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Dynamics of Motor System Excitability during Auditory Anticipation

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Honors Psychology Thesis

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London, Ontario, CANADA

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Abstract

The ability to anticipate complex sounds, like words in speech or the beat in music, is an important aspect of human perception. However, the changes of excitability in the motor system during auditory anticipation have not been characterized. Here, we applied single-pulse Transcranial Magnetic Stimulation (TMS) to the primary motor cortex to elicit motor evoked potentials (MEPs) from the first dorsal interosseous muscle, the amplitude of which indexes motor system excitability. Healthy right-handed participants (N = 20) underwent TMS stimulation during listening to regular (periodic) tone sequences at three rates (200ms, 550ms, and 900ms) and irregular tone sequences. We assessed MEP amplitudes over time, to test fluctuations in excitability during auditory anticipation (listening to regular sequences), and in the absence of auditory anticipation (listening to irregular sequences). We hypothesize that motor system excitability fluctuates at the rate of auditory stimulation, and peaks in anticipation of regular sounds. Results do not show evidence that motor system excitability fluctuates at the rate of regular or irregular auditory tones. Also, the results do not show evidence of an increase in excitability in anticipation of regular or irregular sounds. These results do not suggest synchronization of motor system excitability to regular sounds, informing our understanding of auditory-motor integration.

Fluctuations of Motor Excitability by Isochronous Tone Sequences

Listening to music is an activity most people partake in on a daily basis. There are also many situations where we are required to integrate auditory information into a motor response such as in dance or when playing a musical instrument. Auditory-motor integration is also involved in conversation, where music is thought to share some underlying mechanisms with language such as perception of temporal patterns (Fedorenko, Patel, Casasanto, Winawer, & Gibson, 2009). Some of the more evident mechanisms involved with auditory-motor integration are the perception of temporal patterns, and then the anticipation of future tones to coordinate synchronized movement. Perception of temporal patterns and anticipation are fundamental to normal hearing, speech, motor control, and music. This study aims to learn more about the underlying neural correlates behind the auditory-motor integration processes of perception and anticipation.

Auditory-Motor Interactions

We often see interactions between the auditory system and the motor system, such as when we listen to music, and are then able to tap along to it. There is a noticeable difference between tapping to an irregular beat, and tapping along to a beat with regular intervals (isochronous). Tapping to an irregular beat is often reactive, meaning that the movement is initiated after the stimulus. With isochronous tones, tones allow for anticipatory movements to tap at the same time as the stimulus. Brain areas found to be involved in movement initiation such as the basal ganglia and supplementary motor areas (SMAs) are also involved in motor prediction (Rao et al., 1997). Previous studies have looked at motor system activation with movement to tempos (length of temporal interval), such as the study by Keiichiro et al. (2002), which found greater motor activation for faster movements and tempos. As tempos increased

from slow to fast, the relationship between movement and tone switched from synchronized to syncopated. This shows that anticipation effects are more likely in faster tempos, than very slow tempos.

Imaging studies have shown that the motor system is activated while listening to rhythms, even when there is no action being performed, in particular the supplementary motor area (SMA), basal ganglia, cerebellum, and the premotor cortex (Grahn & Brett, 2007). The fMRI study by Grahn and Brett (2007) used rhythms to investigate which specific motor regions respond to the beat (regular, underlying pulse) in music. They demonstrated that motor areas are not only active in the production of music by movement, but also in the perception of music. These activations were found to be different in response to different stimuli, such as stronger activation for rhythms with strong regular accents. The strong regular accents can be compared to isochronous tones in their property of a constant interval between stimuli.

Other imaging studies have looked at neural representations of temporal patterns in performing movement. A study by Fujioka et al. (2012) found that activity in auditory cortices and motor-related areas increases in anticipation to isochronous tones, and synchronizes to tone rates. Using human magnetoencephalography (MEG) in a task of listening to tones with no movement, the study found modulation of beta amplitude in synchronization with the tempo of sound stimulation in brain areas such as the sensorimotor cortex, inferior-frontal gyrus, SMAs, and cerebellum. These changes in beta amplitude represent periodic waves where the periods match the tempo; as the temporal intervals increased from 390ms, 585ms, to 780ms, a pattern is seen. There is a decrease in the excitability wave directly after a stimulus, and a subsequent rebound where excitability increases until the next stimulus in anticipation. The rebound slope in excitability depended on stimulus rate, suggesting anticipatory effects from an internalized

temporal interval. The beta waves are made up of beta bands which are waves of electrical activity constant in the brain at a frequency of 25-30 Hz. Normally they are desynchronized, but it was found that they synchronize to auditory rhythms and create the characteristic beta waves. Beta waves were found to play a role in functional auditory-motor communication. The patterns of brain activity shown in the study by Fujioka et al. (2012) show synchronization of neuronal activity primarily in auditory systems. Due to auditory-motor interactions, there is strong evidence for a possibility for patterns of synchronization in motor systems, which may provide more insight into the mechanism for being able to synchronize movements with auditory stimuli.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a method for inferring causal relationships between brain structures and their functions. TMS consists of non-invasive stimulation of the brain using a transient magnetic field generated by triggering an electrical current through the coil. When the TMS coil is placed over the primary motor cortex, it can produce motor evoked potentials (MEPs), which when large enough, can be seen as a muscle twitch. MEPs are measured used an electromyogram (EMG) machine. A methodological basis for using TMS-elicited MEPs as a measure of motor excitability to auditory stimuli is the study by Watkins and Paus (2004). This study measured the increase in the excitability of the orofacial motor system during speech perception. They combined positron emission tomography (PET) with TMS to investigate motor areas activated during speech perception. They found increased excitability in the motor areas underlying speech production in response to speech perception with no speech output required. This proposed that there are motor areas which prime the motor system to respond to auditory stimuli. The study also showed a larger MEP to M1 stimulation of the face area which correlated with cerebral blood flow in the language area. This provides support for

TMS not only being able to infer causal relationships between brain areas and their function, but also measuring changes in excitability as a function of differences in MEP amplitude, where the amplitude of MEPS is able to index real-time excitability in the motor system.

Studies have shown that several motor areas respond to the presence of a regular beat. Since the premotor cortex and the SMA feed into the primary motor cortex (M1), we expect subthreshold excitability changes in M1. The changes in amplitude of an MEP can be used as a measure of changes in motor cortex excitability. Greater excitability of M1, due to greater activation in premotor cortex and SMA, results in larger MEPs.

A study by Cameron, Stewart, Pearce, and Grube (2012) used metrically strong music, metrically weak music, or tone sequences. While listening to these sounds, TMS pulses were timed to fire either on the beat or before the beat. MEPs were measured in two leg muscles, the lateral gastrocnemius (LG) and the tibialis anterior (TA). They found that the amplitudes of the MEPs elicited by TMS stimulation depended on the metrically of the auditory stimuli and the position of the stimulus sequence at which the TMS was fired. Motor excitability showed temporal specificity, with a larger MEP on the beat and a smaller MEP off the beat in metrically strong tone sequences. The study also found larger MEPS for metrically strong than metrically weak music when TMS was fired on the beat. It is expected that there will be larger MEPS elicited on and before the beat or tone stimulus, compared to MEPs in positions further from the beat.

