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ABSTRACT

THE USE OF AUDIO STIMULATION TO AFFECT SENSORIMOTOR LEARNING

**by
Gregory Nicholas Ranky**

Sensorimotor learning for the hand and fingers can be conducted using both hardware and software components, but the training regime is also important. Using repetitive sequence tapping allows measurement of defined metrics in a controlled, safe environment, and therefore statistical indications for subject improvement.

The process of entrainment, when a subject's own movements synchronize to an external signal, has been tested in prior studies for memorization and recognition, but has not been investigated for correlation with sensorimotor learning.

This is tested with selected custom isochronic audio tones, combined with sequential finger tapping on a standard computer keyboard.

Whilst there were no significant differences between specific frequencies, testing blocks done during tone conditions show subject improvement in reduced mean sequence times compared to pre-stimulation, with no significant change in subsequent post-stimulation blocks.

**THE USE OF AUDIO STIMULATION
TO AFFECT SENSORIMOTOR LEARNING**

**by
Gregory Nicholas Ranky**

**A Dissertation
Submitted to the Faculty of
New Jersey Institute of Technology
and Rutgers University Biomedical and Health Sciences – Newark
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Biomedical Engineering**

Department of Biomedical Engineering

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APPROVAL PAGE

**THE USE OF AUDIO STIMULATION
TO AFFECT SENSORIMOTOR LEARNING**

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It is difficult to predict the end result of focused, exploratory research, regardless of the subject, and I've found that's true for life as well. For in the words of the late, great Isaac Asimov: 'The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' (I've found it!), but 'That's funny'.

I expected when first going into this dissertation that I would make a grand discovery, one that would change my field and inspire future work, and through the course of this dissertation, I found both results that I had hoped for, and results that surprised me and made me think.

Having just finished this and looking back at this moment, I can't say right now how beneficial my efforts were, as despite all my work I don't know the full effects of what I've done, and whether the results are significant enough for anyone to take notice in the future, or to build on it further. But in all honesty, I've come to conclude that every researcher, student or not, academic or not, has the belief that their work will be grand at some point, and that it's fine to believe in that possibility.

Over the past four years, I've spent not just time and money, but I've invested much of my peace of mind and self-worth too; when this dissertation is over and done with I want some of it back, as much as possible in fact. And whatever I won't be able to get back, I want to leave this work knowing that what I've traded for it is worthwhile. But once again, it's difficult to tell right now exactly what the end result will be.

What I can say however, is that I've experienced the key elements of research, stepping forward with one foot into the unknown, testing out what you expect to see if it is true outside of your own mind, and trying to convince others, many of whom you've never met, that your efforts were worthwhile. Research has taught me that learning is

indeed life-long, far beyond the confines of the classroom, and that the answers we end up having are rarely multiple choice, or simple enough to boil down into one pithy sentence, like the ones I'm trying to include here.

For anyone who's reading this dissertation, I advise you to think carefully about what you're planning to do with the degree you'll earn from this, because work on this scale will take space, time and peace of mind to accomplish. And if you do decide to follow through, don't be afraid to ask for help, because as insurmountable as it seems day after day, it is possible to finish, even if you don't find the results that you expected to.

In the end, your work can enrich the lives and understanding of those beyond you, and if this work that you're reading just now can do that for you, then I will consider my efforts have been worthwhile.

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LIST OF SYMBOLS

X	Y
ADL	Activities of Daily Living
AVS	Audiovisual Stimulation
CBF	Cerebral Blood Flow
CLT	Cognitive Load Theory
EEG	Electroencephalography
EOG	Electrooculography
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
FOT	Finger Oscillation Test
FTT	Finger Tapping Test
GFP	Global Field Power
GMFP	Global Mean Field Power
NT	No-Tone
OSHA	Occupational Safety and Health Administration
STD	Standard Deviation
tACS	Transcranial Alternating Current Stimulation

CHAPTER 1

INTRODUCTION

1.1 Objective

The objective of this dissertation is to investigate the effects of isochronic audio tones on upper extremity sensorimotor learning and activity, specifically to determine whether these are primarily assistive, restrictive or negligible. This was tested using neurologically healthy typical subjects with normal or corrected to normal vision and hearing, and no history of head trauma, seizures, or injuries or surgeries to the fingers, hands or arms.

This was first tested using four evenly spaced audio tones based on prior art, combined with the 9-Hole Peg Test, testing both the dominant and non-dominant hands.

Next, the same four tones were tested in combination with Thin Force sensors to measure both mean tapping speed and a preset finger sequence with subjects' non-dominant hand.

Finally, two of the four tones were tested using a preset keyboard sequence with subjects' non-dominant hands.

1.2 Problem Statement

The goal of this study is to utilize isochronic audio frequencies to determine their effects on upper extremity sensorimotor performance and learning. This was tested in adult subjects without physical or neurological impairments by using established cognitive tests and physiological measurements.

Despite the relative dearth of prior art in this testing of combinations of isochronic audio tones and upper extremity sensorimotor activity, there are real-world and clinical applications for the resulting work. Specifically, any activity with repetitive upper extremity movement may be assisted or hindered by external sounds, whether intended or not, such as noise or vibration from surroundings. This can assist by allowing synchronization of movements, or hinder by distracting or interfering in a person's optimal rhythm. This has potential applications in both ergonomics and rehabilitation; the full extent of which is not fully known.

1.3 Background Information

Because human working memory is limited, multiple cultures across the world have independently developed physical and behavioral tools to aid in memorization. Amongst the oldest and most widespread of these is the use of music and rhythm to encode information for future use. As both music and dance contain repeating sound and motion patterns, learning to play or keep time with music requires the practitioner to maintain rhythms by using internal synchronization and body movements, whether in dance or playing instruments.

A specific example of this involves the synchronization of brain activity to external rhythmic stimuli, known as entrainment. Historical examples of using entrainment extend beyond the personal scale, such as the Hypogeum of Hal-Saflieni, a subterranean structure on the island of Malta. Within one of the side chambers, known as the Oracle Room, where reverberations could be induced, and chanting at a 110Hz frequency has been found to induce a trance-like state in the speaker. As an aside, the

reverberations have been found only to occur at the frequency range of 95-120Hz, which could only be produced by a male voice.

Whilst prior work has found that using entrainment in combination with additional tasks has led to changes in recognition and memorization, the use of specific patterns, tones and frequencies and their effects on brain activity and sensorimotor learning however have had comparatively little study. In order to discuss entrainment, it is necessary to distinguish it from the similar concepts of Flow and Cognitive Load Theory.

1.3.1 Consciousness and Attention Optimization

The idea of a specific state of consciousness that optimizes learning and application was also explored by Professor Mihaly Csikszentmihalyi. He used the term Flow to refer to a state where a person's abilities and skills are comparable to meeting the challenges of presented tasks, with both greater than the levels of baseline daily activities. This is found in both genders, multiple ages, professions and nationalities. All instances of Flow that he discovered had common elements: feedback was immediate, goals were clear, and the perception of time was less relevant (though there were exceptions with this last element, such as in sprinting, where minimizing time spent was a goal).

1.3.2 Cognitive Load Theory

Cognitive Load Theory (CLT) was developed in the 1950s from the work of G.A. Miller,

then elaborated on in the 1980s by John Sweller; and posits that human working memory is limited, and therefore requires organizing input in order to make full use of it.

CLT provides an estimate of the maximum units of information that humans can process in a given amount of time at seven 'chunks' of information, with a gap of 1/18th of a second, giving 126 bits per second per person max, though this can be affected by distractors or fatigue (Sweller and Van Merriënboer, 2009). The concept of Flow agrees with CLT, in that human working memory is limited, and is subdivided into three types of load: task complexity, task presentation, task learning process. Given these conditions, there exists the possibility of a methodology or set of quantified elements that can achieve this state in order to thoroughly and consistently develop specific skills, even within the limits of human working memory.

The reason for this has been proposed to be a function of the brain's memory processing (Lisman, 2013). In this hypothesis, short-term memories are continuously refreshed to maintain their presence, at a rate of 30-100Hz, whilst long-term memories are refreshed at approximately 4-7Hz. Given these constraints, a short-term memory can cycle approximately seven times for each long-term refresh cycle. Whilst this has similarities to Flow, the primary difference is that CLT is used to analyze and optimize learning at an intellectual level, whilst Flow concerns itself with application and the overall state of participant consciousness. Both of these have an overlap with the use of rhythm to present information.

1.3.3 Neurofeedback and Audiovisual Entrainment

Entrainment is the matching of brain activity frequencies to external rhythms. This can

occur through sensory means using audio, visual or tactile input, or applied means such as tACS (transcranial alternating current stimulation).

Whilst prior work has found that using entrainment in combination with additional tasks has led to changes in recognition and memorization, the use of specific patterns, tones and frequencies and their effects on brain activity and sensorimotor learning however have had comparatively little study. A list of related work via PubMed is summarized below in Table 1.1.

Table 1.1 Background on Entrainment via PubMed

Category	# Papers Reviewed Prior to Testing
EEG and fNIRS	35
Rhythm – Audio – Mu and Theta	46
Neurofeedback and Brainwave entrainment	30
Ghilardi metrics	9
9-Hole Peg Test	22
Fitt’s Law	27
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Whilst the brain has multiple frequency ranges depending on the activity, it is necessary to evaluate prior entrainment work. A list of prior studies and their stimulation

frequencies is summarized below in Table 1.2.

Table 1.2 Prior Entrainment Frequencies and Modality

Researchers	Modality	Frequency Range	Study Results
Fox and Raichle (1984)	Visual	0-7.8Hz	Positive correlation with cerebral blood flow (CBF) in the striate cortex from 0 to 7.8Hz
Gomex-Ramirez et al. (2011)	Visual	0.67Hz	Entrainment occurred at 1.33Hz, reflected in FFT-spectrum, alpha amplitude increased in auditory cortex when vision attended
Lane (1998)	Audio	1.5,4,16,24Hz	Beta frequency gave more correct target detection than theta/delta beats
Mentis et al. (1997)	Visual	0,1,4,7,14Hz	Frequencies of 0,1,4,7, and 14Hz, results showed increase in striate cortex activity at 7Hz, with a decline at 14Hz
Padmanabhan (2005)	Audio	0-4Hz	Acute anxiety was ~50% less after 30min
Thomas & Siever (1989)	Visual	10Hz	Produced masseter relaxation in subjects with chronic temporomandibular joint disorder
Wach (2012)	tACS	10,20Hz	10Hz tACS increased movement variability over 30min post-stimulation, 20Hz tACS caused movement slowing directly after stimulation
Williams (2006)	Visual	9.5-11Hz	Optimal visual frequencies to improve word recognition from 9.5-11Hz, with peak power at 10.2Hz

The brain itself has the ability to change its active wave frequencies to match external audio, visual or tactile rhythms and is defined as entrainment (Siever, 2003). And it has been found that audiovisual entrainment in humans has a correspondence with the stimulation frequency. One example of this is the presence of entrainment at 2x the stimulation rate (Gomez-Ramirez et al., 2011), with entrainment occurring at 1.33Hz as

measured via Electroencephalography (EEG), when stimulation was presented in the sub-delta band at 0.67Hz. Another study (Fox, 1984) varied light flash frequencies, and found a positive correlation with cerebral blood flow (CBF) in the striate cortex from 0 to 7.8Hz, with a decrease in CBF above this frequency and a 20-30% increase in CBF at a 7.8Hz frequency of stimulation.

In addition to audio and visual stimulation, transcranial alternating current stimulation (tACS) has been utilized in recent work, on the M1 region of the brains of 15 right-handed subjects (Wach, 2012). It was discovered that 10Hz stimulation increased movement variability over 30 minutes post-stimulation, and 20Hz stimulation caused movement slowing directly after stimulation. The conclusion drawn from this was that a 10Hz neural oscillation interferes with inhibitory circuits, therefore increasing movement variability, an undesired result which would decrease subjects' precision.

Most significantly, regional cerebral blood flow has been measured using positron emission tomography (PET) during a pattern-flash visual stimulation at frequencies of 0,1,4,7, and 14Hz, (Mentis, 1997). The results showed increase in striate cortex activity at 7Hz, with a decline at 14Hz. Likewise, a study centered on a word recognition memory task with elderly participants (Williams, 2006), discovered optimal visual frequencies from 9.5-11Hz for increased word recognition, with optimal recognition close to 10.2Hz. Whilst these results point to the effects of optimal frequencies using visual entrainment, there has been no verification for the use of audio only at these same frequencies.

The frequency of 7.8Hz may have physiological significance aside from CBF, as it lies adjacent to both the Theta (4-7Hz) and Alpha (8-12Hz) bands within

Electroencephalography (EEG), which correspond to response inhibition with possible links to learning and memory and wakeful relaxation respectively. In addition, a subset of the Alpha band called the Mu wave (8-12Hz) is located over the sensorimotor cortex, which is reduced during actual or intended body movements (Ogoshi, 2013).

