Using Transcranial Magnetic Stimulation to Assess Fluctuations in Motor System Excitability While Hearing and Internally Generating a Beat

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Abstract

When listening to music people often move to the beat. Recent studies using transcranial magnetic stimulation (TMS) technology have shown that motor system excitability, an index of motor system activation, fluctuates while listening to music even while not moving. However, the pattern of these fluctuations has not been characterized yet. Building on the designs of previous studies, in this experiment participants listened to an isochronous beat followed by a period of silence and a delayed probe tone. Participants maintained the timing of the beat during the silent period and judged whether the probe tone was on beat or off beat in relation to the timing of the auditory beat. TMS was delivered once each trial during a fixed window consisting of the final two auditory beat-to-beat intervals and the following silent period (including the probe tone) to assess how motor excitability fluctuates differently under conditions of hearing auditory stimuli and internally generating auditory stimuli during silence. It was hypothesized that motor excitability would linearly decrease over the inter-beat interval. It was also hypothesized that fluctuations in motor system excitability would synchronize to the tempo of the beat to a greater degree and have greater magnitude when the beat was internally generated as opposed to heard. Results did not support either hypothesis.

When listening to music, we often tap along to the beat. We use our auditory perception and motor systems to identify the timing of the beat and then make tapping movements at this timing. In this study, the patterns of activation of the motor system in relation to perceiving auditory stimuli were examined. Determining precisely how motor activation fluctuates in relation to the timing of a beat can increase our knowledge of the ways that auditory perception and motor processes are linked, opening the door for further research in the field. Understanding the effects of perceiving auditory stimuli on motor activation can also inform the creation of auditory therapy methods for individuals with gait-related conditions such as Parkinson's disease.

The property of auditory stimuli that is of interest in this study is the beat. A beat is the basic unit of time of any auditory stimuli, the underlying rhythm separated by a fixed interval. In this study the auditory stimuli were isochronous tone sequences which consisted of a series of uniform tones separated by a fixed interval. Individual beats in auditory stimuli that are accented are called on-beats; these are the beats that listeners would tap along to. These beats collectively are referred to as being on beat, while the portions of the beat that aren't accented are referred to as being off beat. The interval between two consecutive on-beats is called the inter-beat interval. Patterns of motor system activation over the course of the inter-beat interval were assessed in this study.

The motor system is the part of the central nervous system that controls movement. When the motor system is activated it does not necessarily mean that movement will occur, but that the system is primed for potential movement. Motor system activation can be assessed by measuring motor excitability. Motor excitability is a quantifiable measure of readiness for motor system-controlled movement of muscles in the body. Using brain stimulation techniques and

electromyography, motor excitability can be measured at time points down to the millisecond. Measuring motor excitability and its pattern of change provides an index of changes in motor system activation over time.

The relationship between auditory perception and motor system activation has been prominently studied in recent years. Previous research has indicated that the primary motor cortex is involved in perceiving rhythmic auditory stimuli, such that patterns of motor activation while listening to auditory stimuli are moderated by the presence of a perceptible beat (Cameron, Grube et al., 2012). Motor activation has also been found to be greater on beat than off beat while one is listening to a musical rhythm. (Fujioka, Trainor et al., 2012; Cameron, Grube et al., 2012). However, the patterns of motor excitability over the course of an inter-beat interval have not been characterized as of yet.

These findings of increased motor excitability on beat could be hallmarks of multiple patterns of activation from the onset of one beat to another. The observation of greater motor activation on beat could be the culmination of an upward trend where motor excitability increases linearly leading up to the beat; alternatively this could be part an oscillatory trend where motor excitability fluctuates throughout the inter-beat interval, or a combination of both linear and oscillatory patterns.

Changes in motor excitability over time can be evaluated using Transcranial Magnetic Stimulation (TMS). TMS is used to stimulate a precise location of the brain with an electromagnetic pulse. One of the uses of TMS is precise motor area stimulation, which is of interest in this study. Stimulation of the primary motor cortex elicits a Motor Evoked Potential (MEP) in the index finger. An MEP is a neuroelectric signal produced by a muscle in the body in response to electrical stimulation, which can be recorded using electromyography (EMG).

Recorded MEPs appear as waveform data when displayed visually, and the amplitude of the wave is measured to quantify motor excitability at the time of the TMS pulse. Measuring goodness of fit of motor excitability data to a cosine function at the rate of the tempo of stimuli is a method of evaluating the degree that fluctuations in motor excitability synchronized to the tempo the stimuli. The r^2 values of goodness of fit of the data to cosine functions at the rate of the tempo must be significantly greater than corresponding r^2 values for functions at rates unrelated to the tempo for motor excitability fluctuations to be considered synchronized to the beat In the studies that are discussed below, stimulation is delivered to individuals who are hearing or observing music being played, to investigate the temporal relationship between perception of auditory stimuli and motor excitability.

Previous studies have used TMS to evaluate motor system activation while listening to music. Cameron, Grube et al. (2012) investigated how perceiving auditory rhythms affected motor excitability by using TMS to elicit an MEP as discussed above. MEP amplitudes were greater when TMS was delivered on beat as opposed to off beat, indicating greater motor excitability at the time of the beat. This effect was especially pronounced when rhythms had strong underlying beats. Similar results were found in a TMS study by Stupacher, Hove et al. (2013), who observed greater on beat motor excitability among musicians who were listening to music that they rated as having high groove; music pieces with high groove tend to also have a strong beat.

Previous literature has also indicated that the motor system can be activated while observing visual cues for auditory stimuli. Vicarious activation of the motor system was found in individuals who observed others playing music without hearing the music (Avenanti, Candidi & Urgesi, 2013). Another study examining motor activation and the access of motor representations

in response to visual stimuli found similar results, such that among expert pianists, motor excitability was greater directly after an error in muted piano fingerings was observed (Candidi, Sacheli, et al., 2012). These results show that cues for auditory stimuli perceived visually can elicit motor activation in the brain similarly to auditory stimuli. Furthermore, a study found that fluctuations in brain activity (beta band oscillations) as measured by EEG synchronized to the timing of beats that were represented only by visual stimuli (Okawa, Suefusa et al., 2017). This suggests that brain activity fluctuations can be moderated by visual stimuli symbolizing a beat in the same way that a prominent auditory beat can moderate motor activity. Together these studies suggest that non-auditory stimuli can moderate brain activity and motor activation in similar ways to auditory stimuli. This may be due to the perceiver internally generating auditory stimuli based on timing cues from visual stimuli; more research is needed about internal generation to determine this.

Previous studies in the Grahn Lab (within Western University's Brain and Mind Institute) have used TMS to evaluate the relationship between motor excitability and auditory beat perception. By delivering TMS across a comprehensive sampling of precise time points across an interval, trends and fluctuations of motor excitability can be evaluated. One study used repetitive TMS to determine how motor excitability relates temporally to beat perception (Teselink, Grahn et al., 2017). Participants were asked to rate the strength of auditory beats after to induce mental synchronization to the beat, while TMS was used to evaluate motor excitability. The results showed that motor excitability did not increase significantly over the course of an inter-beat interval, and fluctuations in motor system excitability did not show significant differences in goodness of fit to the rate of the tempo of stimuli, or rates that were twice and four times the tempo of stimuli.

Another study similarly examined motor activation while participants listened to sequences of isochronous tones of varying tempos using TMS (Czajka, Grahn et al., 2017). Participants passively listened to auditory stimuli at 4 different tempos (200 ms, 550 ms, 900 ms and jittered/inconsistent tempo), while TMS was used to evaluate motor excitability. This study found a moderate decrease in motor excitability in anticipation of the beat in the 550 ms condition. Interestingly, when fluctuations in motor system excitability over the course of the inter-beat interval were analysed, fluctuations synchronized significantly better to a 200 ms fitted rate than a 550 ms fitted rate in stimulus conditions with tempi of both 200 ms and 550 ms. This was expected in the 200 ms stimulus condition as it indicated that motor system excitability synchronized to the tempo of the stimuli, but this was an unexpected result in the 550 ms condition.

