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Is Motor Excitability Modulated by Isochronous Rhythms?

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Abstract

Humans perceive and synchronize to regularity in auditory temporal sequences. Auditory regularity activates motor areas, but how the timing of motor responses relates to the regularity is unclear. Thus, we examined whether motor excitability, an index of motor activity, fluctuated to an isochronous sequence and characterized the timing of these fluctuations. Participants heard isochronous tones followed by a short silence, during which they imagined the tones continuing. Using single pulse transcranial magnetic stimulation (TMS), we indexed excitability throughout the sequence. Cosine models were fit to constructed excitability timecourses to quantify periodicity of the excitability fluctuations. Motor excitability did not fluctuate at the stimulus frequency during either listening or silent portions. Thus, the study does not provide evidence for motor excitability fluctuations during isochronous tone perception or generation. Future work may reduce measurement noise by acquiring more samples over a shorter time or using a more engaging stimulus.

Keywords

Rhythm, auditory-motor coupling, motor excitability, corticospinal excitability, regularity, movement, music, motor cortex, transcranial magnetic stimulation, motor evoked potentials, periodicity.

Summary for Lay Audience

Humans can perceive and synchronize their movements with regularly repeating patterns in sound. For instance, people can spontaneously tap their feet or bob their heads to the beat in Western music. In recent decades, researchers have tried to determine how the human brain accomplishes this feat. Studies using brain scanning technology show that motor areas of the brain (areas involved in generating and coordinating movement) are active when people listen to rhythms containing a beat, even while they remain still in the scanner. Other studies suggest that motor excitability (i.e., the readiness of neurons in the motor regions to 'fire' or activate) fluctuates at the same rate or 'tempo' as the regularly repeating sounds. However, no study so far has directly monitored motor excitability over the course of a rhythm. So, in the present study, we set out to address this gap in research and determine whether motor excitability does indeed fluctuate at the same rate as a regularly repeating sound sequence. In this study, we used a 10-tone isochronous sequence (a simple sequence in which tones are equally spaced apart in time, similar to a metronome). While participants were listening to the sequence, we stimulated their brains using a non-invasive technology known as transcranial magnetic stimulation, or TMS. When performed over a specific region of the brain known as the primary motor cortex, this stimulation causes a muscle twitch in the participants' hands, which can be quantified and used to assess the degree of motor excitability. By stimulating at many time points throughout the tone sequence, we were able to observe how excitability changes as people listen to the tone sequence. We found that motor excitability does not fluctuate at the same rate as the isochronous sequence. Although we did not get the results we expected, these findings still help clarify how exactly the motor regions of the brain are involved in perceiving regularity. Future studies can now build on these findings and continue to explore the intersection between regularity and movement.

Acknowledgments

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Chapter 1

1 Introduction

Regularities in sound are present in nature, as well as in man-made sounds such as the regular beat in music. Humans predict and synchronize their movements to these regularities (Peters, 1980; Keele et al., 1985; Truman & Hammond, 1990; Repp, 2005). When listening to a regular (isochronous) sequence of tones, humans are able to tap closer to the tone onset time than when listening to a jittered, unpredictable sequence, which suggests that humans anticipate the regularity and use it to improve their temporal accuracy. Interestingly, the ability to perceive and predict regularity also extends to rhythms in which the underlying regular pulse does not always correspond one-to-one with auditory events. For example, the beat in music can be tapped even through gaps in the music or after the music stops. This 'internal generation' of the beat is thought to support beat perception and synchronization. Studies of beat perception find activity in motor areas in response to rhythmic auditory stimuli, even in the absence of movement, suggesting that these areas may be part of the neural mechanism underlying beat perception (Penhune et al., 1998; Grahn & Brett, 2007; Chen et al., 2008; Teki et al., 2011, Parsons, 2012). While the evidence for motor involvement is robust, it is not clear *when* motor activity changes during the perception of regular auditory sequences. For example, do motor areas respond in advance of regular tones, suggesting a role in anticipation or prediction, or do they respond after the tone? The current research project addresses this question by investigating whether there are periodic fluctuations in motor (or corticospinal) excitability in human adults in response to a regular isochronous sequence and by characterizing the time course of these changes. Detecting regularity in an isochronous sequence may not involve the same mechanism as detecting regularity in a more complex (non-isochronous) rhythm such as those found in music, in which the regular beat may at times coincide with silence. However, given that both isochronous and non-isochronous rhythms lead to perception of and synchronization to regularity, studies using both types of stimuli have been included in the following review of the literature.

1.1 Sensorimotor synchronization

Humans are able to synchronize movements to auditory events in isochronous sequences as well as the beat in more complex rhythms. However, there are limited rates at which they accurately perform synchronization tasks (such as tapping along to an isochronous sequence or the perceived beat of a non-isochronous rhythm). The lower limit for synchronizing to temporal regularity is thought to be 100-200 ms and may correspond either to the perceptual threshold for detecting individual events (Carver et al., 2002) or motor-related constraints (Keele & Hawkins, 1982; Peters 1985; Gross et al., 2002). The upper limit (slowest rate) for perceiving regularity is around 1.8 s, beyond which responses are no longer anticipatory (Engstrom et al, 1996; Mates et al., 1994; Miyake et al., 2004). Beyond this upper limit, motor responses start occurring after the auditory event. When these responses occur 100 ms or more after the event, they indicate a reaction to the auditory event rather than anticipation of it. Thus, the present study focuses on sensorimotor synchronization to beat-based rhythms or isochronous sequences spanning a limited range of tempi (100 ms to 1.8 s).

Movement plays an important role in perceiving temporal regularity at sub-second scales. For instance, when participants hear isochronous sequences with missing tones and must extract the perceived regular pulse, being allowed to overtly move (for example, bob their heads) improves accuracy of pulse finding (Su & Poppel, 2012). Along similar lines, movement was found to increase the accuracy of judgements about isochronous rhythms in a time-keeping task (Manning and Schutz, 2013). In the task, participants listened to an isochronous series of intervals followed by a silent, time-keeping period several intervals long. Finally, a ‘probe’ tone was played either at the correct time (the time the final tone would have occurred if the isochronous sequence had continued playing) or the incorrect time (earlier or later than the final tone would have occured). Judgements about the final tone were more accurate when participants were allowed to tap their fingers through the silent period than when they were asked to not move. The influence of movement on perception of such regularities can even be detected in early childhood. Phillips-Silver and Trainor (2005) trained two groups of 7-month-old infants to perceive accents on either every second or third tone in an isochronous sequence by bouncing the babies

every second or third tone, respectively. After training, babies' listening preferences were tested: they heard intensity-accented versions of the isochronous sequence corresponding to the two conditions, and preference was assessed with a head-turn procedure. Each group of babies preferred to listen to the sequences that were accented according to their bouncing pattern during training. Taken together, these studies suggest that movement enhances the experience of 'feeling a beat' and this enhancement can be quantified in behaviour.