There is evidence that TMS can been used to look at motor excitability in an on/off fashion, where there is a larger amplitude MEP on the beat than off the beat. There has been no past research in the time course of these changes in MEP amplitudes, or how motor excitability is changing over time. As mentioned earlier in the paper by Fujioka et al. (2012), activity over

time was measured using fMRI, where there is evident synchronization to isochronous tones in the auditory system. Like the Fujioka paper, we will also be using isochronous tones as the auditory stimuli. The piece of information which is missing, is whether the motor system is also synchronizing in a similar way as the auditory system in response to isochronous tones. Using a similar approach to the paper by Cameron et al. (2012), we will be stimulating M1 with TMS, except at more time points, to observe the changes in motor excitability over time.

The aim of the current research is to investigate motor excitability to regular (isochronous) and irregular (jittered) tone sequences in the primary motor cortex (M1) over time. The method of investigation uses transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) while listening to auditory stimuli and measuring elicited muscle twitches, or motor evoked potentials (MEPs). The project will measure the differences in amplitudes of resultant MEPs in the first dorsal interosseous (FDI) muscle of the dominant hand. MEPs will be measured at different rates of isochronous sequences (200ms, 550ms, and 900ms), and during a jittered, control condition. There are certain characteristics of excitability of the motor cortex which we are looking for. We hypothesize that excitability will increase in anticipation of each tone for the isochronous sequences, as a neural correlate of behavioural motor anticipation. We also hypothesize that excitability in the moot cortex will synchronize to fluctuate at the tone rate.

This study will improve our understanding of auditory motor integration, and show insight to the time course of motor system excitability while listening to isochronous tones. The present study will also improve our understanding of how and why people synchronize their movements to repetitive regular sounds, and hold applications in understanding motor and speech disorders where there is impairment in discriminating temporal intervals such as Parkinson’s disease, dyslexia, and stutters.

Method

Participants

Final analysis included 20 self-reported right-handed, healthy participants aged 18-38 (M = 21.42, SD = 4.35; 13 females and 6 males). All participants were recruited through posters displayed across campus at Western University (Appendix A). Everyone passed the initial pre-screening form (Appendix B) for possible project exclusion criteria, i.e. hearing problems, epilepsy, pregnancy, or a history of migraines. All participants provided informed consent for a protocol approved by the Western University Institutional Review Board (Appendix C). Participants also filled out a TMS/fMRI form (Appendix D), and filled out a handedness questionnaire (Oldfield, 1971). For the handedness questionnaire, a score 70 or more out of 100 confirmed right-handedness. Testing lasted approximately three hours and participants were compensated 25 dollars per hour for their time, upon successful completion.

A subsequent demographics questionnaire collected information about years and type of music and dance experience to determine amount of formal music training. A study by Stupacher et al. (2013) found differences in motor excitability between musicians and non-musicians, which this study also aims to observe.

Auditory Stimuli

Stimuli consisted of 120 trials of four different sequences (200ms, 550ms, 900ms, jittered). The sequences with even tone intervals are considered isochronous and represent an anticipation condition. The jittered condition was composed of interstimulus intervals the length of 200ms, 550ms, or 900ms, in a random order and a jittered sequence was always presented after a 550ms condition. The jittered sequences represent a no anticipation condition. Sequence length ranged from 30 seconds to 40 seconds, depending on condition. The tone used in all the

sequences was a 6ms clip of a generic snare drum sound sample (GarageBand). Stimuli were presented in a random order to prevent any potential order effects, and through in-ear noise-reduction earphones (ear tips, Etymotic Research) to reduce external noise and experimenter bias.

Electromyography (EMG)

EMG equipment (AC Amplifier EMG system, amplification; Micro1401-3 data acquisition unit, reading transmission; Signal software, display and recording) was used to record motor evoked potentials (MEPs) the first dorsal interosseous (FDI) muscle on the right hand. The G1 and G2 (positive and negative) electrodes were placed at either end of the FDI muscle, while the ground (reference) electrode was placed on the styloid process of the ulna.

Transcranial Magnetic Stimulation (TMS)

TMS was delivered using a Magstim Single Pulse Super Rapid TMS machine (Magstim Company Ltd, Carmarthenshire, UK) and a figure-eight TMS coil. The head was first measured to find the point of stimulation in the primary motor cortex (M1). The midpoint of nasion-inion distance, and of the inter-auricular distance was marked. Application of stimulations was started at the point 2 cm rostral and 5 cm left from the midpoint mark, at M1. The motor hotspot for the right FDI muscle was found by adjusting the intensity, location, and angle of the TMS coil, and examining the resulting MEP measurements. Testing was conducted at 110% of motor threshold, where motor threshold is defined as the intensity at which 50% of MEPs are greater than 50mV.

TMS pulses were delivered randomly throughout the tone windows (time between tonal stimuli), so that at the end of the experimental session, there were two data points collected from each of 100 evenly spaced positions throughout the tone to tone window in each condition. 200 data points were collected from each condition. TMS pulses were delivered 6 (n=8 sequences at

each tempo), 7 (n=8), or 8 (n=12) times throughout each isochronous sequence, and 5 (n=16) or 6 (n=20) times in each jittered sequence.

Procedure

Subjects were informed that they would be sitting in a chair listening to auditory stimuli while having their motor cortex stimulated with a coil. They were instructed to passively listen to the tone sequences, while resting their hand on the arm rest or on their lap. Participants were also told that their participation was completely voluntary and that they could choose to end the experiment at any point if they feel uncomfortable. Once the participant had inserted their headphones, the sequences of auditory stimuli and TMS stimulation triggers started by running the appropriate MATLAB script. The order of auditory conditions was randomly selected by MATLAB, with each condition being presented no more than two times in a row. The duration of one 30s condition sequence was referred to as one trial. Every six trials there was a programmed break which the participant could choose to take or to continue. There was a total of 180 trials, or 20 blocks.

Isochronous tapping task. Behavioural tasks were administered using E-Prime® 2.0 (Psychology Software Tools Inc, Sharpsburg, PA) software**.** In the tone tapping task, participants were instructed to tap along to tones, that they heard over headphones, with the index finger of their right hand. Participants tapped using the ‘m’ key of the keyboard. Tone sequences were the same ones used in the main experiment (200ms, 550ms, 900ms, jittered). There were two trials for each isochronous condition and four trials of the jittered condition, totaling 10 trials, and trials were randomized. Tapping was assessed in terms of accuracy (stimulus-tap asynchrony as a proportion of mean inter-tap interval) and variability (coefficient of variation of inter-tap intervals). To find the coefficient of variation the standard deviation of the inter-tap interval was

divided by the mean. This task was used to measure individual differences in motor tone anticipation.