Based on these studies, there is some evidence that motor system excitability decreases linearly over the course of an inter-beat interval while listening to auditory stimuli with a tempo of 550 ms. Results also showed that motor system excitability fluctuations had a greater fit to a rate of 200 ms than 550 ms, for auditory stimuli at both of those tempi. These findings were examined further in the current study. These studies also informed design elements that were used in the current study. Use of a manipulation to maintain participant attention to the beat is important when assessing the relationship between auditory stimuli and motor excitability; the beat strength rating task described above (Teselink, Grahn et al., 2017) was built upon in this study. In addition, both of these studies used a design where TMS pulses were delivered at 1 of 100 possible time points within inter-beat intervals. This allowed for a comprehensive sampling of time points within an inter-beat interval, while using a randomized delivery order limits order and fatigue effects. In the current study these elements were combined with an experimental

design called a delayed probe tone paradigm (Manning & Schutz, 2013). In a delayed probe tone paradigm, participants initially listen to and focus on the timing of an auditory beat. They then maintain the timing of the beat internally during a silent period until a probe tone is sounded, after which participants must indicate if the probe tone was on beat or off beat. This design has previously been used to evaluate the correlation between moving and beat keeping abilities, with results indicating that moving to the beat improves timing accuracy (Manning & Schutz, 2013). This design has not been used in conjunction with TMS before.

This study built on previous research by using TMS to investigate how motor activation varies not only in relation to timing of the beat, but also due to the difference between hearing an auditory beat and internally generating a beat. The experiment made use of Manning & Schutz's (2013) delayed probe tone paradigm to create three conditions of inter-beat interval: auditory intervals, silent intervals, and the final silent interval (a silent interval ending with the probe tone). In the auditory intervals the participant is hearing an isochronous tone sequence and focusing on the timing of the beat (a tempo of 550 ms); in the silent intervals the participant is internally generating the beat using this timing; and in the final interval, the participant is continuing to internally generate the beat until the probe tone occurs, then making a judgement of whether the probe tone is on beat or not. During each trial a TMS pulse was delivered once within a window consisting of the 6 inter-beat intervals: the last 2 auditory intervals, the first 3 silent intervals, and the final silent interval ending with the probe tone. Over the course of the experiment, TMS pulses were delivered at each of the 600 possible time points within this window (100 time points per interval x 6 intervals) to evaluate patterns of motor excitability in all interval conditions.

The research questions being asked were as follows. How does motor excitability fluctuate over the course of an inter-beat interval? Does motor excitability increase linearly in anticipation of a beat? Does motor excitability fluctuate regularly at the tempo of stimuli? How do patterns of motor excitability vary when one is hearing auditory stimuli as opposed to internally generating auditory stimuli during silence, and are there any differences during the interval where the participant must also make a judgement about the timing of a probe tone?

The independent variable was the timing of the TMS pulse: when within an inter-beat interval it was delivered, and which interval condition it was delivered in (auditory, silent or final). The dependent variable was motor excitability, assessed by measuring the amplitudes of MEPs elicited by TMS.

Within each condition of interest, the pattern of motor excitability within an inter-beat interval was assessed. This was done by averaging all obtained MEPs within all intervals in a condition into a single interval using a sliding window technique and assessing the goodness of fit of this data using both linear and cosine functions of goodness of fit. This provided a measure of the general linear trend of the data within an interval, as well as the goodness of fit and amplitude of fitted cosine functions to the fluctuations de-trended motor excitability data. Data was assessed for goodness of fit to cosine functions fitted at the rate of the tempo of stimuli as well as two unrelated rates. This allowed us to assess the extent to which fluctuations in motor excitability were synchronized to the stimuli, as opposed to occurring at other rates.

Hypotheses were made regarding the linear and oscillatory trends of motor excitability during an inter-beat interval. It was hypothesized that motor excitability would linearly decrease significantly over inter-beat interval in the auditory condition, based on the findings in the 550 ms condition of Czajka, Grahn et al. (2017). Regarding the oscillatory trend of motor

excitability, it was hypothesized that fluctuations in motor excitability would synchronize to the tempo of the stimuli more in the silent and final interval conditions than the auditory condition. This was based on the lack of synchronization of motor excitability fluctuations to the tempo of isochronous tone sequences found previously (Czajka, Grahn et al., 2017; Teselink, Grahn et al., 2017) as well as the findings that brain activity synchronized to the tempo of beat stimuli when perceivers only had visual cues, requiring use of internal generation (Okawa, Suefusa et al., 2017). It was also hypothesized that fluctuations in motor system excitability fluctuations would synchronize significantly better to the rate of the tempo of stimuli than to all unrelated rates across all conditions, due to the requirement of participants to assess the timing of the beat during auditory intervals and then to continue to internally generate the beat at that timing during silent and final intervals. This requires synchronization to the tempo of the beat throughout the whole trial, which is expected to be reflected in the synchronization of fluctuations in motor system excitability to the tempo of the stimuli (when averaged across all interval conditions). Also regarding the oscillatory trend of motor excitability, it was hypothesized that greater amplitudes of fluctuations in motor excitability data would be observed in silent and final intervals compared to auditory intervals. This was due to the required active use of internal generation in this condition which was expected to result in greater fluctuations than those in the auditory condition when participants did not need to use internal generation.

Method

Participants

17 participants were tested (10 male, 7 female) with an age range of 18-27 years (M = 22.52, SD = 3.16). Participants were recruited by word and of mouth and through the SONA database of

first year psychology students. Participants were students at Western University or residents of London, Ontario. Participants varied in cultural background and musical experience. All participants gave informed consent (see Appendix A) and were compensated for their time. Individuals were excluded from participating if they had a history of neuropsychiatric disorders that could be aggravated by persistent stimulation to the head, if they were subject to frequent migraines, or if they had any metal objects other than dental work embedded on their person (See Appendices B and C). This was done to prevent potential participants from being feeling discomfort during the experiment due to magnetic stimulation. Participants were also excluded if their left hand was dominant as assessed by a handedness screening form (See Appendix D) in order to maintain consistent hemispheric and hand dominance across all participants.

Materials

Screening Forms. Participants completed screening forms to assess suitability for the experiment as discussed above (See Appendices A-C).

Stimuli. Auditory stimuli used for experimental trials consisted of a single isochronous rhythm with a tempo of 550 ms per beat. The rhythm consisted of 9 repetitions of a single Waveform audio clip (a standard computer “click” sound) that was created using Garage Band software (Apple Inc., Cupertino, USA). Following the 8 inter-beat intervals (separating the 9 beats) of the auditory stimuli, there was a silent period the length of 4 inter-beat intervals. At the end of the silent period there was a single click that acted as the probe tone; this click was either synchronized with the timing of the prior auditory beat, early by 30% of the inter-beat interval or late by 30% of the inter-beat interval. The timing of the probe tone was the only difference between stimuli used. The three possible timings of probe tone occurred in 200 trials each, randomly distributed throughout the 600 trials of the experiment.

Experimental Programs. The primary experimental program was run using MATLAB 2015b on the main computer, which controlled the timing of all auditory and TMS stimuli. A response tracking script was also run using MATLAB 2015b (Mathworks, Natick, USA). A beat-based computer keyboard tapping task following the main experiment was run using E-Prime 2.0 (Psychology Software Tools, Sharpsburg, PA).

Audio Equipment. Auditory stimuli was played through in-ear headphones, fitted with earplugs to reduce noise from the TMS coil.

