis, when we refer to "attention" we mean the process of allocating resources required to backwards count as defined by the "serial sevens" task (backwards counting from 100 by 7), which serves as the cognitive load used in our experiments as described in more detail below. Serial sevens is widely considered to be an attentional task[103-106] although motivation, calculation[107] and working memory[108] have also been suggested to play a role and the verbal response may require motor resources. To the best of our knowledge, this is one of the first attempts (perhaps the first) to use computational modeling to identify a strong and potentially causal link between cognitive function and a behavior measured by a commonly administered neuropsychological test.

In the following, we introduce the work described in this thesis. We start by discussing the need to study sensorimotor function and discussing the link between motor, cognitive, and physical function. We then discuss in detail one of the most commonly administered neuropsychological tests of motor function, the Halstead Reitan finger tapping test (FTT), which is the observed motor behavior for which we build a computational model. We then discuss the objectives and significance of our work, followed by an overview of the rest of this thesis.

## 1.1 Motor, Cognitive, and Physical Function

The study of sensorimotor function is vital for a variety of reasons. In the clinical setting, motor function has been used to monitor and assess behavioral or functional change associated with aging[2, 3], including identification of pathological conditions that may require increased levels of patient care. Measures of motor function have also been used extensively for diagnosis and assessment of neurodegenerative disease such as Alzheimer's[4] or Parkinson's disease[5], the two most common and perhaps most devastating of the neurodegenerative diseases. Motor function has also been used as an objective assessment of an individual's health status, which may be more accurate than subjective patient complaints. Outside of the clinical setting, the manipulation of motor tasks is used to discover relationships between sensory, motor, and cognitive function[6, 7], which help further our understanding of the interplay between these complex processes.

Substantial research has also shown motor function to be an important predictor and indicator of both cognitive and physical function. For example, motor slowing in elderly patients has been shown to precede cognitive impairment [8-10] and is a risk factor for future hospitalization[11, 12]. Motor speed has also been linked to cognitive function[13, 14] and risk of future disability[15, 16]. Measured levels of motor dysfunction have been used to differentiate between normal aging and different levels of dementia[17, 18], and excessive motor speed asymmetry has been seen in patients diagnosed with probable Alzheimer's disease [19]. Other motor phenomena, such as variability and accuracy, are sensitive to aging[20, 21] and predictive of future cognitive decline[22], are impaired in early stage dementia[23], and are related to cognition[24]. Although the literature implicates motor function for these relationships, the observed relationships likely also depend on the sensory and possibly cognitive components of the measured motor tasks [25-27].

Motor function is measured in a variety of different ways, but perhaps the most commonly used research and clinical assessments involve gait or tapping tasks, which we describe in turn below. Gait, in addition to being a complex motor task, is also widely regarded as a complex cognitive task[28], although this was not always the case. Recently, gait was considered to be produced primarily by a central pattern generator (a neural circuit producing rhythmic output) [29-34] with minimal cognitive involvement. However, numerous studies have linked gait to executive function[28, 35-37] and function in other cognitive domains[38-40]. Studies have also associated gait with cognitive decline[41, 42] and disability[43]. Gait has been linked to falls[44, 45], and abnormal gait patterns have been associated with dementia[46] and the loss of focalized gray matter[47]. Further, various facets of gait have been linked to specific cognitive domains, thus helping to elucidate how specific or diminished cognitive resources modulate gait. For example, one study linked the pace and rhythm of gait to executive function and memory, respectively[48]. Another study found that visuospatial ability, processing speed, and executive function were associated with greater variability in the double support phase of gait (when both feet are on the ground)[40]. Additionally, pathological gait has been studied and identified for many different neurodegenerative and other diseases allowing qualitative gait analysis to distinguish some disease states from healthy states[49] such as festinating gait[50] or freezing of gait in Parkinson's disease[51].

Unlike gait, finger tapping, is generally considered to be a simple motor task with minimal cognitive involvement[28]. In the remainder of this thesis we do not further discuss gait, but note that the trajectory of understanding about gait - from being considered a simple repetitive task with minimal cognitive involvement to a complex cognitive task – is very similar to what we find about finger tapping. Many different finger tapping tasks exist and are routinely used in studying movement disorders [52-55], dementia research [23, 56, 57], and for aging and dual-task experimentation [58-60]. One study showed patients with essential tremor have impaired tapping speed and frequency when compared to age and sex matched controls[61]. A finger tapping task is also included in the motor subscore (Part III) of the assessment of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale[62] and is often used in neuropsychological testing[1, 63]. Despite the perception of tapping as a simple motor task, it has also been widely linked to sensory and cognitive function [9, 17, 18, 52, 56, 64]. However, in contrast to the rich results in the gait literature, these results have all been *correlational* in nature, linking some measure of finger tapping performance, such as absolute speed [9, 17, 18, 52, 56, 64], to function or a disease state - with no specific link elucidated between finger tapping and the specific cognitive and motor components underlying it. Better understanding of the relationship between finger tapping and the cognitive and sensory components underlying it would greatly improve the sensitivity and specificity of tapping as both a diagnostic and research tool.

## 1.2 The Halstead Reitan Finger Tapping Test

By far the most commonly administered tapping task for neuropsychological evaluations and diagnoses [63, 65] is the Halstead-Reitan Finger Tapping Test (FTT) [66], which is widely used to detect both motor and cognitive impairments [1]. The FTT, also called the finger oscillation test[67], is considered to be a relatively pure task of gross motor speed[68, 69] (although it has been suggested that the FTT is affected by alertness, attention, problems with task initiation, and general slowing of responses[1]).

The FTT is scored as the average number of times a patient depresses a key with his or her index finger (each hand is tested separately) during 5 trials on a manual finger-tapping device, where each trial lasts 10 seconds. The test nominally consists of 5 tapping trials, but will continue until either the counts on any five trials are within five of each other or 10 trials are administered[1], although variants on the basic instructions have also been reported[70].

The test is sensitive to brain damage[71, 72], age[73], gender[74], and handedness[75]. The FTT is also sensitive to cognitive decline[9, 76] and mild or early stages of dementia[23, 57]. However, while the test is sensitive to a wide variety of conditions, it lacks specificity. For example, while finger tapping scores could distinguish between healthy controls and patients with motor dysfunction (cerebellar diseases, parkinsonian patients, or hemiparesis of cerebral origin), it could not distinguish between the different motor dysfunctions[75] (note: a non-standard apparatus was used for tapping in this study). Further, it is unclear whether the reduced performance in tapping in early-stage dementias are truly a result of motor slowing, or whether cognitive declines associated with the impairment are directly affecting test performance. In general, the underlying interplay between cognitive and motor function during tapping is not well understood. A more comprehensive understanding of how the tapping task is related to an individual's motor and cognitive abilities (and changes in these abilities over time) is needed to improve the specificity of the task as a diagnostic tool and aid in understanding how certain disease states manifest in tapping behavior.

The FTT also suffers from other problems common to many neuropsychological and clinical assessments. First, the reported outcome is a single number for each trial, which is then averaged across trials. No information about tap-to-tap variability, trial-to-trial variability, or slowing during a trial is measured. However, recent research suggests that measures unrelated to tapping speed, such as variability and accuracy, are related to cognitive ability [22-24], and may be more sensitive to cognitive change than absolute speed. Additionally, the test is performed infrequently – typically, six months or more pass between assessments. As a result, the FTT cannot reliably detect motor changes at the time of onset or distinguish between acute changes and slower changes that have occurred over time. The need for a trained clinician to administer the test using a stopwatch and manual finger tapper can cause issues with inter-rater reliability [74] and makes it more difficult to administer the test outside of a clinical or laboratory setting. A computer based FTT has been proposed to make test administration more precise [77, 78], but does not address the other reported issues. Another shortcoming is that the FTT can confound motor ability with short-term fatigue, which is especially noticeable after several trials. Last, the FTT is not a task naturally performed in daily life, thus lacking ecological validity.

## 1.3 Objectives and Significance

Two main groups of problems have been outlined in the prior two sections of this thesis. The first is the lack of understanding of the interplay between cognition, sensory perception, and motor function during the simple activity of finger tapping. The second is related to test administration shortcomings and ecological validity. In this thesis, we address each issue for the finger tapping during the FTT.

### *1.3.1 Objective 1: Differentiating the Cognitive and Motor Aspects of Tapping*

Our approach to differentiating between the cognitive and motor aspects of finger tapping is based on a novel decomposition of the tapping task into a sequence of component tasks, or phases, that appear to be most heavily influenced by cognitive or motor function. We developed a computational statistical model for the durations of the different component tasks required to effectively tap during the FTT, which allows characterization and independent assessment of the cognitive and motor aspects of tapping. In addition, the model allows determination of fatigue, learning, and variability (tap-to-tap, trial-to-trial, and among the different phases of tapping).

The five individual tasks, or phases, of tapping can be grouped into three parts. The first is the initial reaction time (IRT), consisting of the time to initiate tapping after being directed to tap, which is widely considered to be a measure of (cognitive) processing speed[79]. The next two phases appear to be most heavily influenced by motor function and are defined as down transition (DT) and up transition (UT). These components consist of the time which the flexion/extension of the finger drives the lever from the top position to the bottom (flexion) position or releases the lever from the bottom position to the top (extension). The last phases of tapping are the two that appear to recruit sensory resources and involve cognitive processes: up dwell (UD) and down dwell (DD). These components consist of sensing the top or bottom of the lever and initiating a motor movement in the opposite direction. With this decomposition, an FTT trial (with each tap performed correctly) consists of the following sequence of phases: IRT (first tap only)->DT->DD->UT->UD->…, where each set of four phases DT->DD->UT->UD-> represents a single tap and repeats until the FTT trial is complete. The need for two dwell phases and two transition phases comes from the lack of symmetry in the task. The dwell phases differ in terms of the sensory input available to the finger (the up dwell phase depends on sensing when the finger leaves the tapping lever whereas the down dwell phase depends on sensing when the lever has reached the minimum position, where the lever "hard stops" at the lowest possible lever position). The transition phases differ in terms of the activated muscles (the up transition phase is dependent on finger extension, and the down transition phase is dependent on finger flexion).

The importance of this decomposition is in the ability to group phases into specific cognitive and motor components, and then to use the time in each phase as a way to *characterize* each component. This characterization allows an independent assessment of the different resources recruited during the task (motor and cognitive), and allows assessment of the change in different components due to differing levels of cognition. Example uses include evaluating differences between a patient group and control group (e.g., mild cognitively impaired versus cognitively intact), an individual under a dual task condition (e.g., tapping only versus tapping while backwards counting) or an individual over time (longitudinal assessment). Further, by looking at how time spent in each phase changes over the course of an FTT trial and/or across trials, one can investigate fatigue and learning effects[80, 81], which both can influence the traditional scoring method of the FTT as well as other neuropsychological tests.

One specific question that our research answers using the statistical model of tapping is whether and to what extent finger tapping changes when attentional resources are diminished, using a dual task paradigm. Related to this, we report three specific results tested prospectively in a cohort of 20 elderly subjects. First, we confirm that a

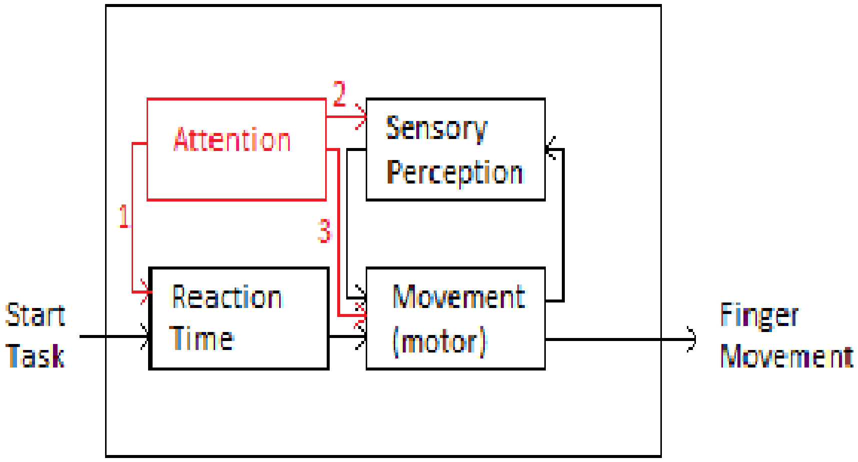

**Figure 1.1. Diagram of finger tapping task decomposition (black) into initial reaction time, motor (down/up transition phases), and sensory components (down/up dwell phases). Red blocks and numbered red arrows show possible ways attention may modulate tapping. We hypothesized and found that attention modulates sensory perception and processing speed, but not speed of movement. This corresponds to red paths 1 and 2 being connected, whereas path 3 is not.**

decrement in tapping (i.e., a lower score) exists and is detected in the dual-task condition compared to tapping only, which is consistent with a body of dual-task research [59, 60, 82, 83]. Second, we found that the observed decrement in tapping is divided between slower task initiation and slower average tapping during the task. Third (see fig 1.1), we determined that time spent in both dwell phases of tapping is longer during dual task, but the time spent in the transition phases is not. These results show, in particular, that the dwell phases are sensitive to an individual's available cognitive resources as measured by reduced attention during the dual-task condition. More generally, these results also suggest that tapping is more than a simple motor task and requires substantial cognitive involvement, like gait[28].

### *1.3.2 Objective 2: Measuring Motor Speed Continuously and Objectively*

In order to overcome the limitations of the clinical test methodology for finger tapping, we proposed and validated typing on a computer keyboard during normal, everyday computer use in a person's own home as a surrogate for finger tapping. Typing has face validity for tapping – the flexion and extensions of normal typing are the same as those used for depressing the finger tapping lever – and is ecologically valid in the sense that using a computer is a normal activity performed regularly. Specifically, in an elderly cohort we show a high correlation between the speed of tapping and the speed of typing, suggesting that much of the motor and cognitive resources involved in tapping overlap with those used during typing. This approach to measuring motor speed overcomes issues with test-retest reliability, inter-rater reliability, infrequent test administration (typing can be monitored as often as it occurs naturally), ambiguity in detected differences, and does not require a trained administrator.

### *1.3.3 Specific Contributions*

This thesis presents three main contributions – an engineering contribution, a basic science contribution, and an application to in-home monitoring. These are:

1) (engineering contribution) A novel computational/statistical model of finger tapping that decomposes the task of tapping into independent behavioral components and comprehensively characterizes an individual's finger tapping behavior from a series of FTT trials.

2) (basic science contribution) Results linking decreased attention (experimentally changed during a dual-task experiment) to an increase in the dwell phases of tapping while the transition phases remain unaffected. Particularly, we find we can induce a change in tapping performance by reducing the attention available to the task, which implicates an important aspect of cognitive function in the performance of specific, independent components of tapping behavior.

3) (applied contribution) Face validity and results demonstrating high correlations between tapping speed measured clinically and the speed of typing in the home demonstrate that tapping and typing share much of the same underlying cognitive and motor resources, and suggest that measuring typing is a viable alternative for measuring motor function.

### *1.3.4 Significance*

The proposed model of finger tapping based on a novel task decomposition, the new results implicating sensitivity of dwell phases of tapping to attention, and typing as an alternative measure of motor function, may have significance in several areas:

- Demonstrating the power of computational modeling in neuropsychology: Detailed observations and precise modeling combined facilitated a direct and possibly causal link between motor behavior and cognitive function (in that we can cause change in tapping by reducing available attentional resources to the task), and has the potential to provide precise and direct inference of other aspects of cognitive function.

- Facilitating precise inferences about cognitive and functional declines associated with tapping: The proposed model has the potential to identify what specific aspect of tapping is impaired when impairment is detected.

- Greater test specificity: The model may be able to distinguish between different motor/cognitive disease states by allowing a characterization of how tapping is affected in different diseases.

- Providing greater understanding of tapping as more than just a simple motor task: Our work provides some of the first steps towards identifying the behavioral characteristics of typing and how differing levels of cognitive and motor function influence them.

- Removing non-patient specific variability from clinical assessments: Measuring typing instead of tapping has the potential to provide a more precise and objective measure of motor (and cognitive) functions.

- Detecting cognitive and motor deficits earlier: Continuous measurement of motor/cognitive function has the potential to detect subtle change earlier than is done clinically with infrequent measurements.

## 1.4 Thesis Overview

The remainder of the dissertation is organized into the following sections:

Chapter 2 (Background) defines and surveys other frequent applications of tapping such as to characterize sensorimotor synchronization and measure spontaneous motor tempo. The brain regions implicated in tapping are then reviewed, and the chapter concludes with a discussion of tapping research more closely related to ours.

Chapter 3[1] (A Statistical Characterization of the Finger Tapping Test: Modeling, Estimation, and Applications) provides a detailed description of the finger tapping task decomposition and the statistical model for the phases that results in a 29 parameter characterization of tapping. Some preliminary applications of the model in a pilot study

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[1] Chapters 3-5 read like journal articles as opposed to chapters. This is because chapter 5 has been published, chapter 3 is under review, and chapter 4 is in preparation. In an effort to keep consistency throughout the thesis (and to alleviate copyright concerns), each of the chapters has the same structure.

of healthy subjects are presented including measurement of fatigue and the first steps toward measuring the effect of attention on tapping.

Chapter 4 (The Role of Attention in the Halstead Reitan Finger Tapping Test) presents the main results linking motor function, sensory perception, and attention. In addition to presenting precisely the results outlined above (1.3.1 Objective 1: Differentiating the Cognitive and Motor Aspects of Tapping), results further characterizing this relationship are presented. This includes the link between tapping variability and attention and the relationship between several neuropsychological tests of attention and tapping.

In chapter 5 (Measuring Motor Speed Through Typing: A Surrogate for the Finger Tapping Test) a case is made for measuring motor speed during typing as a surrogate for tapping. Many of the shortcomings in test administration are presented along with a case for typing at the keyboard having face validity to finger tapping. A strong correlation is also presented between the speed of typing and the speed of tapping in both the dominant and non-dominant hands, suggesting significant overlap in the cognitive and motor resources underlying both typing and tapping.

In chapter 6 (Summary and Conclusion), the main findings of my thesis are summarized along with a brief discussion of future directions.

# Chapter 2: Background

In this chapter, we provide background information on areas of research related to finger tapping. In section 2.1, we discuss two non-clinical uses for finger tapping: to study sensorimotor synchronization and to measure spontaneous motor tempo. We then present and discuss imaging studies that have helped identify cortical areas involved in finger tapping before discussing the dual-task paradigm and attention. This is followed by a discussion of work similar and perhaps most relevant to ours, which is intended to address some of the shortcomings associated with current measurements of finger tapping, and highlight some of the advantages and applications of our work not addressed by these other contributions.

## 2.1 Other Applications of Finger Tapping

In this section we discuss two common, non-clinical areas that extensively use finger tapping tasks – the study of sensorimotor synchronization and spontaneous motor tempo. Both research areas are important but fundamentally different from the work we present in this thesis as we discuss below.

### *2.1.1 Sensorimotor Synchronization*

Sensorimotor synchronization (SMS) is the rhythmic coordination of perception and action[84]. SMS is studied frequently in the laboratory with tapping tasks that require a subject to tap – often with the index finger – in time with a metronome or other auditory stimulus. This type of tapping task is popular in large part because of the simplicity of the task and the ability to conveniently study basic mechanisms of SMS[85]. Some of the important findings have been the understanding of rate limits for SMS, where a frequency range of 0.55 Hz – 5 Hz has been reported[84]. In musically trained participants, the ability to maintain synchronization at higher frequencies has been investigated, with an upper threshold of 8.3-10 Hz reported[86]. Other studies have investigated negative mean asynchrony (the tendency for finger taps to slightly precede the metronome/auditory tone) in musically trained and untrained participants[87, 88], examined variability in response timing[89], and investigated the neurobiology of rhythmic motor timing[90]. While work in this area is certainly important and exciting, the fundamental questions being investigated are substantially different from those investigated clinically, and the tapping task is inherently different from the FTT. In particular, our work with finger tapping is not concerned with synchronization; rather we investigate the role of attention in unsynchronized tapping performed as fast as possible.