Data Analysis

The peak to peak amplitude value was measured for collected MEPs in the 10-80 ms window after the onset after the visible TMS artifact. MEP amplitude data was excluded if the amplitude was less than 50 mV/ms or if it was more than 3 standard deviations away from the mean amplitude of the individual participant. This was to remove outlier data, or very small amplitudes.

For each condition for each participant, the two sets of 100 data points were separated into two inter-tone windows, and MEP amplitude values were averaged across in a sliding window technique, to smooth the data.

The first analysis was that of linear fit where a linear equation was fitted to the data of one of the inter tone windows and the slope was calculated for each condition. This represents the increase in excitability of the motor system over time between two stimuli. A one sample t-test was performed to determine the significance of the difference of the slope from 0.

The next step was to detrend the data so that the slope was back to 0. This allowed us to fit cossinusoidal waves to the inter-tone window to see whether excitability fluctuates in relation to the tone rate. The three cosine frequencies used were 200ms, 550ms, and 900ms. These frequencies matched the stimulus frequencies and allowed each tone rate to act as a control for the other conditions. The cosine fits allowed for the observation of whether excitability fluctuates at the stimulus rate. The values obtained in this analysis were the amplitude and goodness of fit of the data. The amplitude of the fitted cosine curves was defined as the depth from 0 of the curve which closest fit the data points. The goodness of fit (r^2) was defined as how well the

cosine wave fit the data by calculating the difference between the collected data points and the expected value based on the fitted wave. Both the amplitude of the fitted cosine and the goodness of fit were analyzed using a sequence rate (200ms, 550ms, 900ms, jittered) x fitted rate (200ms, 550ms, 900ms) repeated measures analysis of variance (ANOVA). Greenhouse-Geisser corrections were applied to reduce type 1 error and significant ANOVAs were followed up with Tukey Post-hoc analysis. Results were also analyzed between participants who received less or more formal training than the median. A p value of 0.05 was used for all tests of significance. IBM SPSS software was used for all statistical analysis.

Results

Beat Tapping Data

Two measures were collected from the beat tapping task; the coefficient of variation of the inter-tap interval (CV ITI), and the stimulus-tap asynchrony as a proportion of mean inter-tap interval (proportionate asynchrony). A one-way repeated measures ANOVA on the CV ITI and condition (200ms, 550ms, 900ms, jittered) revealed a main effect of condition, $F(2,41) = 341.56$, $p < .001$. Following up on the coefficient of variation with *post hoc* comparisons using one-tailed paired *t*-tests, the inter-tap interval of the jittered condition (M = 0.23, SEM = 0.01) was more variable than the 200ms (M = 0.08, SEM = 0.01; $t(19) = 25.24$, $p < 0.01$), 550ms (M = 0.07, SEM = .005; $t(19) = 29.70$, $p < 0.01$), and 900ms (M = 0.23, SEM = 0.006); $t(19) = 19.01$, $p < 0.01$) isochronous conditions, as seen in figure 1. A one-way repeated measures ANOVA on the proportionate asynchrony and condition (200ms, 550ms, 90ms, jittered) also revealed a main effect of condition, $F(2,35) = 40.52$, $p < .001$. Following up on the proportionate asynchrony with *post hoc* comparisons using one-tailed paired *t*-tests, the inter-tap interval of the jittered

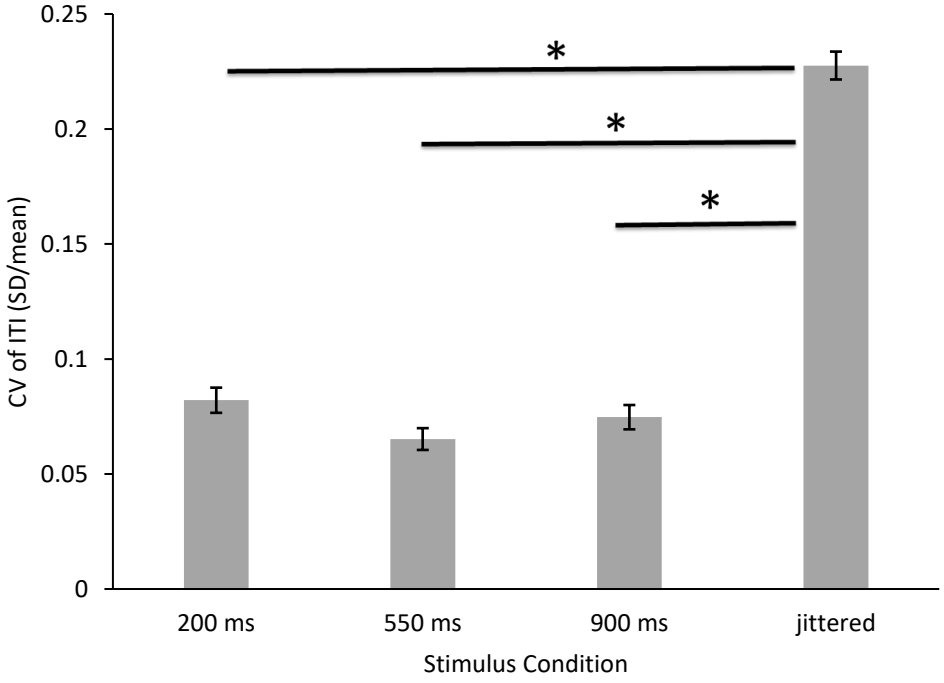

Figure 1. Coefficient of variation of inter-tap intervals (SD/mean), while listening to isochronous rhythms (200ms, 550ms, 900ms) and a jittered condition. One-tailed paired samples *t*-test, *$p < 0.05$.

condition (M = 0.25, SEM = 0.002) was less accurate than the 550ms (M = 0.14, SEM = .02; $t(19) = 5.64$, $p < 0.01$) and 900ms (M = 0.11, SEM = 0.01); $t(19) = 9.04$, $p < 0.01$) isochronous conditions, but not more accurate than the 200ms condition (M = 0.25, SEM = 0.01; $t(19) = 0.27$, $p = 0.40$), as seen in figure 2.

MEP Amplitudes of TMS Data

Slope. The slope of the linear fit represents an increase or a decrease in excitability over the inter-tone interval. A one-way repeated measured ANOVA with slope and condition (200ms, 550ms, 90ms, jittered) did not reveal a main effect of condition; the slopes of each of the linear fits were not significantly different between conditions, $F(2,47) = 1.22$, $p = .309$. A two-tailed paired two sample *t*-test comparing each condition to 0 found a significantly negative slope for 550ms (M = -0.06, SEM = 0.02; $t(19) = 2.48$, $p = 0.02$), but not for 200ms (M = 0.007, SEM = 0.04; $t(19) = -0.19$, $p = 0.85$), 900ms (M = 0.01, SEM = 0.03; $t(19) = -0.40$, $p = 0.69$), or the jittered conditions (M = -0.04, SEM = 0.03; $t(19) = 1.23$, $p = 0.24$), as seen in figure 3.