TMS Equipment. A Magstim Rapid transcranial magnetic stimulator and a focused magnetic stimulation coil (Magstim Co Ltd, Whitland, UK) were used to deliver single-pulse TMS to the primary motor cortex via the scalp. During each experimental trial a single TMS pulse was delivered at 1 of 600 time points within the TMS pulse window (the last two auditory intervals and the four silent intervals concluding with the probe tone). The TMS pulse was delivered at each time point once throughout the 600 trials of the experiment in random order.

EMG Equipment. Three electrodes were applied to the participant's hand (see Figure 1) using adhesive gauze pads. Prior to the application of electrodes the participant's hand was sanitized using standard isopropyl rubbing alcohol and cotton swabs. Electrodes were connected by separate cables to a Quad AC Amplifier EMG system to obtain MEP data. Data was relayed to a computer through a Micro1401-3 data acquisition unit. Data was displayed and recorded on the computer using Signal software (CED Ltd., Cambridge, UK).

Questionnaires. A demographics and supplementary information questionnaire consisting of background information was administered using E-Prime 2.0. The questionnaire contained questions about standard demographic information, musical training history and strategies used to complete the experimental tasks.

Procedure

Prior to starting the experiment, all participants completed informed consent forms and suitability screening forms. Given the neurological nature of the study, consent forms also acted as debriefing forms. Upon successful completion of these, electrodes were applied to the first dorsal interosseous muscle and the pisiform bone on the wrist as shown in Figure 1.

Before beginning trials, the relative location of the primary motor cortex on the scalp was determined using fixed points marked with a carbon pencil. The centre of the head was determined and marked using measurements from the nasion to the inion and from the left tragus to right tragus. An "X" was drawn 5 cm to the left and 2 cm forward of the marked centre point, indicating the relative location of the primary cortex. The precise location of the primary cortex within this circle was localized through trial and error using the test mode of the Signal software application, which sent TMS pulses intervals of 2 seconds continuously. When MEPs were consistently observed within the delineated range in the Signal software, the precise location of the motor cortex was marked on the scalp. After this, the appropriate threshold of stimulation from the TMS for the experiment was determined. This was carried out by finding the minimum threshold that produced an MEP reaching the predetermined MEP baseline in the Signal software application on half the test trials, defined as five out of ten consecutive pulses. This threshold was increased by a factor of 10% to determine the motor threshold, which was used for all experimental trials. The experimental equipment setup is illustrated in a diagram in Figure 2.

Participants were told that on each trial they would hear an auditory rhythm, followed by a period of silence and a probe tone. They were instructed to identify the beat of the rhythm, and to maintain the timing of this beat during the following silent period until the probe tone sounded. After the probe tone had sounded, participants were asked to indicate whether the probe

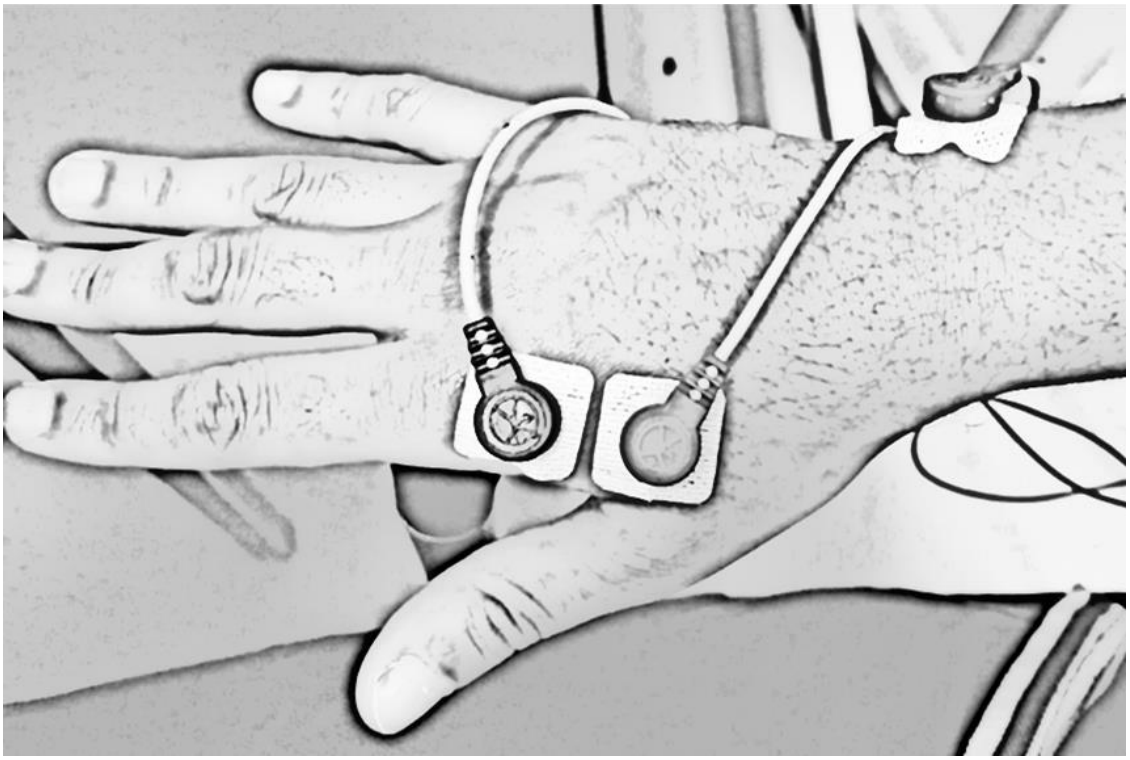

Figure 1. Electrode configuration for EMG recording.

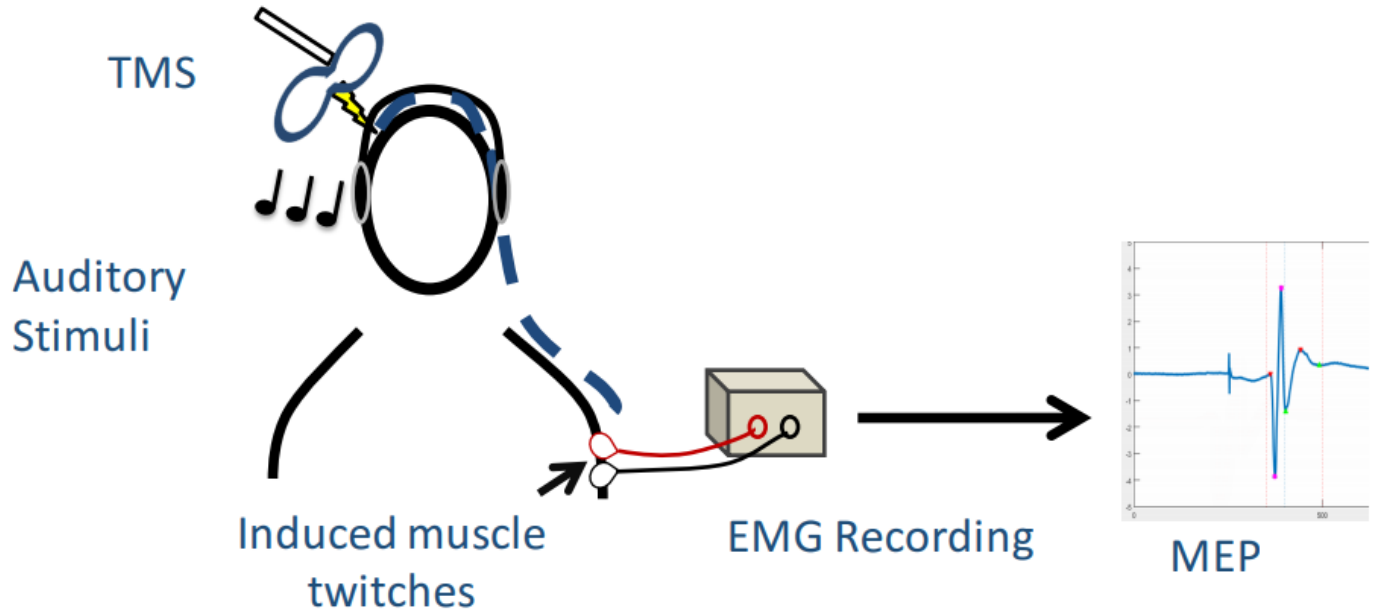

Figure 2. Diagram of experimental setup and procedure.