1.3.4 Optimal Frequencies for Movement

The presence of optimal or default frequencies for body movements as well as brain activity has also been investigated historically. This has led to discoveries such as a resonance for human walking at approximately 120 beats per minute, or 2Hz, though the discoverers concluded that the biomechanics of the arm and hand may give different frequencies (Van Noorden, 1999). Other work has found an optimal tapping frequency for single finger tapping of ~600ms or 1.667Hz; as this has not been examined for sequences, there may be additional correlations with multiples of this frequency (Keele, 1987). However, there is a difficulty here due to this being a repeating decimal, and it is unknown if there will be effects on tone creation due to rounding errors.

As the possible frequencies for optimal repetitive upper extremity and finger motion may not necessarily be identical to those for walking, they may span a range of values, or be a multiple of existing optimal frequencies. The discovery and use of optimal frequencies for repetitive movements has implications for such fields as sports medicine, workplace ergonomics and rehabilitation. Movements conducted at an optimal frequency would lead to greater efficiency of movement, fewer repetitive strain injuries, and reduced fatigue.

It is important to note that the frequencies that proved most effective in assisting recognition and memorization may not be optimal for upper extremity sensorimotor activity. Nevertheless, it is important to prioritize subject safety, and focus on finding as direct a correlation as possible between audio tones and upper extremity sensorimotor activity.

1.3.5 Workplace Safety and Ergonomics

In addition to potential effects on human performance, there is also the issue of safety and comfort, whether the workplace is an office, a mine or a factory floor.

Workplace noise has been found to be an explanatory factor in fatal industrial accidents between 1990 and 2005 (Deshaies, 2015), especially if worker communication was involved. In a less obvious example, worker performance and comfort can suffer with the presence of disruptive or unwanted noise; a survey conducted within eight European nations with 7441 participants revealed ‘noise’ as the variable with the highest association with occupants’ comfort (Sakellaris, 2016). Finally, noise has been found to affect recognition memory, which can lead to diminished performance or accidents by diminishing vigilance (Molesworth, 2015).

1.3.6 Significance

Whether there exists a correlation-positive or negative-between audio tones and upper extremity activity, the result is significant in either case. We are surrounded by a multitude of sounds-both repetitive and random, and if there are any effects on our

behavior or physiology, then it is necessary to determine what these are. It is also possible that there are related effects with other subject factors, such as handedness, gender or formal musical training.

In the event of a positive correlation, then the presence of isochronic tones may enhance concentration, improve sensorimotor activity or learning, or reduce fatigue, whilst a negative correlation may do the reverse.

If there is no correlation, then the results are significant nonetheless, as it permits the presence of a range of ambient sound frequencies in our working environment. Many of these may be unavoidable or costly to reduce, and so their presence would not detract from the quality of work or living by those in the proximity.

CHAPTER 2

9-HOLE PEG TEST

2.1 Chapter Introduction

As the ultimate objective of this work is to determine the effects of isochronic tones on sensorimotor activity, it is necessary to begin with an accepted, standardized test with which to combine audio tones. This allows minimization of variables in order to determine possible causality.

The test administered required a short setup time to minimize subject fatigue, be accepted by clinicians as valid, and be sufficiently challenging in order to demonstrate subject progression. Existing tests that matched these criteria include: the Jebsen Hand Function Test, the Perdue Pegboard Test, and the 9-Hole Peg Test. Also, as it is necessary to assess changes in neurotypical subjects before the possibility of requesting post-stroke subjects, the tests must not be too familiar to daily life. If these prove to be insufficient in some way, then a more localized test may be needed.

2.2 Established Upper Extremity Tests

The Jebsen Hand Function Test consists of seven subtests to assess unimanual hand functions for activities of daily living (ADLs), such as stacking checkers, card turning and picking and placing small common objects such as paper clips. Each subtest has a maximum of 120 seconds allotted, with a total testing time of at least 14 minutes and a lower time score corresponding to a greater function. Whilst this test does cover multiple unilateral hand functions, it only measures subject speed, not the quality of their

performance, therefore limiting its value. Also, as all the activities are performed by neurotypical subjects, it is unlikely to present a sufficient challenge for evaluation.

The Purdue Pegboard test consists of a rectangular board with two columns of 25 holes and four concave cups at the top. Subjects are asked to place small metal pegs from the cups on the testing side into the holes on the same side. Scores are determined by the number of pegs placed in 30 seconds, with a total of 5 minutes for the test.

The 9-Hole Peg Test consists of a rectangular plastic board with a concave cup at one end and nine evenly spaced holes at the other end arranged in a square. A sample image is shown below in Figure 2.1.



Figure 2.1 The 9-hole peg test.

Source: <http://www.euromedical.co.uk/section25/product328/9-hole-peg-test.html> (accessed 12/12/2016).

The board is placed at the subject's midline with the container holding the pegs on the same side as the hand being tested. Scoring is measured either by the time taken to

place all the pegs in their slots and remove them, or the total number of pegs placed in 50 or 100 seconds; the time taken is given from when the subject touches the first peg to when the last peg hits the container.

As all of these tests utilize completion time as their metric, they are limited in their ability to assess changes; however, the 9-Hole Peg Test has the advantage of compact size and shorter completion time over the other tests, thereby allowing a greater number of subjects to be tested in the same amount of time.

2.3 Modified 9-Hole Peg Test

Whilst the 9-Hole Peg Test appeared to be the most promising candidate to assess the effects of isochronic audio tones, the standard test required additional modifications to increase the challenge for neurotypical subjects.

The main difference in the Modified Test was the inclusion of a sequence order; the standard 9-Hole Peg Test only measures time to place the pegs in their slots, the Modified Test included a placement order where the subject added pegs row by row, bottom row first with the starting side opposite to the hand being used, and then removed them in the same order. The board was still placed at the subject's midline, but the concave dish was directly in front of the user in order to decrease peg placement distance and therefore decrease fatigue. Subjects wore earphones during this procedure, which were disinfected after each test session.

In terms of sound, there were a total of four conditions combined for the different protocols, each for 5min blocks: silence, a 5Hz isochronic tone, a 10Hz isochronic tone, white noise. An isochronic tone is listed by its isochronic frequency, here as either 5 or

10Hz, which is the rate at which the tone is turned on and off. However, each also has a carrier frequency, which is significantly higher due to the average human hearing range extending from 20Hz to 20kHz. The white noise was obtained from simplynoise.com, and the tones used were commercial tones from Goodvibras.com, each with a carrier frequency of 44.1kHz. The sound volume during testing met OSHA safety levels using the TooLoud smartphone app. The Protocol specifics are listed below in Table 2.1. All subjects were tested for both hands. In Protocol 3, hand order and tone order were determined for each subject using the random number generator function in Microsoft Excel.

Two-Way ANOVA was performed on Completion Time with the repeated measures of Stimulation and Hand Used (Left, Right). For Protocol 1, Stimulation had three levels (10Hz, 5Hz, 0Hz), for Protocol 2, Stimulation had two levels (White Noise, None), and for Protocol 3, Stimulation had three levels (10Hz, 5Hz, 0Hz).

Each subject was recruited from the NJIT student population, all had normal or corrected-to-normal vision and hearing. Before testing, each answered a questionnaire to determine their age in years (rounded up), their gender, and handedness as well as formal musical training (if applicable), and if they still continued to the present time. As described above, scoring was determined by the total time to place all nine pegs and then remove all of them once, with placement beginning in the top row on the opposite to the hand used, and removal done in the reverse order to placement. Each subject performed each combination (left/right hand, tone/no-tone) three successive times, and the means were extracted. Combinations are listed below in Table 2.1.

Table 2.1 Modified 9-Hole Peg Test Protocols

	Hand Order	Tone Conditions	# Subjects
Protocol 1	Alternating, non-dominant first	Fixed Tone Order; Non-dominant: None, 5Hz, 10Hz Dominant: None, 10Hz, 5Hz	7
Protocol 2	Alternating, non-dominant first	No Tones; White Noise, White Noise	6
Protocol 3	Random Hand Order	Random Tone Order; None, 5Hz, 10Hz	6

2.4 Results

The significant results for each of the three Protocols are shown in Figures 2.2 to 2.6

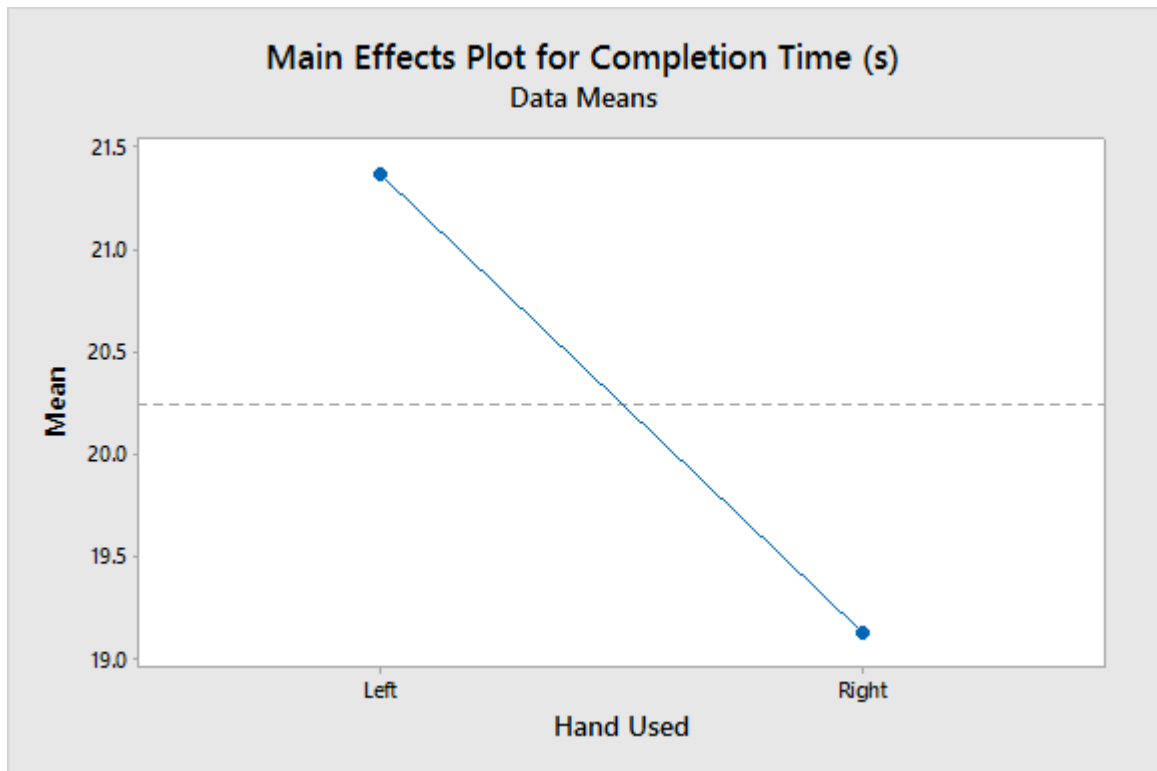


Figure 2.2 Protocol 1: main effects plot - completion time (s) vs. hand used.

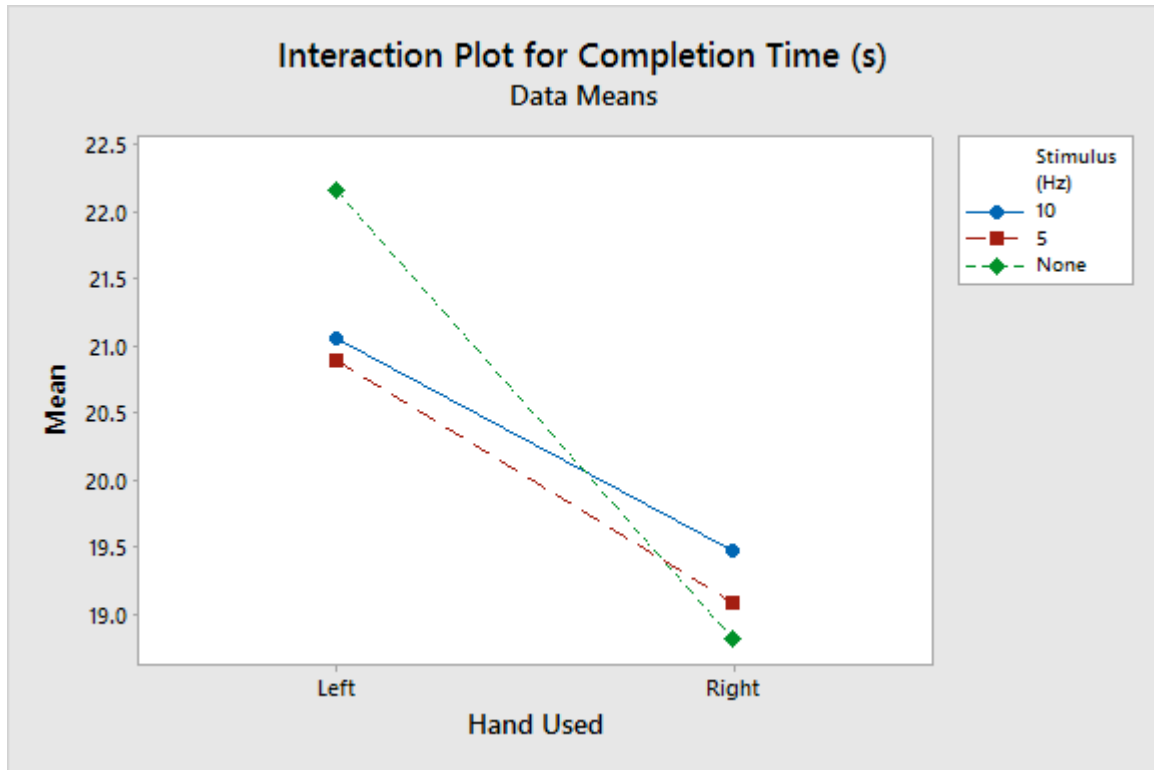


Figure 2.3 Protocol 1: interaction plot - completion time (s) vs. stimulus(hz)*hand used.