The role of movement in synchronization can also be studied in people with movement-related deficits, such as people with Parkinson's disease (PD). One such study compared performance on a rhythm discrimination task between patients with PD and healthy controls (Grahn, 2009). Some of the rhythms induced a strong sense of beat and others induced a weak sense of beat. Healthy controls detected changes in strong-beat rhythms more accurately than weak-beat rhythms, but the PD patients were similarly accurate across the two types of rhythms. Additionally, PD patients performed worse on isochronous tapping tasks than controls (O'Boyle et al., 1996; Harrington et al., 1998). The authors of these studies suggest that the rhythm deficits relate to the degeneration of basal ganglia structures in PD. Thus, damage to motor areas of the brain appears to impair rhythm perception and production.

1.2 Neural correlates of beat perception

As mentioned above, neuroimaging studies have found that various movement-related areas are involved in rhythm and beat perception. In one study, participants listened to regular (isochronous) and irregular (jittered) tone sequences while functional magnetic resonance imaging (fMRI) was used to measure brain activity (Teki and colleagues, 2011). When subjects listened to regular compared to irregular sequences, activity was higher in several motor brain regions, such as the supplementary motor area (SMA), premotor cortex (PMC), and striatum. Other studies have investigated rhythms that are temporally organized to either induce beat perception or not. Compared to rest, listening to rhythms activated several motor areas, such as the basal ganglia, cerebellum, SMA, and PMC (Grahn and Brett, 2007). Since participants were instructed not to move during the scan acquisition period, the motor responses were elicited by only the perception of

rhythm. Additionally, activation in the SMA and the basal ganglia was higher while participants heard rhythms that conveyed a strong compared to a weak sense of beat. Other work has shown that SMA and dorsal PMC activity covaried with rhythm task performance (Chen et al. 2008). Finally, the role of the SMA in rhythm perception is further reinforced by studies showing a correlation between beat perception ability and SMA activity (Grahn and McAuley, 2009; Grahn and Schuit, 2012) and deficits in rhythm reproduction in patients with lesions to the SMA and PMC (Halsband et al., 1993). These studies strongly suggest the involvement of a striato-thalamo-cortical network in the perception of auditory temporal regularity and highlight an important role played by motor areas in this process.

Other neuroimaging work has highlighted the role of the motor system in processing temporal information at the sub-second timescale, which is relevant because beat perception takes place at this timescale. A review of the neuroimaging literature on time perception suggests that motor areas are uniquely involved in 'automatic timing', which the authors describe as timing on a sub-second scale, when the stimulus is continuous (repeating in some predictable way; Lewis and Miall, 2003). In one study that supports this view, participants made judgements about the duration of an interval that was either preceded by an isochronous sequence or a jittered sequence, supposedly tapping into distinct timing systems (Teki et al., 2011). Different brain areas were active based on the preceding sequence, with several motor areas (SMA, PMC, striatum) showing increased activity during trials when the isochronous sequence was presented. In another study, participants listened to rhythms at a sub-second (600 ms inter-beat interval) and supra-second (1500 ms) tempo (McAuley, Henry, Tkach, 2012). When participants heard rhythms at the sub-second tempo (one that induces beat perception more strongly) compared to the supra-second tempo, SMA, PMC, and basal ganglia were more active. These studies suggest that motor areas respond to auditory sequence regularities at small, usually sub-second intervals. These findings may correspond to the temporal limits of sensorimotor synchronization discussed earlier and demonstrate the overlap between time perception at sub-second scales and the perception of regularity.

1.3 Changes in motor activity over time

To understand motor involvement in regularity perception, researchers have examined how motor activity changes as a function of time. This research has largely been pursued using electrophysiological methods, which allow for detection of changes in electrical activity (and thus neural activity) at a high temporal resolution. Using intracranial electrodes, researchers have recorded local field potentials from the SMA in Rhesus monkeys while they internally maintain an isochronous visual metronome at various tempi (Cadena-Valencia et al., 2018). Rhythmic bursts of gamma band activity (30-40 Hz neural oscillations) corresponded to the tempo of the isochronous stimulus. Additionally, the frequency of gamma band fluctuations predicted whether the monkeys would make the correct or incorrect temporal judgements in the task, strongly suggesting that gamma band activity in the SMA represented an internal timer. In addition, populations of neurons in the monkey pre-SMA and SMA show periodic activation patterns (Gamez et al., 2019). While these studies provide valuable insight into how the activity in motor areas changes over time, the same question is more difficult to answer non-invasively in humans.

In humans, non-invasive techniques such as MEG are used to detect changes in large populations of neurons with high temporal resolution. One study found that beta-band activity in participants' brains fluctuated periodically in a way that corresponded to the tempo of the isochronous sequence that they listened to (Fujioka et al., 2012). The power in the beta band decreased after each tone at a uniform rate, regardless of tempo, but subsequently increased at a tempo-dependent rate, returning to peak power at the same point relative to the tone. Using source localization, it was discovered that signals originated from motor areas including the SMA and sensorimotor cortex, in addition to auditory areas. These findings suggest that activity in motor areas is modulated periodically, at the stimulus frequency, when people listen to an isochronous sequence.

1.4 Changes in motor excitability over time

Transcranial magnetic stimulation (TMS) provides another time-sensitive measure of motor excitability when applied to the primary motor cortex. The TMS pulse elicits a

muscle response, known as a motor evoked potential or MEP, the amplitude of which indexes excitability of the motor system. When listening to rhythms that convey a strong sense of beat, motor excitability is higher just preceding beat positions (100 ms earlier than the beat position) than at randomly sampled other points in the sequence (Cameron et al., 2012). These findings suggest that motor excitability fluctuates over the time course of a rhythm, with higher excitability just prior to beat positions and lower excitability between beat positions. Several follow-up studies attempting to characterize these fluctuations have showed mixed results. In one study, participants were stimulated at several time points just prior to the beat position in the rhythm (Wu et al., 2015). No change in MEP amplitude was observed across the various time points. In another study, participants listened to isochronous sequences of varying tempi while they were stimulated at various time points relative to the two tones that defined the inter-onset interval (Czajka et al., 2017). Linear and cosine fits were made to the elicited MEPs across the inter-onset interval but these fits were not significant, thus providing no evidence for motor excitability fluctuations that were time-locked to the isochronous tones. Lastly, a study with a similar design was conducted using metrical rhythms. Cosine fits at the beat rate fit the MEP data better than fits at twice and four times the beat rate (Teselink et al., 2017). However, this effect was only present in metrically complex rhythms, in which the beat is less salient, but not in metrically simple rhythms, which have a clear beat. The authors suggested that perhaps the internal generation of the beat was stronger in the complex than simple rhythms, to compensate for the beat being less clear in the stimulus, and that this internal generation may have increased the excitability of motor areas.

1.5 Present study

The aim of the present study is to determine whether motor excitability fluctuates when humans listen to and generate an isochronous sequence, and to characterize this response. While a similar previous study using isochronous sequences returned null results (Czajka et al., 2017), it is possible that these sequences were too simple, and participants did not need to engage enough for a change in motor excitability to be detectable. The sequences consisted of identical tones presented over a long duration (30 to 40 second trials), which

may have caused the participants to disengage. Additionally, participants passively listened, and did not perform a task, which may also have contributed to disengagement. Because complex rhythms seemed to show a trend toward eliciting periodic fluctuations in excitability (Tesselink et al., 2017), internal generation may engage the motor system more than passively listening to regular sequences.