tone occurred on or off the beat of the rhythm (participants asked to identify whether a probe tone was on-beat or off-beat; they were not asked to identify if an off-beat probe tone was early or late). Participants used a laptop computer to enter their responses manually, by entering a 'Y' to indicate a probe tone that was on-beat or an 'N' to indicate a probe tone that was off-beat. Within the window consisting of the last 2 inter-beat intervals of the auditory rhythm and the following silence (the silent period being the equivalent of 4 inter-beat intervals), one TMS pulse was delivered to the primary motor cortex. The TMS pulse was delivered randomly at 1 of 600 potential timepoints on each trial, made up of 100 evenly spaced out time points within each inter-beat interval. Participants were directed to ignore the TMS pulse and to focus on maintaining the beat of the stimuli in order to make a response regarding the probe tone. A diagram of an experimental trial is shown in Figure 3.

This procedure was repeated for 600 trials, sectioned into ten blocks lasting about 10 minutes apiece. Participants were offered the opportunity to take a break between each block of trials. Upon completion of all experimental trials, participants completed a manual beat tapping task delivered on a laptop computer. Following this, participants completed a computer-delivered demographics questionnaire including questions about prior musical training and any strategies employed to maintain the timing of beats during the experiment.

During each trial, data was recorded in multiple ways. The MATLAB script commanding the playing of auditory stimuli and TMS pulses recorded the timing of the TMS pulse and the timing of the probe tone for each trial. The Signal software application recorded MEP data at the time of the TMS pulse on each trial. The MATLAB script for recording participants' responses to the probe timing recorded whether the participant thought the probe tone was on-beat ('Y') or off-beat ('N') for each trial.

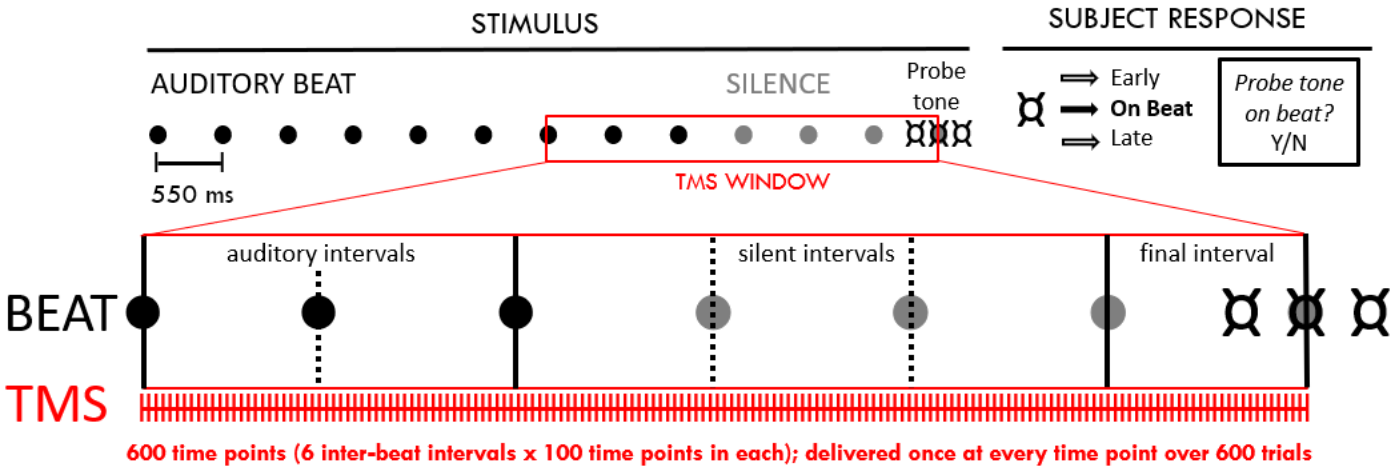

Figure 3. Visual representation of an experimental trial. TMS pulse is delivered within window consisting of last 2 auditory intervals, 3 silent intervals and final interval ending with probe tone

Results

Manual beat tapping data. Participants generally had a high rate of accuracy in the manual beat tapping task. Participants tapped along to 3 beats, all with a tempo of 550 ms. The mean accuracy percentage of inter-tap intervals proportional to the inter-beat interval of 550 ms was 93.3%, with a standard deviation of 13.3% accuracy. 15 out of 17 participants had an overall accuracy percentage above 93%. This is an indication that participants were capable of synchronizing motor action to a beat at the tempo of 550 ms.

Response data. Participants correctly responded "On-Beat" at a rate of 69.0 % in the On-Beat probe tone condition, and incorrectly responded "On-Beat" at rates of 48.3% and 60.3% in the early and late probe tones respectively. These response rates represent a significantly greater proportion of responses of on-beat than expected in the early and late probe tone conditions, however these results are not vastly different from those obtained by Manning and Schutz (2013) in their study that used the same paradigm (see Figure 4). D prime scores comparing the rate of "hits" (responding "on-beat" when the probe was on-beat) were proportionally greater than the rate of "false alarms" (responding "on-beat" when the probe was not on-beat) by an average of 0.50 standard deviations (M= 0.497, SEM = 0.485).

A one-way repeated measures ANOVA (comparing 6 intervals that TMS pulse was delivered in, see Figure 5) was performed to determine how response accuracy percentage varied based on the timing of the TMS pulse. The results were significant ($F(5,80) = 4.804$, $p = .008$) and post hoc comparisons were performed comparing all possible pairs of the six intervals (first: M = 54.47, SEM = 3.06; second: M = 51.88, SEM = 2.30; third: M = 52.53, SEM = 2.23; fourth: M = 53.82, SEM = 2.24; fifth: M = 51.53, SEM = 2.09, sixth: M = 46.71, SEM = 2.16; all values given as a percentage). Two-tailed paired samples t-tests determined that participants were