Best fit. The best fit or R^2 of the cosine waves to the stimulus conditions indicates their amount of matching, and how well each of the cosine waves represents the condition. A high degree of matching between a particular wave rate and condition rate indicates synchronization. A two-by-two repeated measures ANOVA on R^2 data, with fitted rate (200ms, 550, 900ms) and stimulus rate (200ms, 550ms, 900ms, jittered) did not reveal main effects of stimulus rate, ($F(2,62) = 1.49$, $p = .234$), but did reveal main effects of fitted rate ($F(1,62) = 4.50$, $p = .044$), as well as an interaction effect between stimulus rate and fitted rate ($F(3,62) = 3.53$, $p = .017$). Due to the interaction effect, main effects should be interpreted with caution. The significant interaction effect indicates that at least one fitted rate showed better fit for at least one stimulus rate, as seen in figure 4. Following up on the best fit data with *post hoc* comparisons using one-

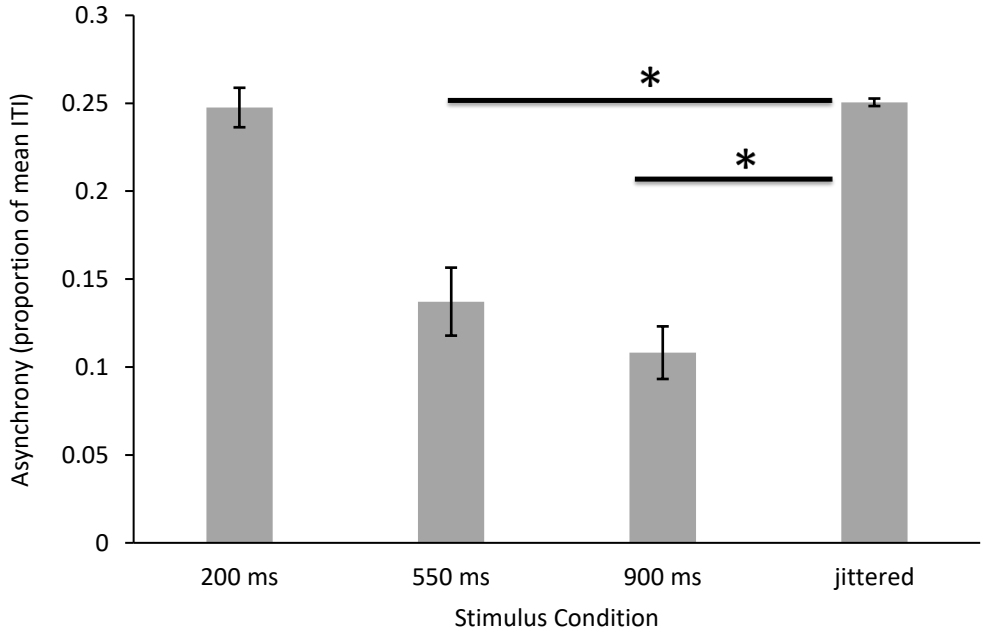

Figure 2. Proportion of asynchrony of the inter-tap interval while listening to isochronous rhythms (200ms, 550ms, 900ms) and a jittered condition. One-tailed paired samples *t*-test, *$p <$ 0.05.

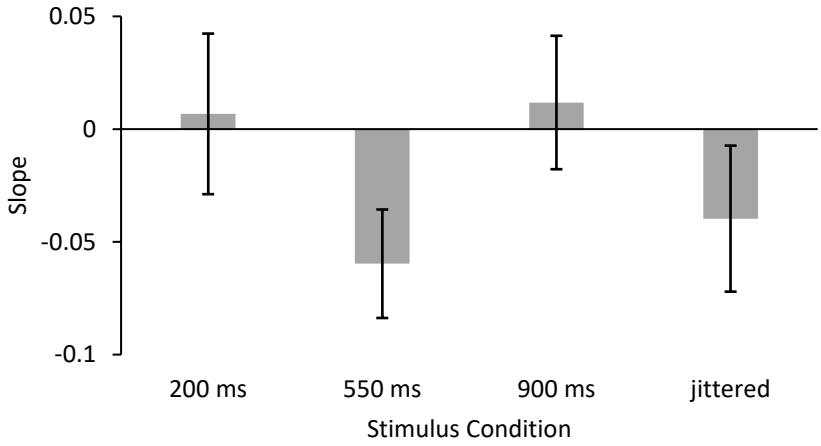

Figure 3. Slopes from linear fits to smoothed MEPs as a function of time within inter-tone interval. No slopes are significantly greater than zero. $p < 0.05$.

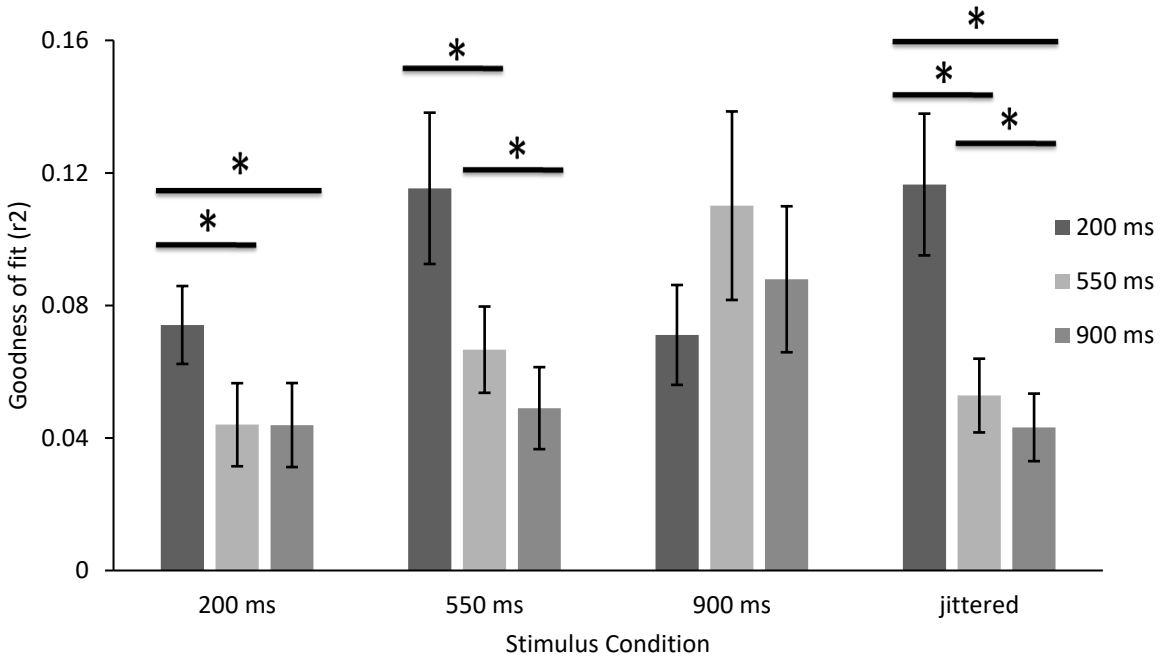

Figure 4. Goodness of fit (R^2) for cosine fits to smoothed MEPs as a function of time within inter-tone interval. The 3 (Fitted rate) x 4 (Sequence rate) interaction, $F(3,62) = 3.52$, $p = .017$, indicated that the 200ms fitted rate matched the corresponding sequence rate best, however, the predicted correspondence between stimulus and fitted rates was not seen for the rest of the MEP data.