### *2.1.2 Spontaneous Motor Tempo*

Spontaneous motor tempo (SMT) is often measured by an unpaced tapping task, where individuals' are asked to tap at a rate that feels natural and comfortable[91]. SMT is thought to be biologically determined[91, 92] and to reflect an internal timekeeper[93]. SMT has been shown to slow with age[94]. One recent use of SMT was to assess differences in the underlying mechanisms of duration production (estimating a length of time) and reproduction (estimating a previously observed length of time). The study investigated the role of the internal clock and working memory in duration production and reproduction. The results suggested that duration production was only correlated with SMT while working memory was only correlated with reproduction, suggesting different mechanisms underlying duration production and reproduction[95]. Other studies have found an age-related slowing in SMT, but that SMT is stable within a given age[91, 96]. In general, work using unpaced tapping and the study of SMT is closely related to tapping tasks for SMS in the sense that the intent of using tapping tasks is for timing (e.g., producing and reproducing intervals), as opposed to the study of motor function or for clinical diagnoses. However, the work on SMT differs substantially from ours in that we seek to investigate the role of attention in a speeded finger tapping task as opposed to investigating the nature of an internal timekeeper.

## 2.2 Cortical Regions Implicated in Finger Tapping

In addition to measuring motor phenomena and aspects of human timing, finger tapping has also been used extensively to study the anatomical human motor system[97, 98]. A recent meta-analysis of 38 imaging studies with varying finger-tapping tasks suggested the primary sensorimotor cortices, supplementary motor area, premotor cortex, inferior parietal cortices, basal ganglia, and anterior cerebellum are all neurocorrelates of finger-tapping[99]. Other studies have focused on specific tapping tasks to elucidate the neural correlates specific to these tasks. For example, one study found increasing regional blood flow in the primary sensorimotor cortex with increasing tapping frequency, whereas the pre-supplementary motor area and cingulate motor area showed increased activity only when tapping frequency deviated from the subjects' own comfortable pace[100]. The authors suggested that the pre-supplementary and cingulate motor areas may be involved in motor control under difficult conditions as opposed to movement execution. Another study reported that index finger flexion during repetitive self-paced tapping activates the supplementary motor area, premotor cortex, and cingulate motor area with increased activation in the supplementary motor area compared to the cingulate motor area, suggesting that the supplementary motor area plays a more integral role in self-paced tapping[101]. Perhaps the most relevant to the research presented in this thesis is a study that investigated how attention modulates cortical activity in sensorimotor areas. Using a backwards counting task (considered to be an attentional task) as a distractor dual-task, it was shown that the reduction in attention to the tapping movement as a result of the distractor task resulted in a negative interaction (less activation in the region compared to the sum of activation from the individual tasks – tapping and counting) in the supplementary motor area, cingulate cortex, insula, and post-central gyrus[82]. While our thesis does not confirm or pursue the neural correlates of tapping and attention, it does describe behavioral correlates of tapping and attention, thus enriching the imaging studies with similar behavioral results.

## 2.3 Closely Related Work

The key to interpreting the experimental results we present in chapter 4 lies in understanding the dual-task paradigm. Additionally, some work – most notably in the study and assessment of Parkinson's disease – has addressed shortcomings similar to those outlined for the FTT. In this section, we discuss dual-tasking and other work in tapping most closely related to ours.

### *2.3.1 Dual Task Paradigm*

The dual-task paradigm consists of having participants perform two tasks separately, and at the same time to determine whether there is interference between tasks. In particular, performance on the individual tasks are compared to performance on the dual-task, and if performance is degraded on the dual-task as compared to one or both individual tasks, then we can infer some overlap exists in the required resources (e.g., cognitive) for both tasks. Often when only one task is of interest, the second task is considered a distractor task and the investigator only focuses on performance in the first task alone and under dual-task.

This paradigm has been used extensively with motor tasks to study the role of cognitive control of motor systems. For example, one study compared the difference in stride velocity and stride variability between walking and walking while counting backwards[102]. The study found that stride velocity decreased and stride variability increased during the dual task – especially in older adults – and concluded that cognitively demanding tasks can destabilize normal gait, which may increase the risk of falls. Other studies have found similar results in cognitively impaired subjects when counting backwards[26] or performing a working memory task[25]. One fMRI study also looked at the role of attention to movement in finger tapping[82] and found that tapping slowed during the attentional dual task (serial subtraction), although the main purpose was mapping the brain regions modulated by the attentional task by monitoring blood flow in the brain. Thus the change in tapping was not well characterized – only slower mean tapping was reported.

As will be described in more detail in chapter 4, our study uses a dual task paradigm combining tapping with a variant of the so-called serial seven's task of counting backwards from 100 by 7s. This task is widely considered to be an attentional task[103-106] (although calculation[107] and working memory[108] have also been suggested to play a role in backwards counting). The dual-task methodology will be used to investigate the role of attention in finger tapping from a *behavioral* viewpoint, which will enrich studies such as [82] by providing a behavioral analogue of changes seen in blood flow in the brain while also suggesting that finger tapping, like gait, may be more cognitively complex than previously believed.

### *2.3.2 Overcoming Limitations of Tapping Tests*

Several attempts have been made to make finger tapping tests or their analyses more comprehensive in assessing disease states from healthy states. Most often, this is done by proposing a new test or test variant that is more amenable to analysis or using new equipment in the measurements (or both). One study proposed the use of an image based motion analyzer to track finger movement and proposed a new score based on speed and regularity of the movements that appeared to be useful for staging of Parkinson's disease patients in a small cohort[55]. Another group suggested using a time-frequency approach to track the potentially non-stationary movement that can occur within a single finger tapping trial[109] (although they did little more than demonstrate the approach on a few single trials of data). Other groups have used magnetic sensors placed on the fingers[110] or an accelerometer and touch pad sensor[54] for assessment of disease severity in Parkinson's.

Another body of work has had substantially more success in clinical research. One group proposed using a Musical Instrument Digital Interface (MIDI) keyboard to measuring finger tapping on an alternating finger taping task, where a participant is asked to alternate between striking one key with the index finger and one key with the middle finger for the duration of the test. The task combined with derived performance measures is called Quantitative Digitography (QDG), and it was shown to be sensitive to motor control in idiopathic Parkinson's [111]. In a follow up paper, it was demonstrated that the velocity of finger movement had a strong, negative correlation with the Unified Parkinson's Disease Rating Scale part III (UPDRS III [62], a measure of motor function) score (faster finger movement during tapping is associated with better motor function), and the coefficient of variation in the duration of the key press had a strong positive correlation with the UPDRS III score, suggesting that more variability in tapping is associated with poorer motor function in Parkinson's[112]. Several other applications followed including the quantification of bradykinesia (slowness of movement)[113-115] and the study of the effectiveness of deep brain stimulation for relief of Parkinson's symptoms[116].

While these approaches provide a more comprehensive characterization of motor function, they do not elucidate the underlying phenomenon of tapping. These approaches also introduce new test methodologies that have not been widely used clinically, perhaps due to the small "proof-of-concept" validation studies, lack of normative data, and need for clinicians to acquire new equipment and learn to interpret and use the results from these tests. In contrast, we instrumented a widely used neuropsychological test (the Halstead Reitan finger tapping test) with a potentiometer to measure the angle of the finger tapping lever, which is proportional to lever position[65], and created a statistical model that can be applied to the newly attained data. This permits researchers to continue using an established test and the normed results, while benefitting from a more complete characterization of the subjects’ performance.

# Chapter 3: A Statistical Characterization of the Finger Tapping Test: Modeling, Estimation, and Applications

Daniel Austin, James McNames, Krystal Klein, Holly Jimison, and Misha Pavel

## 3.1 Abstract

Sensory-motor performance is indicative of both cognitive and physical function. The Halstead-Reitan finger tapping test (FTT) is a measure of sensory-motor speed commonly used to assess function as part of a neuropsychological evaluation. Despite the widespread use of this test, the underlying motor and cognitive processes driving tapping behavior during the test are not well characterized or understood. This lack of understanding may reduce test sensitivity in clinical assessments intended to discriminate between health and disease states because it ignores important aspects of the task such as variability or fatigue. To overcome these limitations, we enhanced the tapper with a sensor that enables us to more fully characterize all the aspects of tapping. This modification enabled us to decompose the tapping performance into 6 component phases and represent each phase with a set of parameters having clear functional interpretation. This results in a set of 29 total parameters for each trial, including change in tapping over time, and trial-to-trial and tap-to-tap variability. These parameters can be used to more precisely link different aspects of cognition or motor function to tapping behavior. We demonstrate the benefits of this new instrument with a simple hypothesis-driven trial comparing single and dual-task tapping.

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### 3.2 Introduction

Sensory-motor function is an important predictor of cognitive and physical function, both of which are key indicators of an individual's current and future health status. For example, motor slowing in elderly patients has been shown to precede cognitive impairment [8-10] and is a risk factor for future hospitalization [11, 12]. Motor speed has also been linked to cognitive function [13, 14] and risk of future disability [15, 16]. Measured levels of motor dysfunction have been used to differentiate between normal aging and different levels of dementia [17, 18]. Excessive motor speed asymmetry has been seen in patients diagnosed with probable Alzheimer's disease [19]. We note that although the literature faults motor function, the observed functionality depends on sensory and possibly cognitive functions [25-27].

One specific task often used to assess motor function in the clinical setting is finger tapping. Various finger tapping tasks are routinely used in Parkinson's disease research [52-55], dementia research [23, 56, 57], and for aging and dual-task experimentation [58-60]. The most commonly administered tapping task for neuropsychological evaluations and diagnoses [63, 65] is the Halstead-Reitan Finger Tapping Test (FTT) [66], which is widely used to detect both motor and cognitive impairments [1]. The test is scored as the average number of times a patient depresses a key with his or her index finger during five 10-second trials on a manual finger tapper, which is treated as a measure of motor speed. Each hand is tested separately. The test nominally consists of 5 tapping trials, but will continue until either the counts on 5 trials are within 5 of each other or 10 trials are administered [1]. Variants on the basic instructions have been reported.

Despite the widespread use of the FTT, it suffers from two main drawbacks. First, the reported outcome is a single number for each trial, which is then averaged across trials. No information about tap-to-tap variability, trial-to-trial variability, or slowing during a trial is measured. However, recent research suggests that measures unrelated to tapping speed, such as variability and accuracy, are related to cognitive ability [22-24], and may be more sensitive to cognitive change than absolute speed. Second, the underlying phenomenon of tapping is not well understood. In particular, results linking finger tapping to sensory, cognitive or physical function have been *correlational* in nature, linking some measure of finger tapping performance, such as absolute speed [9, 17, 18, 52, 56, 64], to function or a disease state with no specific link elucidated between finger tapping and the specific cognitive and motor components underlying it. Understanding how performance on the tapping task is related to motor and cognitive abilities could improve the sensitivity of the task as a diagnostic tool.

Several studies have proposed methods to address shortcomings such as these [54, 55, 75, 117] in other areas of research, primarily by utilizing novel tests or measurement apparatuses to measure motor function more accurately or comprehensively. For example, a MIDI keyboard has been used to assess several characteristics of tapping, such as velocity and dwell time on the tapping key, during an alternating finger tapping task in Parkinson’s disease patients [111, 112]. While these approaches provide a more comprehensive characterization of motor function, they do not elucidate the underlying phenomenon of tapping. These approaches also introduce new protocols that lack historical publications and familiarity. For these reasons, new tests are often slow to be adopted clinically and it often requires many years before sufficient validation, understanding, and familiarity lead to widespread adoption.

To explore the phenomenology underlying tapping, we instrumented the widely used neuropsychological finger tapping test (FTT) with a potentiometer to measure the angle of the finger tapping lever, which is proportional to lever position [65]. We then model and characterize tapping based on a decomposition of the recorded tapping movement into six different phases that may be related to different aspects of cognition, perception, and motor ability. This permits researchers to continue using an established test and the normed results, while benefitting from a more complete characterization of the subjects' performance.

## 3.3 Methodology

### *3.3.1 Instrumentation*

The finger-tapper was constructed by John Hunt (OHSU) as an exact replica of the Reitan Neuropsychology Laboratory manual tapper (www.reitanlabs.com). A potentiometer was installed on the shaft of a Veeder-Root brand counter (model 0727235-002). The angular displacement of the potentiometer then represents the angular displacement of the counter, while requiring a negligible additional force in relation to the counter. The wiper arm of the potentiometer was connected to a USB-1208FS DAQ (Measurement Computing, Norton, MA) to sample the voltage at a (user programmable) sampling frequency of 512 Hz. Matlab R2012a was used to record from the device and perform subsequent analyses described below. The voltage measured at the potentiometer is proportional to the angular position of the finger tapping lever, and is converted to degrees to represent the deflection of the lever from the resting position (the top position of the lever). The length of the lever is one inch from the shaft to the tip, and has a maximum arc length of 45º. A minimum arc length of 40º is required to add one count to the mechanical counter. In the conversion from voltage to degrees, we set the top lever position as 0º and the bottom lever position as -45º, thus the resulting measurements are the angle of deflection of the lever from the top position. The hardware is shown in figure 3.1. Further details can be found in [118].

### *3.3.2 Model*

Our statistical characterization of tapping is based on decomposing the tapping task into a set of non-overlapping component parts, or phases of tapping. The underlying model of tapping performance is based on these phases occurring in a specific order with (idealized) instantaneous switching times between phases. We then characterize each phase with a set of parameters that represent metrics of performance (e.g. time intervals), thus producing a parametric model of tapping. The six phases of tapping are as follows:

1. **Initial Reaction time (IRT)**, the time from when the tapping task begins to when tapping starts.
2. **Down transition (DT)**, the time during which the finger drives the lever from the top position down to the bottom position.
3. **Down dwell (DD)**, the time during which the lever is depressed.
4. **Up transition (UT)**, the time during which the finger releases the lever and returns to the top position.

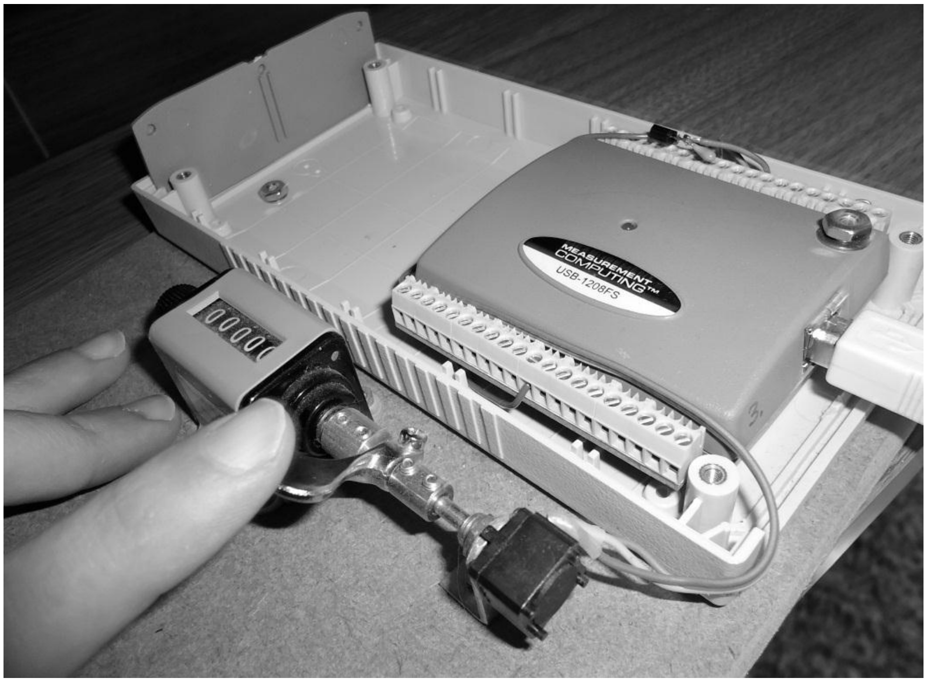

**Figure 3.1. A close up of the instrumented replica of the Halstead-Reitan manual finger tapper. The cover has been removed to show the internal electronics.**

5. **Up dwell (UD)**, the time during which the lever has been fully released.
6. **Incomplete tap (IT)**, during which the lever is either not fully depressed or not fully released.

The normal flow of tapping consists of the following phase transitions: IRT→DT→DD→UT→UD…, with DT→DD→UT→UD→ repeating until the task stops. Note there is only one reaction time phase for each trial. Taps are considered incomplete when either the down dwell or up dwell phases are skipped, indicating the task was not performed correctly. Figure 3.2 shows a segment of raw tapping data and the start of different phases (the phase is considered to last until the beginning of the next phase) for a participant who performed a 10 second tapping trial. As can be seen from figure 3.2, partitioning the signal into phases allows determination of the time, or duration, spent in each phase over the course of a trial.

To characterize the individual component phases of tapping, we represent each by a random variable that represents the duration of time spent in that phase of tapping, except for IT. For simplicity, IT is characterized by the number of occurrences. The IT phase is treated differently for two reasons. First, time spent in the IT phase can vary depending on how many taps in a row are performed incorrectly. Second, this phase does not always occur in a tapping trial. We also explicitly model the tapping cycle, TC (a sequence of DT→DD→UT→UD), as a random variable representing the sum of the durations of time spent in each of the (sequentially performed) component phases.

### *3.3.3 Algorithms – Tapping Segmentation*

Before we can statistically characterize a person's finger tapping, the tapping signal from each trial must be segmented into the different phases. To do so, we estimate the start and

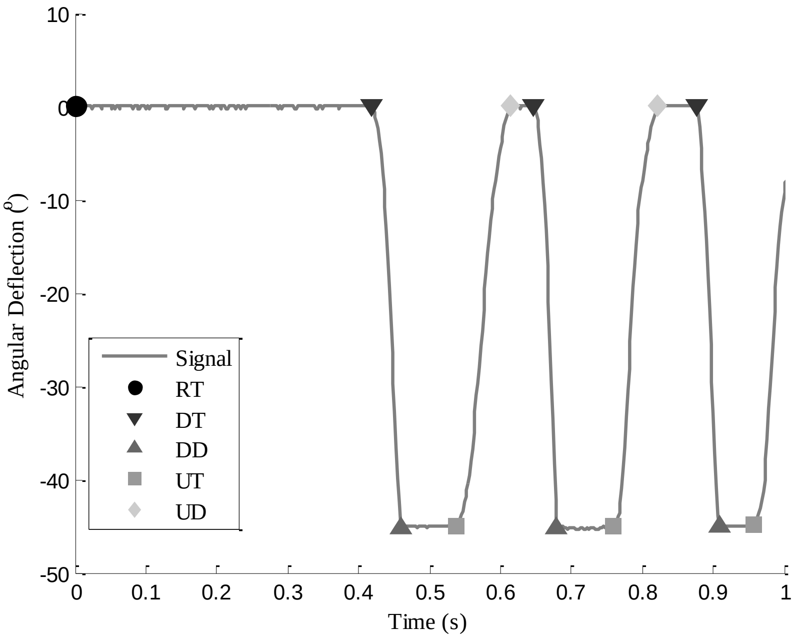

**Figure 3.2. Finger tapping data (gray line) with the start of each of the phases described in the text: initial reaction time (IRT; circle), down transition (DT; upside down triangle), down dwell (DD; triangle), up transition (UT; square), and up dwell (UD; diamond). Incomplete tap (IT) is not depicted.**

end of each phase for each tapping trial, and then estimate the durations as the time between the estimated start and end points. This consists of several steps, but the main idea is to find the best estimates of the start and end times for the UD and DD phases based on thresholds of the device (top and bottom lever positions), then label the durations between these phases as incomplete, motor down, or motor up based on a simple set of rules identifying the phases.