The current study addresses the limitations of previous studies by using an isochronous stimulus that is more engaging and adding a task requirement that would encourage internal generation of the stimulus. The stimulus was an isochronous sequence with tones of varying pitch, to add hierarchical structure to the sequence and thus aid in feeling the pulse, and a silent 'time-keeping' period to promote internal generation of a beat (Manning & Schutz, 2013). The position of the final tone was varied in time and participants were required to make judgements about whether the final tone was on-beat or off-beat. In addition to the listening task performed during TMS stimulation, an offline synchronization-continuation tapping task was included to measure participants' ability to perceive and generate regularity, such that we could determine whether tapping performance and motor excitability were related.

Participants performed the task while the primary motor cortex was stimulated using TMS. Over the course of the experiment, stimulation was administered at 600 time points, equally distributed across six intervals of the sequence. Three of these intervals were audible (bounded by audible tones) while three were silent (bounded by imagined tones), thus requiring internal generation from the participants. MEP amplitudes were then concatenated to create a single time series across the six intervals and periodicity of the signal was quantified using cosine fits at various frequencies.

We hypothesized that motor excitability would fluctuate periodically in response to the isochronous rhythm. In line with this hypothesis, we predicted that a cosine model at the stimulus frequency would fit to changes in motor excitability better than cosine models at unrelated frequencies. We also hypothesized that motor excitability would fluctuate at a higher amplitude during internal generation than during passive listening, thus predicting that the amplitude of fit of cosine models would be higher for the silent 'timekeeping'

portion of the rhythm than the audible portion. Lastly, we hypothesized that behavioural performance would be better for individuals whose motor excitability fluctuated in a more periodic fashion. This relationship would be indexed by a correlation between behavioural performance on the synchronization portion of the tapping task and cosine fits to the audible portion of the isochronous sequence, as well as a correlation between performance on the continuation portion with cosine fits to the silent portion of the sequence.

Chapter 2

2 Materials and Methods

2.1 Participants

Fifty-four healthy participants were recruited for the study. A TMS screening questionnaire based on published safety regulations (Rossi et al., 2009) was used. Participants were excluded from participating if they met any of the following criteria: claustrophobia, pacemakers or other electronic implants, metallic implants, welders or soldiers, injured by a metallic object that was not removed, pregnant or trying to conceive, cerebral aneurysm clips, a history of neurological, psychiatric, heart or lung disease, epilepsy or a history of seizures, use of psychotropic medication, and migraines or susceptibility to headaches. Of the 54 adults recruited, 30 did not complete the study (lack of reliable MEPs, detailed in next section) and the data from 2 participants was unusable due to technical issues. Thus, data collected from the 22 participants (mean age: 25.6, range: 18 – 64, 14 females) was analyzed in the study. We also conducted exploratory analyses to determine whether musicianship influences our measures. For musicianship analyses, participants were divided into musicians (those with 5 or more years of experience playing an instrument) and non-musicians (fewer than 5 years of experience). This split resulted in 10 musicians and 12 non-musicians.

2.2 TMS and EMG recordings

Single-pulse TMS was delivered to the scalp using a 70 mm figure-of-eight coil connected to a Magstim Rapid 2 stimulator (Magstim, Whitland, UK). To ensure consistency in placement of the coil, a standard template structural MRI scan was calibrated to each participant's head using BrainSight software (Rogue Research, Montreal, Canada). Infrared markers on BrainSight goggles tracked participants' head movements while infrared markers on the coil tracked coil position relative to the head. To record EMG, disposable Ag/AgCl electrodes were placed on the first dorsal interosseus (FDI) muscle of the right hand, while a ground electrode was placed on the styloid process of the right ulna. The EMG signal was sampled at 1000 Hz, amplified

1000 times, band-passed between 30 and 1000 Hz, and line-filtered. One-second sweeps of EMG activity (triggered by the TMS pulse) were recorded and peak-to-peak MEP amplitude quantified using Signal (CED, Cambridge, UK) and Matlab software (Matlab, Natick, USA). The motor hotspot, which is the location of the coil on the scalp that elicited maximal FDI muscle response, was determined by varying the location of the coil (starting 5 cm left of the vertex, and 1 cm anterior) and observing responses (while keeping intensity constant) until the coil location that led to the largest response was determined. Coil position at the motor hotspot was then marked and targeted on the BrainSight software as a coordinate in three-dimensional space and maintained for the duration of the experiment. Resting motor threshold was defined as the intensity at which at least 50% of MEPs (5 out of 10) were above the threshold value (100 uV) based on previous work (Rossini et al., 1994). For 30 participants, testing was discontinued either because a motor hotspot could not be found or the MEP amplitude at near-threshold intensities was highly variable (on the order of millivolts of difference in peak to peak amplitude). During the subsequent tasks, participants were stimulated at 110% of their respective resting motor threshold intensity.

2.3 Motor imagery and synchronization-continuation tasks

To validate whether motor system excitability reliably altered MEP amplitude with our equipment set-up, MEPs were measured during a motor imagery task. The motor imagery task always occurred after the synchronization/continuation task. MEP amplitude was measured in two separate blocks: one rest block and one motor imagery block (adapted from Kasai et al., 1997). For each block, 10 TMS pulses were delivered. Pulses were delivered with an inter-pulse interval of 6 seconds and each block took approximately 1 minute to complete. The order of the rest and imagery blocks was counterbalanced across participants. During the rest block, participants were instructed to remain still and focus on the crosshairs on the computer screen. During the motor imagery block, participants visualized moving their FDI muscle. Previous studies find that motor imagery reliably increases MEP amplitudes compared to rest (Kasai et al., 1997, Fadiga et al., 1999, Tomassino et al., 2008), therefore we expected to observe similar increases during

imagery compared to rest. The MEP amplitudes from the imagery and rest blocks were compared using a paired-samples t test.

Prior to the start of the experimental task, participants completed a synchronization/continuation task (Fig. 1). The task was included in the study to assess beat perception and production abilities, using a sequence with the same features as the sequence used in the experimental task. The sequence consisted of 50-ms isochronous tones, with an inter-onset interval (IOI) of 400 ms. The first of each group of 4 tones was 522 Hz, and the other tones were 392 Hz, implying a hierarchical structure to aid with beat tracking, as intended in the study from which the experimental task was adapted (Manning & Schutz, 2013). For each trial, there was a synchronization portion of 11.2 seconds, during which 28 tones were heard, directly followed by a continuation portion of 11.2 seconds, during which no tones were played. Participants were instructed to tap along to the sequence as soon as they were able to during the synchronization portion, and to continue tapping at the same rate during the continuation portion, until the end of the trial. The coefficient of variation (CoV; a measure of the variance in inter-tap interval) was calculated ($SD_{IOI}/Mean_{IOI}$) separately for synchronization and continuation (herein referred to as $CoV_{synchronization}$ and $CoV_{continuation}$, respectively) and compared using a paired-samples t test.