With Protocol 1, alternating hand order and fixed tone order, there is a significant effect on Completion Time both for Hand Used and for the combination of Hand Used and Stimulus (see Figure 2.2). For Hand Used [$F(1,6) = 65.05, p < 0.001$], When examining the mean (STD), Subjects gave shorter completion times with the Right Hand at 19.124 (1.794) seconds than the Left Hand at 21.368 (2.652) seconds, and with less variation shown by the smaller STD. In terms of the combined effects of Tone Frequency and Hand Used [$F(2,6) = 3.91, p = 0.023$], Right Hand Completion Times were shorter than those for the Left Hand across all frequencies (see Figure 2.3), with 19.467 (1.840) vs. 21.057 (2.734) seconds for 10Hz, 19.086 (1.626 vs. 20.890 (2.645) seconds for 5Hz, and 18.819 (1.929) vs. 22.157 (2.517) seconds for 0Hz/No-Tone. In addition, the Right Hand results had smaller STDs for each frequency, and all Right Hand

STDs were smaller than those from the Left Hand.

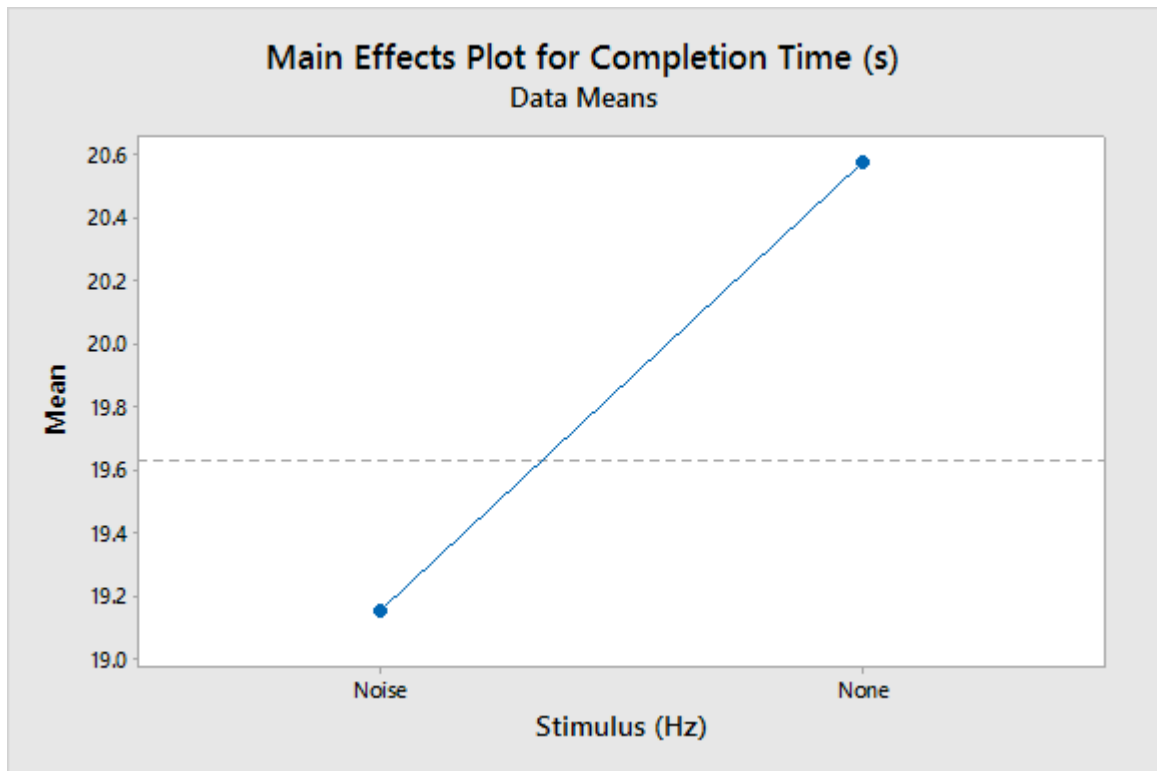


Figure 2.4 Protocol 2: main effects plot - completion time (s) vs. stimulus (hz).

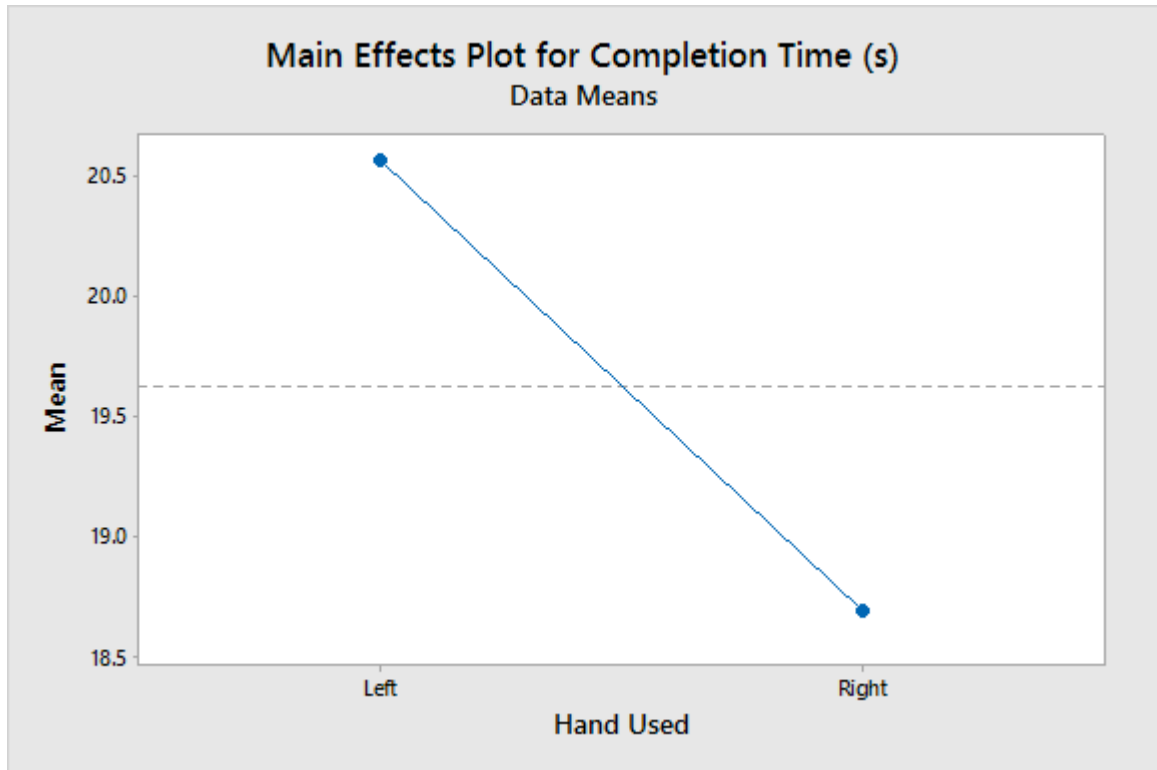


Figure 2.5 Protocol 2: main effects plot - completion time (s) vs. hand used.

With Protocol 2, alternating hand order and fixed white noise order there is a significant effect on Completion Time both for Stimulus and for Hand Used. For Stimulus [$F(1,5) = 39.88, p < 0.001$], White Noise gave shorter completion times and a smaller STD, 19.151 (1.762) vs. 20.575 (2.078) seconds. For Hand Used [$F(1,5) = 78.60, p < 0.001$]. The Right Hand gave shorter completion times and a smaller STD, at 18.689 (1.334) seconds vs. 20.563 (2.088) seconds.

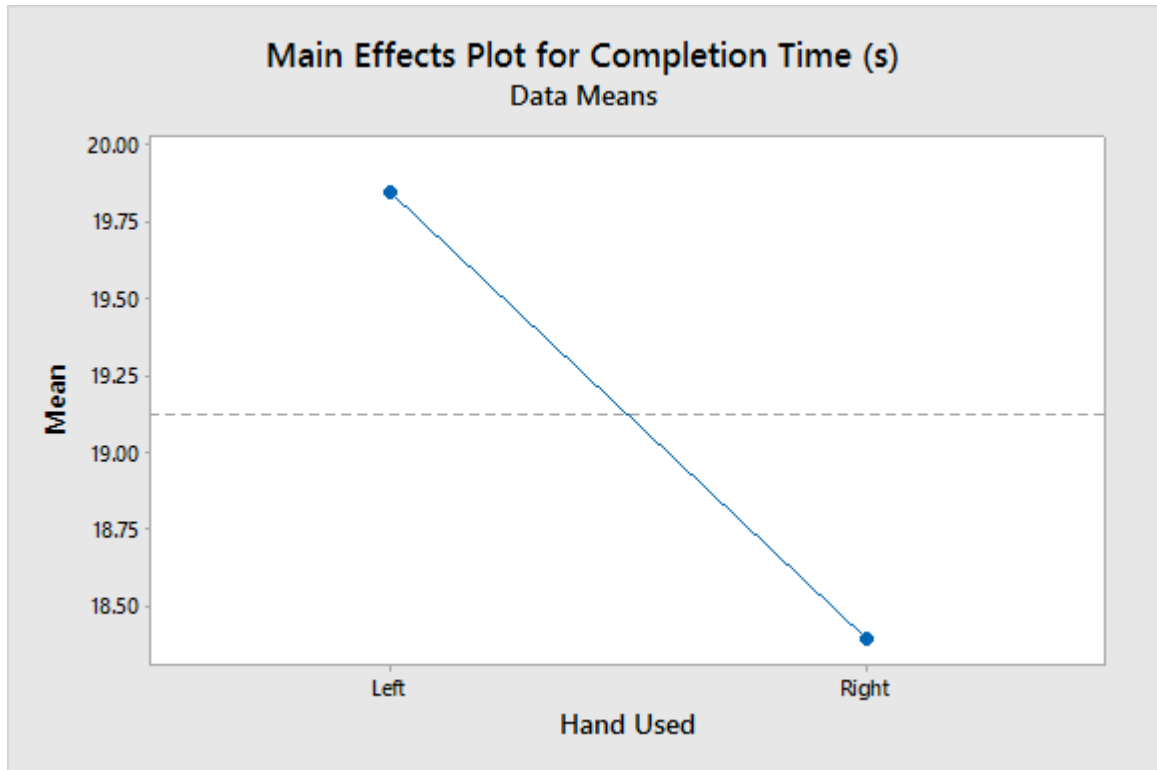


Figure 2.6 Protocol 3: Main effects plot - completion time (s) vs. hand used.

With Protocol 3, random hand and tone order, order there is a significant effect on Completion Time for Hand Used, [$F(1,5) = 17.66, p < 0.001$], where the Right Hand gave shorter Completion Times at 18.394 (2.288) seconds vs. 19.848 (2.297) seconds, and had a smaller STD.

Collectively, there exist consistent outcomes across the three Protocols, most apparent is that Subjects achieve shorter Completion Times with the Right hand. This is to be expected, as Subjects use the dominant hand for activities that require greater dexterity. Because of this, it is more difficult to gauge progress in activities, whilst using the non-dominant hand provides a greater challenge and therefore allows a clearer progression in testing. Within this testing there were no significant differences in Completion Time between multiple tone frequencies in those Protocols that had more

than one No-Tone condition, specifically Protocols 1 and 3. However, in Protocol 2 there were significant differences between White Noise and No-Tone, specifically that improved Completion Time and reduced the standard deviation. This shows the potential for the use of audio stimulation on upper extremity motor activity, even if the audio is not directly tied to the activity itself.