The segmentation algorithm has several steps. The angular position signal is represented as $s_k$, where $k$ is the sample index. The algorithm first estimates the upper and lower thresholds, $\theta_U$ and $\theta_L$, respectively, from $s_k$ by finding the most frequently occurring signal value in the top half (upper threshold) and bottom half (lower threshold) of the signal range. This is done by constructing a histogram with the number of bins equal to the number of samples in a finger tapping trial, and identifying the histogram peaks corresponding to the largest and smallest values. Because the analog to digital converter discretizes $s_k$, the largest number of samples of the same value occurs when the tapping lever is at the device top and bottom, confirming the validity of the histogram method. In addition to the upper and lower thresholds, a noise tolerance $\theta_N$ is calculated as:

$$\theta_N = \max\big(0.018°, \min\big(\max(s_k) - \theta_{U,} \theta_L - \min(s_k)\big)\big) \tag{3.1}$$

where 0.018º is an empirically chosen level for the minimum noise threshold. After estimating the thresholds, each $s_k$ potentially belonging to the UD and DD phases are identified as

$$s_k \in \{ \begin{matrix} UD \text{ if } s_k > \theta_U - \theta_N \\ DD \text{ if } s_k < \theta_L + \theta_N \end{matrix} \tag{3.2}$$

The next step ensures all individual samples falling within the previously classified UD and DD phases are correctly classified. Any unclassified samples falling between two UD samples with no DD samples in between that are also separated by less than 19.5 ms, are classified as UD. An analogous step is performed to search for unclassified DD samples. This smoothing mitigates classification errors from (3.2) due to noise, where the 19.5 ms sample was determined empirically from early pilot data from two instrumented tappers. The classification of UD and DD phases is finished by refining the start and end points by up to one sample, to make sure that they coincide with crossing the device thresholds, $\theta_U$ and $\theta_L$, and are not affected by noise. The start point of each set of points labeled UD is removed from the set if the tapping signal derivative, $s'_k > 0$ and $s_k < \theta_U$, as this set of conditions corresponds to detecting the start of the UD phase too early. An analogous set of checks is used to refine the end points of all UD phases, and start and end points of the DD phases.

At this point, all signal samples corresponding to the UD and DD phases are labeled. To label the remaining phases, we iterate sequentially through the signal and use the following rules (ignoring unlabeled points): 1) if UD is followed by DD, the unlabeled time from the end of the UD phase to the start of the DD phase is labeled as DT, 2) if DD is followed by UD, the unlabeled time from the end of the DD phase to the start of the UD phase is labeled as UT, 3) the time from the first sample to the first DT phase is labeled as IRT if no other phase has been labeled in between, and 4) everything else is labeled as IT. Figure 3.2 shows an example of applying this algorithm to the first second of tapping data from one trial of tapping. Once the data is partitioned into phases, the durations of each phase are calculated as the difference in end time and start times.

### *3.3.4 Algorithms – Session Analysis*

Given a characterization of the individual movements, it is possible to analyze the detailed performance of each individual subject over the course of trials and for the entire session. This is important in order to assess move-to-move variability as well as learning and fatigue effects. Our statistical analysis is based on two additional assumptions. First, we model any changes that occur over the duration of the trial as linear. This assumption is appropriate because any changes in duration that occur during a 10 s trial are gradual relative to the variability from tap to tap; nonlinear trends are not apparent and difficult to estimate. Second, we assume the durations are Gaussian random variables with a potentially small amount of impulsive noise contamination. The impulsive noise part of the second assumption models incorrectly segmented phases and phenomena such as attentional lapses, which occur infrequently and result in isolated instances of uncharacteristically slow or fast phase durations. These outlier data are identified and removed via an iteratively re-weighted least squares[119] approach: each set of phase-trial data is robustly regressed onto time, and data points whose residual from the regression is greater than 1.5 times the interquartile range of the residual distribution, are removed. By assuming a normal distribution, the form of the phase densities is constrained, facilitating estimation. We model the time course of durations in each phase and across trials using a mixed effects model [120], comprising a combination of fixed average population effects and random trial-specific effects:

$$y_{ij} = (b + b_i) + t(m + m_i) + \varepsilon_{ij} \tag{3.3}$$

where $y_{ij}$ is the *j*th duration of a phase for the *i*th tapping trial, *t* is time during the trial, $b$ (offset) and $m$ (slope) are the fixed effects representing the average tapping behavior independent of trial number. Each phase is modeled and fit separately. The trial-specific offset and slope, $b_i$ and $m_i$, are random effects representing trial-specific effects, and are drawn from a Gaussian distribution:

$$\begin{bmatrix} b_i \\ m_i \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_b^2 & \sigma_{bm} \\ \sigma_{mb} & \sigma_m^2 \end{bmatrix}\right) \tag{3.4}$$

The noise component

$$\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^{\ 2}) \tag{3.5}$$

is also drawn from a zero-mean Gaussian distribution. The statistical model described by (3.3)-(3.5) can then be estimated via maximum likelihood or other methods [120] in readily available software packages. Further, most packages report whether the entries in the covariance matrix in (3.4) are statistically different than 0 (or this can be readily computed from the output of most statistical packages), which indicates whether the

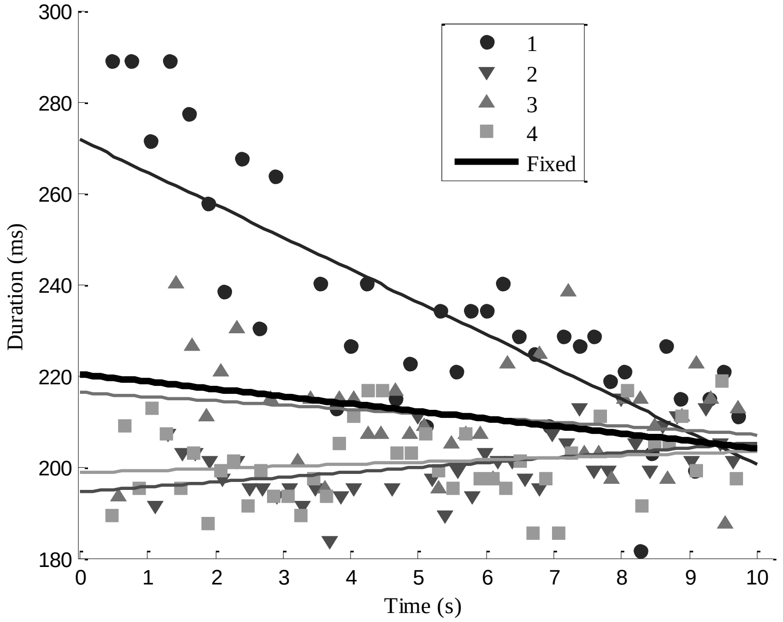

**Figure 3.3. Raw data (symbols) and best fit lines (solid traces) for tapping cycle duration over four finger tapping trials (trial number represented by shades of gray and symbol style) as well as the population line ("fixed effect line"; thick black).**

random effects can be omitted from the model and the fixed effects can be estimated with the pooled estimator (pooling all the samples into a standard linear regression). An example of raw tapping cycle data and the linear fits described by (3.3) for a participant who completed four tapping trials is shown in figure 3.3.

The parameters estimated from the model characterizing each phase of tapping and the tapping cycle are $b$, $m$, $\sigma_b$, $\sigma_m$, and $\sigma_\varepsilon$. Each has an intuitive physical interpretation: $b$ represents the average phase duration at the beginning of a trial, $m$ represents change in phase duration over the period of a single trial, $\sigma_b$ represents trial-to-trial variability in starting duration, $\sigma_m$ represents trial-to-trial variability in change over the period of a single trial, and $\sigma_\varepsilon$ represents tap-to-tap variability (as each phase happens once per tap). In addition to these 25 parameters (5 parameters for each of 4 phases and TC), we also calculate the average and standard deviation of the IRT phase, $\mu_{IRT}$ and $\sigma_{IRT,}$ which serves as a measure of central processing speed. Finally, we also calculate the

**Table 3.1. List of all 29 finger tapping Test parameters (SD is standard deviation).**

| Phase | Parameters | Description |
|---|---|---|
| Tapping Cycle | $b_{tc}$, $m_{tc}$, $\sigma_{\mu,tc}$, $\sigma_{m,tc}$, $\sigma_{\varepsilon,tc,}$ | Initial duration, slope, SD of average across trials, SD of slope across trials, SD of residuals. |
| DT | $b_{DT}$, $m_{DT}$, $\sigma_{\mu,DT}$, $\sigma_{m,DT}$, $\sigma_{\varepsilon,DT}$ | Initial duration, slope, SD of average across trials, SD of slope across trials, SD of residuals. |
| DD | $b_{DD}$, $m_{DD}$, $\sigma_{\mu,DD}$, $\sigma_{m,DD}$, $\sigma_{\varepsilon,DD}$ | Initial duration, slope, SD of average across trials, SD of slope across trials, SD of residuals. |
| UT | $b_{UT}$, $m_{UT}$, $\sigma_{\mu,UT}$, $\sigma_{m,UT}$, $\sigma_{\varepsilon,UT}$ | Initial duration, slope, SD of average across trials, SD of slope across trials, SD of residuals. |
| UD | $b_{UD}$, $m_{UD}$, $\sigma_{\mu,UD}$, $\sigma_{m,UD}$, $\sigma_{\varepsilon,UD}$ | Initial duration, slope, SD of average across trials, SD of slope across trials, SD of residual. |
| IRT | $\mu_{IRT}$, $\sigma_{IRT}$ | Mean, SD across trials. |
| IT | $\mu_{IT}$, $\sigma_{IT}$ | Mean, SD across trials. |

average and standard deviation of the number of incomplete taps, $\mu_{IT}$ and $\sigma_{IT}$, which serves to measure adherence to the task. Altogether, a total of 29 parameters characterize a set of tapping trials for a subject. These are summarized in Table 3.1.

### 3.4 Example

One practical application of the proposed characterization is that it allows for substantially more precise inferences about tapping than can be made using the average number of taps, which is the current clinical standard. To demonstrate this, we performed a small pilot study to investigate fatigue during tapping and the effects of attention on tapping. Eleven subjects were recruited from among the students and staff at the Oregon Health & Science University (Portland, OR, USA) to perform a series of eight tapping trials. This study was approved by the OHSU institutional review board. Four of eight trials simply required subjects to tap. The remaining four trials required subjects to tap under a dual-task condition where subjects were asked to simultaneously count backwards by seven from a number randomly selected between 100 and 110. The backwards counting is a variant of the commonly used “serial-sevens” task which is considered to be a measure of attention [108]. In the dual-task condition we seek to reduce the amount of attention available for the tapping task. Subjects performed the tasks in alternating order with 75 seconds of rest between each trial. Subjects were instructed to tap as quickly as possible during tapping only trials and to tap as quickly as possible while counting backwards as quickly and accurately as possible during dual-task trials. We intended for subjects to put equal emphasis on performing each task well. The entire experiment took approximately 10 minutes per subject.

In addition to recording tapping with the instrumented tapper, we also recorded the number of taps completed in each trial as is done during typical clinical administration of this test. Data from one subject was completely excluded for not following instructions tap as fast as possible. Two subjects had their fourth trial of each condition excluded for late starts. This left 38 trials each of tapping only and dual task across 10 subjects.

After characterizing each subjects' tapping data, we tested several research hypotheses we made prospectively about fatigue during tapping and the relationship between tapping and attention, which we describe in more detail below. We used both count data recorded from the manual tapper (the clinical test scores) and various parameters from the statistical characterization of tapping, described in more detail below. In the analyses that follow, the statistical tests used to test our research hypotheses are *t*-tests if the data are approximately normally distributed (assessed via Lilliefors' test for normality and inspection of histograms), and Wilcoxon signed rank tests [121] otherwise. Both these tests assess whether there is a difference in central tendency between groups or when compared to 0. Statistical significance was assessed at the 5% level.

First, we tested the hypothesis that subjects slow during tapping trials. This cannot be determined by clinical test administration and scoring. We tested our hypothesis by determining whether the mean slope of the fixed effects for tapping, $m_{tc}$, across subjects was greater than 0 using a one-sided *t*-test. We tested tapping only and dual-task conditions separately, and found that, in both cases, the slope was positive and

**Table 3.2. The results of hypothesis testing: tests 1-5 are paired *t*-tests; 6 - 9 are paired Signed Rank tests.**

| Hypothesis | Effect size | Standard error | Degrees of freedom | Test Stat | *p* value |
|---|---|---|---|---|---|
| 1) Subjects fatigue within tapping trials. | 2.2 ms/s | 0.68 | 9 | 3.25 | 0.00500 |
| 2) Subjects fatigue within dual task trials. | 3.0 ms/s | 0.45 | 9 | 6.7 | 0.00004 |
| 3) FTT score is lower in dual task. | -3.6 | 0.86 | 9 | -4.14 | 0.00130 |
| 4) Tapping cycle is slower in dual task. | 10.6 ms | 5.04 | 9 | 2.09 | 0.03300 |
| 5) IRT is slower in dual task. | 302 ms | 79.48 | 9 | 3.8 | 0.00200 |
| 6) DD is slower in dual task. | 7.49 ms | - | - | 15 | 0.11621 |
| 7) UD is slower in dual task. | 7.74 ms | - | - | 15 | 0.11621 |
| 8) DT is slower in dual task | -0.55 ms | - | - | 27 | 0.50000 |
| 9) UT is slower in dual task | 0.42 ms | - | - | 24 | 0.38477 |

significantly different than 0, indicating slowing. We also found a more robust slowing during dual-task, as shown in table 3.2 (tests 1 and 2).

Next, we tested the hypothesis that attention modulates tapping by slowing both reaction time and tapping speed. We first compared whether the clinical score (average number of taps) was lower (indicating slower tapping) under dual-task condition than during tapping only. We used a one-sided paired *t*-test, and found that the average number of taps recorded was 3.6 fewer during the dual-task condition. This difference could have been caused by slower reaction time, slower tapping speed, or both. To test our research hypothesis, we tested (statistically) both the difference in initial reaction time, $\mu_{\text{IRT}}$, and the difference in average tapping cycle speed defined as $b_{tc}+5m_{tc}$ (the initial speed plus the slope halfway through the test) between task conditions. Both tests were conducted using one-sided, paired *t*-tests. We found both components of tapping were significantly slower during dual task, which indicates that the slowing is due to both slower task initiation and slower average tapping, thus confirming our hypothesis as accurate.

The last research hypothesis we made regarding the effect of attention on tapping was that attention would differentially affect some of the phases of tapping. As attention is an aspect of cognition, we hypothesized that both dwell durations, DD and UD, would be affected by the dual-task condition, as this appears to be where cognition would play the largest role during the tapping cycle. In particular, the dwell durations consist of sensing the top/bottom of the tapping lever followed by initiating a motor command to move the finger in the opposite direction. On the other hand, we hypothesized that the transition times, UT and DT, would not be affected by the dual task as they are simple motor functions: driving/releasing the lever is done via a simple flexion/extension of the finger. To test the dwell-duration hypothesis, we tested (statistically) whether the initial values of the dwell phases, $b_{DD}$ and $b_{UD}$, were slower in dual task compared to tapping only. We completed analogous tests for $b_{DT}$ and $b_{UT}$. All four tests were done using a paired one-sided signed rank test. We found that, while not reaching significance ($p=0.116$ for both), the dwell durations showed a trend towards slowing, while the transition times appeared not to change, as shown in table 3.2 (tests 6-9). This is also shown in Fig.3.4, where the tapping only data has been plotted against the dual task data for each of the four hypotheses 6-9. For hypothesis 6 and 7, the majority of the data lie above the x=y line suggesting a decrement in performance, whereas the data for hypotheses 8 and 9 cluster on or near the x=y line suggesting no difference. Based on the *p*-values and Fig. 3.4, it appears the lack of significance for dwell durations (hypotheses

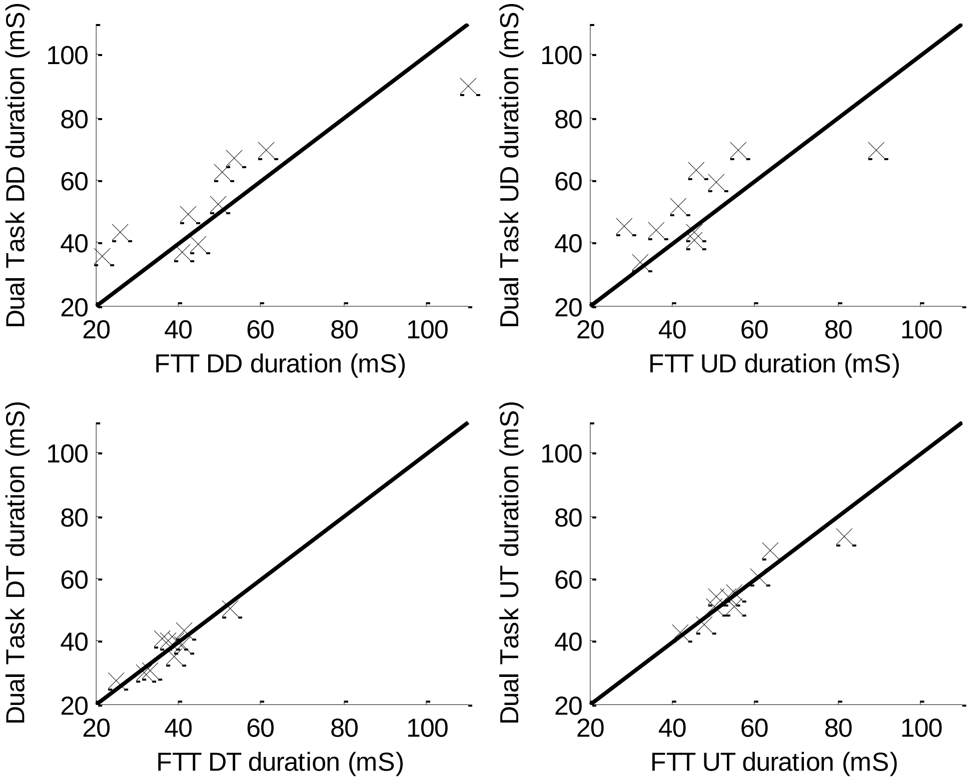

**Figure 3.4. Scatter plots of raw data for dual task dwell times plotted against tapping only (FTT) dwell times for the four repeated phases of tapping in experiments along with the x=y line for reference (solid black).**

6-7) was likely due to the small number of subjects used in this pilot study and the loss of statistical power by using a non-parametric test.

### 3.5 Discussion

In our study, only 2.9 outliers were removed per trial on average, out of an average of 39 durations per trial. This suggests a small proportion of contamination due to poor signal segmentation, attentional lapses, or other unmodeled effects. During model fitting, this contamination was enough to leverage the parameter estimates and required removal for the mixed effects model's distributional assumptions to hold. The purpose of the model is to capture the general character of a person’s tapping behavior, so the removal of a small portion of points inconsistent with this general behavior is justified. However, in some patient populations, the number of outliers may be large or the data distributed in a way that violates some of the distributional assumptions of the model. For these cases, the model can be fit with robust methods [122]. Additionally, in certain other cases the outliers themselves may be informative, in which case they can also be represented in the tapping characterization.

The tapping characterization consists of 29 parameters, which is large compared to the single count outcome currently used clinically from the same test. However, each of the parameters has a clear physical and neuropsychological interpretation covering a different aspect of the tapping process, making each parameter potentially useful in clinical diagnosis or research investigations. Further, not all parameters need to be used or even estimated in every investigation. For example, studies of fatigue may only require estimation of the slopes. The variety of parameters that can be used to characterize the tapping is precisely the advantage of the proposed approach over a single clinical score. There are several outcomes that have been linked to lower tapping scores spanning the range from cognitive deficits to adverse health outcomes [8-16]. However, it is unclear what aspect of tapping is causing the lower scores in each case, or which is/are most sensitive to cognitive decline or poor health outcomes. Our characterization of tapping overcomes this by explicitly allowing investigators to study different aspects of tapping that are specific to patient populations or interventions. Further, our characterization of tapping includes parameters describing trial-to-trial and tap-to-tap variability, which may be more sensitive to detecting cognitive change [22, 24] than absolute measures, such as average number of taps.