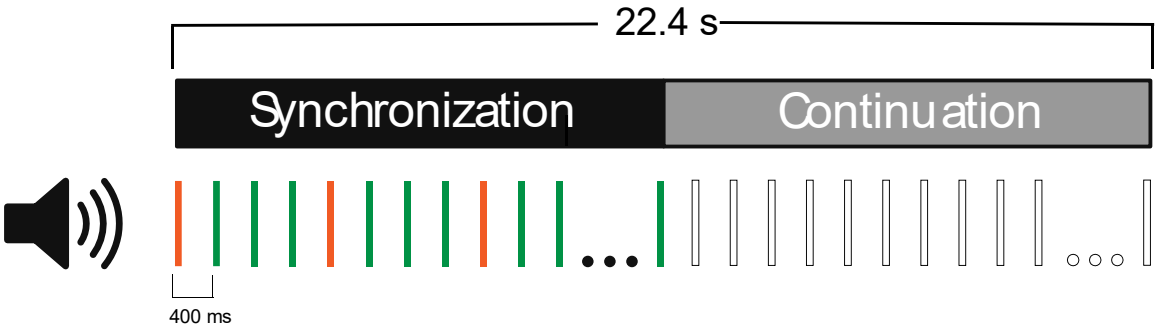


Figure 1: Schematic diagram of synchronization-continuation task. The filled bars represent isochronous tones (400 ms IOI) while the empty bars represent the continuation of the 400-ms timing of the intervals during silence. Orange bars represent accented tones while green bars represent unaccented tones. During the continuation portion, participants

were instructed to continue tapping at the same rate as the synchronization portion, but in the absence of sound.

2.4 Experimental task

During the experimental task, participants listened to an isochronous sequence while single pulse TMS was delivered to their primary motor cortices (M1), eliciting MEPs. The auditory sequence, modified from Manning & Schutz (2013), consisted of 10 isochronous tones (duration: 50 ms) with an inter-onset interval (IOI) of 400 ms (Fig. 2A). Herein, the word 'tone' refers to an auditory event lasting 50 ms, and 'interval' refers to the period after the onset of a tone and before the onset of the next tone. Like the sequence in the synchronization/continuation task, the first of each group of 4 tones was accented (by raising the frequency of the tone: 522 Hz; unaccented tones: 392 Hz) to imply a hierarchical structure in the sequence. After the 9th tone (i.e. 8 intervals), there was a silent, or 'time-keeping' period that lasted the duration of 4 intervals (1.6 s). During this time-keeping period, participants were asked to imagine the continuation of the sequence, internally generating the beat. The purpose of the time-keeping interval was to encourage participants to internally generate the sequence, enabling us to measure whether fluctuations in excitability differed between perceiving an external beat and generating an internal one. The time-keeping period was followed by a final 'probe' tone which either occurred at the beat position (where it would have occurred had the 3 tones of the sequence continued through the time-keeping period) or at one of two off-beat positions: 160 ms earlier or later than the beat position. On each trial, participants were asked to judge whether the probe tone was on-beat or off-beat. A visual representation of the sequence can be found in Figure 2B. One-third of the trials contained an on-beat probe tone, while two-thirds of the trials contained off-beat probe tones – a third each of early and late tones. Participants were not informed of the chance of the probe tone being on- versus off-beat. Participants completed 600 trials of the task divided into 5 blocks. Each block spanned 120 trials, and participants were given breaks between blocks to rest and recover. Visual feedback indicating whether their responses were correct appeared on the screen immediately after their response to each trial.

A single TMS pulse was delivered during each trial at a pseudorandomly selected timepoint during one of the last 6 intervals of the sequence. MATLAB was used to pre-program the timing of the TMS pulses across trials such that, over the entire experiment, 600 timepoints were sampled once. The sampled timepoints were spaced 4-ms apart, and one timepoint was selected for pulse delivery on each trial. This resulted in a cumulative resolution of 100 pulses/400-ms interval (across the 600 pulses delivered over the entire experiment), which translated to an effective resolution of 250 Hz (average inter-pulse interval of 4 ms). Due to a Gaussian jitter in the TMS system, pulses were not always delivered exactly when they were programmed to be delivered. This Gaussian jitter had a standard deviation of 3 ms. To account for the jitter and ensure that MEP readings reflected excitability at the correct timepoints, the sound of the TMS pulses was recorded using Apple earbuds (Apple, Cupertino, USA) on Audacity software (Audacity®). The isochronous tones were concurrently recorded using a loop cable connected to an external sound card (Steinberg UR22mkII; Steinberg, Hamburg, Germany). Post-hoc analyses show that TMS pulses were jittered as expected, with an average duration of 4 ms between adjacent pulses.

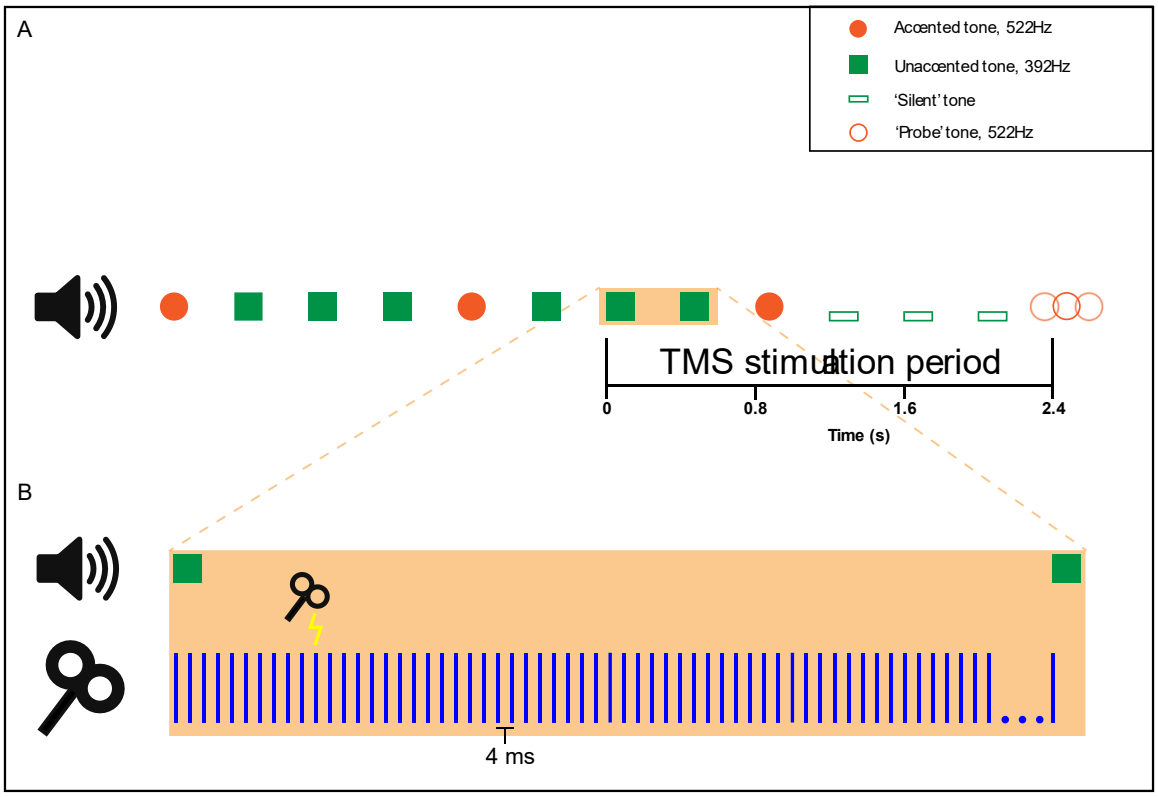


Figure 2: Schematic diagram of the experimental task and timing of TMS pulses. A) is a visual representation of a single trial. Orange circles represent accented tones, green squares represent unaccented tones, empty green rectangles represent silent 'tones', and the empty orange circles represent the possible positions that the final probe tone could occur (160 ms 'early', on time, or 160 ms 'late'). A single TMS pulse was delivered during the TMS stimulation period (during one of the last six intervals of the sequence). B) A visual representation of the potential timepoints of stimulation (blue lines) in a sample interval. An example position for one TMS pulse in a given trial is denoted by the small coil and yellow bolt above it. By the end of the experiment, 100 pulses had been delivered within each of the last 6 intervals, for a total of 600 pulses over the final 6 intervals. Pulse times accumulated over the experiment resulted in an effective sampling rate of 250 Hz (pulses 4 ms apart).