tailed paired t-tests, in the 200ms condition, the 200ms fitted rate (M = 0.07, SEM = 0.01) fits better than the 550ms (M = 0.04, SEM = 0.01; $t(19) = 3.13$, $p < .001$) and the 900 ms conditions (M = 0.04, SEM = 0.01; $t(19) = 3.08$, $p < .001$). For the 550ms condition, the 200ms fitted rate (M = 0.11, SEM = 0.02) fits better than the 550ms (M = 0.07, SEM = 0.01; $t(19) = 1.76$, $p = .047$), and the 550ms fits better than the 900ms condition (M = 0.05, SEM = 0.01; $t(19) = 4.28$, $p < .001$). In the 900ms condition, the 900ms fitted rate (M = 0.09, SEM = 0.02) does not fit better than the 200ms (M = 0.07, SEM = 0.01; $t(19) = 0.57$, $p = .289$) or the 550ms conditions (M = 0.11, SEM = 0.03; $t(19) = -1.55$, $p = .068$). In the jittered condition, the 200ms fitted rate (M = 0.12, SEM = 0.02) fits better than the 550ms (M = 0.05, SEM = 0.01; $t(19) = 2.56$, $p = .010$) and the 900ms conditions (M = 0.04, SEM = 0.01; $t(19) = 2.91$, $p = .004$), and the 550ms fitted rate fits better than the 900ms fitted rate ($t(19) = 2.15$, $p = .022$). The results demonstrate an interaction effect between stimulus rate and fitted rate, with selective fluctuation of 200ms in the 200ms condition, and no other corresponding selective fluctuation at the other stimulus rates. The 550ms and jittered stimulus rates selectively fluctuate at a 200ms fitted rate, while the 900ms stimulus rate selectively fluctuated at a 550ms fitted rate. Best fit values were not found to selectively synchronize to corresponding fitted rates.

Amplitude. Amplitude indicates how deep the cosine waves are when they best fit the data. Amplitude is another indication of synchronization. A two-by-two repeated measures ANOVA on amplitude, with fitted rate (200ms, 550, 900ms) and stimulus rate (200ms, 550ms, 900ms, jittered) revealed main effects of stimulus rate, ($F(1,24) = 14.88$, $p < .001$), main effects of fitted rate ($F(1,26) = 25.92$, $p < .001$), as well as an interaction effect between stimulus rate and fitted rate ($F(1,623) = 19.09$, $p < .001$). Due to the interaction effect, main effects should be interpreted with caution. The significant interaction effect revealed that at least one fitted rate

showed a larger amplitude for at least one stimulus rate, as seen in figure 5. Following up on the amplitudes with *post hoc* comparisons using one-tailed paired t-tests, in the 200ms condition, the 200ms fitted rate (M = 0.07, SEM = 0.01) has a significantly smaller amplitude than 550ms (M = 0.04, SEM = 0.01; $t(19) = -4.26$, $p < .001$) and the 900ms conditions (M = 0.04, SEM = 0.01; $t(19) = -4.91$, $p < .001$). For the 550ms condition, the 550ms fitted rate (M = 0.07, SEM = 0.01) has a significantly smaller amplitude than the 900ms (M = 0.05, SEM = 0.01; $t(19) = -1.93$, $p = .034$), but not the 200ms condition (M = 0.11, SEM = 0.02; $t(19) = -1.27$, $p = .110$). In the 900ms condition, the 900ms fitted rate (M = 0.09, SEM = 0.02) does not have a higher amplitude than the 200ms (M = 0.07, SEM = 0.01; $t(19) = 0.10$, $p = .461$) or the 550ms conditions (M = 0.11, SEM = 0.03; t(19) = -0.48, p = .319). In the jittered condition, the 200ms fitted rate (M = 0.12, SEM = 0.02) has a larger amplitude than the 550ms (M = 0.05, SEM = 0.01; $t(19) = 2.30$, $p = .016$), but not the 900ms conditions (M = 0.04, SEM = 0.01; $t(19) = 0.75$, $p = .232$), and the 550ms amplitude is smaller than the amplitude of the 900ms fitted rate ($t(19) = -2.83$, $p = .005$). The results demonstrate an interaction effect between stimulus rate and fitted rate, with no corresponding selective amplitudes between stimulus rate and fitted rate. There is selective amplitude of 900ms in the 200ms condition, however none of the other stimulus rate have a selectively significant amplitude of fitted rate. Amplitudes of fitted rates were not found to selectively synchronize to corresponding stimulus rates.

Musician status. When years of musical training was used as a covariate variable for R^2, there was no main effect of R^2 for stimulus rate ($F(2,38) = .51$, $p = .634$), fitted rate ($F(1,17) = .01$, $p = .989$), and no interaction effect ($F(3,51) = .42$, $p = .752$). Years of musical training was not found to influence synchronization to auditory tone rates.