The model described by (3.3) is very general and can be changed to account for phenomena not included here that may be important in certain cases. For example, our experimental paradigm gives fixed and lengthy rest periods between tapping trials in a cohort of healthy adults. As a result, there is no reason to expect slowing over consecutive trials. However, in certain populations this may be an important aspect of the model, especially in populations who may fatigue and not fully recover between consecutive tapping trials. This systematic effect of trial order can be added to the model by adding additional terms, such as slopes and/or offsets, to account for this ordering. In a test scheme with little to no rest between trials, we may propose that the model should be:

$$y_{ij} = (b + b_i + ic) + t(m + m_i + id) + \varepsilon_{ij} \tag{3.6}$$

where the parameter $c$ represents an offset that is trial dependent and $d$ represents a slope that is trial dependent. Other phenomena not considered here may also be included by adding parameters to (3.3) or deriving additional measurements from the raw tapping data.

In addition to the advantages of the proposed tapping characterization, there are also some shortcomings. First, the proposed methodology is more expensive due to the additional instrumentation and computer that are required to collect the data. Second, the distributional assumptions for the mixed effects model must be satisfied for the model to give meaningful estimates of the 29 parameters estimated in this framework. Third, special software is required to analyze the data. We believe that the advantages of the proposed approach significantly outweigh the disadvantages.

### 3.6 Summary

In this paper, we presented a novel adaptation of the Halstead Reitan Finger Tapping Test; one of the most commonly used neuropsychological assessments. This approach is based on decomposing a tapping signal recorded from an instrumented manual tapper into different, non-overlapping phases that may be related to different aspects of cognitive and motor function. We provided algorithms to segment and estimate a total of 29 parameters that characterize tapping, while also suggesting how other aspects of tapping may be incorporated into the model. We also gave a detailed example demonstrating how this type of characterization can be used to test specific hypotheses about the relationship between tapping and attention, and also to investigate the effects of fatigue. We further outlined the benefits and shortcomings of the proposed approach with specific emphasis on the ways in which the approach can be used to make inferences that cannot be made by the current clinical testing methodology.

# Chapter 4: The Role of Attention in the Halstead Reitan Finger Tapping Test

## 4.1 Abstract

The Halstead-Reitan finger tapping test has long been considered to be a simple test of motor speed. Despite this consensus, the test has repeatedly been linked to cognitive function, future cognitive decline, and the diagnosis and staging of neurodegenerative diseases. Despite the numerous connections between finger tapping and cognition, the findings have been correlational in nature, linking some aspect of performance – such as speed of tapping – with cognitive function or decline. As a result, it is unclear whether the declines in tapping performance are related to declines in motor function coinciding (or preceding) declines in cognitive function, or whether the cognitive declines themselves are modulating tapping performance. More generally, it is unclear whether and to what extent cognitive function plays a role in simple repetitive finger tapping during the finger tapping test. Recently, a new statistical characterization of tapping was presented that decomposed the tapping task into different physical components that appear to be mostly influenced by cognitive or motor function. In this paper we use this new characterization with a dual-task paradigm (attentional dual task) in a cohort of elderly patients to study the role of attention – one domain of cognitive function – on finger tapping. We find that specific phases of tapping, called dwell phases, are sensitive to reduced levels of attention while other phases of tapping, called transition phases, are not. These results suggest both that finger tapping is a cognitively demanding task, and

that different physical aspects of finger tapping can be linked independently to cognitive and motor function.

## 4.2 Introduction

Finger tapping is generally considered to be a simple motor task with minimal cognitive involvement[28, 68]. Many different finger tapping tasks exist and are routinely used in studying movement disorders [52-55], dementia research [23, 56, 57], and for aging and dual-task experimentation [58-60]. A finger tapping task is also included in the motor subscore (Part III) of the assessment of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale[62] and is often used in neuropsychological testing[1, 63]. Despite the perception of tapping as a simple motor task, it has also been widely linked to sensory and cognitive function [9, 17, 18, 52, 56, 64]. However, these results have all been correlational, linking some measure of finger tapping performance, such as absolute speed [9, 17, 18, 52, 56, 64], to function or a disease state with no specific link elucidated between finger tapping and the specific cognitive and motor components underlying it. As a result, the underlying interplay between cognitive, sensory, and motor function is not well understood.

By far the most commonly administered tapping task for neuropsychological evaluations and diagnoses [63, 65] is the Halstead-Reitan Finger Tapping Test (FTT) [66], which is widely used to detect both motor and cognitive impairments [1]. The FTT, also called the finger oscillation test[67], is considered to be a relatively pure task of gross motor speed[68, 69] (although it has been suggested that the FTT is affected by alertness, attention, problems with task initiation, and general slowing of responses[1]).

The FTT is scored as the average number of times a patient depresses a key with his or her index finger (each hand is tested separately) during 5 trials on a manual finger-tapping device, where each trial lasts 10 seconds. The test nominally consists of 5 tapping trials, but will continue until either the counts on any five trials are within five of each other or 10 trials are administered[1], although variants on the basic instructions have also been reported[70].

While FTT is sensitive to cognitive decline[9, 76] and neurodegenerative diseases[23, 57], it lacks specificity[75] as multiple conditions can cause similar changes in overall tapping performance. Further, it is unclear whether the reduced performance in tapping in neurodegenerative diseases, such as Alzheimer's disease, is truly a result of motor slowing or whether cognitive declines associated with the impairment are directly affecting test performance. In general, the underlying interplay between cognitive and motor function during tapping is not well understood. A more comprehensive understanding of how the tapping task is related to an individual's motor and cognitive abilities (and changes in these abilities over time) could improve the specificity of the task as a diagnostic tool, for example in distinguishing between different neurodegenerative diseases, by understanding how certain disease states manifest in the physical process of tapping..

Recently, a new statistical characterization of finger tapping was presented that decomposes the task of tapping into a set of distinct physical components, or phases of tapping[123]. In this chapter, we use this characterization of tapping with a dual-task paradigm to examine the role of attention on tapping in an elderly cohort. Among other things, we find that certain phases of tapping that appear to be predominantly related to sensory perception and task switching, called dwell phases, are sensitive to attention while other phases of tapping that appear to be predominantly influenced by motor function, called transition phases, are not. In particular, we find that when we reduce attention available to the tapping task with a dual task paradigm, the dwell phases of tapping to become slower and more variable when compared to tapping only. In contrast to prior studies, these results demonstrate a possibly *causal* relationship (in that we can cause changes in tapping performance by reducing attentional resources). In particular, we reduce avaliable cognitive resources (predominately attentional, as defined by the resources required to perform the "serial seven's" task[103-106]) with a dual task and then measure a coincident change in tapping behavior in a *specific* and independent aspect of the physical process of tapping. This further demonstrates that the FTT is a cognitively demanding task and provides the first results in what we expect to be a comprehensive characterization of finger tapping as a complex cognitive and motor task.

## 4.3 Methods

### *4.3.1 Subjects*

Twenty subjects were recruited from a cohort of 33 subjects who were enrolled in a health coaching study. The Oregon Health & Science University's institutional review board approved this study (IRB #00007466). Mean subject age was 80.5 years with a standard deviation of 8.33 years, 10 subjects were female, 17 were Caucasian, 3 were black, and 2 were left-handed by the Handedness Inventory[124]. Average education was 14 years (SD 3.14 years). No subjects were demented as measured by the clinical dementia rating scale[125] (CDR=0 for all participants). All subjects had a comprehensive neuropsychological examination within a year of recruitment for our experiment. The details of the neuropsychological examination are described elsewhere[126]; we describe the neuropsychological data used in this study below. Each subject was compensated for their time (approximately 15 minutes) with a $25 gift card. One subject tapped two or fewer times during all four dual task trials and was excluded from the analysis due to insufficient data (our model of tapping cannot be fit with so few data points), leaving data from 19 subjects for comparison.

### *4.3.2 Experimental Design*

Subjects were asked to complete a series of four experimental blocks consisting of three, ten second trials in each block. Each block consisted of one FTT trial with the dominant hand, one trial of backwards counting by seven from a number randomly selected between 100 and 110 (no numbers were repeated within subject trials), and one dual-task trial of tapping while backwards counting. The tapping task was performed using an instrumented manual finger tapper designed as an exact replica of the Reitan Neuropsychology Laboratory manual tapper (www.reitanlabs.com), described in detail elsewhere[118] (see also below). The backwards counting task was a slight variant of the so-called “serial seven’s” task where subjects were given a random number between 100 and 110 to count from. This was used to reduce memorization and learning effects during the eight total counting trials. This task is considered to be an attentional task[103-106] (although calculation[107] and working memory[108] have also been suggested to play a role in backwards counting). This task was chosen because it can be performed on the same time-scale as an FTT trial (10 seconds) and uses an auditory response, which is less likely to confound the motor task than another motor response.

Subjects were randomly assigned to one of two starting groups. Ten subjects started with the counting only task and the remaining ten with the tapping only task. The last task for all subjects in each block was the dual-task to allow subjects to do both single tasks in each trial before attepting the more challenging dual-task. The tasks were all explained and demonstrated for each subject prior to beginning the first experimental block, and subjects were encouraged to use the manual tapper and count backwards prior to beginning the experiment. The time between tasks was set so that 75 seconds elapsed between each tapping trial - whether tapping only or dual task – to reduce sensorimotor fatigue. All tasks were initiated visually using custom software written in Matlab (MATLAB Release 2012a, The MathWorks, Inc., Natick, Massachusetts, United States). The operating system used was Windows 7, which is not a real-time operating system and can introduce additional variability in the specific start time of the task. As a result, there is some additional variability – on the millisecond level – in when the task started, but each task was recorded for 10 seconds.

Before each trial, a fixation point (a large X) was displayed on the screen for 3 seconds. After 3 seconds were up, a large “GO!” (for the tapping only task) or number between 100 and 110 was displayed (dual-task and counting only), which served to alert the subject to initiate the appropriate task. Instructions were given between each trial about which task would be performed next. When tapping, subjects were instructed to tap as quickly as possible with the dominant hand. During counting, subjects were instructed to state the number shown on the screen and then to count backwards from this number by 7’s out loud as quickly and accurately as possible until the task was over. During the dual-task condition, subjects were instructed to tap as fast as possible while simultaneously counting backwards as fast and accurately as possible, with the additional instruction to put equal emphasis on each task. These instructions combined with the short 10 second trials helped mitigate the effects of test strategy on the task (e.g., pacing versus an all-out approach), although subjective instructions such as this can increase variability between subjects. The task ended when the “GO!” or number was removed from the screen. A video camera was used to capture auditory counting responses and to record the motion of the hand during tapping.

### *4.3.3 Data*

Several data were collected for this experiment. Demographic information was collected from the subjects prior to the experiment (age, gender). Custom Matlab software collected a voltage proportional to the angle of the shaft on the manual finger tapping lever at a rate of 512 Hz during the tapping tasks, which was processed to estimate a set of parameters that characterize tapping[123]. Auditory recordings for all counting tasks (counting only or dual-task) were annotated into a list of numbers corresponding to subjects counting responses. The number of taps counted by the manual tapper (as used clinically) for all subjects and all counting trials were recorded.

Additionally, several neuropsychological variables from each subjects’ most recent neuropsychological evaluation were gathered. Three common and widely used measures of attention and processing speed were collected – trail making test part A[127], digit span forward[128], and digit symbol test[129]. An attention “z-score” was constructed as the average of normalized versions of each of these three tests—normalized with respect to the group specific mean and standard deviations of the ISAAC[126] cohort at baseline enrollment. Additionally, a global cognitive z-score – providing a summary estimate of a person's overall cognitive function – was calculated from 13 neuropsychological tests spanning the range of cognitive domains: executive function, working memory, attention/processing speed, memory, and visuospatial. We also used the time to walk 30 feet as a measure of motor function. All analyses of the data presented below used the bootstrap[130] to calculate significance (the *p*-value for statistical tests and correlations) as the data (except for the z-scores) described in this section are not well approximated by normal distributions and non-parametric methods may reduce statistical power for the added distributional generality. More specifically, *p*-values were estimated as follows – 10,000 bootstrap replicates (each the same size as the original data set) were constructed by randomly sampling with replacement from the original data. The test statistic is then calculated for each replicate (e.g., the correlation coefficient), the empirical distribution of the test statistic is approximated from these bootstrap replicated test statistics, and the *p*-value can be estimated from the empirical distribution. Further description of this procedure can be found in many places, for example chapter 16 of[130].

### *4.3.4 Statistical Characterization of the FTT*

Recently, a characterization of the FTT was proposed and validated that decomposes the physical process of tapping into non-overlapping component parts, and models these parts separately in a statistical framework. A full description is available elsewhere[123];

here we give a summary for completeness. The proposed characterization provides parameters for within and across trial characterization of cycle time (CT; time to complete a finger oscillation), initial reaction time (IRT – the time from when the tapping task starts to when the subject starts tapping), down transition (DT – the time to fully depress the lever), down dwell (DD – the time between when the lever is completely depressed until it is first released), up transition (UT – the time to fully release the lever), and up dwell (UD; the time between when the lever is fully released and when it is first depressed again). IRT is characterized by the mean and standard deviation across trials, whereas CT, DT, DD, UT, and UD are all characterized by initial values (the duration of the phases at the start of the task), change over time (a linear slope characterizing average change within trial), and tap-to-tap variability in the duration (a standard deviation describing how much left over variability exists after fitting a line to the data). These parameters allow investigation of finger tapping during the FTT at a microscopic level previously unavailable. Hypotheses involving specific aspects of tapping as outlined below are tested using the parameters provided by this new characterization of tapping.

## 4.4 Results and Discussion

### *4.4.1 Prospective Hypotheses*

The design of this study was driven by three main research hypothesis that were investigated prospectively with a set of 11 statistical tests. The first hypothesis was that tapping would be faster when only tapping compared to the dual task, as measured clinically (by FTT score). This was tested with a one-sided, paired difference bootstrap test on the tapping scores. The second hypothesis was that both task initiation (IRT) and true speed of tapping (CT) would be slower during the dual-task condition compared to tapping only. Both of these were also tested with one-sided, paired difference bootstrap tests on the mean IRT and mean CT, respectively.

The last hypothesis was that the physical aspects of tapping that appear to be most heavily related to cognitive processing[123] (DD and UD) would be slower in the dual-task compared to tapping only whereas the physical aspects of tapping that appear to be most heavily influenced by motor function (DT and UT) would not be slower. This research hypothesis was tested with eight statistical tests broken into two sets of four tests. The first set of four tests examine this research hypothesis at the beginning of the tapping tasks with one-sided, paired difference bootstrap tests on the *initial* values for DT, DD, UT, and UD, respectively. The second set of four tests examine this research hypothesis at the *midpoint* (or average; calculated as the initial value plus half of the linear change over the course of the test) of the tapping tasks – when fatigue or learning

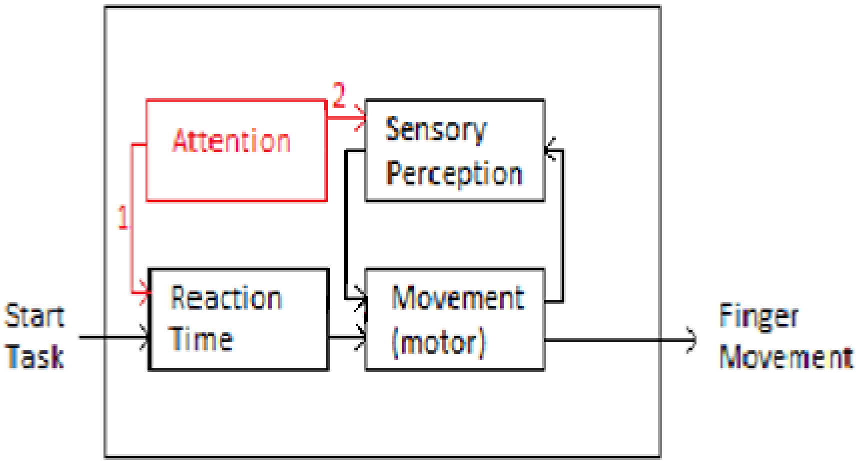

**Figure 4.1 Diagram of finger tapping task decomposition (black) into initial reaction time, motor (down/up transition phases), and sensory components (down/up dwell phases). Red blocks and numbered red arrows show the hypothesized way attention modulates tapping. We hypothesized and found that attention increases variability and slows sensory perception, and also slows processing speed, but does not modulate time spent in movement as indicated here.**

effects may have come into play – with one-sided, paired difference bootstrap tests on the average values for DT, DD, UT, and UD, respectively. Our hypothesized process model demonstrating our hypotheses and potential alternatives is shown in figure 4.1.

The test number, description and results for all 11 prospective tests are shown in table 4.1. Tests 1-5, 8, and 9 in table 4.1 are considered significant at the 5% level if the p-value is smaller than a Bonferroni correction for seven multiple comparisons ($p < 0.0071$). Tests 6, 7, 10, and 11 are considered significant if they reject the null hypotheses at the uncorrected 5% level ($p < 0.05$). We corrected for seven comparisons instead of eleven because tests 6, 7, 10, and 11 are consistent with our research hypotheses if the null are *not* rejected. As a result, we do not seek to make the null more

**Table 4.1. Results of prospective hypothesis tests. For tests 4-11, in addition to the effect size the proportion of change is shown (average change divided by average tapping only duration) to aid in interpreting the results.**

| Test | Null Hypothesis / Description | Effect Size | p value |
|---|---|---|---|
| 1 | Tapping is not faster (score is higher) in tapping task than dual task | 14.199 taps | <0.0001 |
| 2 | Initial reaction time is not longer in dual task than tapping task | 811.27 ms | <0.0001 |
| 3 | Cycle duration is not longer in dual task than tapping task | 62.936 ms | <0.0001 |
| 4 | Initial Down Dwell duration is not longer in dual task | 20.601 ms<br>(27.16%) | <0.0001 |
| 5 | Initial Up Dwell duration is not longer in dual task | 18.862 ms<br>(29.36%) | 0.0030 |
| 6 | Initial Down Transition is not longer in dual task | 5.744 ms<br>(11.69%) | 0.1734 |
| 7 | Initial Up Transition is not longer in dual task | 5.4476 ms<br>(7.29%) | 0.2512 |
| 8 | Average Down Dwell duration is not longer in dual task | 18.736 ms<br>(26.77%) | <0.0001 |
| 9 | Average Up Dwell duration is not longer in dual task | 14.239 ms<br>(20.01%) | 0.0161 |
| 10 | Average Down Transition is not longer in dual task | 5.9515 ms<br>(12.46%) | 0.0036 |
| 11 | Average Up Transition is not longer in dual task | 4.527 ms<br>(6.25%) | 0.1529 |

difficult to reject for these tests, as this would unfairly bias the results in our favor.

Research hypotheses one and two are confirmed by the results in table 4.1 (test 1-3). Slower tapping during an attentional dual task has been reported elsewhere with a different tapping task[82], thus our results for the first research hypothesis are consistent with and support the prior literature[123]. The positive results of the second research hypothesis, which is untestable from the current clinical method for scoring tapping, suggest that attention modulates the task in different ways—it slows task initiation and interferes directly with the physical process of finger tapping. This result.is important because it suggests that tapping is sensitive to diminished cognitive resources, but still does not elucidate whether the slowing is general or specific to certain aspects of tapping.