2.5 Data analysis

Motor excitability was quantified by calculating the peak-to-peak amplitude of the measured MEPs (indexed as EMG activity between 20 and 40 ms following the delivery

of the TMS pulse). Thus, each TMS pulse and the corresponding MEP gave a measure of motor excitability at one time point during the final six intervals of the temporal sequence (shown in the 'TMS stimulation period' in Figure 2). The time course of motor excitability over the six intervals was constructed for each participant from the peak MEP amplitudes acquired at each timepoint. The beginning of the time course coincided with the onset of the 7^{th} tone of the sequence (the beginning of the final six intervals) and continued for 2.4 s, to the end of the sequence. Thus, for each participant, when the MEPs at each timepoint (spaced on average every 4 ms) were concatenated, a 2.4-second timecourse of MEP amplitudes was obtained, representing motor excitability during the last 6 intervals of the isochronous sequence. This raw MEP data was then smoothed using a sliding Gaussian kernel (width: 80 milliseconds) to remove high frequency noise. The smoothing algorithm acted as a low pass filter, smoothing over high frequency fluctuations in the raw data.

To test the primary hypothesis that motor excitability fluctuated at the rate of the auditory isochronous sequence, we used a curve-fitting approach. Cosine waves of varying frequencies (0.05 Hz to 25 Hz in intervals of 0.05 Hz) were fit to the smoothed data while optimizing for phase and amplitude, and a goodness of fit (R^2) value was obtained for each frequency. To statistically test whether peaks in the frequency spectrum were the result of time-dependent relationships in the data rather than noise, a permutation test was used. For each permutation, a participant's raw MEP data was scrambled by randomly shuffling the MEP amplitude data points along the time axis. Then, the raw data was smoothed, and the smoothed data was curve fitted in the same manner as for the real (non-permuted) data, resulting in an R^2 value for each permutation. Following 10,000 permutations, a null exponential distribution of R^2 scores was created. The p-value for the observed R^2 was determined relative to the null distribution for each participant. To average across the group, each participant's z-score was calculated based on their p-value. An average z-score was calculated for the group and converted back into a p-value. This procedure was done for one curve-fitting frequency at a time. In addition to predicting that excitability would fluctuate at the sequence rate, we predicted that excitability would be higher at beat positions and lower between beats. To investigate this, we obtained phase information of the best fitting sinusoid at the stimulus frequency

for each participant and plotted these phases on a circular phase plot to allow for detection of any patterns in phase concentration. For example, if the phase of motor excitability fluctuations is consistently related to the tones, there would be a high concentration of phases in one part of the circular plots. Alternatively, if the phase is inconsistent, the phase data points would be spread out across the plot.

Differences between listening to the tones and internally generating the tones were explored by dividing the excitability time course over the six intervals into two halves. The first half consisted of the time course across the three audible tones and one silent tone (the first three intervals of the 6-interval timecourse). The third of those three intervals was considered part of the 'listening' half because the silence occurred at the very end and processes occurring due to audible isochrony were expected to continue through the interval. The second half consisted of 3 silent tones and the final 'probe' tone (the last three intervals of the 6-interval timecourse). The last interval was considered part of the 'silent' half because internal generation processes were expected to be unaffected by the final tone, save for the possibility of a hazard function (i.e., anticipation of the final tone causing a steady increase in excitability during the entire silent period). MEP data suggests there was no such increase in excitability during the silent period. The same methodology as the full 6-interval sequence curve-fitting was applied to the 3-interval audible and silent halves separately, to determine the statistical significance of time-dependent relationships between the tone sequence and changes in excitability.

To address our secondary hypothesis that the magnitude of excitability was higher during internal generation than listening, we compared the amplitude of fit (the amplitude of the optimized curve-fitting function at the stimulus frequency) between the audible and silent portions. For effect size analyses, Cohen's *d* was used when comparing means and r^2 was used for correlations.

Chapter 3

3 Results

3.1 Motor imagery and synchronization-continuation task

A motor imagery task was used to ensure motor excitability changes were measurable with the equipment set-up. Ten MEPs were collected during rest and ten while participants imagined moving their FDI muscle. MEP amplitude was higher during imagery than rest ($t(21) = 2.84$, $p < 0.05$, $d = 0.84$). Participants also performed a synchronization-continuation task prior to the experimental task to provide a behavioural measure of rhythmic tapping ability (Fig. 3). The coefficient of variance (CoV), a measure of the consistency of tap timing, was higher for continuation than synchronization ($t(21) = 4.36$, $p < 0.05$, $d = 0.75$).

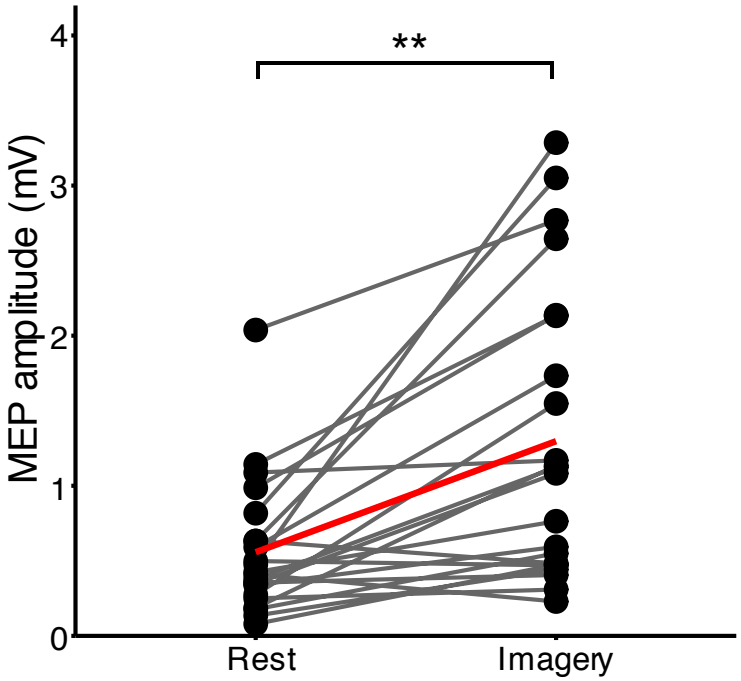


Figure 3: MEP amplitude during rest and imagined movement of the FDI muscle. Condition means are shown in red**,** black dots represent individual amplitudes, and grey lines connect the same individual's data points. The significant difference between the

two conditions indicates that the M1 was being stimulated and participants' excitability changed, as expected, based on the established phenomenon of motor imagery.