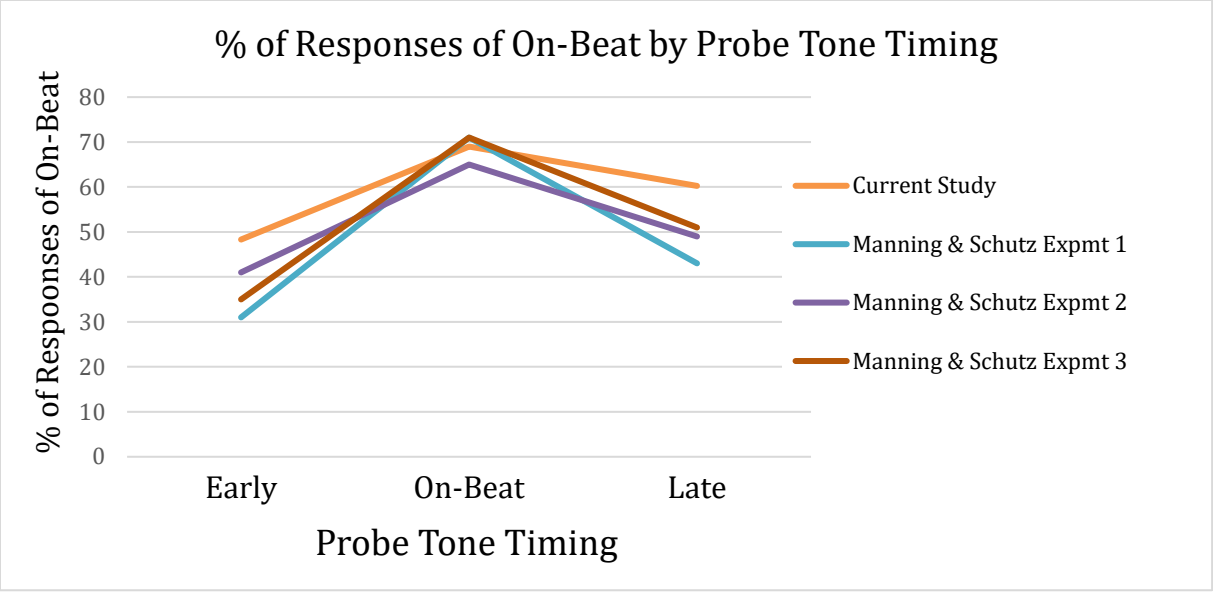

Figure 4. Percentage of responses of on-beat within early, on-beat and late probe tone conditions for this study and 3 experiments from a previous study using the same paradigm (Manning & Schutz, 2013).

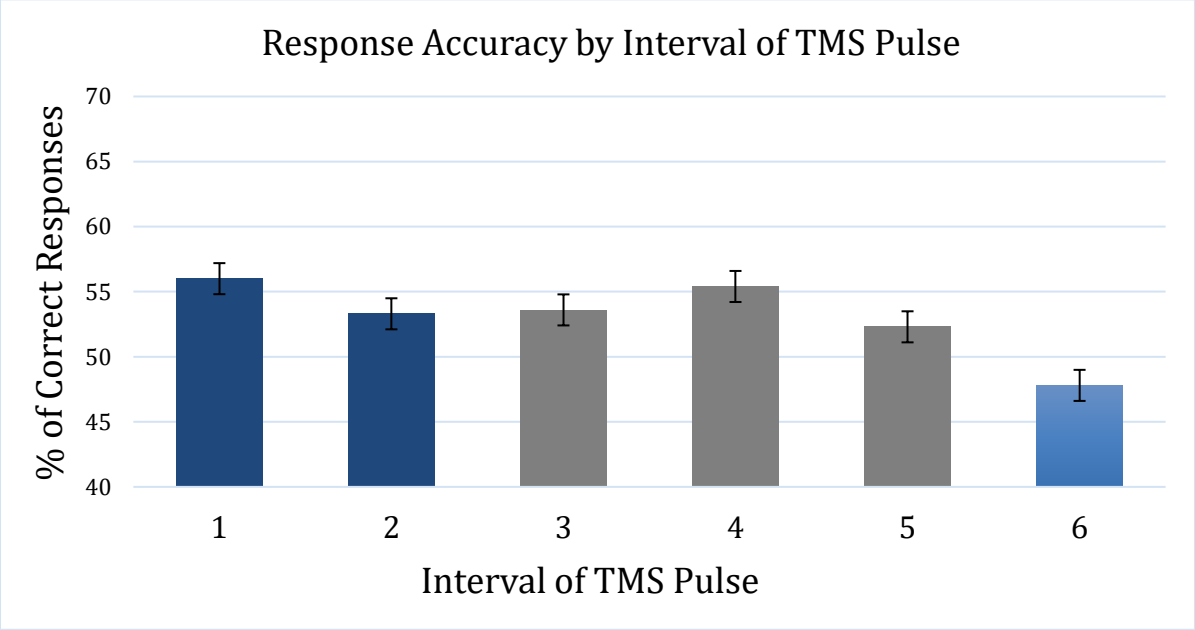

Figure 5. Percentage of correct responses based on which interval the TMS pulse was delivered in. Intervals 1 or 2 were in the auditory condition; intervals 3, 4 and 5 were in the silent condition; interval 6 was in the final condition.

significantly more accurate when the TMS pulse was delivered in the first, third and fourth intervals than in the final interval (($t(16) = 4.395$, $p < .003$; $t(16) = 3.973$, $p < .003$; $t(16) = 4.591$, $p < .003$ respectively for first, third and fourth intervals compared to sixth). Participants had greater response accuracy percentages when the TMS pulse was delivered in the second and fifth intervals than in the sixth interval, but the differences did not reach significance ($t(16) = 3.072$, $p = .007$; $t(16) = 2.272$, $p = .037$ respectively for second and fifth intervals compared to sixth). No other comparisons were statistically significant ($t(16) < 1.76$, $p > .083$). Lower accuracy when the TMS pulse is delivered in the final interval compared to multiple earlier intervals suggests a disruptive effect of the TMS pulse on accuracy when delivered in close proximity to the probe tone. This may be due to the sound and/or induced hand movement that results from the TMS pulse, which may disrupt internally maintained timing of the beat. TMS has been observed to disrupt timing assessment abilities previously (Novembre, Ticini et al., 2013).

MEP data analysis. MEP amplitudes were selected by a MATLAB script. Peak to peak amplitudes within the MEPs were excluded from the analysis if no distinct MEP was elicited, if the amplitude was below 100 μv, or if the amplitude was more than three standard deviations above the mean amplitude for the participant. As a result, 25.2 % of MEPs were discarded from the analysis. A MATLAB script was used to analyze MEP amplitudes based on relative timing within the inter-beat interval. Participants' data sets were excluded from the analysis completely if more then 40% of MEPs from the data set had been discarded; this resulted in the exclusion of 5 participants' data sets from the analysis.

For each participant, amplitude data was plotted across all trials by pulse timing and separated into beat to beat intervals within three conditions: auditory intervals, silent intervals

and the final interval (during or after which the probe tone occurred). Within each condition amplitude data was combined into a single beat to beat interval and analysed using a sliding window technique. The medians of amplitudes from adjacent periods of 5 pulse time points, centred on 50 points evenly spaced out points across each interval condition, were plotted on a graph. Data within each interval condition was then analyzed for general linear trend, and cosine fit at the rate of tempo of the stimuli as well as 2 non-harmonic rates to assess if MEP fluctuations were analogous to the tempo of the stimuli or fluctuating at an unrelated rate. Data was initially analysed within each interval condition for slope of linear fit. Once the slope of linear fit had been determined, data within each interval condition was detrended linearly by the value of the slope and analysed for goodness of cosine fit at 3 period rates of cosine function: 550 ms (the tempo of the auditory stimuli), 200 ms and 900 ms. Slope data was analyzed by one-way repeated measures ANOVA (3 interval conditions), while goodness of fit data and amplitude data was analyzed using a two-way repeated measures ANOVA (3 interval conditions x 3 fitted rates).

Slope. Slope data was analysed using a one-way repeated measures ANOVA by interval condition (auditory, silent, final). No main effect of interval condition was found, as slopes of linear fit did not significantly differ between any conditions, $F(2, 22) = 1.535$, $p = .239$. No slopes were found to be significantly different from 0, $t(11) < 2.29$, $p > 0.02$, see Figure 6.