The results for tests 4-11 in table 4.1 help further determine the role of attention in tapping. The first set of tests, tests 4-7, demonstrate that when the task starts, the dwell phases of tapping are significantly slower during dual task (between 27-29% slower during dual task with respect to tapping only) while the transition phases of tapping were not changed by the attentional task. However, at the test midpoint this relationship does not quite hold (tests 8-11) as the UD phase becomes marginally non-significant against the Bonferroni correction and the average DT phase becomes significantly slower in dual task. Further, the *p*-value for the average UT phase has lowered, suggesting it may reach significance in a larger sample size. Despite this, the effect size as a percent change in transition phases is only 6-12% whereas it is 20-26% for the dwell phases, suggesting a larger effect on the dwell phases than tranistions, even if it is not as clearly delineated by the statistics as at task intiation. This suggests that the robust effect of attention only in the dwell phases of tapping becomes diluted as fatigue and learning effects (represented as linear slopes in the tapping characterization[123]) modify initial performance. However, the clear and robust results demonstrating the selective modulation of attention on the dwell phases of tapping during task *initiation* demonstrate that the phases of tapping that appear to predominately utilize cognitive and sensory resources are affected by diminished attention while the phases that appear to most heavily use motor resources are not affected. Specifically, the dwell phases in tapping *at the start of the task* are robustly sensitive to attentional resources (as measured by serial seven's), demonstrating that tapping is substantially more cognitively demanding than previously thought.

### *4.4.2 Post-Hoc Analyses*

After analyzing the data prospectively, we identified 15 additional hypotheses to test post-hoc to further elucidate the relationship between tapping, attention, cognitive function, and motor function. The large number of post-hoc tests results from the fact that this type of data has never before been available, thus this section describes exploratory analyses designed to discover strong novel relationships in the data, and weaker relationships that may be confirmed in future studies. As with the prospective tests, we use the Bonferroni correction for an experiment wide 5% error. For 15 multiple comparisons, the correction gives $p < 0.00333$ to be considered statistically significant. All tests/correlations were done using the bootstrap – correlations are Pearson correlations for linear relationships – and all $p$-values reported are 2-sided. These tests also naturally break into groups characterizing different aspects of tapping which are listed with the results in table 4.2. All variability measures are standard deviations. Tests 1-5 in table 4.2 used data from all 19 subjects, tests 6-15 used data from 18 subjects (one subject's neuropsychological test scores were missing and the subject was therefore excluded).

We first sought to determine whether variability in tapping speed was different between tapping only and the dual-task condition. The results indicate that variability on a tap-to-tap basis was significantly different and more than twice as large in the dual task

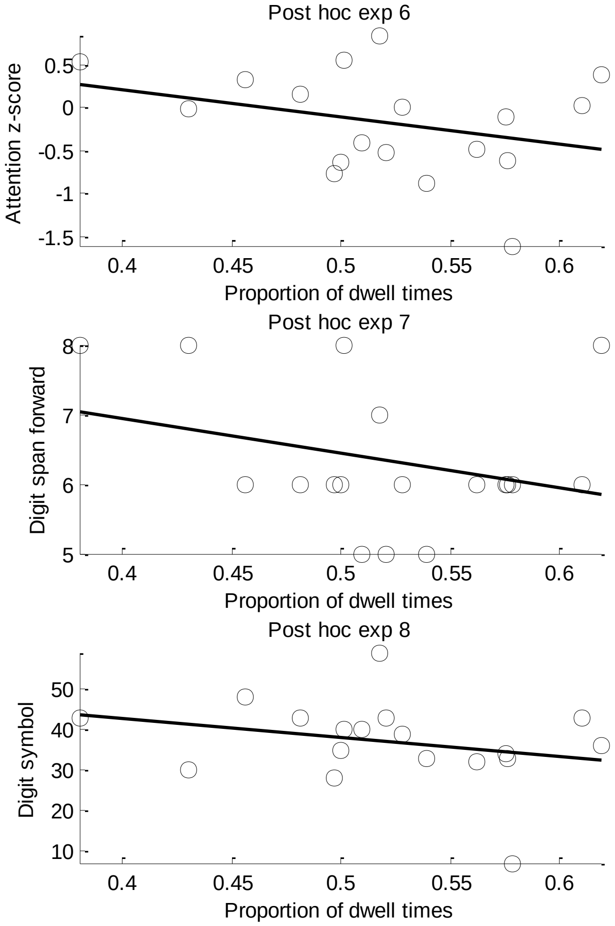

**Figure 4.2 Scatter plot of neuropsychological tests (attentional z-score, digit span forward, and digit symbol, respectively) against the proportion of dwell times along with the best fit line. These data represent post hoc experiments 6-8 and show the trends towards significance in the negative correlations between proportion of dwell times and the neuropsychological tests (longer dwell times are negatively correlated with attention).**

test condition than during tapping only, but that neither variability in initial tapping speed nor variability in the change in tapping speed (both calculated across trials) differed significantly between the tasks (tests 1-3, table 4.2). This suggests that reduced attention increases variability in each tap, but does not increase variability in performance across trials.

We then analyzed the differences in counting performance between the counting only trials and the dual task trials. We found that during dual task, participants tended to give the correct counting response 10% less often than during counting only, and also tended to follow the directions (reading the number shown on the screen at the beginning of the task, before commencing counting) about 10% less often (tests 4-5, table 4.2), although neither result quite reached statistical significance.

Next, we sought to determine whether the proportion of time spent in the dwell phases of tapping during tapping only correlated with clinical tests of attention. This was driven largely by the fact that the dwell phases of tapping appear to be sensitive to attentional resources as demonstrated prospectively. As outlined above, there are three main tests of attention in addition to the composite attentional z-score (higher is better) used in our cohort. The scores used as measures of attention are: digit span forward (higher is better), digit symbol (higher is better), and trails making part A (lower is better). While none of the correlations reached significance, we found that the calculated correlations for three of the measures of attention were in the expected direction as shown in Fig. 4.2 (tests 6-8, table 4.2). Trail making A did not seem to be associated at all with the proportion of time spent in the dwell phases of tapping. We also investigated the correlation with a global (cognitive) z-score calculated from a composite of domain specific z-scores. The calculated correlation was in the expected direction (larger z-score corresponds to "better" cognitive function) but was small and failed to reach significance (test 10, table 4.2).

We then looked at the relationship between the dwell phases of tapping and gait, calculated as the time to walk 30 ft. We found that neither proportion of time spent in the dwell phases of tapping nor larger tap-to-tap variability were associated with time to walk (tests 11-12, table 4.2).

Next, we looked at whether variability in the dwell phases of tapping was different during dual task than tapping only and whether variability in the transition phases was different during dual task than tapping only. We found that variability during the dwell phases of tapping was moderately greater in dual task – just missing significance with the Bonferroni correction – but that the variability in the transition phases did not differ between task conditions, strengthening the prospective result that time spent in the dwell phases of tapping is sensitive to attention (tests 13-14, table 4.2). That is, both duration and variability in the dwell phases are sensitive to attention, but neither is sensitive to attention in the transition phases of tapping. The last relationship we looked at was whether the variability in the dwell phases of tapping are correlated with the attentional z-score. We found a small to moderate negative correlation, suggesting that increased variability is associated with poorer attention, although this did not reach significance (test 15, table 4.2).

### *4.4.3 Further Discussion*

Taken together, the results of the prospective and post-hoc analyses demonstrate the importance of the dwell phases of tapping as sensitive measures of the attentional

**Table 4.2. Results of post-hoc analyses. DT is dual task, ST is single task (tapping only or counting only as the description indicates), and NP is neuropsychological. Group means are not reported for correlations.**

| Test | Null hypothesis/Description | DT Group Mean | ST Group Mean | Effect Size | *p*-value |
|---|---|---|---|---|---|
| 1 | Tap-to-tap variability is not greater in dual task compared to tapping only. | 29.917 ms | 13.882 ms | 16.09 ms | 0.0012 |
| 2 | Initial tapping (cycle) speed variability across trials is not greater in dual task than tapping only. | 47.161 ms | 23.432 ms | 23.7 ms | 0.2736 |
| 3 | Variability of change in tapping speed (slope) across trials is not greater in dual task than tapping only. | 2.3594 ms | 1.2664 ms | 1.0946 ms | 0.3610 |
| 4 | The proportion of correct responses during backwards counting is not smaller in dual task compared to tapping only. | 0.7029 | 0.8049 | -0.1015 | 0.0138 |
| 5 | Backwards counting task-adherence is not worse in dual task compared to tapping only. | 0.6528 | 0.7407 | -0.0881 | 0.0636 |
| 6 | There is no correlation between time spent in dwell phases of tapping and attentional z-score (NP composite score). | - | - | -0.3197 | 0.1286 |
| 7 | There is no correlation between proportion of time spent in dwell phases of tapping and digit span forward test. | - | - | -0.2749 | 0.3366 |
| 8 | There is no correlation between proportion of time spent in dwell phases of tapping and digit symbol test. | - | - | -0.2734 | 0.1546 |
| 9 | There is no correlation between proportion of time spent in dwell phases of tapping and Trails A test. | - | - | 0.0475 | 0.8284 |
| 10 | There is no correlation between proportion of time spent in dwell phases of tapping and global (cognitive) z-score (NP composite score). | - | - | -0.1030 | 0.5888 |
| 11 | There is no correlation between the proportion of time spent in the dwell phases of tapping and gait speed (time to walk 30 ft.). | - | - | 0.1252 | 0.6880 |
| 12 | There is no correlation between tap-to-tap variability and gait speed (time to walk 30 ft.). | - | - | 0.0770 | 0.6296 |
| 13 | The variability in the dwell phases of tapping is not greater in dual task than tapping only. | 31.448 ms | 23.97 ms | 7.4247 ms | 0.0096 |
| 14 | The variability in the transition phases of tapping is not greater in dual task than tapping only. | 15.943 ms | 13.109 ms | 2.8313 ms | 0.1494 |
| 15 | The variability in the dwell phases of tapping is not correlated with the attentional z-score. | - | - | -0.2783 | 0.1502 |

resources required for tapping. These analyses also demonstrate that the transition phases of tapping are unaffected by diminished attentional resources. This is intuitively appealing as the transition phases of tapping appear mostly to require pure motor function (flexion/extension of the finger to drive the tapping lever) whereas both dwell phases appear to require mostly sensory and cognitive functions (e.g., sensing the finger leaving the lever at the top or sensing/reacting to the lever stopping at the bottom position followed by issuing a new motor command for the finger to begin going in the opposite direction). Besides demonstrating the interplay between attention and certain aspects of tapping, this further suggests that finger tapping is a cognitively demanding task, which flies in stark contrast to the popularly held belief that it is a simple motor task with minimal cognitive demands[28, 68]. Further, a recent study on Parkinson's disease showed that the equivalent of what we call transition phases were sensitive to motor function[112]. Taking these results together suggest that by monitoring different aspects of tapping, we may be able to independently assess both motor and cognitive function. However, the interpretation of the results comes with some caveats we discuss here.

First, we used a slight variant of serial seven's as the attentional task. As outlined above, this task is widely considered to be a measure of attention[103-106] but it has been suggested that calculation[107] and working memory[108] also play an important role. As a result, it is possible that the effect of attention on the dwell phases of tapping are confounded by calculation and/or working memory. This does not invalidate the main result that tapping is a cognitively demanding task, but future studies are needed to investigate potential effects of calculation and working memory on tapping.

Second, many of the post-hoc tests did not reach significance. Part of this is due to the aggressive conservatism of the Bonferroni correction combined with the large number of post-hoc tests, and part of this is because we designed the experimental paradigm to test the prospective hypotheses, not the post-hoc tests. However, some of it was also likely because the neuropsychological examinations were not given at the same time as the experiment. In particular, the neuropsychological examinations were only guaranteed to be given within one year from the administration of the experiment, and the time between the experiment and neuropsychological exams varied across subject. This additional heterogeneity in the data combined with a relatively small cohort may have weakened the results of some of the post-hoc tests, and future studies are needed to determine whether the results of the post-hoc tests are repeatable or become significant in larger and more controlled experiments specifically investigating these other relationships.

Some additional potential confounds are the inability to determine whether subjects' test strategies (e.g., going all out from the beginning or pacing) changed from the single tasks to the dual tasks, whether the strategies were the same across subjects, and whether subjects followed the directions. Our analyses assume that test strategy remained constant, were the same across all subjects, and that all subjects followed instructions to the best of their ability. This allowed us to attribute change in performance to change in the cognitive resources available to the task. The instructions issued to the subjects prior to task administration attempted to mitigate these potential confounds, and the fact that both tapping and counting performance were diminished during dual task suggests that subjects were following instructions and using the same or similar strategies, but we could not directly measure the subjects' task strategies or task adherence.

### 4.5 Conclusion

In this paper, we demonstrated that the Halstead-Reitan finger tapping test, a task largely considered to be a measure of simple motor speed, has a substantial attentional component. This was shown by identifying specific physical aspects of finger tapping – the dwell phases – that are sensitive to the reduction of attentional resources, while also demonstrating that the transition phases are not sensitive to reduced attention. This suggests a substantial and specific cognitive component underlying the tapping task, whereby the sensory components of tapping are differentially modulated by attention and the motor aspects remain unaffected. This result combined with a study using a similar tapping task in Parkinson's disease that showed the equivalent of what we call transition phases were sensitive to motor function[112], suggest that finger tapping may be independently and simultaneously able to assess both motor and cognitive function. While these results are promising in demonstrating the importance of attention in finger tapping, we expect that future work will further characterize the underlying interplay between motor and cognitive resources during the test, which may increase sensitivity and specificity in the diagnosis and staging of neurodegenerative and other diseases states.

# Chapter 5: Measuring Motor Speed Through Typing: A Surrogate for the Finger Tapping Test

Daniel Austin, Holly Jimison, Tamara Hayes, Nora Mattek, Jeffrey Kaye, and Misha Pavel

## 5.1 Abstract

Motor speed is both an important indicator and predictor of cognitive and physical function. One common assessment of motor speed is the finger tapping test (FTT), which is typically administered as part of a neurological or neuropsychological assessment. However, the FTT suffers from several limitations including infrequent in-person administration, the need for a trained assessor and dedicated equipment, and potential short term sensory-motor fatigue. In this paper we propose an alternative method of measuring motor speed with face validity to the FTT that addresses these limitations based on measuring the inter keystroke interval (IKI) of familiar and repeated login data collected in home during subject's regular computer use. We show significant correlations between the mean tapping speed from the FTT and the median IKIs of the non-dominant (r=0.77) and dominant hand (r=0.70), respectively in an elderly cohort of

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subjects living independently. Finally, we discuss how the proposed method for measuring motor speed fits well into the framework of unobtrusive and continuous in-home assessment.

## 5.2 Introduction

Sensory-motor speed is an important predictor of cognitive and physical functionality, which are some of the key determinants of individuals' well-being. For example, motor slowing, as indicated by finger tapping speed and walking speed measurement, have been shown to precede cognitive impairment in the elderly [9], and slow motor speed has been shown to be a risk factor for fractures during falls [11]. One common assessment of motor speed is the finger tapping test (FTT). The FTT is frequently used as part of a neuropsychological examination to detect both motor and cognitive impairment [1]. This test is typically scored as the average number of times a patient can depress a key with their index finger (each hand is tested separately) on a manual finger tapping device in 10 seconds. The test nominally consists of 5 tapping trials subject to the constraint that either the counts on all trials are within 5 of each other or no more than 10 trials are administered [1]. Under this procedure, extra trials are administered only if the first condition is not met, although there are many other variants described in the literature.

The FTT and similar tests have been used for assessment of slowing of movement related to aging in general [64, 131, 132] as well as in a number of medical conditions including in stroke [133], essential tremor [61], and Alzheimer's disease [56, 57]. This type of testing may be especially useful in high risk patient populations, such as patients with mild cognitive impairment who are at greater risk to convert to Alzheimer's disease [76, 134] or elderly who are at increased risk for many adverse outcomes.

Despite the utility and successful application of the FTT, the test still suffers from several short comings. First, because the test is performed with an in person assessor, the test is usually administered infrequently – typically no more often than once every 6 months, and frequently a year or more passes between assessments. Second, a trained assessor is required to administer the standard test using a stopwatch and manual finger tapper; using alternative computerized tapping test apparatus still requires an assessor to instruct the test volunteer. As a result of the first limitation, the FTT cannot reliably detect motor changes at the time of onset or distinguish between acute changes and slower changes that have occurred over time. Further, when a change is detected between two visits, it is difficult to determine whether this was caused by inherent test performance variability between the two examination dates or whether there has been a true change in motor function. The requirement for an in-person test administrator on repeated examinations adds to the expense of administering the FTT and also introduces concerns with inter-rater reliability [74]. There has been some attempt to standardize the FTT into a computer-based test [77, 78] that would solve the inter-rater issues, but the computer-based methods still require trained personnel to give the test and do not solve the issue of infrequent measurements. In addition to these shortcomings, the results of FTT confound motor ability with short term fatigue, which is especially noticeable after several trials. Finally, the FTT itself is not a natural task, i.e., we do not normally perform tapping movements, which limits its everyday or ecological validity.

In this paper we propose a surrogate for the finger tapping test based on monitoring the inter keystroke interval (IKI) of repeated computer login data and validate this measure in a group of 22 elderly subjects who live alone and are monitored remotely and unobtrusively in their homes. Specifically, we compare the relationship between the average tapping speed calculated from the FTT scores (denoted as $T_{FTT}$) of both dominant and non-dominant hands with the median IKI from the keystrokes executed while entering over-learned and familiar sequences such as the user name string typed during each computer login. Prior research suggested that typing familiar words, e.g. words with a high frequency of occurrence, is much faster than typing low frequency words or random letters [135, 136]. By minimizing the cognitive load and keyboard search time during the execution of these over-learned sequences, we hypothesized that median IKIs are a potentially valid measure of raw motor speed. The action of typing also has face validity in that the flexion and extension of the finger required to depress and release a key is similar to that required to depress and release the lever on the manual finger tapper board. Additionally, with more and more people owning personal computers and laptops, collecting IKI data can be as simple as installing a software key logger onto a patient's personal computer with known login sequence or providing a patient with a computer that has software already installed. This new approach offers a low cost measure of motor speed with reduced subject burden. In addition, repeated measures in a natural environment allow us to measure within subject trends over time and potentially detect problems much earlier than traditional methods. This ultimately may facilitate continuous assessment of high risk patients and frequent and widespread assessment of subjects in clinical trials with reduced cost and objective measurements.

## 5.3 Method

Our subject pool consisted of the computer arm of the Intelligent Systems for Assessing Aging Changes (ISAAC) cohort of 225 elders living in homes and retirement communities in the Portland, Oregon (USA) metropolitan area. The overall ISAAC study and cohort is described in more detail elsewhere[126]; our description will consist only of the details related to computer use and the data inclusion criteria for the subjects used in the present analysis. Subjects who lived alone and who used their computer frequently during a 28 day window centered on the date of their in-person administered FTT assessment were considered for inclusion. To ensure that sufficient keystroke data were available for analysis, we further required that subjects had entered at least 80 characters of user name data during the 28 day window centered on the associated FTT date. This corresponds roughly to the requirement that the subject login to the computer on at least half of the days in the data window (mean user name length was 5.7 characters, 80/5.7 is approximately 14 logins). These criteria ensured that the key capture data obtained from the subject's login belonged to the subject and that there was enough data to calculate a reasonable measure of central tendency of IKIs near each FTT date for comparison.

One final exclusionary criterion was used as a method for outlier identification based on the residual error from the linear regression (described in more detail below). We identified as outliers those data points with the 95% confidence interval on the residual as not containing 0. One data point (and thus one subject) was identified as an outlier. Further investigation revealed that the subject associated with this data point had a transient ischemic attack within a few days of the FTT assessment and thus the relationship between the median IKI over the 28 day interval and the average tapping speed was affected by this event. As a result, we removed this subject from the analysis.