3.2 MEP time course concatenation and visualization

During each trial, a single TMS pulse was delivered at a random point during the last 6 intervals of the isochronous sequence. The MEP amplitudes collected across each of the 600 trials (one MEP measurement per trial) were concatenated to produce a linear timecourse over the six intervals. That is, each MEP amplitude was plotted at the time of TMS pulse delivery relative to the isochronous sequence (Fig. 4A). Subsequently, the raw MEP time course was smoothed using a sliding gaussian kernel to remove high frequency fluctuations. The smoothed timecourse (averaged across participants) is shown in Figure 4B.

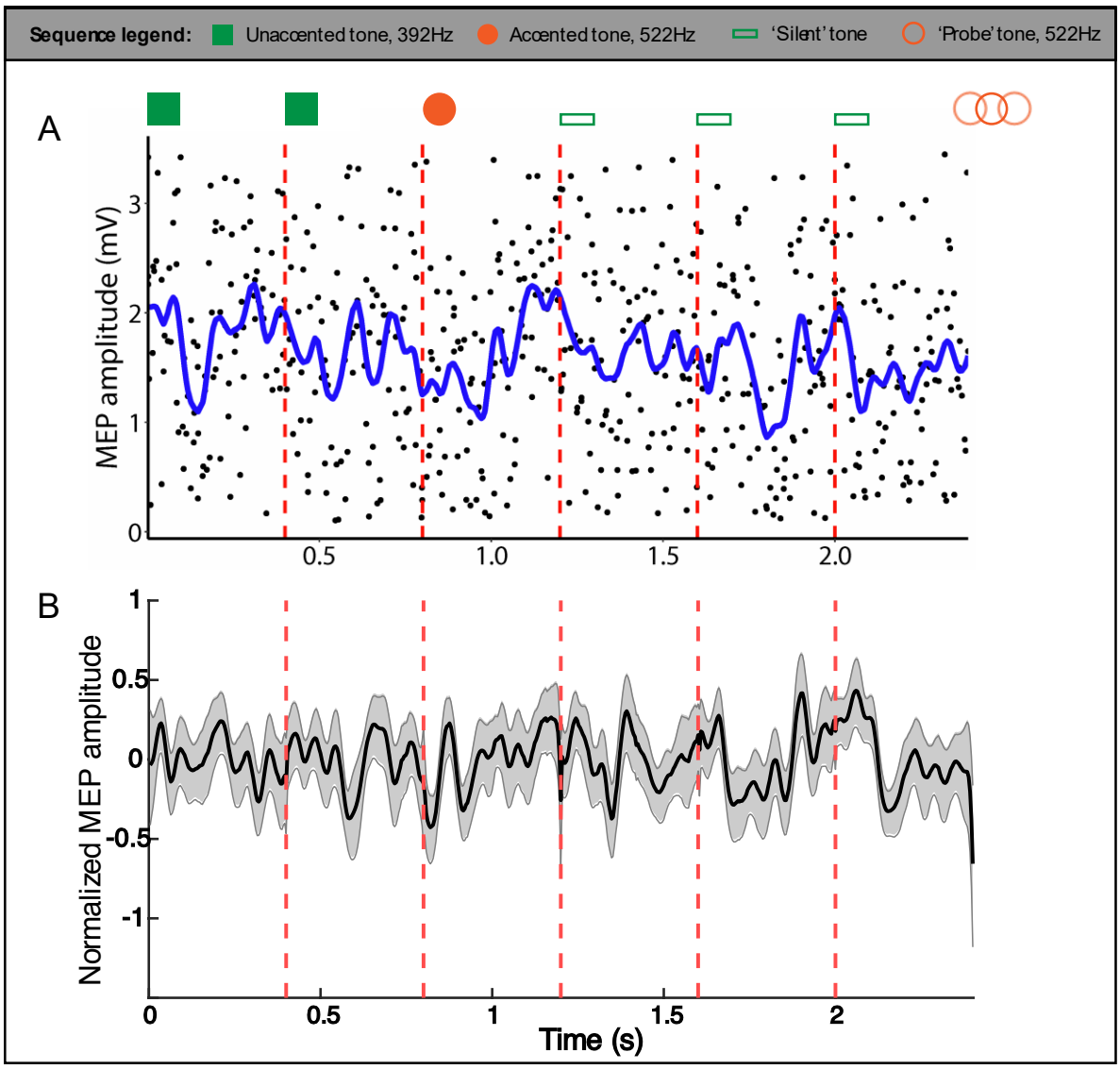
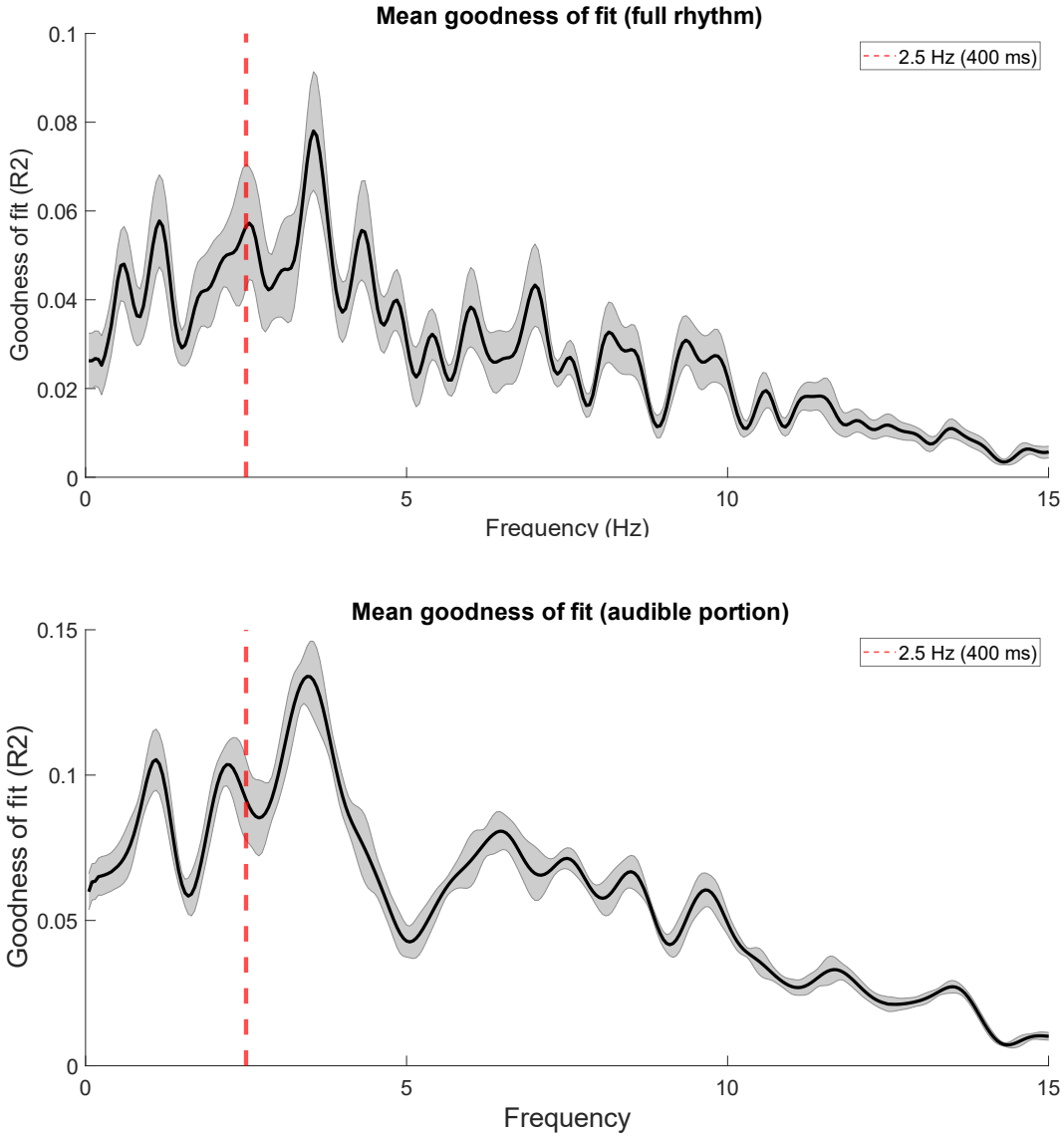