To summarize, whilst there exist differences in completion times between Tone vs. No-Tone, and between different isochronic tone frequencies, the 9-Hole Peg Test is not the ideal test to determine the specifics of this. Furthermore, the distribution shape of completion times vs. tone frequency remaining unclear, whether the relationship is linear, parabolic, plateauing, or another shape, or possibly random.

2.5 Discussion

Whilst the 9-Hole Peg Test is an established test for clinical use, it has disadvantages that are not immediately obvious; specifically that extended use causes the pegs to become slippery from contact with subjects' hands, and the emphasis on speed causes subjects to slip, and unintentionally drop them. This not only causes delays and requires subjects to repeat testing blocks, and therefore reduces the possible effects of entrainment if the testing block needs to be repeated.

Another disadvantage is the metrics available from the test. An optimal test is able to supply several metrics for analysis, which is especially necessary when examining potential effects of isochronic tones, as changes may be present in one metric, but not in others. Whilst the 9-Hole Peg Test allows the measurement of testing times, it does not directly supply accuracy or time for placement alone if performing peg placement and

removal with a single timer.

In terms of tones used, the optimal tones for upper extremity sensorimotor activity may not be the same as those found to be useful in prior literature. Nevertheless, future testing should include at least two tone variations in addition to a silence/no-tone condition, in order to determine if isochronic frequency has any significant effect on subject metrics.

Whilst it is possible to use additional equipment to record subject hand and finger position and joint angles, such as the CyberGlove®, this increases setup time and reduces subject dexterity. Also, the majority of upper extremity motions in daily life are performed without gloves, and therefore additional layering on a subject's hands may negate or obscure potential changes, especially if the starting pool consists entirely of neurotypical subjects. For similar reasons, the use of motion tracking equipment such as the OptiTrack would cause interference with subjects' finger motions due to the need for marker placement, and their unfamiliarity with the system. Future use is not completely discounted, but for the above reasons, successive testing will need minimization of variables.

A final mention is needed for subject handedness; all of the subjects in these Protocols were right-handed. Whilst all subjects had both hands tested, and the totality of the protocols-specifically Protocol 3-included cases where either the dominant or the non-dominant hand was tested first, there may be asymmetrical effects depending on subject handedness. Future testing may include a number of left-handed subjects, and any effects this may have on protocol metrics remains unclear at this time.

With these results in mind, it is necessary to use a testing method that

compensates for the difficulties experienced thus far, allowing a greater number of metrics with shortened setup time and ease of use.

CHAPTER 3

SEQUENTIAL FINGER TAPPING WITH FOUR TONES

3.1 Chapter Introduction

In order to determine possible correlation or causality between upper extremity activities and audio tones, it is necessary to use a testing protocol with high repeatability and clearly defined metrics. Therefore, the protocol utilized for the next stage was sequential finger tapping, combined with customized audio tones.

Whilst single-, and sequential-finger tapping is an accepted testing method in the biomedical community, the abundance of literature means that innovating using this method is subsequently more difficult. Nevertheless, it is possible to use finger tapping to bridge accepted testing with the experimental work performed in this dissertation.

3.2 Tone Customization

Although isochronic tones are available from commercial sources, being able to customize characteristics of each tone such as duration, waveform shape and internal frequencies entails creating specific audio files for testing purposes. The availability of software and online tutorials for this purpose allows for ease of use.

The tones used in this experiment were made specifically for this dissertation using Audacity® software, this allowed the creation of tones where not only the isochronic frequency, but the carrier frequency, duration, and overall shape can be customized; online tutorials also exist for the creation of specific waveforms. The carrier frequency was chosen to be 256Hz, which represents the note of middle C in Scientific

pitch. This differs from middle C at 261.62Hz as used by concert orchestras, as 256Hz is a whole number in the binary system, and allows all the octaves of C (an octave is 50% or 200% of a note's frequency) to remain whole numbers in both binary and decimals down to 1Hz. Middle C was also chosen because it exists within the average human hearing range, and can also be sung. Unlike the commercially available tone used previously, the resulting custom tone did not have tapering in volume at the beginning or end of the block. However, even though it is possible to include tapering in custom tones, it introduces additional variables to adjust, such as the time from silent to full volume, and the shape of the volume increase. As this is experimental, it is prudent to minimize testing variables until a clearer model can be established.

As an aside, Scientific pitch was first proposed in 1713 by French physicist Joseph Sauveur, and was promoted by the Italian composer Giuseppe Verdi; during its advocacy by the Schiller Institute, opera singer Stefan Zucker claimed that the Institute offered a bill in Italy for confiscation of all other tuning forks for state-sponsored musicians.

With the carrier frequency chosen as a constant, the next step was to determine a selection of isochronic frequencies to vary. As stated in Chapter 1, prior art gives a number of choices for frequencies to use, and for this round of testing, having frequencies with even spacing between them will allow the recording of changes in a more even distribution. Therefore, the frequencies tested here were 4, 8 and 12Hz; 10Hz was also included, as it has been used as a visual frequency in prior art, and falls within the specified frequency range. In order to ensure subject safety, it is necessary to exclude potential subjects who have a history of seizures, but also to minimize this risk within the

testing procedure itself; this is one of the primary reasons why the tones are presented in audio as opposed to visual. The key frequency to avoid is 15Hz, which is given in prior art as the frequency with the greatest risk of seizures, with the risk decreasing linearly on either side. Further seizure risks not covered in this dissertation include the color red, stripes, and alternating light and dark patterns (Fisher, 2005). Although this has been primarily reported in visual stimulation only so far, it is important not to undergo unnecessary risks in experimental work. Specifically, reflex epilepsy can be triggered by environmental stimuli, not only visual, or photosensitive epilepsy, but also audio from music or human voices.

3.3 Finger Tapping for Evaluation

Finger tapping has several advantages that allow for repeatability, which include but are not limited to: limited fatigue due to reduced body movement, a high degree of conscious control, and customization in movement patterns.

Finger tapping is a method to investigate upper extremity motor planning and execution, and has the advantage of having metrics in both behavioral changes and neuroimaging. This has been utilized to investigate procedural learning, such as work by Squire (1986), who investigated connections in human memory functions, and accepted motor tests such as the Halstead-Reitan Neuropsychological Battery are used to assess the observable physical effects of neurological damage.

3.4 Equipment and Metrics

In order to test a fixed unimanual sequence with force input, it is necessary to utilize a

pressure sensor to convert finger taps into a measurable, recordable signal for later software analysis.

The testing apparatus for the subjects was a Phidget Thin Force Sensor, which is listed as being able to measure forces from 1-100N or up to 2kg. This was connected to a Phidget Interface Kit, which sent the measured forces to a PC via a USB port. The default sampling rate for each sensor is 100Hz, and can go up to 500Hz. This is more than sufficient to satisfy the Nyquist Theorem, which states that a signal composed of sinusoidal waves must be sampled at least twice the rate of the highest frequency to accurately record it. The interface for the sensor functions via MATLAB, and input force data can be saved and processed for other software formats. The sensor itself was attached to a table in front of the seated subjects via double-sided Scotch® Heavy Duty Mounting Tape, to prevent the pad from slipping during repeated tapping. The sensor is shown below in Figure 3.1.

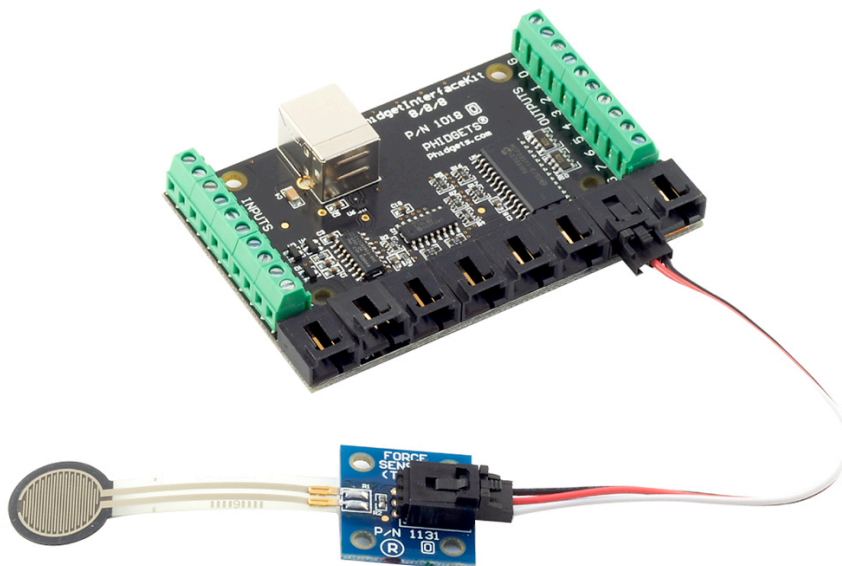


Figure 3.1 Phidget thin force sensor interface with usb port.

Source: <http://www.robotshop.com/media/files/images/phidgets-thin-force-sensor-large.jpg> (accessed 12/12/2016).

Commercial headphones were used to transmit white noise and Isochronic tones to the subjects whilst minimizing background noise. These were inserted and removed by the subjects themselves to minimize discomfort. The headphone wires were looped around the subjects' head and around the non-dominant hand to avoid interference with finger tapping motion.

The loudness of the audio administered through the headphones conformed to OSHA standards to remain below 85dB, using the TooLoud iPhone app. For reference, 90dB is the approximate level of a hair dryer or lawnmower, over 8 hours of which per day is considered harmful. As the tests themselves will take an estimate of 1-2 hours per subject with a week between sessions, this minimizes risks to hearing.

3.5 Procedure

Volunteers for this stage of testing came from the student population of NJIT. The subjects were seated in a non-swiveling chair in an upright position, and performed the Edinburgh handedness inventory. Once they were seated comfortably, they were presented with 5 minutes of white noise at an OSHA-safe audio level to achieve a relaxed state. After this, they performed a Crossover Study, in which they had to tap to maintain a steady rhythm as fast as they can using the index finger on their dominant hand. First they tapped for 6 minutes without a tone, then for 6 minutes to one of four randomized custom Isochronic tones presented equally to both ears, then for 6 minutes without the tone.

This study had 3 trials per frequency-before, during and after a tone adding up to 12 trials for single finger tapping using the index finger of the dominant hand. The order

of the testing frequencies was randomized in both sessions for each subject to minimize the effects of motor learning, fatigue and data contamination, and breaks of 5-10 minutes were provided if the subject felt fatigued.

Two-Way ANOVA was performed on Mean Tapping Frequency with the repeated measure of Stimulation (Tone, No Tone).

3.6 Results

A total of four subjects were recruited from the NJIT student population and tested for this procedure.

The Two-way ANOVA performed here did not reveal any significant effects of either Tone vs No Tone [$F(1,3) = 2.22, p = 0.145$]. A Main Effects plot for Stimulation is shown below in Figure 3.2, and whilst this does show an overall decrease in Mean Tapping Frequency during Tone conditions, it is not large enough to be significant.

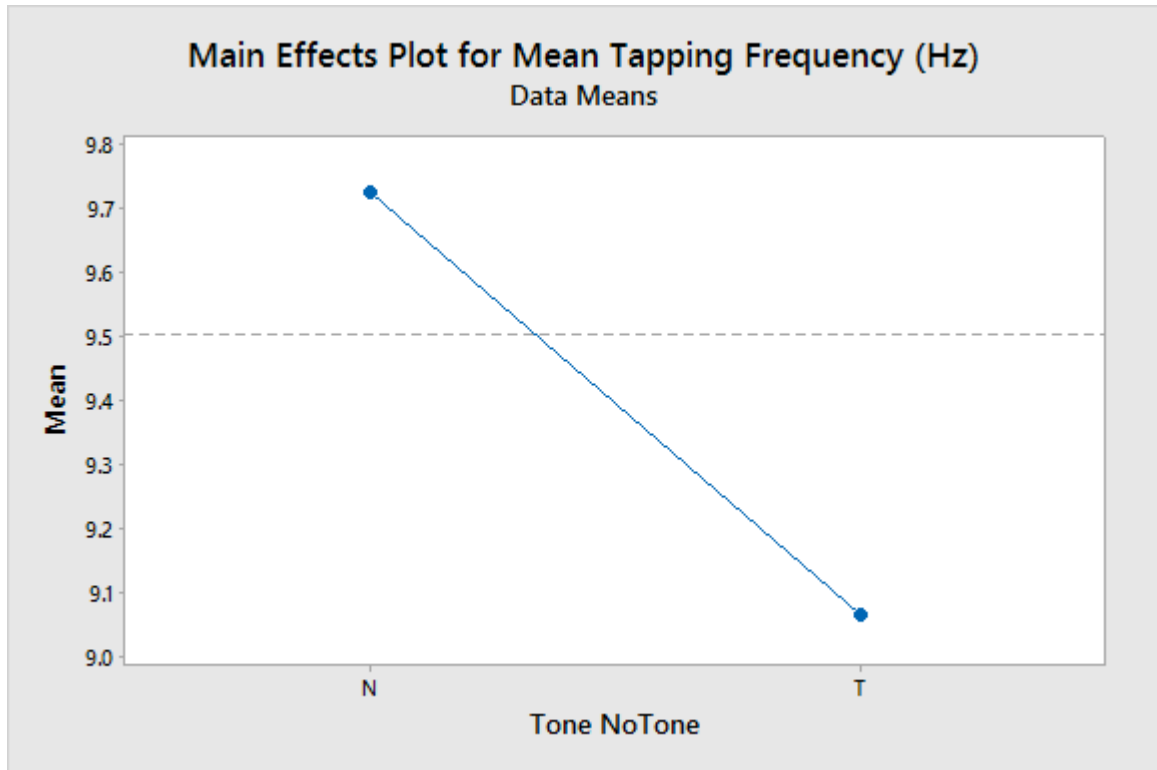


Figure 3.2 Main effects plot for mean tapping frequency (hz) vs. stimulation, n and t denote the no-tone and tone testing blocks, respectively.