Of the 225 subjects fully enrolled in the ISAAC study (164 female, 61 male), 115 were living alone since the beginning of the study (103 female, 12 male). Of these 115, 13 did not receive a study computer as they opted to use their own. While we were able to install some software unrelated to the present analysis on these 13 subjects' personal computers, the key logging software was not installed. This left a total of 102 subjects from which we identified 22 who met the exclusionary criteria described above and whose data was included for the present analysis. Most of the excluded subjects were excluded due to the lack of a sufficient amount of computer login data within the window for comparison with the FTT. Since the ISAAC study is a natural history study of activity and computer use monitored unobtrusively overtime to detect normative cognitive and motor change with aging, no attempt was made to encourage subjects to use the computer more frequently than their normal patterns dictated. While requiring that a certain amount of login data fall within a window of an FTT examination is necessary to validate the proposed methodology, we note that in practice this is not required. In the ISAAC cohort, 40% of the subjects are daily computer users and almost all use the computer on a weekly or monthly. As a result, the proposed method can be employed on most subjects in our cohort even though the validation to the FTT can only be demonstrated on the subset meeting the exclusionary criteria. All subjects were consented in accordance with the IRB approved procedure. The mean age of the subject population was 83.5 ± 4.0 (SD) years and ranged from 73.4 – 89 years of age. Mean education level was 15.8 ±2.5 (SD) years and ranged from 12 – 20 years of education. Twenty subjects were woman. Twenty subjects were right handed using the Handedness Inventory. All subjects were cognitively intact (no dementia or mild cognitive impairment) with a Clinical Dementia Rating scale [125] score of 0. No subjects possessed symptoms of Parkinson’s disease (as clinically assessed by a combination of informant report, subject history, medical records, and observation) or stroke. Three subjects were identified as having symptoms of depression within the last two years (also as clinically assessed by a combination of informant report, subject history, medical records, and observation). At the start of the ISAAC study, all subjects who were unable to independently compose and send email or who requested computer instruction participated in a six session training program on basic computer use. Others who were enrolled after the study began were provided with individual computer training. All subjects had a personal computer provided in their home as part of the ISAAC study or opted to use their own computer. All subjects had a computer in the home for at least two years with the same login user name prior to the earliest computer data used in this study.

### *5.3.1 The FTT and Test Administration*

The FTT procedure used in this study was a slight variant of that described in the Introduction. Instead of asking the subject to complete five trials, only three trials were administered for both the dominant and non-dominant hands. Each trial consisted of the subject placing their palm flat on the manual finger tapper with the index finger of the hand under test placed on the lever. The subject was then instructed to tap as many times as possible in a 10 second interval while a clinician timed the 10 second trial with a stop watch. The manual finger tapper boards used were obtained from Reitan Neuropsychology Laboratory (www.reitanlabs.com). The same clinician administered all the tests. The FTT score is reported as the mean number of taps recorded during the three trials, for each hand. In order for a direct comparison of the FTT with the inter keystroke intervals (defined in the next subsection) we calculated the average tapping time, $T_{FTT}$, as

$$T_{FTT} = \frac{10 \text{ seconds}}{N} \tag{5.1}$$

where *N* is the number of taps recorded for the FTT.

### *5.3.2 Inter Keystroke Interval Collection and Preprocessing*

The personal computer in each subject's home was preloaded with computer software developed by the Oregon Center for Aging and Technology (ORCATECH) that presented a study-specific login screen and logged the timestamp and key pressed for each keyboard event during the login. The inter keystroke interval (IKI) was defined as the time interval between the initial contact of the first key to the initial contact of the second key. From this set of data, we used only the assigned computer login user name characters corresponding to a successful login event that were also typed without errors (for example, mistyped user names where the subject needed to delete and retype some characters were not included). Figures 5.1 and 5.2 show scatter plots of the IKI plotted

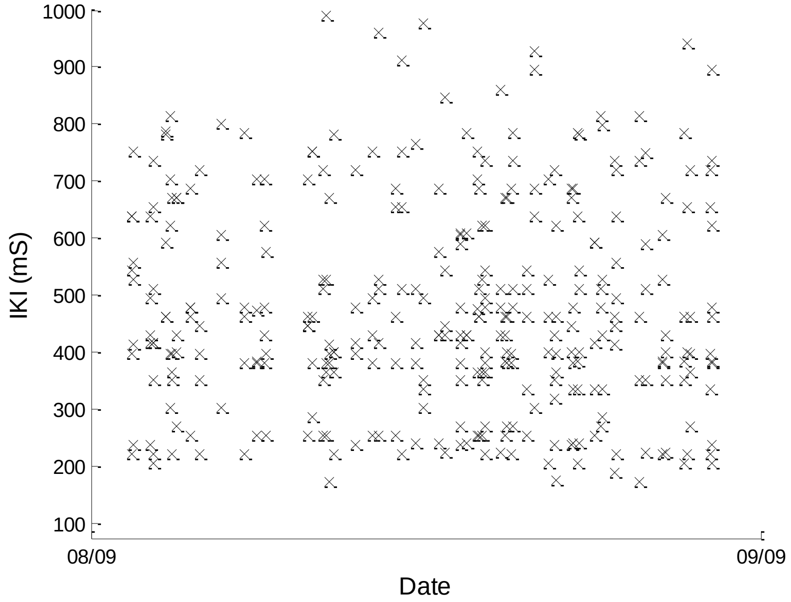

**Figure 5.1. User name login IKI versus date for one subject with highly variable times in the 28 day window centered on the associated FTT test date.**

against date for two of the subjects. These two figures represent the extremes of the data seen across our subject population. The data in figure 5.1 is from a subject who shows large variability in IKIs whereas figure 5.2 shows data from a subject with much less and more typical variability in keystrokes. The median of all IKIs in the 28 day window centered on the corresponding FTT administration date is the measure of central tendency used for comparison to the average tapping time ($T_{FTT}$) for each subject.

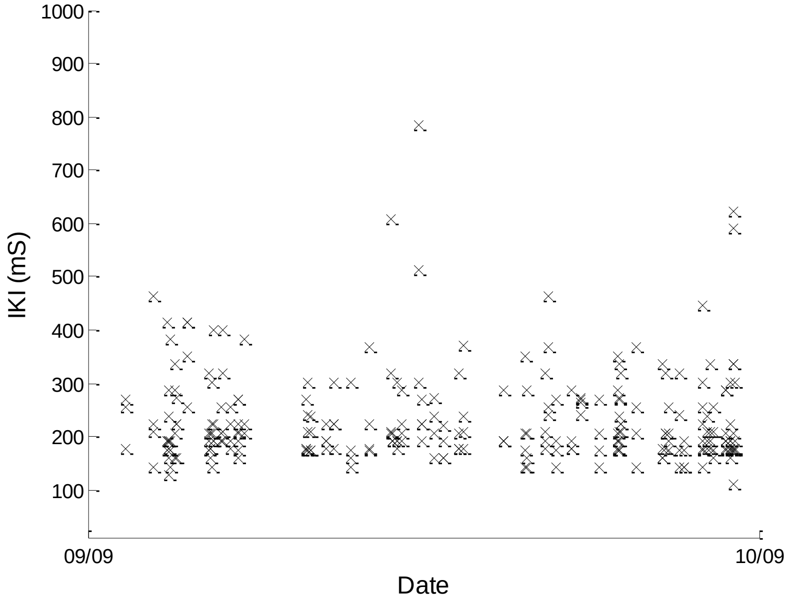

**Figure 5.2. User name login IKI versus date for another subject with more typical variability for the 28 day window centered on the associated FTT test date.**

## 5.4 Results

Due to the face validity of the finger flexion and extension required to generate IKI's while typing highly repeated and over-learned sequences, we hypothesized a positive correlation between the typing speed and average tapping time across subjects. To test this hypothesis we regressed the $T_{FTT}$ times for both dominant and non dominant hands (separately) onto the median IKI, and calculated the Pearson correlation coefficient *r*. To assess the significance of the results we tested the one sided hypothesis that the correlation is positive versus the null hypothesis that the correlation is not positive using a Student's *t*-test separately for both dominant and non-dominant hand. To further quantify the value of the correlation coefficient we calculated confidence intervals using the Fisher z transform method. All data analysis was done using Matlab version 7.6.0 (R2008a, The Mathworks Inc.).

Table 5.1 shows population means and standard deviations (SD) for both FTT scores and mean tapping speed $T_{FTT}$ (dominant and non-dominant hand), and median IKI times. The regression line from the median IKI to the non dominant and dominant hand $T_{FTT}$ times are shown in figures 5.3 and 5.4, respectively. The correlation, p value from the hypothesis test, and confidence intervals are shown in table 5.2. The calculated values of correlation coefficient of 0.77 and 0.70 between the non dominant and dominant hand, respectively, show that much of the variability in the $T_{FTT}$ is explained by the median IKI. In both cases, the hypothesis tests showed that the positive correlation was significant at the 5% level ($p<0.0001$ and $p<0.0002$ for non dominant and dominant hand, respectively). For further comparison we calculated the sample correlation between dominant and non-dominant FTT in the entire 225 subjects of the ISAAC cohort and tested significance at the 5% level. This correlation was 0.75 ($p<0.0001$), which is close to the correlations between $T_{FTT}$ and median IKIs for both hands. In the literature, the test-retest reliability of the FTT has been reported to be between 0.58 and 0.93 [1] over a variety of studies including both patient and normal populations. This places the median IKI to $T_{FTT}$ correlations firmly within the test-retest range of the FTT for both the non-dominant and dominant hand.

**Table 5.1. Population mean and standard deviation (SD) for FTT scores and mean tapping speed TFTT (for both dominant and non-dominant hand), and median IKI times.**

| | Mean | SD |
|---|---|---|
| FTT Dominant Hand (score) | 39.7 | 8.2 |
| FTT Non-Dominant Hand (score) | 35.8 | 8.2 |
| $T_{FTT}$ Dominant Hand (ms) | 264 | 61 |
| $T_{FTT}$ Non-Dominant Hand (ms) | 295.1 | 73.8 |
| Median IKI (ms) | 356.2 | 155.2 |

**Table 5.2. Correlation coefficient estimate between median IKI time and TFTT for dominant and non dominant hands, p value for hypothesis test of significance of positive correlation, and 95% confidence intervals of the correlation estimates.**

| | *r* | p value | 95% Confidence Intervals |
|---|---|---|---|
| Non-Dominant Hand | 0.77 | <0.0001 | (0.516,0.90) |
| Dominant Hand | 0.70 | <0.0002 | (0.395,0.866) |

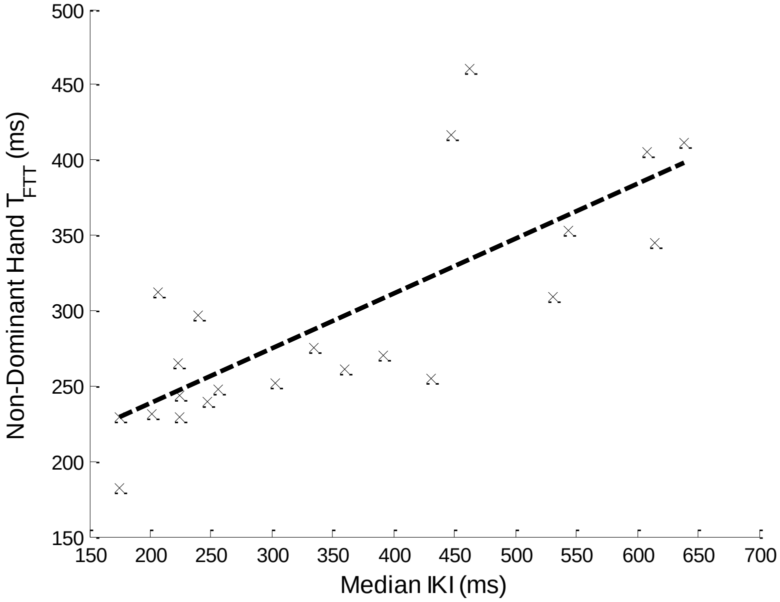

**Figure 5.3. Regression line (black dashed line) from the predictor variable, median IKI, to the non-dominant hand average tapping speed (TFTT) calculated from the FTT for 22 subjects along with individual measurement pairs (black x) for each subject.**

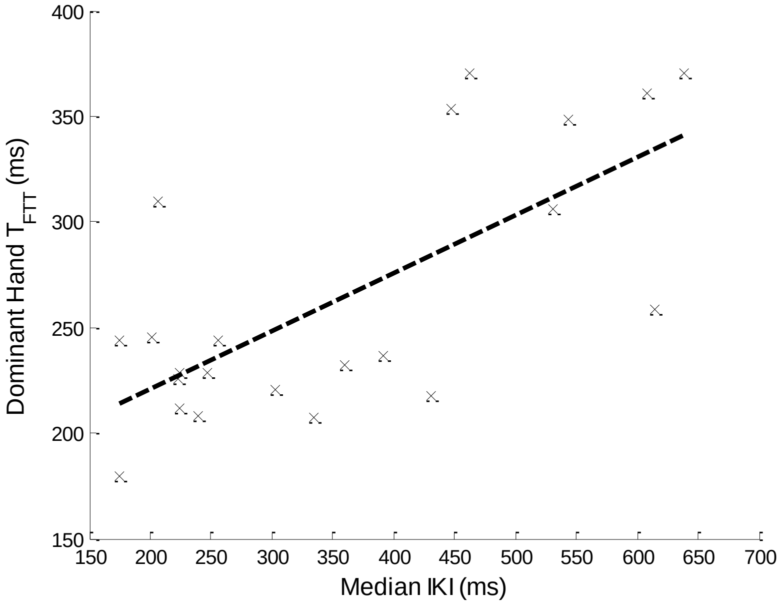

**Figure 5.4. Regression line (black dashed line) from the predictor variable median IKI to the dominant hand average tapping speed ($T_{FTT}$) for 22 subjects along with individual measurement pairs (black x) for each subject.**

## 5.5 Discussion

In this study, the median inter keystroke intervals of the memorized and frequently used computer login user name was proposed as a measure of simple motor speed and compared as a surrogate for the average tapping speed derived from the FTT score with initial validation in an elderly subject population living independently. The results of the correlation analysis were significant and show that the proposed method accounts for much of the variability in the FTT across subjects. Further, the fact that the correlation is within the range of the test-retest reliability for both the non-dominant and dominant hands combined with the face validity of the typing motion suggests that the proposed method has capabilities similar to the FTT for assessing simple motor speed.

The reason we selected the median as a suitable measure of central tendency - instead of the mean, which is a more intuitive choice to compare with mean tapping speed – is because of the large variability in the IKI distributions of some subjects (such as the one whose data is shown in figure 5.1). The median is much more robust to this wide spread of data than the mean, and it was this robustness property that we desired in an estimator of central tendency for this highly variable data. Further, since the support of the distribution underlying this data is the positive real line there is a natural skewness associated with the IKI distributions. Specifically, things such as pauses between letters not associated with the motor aspect of typing (i.e., if someone sneezes or hears the phone ring during the login sequence) will show up as slower IKIs and cause outliers only on one side of the distribution. The effect of these types of events is what we sought to minimize with the median IKI as the measure of motor speed.

To understand the difference in correlation between the median IKIs and the dominant and non-dominant hand $T_{FTT}$ times, we considered the keyboard placement of the most commonly used letters that appeared in the user name character strings of the 22 subjects. Due to the well known property of the QWERTY keyboard where the most common letters appear on the left side, any touch typist would use their left hand more frequently than their right. While our subjects are not all trained typists, it is reasonable to assume that many of the characters closer to the left hand are pressed by the left hand even in non-skilled typing styles. Since 20 of our 22 subjects are right handed more of the data used in our study was generated by the non-dominant hand which may account for the better correlation between the median IKI and the non-dominant hand.

Although these results along with the similarity of typing and tapping show both the accuracy and the face validity of the proposed method as a possible early screening tool or surrogate for the FTT, the main advantage of this technique is in its ability to assess behavioral measures unobtrusively and frequently. In particular, the IKI data can be collected unobtrusively in a subject's or patient's residence on a frequent basis without the need for a trained assessor to administer testing. In contrast to finger tapping tests, this type of assessment is not subject to inter-rater variability. As a result, within subject trends in motor speed may allow us to detect problems much earlier than traditional psychomotor tests. Changes in motor speed can be detected when they occur - either in real time as part of a clinical alerting system or retrospectively through offline data analysis and interpretation. Further, intraindividual variability in motor function manifested as variability in IKIs may themselves be an important indicator or predictor of function [24]. This is something that is not currently collected as part of the FTT and cannot be evaluated until many FTTs have been administered over many years. Thus the proposed method would allow both short term and long term variability to also be assessed. This issue of periodic and infrequent assessments has been discussed in the context of dementia prevention trials [137] for assessment methods in general and addressing these issues in commonly administered tests (such as the FTT) with in-home monitoring may introduce new analysis tools and diagnostic aids for both researchers and clinicians.

Despite the promise of the proposed method and the validity demonstrated in the ISAAC cohort, there are some limitations. First, some of the uses of the FTT are based on assessing differences in performance between hands such as when detecting the presence of brain lesions [1]. The currently proposed method does not distinguish between hands (or fingers) since we use the same predictor for both dominant and non dominant $T_{FTT}$. Second, focusing only on the sequential depression of the same set of computer keys (user name string) greatly reduces the use of the wide variety of key capture data that can be obtained over the course of monitoring computer sessions over time. Additionally, the validation of the proposed methodology was conducted with healthy elderly subjects who live independently. While these subjects are potentially at high risk for adverse outcomes, generalization of this technique to other patient populations across a wider age and demographic profile will require further studies. Another apparent shortcoming of the proposed technique is the fact that unobtrusive measurements are subject to significantly higher variability than those performed in controlled environments. The results of the analysis presented in this paper suggest that this variability is well compensated for by the very large number of samples. It is also possible to speculate that the variability of the raw IKI data itself can be eventually used for additional assessment of cognitive as well as motor functionality of continuously monitored individuals [24].

## 5.6 Conclusion

In this paper we proposed a new method for assessing motor speed based on computer inter keystroke intervals of highly learned and frequently repeated sequences and demonstrated that the data collected using this method correlates well with the average tapping speed derived from the FTT. The resulting significant correlation across subjects suggests that the IKI measure is a useful alternative to the conventional FTT test overcoming some of its limitations in current use. Moreover the IKI-based technique may enable nearly continuous assessment and thereby be used for early detection of changes in motor and related function. Since the IKI during regular typing can incorporate cognitive aspects of function, the IKI based approach may also provide sensitive, unobtrusive measures of cognitive function as well.

# Chapter 6: Summary and Conclusions

## 6.1 Summary

One of the great challenges facing modern science is the ability to measure and make direct inferences about cognitive processes and individuals' cognitive function. Currently cognitive function cannot be directly measured, thus there is a need for mechanisms allowing inferences to relate cognitive processes to observations, such as those obtained from measuring behavior. In this thesis we used computational modeling as an overarching theme to drive our investigation into the relationship between cognitive and motor function.

Motor function has repeatedly been shown to be an important predictor and indicator of both cognitive and physical function. Motor slowing precedes cognitive impairment, has been linked to cognitive function, and is associated with and predictive of adverse health outcomes, such as risk of future hospitalization and disability. Among other things, motor function has been used for diagnosis and staging of neurodegenerative disease, monitoring normal and pathological functional changes associated with aging, and objective assessment of health status. Although the literature implicates motor function for these relationships, the observed relationships likely also depend on the sensory and possibly cognitive components of the measured motor tasks.

One of the most commonly used neuropsychological assessments of motor function is the Halstead-Reitan finger tapping test (FTT). This test is widely considered to be a measure of simple motor speed with minimal cognitive involvement, despite the many studies linking speed or variability of tapping to a diverse array of sensory and cognitive outcomes. This disconnect between the perception of minimal cognitive involvement during the FTT and the literature implicating the test with cognitive function suggests a fundamental lack of understanding in the interplay of cognitive, sensory, and motor function during tapping. Further, in spite of the importance of assessing motor function with the FTT, the current clinical assessment methodology suffers from several shortcomings including the infrequency of test administration, the need for a trained clinician to administer the test, the confounding of sensorimotor fatigue on repeated trials with minimal rest, and the lack of ecological validity of the test. In chapter 1, we surveyed the importance and shortcomings of assessment of motor function and the FTT in particular, and discussed the need for a comprehensive understanding of the role of cognition during finger tapping.