Discussion

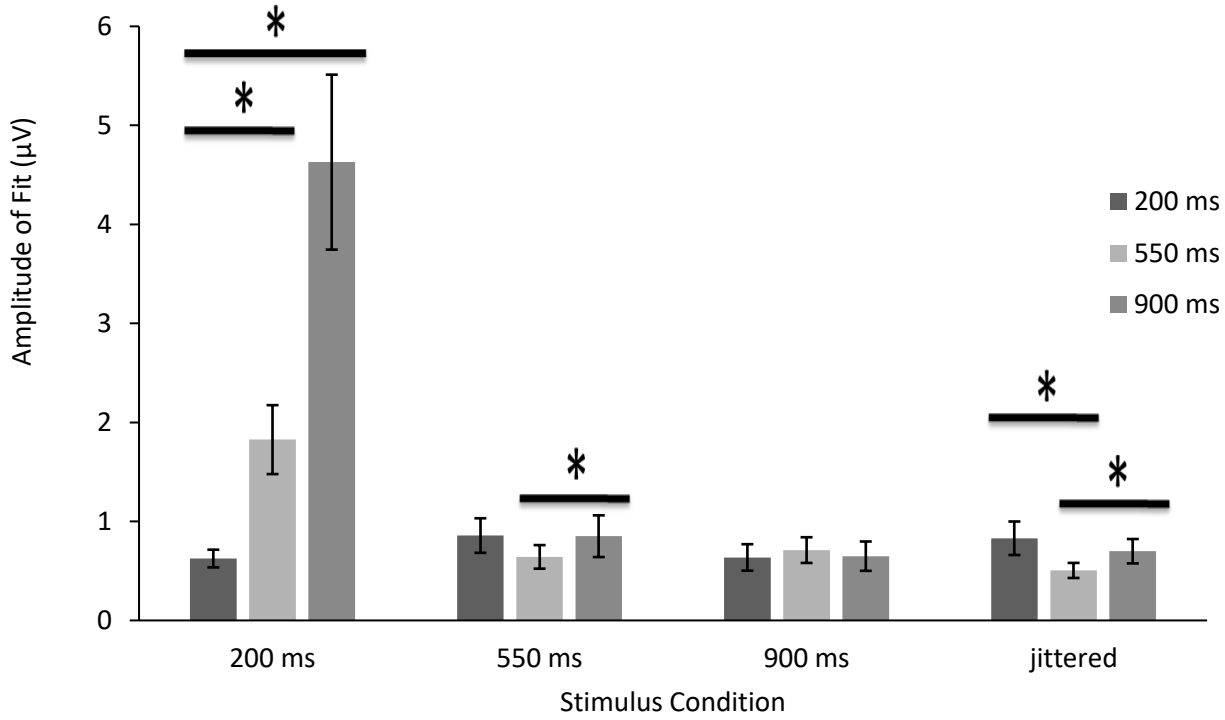

Figure 5. Mean amplitude parameter values (±SEM) from cosine fits to smoothed MEPs as a function of time within inter-tone interval. The 3 (Fitted rate) x 4 (Sequence rate) interaction, $F(1,23) = 19.09$, $p < .001$, indicated that MEPs fluctuated to different extents depending on the frequency of the stimulus rate (or whether the rhythm was jittered) and the rate of the fitted cosine, however the differences between fits did not match the predicted correspondence between stimulus and fitted rates.

The purpose of this study was to examine changes in excitability of the motor system in anticipation of isochronous tones, and to determine if excitability increased over the inter-tone interval, and if excitability synchronized to fluctuate at stimulus rates. This was done by measuring MEPs elicited by TMS at 100 time points across the inter-tone interval while listening to isochronous sequences of varying rates. The results show patterns of changes in motor system excitability over the inter-tone interval and when listening to the different tone sequences (200ms, 550ms, 900ms, and jittered). However, the patterns of changes are not in the predicted directions, and we did not find evidence of an increase of motor system excitability in anticipation of the tone, or evidence of selective fluctuation between corresponding stimulus and fitted rates.

We did not find evidence of an increase in motor system excitability in anticipation of the tone onset as predicted, although there was a marginally significant decrease in excitability in anticipation of tone onset in the 550ms stimulus rate condition. The anticipatory pattern is predicted based on MEG studies which show that activity in the auditory system increases as in approaches tone onset when listening to isochronous tones (Fujioka et al., 2012). One of the possible reasons we did not see this pattern could be because the passive listening task the participants were engaged in did not provide any attention cues, therefore participants could have not been paying attention to the sounds. One way of increasing attention during the experiment is to provide random tones of a different pitch, which the participant must listen for and indicate when they occur. These different tones motivate participants to listen attentively even during long testing sessions. Evidence that some participants were not paying attention was when they would fall asleep during the testing session. We did control for any medication with drowsiness-related effects, did not test very early or very late, provided frequent participant-controlled

breaks, and controlled for alcohol intake in the past 24 hours. Even with all of these preventative measures, the monotonous and prolonged nature of the experiment can also cause drowsiness. Another possible reason why we did not see an increase in excitability could be due to the passive nature of the experiment. The motor cortex has been found to be more excitable in anticipation of strong beats rather than weak beats in rhythmic sequences, as well as for sound patterns which require more effort for perception (Grahn & Brett, 2007). Isochronous sequences do not require much effort to perceive temporal rates, compared to rhythms of varying inter-stimulus intervals. While many studies have measured motor during passive listening of sounds, using more novel stimuli such as rhythms rather than isochronous sounds, may induce more motor system excitability.

We did not find evidence of synchronization of motor system excitability to the rates of regular tone sequences. Based on the findings in the Fujioka et al. (2012) study, we were expecting selective fluctuation at the tone rate. Evidence of this in our study would have been a significant interaction between stimulus rate and fitted rate, as well as selective fluctuation between corresponding stimulus and fitted rates, which we did not find. As before, this lack of significance may be due to lack of attention to the listening task, as well as insufficient difficulty in perception to induce large enough excitability to be measurable. Another possible explanation for this lack of evidence is that activity of the motor system does not correlate with temporal properties of regular tones. Perhaps there is another neural mechanism which allows for the ease with which we are able to perceive musical tempos and anticipate sounds to coordinate our movements with what we hear.

TMS is beneficial because it provides a causational relationship between stimulus and response compared to imaging methods which only provide correlational results between

stimulus and response. However, TMS is a very sensitive technique, and may have produced a variability of MEPS which were not due to auditory perception. TMS can be influenced by changes in the environment which affect the electric field generated by the coil, such as the shoes of the experimenter and their ability to ground the electric field. TMS also has a very specific depolarization field, 1cm by 1cm, and the exact location of TMS stimulation depends on coil location, angle, and rotation relative to participants' brain/skull structure (Laakso, Hirata, & Ugawa, 2013). There are some ways to improve the reliability of TMS testing. One of these ways is to image the brain to locate the specific location of the area of interest. Unfortunately, this method is very expensive and time consuming. Another way to improve TMS reliability and reduce participant movement is to use a chin rest and a TMS coil stand. Unfortunately, a chin rest is not very comfortable for very long protocol such as the one used in this study, and by fixing the coil in one location, it is more difficult to make adjustments. Fortunately, this experiment allowed us to see when the TMS was applied in the correct location by a motor evoked potential in the FDI muscle, and holding the coil in place manually allowed for constant adjustment. Another drawback of using TMS to measure motor excitability, is that we are not directly testing our areas of interest. According to fMRI data (Grahn & Brett, 2007), the areas which are most active while listening to sounds are the SMA, basal ganglia, cerebellum, and the premotor cortex. The amplitudes of the MEPS elicited by TMS are measuring the excitability of the primary motor cortex (M1) at the time of stimulation. Without movement influencing excitability of M1, the changes in excitability are due to sub-threshold neuronal excitabilities, based on activity in premotor areas connected to the primary motor cortex such as the SMA and premotor cortex. An indirect method of measurement such as the one displayed in the present experiment leaves the results open to influence by many other factors. A more direct method of

measurement or motor system excitability would leave the results less susceptible to influence by confounding factors.

The behavioural tapping data allowed us to show a difference in tapping variability and accuracy for regular tone interval sequences which use anticipation, and irregular tone interval sequences where anticipation is not present. In the tapping data, the jittered condition showed more variability and lower accuracy than the isochronous conditions, indicating an effect of anticipation. The tapping results provide evidence for the use of anticipation in the isochronous tones, but not for the jittered sequences, providing support for the sequences used.