Whilst useful in terms of testing using custom isochronic tones, the remainder of this procedure has too much variability to be used for further testing.

Firstly, the mean human tapping frequency is given to be approximately 1.667 Hz (Keele, 1987), and therefore the majority of given means is above this. As the force sensor used here has a range of values instead of a clear binary state, this is not the most appropriate choice to measure finger tapping accurately.

It was also discovered post-testing that subjects 3 and 4 may have had caffeine prior to their testing session. Whilst it is unlikely that this affected the mean frequency ranges in this procedure given the 5x greater than 1.667Hz frequency means, it will be necessary to confirm with recruited subjects ahead of time to abstain from caffeine for at least two hours as a prior study from the University of Barcelona has found that the

effects have that duration (Adan, 2008).

Although these limited results can be partially justified due to a dataset from only four subjects, if further testing with a greater number of subjects will be undertaken, it is important to determine the likelihood of significant results to avoid misspent time and effort.

3.7 Discussion

Although self-paced unimanual finger tapping is useful overall, having examined preliminary testing, a number of changes need to be implemented in order to improve accuracy in results.

Although a Force Sensor allows for a greater number of metrics than completion speed alone-and in this particular case, the measurement of rhythm/frequency-the measured instances to press each sensor gave too much uncertainty. Therefore, using keystrokes to measure sequences is far less ambiguous, as the resulting action is binary-either yes or no. This does not discount the possibility of using force sensors for future studies, but when working to test new hypotheses it is necessary to reduce ambiguity in testing metrics with appropriate choice of hardware and metrics, as it is difficult to extract a relationship between tone frequency and finger tapping performance.

Furthermore, subjects using the dominant hand may not be providing a significant challenge, as each has had a lifetime to practice and improve skills on this hand. Therefore, the next step is for subjects to perform a unimanual sequence using their non-dominant hand to provide a significant challenge for a previously unknown sequence.

CHAPTER 4

SEQUENTIAL FINGER TAPPING WITH 2 TONES AND A FIXED SEQUENCE

4.1 Chapter Introduction

With the difficulties encountered thus far in testing, it is necessary to reduce testing session time and the accompanying subject fatigue, as well as focus on more clearly defined metrics.

As mentioned in the discussion of Chapter 2, using four tones per session likely causes fatigue effects that overshadow smaller, more subtle changes in subject behavior. Therefore, it is necessary to change to two tones per session, thereby reducing fatigue effects. This will also reduce testing time by approximately 50%, allowing a greater number of subjects to be tested. In addition, comparing metrics obtained from the first and last testing blocks will allow evaluation of potential fatigue effects.

The decision was made to use 10Hz as one of the two frequencies due to being close to a multiple of 6x the listed maximum for human finger tapping, or 10.002Hz. Out of the four prior frequencies, this has the least deviation from a multiple of 1.667Hz. Using 4Hz as the other frequency was done due to its use in prior art as an audio stimulation frequency, and to give the largest possible frequency difference out of the prior four testing frequencies.

Also worth noting is the position of 10Hz in the Mu band for EEG frequencies, which as stated previously in Chapter 1 is reduced during actual or intended body movements, and lies within the frequency range for optimal visual entrainment. Although audio and visual signals do pass into the thalamus via different pathways,

because entrainment can occur in either case, it is necessary to have a point of comparison before moving further. In order to maximize the difference between frequencies, it is necessary to choose the 2nd frequency as being as far as possible from 10Hz, the choice here being 4Hz. Furthermore, 4Hz is near to the maximum human finger tapping frequency of approximately 600ms or 1.667Hz (Keele, 1987), and may therefore have a more pronounced effect.

For this modified procedure, testing metrics were wholly keyboard-based in order to minimize ambiguity in measurement, as a keystroke is a digital event-either yes or no-and can be more easily recorded and analyzed.

4.2 Procedure

A total of 30 subjects were tested for this specific procedure, and each was compensated \$20 for their time. All subjects were college students with no history of neurological disorders and were right-hand dominant. Out of the 14 subjects who answered ‘Yes’ to Formal Musical Training, two replied that their training was vocal only. The remaining 12 had either a mixture of instruments and vocal training or instruments only. All the instruments listed required the use of the fingers of both hands.

Each subject performed a sequence of 3 blocks of continuous typing of the ‘[a f s d a d f]’ sequence with their non-dominant, left hand. During the second block, auditory stimulation of either 4 Hz or 10 Hz was provided. Then the sequence of three blocks was repeated, and the auditory stimulation was once again provided during the second block, with a frequency of either 10 Hz or 4 Hz. The presentation order for the two stimulation frequencies were randomized across subjects. Each 370 s testing block had two recorded

files - the keystroke sequence and corresponding time codes - from which MATLAB extracted several metrics: the % Accuracy, defined as the total number of correctly performed sequences divided by the total number of performed sequences, then multiplied by 100; the Mean Sequence Time, defined as the time in seconds to perform a correct sequence; the Total # of Error States, a unitless value where each Error State is defined from the beginning point of an incorrect sequence to the beginning of the next correct sequence.

In order to gain familiarity with the testing sequence, subjects performed a single testing block prior to recording any of the metrics. Subjects were allowed to see the typing sequence to perform before and after this practice block, but at no point after this. They were also instructed to prioritize accuracy before speed.

The key sequence utilized involved all four fingers of the subjects' non-dominant hand, instead of the index finger of the dominant hand, and involved a fixed, repeated sequence instead of a single-finger self-paced rhythm.

In order to reduce visual distractions, subjects also used their non-dominant hand both to increase challenge, and provide a more easily observed change in performance before and after testing.

Prior art for unimanual sequential finger tapping focuses on five-digit sequences using the four fingers of the left hand: the left index finger corresponds to '1', the left middle finger to '2', the left ring finger to '3' and the left pinky to '4'. This gives the most common sequence found as '[4-1-3-2-4]'. This sequence has the advantage of providing challenge by avoiding more than two adjoining keys in a sequence, and difficulty can be increased further to a 7-digit sequence. In order to avoid two adjoining

keys once again both in sequence and for successive sequences, the modified sequence is [4-1-3-2-4-2-1]. To use this on a standard keyboard, and as the majority of subjects are right-handed, the keys used for the non-dominant/left hand were the ‘a s d f’ location, which is taught as the starting position for the left hand when typing. The resulting sequence, when translated to these keys is ‘[a f s d a d f]’, and the two tones (4 Hz and 10 Hz) were randomized across the subjects using Microsoft Excel’s RAND function.

The tones used in this experiment were made using Audacity® software, this allowed the creation of tones where not only the isochronic frequency, but the carrier frequency, duration, and overall shape can be customized for this study. The carrier frequency was chosen to be 256Hz, which represents the note of middle C in Scientific pitch. This differs from middle C at 261.62Hz as used by concert orchestras, as 256Hz is a whole number in the binary system, and allows all the octaves of C (an octave is 50% or 200% of a note’s frequency) to remain whole numbers in both binary and decimals down to 1Hz. Middle C was also chosen because it exists within the average human hearing range, and can also be sung. Unlike the commercially available tone used previously, the resulting custom tone did not have tapering in volume at the beginning or end of the block. Whilst it is possible to include tapering in custom tones, it introduces additional variables to adjust, such as the time from silent to full volume, and the shape of the volume increase. As this is experimental, it is prudent to minimize testing variables until a clearer model can be established.

With the carrier frequency chosen as a constant, the next step was to determine a selection of isochronic frequencies to vary. As shown earlier, prior art gives a number of choices for frequencies to use, and for this round of testing, having frequencies with even

spacing between them will allow the recording of changes in a more even distribution. Therefore, the frequencies tested here were 4, 8 and 12Hz; 10Hz was also included, as it has been used as a visual frequency in prior art, and falls within the specified frequency range. In addition, this is close to a multiple of six times the listed maximum for human finger tapping, or 10.002Hz.

In order to ensure subject safety, it is necessary to exclude potential subjects who have a history of seizures, but also to minimize this risk within the testing procedure itself; this is one of the primary reasons why the tones are presented in audio as opposed to visual. The key frequency to avoid is 15Hz, which is given in prior art as the frequency with the greatest risk of seizures, with the risk decreasing linearly on either side. Further seizure risks not covered in this study include the color red, stripes, and alternating light and dark patterns (Fisher, 2005). Whilst this has been primarily reported in visual stimulation only so far, it is important not to undergo unnecessary risks in experimental work. Specifically, reflex epilepsy can be triggered by environmental stimuli, not only visual, or photosensitive epilepsy, but also audio from music or human voices.

Separate four-way ANOVA was performed on each of the three outcome measures (% Accuracy, Mean Sequence Times, Total # of Error States) with two between factors Gender (Male, Female) and Formal Musical Education (Training, No Training), and two repeated measures factors Repetition (First, Second) and Block (Pre, Stimulation, Post).

Subsequently, to investigate the effects of different frequencies of stimulation, data from the conditions where auditory stimulation was present were analyzed. Separate three way repeated measures ANOVAs were performed on each of the three Responses

(% Accuracy, Mean Sequence Times, Total # of Error States), with two between factors of Gender (Male, Female) and Formal Musical Education (Training, No Training) and the repeated measure factor of Tone Frequency (4Hz, 10Hz).

All variance analyses performed on the data used $p < 0.05$ as the probability level to accept statistical significance. Post hoc comparisons used Bonferroni correction for multiple comparisons. For % Accuracy and Mean Sequence Times, $n=30$, for Total # of Error States, $n=27$, as three subjects had to be excluded due to technical reasons.

4.3 Results

Three separate ANOVAs with two repeated measures (Time (Pre, Stimulation, Post) and Repetition (1, 2)) were used to investigate the effects of auditory stimulation and motor learning on three outcome measures: Mean Sequence Time, Accuracy and Number of Error States.

Both main effects of Time and Repetition on Mean Sequence Time were significant ($F(2,52)=37.94$, $p < .0001$ and $F(1,26)=54.83$, $p < .0001$, respectively). Speed of typing increased during the second half of the experiment, with the mean (SD) Sequence Time reduced from 2.51 (.08) sec during the first three blocks (Repetition 1) to 2.19 (.66) sec during the last three blocks of trials (Repetition 2).

For the factor Time, post hoc comparisons showed that Mean Sequence Time averaged across the two repetitions was significantly shorter in the two Stimulation blocks of trials with auditory stimulation (mean (SD) of 2.27 (.72) sec) than during the preceding Pre blocks of trials without the stimulation (mean (SD) of 2.53 (.74) sec).

However, Mean Sequence Time was not different in the Post trial blocks (2.25 (.67) when compared to the Stimulation blocks (see Figure 4.1).