Slopes of linear fit of smoothed MEP amplitude data did not differ significantly between interval conditions, indicating that motor excitability is not significantly affected by whether a beat is heard or maintained internally. All slope values were neither significantly positive or negative, indicating that MEP amplitudes are not increasing or decreasing over these intervals. This means that motor excitability is not changing significantly in a linear fashion from onset of

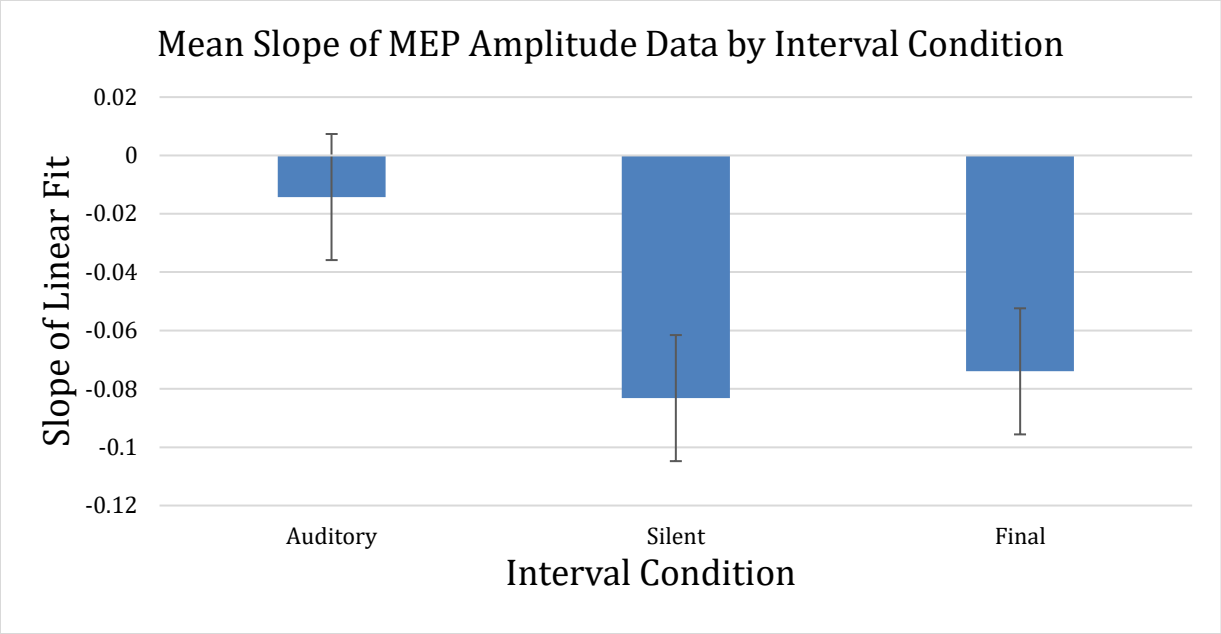

Figure 6. Mean slope of linear fit of smoothed MEP amplitude data within each condition. Differences between slopes were not significant; slopes in silent and final conditions were significantly less than 0.

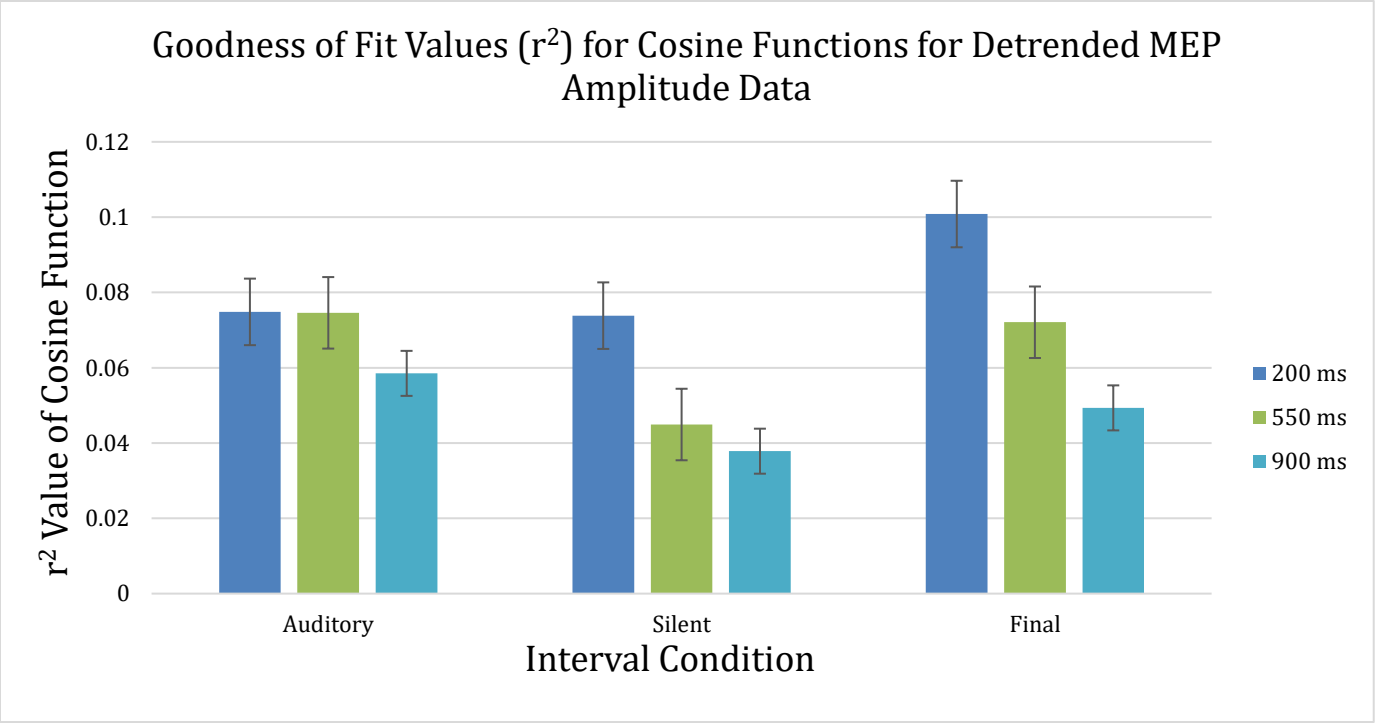

Figure 7. Mean r2 values of cosine functions fitted to detrended MEP amplitude data at fitted rate of tempo of stimuli (550 ms) and two unrelated fitted rates (200 ms and 900 ms) within each interval condition.

the final silent beat until the time of the probe tone. Results for all conditions are contrary to our hypothesis that motor excitability increases from the onset of a beat until the onset of the next, regardless of whether a beat is heard or maintained and whether there is a probe tone that must be evaluated. These results suggest that motor excitability does not follow any linear trend within an inter-beat interval, potentially only fluctuating in an oscillatory manner.

Goodness of cosine fit. Cosine fit data was analyzed using a two-way repeated measures ANOVA comparing effects of interval condition (auditory, silent, final) and fitted rate of cosine function (200 ms, 550 ms, 900 ms). There was not a significant main effect of interval condition, $F(2,22) = 0.596$, $p = 0.536$, while there was a significant main effect of fitted rate, $F(2,22) = 9.701$, $p = 0.007$. There was no significant interaction between interval condition and fitted rate, $F(2,22) = 0.475$, $p = 0.631$. Based on the results of the repeated measures ANOVA, post hoc comparisons were completed to compare averaged means within each fitted rate condition across all interval conditions. Two-tailed paired two sample t-tests revealed that r^2 values at rates of 200 ms (M = 0.083, SEM = 0.014) and 550 ms (M = 0.064, SEM = 0.011) were both significantly greater than those at 900 ms (M = 0.049, SEM = 0.009; $t(11) = 4.78$, $p = 0.001$; $t(11) = 3.82$, $p = 0.003$), see Figure 7.

r^2 values represent how closely cosine functions at three fitted rates model the fluctuations of MEP amplitudes over an inter-beat interval, and thus how well fluctuations in each interval are synced to either the tempo of stimuli or unrelated rates. The lack of a significant main effect of interval condition on r^2 values means that fluctuations in motor system excitability did not have greater regularity across all rates within any interval condition. This indicates that the rate of motor excitability fluctuation did not vary significantly between when beats were

heard, beats were internally maintained, or in the final interval containing the probe tone about which a judgement must be made.