Limitations and Conclusion

As mentioned above, some of the limits of our study included a deficit in attention to the experimental stimuli. While this seemed to be the most significant deficit there was also lack of effort required to perceive the temporal rates of the stimulus sequences. Future studies can modify the current methodology to include attention cues dispersed in the testing protocol, where participants must pay attention and indicate the presence of a tone of a different pitch. This is one way to keep participants more focused on the passive listening task rather than fall asleep. Another change to make in future studies would be to use different stimulus sequences, such as rhythm sequences or popular songs. The present isochronous sequences do isolate timing, and separate the perception and anticipation of rates from all other properties of music. One of the drawbacks of using these simple regular tones is that they are not very representative of what people normally listen to. The music people listen to involves rhythm, beat (underlying pulse of music), and varying pitch. These characteristics of music which people commonly listen to have more groove (emotionally communicative rhythmic quality of music). Sequences with more groove evoke more motor system activation (cite). Since the stimulus sequences used in this

study did not have much groove, excitability of the motor system may not have been large enough to be able to measure fluctuations. Therefore, future studies should investigate motor system excitability while listening to rhythms sequences or popular songs, which are more representative of what people normally listen to.

As mentioned previously, TMS testing has many flaws and small alterations can result in large variability in results. Future studies can consider a different way of measuring motor system excitability. One alternative to TMS is using a "Go/no-go" task, which is used in other studies to measure motor excitability (Draper, Jude, Jackson, & Jackson, 2015). Reaction times in "Go" trials can be used as a measure of how excitable the motor cortex was at the time of stimulus presentation. If there are sounds playing while performing this task, fluctuations in excitability of the motor system due to the properties of the auditory stimuli can influence reaction time of motor responses, which can be measured as the delay time between stimulus onset and movement.

During listening to regular sounds, we did not observe that excitability in the neural motor system increases in anticipation of regular sounds or selectively fluctuates with regularity in correspondence to the perceived rate. This study informs our understanding of auditory-motor integration, of the role of the motor system in auditory timing. Future studies with improved methodology are required to learn more about the dynamics of motor system excitability to sounds.

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Appendix A

Western

Western
The Brain and
Mind Institute

Neuroscience of Music Study

The laboratory of Professor Jessica Grahn in the Brain and Mind Institute at the University of Western Ontario is seeking volunteers for a study that involves Transcranial Magnetic Stimulation (TMS). The goal of the study is to understand how different brain areas contribute to different aspects of music perception. Participants will be compensated for their time. For more information, please contact the Grahn Lab TMS e-mail at neuromusicTMS@gmail.com. Be sure to include your name and phone number where you can be contacted. Unfortunately we **cannot** accept anyone who: is hearing impaired, has a pacemaker or any metal implants in their body, has blackouts or has had seizures, has claustrophobia, is pregnant and has piercings that cannot be removed. Safety screening will be conducted prior to TMS.

Neuroscience of Music Study
Grahn Lab
neuromusicTMS@gmail.com

Appendix B

Western
The Brain and
Mind Institute

Participant Screening Form

Name: _____

Phone: _____

Age: _____

Transcranial Magnetic Stimulation Adult Safety Screen (TASS)

1. Have you ever had an adverse reaction to transcranial magnetic stimulation (TMS)?
(YES/NO)
If YES, please elaborate: _____

_____

2. Have you ever had a seizure?
(YES/NO)
If YES, please elaborate: _____

_____

3. Have you ever had a stroke?
(YES/NO)
If YES, please elaborate: _____

_____

4. Have you ever had a head injury (include neurosurgery)?
(YES/NO)
If YES, please elaborate: _____

_____

5. Do you have any metal in your head (outside of the mouth), such as shrapnel, surgical clips, or fragments from welding or metal work?
(YES/NO)
If YES, please elaborate: _____

_____

6. Do you have any implanted devices such as cardiac pacemakers, medical pumps or intercardiac lines?
(YES/NO)
If YES, please elaborate: _____

_____

7. Do you suffer from frequent or severe headaches?
(YES/NO)

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If YES, please elaborate: _____

_____

8. Have you ever had any other brain-related condition?
(YES/NO)
If YES, please elaborate: _____

_____

9. Have you ever had any illness that caused brain injury?
(YES/NO)
If YES, please elaborate: _____

_____

10. Are you taking any medication (YES/NO), including:

a) Prescription medication (including but not limited to antidepressants, antipsychotics, antibiotics)? (YES/NO)
b) Over-the-counter drugs or herbal remedies? (YES/NO)
c) Street/Recreational drugs (i.e., cocaine, ecstasy, etc.)? (YES/NO)

Have you consumed any alcohol in the past 24 hours? (YES/NO)

Are you experiencing any alcohol or drug withdrawal symptoms? (YES/NO)

If you answered YES to any questions about drug and alcohol use, please elaborate:

_____

_____

11. If you are a woman of childbearing age, are you sexually active, and if so, are you *NOT* using a reliable method of birth control?
(YES/NO)
If YES, please elaborate: _____

_____

12. Does anyone in your family have epilepsy?
(YES/NO)
If YES, please elaborate: _____

_____

13. Do you need further explanation of TMS and its associated risks?
(YES/NO)
If YES, please elaborate: _____

_____

Appendix C

Western The Brain and Mind Institute | Department of Psychology | Western SocialScience

LETTER OF INFORMATION FOR PARTICIPANTS

The Effects of Transcranial Magnetic Stimulation on Auditory Rhythm and Beat Perception

Principal Investigator:

Jessica Grahn, Ph.D.
Brain and Mind Institute
Room 229, Natural Sciences Building
University of Western Ontario
London, Ontario, N6A 5B7
Email: jgrahn@uwo.ca
Phone: 519-661-2111 x84804

Introduction:

You are invited to voluntarily participate in a research study investigating the role of brain areas known to contribute to the perception of rhythm and beat in music, using transcranial magnetic stimulation, or TMS. The purpose of this study is to determine how specific brain regions may be responsible for different aspect of musical perception and experience. This letter of information will provide you with further information about behavioural tasks and techniques that will be used during the experiment allowing you to make an informed decision regarding participation in this research.

Research Procedures:

If you agree to participate in this study, your participation will involve behavioural tasks that include:

Rhythm/ Beat Perception Tasks:

During the study, you will hear stimuli that fall into three categories: metronomic/ isochronous beeps, metric or non-metric rhythms, and music clips (e.g. clips from recorded musicians). Tasks fall into four categories: discrimination, passive listening, beat-tapping, and reproduction tasks. You will hear stimuli and may be asked to simply listen passively, or to make perceptual judgments about the sounds, and/or make responses to the sounds. If the task is complex, you will be given a chance to practice before the session begins. You may be completing these tasks before and after TMS is applied to the scalp (offline TMS), or at the same time as TMS is applied (online TMS). Overall, these experiments will inform us about the role of different brain areas in music processing.