Table 4.1 Means Table for Sequence Time Effect: Repetition

**Means Table for Sequence Time
Effect: Repetition**

	Count	Mean	Std. Dev.
first	90	2.511	.736
second	90	2.195	.660

Table 4.2 Means Table for Sequence Time Effect: Time

**Means Table for Sequence Time
Effect: Time**

	Count	Mean	Std. Dev.
before	60	2.534	.736
stim	60	2.272	.716
post	60	2.254	.668

Table 4.3 Means Table for Sequence Time Effect: Repetition*Time

**Means Table for Sequence Time
Effect: Repetition * Time**

	Count	Mean	Std. Dev.
first, before	30	2.770	.706
first, stim	30	2.404	.746
first, post	30	2.360	.708
second, before	30	2.298	.699
second, stim	30	2.140	.671
second, post	30	2.148	.618

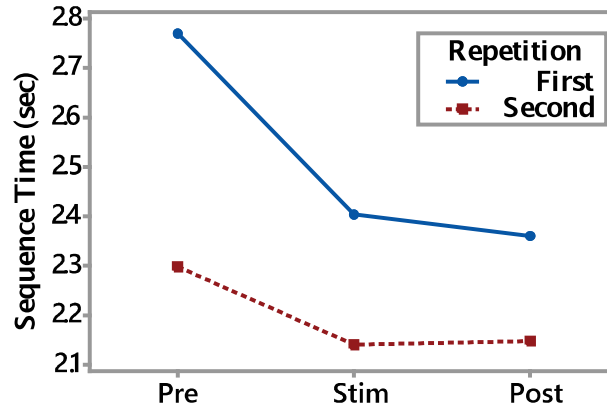


Figure 4.1 Interaction plot for mean sequence time

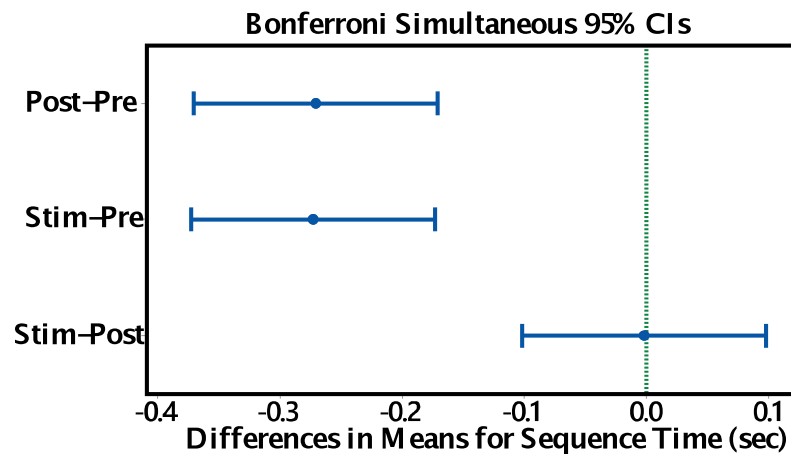


Figure 4.2 Bonferroni comparison plot for mean sequence time

Finally, there was a significant Repetition by Time interaction ($F(2,52)=6.66$, $p=.003$). Post hoc comparisons show that the decrease in sequence time in the Stimulation block (when compared to the Pre block) was more pronounced during the first Repetition than during the second Repetition.

Post hoc analysis using the Bonferroni multiple comparison procedure demonstrated that Mean Sequence Time was shorter in both blocks of trials where

auditory stimulation was present when compared to the preceding blocks with no auditory stimulation (blocks 1 and 4, respectively). At the same time, Mean Sequence Time was not different between these two blocks with stimulation and the two subsequent blocks, as shown in Figure 4.1, where there is not a significant difference between Stimulation and Post blocks.

There were no significant main or interaction effects on Accuracy except for the Gender by Musical Education interaction effect ($F(1,26)=5.43, P=.03$).

Table 4.4 Means Table for Accuracy Effect: Gender * Music

Means Table for Accuracy
Effect: gender * music

	Count	Mean	Std. Dev.
Female, No	30	94.152	4.744
Female, Yes	36	85.537	17.936
Male, No	72	86.083	11.649
Male, Yes	42	94.244	2.797

The effect of Time on Number of Error States was significant ($F(2,46)=5.71, p=.006$). Post hoc comparisons revealed that the number of error states was not different between the Pre and the Stimulation blocks of trials. The same was true for the Stimulation versus Post comparison. However, the difference between the Pre and the Post blocks reached significance, probably because of the overall increased number of typing sequences due to faster typing at the end of the experiment.

Table 4.5 Means Table for Error States Effect: Time

Means Table for Error States
Effect: Time

	Count	Mean	Std. Dev.
before	54	20.148	17.216
stim	54	22.556	14.819
post	54	25.056	17.565

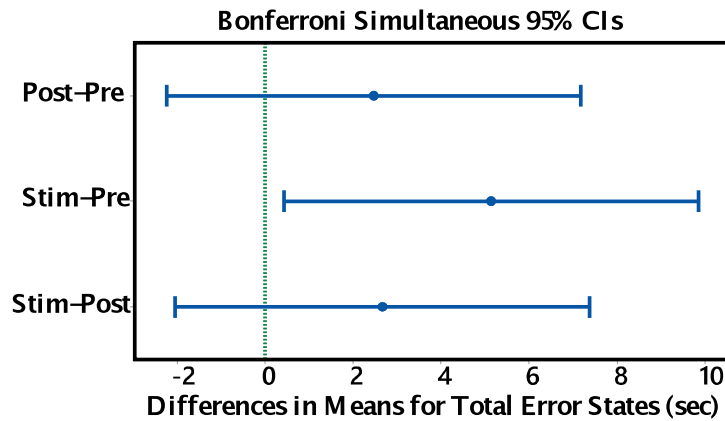


Figure 4.3 Bonferroni comparison plot for total error states

In a subsequent analysis of only the trials where auditory stimulation was present, we investigated the potential differential effects of stimulation frequency (4Hz versus 10Hz) on the three main responses. The three-way ANOVA with factors Stimulation Frequency, Gender and Formal Musical Training did not reveal any significant main or interaction effects of frequency stimulation.

4.4 Discussion

Although the use of isochronic tones on upper extremity sensorimotor learning and activity were not as pronounced as expected, the results were nonetheless significant.

Whilst Tone Frequency did not have any significant effects on the three metrics chosen for this protocol, Tone vs. Pre-stimulation conditions displayed a positive effect for Mean Sequence Times, giving shorter times regardless of gender or Formal Musical Training. The lack of significant increase or decrease in this metric for both Post-stimulation conditions indicates a degree of retention of the effects of applied Tones. Also, whilst there was an overall decrease in Mean Sequence Times from the first to the last block for each subject, the Tone block effects were more pronounced during the first Tone block, regardless of frequency. As for an explanation for the reduction in sequence time during Tone blocks, the cause is unlikely due to the Tone being a distraction, as Post-Tone blocks are not significantly lower or higher than the immediately preceding Tone blocks, and the overall decrease of Mean Sequence Time from Block 1 to Block 6 for each Subject occurs regardless. This supports the explanation that the presence of a Tone enhances a process that is already present in each Subject. A likely explanation is that Tones affect or enhance Subject vigilance, and keep them alert to allow them to acclimate faster to performing a repetitive upper extremity unimanual task.

Despite the lack of significant effects on Accuracy due to Tones, the interaction effect of Formal Musical Training and Gender did reveal within each gender, higher Accuracy and a smaller Standard Deviation for Female Subjects without training, whilst Male Subjects demonstrated lower Accuracy, and a larger Standard Deviation. Though this result alone cannot universally support the assertion that Formal Musical Training assists with repeating sequences and doing so with reduced variation, there is room in possible future studies to examine this further.

The metric of Total Error States was not affected significantly by Tone vs. No-

Tone conditions. The only noteworthy finding here is that it is significantly affected by fatigue, with Post-testing blocks on average giving more Error States than Pre-testing, though whether the length or distribution of these Error States within each block is significantly affected is a topic for future research. Furthermore, whilst all the tones in this experiment utilized sine waves as components, it may be the case that square or triangular waves have different effects on subject metrics if all other tone parameters remain unchanged.

Finally, in examining Tone testing blocks only, the lack of significant effects on any of the three metrics shows that the frequencies chosen for this study are not significantly different, though this does not preclude other frequencies from being significantly different, especially those closer to the maximum human tapping rate.

It is also useful to note that in prior work by Mentis et al. in 1997, the use of audio tones was presented for longer durations than the 6min used in this study, such as 10min or 30min; therefore, it may be necessary to have a longer stimulation duration to achieve more statistically significant effects. The difficulty here is that including the before, during and after conditions for each additional specific frequency adds time spent on a session, and to avoid subject fatigue or acclimation to the sequence it is necessary to avoid a total testing time longer than approximately an hour. Having a subject test on successive days to try different sequences is a possibility, but the effects of acclimation are greater, as is the difficulty of fitting testing sessions to conform to subjects' schedules. There may be combinations of varying the durations of each of the a-b-c conditions such as maintaining the b/during condition for 6min and reducing the a/before and c/after each to under 6min, but at this stage it is unclear which combinations to aim

for.

Also, as mentioned previously, given the maximum human finger tapping speed of 1.667Hz, none of the audio frequencies used thus far overlap directly with this tapping range. It may be that for repetitive motor actions, audio frequencies that overlap with motion range have a significantly more pronounced effect on successive motions than on frequency ranges for brain activity.

As stated in earlier chapters, the use of neurotypical subjects may not display significant effects in all metrics, and instead those with deficits, such as chronic post-stroke subjects, may display greater changes.

Future work may also need to include an isochronic tone closer to the measured optimal human finger tapping rate of 1.667Hz as determined by Keele et al., to determine if entrainment effects occur at a lower frequency range for the fingers than what has been used thus far. Alternatively, using tones with each of the isochronic frequencies chosen from multiples of 1.667Hz may have noticeable effects.

Though not as strenuous as walking, typing requires integrating audio, visual and tactile information. As this was a self-paced activity, subjects' attention was split between perception of external stimuli and internal rhythm generation (Hao, 2015).

It has been found in prior work that closed-loop auditory feedback on walking with Parkinson's subjects, results in improved walking speed and stride length; and compared to open-loop it has residual effects-suggesting that it could be integrated into existing therapy programs (Baram, 2016). In contrast, because the activity performed in this study gave tactile feedback in a closed-loop fashion, whilst the auditory Tone stimulation was open-loop, it is plausible that their sequence tapping negated a portion of

the effects due to the Tones.

Using custom isochronic tones allows precision over the testing materials in not only frequency but in duration and waveform shape. Combining this with keyboard-derived unimanual sequential finger tapping metrics allows the measurement of significant changes across subjects.

CHAPTER 5

CONCLUSION

Although the use of isochronic tones on upper extremity sensorimotor learning and activity were not as pronounced as expected, the results were nonetheless significant.

The 9-Hole Peg Test was useful as preliminary testing, and demonstrated that audio stimulation can have an effect on the completion time of an upper extremity unimanual task, and that overall performance is more pronounced in subjects' non-dominant hand. Although the specific effects of each frequency were not significant across protocols, this was addressed in subsequent testing using additional metrics and the use of finger tapping instead.

Using custom isochronic tones allows greater precision over the testing materials in not only frequency but in duration and waveform shape. Combining this with multiple force sensors allowed measurement of additional metrics to sequence completion times, such as tapping frequency, but also introduced uncertainty in recording precise waveform shape, and revealed no significant changes. Therefore, a more clearly-defined test needed to be implemented for finger motion.

The further procedure change from using four tones to two allowed for shorter testing session time and reduced subject fatigue, and whilst there were no statistically significant effects of Tone frequency on % Accuracy, Mean Sequence Time or Total Error States, Tone conditions did result in shorter Mean Sequence Times compared to Pre-Stimulation conditions.

In summary, it is highly unlikely that there is entrainment occurring during audio tones with isochronic frequencies above the maximum human finger tapping speed, as

the pace is simply too fast for the human hand to match and stay in time to. However, if testing is performed in 6-minute blocks accompanied by isochronic frequencies above the maximum human finger tapping speed, a self-paced unimanual task will not be affected by tone frequency, but the use of audio tones will result in improved Mean Sequence Time.

Potential future studies can include using one or more isochronic tones below that of maximum human finger tapping rates, or combining these with more complicated upper extremity sensorimotor tasks. In addition, whilst retention was not tested directly during this study, it remains a potential attribute to test for future work. Ultimately, if there exist larger effects under more specific circumstances, then it is necessary to clarify and study these for potential benefits to workplace activity; and the results found here can provide a foundation for future work.

APPENDIX A

SEQUENTIAL FINGER TAPPING WITH 4 TONES AND A FIXED SEQUENCE UNDER EEG

Electroencephalography (EEG) allows the recording of brain activity by monitoring voltage changes in clusters of neurons using scalp electrodes. Its high temporal resolution and non-invasive monitoring allow for real-time monitoring of brain activity. EEG activity is distinguished by multiple frequency ranges, each corresponding to different states of mind and internal activity, with lower frequencies correspond to reduced states of consciousness. The frequency ranges most relevant to this work are generally defined as follows: Delta (<4Hz), Theta (4-7Hz), Alpha (8-15Hz) and Mu (8-12Hz). In order to evaluate the possible use of EEG to gauge changes in brain activity during repetitive upper extremity activity, the wireless Emotiv EPOC™ headset by Emotiv Systems, Inc was tested in the Summer of 2014 during sequential unimanual finger tapping.