The significant main effect of fitted rate on r^2 values and the subsequent post-hoc comparisons mean that fluctuations of motor excitability are fit better by cosine functions at rates of 200 ms and 550 ms than at 900 ms. This indicates that motor excitability did not fluctuate at a rate of 900 ms. However, significant differences were not found between corresponding r^2 values for rates of 550 ms and 200 ms, suggesting that across all interval conditions, motor excitability fluctuations may not have been synchronized to the tempo of the stimuli.

The lack of significant interaction between interval condition and fitted rate means that r^2 values did not vary systematically based on the combined effects of both conditions. A significant interaction between interval condition and fitted rate could have potentially revealed significant differences in r^2 values at fitted rates within only one or only two conditions. Had a significantly greater value of goodness of fit for the 550 ms rate been found in only one or two interval conditions, this would indicate that motor excitability fluctuations synchronized to the tempo of stimuli in a certain condition or condition(s) only. It was hypothesized that motor excitability would be more synchronized to the tempo of the beat during silent and final intervals than in other conditions, which would have been indicated by greater r^2 values for 550 ms than both other rates only within the silent and final interval condition. However, the lack of significant interaction means that this or any other differences in synchronization of motor excitability to the beat moderated by interval condition were not found.

Amplitude of cosine fit. Amplitude data of cosine functions of goodness of fit was also analyzed using a two-way repeated measures ANOVA bv interval condition (auditory, silent, final) and fitted rate of cosine function (200 ms, 550 ms, 900 ms). A significant main effect of

interval condition was discovered, $F(2,22) = 8.626$, $p = 0.002$. No significant main effect of fitted rate was found, $F(2,22) = 0.659$, $p = 0.444$. There was no significant interaction between interval condition and fitted rate, $F(2,22) = 0.096$, $p = 0.886$. Post hoc comparisons were performed to compare means within each of the three interval conditions, across all fitted rates. Two-tailed paired two sample t-tests revealed that amplitudes in the final interval (M = 1.93, SEM = 0.29) were significantly greater than those in silent intervals (M = 0.75, SEM = 0.12; $t(11) = 4.24$, $p = 0.001$). Amplitudes in the auditory intervals (M = 1.33, SEM = 0.22) were numerically greater than those in silent intervals, but this difference did not reach significance ($t(11) = 2.31$, $p = 0.04$). Amplitudes in the final interval were not significantly greater than those in the auditory intervals ($t(11) = 1.88$, $p = .09$), see Figure 8.

The main effect of interval condition on amplitude and following post hoc comparisons means that motor excitability had larger fluctuations in the final interval than in silent intervals, regardless of the rate of fit of cosine function. Amplitude of the cosine functions of best fit within an interval is a measure of the magnitude of fluctuations in motor excitability. The greater amplitudes in the final condition than in the silent condition indicate that motor excitability in fluctuated to a greater extent in the final interval compared to the three silent intervals prior.

The lack of main effect of fitted rate on amplitude of goodness of fit functions indicates that amplitude did not vary significantly among fitted rates. The lack of interaction between interval condition and fitted rate indicates that amplitude of goodness of fit functions did not vary systematically within any condition based on fitted rate or vice-versa. These were expected, as the amplitude of cosine functions for detrended data is determined by the extent of the variance of MEP amplitude values (along the y-axis) within the interval, without the influence of timing of those values (along the x-axis).

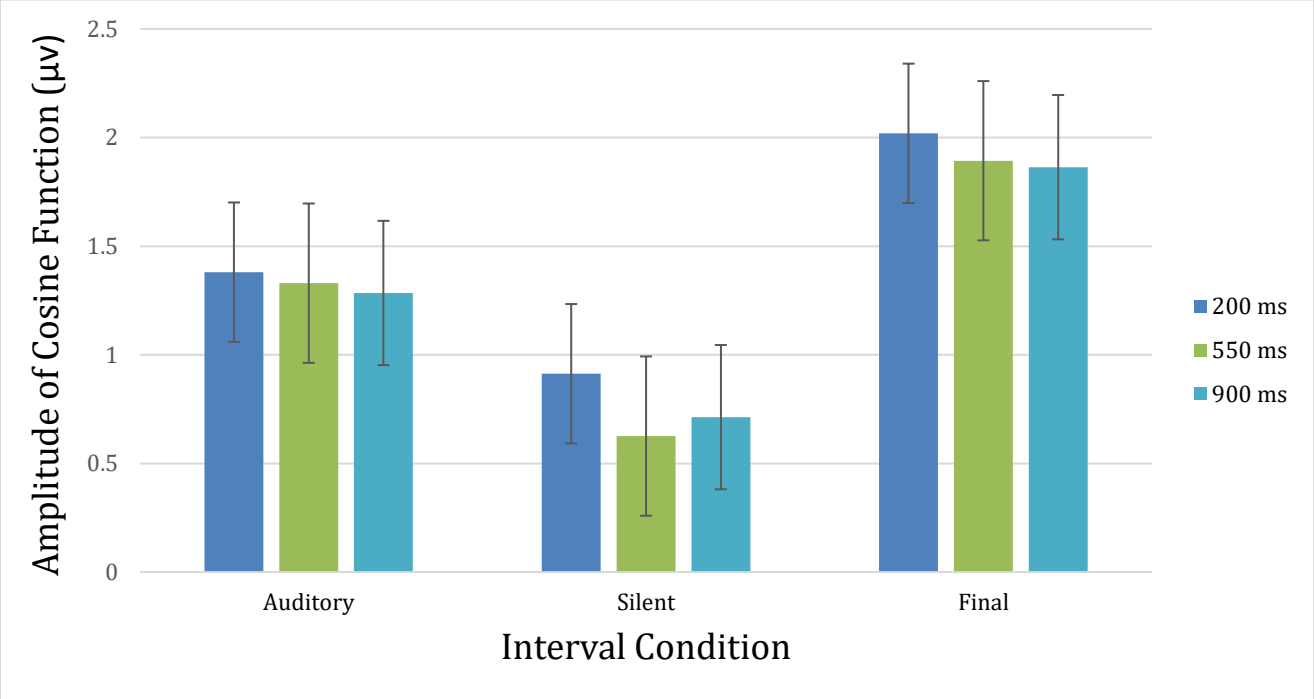

Figure 8. Amplitudes of cosine functions fitted to detrended MEP amplitude data at fitted rate of tempo of stimuli (550 ms) and two unrelated fitted rates (200 ms and 900 ms) within each interval condition.

Discussion

Restating, the hypotheses of the study were as follows: motor excitability would show a significant linear trend of decreasing over the inter-beat interval in the auditory condition; motor excitability would synchronize significantly better to the rate of the stimuli than to unrelated rates in the silent and final conditions; motor excitability would synchronize significantly better to the rate of stimuli than to all unrelated rates when averaged across all interval conditions; and motor excitability fluctuations would be greater in the silent and final conditions than in the auditory condition.

The hypothesis that motor excitability would decrease at a significant rate leading up to a beat in the auditory condition was not supported, as the slope of linear fit of MEP data was not significantly less than 0 in the auditory intervals. This may indicate that motor excitability does not follow a downward trajectory from the onset of one auditory beat to the onset of another, with the only significant changes following an oscillatory pattern. Alternatively, motor system excitability may increase at the time of a beat without a gradual buildup or drop in motor excitability over the course of the inter-beat interval. This would be displayed as a pattern of flatness in motor excitability with narrow peaks on each beat; this data may not show a general trend over the course of the interval nor as a regular cosine function, but motor excitability would nonetheless be greater on beat as opposed to off beat.