In addition to neuropsychological assessment, several other uses for finger tapping exist. Tapping tasks are used to measure the sensorimotor system's ability to coordinate, or synchronize, movement with perception in the study of what is referred to as sensorimotor synchronization, or SMS. An unpaced tapping task is used to measure spontaneous motor tempo – an individual's preferred rate of tapping – which is thought to be biologically determined and measures the speed of an internal clock. Various tapping tasks have also been used in imaging studies with the intent to map out the cortical areas of the human motor system. Some of these studies involve a dual-task paradigm, which have extensively been used to determine both cortical regions implicated in – and physical aspects of – cognitive control in the human motor system. Some studies have attempted to overcome the shortcomings of tapping by utilizing new devices or test methodologies, most notably for Parkinson's disease research. Despite the success of some of these approaches, many limitations remain or are introduced such as the lack of clinical validation for new procedures or devices and the lack of normative data to aid in understanding test results. Further, none of these approaches addresses the fundamental lack of understanding of the role of cognition in the various finger tapping tasks. Research surrounding those areas closely related to our work were described in detail in chapter 2.

In chapter 3, we described and validated a comprehensive statistical model for the FTT. This model is based on decomposing the finger tapping task into five different, distinct physical components, each of which appears to be most heavily influenced either by sensory and cognitive function, or by motor function. Each of the four repeating phases is independently characterized both within trial (over time) and across trial in a mixed-effects model. The phases that do not occur regularly or repeatedly are characterized independently by a mean and standard deviation (taken across trials). This characterization results in a set of 29 parameters characterizing tapping, including such features as: change over time, tap-to-tap variability and variability across trials, and average values at task initiation for each of the phases. In addition to describing the model, we provided applications to the measurement of within trial sensorimotor fatigue, which cannot currently be measured clinically.

In chapter 4, we used the characterization of tapping to investigate the role attention – one aspect of cognition – on finger tapping. We employed a dual-task paradigm to reduce the amount of attention available during several trials of finger tapping, and compared the performance during the dual task to the baseline levels seen during a series of tapping only trials. The results demonstrated that the reduction in attention caused by the dual task induced diminished (slower) tapping performance during the dwell phases of tapping only; the transition phases were unaffected. A series of post-hoc tests rounded out this result by demonstrating an increase in variability in the time spent in the dwell phases of tapping when attention is diminished. These tests also further explored the relationship between motor and cognitive components during tapping. The results in this chapter demonstrated that the FTT, despite being widely perceived as a simple motor task with minimal cognitive involvement, is in fact a cognitively demanding task. This further provides a basis for understanding the interplay between attention, one domain of cognitive function, and the sensory and motor components of tapping. Additionally, certain phases of tapping were shown to be independently related to cognitive function, which – when combined with prior research in a related task – suggests that the different phases of tapping may be able to provide independent assessments of both motor and cognitive function from the same task.

In chapter 5, we argued for overcoming the shortcomings associated with assessing motor function clinically by using typing at the keyboard measured unobtrusively in the home setting as a surrogate for the finger tapping test. We argued that the unobtrusive assessment of a naturalistic task has ecological validity and provides an objective assessment of function, as keystrokes measured at the keyboard can be measured with millisecond accuracy and thus does not suffer from issues with test-retest reliability or inter-rater reliability. Additionally, we demonstrated how monitoring typing continuously – that is, whenever it occurs – overcomes the problems associated with infrequent clinical assessments, such as the inability to distinguish between abrupt and slow changes, or to reliably evaluate baseline performance and estimate variability. We further demonstrated the face validity of typing with tapping by arguing that the flexion and extensions used to type are the same as those used to drive the tapping lever during the FTT.  We supported these arguments with a quantitative assessment of the relationship between typing and tapping by demonstrating the high correlation between the speed of tapping and the speed of typing.  These high correlations suggest substantial overlap between the cognitive and motor resources underlying the tapping task and typing on the keyboard in the home setting.  In addition to overcoming the shortcomings of formal, clinical assessment of motor function, monitoring motor function continuously in the home setting allows for the detection of pathological declines of motor function *when they occur*, thus facilitating detection and diagnosis of, for example, neurodegenerative diseases, at the earliest possible time point.  While we did not explicitly demonstrate how the model for finger tapping could be used in typing speed measurements, we believe that this can be done and will be an area of future work. Specifically, highly overlearned typing sequences – such as those used to login to the computer – appear to have minimal cognitive involvement and may become automatic over time.  This suggests that we may be able to measure motor speed with certain typing speeds (akin to the transition phases), which may then be used to begin to disentangle the potential slowing in typing due to increased cognitive load (akin to the dwell phases) – such as from mental message composition during spontaneous (non-transcription) typing.

One main shortcoming with this work is that we did not explicitly demonstrate that instrumenting the test leads to improved detection of cognitive or motor decline.  In particular, if the duration spent in UD and DD phases change for a pateint while the UT and DT phases do not, the overall test score will be sensitive to this same change.  Future work is needed to investigate whether change in tapping performance caused by cognitive decline, neurodegenerative disease, and motor impairment can be detected with greater sensitivity and distinguished with greater specificity using the proposed model.

## 6.2 Contributions

The combined work in this thesis provides three new results influencing basic science and supporting new medical and diagnostic applications. First, we implicated substantial cognitive involvement in the Halstead-Reitan finger tapping test; a test widely considered to be a simple motor test with minimal cognitive involvement. Second, we increased the understanding of the interplay between cognitive sensory, and motor function underlying finger tapping. Third, we presented a novel approach to objective, accurate, and timely assessment of motor speed through unobtrusive in-home monitoring, which may have substantial application in early detection and diagnosis of neurodegenerative diseases.

The contributions described in this thesis leading up to these insights include:

- Developing and validating a novel characterization of the finger tapping test. This characterization combines a decomposition of the physical process of tapping into component phases and a statistical model to summarize these components both inter-trial and across trials, resulting in a 29 parameter characterization of tapping. Among other things, this decomposition allows detection and measurement of fatigue and learning effects during the test, and allows independent assessment of the different physical aspects of tapping. This may provide a more specific and comprehensive picture of motor and cognitive function from a single test, while also potentially increasing specificity in diagnosing and monitoring the time course of neurodegenerative and other diseases.

- Characterizing the role of attention on the physical aspects of finger tapping. Using a dual-task paradigm, we demonstrated not only that finger tapping is a cognitively demanding task, but also assessed the role of attention on finger tapping using a dual-task paradigm. Analysis of the experimental data showed that certain phases of finger tapping, called dwell phases, slow down and become more variable when the amount of attention available to the task is reduced. This has two main implications for basic science. First, this shows that finger tapping is a cognitively demanding task, despite the widespread idea that it is a simple motor task with minimal cognitive involvement. Second, our work takes the first steps toward discovering the interplay between sensory, cognitive and the motor function during finger tapping.

- Proposing and validating an alternative test strategy for measuring motor function as currently assessed by the finger tapping test, by continuously and unobtrusively measuring the speed of typing at the keyboard during normal, everyday computer use. Moving the assessment of motor function into the home during everyday activities promotes objective assessment of motor function and the continuous monitoring of high-risk patient groups for declines associated with pathological conditions such as neurodegenerative diseases. It will also increase the ability to detect change *when it occurs* and therefore represents a methodology for the detection of disease at the earliest possible stages. Additionally, this methodology promotes more frequent, longitudinal monitoring of age-related and other changes in function. This methodology also may have applications in long-term clinical trials requiring frequent and objective assessment of changes associated with, for example, dementia or pain medication.

### 6.3 Conclusion and Future Work

The results presented in this thesis provide a comprehensive characterization of the role of attention in finger tapping. More general, we present some of the first work towards understanding the interplay between cognitive, sensory, and motor function in a tapping task commonly considered to require little cognitive involvement. To support these results, we developed and validated a new characterization of the physical process of finger tapping, which allows investigation into basic physical components required to finger tap. Future work will include characterizing the physical process of tapping in neurodegenerative disease states, such as mild cognitive impairment and Alzheimer's disease, to promote improved accuracy and specificity in clinical diagnosis of these diseases. Additionally, investigating the role of other cognitive domains – such as working memory and executive function – will help provide a more comprehensive picture of the role cognitive function plays in repetitive finger tapping.

# References

[1] E. Strauss, E. M. S. Sherman, and O. Spreen, *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, 3 ed: Oxford University Press, 2006.

[2] V. Kolev, M. Falkenstein, and J. Yordanova, "Motor-response generation as a source of aging-related behavioural slowing in choice-reaction tasks," *Neurobiol Aging*, vol. 27, pp. 1719-30, 2006.

[3] M. Falkenstein, J. Yordanova, and V. Kolev, "Effects of aging on slowing of motor-response generation," *Int J Psychophysiol*, vol. 59, pp. 22-9, 2006.

[4] A. F. Pettersson, E. Olsson, and L. O. Wahlund, "Motor function in subjects with mild cognitive impairment and early Alzheimer's disease," *Dement Geriatr Cogn Disord*, vol. 19, pp. 299-304, 2005.

[5] E. R. Barbosa, J. C. Limongi, and J. L. Cummings, "Parkinson's disease," *Psychiatr Clin North Am*, vol. 20, pp. 769-90, 1997.

[6] T. Asai, S. Misu, T. Doi, M. Yamada, and H. Ando, "Effects of dual-tasking on control of trunk movement during gait: Respective effect of manual- and cognitive-task," *Gait Posture*, 2013.

[7] D. Simoni, G. Rubbieri, M. Baccini, L. Rinaldi, D. Becheri, T. Forconi, E. Mossello, S. Zanieri, N. Marchionni, and M. Di Bari, "Different motor tasks impact differently on cognitive performance of older persons during dual task tests," *Clin Biomech (Bristol, Avon)*, 2013.

[8] O. Beauchet, G. Allali, G. Berrut, C. Hommet, V. Dubost, and F. Assal, "Gait analysis in demented subjects: Interests and perspectives," *Neuropsychiatr Dis Treat*, vol. 4, pp. 155-60, 2008.

[9] R. Camicioli, D. Howieson, B. Oken, G. Sexton, and J. Kaye, "Motor slowing precedes cognitive impairment in the oldest old," *Neurology*, vol. 50, pp. 1496-8, 1998.

[10] R. Camicioli, Y. Wang, C. Powell, A. Mitnitski, and K. Rockwood, "Gait and posture impairment, parkinsonism and cognitive decline in older people," *J Neural Transm*, vol. 114, pp. 1355-61, 2007.

[11] R. Shigematsu, T. Rantanen, P. Saari, R. Sakari-Rantala, M. Kauppinen, S. Sipila, and E. Heikkinen, "Motor speed and lower extremity strength as predictors of fall-related bone fractures in elderly individuals," *Aging Clin Exp Res*, vol. 18, pp. 320-4, 2006.

[12] S. Studenski, S. Perera, D. Wallace, J. M. Chandler, P. W. Duncan, E. Rooney, M. Fox, and J. M. Guralnik, "Physical performance measures in the clinical setting," *J Am Geriatr Soc*, vol. 51, pp. 314-22, 2003.

[13] A. L. Fitzpatrick, C. K. Buchanan, R. L. Nahin, S. T. Dekosky, H. H. Atkinson, M. C. Carlson, and J. D. Williamson, "Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons," *J Gerontol A Biol Sci Med Sci*, vol. 62, pp. 1244-51, 2007.

[14] R. Holtzer, J. Verghese, X. Xue, and R. B. Lipton, "Cognitive processes related to gait velocity: results from the Einstein Aging Study," *Neuropsychology*, vol. 20, pp. 215-23, 2006.

[15] J. M. Guralnik, L. Ferrucci, C. F. Pieper, S. G. Leveille, K. S. Markides, G. V. Ostir, S. Studenski, L. F. Berkman, and R. B. Wallace, "Lower extremity function

and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery," *J Gerontol A Biol Sci Med Sci*, vol. 55, pp. M221-31, 2000.

[16] J. M. Guralnik, L. Ferrucci, E. M. Simonsick, M. E. Salive, and R. B. Wallace, "Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability," *N Engl J Med*, vol. 332, pp. 556-61, 1995.

[17] A. Kluger, J. G. Gianutsos, J. Golomb, S. H. Ferris, A. E. George, E. Franssen, and B. Reisberg, "Patterns of motor impairement in normal aging, mild cognitive decline, and early Alzheimer's disease," *J Gerontol B Psychol Sci Soc Sci*, vol. 52, pp. P28-39, 1997.

[18] A. Kluger, J. G. Gianutsos, J. Golomb, S. H. Ferris, and B. Reisberg, "Motor/psychomotor dysfunction in normal aging, mild cognitive decline, and early Alzheimer's disease: diagnostic and differential diagnostic features," *Int Psychogeriatr*, vol. 9 Suppl 1, pp. 307-16; discussion 317-21, 1997.

[19] P. J. Massman and R. S. Doody, "Hemispheric asymmetry in Alzheimer's disease is apparent in motor functioning," *J Clin Exp Neuropsychol*, vol. 18, pp. 110-21, 1996.

[20] W. G. Darling, J. D. Cooke, and S. H. Brown, "Control of simple arm movements in elderly humans," *Neurobiol Aging*, vol. 10, pp. 149-57, 1989.

[21] J. D. Cooke, S. H. Brown, and D. A. Cunningham, "Kinematics of arm movements in elderly humans," *Neurobiol Aging*, vol. 10, pp. 159-65, 1989.

[22] A. A. Bielak, D. F. Hultsch, E. Strauss, S. W. Macdonald, and M. A. Hunter, "Intraindividual variability in reaction time predicts cognitive outcomes 5 years later," *Neuropsychology*, vol. 24, pp. 731-41, 2010.

[23] G. Muller, S. Weisbrod, and F. Klingberg, "Finger Tapping Frequency and Accuracy Are Decreased in Early Stage Primary Degenerative Dementia," *Dementia*, vol. 2, pp. 169-172, 1991.

[24] A. A. Bielak, D. F. Hultsch, E. Strauss, S. W. MacDonald, and M. A. Hunter, "Intraindividual variability is related to cognitive change in older adults: evidence for within-person coupling," *Psychol Aging*, vol. 25, pp. 575-86, 2010.

[25] M. Montero-Odasso, H. Bergman, N. A. Phillips, C. H. Wong, N. Sourial, and H. Chertkow, "Dual-tasking and gait in people with mild cognitive impairment. The effect of working memory," *BMC Geriatr*, vol. 9, pp. 41, 2009.

[26] M. Montero-Odasso, A. Casas, K. T. Hansen, P. Bilski, I. Gutmanis, J. L. Wells, and M. J. Borrie, "Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study," *J Neuroeng Rehabil*, vol. 6, pp. 35, 2009.

[27] J. Verrel, M. Lovden, M. Schellenbach, S. Schaefer, and U. Lindenberger, "Interacting effects of cognitive load and adult age on the regularity of whole-body motion during treadmill walking," *Psychol Aging*, vol. 24, pp. 75-81, 2009.

[28] J. M. Hausdorff, G. Yogev, S. Springer, E. S. Simon, and N. Giladi, "Walking is more like catching than tapping: gait in the elderly as a complex cognitive task," *Exp Brain Res*, vol. 164, pp. 541-8, 2005.

[29] T. Zielinska, "Coupled oscillators utilised as gait rhythm generators of a two-legged walking machine," *Biol Cybern*, vol. 74, pp. 263-73, 1996.

[30] C. L. Vaughan, "Theories of bipedal walking: an odyssey," *J Biomech*, vol. 36, pp. 513-23, 2003.

[31] F. S. Stafford and G. M. Barnwell, "Mathematical models of central pattern generators in locomotion: I. Current problems," *J Mot Behav*, vol. 17, pp. 3-26, 1985.

[32] M. MacKay-Lyons, "Central pattern generation of locomotion: a review of the evidence," *Phys Ther*, vol. 82, pp. 69-83, 2002.

[33] H. J. Chiel, R. D. Beer, and J. C. Gallagher, "Evolution and analysis of model CPGs for walking: I. Dynamical modules," *J Comput Neurosci*, vol. 7, pp. 99-118, 1999.

[34] R. D. Beer, H. J. Chiel, and J. C. Gallagher, "Evolution and analysis of model CPGs for walking: II. General principles and individual variability," *J Comput Neurosci*, vol. 7, pp. 119-47, 1999.

[35] A. Ble, S. Volpato, G. Zuliani, J. M. Guralnik, S. Bandinelli, F. Lauretani, B. Bartali, C. Maraldi, R. Fellin, and L. Ferrucci, "Executive function correlates with walking speed in older persons: the InCHIANTI study," *J Am Geriatr Soc*, vol. 53, pp. 410-5, 2005.

[36] P. L. Sheridan, J. Solomont, N. Kowall, and J. M. Hausdorff, "Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease," *J Am Geriatr Soc*, vol. 51, pp. 1633-7, 2003.

[37] M. B. van Iersel, R. P. Kessels, B. R. Bloem, A. L. Verbeek, and M. G. Olde Rikkert, "Executive functions are associated with gait and balance in community-living elderly people," *J Gerontol A Biol Sci Med Sci*, vol. 63, pp. 1344-9, 2008.

[38] A. Soumare, B. Tavernier, A. Alperovitch, C. Tzourio, and A. Elbaz, "A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people," *J Gerontol A Biol Sci Med Sci*, vol. 64, pp. 1058-65, 2009.

[39] G. Yogev-Seligmann, J. M. Hausdorff, and N. Giladi, "The role of executive function and attention in gait," *Mov Disord*, vol. 23, pp. 329-42; quiz 472, 2008.

[40] K. L. Martin, L. Blizzard, A. G. Wood, V. Srikanth, R. Thomson, L. M. Sanders, and M. L. Callisaya, "Cognitive function, gait, and gait variability in older people: a population-based study," *J Gerontol A Biol Sci Med Sci*, vol. 68, pp. 726-32, 2013.

[41] N. Deshpande, E. J. Metter, S. Bandinelli, J. Guralnik, and L. Ferrucci, "Gait speed under varied challenges and cognitive decline in older persons: a prospective study," *Age Ageing*, vol. 38, pp. 509-14, 2009.

[42] M. Inzitari, A. B. Newman, K. Yaffe, R. Boudreau, N. de Rekeneire, R. Shorr, T. B. Harris, and C. Rosano, "Gait speed predicts decline in attention and psychomotor speed in older adults: the health aging and body composition study," *Neuroepidemiology*, vol. 29, pp. 156-62, 2007.

[43] G. Abellan van Kan, Y. Rolland, S. Andrieu, J. Bauer, O. Beauchet, M. Bonnefoy, M. Cesari, L. M. Donini, S. Gillette Guyonnet, M. Inzitari, F. Nourhashemi, G. Onder, P. Ritz, A. Salva, M. Visser, and B. Vellas, "Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force," *J Nutr Health Aging*, vol. 13, pp. 881-9, 2009.

[44] J. Verghese, R. Holtzer, R. B. Lipton, and C. Wang, "Quantitative gait markers and incident fall risk in older adults," *J Gerontol A Biol Sci Med Sci*, vol. 64, pp. 896-901, 2009.

[45] A. Weiss, M. Brozgol, M. Dorfman, T. Herman, S. Shema, N. Giladi, and J. M. Hausdorff, "Does the Evaluation of Gait Quality During Daily Life Provide Insight Into Fall Risk?: A Novel Approach Using 3-Day Accelerometer Recordings," *Neurorehabil Neural Repair*, 2013.

[46] J. Verghese, R. B. Lipton, C. B. Hall, G. Kuslansky, M. J. Katz, and H. Buschke, "Abnormality of gait as a predictor of non-Alzheimer's dementia," *N Engl J Med*, vol. 347, pp. 1761-8, 2002.

[47] C. Rosano, H. Aizenstein, J. Brach, A. Longenberger, S. Studenski, and A. B. Newman, "Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults," *J Gerontol A Biol Sci Med Sci*, vol. 63, pp. 1380-8, 2008.

[48] J. Verghese, C. Wang, R. B. Lipton, R. Holtzer, and X. Xue, "Quantitative gait dysfunction and risk of cognitive decline and dementia," *J Neurol Neurosurg Psychiatry*, vol. 78, pp. 929-35, 2007.