Figure A.1 The emotiv epoc™ eeg headset.
Source: <https://emotiv.com/epoc.php> (accessed 12/12/2016).

Subjects, each performed a fixed sequence ‘[a f s d a d f]’, using their non-dominant hand for each of four tone frequencies, 4,8,10 and 12Hz, the order randomized for each subject using Microsoft Excel’s RAND function. Each tone had a before-during-after block, with each block 6 minutes long, giving a total of 72 minutes per subject. EEG signal processing and analysis were performed using EEGLAB, an open source MATLAB toolbox, and subjects were monitored for changes in brain activity by using the Emotiv EPOC™ headset, sampling at 128Hz. Saline solution was applied to the scalp electrodes to improve conduction, but no adhesive tape or invasive attachment was needed. Subjects were asked to abstain from caffeine for at least 2 hours prior to testing, as prior art from the University of Barcelona has found that the effects have that duration.

The metrics from this experiment came from two sources: the EEG headset and the keyboard, which gave the total number of Error States. The initial metric give by the headset was Global Mean Field Power (GMFP), first introduced in 1979 to describe global EEG activity without requiring a specific reference electrode (Lehmann, 1979). An equation for calculating it is show below in Figure A.2, (Esser, 2006).

$$\text{GMFP}(t) = \sqrt{\frac{[\sum_i^k (V_i(t) - V_{\text{mean}}(t))^2]}{K}},$$

Figure A.2 The gmfp equation.

Source: http://www.fieldtriptoolbox.org/tutorial/tms-ee#global_mean_field_power (accessed 12/12/2016).

A total of five subjects were recorded during this experimental setup, and each

was compensated \$15 for their participation.

Subjects were examined for % changes in activity in one of four frequency bands for each of the four tones, both in no-tone/pre-stimulation to tone/stimulation, and tone/stimulation to no-tone/post-stimulation. These can each be represented by a topoplot, an example of which is given below in Figure A.3 and was obtained via EEGLAB, a toolbox for MATLAB.

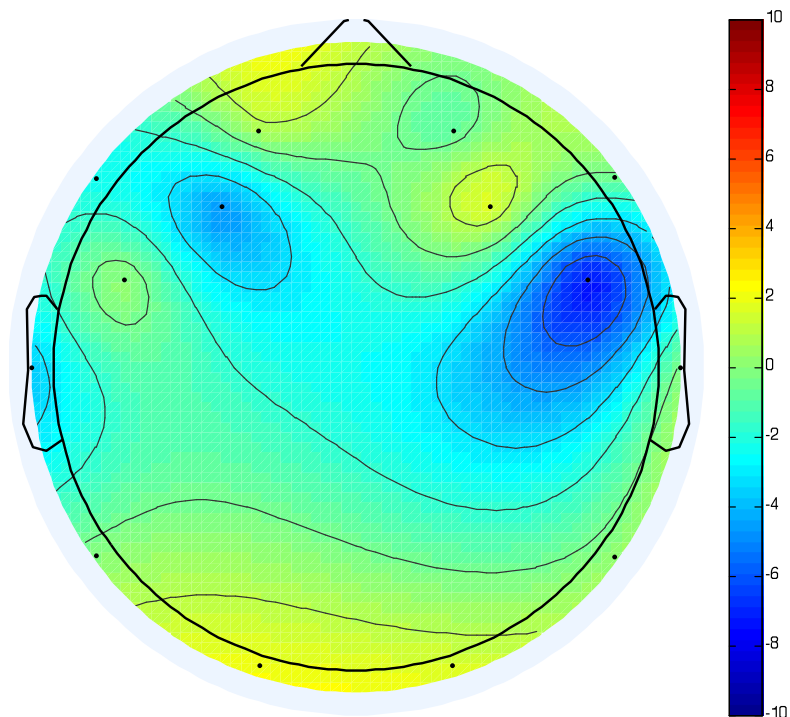


Figure A.3 Example of a topoplot.

A topoplot is a scalp map of an EEG for a combination of a specific frequency range such as alpha or theta, and a given condition; in this case, the condition is one of the four chosen isochronic tones. The map shows a top-down view with the subject's face at the top, and the right and left sides on the body matching the right and left sides of the map. Here, each of the electrodes has a scalar value, and the remaining color changes are interpolated from these values. The color bar here represents % changes in power, with green being 0% change, and each end representing in an increase of +10% for red, and -10% for blue, respectively.

After examining the EEG GMFP across five subjects shows that whilst there are subtle differences from No-Tone to Tone, and Tone to No-Tone, the differences are not significant enough in the measured frequency bands. The majority of GFP values have an absolute value change less than 1 per tone condition, which is not statistically significant. Examination of the Total Error States for each subject also did not show any statistical significance.

From the topoplots, the Group mean from No-Tone to Tone showed that the greatest changes overall were in the 4Hz and 10Hz conditions, and the greatest changes being in the Delta range over all the four tone frequencies-mostly decreases as indicated by the overall shifts to blue, and in the Theta range during 4Hz. The group mean from Tone to No-Tone showed that the largest changes are in the Delta range over all the four tone frequencies, as decreases during 4Hz and 10Hz, and as increases during 8 and 12Hz. There were also significant increases in the 10Hz condition during 10Hz.

Nonetheless, it is difficult to determine from these results whether entrainment is occurring in any of the subjects, as the EEG measurements here are primarily for changes

in global electrical activity. The EEG frequency range that shows the greatest change-Delta in this case-is associated with slow-wave sleep, and so a decrease in this would correlate with increased attention to one's surroundings. With a group sample size of only five subjects, it is difficult to draw further conclusions, but a less ambiguous series of metrics would be needed in order to determine the direction of further testing.

It could be that entrainment is fundamentally difficult when combining isochronic audio tones with sequential finger tapping and the frequency ranges of mental activity. Specifically, because the maximum human finger tapping frequency is approximately 1.667 Hz from prior art, and supported by prior work in this dissertation in Chapter 3, but the corresponding frequency range in brain activity is Delta at 0.1-3Hz, which corresponds to slow wave sleep, and the adjoining frequency range of Theta at 4-7Hz corresponds to drowsiness. Therefore, asking subjects to concentrate on maintaining a steady rhythm may negate any entrainment effects unless they maintain a slower rhythm.

In addition, due to testing subjects with four tones per session, the session is over an hour long, and effects due to fatigue may be too prominent. Therefore it is necessary to use fewer tones per session in order to determine possible effects on upper extremity sensorimotor activity.

Utilizing EEG allowed additional monitoring of subject responses to Tone vs. No-Tone conditions, but due to the exploratory nature of this dissertation, the resulting effects are inconclusive, and are therefore best left for future work. Also, because all of the subjects in this protocol would be considered neurotypical by their own admission, any visible effects may not be statistically significant with only five subjects. EEG could be utilized in future testing or studies, but for simplicity and reduced setup time, it is

more practical to utilize it only if there are results first confirmed in more clearly defined metrics.

APPENDIX B

MATLAB SOURCE CODE FOR DATA INPUT

In the course of testing, it was necessary to record and extract data from subjects' finger tapping, whether single or sequential. And for this, MATLAB software was used.

The following MATLAB file, 'prasademgmodv1b.m', recorded the input from a USB-connected force sensor, recorded the pressure exerted during self-paced dominant hand unimanual finger tapping, and then extract the mean tapping frequencies and displayed these as histograms.

```
% data=load('gnrrightsingleandsequ481012hzabc.mat');
x = gnrrightsingle4hza;
fs =500;
lc = 30;

N=30;
alpha =.36;

rawemg = x(:,1);
[B,A] = butter(4, lc/(fs/2));
fullemg = filtfilt(B,A, rawemg);

time = (1:length(fullemg))/(lc*2);
time2 = (1:length(rawemg))/fs;
h = (ones(1, N)/N);
Vt = conv(fullemg, h, 'same');
Vt = expinv(1-alpha, Vt);
g = Vt(1:end-1) <= fullemg(2:end);

g1 = [g' 0];
g2 = [0 g'];
onsets = find( g1 == 1 & g2==0);
times = time2(onsets);

figure (1);
plot(time2, rawemg)
hold on;

plot(time2(g), 20*ones(size(time(g))), '*r');
figure(2);
```

```

[n, x]=hist(1./diff(times), 100);
hist(1./diff(times), 100);
xlabel('frequencies in Hz');
ylabel('# of occurrences');
m=(n*x')/sum(n);
title(['mean= ' num2str(m)])

```

In order to determine the testing metrics of Accuracy, Mean Sequence Time and Total Number of Correct Sequences, it was necessary to record keyboard sequences by multiple subjects as well as corresponding timecodes, and then compare the recorded correct sequences to the total possible correct sequences in each block.

The following MATLAB file, 'keytest.m' recorded the keystroke sequence and corresponding timecodes from a 370s testing block, 1 of 7 for each subject; once the block ended with three successive beeps, MATLAB then saved two separate files per block named 'sequence' and 'times', respectively. These were then renamed between testing blocks with a prefix to denote the block order, with 'fp' as the practice block, and then fa through ff for the remaining blocks.

```

global sequence
global times
sequence = [];
times = [];

a = figure;

set(a, 'WindowKeyPressFcn', @onKeyPress);
tic;

%pattmod b = [a f s d a d f];
pause(370);
display('Collection Stopped');
beep;pause(.25);beep;pause(.25);beep;pause(.25);
close(a);

```

The following MATLAB file, 'findsequencesmodstd2.m' extracted the Accuracy,

Mean Sequence Time and Total Number of Correct Sequences for a testing block, 1 of 7 for each subject, with the correct key sequence as 'afsdadf'. If an error state is detected, the first full correct sequence after this error state occurs is considered to be the continuation of the correct sequences.

```
close all;
str='afsdadf';

fullstr=sequence;
fullstr(fullstr=='z')='a';
timeseq = times;
indices = [];
sequencesfound = length(indices);

nfullstr = fullstr;
sequencesfound = 0;
globalstart=0;
while(~isempty(strfind(nfullstr,str)))
    cindices = strfind(nfullstr, str);
    nfullstr = nfullstr((cindices(1)+length(str)):end);

    indices(end+1) = globalstart + cindices(1);
    globalstart = globalstart + cindices(1)+ length(str)-1;
    sequencesfound = sequencesfound + 1;
end

idealnumsequences = floor(length(fullstr)/length(str));

accuracy = (sequencesfound/idealnumsequences)*100

sequencetimes = [];
for i=1:length(indices)
    t1 = timeseq(indices(i));
    t2 = timeseq(indices(i)+length(str)-1);
    sequencetimes(end+1) = t2-t1;
end

meanseqtime = mean(sequencetimes)

keystroketimes = [];

for i=1:length(indices)
    for j = 1:(length(str)-1)
        t1 = timeseq(indices(i)+j-1);
```

```

        t2 = timeseq(indices(i)+j);
        keystroketimes(end+1) = t2-t1;
    end
end

meankeystroketimes = mean(keystroketimes)

% detection of error states
init = indices(1) + length(str);
state = zeros(size(fullstr));
state(init-5:init-1) = 1;

currInd = init;
inNormalState = true;
templateIndex=1;
while(currInd <= length(fullstr))
    currCharac = char(fullstr(currInd));
    desiredCharac = str(templateIndex);
    if(currCharac == desiredCharac)
        state(currInd) = 1;
        templateIndex = templateIndex +1;
        if(templateIndex > length(str)), templateIndex=1; end
    else
        I = find(indices > currInd);
        if isempty(I), break; end
        I = indices(I(1)) + length(str);
        state(I-5:I-1) = 1;
        templateIndex = 1;
    end
    currInd = currInd +1;
end

fstate = [-1, state];
bstate = [state, -1];

I=find((fstate == 1) & (bstate ==0))-1;
I2=find((fstate == 0) & (bstate ==1))-1; %error ending time
errortimes = timeseq(I);
errorendingtimes = timeseq(I2);

if(length(errortimes)> length(errorendingtimes))
    errorendingtimes(end+1) = 370;
end
if(length(errortimes)< length(errorendingtimes))
    errorendingtimes(1) = [];
end

errorlengths = errorendingtimes-errortimes;

```



```
totalerrors = 1:length(errortimes);
normtotalerrors =totalerrors/max(totalerrors);
% plot(errortimes, totalerrors, 'sq');

% [a,b,c] = createfit(errortimes, totalerrors)
% title('Cumulative Error States over Time');
% xlabel('Time(s)');
% ylabel('Number of Error States');

figure;
[an, bn] = createfitnorm(errortimes, normtotalerrors,
timeseq, errorendingtimes);

hold on
numberoferrors = length(errortimes)
disp('done')
```