The hypothesis that fluctuations in motor excitability would synchronize significantly better to the rate of the stimuli than to unrelated rates in the silent and final conditions was not supported. An interaction was expected such that r^2 values of goodness of fit were expected to be greater for the fitted rate at the tempo (550 ms) than other rates (200 ms and 900 ms) in the silent and final conditions. There was no significant interaction, and r^2 values for the 550 ms fitted rate

to data were not significantly greater than r^2 values for all other rates within these conditions. This indicates that motor excitability did not fluctuate at the rate of the stimuli in these conditions. Despite the active internal generation of the beat occurring in these conditions, motor excitability fluctuations were not found to be moderated by the tempo of the beat. The same results were found in the auditory condition when the beat was heard rather than internally generated, indicating that auditory stimuli also did not moderate fluctuations in motor excitability. The hypothesis regarding motor excitability fluctuation showing significantly synchronization to the rate of the tempo than to all other rates was not supported. Across all conditions, motor system excitability fluctuation synchronized more to the rate of the tempo (550 ms) than to one of the unrelated rates that was fitted to the data (900 ms). However, there were no significant differences found when compared to a second unrelated rate (200 ms). There was not enough evidence that fluctuations in motor system excitability synchronized to the tempo of stimuli.

Collectively, the lack of support for the hypotheses regarding synchronization of motor excitability fluctuations to the beat could be due to several factors. This may mean that the focus of participants to the beat was not maintained to a degree where motor system excitability fluctuations synchronized to the stimuli; perhaps participants found the task unengaging or repetitive and did not give the beat their full attention. Participants occasionally missed entering a response to the probe tone, which could show a lack of attention. There is also a possibility of noise within the data that is masking differences in rates of motor excitability fluctuation between different interval conditions. Noise could be due to factors such as differences in participants' ability to focus throughout the experiment, unintentional small movements of the TMS coil causing variation in pulse precision, and interference affecting the EMG equipment.

Alternatively, motor system excitability fluctuation may not be moderated by the tempo of auditory stimuli, whether heard or internally generated. The previous study by Czajka, Grahn et al. (2017) found that motor excitability fluctuations synchronized significantly better to a rate of 200 ms than 550 ms, for stimuli at both of these tempi. In this study values of goodness of fit for the rate of 200 ms were numerically higher than those at 550 ms, but the difference did not reach significance. This provides some evidence that fluctuations in motor system excitability synchronize to a fitted rate of 200 ms more than a rate of 550 ms regardless of tempo. Another study suggested that motor system excitability fluctuations are modulated better by the preferred tempos of participants than other tempos (Michaelis, Wiener et al., 2014). This could make participants more likely to have motor system excitability fluctuations synchronize to a rate different than that of the stimuli (e.g. 200 ms instead of 550 ms) if their preferred tempo differs from the tempo of the stimuli. An experiment with a similar design to this one that determined the preferred tempo of participants and using stimuli at this tempo could potentially produce higher values of goodness of fit for MEP data when fitted to the rate of the tempo of stimuli. More research is required on the moderating factors of fluctuations in motor system excitability that occur while listening to, and internally generating, auditory stimuli.

The hypothesis of greater magnitude of fluctuations in motor excitability in silent and final intervals compared to auditory intervals was not supported. Unexpectedly, motor system excitability fluctuated at a greater magnitude during the final interval that contained the probe tone compared to intervals that were completely silent. This may have occurred due to the approaching onset of the probe tone, as the listener made a greater effort to internally generate the timing of the beat as the probe tone sounded in order to make a response afterwards. However, these results may be biased by the size of data samples as well. As part of the MEP

amplitude analysis script, data was averaged into one interval for each condition based on relative positions within the interval using a sliding window technique. The sliding window technique used a binning process, plotting the median amplitude values from bins of 5 consecutive time points within the averaged interval to form the data set of analysis. Since the auditory condition consisted of 2 intervals, the silent condition consisted of 3 intervals, and the final condition consisted of 1 interval, the number of total values being averaged into a bin varied from condition to condition. Data for the silent condition was composed of the medians of bins consisting of approximately 15 amplitude values as opposed to 5 in the final condition; this could have resulted in data that was generally closer to the mean in the silent condition, resulting in lower values of amplitude for fitted cosine functions. In future studies this may be rectified by having an even number of intervals in each condition; this may necessitate including more probe tones to be judged. This would allow for even sampling of all conditions, potentially increasing the validity of measures such as the amplitude of functions of goodness of fit.

Limitations and Conclusion

This study had a relatively small sample size for the analysis of primary interest. 5 participants were excluded from the analysis of MEP amplitude data based on the high amount of MEP amplitude values that were discarded from their data sets. This diminished a pool of participants that was already smaller than the target sample size due to the invalidity of data tested at certain times based on technical and data acquisition issues. The final analysis included a total of 12 participants, meaning that the repeated measures ANOVA and post hoc tests that were run were limited in their power to determine significant differences. Future studies looking at the same factors would increase chances of finding significant results.

There may have been multiple sources of variance due to procedural effects. The M1 motor hotspot on the scalp has a precise location, and the manually held TMS coil was subject to movement from the hotspot throughout the experiment. This may have caused variation in the amplitude of MEPs that was unsystematic, potentially leading to noise. In addition, technical issues with hardware and/or software from the TMS occasionally compromised the timing of signal recording for TMS pulses. While MEP data could still be collected on these trials, timing of TMS pulses and thus identification of timing of MEPs obtained may have been compromised in some cases.

In conclusion, motor excitability was not found to have a significant linear trend over the course of an inter-beat interval, and fluctuations in motor system excitability were not found to be moderated by the tempo of auditory stimuli to a greater degree when stimuli were internally generated. While this study did not confirm our hypotheses, it has furthered our knowledge of patterns of motor excitability while both hearing and internally generating auditory stimuli. Future studies may be able to refine the design of this study to produce significant results, by manipulating factors of the experiment to optimize testing conditions. Two ways this could be done are by sampling each condition of interest equivalently (i.e. auditory intervals, silent intervals and intervals where a judgement must be made about stimuli such as the final interval) and modifying the tempo of stimuli to be consistent with participant's preferred tempo.

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Appendix A

LETTER OF INFORMATION FOR PARTICIPANTS

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

Principal Investigator:

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Brain and Mind Institute
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University of Western Ontario
London, Ontario, N6A 5B7
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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 three hours. Each experiment within the research project will involve 10-40 participants, and the entire research project will involve approximately 400 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

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, _____.

Appendix B

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	

Appendix C

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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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The Brain and Mind Institute

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 D

Handedness Questionnaire

Research Subject ID Code: _____

Have you ever had any injury or other problem that caused you to change your hand or foot preference? If so, please give the date of the change and the reason for it:

_____

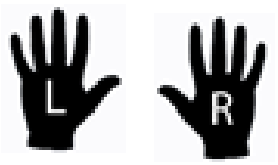
_____

Which hand do you use for each of these things?

If your preference is not that strong, put +

If you would never use the other hand unless forced to, put ++

If you might use either hand put + in both columns



	LEFT	RIGHT
1. Writing	_____	_____
2. Drawing	_____	_____
3. Throwing	_____	_____
4. Scissors	_____	_____
5. Toothbrush	_____	_____
6. Knife (without a fork)	_____	_____
7. Spoon	_____	_____
8. Broom (upper hand)	_____	_____
9. Striking a match (match)	_____	_____
10. Opening box (lid)	_____	_____
11. Which foot do you prefer to kick with?	_____	_____
12. Which eye do you use when using only one? (e.g., for a telescope)	_____	_____

Is anyone in your family left-handed, including parents, siblings, and grandparents? _____

If yes, give relationship(s): _____

_____

_____