Transcranial Magnetic Stimulation (TMS):

TMS allows scientists to stimulate the brain non-invasively by a rapid switching of a current in a coil placed over the head. When triggered, the capacitors send an electrical current through the coil resulting in the generation of a magnetic field. Placed over the head, the magnetic field

passes through the scalp and induces a physiological current, which in turn temporarily affects neural activity in the brain. The procedure is painless because the magnetic field passes through the scalp and skull freely. Activation of the magnetic coil produces a 'clicking' noise. You will wear headphones to protect your hearing. You may undergo two forms of TMS: "single-pulse TMS" and "high-frequency repetitive TMS". "Single-pulse TMS" involves placing the magnetic coil over your scalp and inducing muscle responses in your arm. This will be repeated several times until a minimum intensity to induce movements is determined. This initial procedure (~5 minutes) will enable us to determine appropriate stimulation parameters for subsequent TMS. We will then reposition the TMS coil over one of several different locations on your head and conduct behavioural testing. "High-frequency repetitive TMS" consists of up to six pulses delivered at up to 50 Hz frequency.

Electromyography (EMG):
EMG is a non-invasive measure of electrical activity produced by skeletal muscles. EMG will allow us to measure motor evoked potentials (MEP's), or muscle movement caused by direct stimulation of the motor cortex. Small electrodes will be placed on specific hand, arm, foot, or leg muscles. These electrodes require a small amount of sticky gel-like substance to conduct the electrical current and adhere to skin.

Risks:
There are no reported cases of single-pulse TMS triggering seizures. In susceptible individuals, high-frequency repetitive TMS may cause persistent tension-type headaches. You should not have TMS if you experience migraines and/ or are susceptible to headaches. If you do experience a headache as the result of TMS, these headaches usually respond well to mild analgesics (e.g. Tylenol). There have been a few instances of seizures induced by high-frequency TMS; however, the stimulation parameters (i.e. the combination of stimulation intensity, frequency, and duration) we will be using fall within the safety guidelines recommended by the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation. There are no reported cases of triggering seizures in healthy individuals using the stimulation parameters used in this study. Magnetic stimulation of the human cortex is considered painless, but may produce a mild discomfort when administered to the scalp. If you experience any discomfort, please inform the experimenter; you may stop the procedure at any time.

Benefits:
There is no direct benefit to you from participating in this study. The results from this study may help us to better understand the brain regions underlying human beat perception.

Voluntary Participation:
Participation in this study is voluntary. You may refuse to participate, refuse to answer questions, or withdraw from the study at any time.

Discontinuation of the Study by the Investigator:
At any time during the study, the investigators have the right to stop the study for any reason.

Participant Exclusion Criteria:
This study is intended for healthy individuals. You should not participate in this study if you fall into one of the following categories:

- Claustrophobic subjects

- Subjects with pacemakers or other electronic implants
- Patients with metallic implants
- Subjects who are welders or soldiers
- Subjects injured by a metallic object that was not removed
- Female subjects who are pregnant, trying to conceive, or who are sexually active and are not practicing an effective method of contraception
- Subjects with cerebral aneurysm clips
- Subjects with a history of neurological or psychiatric disorder
- Subjects who have experienced epileptic seizures or who have a family history of epilepsy
- Subjects who require prescribed psychotropic medication or currently take other medication that makes them drowsy
- Subjects who get migraines and/ or are susceptible to headaches
- Subjects with severe heart or lung disease (including susceptibility to arrhythmias)

Estimate of Participant's Time and Compensation:
Each experiment will last one to two hours. Each experiment within the research project will involve 10-25 participants, and the entire research project will involve approximately 200 participants.

Upon completion of all parts of the study, you will receive $25/ hour for your time and inconvenience. If the study has to be stopped for any reason, compensation will be adjusted according to the fraction of the study that was completed.

Confidentiality:
Any information obtained from this study will be kept confidential. Any data resulting from your participation will be identified by a number, without any reference to your name or personal information. Data will be stored on a secure computer in a locked room. After completion of the experiment, data will be archived on storage disks and stored in a locked room for a minimum of five years and a maximum of 15 years, after which they will be destroyed. Representatives of the University of Western Ontario Non-Medical Research Ethics Board may require access to your study-related records or may follow up with you to monitor the conduct of the study.

Contact Information:
A more complete and detailed description of the study is available from the principal investigator, Professor Jessica Grahn, Ph.D. and you are welcome to examine it.

For questions about your rights as a research participant or the conduct of the study you may contact:

Office of Research Ethics
University of Western Ontario
519-661-3036
E-mail: ethics@uwo.ca

 Participant's Initials: _____

CONSENT FOR RESEARCH STUDY

The Effects of Transcranial Magnetic Stimulation on Auditory Rhythm and Beat Perception

I have read the Letter of Information, have had the nature of the study explained to me, and I agree to participate. All questions have been answered to my satisfaction.

Name of Participant (Please print): _____

Signature of Participant: _____

Dated at Western University, London, Ontario, _____.

Name of Investigator: _____

Signature of Investigator: _____

Dated at Western University, London, Ontario, _____.

Participant's Initials: _____

Appendix D

PARTICIPANT SCREENING FORM FOR TMS

The Effects of Transcranial Magnetic Stimulation on Auditory Rhythm and Beat Perception

ID Code: _____

Date: _____

Date of Birth: _____

Handedness: right/ left/ mixed

	YES	NO
Have you previously had an MRI or fMRI scan?		

	YES	NO
Have you ever had surgery? Type:_____		
Have you ever been injured by a metallic foreign body which was not removed (e.g., bullet, BB, shrapnel)?		
Have you ever worked with metal (grinding, fabricating, welding, etc.) or ever had an injury to the eye involving a metallic object (e.g., metallic slivers, shavings)?		
Do you have a cardiac pacemaker or defibrillator?		
Do you have severe heart disease (including susceptibility to arrhythmias)?		
Do you have an aneurysm clip?		
Do you have cochlear (ear) implants?		
Do you have Meniere's disease?		
Do you have dental work other than fillings? Type:_____		
Do you have any tattoos or permanent eyeliner?		
Do you have any body piercings that cannot be removed?		
Do you wear a hearing aid or false teeth?		
Have you ever experienced claustrophobia or a panic attack?		
Have you ever had an epileptic seizure?		
Is there a history of epilepsy in your family?		
Have you ever had a head injury?		
Have you had any visual disorders?		
Do you get migraines and / or are susceptible to headaches?		
FOR WOMEN ONLY:		
Are you pregnant, experiencing a late menstrual period, or at risk of conceiving (i.e., sexually active and not using a reliable form of birth control)?		
Are you breast feeding?		
Do you have an intrauterine device (IUD)?		
Are you wearing an underwire bra?		

PLEASE REMOVE THE FOLLOWING	CHECK
Any jewellery	
Any body piercings	
Your wristwatch	
Any hair pins or barrettes	
Your wallet and credit cards	
Everything from your pockets	