REFERENCES

- 9 Hole Peg Test - Handy Healthcare. (2013, May 31). Retrieved from <http://handyhealthcare.co.uk/9-hole-peg-test-5170.html>
- A440 (pitch standard). (n.d.). In *Wikipedia*. (2016, April 17). Retrieved from https://en.wikipedia.org/wiki/A440_%28pitch_standard%29
- Adan, A., Prat, G., Fabbri, M., Sánchez-Turet, M. (2008). Early effects of caffeinated and decaffeinated coffee on subjective state and gender differences, *Progress in Neuro-psychopharmacology & Biological Psychiatry*, Volume 32, Issue 7, October 2008, p1698-703.
- Albouy, G., Sterpenich V., Vandewalle, G., Darsaud, A., Gais, S., Rauchs, G., Desseilles, M., Boly, M., Dang-Vu, T., Balteau, E., Degueldre, C., Phillips, C., Luxen, A., & Maquet, P. (2012). Neural correlates of performance variability during motor sequence acquisition, *Neuroimaging*, Volume 60, Issue 1, March 2012, p324-331.
- Ali, D.. (2010, October 30). Rehab Measures - Nine-Hole Peg Test. Retrieved from <http://www.rehabmeasures.org/lists/rehabmeasures/dispform.aspx?id=925>
- Audacity. (2013, March 10). Retrieved from <http://www.audacityteam.org/>
- Audio-visual entrainment. (n.d.) .). In *Wikipedia*. Retrieved August 16 2016, from https://en.wikipedia.org/wiki/Audio-visual_entrainment
- Baram Y, Aharon-Peretz J, Badarny S, Susel Z, Schlesinger I (2016) Closed-loop auditory feedback for the improvement of gait in patients with Parkinson's disease. *Journal of the Neurological Sciences*, 2016, April 15;363:104-6.
- Caffeine | C₈H₁₀N₄O₂ – PubChem. (2016, March 11). Retrieved from <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2519>
- Chen, H. M., Chen, C. C., Hsueh , I. P., Huang, S. L., & Hsieh, C. L. (2009). Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. *Neurorehabilitation and Neural Repair* 23(5): 435-440.
- Cognitive Load. (n.d.). In *Wikipedia*. (2016, April 17). Retrieved from https://en.wikipedia.org/wiki/Cognitive_load
- Conway, J. (2016, April 25). TooLoud Pro on the App Store. Retrieved from <https://itunes.apple.com/us/app/tooloud-pro/id425137981?mt=8>
- Csikszentmihalyi, M. (2008). *Flow: The psychology of optimal experience*. New York City: Harper Perennial Modern Classics, 1st edition, 2008. Print (pp.1-1).

- Create Isochronic Tones Using Sine Waves. (2009, February 11). Retrieved from <http://isochronic-tones.blogspot.com/2009/02/create-isochronic-tones-using-sine.html>
- Deshaies P., Martin R., Belzile D., Fortier P., Laroche C., Leroux T., Nélisse H., Girard S. A., Arcand R., Poulin M., Picard M. (2015). Noise as an explanatory factor in work-related fatality reports. *Noise & Health*, 2015 Sep-Oct; 17(78): 294–299.
- Do You Believe in Brainwave Entrainment? Try Online Now!. (2016, April 17). Retrieved from <http://www.goodvibras.com/>
- Electroencephalography. (n.d.). (2016, April 17). In *Wikipedia*. Retrieved from <https://en.wikipedia.org/wiki/Electroencephalography>
- Emotiv EPOC – 14 Channel Wireless EEG Headset. (2016, April 16). Retrieved from <https://emotiv.com/epoc.php>
- Entrainment .(n.d.). (2015, February 24). In *Wikipedia*. Retrieved from [http://en.wikipedia.org/wiki/Entrainment_\(biomusicology\)](http://en.wikipedia.org/wiki/Entrainment_(biomusicology))
- Esser, S. K., Huber, R., Massimini M., Peterson M. J., Ferrarelli F., & Tononi G. (2006). A direct demonstration of cortical LTP in humans: A combined TMS/EEG study, *Brain Research Bulletin Volume 69, Issue 1*, 15 March 2006, 86-94.
- Fisher, R. S., Harding, G., Erba, G., Barkley, G. L., & Wilkins, A. (2005). Photic- and Pattern-induced Seizures: A Review for the Epilepsy Foundation of America Working Group, *Epilepsia*, 46(9):1426–1441, 2005, Blackwell Publishing, Inc.
- Fox, P. T., and Raichle, M. E. (1984). Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *Journal of Neurophysiology*. 51(5): 1109–1120.
- Gomez-Ramirez, M., Kelly, S. P., Molholm, S., Sehatpour, P., Schwartz, T. H., & Foxe J. J. (2011). Oscillatory Sensory Selection Mechanisms during Intersensory Attention to Rhythmic Auditory and Visual Inputs: A Human Electro-Corticographic Investigation, *Journal of Neuroscience* 2011, 31(50): 18556–18567.
- Guclu-Gunduz, A., Citaker, S., Nazliel, B., & Irkeç, C. (2012). Upper extremity function and its relation with hand sensation and upper extremity strength in patients with multiple sclerosis. *NeuroRehabilitation Vol. 30, Issue 4*, 2012, 369-374.
- Hao Q, Ogata T, Ogawa K, Kwon J, Miyake Y (2015) The simultaneous perception of auditory-tactile stimuli in voluntary movement. *Frontiers in Psychology*, 2015 Sep 24;6:1429.

- Holloway, A.. (2014, January 20). The incredible sound effects of Malta's Hypogeum Hal Saflieni. Retrieved from <http://www.ancient-origins.net/news-history-archaeology-mysterious-phenomena/experts-unravel-sound-effects-malta-s-hypogeum-hal>
- Holmes, G.L.. (2013, September) Reflex Epilepsies. Retrieved from <http://www.epilepsy.com/learn/types-epilepsy-syndromes/reflex-epilepsies>
- Human Hearing Range. (n.d.). (2016, April 17). In *Wikipedia*. Retrieved from https://en.wikipedia.org/wiki/Hearing_range#Humans
- Jung, T. P., Makeig, S., Stensmo, M., & Sejnowski, T. J. (1997). Estimating Alertness from the EEG Power Spectrum, *IEEE Transactions on Biomedical Engineering*, Vol. 44, No. 1.
- Keele, S. W., Ivry, R. I., & Pokorny, R. A. (1987). Force control and its relation to timing, *Journal of Motor Behavior*, 19(1):96-114.
- Kidmose, P., Looney, D., & Mandic, D. P., Auditory Evoked Responses from Ear-EEG Recordings, *34th Annual International Conference of the IEEE EMBS*.
- Lane, J. D., Kasian, S. J., Owens, J. E., Marsh, G. R. (1998). Binaural auditory beats affect vigilance performance and mood. *Physiol Behav*. 1998;63(2):249-252.
- Ledberg, A. & Robbe, D. (2011). Locomotion-Related Oscillatory Body Movements at 6–12 Hz Modulate the Hippocampal Theta Rhythm, *PLoS One*, 2011, Vol. 6, Issue 11, 1-10.
- Lehmann, D., & Skrandies, W., Reference-free identification of components of checkerboard-evoked multichannel potential fields, *Electroencephalography and Clinical Neurophysiology*, Volume 48, Issue 6, June 1980, 609-621.
- Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron* 77, 1002–1016. 10.1016/j.neuron.2013.03.007.
- Manns, A., Miralles, R., & Adrian, H. (1981). The application of audiostimulation and electromyographic biofeedback to bruxism and myofascial pain-dysfunction syndrome. *Oral Surgery*, 52 (3), 247-252.
- Mathiowetz, V., Weber, K., Kashman, N., & Volland, G. (1985). Adult norms for the Nine Hole Peg Test of finger dexterity. *Occupational Therapy Journal of Research*, 5, 24–38.
- Mentis, M. J., Alexander, G. E., Grady, C. L., Horwitz, B., Krasuski, J., Pietrini, P.,...Rapoport, S. I. (1997). Frequency Variation of a Pattern-Flash Visual Stimulus during PET Differentially Activates Brain from Striate through Frontal Cortex. *Neuroimage* 5, 116–128.

- Mihaly Csikszentmihalyi. (n.d.). In *Wikipedia*. Retrieved February 24 2015, from http://en.wikipedia.org/wiki/Mihaly_Csikszentmihalyi
- Molesworth B. R., Burgess M., Zhou A. (2015). The effects of noise on key workplace skills. *The Journal of the Acoustical Society of America*. 2015 Oct;138(4):2054-61.
- Musical Notation. (n.d.). (2016, April 17). In *Wikipedia*. Retrieved from https://en.wikipedia.org/wiki/Musical_notation
- Mu Wave. (n.d.). (2016, October 5). In *Wikipedia*. Retrieved from https://en.wikipedia.org/wiki/Mu_wave
- Ogoshi, S., Ogoshi, Y., Momose, S., Takezawa, T., & Mitsunashi, Y. (2013). Mu rhythm suppression during the imagination of observed action, *Engineering in Medicine and Biology Society (EMBC)*, 2013 35th Annual International Conference of the IEEE. September 2013.
- Olsson, C. J., Jonsson, B., & Nyberg, L. (2008). Learning by doing and learning by thinking: an fMRI study of combining motor and mental training, *Frontiers in Human Neuroscience*, June 2008.
- OSHA, Occupational Noise Exposure. (2016, April 27). Retrieved from <https://www.osha.gov/SLTC/noisehearingconservation/>
- Padmanabhan, R., Hildreth, A. J., & Laws, D. (2005). A prospective, randomised, controlled study examining binaural beat audio and pre-operative anxiety in patients undergoing general anaesthesia for day case surgery, *Anaesthesia*. 2005;60(9):874-877.
- Patrick, G. J. (1996). Improved neuronal recognition in ADHD: An application of fifteen sessions of photic-driven EEG neurotherapy. *Journal of Neurotherapy*, 1(4), 27-36.
- Phidgets Inc. (2016, April 16). Retrieved from <http://www.phidgets.com/>
- Raad, J. (2012, August 17). Rehab Measures - Jebsen Hand Function Test. Retrieved from <http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=1025>
- Raad, J. (2014, January 9). Rehab Measures – Purdue Pegboard Test. Retrieved from <http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=1144>
- Sakellaris, I. A., Saraga, D. E., Mandin, C., Roda, C., Fossati, S., de Kluizenaar, Y.,...Bluyssen, P. M. (2016). Perceived Indoor Environment and Occupants' Comfort in European "Modern" Office Buildings: The OFFICAIR Study. *International Journal of Environmental Research and Public Health*. 2016 Apr 25;13(5).

- Scientific Pitch. (n.d.). (2016, April 17). In *Wikipedia*. Retrieved from https://en.wikipedia.org/wiki/Scientific_pitch
- Siever, D. (2003). Applying audio-visual entrainment technology for attention and learning-pan II I. *Biofeedback*, 31, 4. 24-29.
- SimplyNoise The Best Free White Noise Generator on the Internet. (2016, April 17). Retrieved from <https://www.simplynoise.com/>
- Squire, L. R. Mechanisms of memory. *Science*. 1986; 232(4758):1612–1619.
- Thomas, N., & Siever, D. (1989). The effect of repetitive audio/visual stimulation on skeletomotor and vasomotor activity. In Waxman, D., Pederson, D., Wilkie, I., & Meller, P. (Eds.) *Hypnosis: 4th European Congress at Oxford*, 238-245. London: Whurr Publishers.
- Tutorial:tms-eeg - FieldTrip. (2016, April 17). Retrieved from http://www.fieldtriptoolbox.org/tutorial/tms-eeg#global_mean_field_power
- Van Merriënboer J. J. G., & Sweller, J. (2010). Cognitive load theory in health professional education: design principles and strategies. *Blackwell Publishing Ltd*. 2009, *MEDICAL EDUCATION* 2010, 44: 85–93.
- Van Noorden, L., & Moelants, D. (1999). Resonance in the perception of musical pulse, *Journal of New Music Research*, 28 (1): 43-66.
- Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A., & Pollok, B. (2013). Effects of 10 Hz and 20 Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. *Behavioral Brain Research* 241 (2013) 1-6.
- Williams, J. H., Ramaswamy, D., & Oulhaj, A. (2006). 10Hz flicker improves recognition memory in older people, *Neuroscience*. 2006; 7:21.
- Yotsumoto, Y., Watanabe, T., Chang, L. H., & Sasaki Y. (2013). Consolidated learning can be susceptible to gradually-developing interference in prolonged motor learning, *Frontiers in Computational Neuroscience*, May 2013.
- Zimmermann, K. M., Bischoff, M., Lorey, B., Stark, R., Munzert, J., & Zentgraf, K. (2012). Neural Correlates of Switching Attentional Focus during Finger Movements: An fMRI Study, *Frontiers in Psychology*, December 2012.