Figure 4: Excitability time course for a single participant and averaged across participants. A) The raw MEP amplitude at each data point (black) as well as the smoothed time course (blue). B) The averaged smoothed time course across participants. Red dashed lines indicate tone positions (sounded during audible portion of trial and imagined during silent portion of the trial). Shaded area represents standard error. Symbols at the top of (A) represent the tone sequence (see Legend at top of figure).

3.3 MEP fluctuations

Fluctuations in MEP amplitude were quantified using a curve-fitting analysis (Fig. 5). The analysis found that the goodness of fit (R^2) at the stimulus frequency (2.5 Hz) was not significantly different from the permuted null distribution (r^2 = 0.06 p = 0.25). Moreover, separate analyses of audible and silent portions of the sequence also found no significance for the goodness of fit at 2.5 Hz ($r^2_{Audible}$ = 0.09, p = 0.33; r^2_{Silent} = 0.13, p = 0.15).



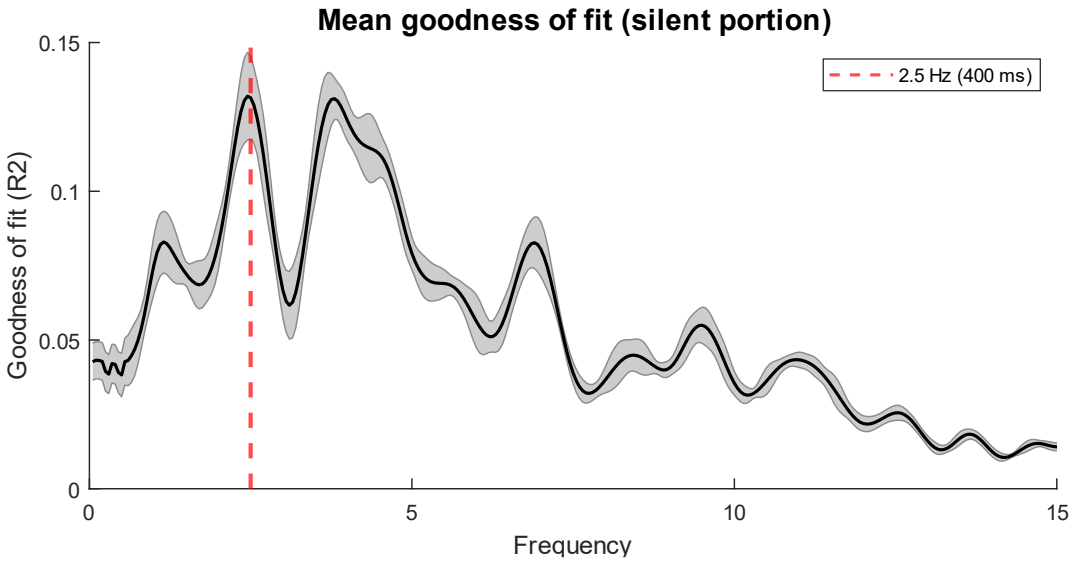


Figure 5: Frequency spectra produced when using a curve-fitting approach. (Top) The full time course (all 6 intervals). (Middle) Only the first half (three intervals—audible portion of trial) of the time course. (Bottom) Only the second half of the time course (three intervals—silent portion of trial).

3.4 Phase of fluctuations

The curve-fitting analysis for quantifying MEP fluctuations automatically optimized for phase, therefore the analyses do not indicate whether there is a consistent relationship between the phase of the MEP amplitude and the stimulus. To examine phase alignment, we plotted the phase for each participant's curve fit at the stimulus frequency (Fig 6). The Rayleigh test of uniformity suggested there was no significant phase concentration ($z = 0.11$, $p = 0.79$), thus no consistent phase relationship between the MEP amplitude fluctuations and the stimulus. Phase was also analyzed for the audible and silent portions separately (Fig 6) and no significance phase concentration was found for audible ($z = 0.24$, $p = 0.29$) or silent portions ($z = 0.09$, $p = 0.83$).

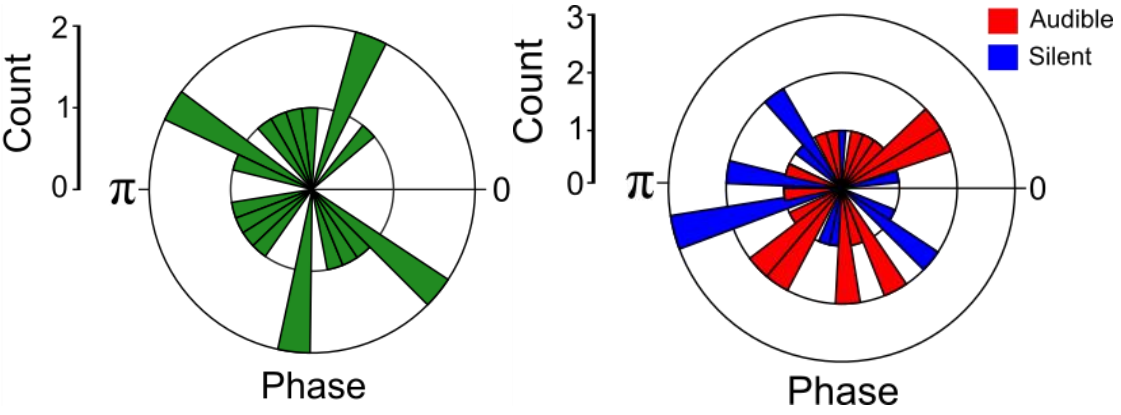


Figure 6: Circular phase plots from curve-fitting data. Left: Distribution of phases from curve-fitting across the whole sequence. Right: Distribution of phases from curve-fitting across audible (red) and silent (blue) portions of the sequence.