[49] M. R. Lim, R. C. Huang, A. Wu, F. P. Girardi, and F. P. Cammisa, Jr., "Evaluation of the elderly patient with an abnormal gait," *J Am Acad Orthop Surg*, vol. 15, pp. 107-17, 2007.

[50] D. Grabli, C. Karachi, M. L. Welter, B. Lau, E. C. Hirsch, M. Vidailhet, and C. Francois, "Normal and pathological gait: what we learn from Parkinson's disease," *J Neurol Neurosurg Psychiatry*, vol. 83, pp. 979-85, 2012.

[51] Y. Okuma and N. Yanagisawa, "The clinical spectrum of freezing of gait in Parkinson's disease," *Mov Disord*, vol. 23 Suppl 2, pp. S426-30, 2008.

[52] S. R. Muir, R. D. Jones, J. H. Andreae, and I. M. Donaldson, "Measurement and analysis of single and multiple finger tapping in normal and Parkinsonian subjects," *Parkinsonism Relat Disord*, vol. 1, pp. 89-96, 1995.

[53] D. J. O'Boyle, J. S. Freeman, and F. W. Cody, "The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease," *Brain*, vol. 119 ( Pt 1), pp. 51-70, 1996.

[54] M. Yokoe, R. Okuno, T. Hamasaki, Y. Kurachi, K. Akazawa, and S. Sakoda, "Opening velocity, a novel parameter, for finger tapping test in patients with Parkinson's disease," *Parkinsonism Relat Disord*, vol. 15, pp. 440-4, 2009.

[55] A. Jobbagy, P. Harcos, R. Karoly, and G. Fazekas, "Analysis of finger-tapping movement," *J Neurosci Methods*, vol. 141, pp. 29-39, 2005.

[56] B. R. Ott, S. A. Ellias, and M. C. Lannon, "Quantitative assessment of movement in Alzheimer's disease," *J Geriatr Psychiatry Neurol*, vol. 8, pp. 71-5, 1995.

[57] J. S. Wefel, B. D. Hoyt, and P. J. Massma, "Neuropsychological functioning in depressed versus nondepressed participants with Alzheimer's disease," *Clin Neuropsychol*, vol. 13, pp. 249-57, 1999.

[58] S. Kemper, R. E. Herman, and C. H. Lian, "The costs of doing two things at once for young and older adults: talking while walking, finger tapping, and ignoring speech or noise," *Psychol Aging*, vol. 18, pp. 181-92, 2003.

[59] M. Crossley and M. Hiscock, "Age-related differences in concurrent-task performance of normal adults: evidence for a decline in processing resources," *Psychol Aging*, vol. 7, pp. 499-506, 1992.

[60] M. Crossley, M. Hiscock, and J. B. Foreman, "Dual-task performance in early stage dementia: differential effects for automatized and effortful processing," *J Clin Exp Neuropsychol*, vol. 26, pp. 332-46, 2004.

[61] F. J. Jimenez-Jimenez, L. Rubio, H. Alonso-Navarro, M. Calleja, B. Pilo-de-la-Fuente, J. F. Plaza-Nieto, J. Benito-Leon, P. J. Garcia-Ruiz, and J. A. Agundez, "Impairment of rapid repetitive finger movements and visual reaction time in patients with essential tremor," *Eur J Neurol*, vol. 17, pp. 152-9, 2010.

[62] C. G. Goetz, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, G. T. Stebbins, M. B. Stern, B. C. Tilley, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A. E. Lang, A. Lees, S. Leurgans, P. A. LeWitt, D. Nyenhuis, C. W. Olanow, O. Rascol, A. Schrag, J. A. Teresi, J. J. Van Hilten, and N. LaPelle, "Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan," *Mov Disord*, vol. 22, pp. 41-7, 2007.

[63] T. Horowitz, P. Schatz, and D. Chute, "Trends in Neuropsychological Test Usage," *Archives of Clinical Neuropsychlogy*, vol. 12, pp. 338-339, 1997.

[64] J. Kaye, B. S. Oken, D. B. Howieson, J. Howieson, L. A. Holm, and K. Dennison, "Neurologic evaluation of the optimally healthy oldest old," *Arch Neurol*, vol. 51, pp. 1205-11, 1994.

[65] W. Camara, J. Nathan, and A. Puente, "Psychological test usage: Implications in professional psychology " *Professional Psychology: Research and Practice*, vol. 31, pp. 141-154, 2000.

[66] R. M. Reitan, *Manual for Administration of Neuropsychological Test Batteries for Adults and Children*. Tucson, Arizona: Reitan Neuropsychology Laboratory, 1979.

[67] W. Halstead, *Brain and Intelligence: A quantitative Study of the Frontal Lobes*. Chicago: University of Chicago Press, 1947.

[68] R. Reitan and L. Davison, *Clinical Neuropsychology: Current Status and Applications* 1974.

[69] M. Bergener and B. Reisberg, "Diagnosis and Treatment of Senile Dementia ", 1989, pp. 416.

[70] D. Austin, H. Jimison, T. Hayes, N. Mattek, J. Kaye, and M. Pavel, "Measuring motor speed through typing: a surrogate for the finger tapping test," *Behav Res Methods*, vol. 43, pp. 903-9, 2011.

[71] A. Vega, Jr. and O. A. Parsons, "Cross-validation of the Halstead-Reitan tests for brain damage," *J Consult Psychol*, vol. 31, pp. 619-25, 1967.

[72] K. Y. Haaland and H. D. Delaney, "Motor deficits after left or right hemisphere damage due to stroke or tumor," *Neuropsychologia*, vol. 19, pp. 17-27, 1981.

[73] S. M. McCurry, L. E. Gibbons, J. M. Uomoto, M. L. Thompson, A. B. Graves, S. D. Edland, J. Bowen, W. C. McCormick, and E. B. Larson, "Neuropsychological test performance in a cognitively intact sample of older Japanese American adults," *Arch Clin Neuropsychol*, vol. 16, pp. 447-59, 2001.

[74] M. W. Morrison, R. J. Gregory, and J. J. Paul, "Reliability of the Finger Tapping Test and a note on sex differences," *Percept Mot Skills*, vol. 48, pp. 139-42, 1979.

[75] I. Shimoyama, T. Ninchoji, and K. Uemura, "The finger-tapping test. A quantitative analysis," *Arch Neurol*, vol. 47, pp. 681-4, 1990.

[76] T. Buracchio, H. H. Dodge, D. Howieson, D. Wasserman, and J. Kaye, "The trajectory of gait speed preceding mild cognitive impairment," *Arch Neurol*, vol. 67, pp. 980-6, 2010.

[77] M. K. Christianson and J. M. Leathem, "Development and Standardisation of the Computerised Finger Tapping Test: Comparison with other finger tapping instruments," *New Zealand Journal of Psychology*, vol. 33, pp. 44-49, 2004.

[78] E. Kiziltan, C. Barut, and E. Gelir, "A high-precision, low cost system for evaluating finger-tapping tasks," *Int J Neurosci*, vol. 116, pp. 1471-80, 2006.

[79] T. A. Salthouse, "Aging and measures of processing speed," *Biol Psychol*, vol. 54, pp. 35-54, 2000.

[80] C. Bartels, M. Wegrzyn, A. Wiedl, V. Ackermann, and H. Ehrenreich, "Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing," *BMC Neurosci*, vol. 11, pp. 118, 2010.

[81] S. S. Dikmen, R. K. Heaton, I. Grant, and N. R. Temkin, "Test-retest reliability and practice effects of expanded Halstead-Reitan Neuropsychological Test Battery," *J Int Neuropsychol Soc*, vol. 5, pp. 346-56, 1999.

[82] H. Johansen-Berg and P. M. Matthews, "Attention to movement modulates activity in sensori-motor areas, including primary motor cortex," *Exp Brain Res*, vol. 142, pp. 13-24, 2002.

[83] R. E. Passingham, "Attention to action," *Philos Trans R Soc Lond B Biol Sci*, vol. 351, pp. 1473-9, 1996.

[84] B. H. Repp, "Sensorimotor synchronization: a review of the tapping literature," *Psychon Bull Rev*, vol. 12, pp. 969-92, 2005.

[85] B. H. Repp and Y. H. Su, "Sensorimotor synchronization: A review of recent research (2006-2012)," *Psychon Bull Rev*, vol. 20, pp. 403-52, 2013.

[86] B. H. Repp, "Rate limits in sensorimotor synchronization with auditory and visual sequences: the synchronization threshold and the benefits and costs of interval subdivision," *J Mot Behav*, vol. 35, pp. 355-70, 2003.

[87] G. Aschersleben, "Temporal control of movements in sensorimotor synchronization," *Brain Cogn*, vol. 48, pp. 66-79, 2002.

[88] B. H. Repp, "On the nature of phase attraction in sensorimotor synchronization with interleaved auditory sequences," *Hum Mov Sci*, vol. 23, pp. 389-413, 2004.

[89] G. Madison, "Variability in isochronous tapping: higher order dependencies as a function of intertap interval," *J Exp Psychol Hum Percept Perform*, vol. 27, pp. 411-22, 2001.

[90] M. Molinari, M. G. Leggio, M. De Martin, A. Cerasa, and M. Thaut, "Neurobiology of rhythmic motor entrainment," *Ann N Y Acad Sci*, vol. 999, pp. 313-21, 2003.

[91] M. Turgeon and A. M. Wing, "Late onset of age-related difference in unpaced tapping with no age-related difference in phase-shift error detection and correction," *Psychol Aging*, vol. 27, pp. 1152-63, 2012.

[92] J. D. McAuley, M. R. Jones, S. Holub, H. M. Johnston, and N. S. Miller, "The time of our lives: life span development of timing and event tracking," *J Exp Psychol Gen*, vol. 135, pp. 348-67, 2006.

[93] M. Turgeon, A. M. Wing, and L. W. Taylor, "Timing and aging: slowing of fastest regular tapping rate with preserved timing error detection and correction," *Psychol Aging*, vol. 26, pp. 150-61, 2011.

[94] S. Vanneste, V. Pouthas, and J. H. Wearden, "Temporal control of rhythmic performance: a comparison between young and old adults," *Exp Aging Res*, vol. 27, pp. 83-102, 2001.

[95] A. Baudouin, S. Vanneste, M. Isingrini, and V. Pouthas, "Differential involvement of internal clock and working memory in the production and reproduction of duration: a study on older adults," *Acta Psychol (Amst)*, vol. 121, pp. 285-96, 2006.

[96] M. Boltz, "Changes in internal tempo and effects on the learning and remembering of event durations," *Journal of Experimental Psychology: Learning, Memory, and Cognition*, vol. 20, pp. 1154-1171, 1994.

[97] R. Kawashima, H. Itoh, S. Ono, K. Satoh, S. Furumoto, R. Gotoh, M. Koyama, S. Yoshioka, T. Takahashi, K. Takahashi, T. Yanagisawa, and H. Fukuda, "Changes in regional cerebral blood flow during self-paced arm and finger movements. A PET study," *Brain Res*, vol. 716, pp. 141-8, 1996.

[98] M. Joliot, D. Papathanassiou, E. Mellet, O. Quinton, N. Mazoyer, P. Courtheoux, and B. Mazoyer, "FMRI and PET of self-paced finger movement: comparison of intersubject stereotaxic averaged data," *Neuroimage*, vol. 10, pp. 430-47, 1999.

[99] S. T. Witt, A. R. Laird, and M. E. Meyerand, "Functional neuroimaging correlates of finger-tapping task variations: an ALE meta-analysis," *Neuroimage*, vol. 42, pp. 343-56, 2008.

[100] R. Kawashima, K. Inoue, M. Sugiura, K. Okada, A. Ogawa, and H. Fukuda, "A positron emission tomography study of self-paced finger movements at different frequencies," *Neuroscience*, vol. 92, pp. 107-12, 1999.

[101] J. Larsson, B. Gulyas, and P. E. Roland, "Cortical representation of self-paced finger movement," *Neuroreport*, vol. 7, pp. 463-8, 1996.

[102] A. W. Priest, K. B. Salamon, and J. H. Hollman, "Age-related differences in dual task walking: a cross sectional study," *J Neuroeng Rehabil*, vol. 5, pp. 29, 2008.

[103] D. V. Espino, M. J. Lichtenstein, R. F. Palmer, and H. P. Hazuda, "Evaluation of the mini-mental state examination's internal consistency in a community-based sample of Mexican-American and European-American elders: results from the San Antonio Longitudinal Study of Aging," *J Am Geriatr Soc*, vol. 52, pp. 822-7, 2004.

[104] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician," *J Psychiatr Res*, vol. 12, pp. 189-98, 1975.

[105] M. Ganguli, G. Ratcliff, F. J. Huff, S. Belle, M. J. Kancel, L. Fischer, and L. H. Kuller, "Serial sevens versus world backwards: a comparison of the two measures of attention from the MMSE," *J Geriatr Psychiatry Neurol*, vol. 3, pp. 203-7, 1990.

[106] R. N. Jones and J. J. Gallo, "Dimensions of the Mini-Mental State Examination among community dwelling older adults," *Psychol Med*, vol. 30, pp. 605-18, 2000.

[107] P. Karzmark, "Validity of the serial seven procedure," *Int J Geriatr Psychiatry*, vol. 15, pp. 677-9, 2000.

[108] J. H. Banos and L. M. Franklin, "Factor structure of the Mini-Mental State Examination in adult psychiatric inpatients," *Psychol Assess*, vol. 14, pp. 397-400, 2002.

[109] W. Liu, L. Forrester, and J. Whitall, "A note on time-frequency analysis of finger tapping," *J Mot Behav*, vol. 38, pp. 18-28, 2006.

[110] K. Shima, T. Tsuji, E. Kan, A. Kandori, M. Yokoe, and S. Sakoda, "Measurement and evaluation of finger tapping movements using magnetic sensors," *Conf Proc IEEE Eng Med Biol Soc*, vol. 2008, pp. 5628-31, 2008.

[111] H. M. Bronte-Stewart, L. Ding, C. Alexander, Y. Zhou, and G. P. Moore, "Quantitative digitography (QDG): a sensitive measure of digital motor control in idiopathic Parkinson's disease," *Mov Disord*, vol. 15, pp. 36-47, 2000.

[112] A. L. Taylor Tavares, G. S. Jefferis, M. Koop, B. C. Hill, T. Hastie, G. Heit, and H. M. Bronte-Stewart, "Quantitative measurements of alternating finger tapping in Parkinson's disease correlate with UPDRS motor disability and reveal the improvement in fine motor control from medication and deep brain stimulation," *Mov Disord*, vol. 20, pp. 1286-98, 2005.

[113] S. Louie, M. M. Koop, A. Frenklach, and H. Bronte-Stewart, "Quantitative lateralized measures of bradykinesia at different stages of Parkinson's disease: the role of the less affected side," *Mov Disord*, vol. 24, pp. 1991-7, 2009.

[114] M. M. Koop, N. Shivitz, and H. Bronte-Stewart, "Quantitative measures of fine motor, limb, and postural bradykinesia in very early stage, untreated Parkinson's disease," *Mov Disord*, vol. 23, pp. 1262-8, 2008.

[115] M. M. Koop, A. Andrzejewski, B. C. Hill, G. Heit, and H. M. Bronte-Stewart, "Improvement in a quantitative measure of bradykinesia after microelectrode recording in patients with Parkinson's disease during deep brain stimulation surgery," *Mov Disord*, vol. 21, pp. 673-8, 2006.

[116] D. T. Brocker, B. D. Swan, D. A. Turner, R. E. Gross, S. B. Tatter, M. M. Koop, H. Bronte-Stewart, and W. M. Grill, "Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease," *Exp Neurol*, vol. 239, pp. 60-7, 2013.

[117] G. P. Prigatano and S. R. Borgaro, "Qualitative features of finger movement during the Halstead finger oscillation test following traumatic brain injury," *J Int Neuropsychol Soc*, vol. 9, pp. 128-33, 2003.

[118] D. Austin, J. Petersen, H. Jimison, and M. Pavel, "A state-space model for finger tapping with applications to cognitive inference," presented at Conf Proc IEEE Eng Med Biol Soc, 2012.

[119] P. Holland and R. Welsch, "Robust regression using iteratively reweighted least-squares," *Communications in Statistics - Theory and Methods*, vol. 6, pp. 813-827, 1977.

[120] J. Singer and J. Willet, *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*: Oxford University Press, 2003.

[121] M. Hollander and D. Wolfe, *Nonparametric Statistical Methods*, 2 ed: Wiley-Interscience, 1999.

[122] J. C. Pinheiro, C. Liu, and Y. N. Wu, "Efficient algorithms for robust estimation in linear mixed-effects models using the multivariate t distribution," *Journal of Computational and Graphical Statistics*, vol. 10, pp. 249-276, 2001.

[123] D. Austin, J. McNames, K. Klein, H. Jimison, and M. Pavel, "A Statistical Characterization of the Finger Tapping Test: Modeling, Estimation, and Applications," *IEEE Transactions on Biomedical Engineering*, vol. Under Review, 2013.

[124] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia*, vol. 9, pp. 97-113, 1971.

[125] J. C. Morris, "The Clinical Dementia Rating (CDR): current version and scoring rules," *Neurology*, vol. 43, pp. 2412-4, 1993.

[126] J. Kaye, S. A. Maxwell, N. Mattek, T. Hayes, H. Dodge, M. Pavel, H. Jimison, K. Wild, L. Boise, and T. Zitzelberger, "Intelligent Systems for Assessing Aging Changes: Home-Based, Unobtrusive and Continuous Assessment of Aging," *Journal of Gerontology*, 2012.

[127] C. R. Bowie and P. D. Harvey, "Administration and interpretation of the Trail Making Test," *Nat Protoc*, vol. 1, pp. 2277-81, 2006.

[128] M. C. Ramsay and C. R. Reynolds, "Separate digits tests: a brief history, a literature review, and a reexamination of the factor structure of the Test of Memory and Learning (TOMAL)," *Neuropsychol Rev,* vol. 5, pp. 151-71, 1995.

[129] S. Joy, E. Kaplan, and D. Fein, "Speed and memory in the WAIS-III Digit Symbol--Coding subtest across the adult lifespan," *Arch Clin Neuropsychol*, vol. 19, pp. 759-67, 2004.

[130] B. Efron and R. Tibshirani, *An Introduction to the Bootstrap* Chapman and Hall/CRC, 1994.

[131] O. Godefroy, M. Roussel, P. Despretz, V. Quaglino, and M. Boucart, "Age-related slowing: perceptuomotor, decision, or attention decline?," *Exp Aging Res*, vol. 36, pp. 169-89, 2010.

[132] F. J. Jimenez-Jimenez, M. Calleja, H. Alonso-Navarro, L. Rubio, F. Navacerrada, B. Pilo-de-la-Fuente, J. F. Plaza-Nieto, M. Arroyo-Solera, P. J. Garcia-Ruiz, E. Garcia-Martin, and J. A. Agundez, "Influence of age and gender in motor performance in healthy subjects," *J Neurol Sci*, vol. 302, pp. 72-80, 2011.

[133] O. Godefroy, S. Spagnolo, M. Roussel, and M. Boucart, "Stroke and action slowing: mechanisms, determinants and prognosis value," *Cerebrovasc Dis*, vol. 29, pp. 508-14, 2010.

[134] A. Levey, J. Lah, F. Goldstein, K. Steenland, and D. Bliwise, "Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease," *Clin Ther*, vol. 28, pp. 991-1001, 2006.

[135] D. R. Gentner, S. Larochelle, and J. Grudin, "Lexical, sublexical, and peripheral effects in skilled typewriting," *Cognitive Psychology*, vol. 20, pp. 524-548, 1988.

[136] L. H. Shaffer, "Latency Mechanisms in Transcription," in *Attention and Performance IV*, S. Kornblum, Ed. London: Academic Press, 1973.

[137] J. Kaye, "Home-based technologies: a new paradigm for conducting dementia prevention trials," *Alzheimers Dement*, vol. 4, pp. S60-6, 2008.