3.5 Magnitude of fluctuation

To determine whether the magnitude of excitability fluctuations was higher during internal generation of than listening to the sequence, the amplitude of cosine fit was compared across the audible and silent portions of the sequence (Fig 7). This difference in amplitude was not significant ($t(21) = 1.29$, $p = 0.10$, $d = 0.29$).

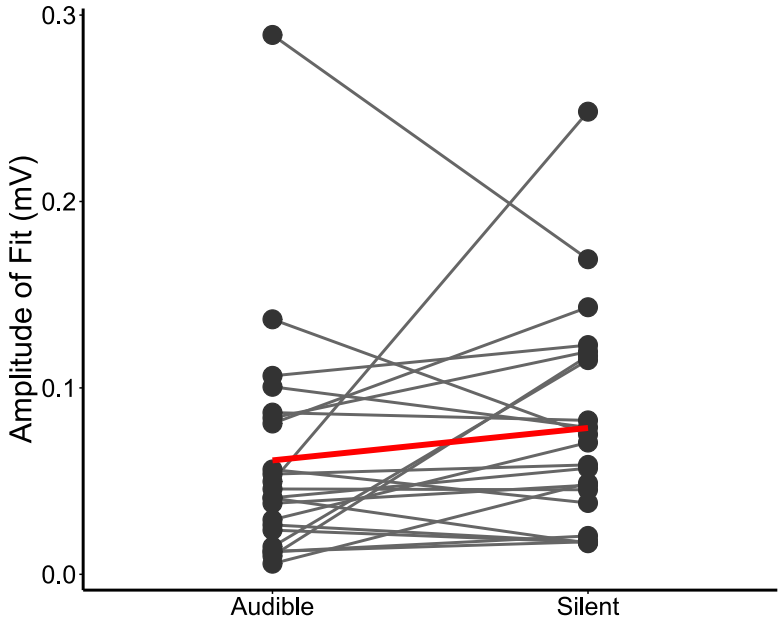


Figure 7: Amplitude of fit across audible and silent portions of the sequence. Values indicate the amplitude of the best fitting curve at the stimulus frequency. Red line indicates group means.

3.6 Correlations between neural data and behavior

We analyzed whether goodness of fit and amplitude of fit at the 2.5 Hz stimulus frequency was linearly correlated with tapping data from the relevant portion of the synchronization-continuation task (Fig 8). That is, goodness and amplitude of fit from the audible portion of the tone sequence were correlated with synchronization tapping performance, and goodness and amplitude of fit from the silent portion were correlated with continuation tapping performance. These the correlations yielded no notable relationship and none of the correlations were significant (goodness of fit audible vs $CoV_{synchronization}$ (r = 0.05, p = 0.88), goodness of fit silent vs $CoV_{continuation}$ (r = -0.04, p = 0.86), amplitude of fit silent vs $CoV_{continuation}$ (r = -0.04, p = 0.87), amplitude of fit audible vs $COV_{synchronization}$(r = 0.14, p = 0.51).

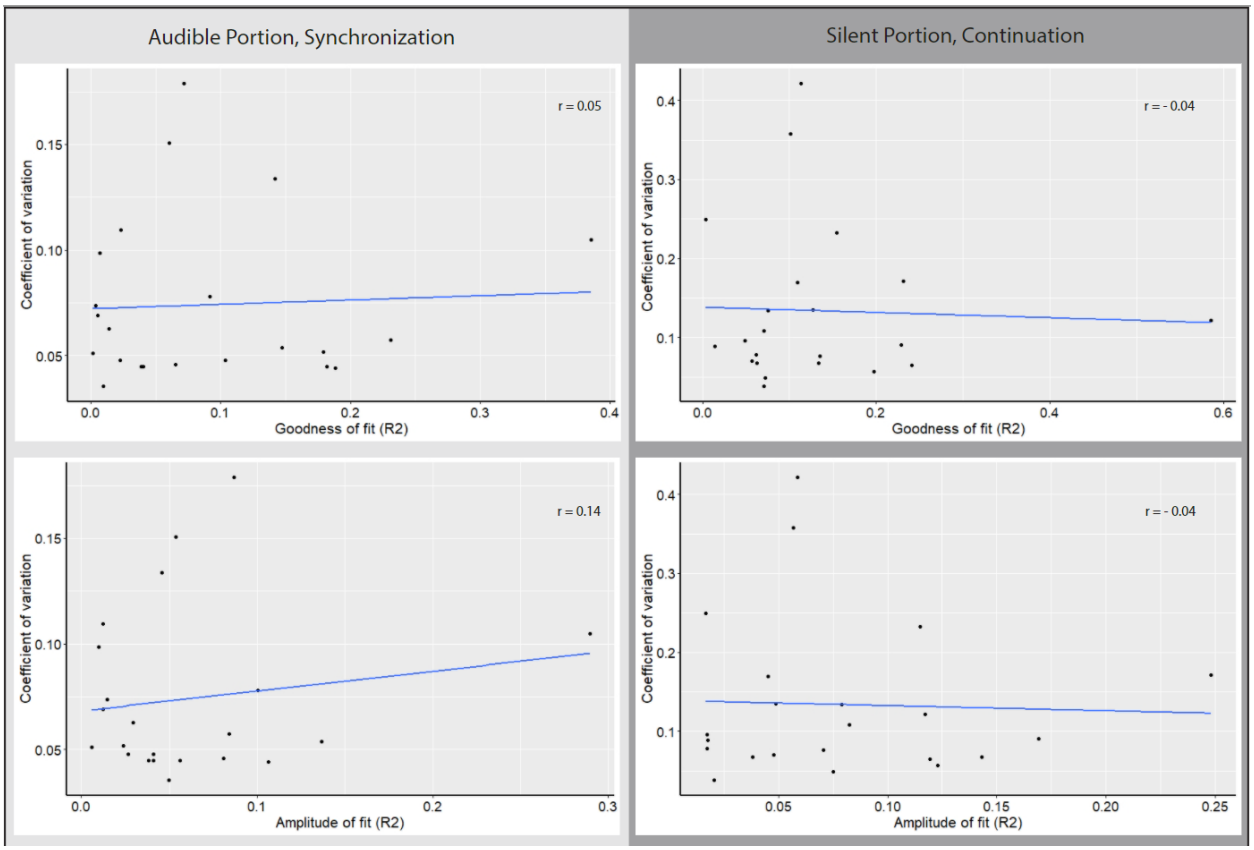


Figure 8: Correlations between tapping data and goodness and amplitude of fit. Participants' tapping performance during the synchronization portion was correlated with measures form the audible portion of the sequence (left), while performance during the continuation portion was correlated with measures from the silent portion of the sequence (right).

3.7 Influence of musicianship

Since musical training and practice may alter neural responses to rhythms, we probed the influence of musicianship on our neural measures (Fig 9). Comparing goodness of fit at the stimulus frequency between musicians and non-musicians yielded no significant differences ($t(21) = 0.01$, $p = 0.99$, $d = 0.07$). Although we did not plan on it a priori, we repeated the same analysis for goodness of fit at 3.6 Hz due to its prominence in comparison to the peak at stimulus frequency. Goodness of fit at 3.6 Hz was significantly higher in non-musicians than musicians ($t(21) = 2.44$, $p = 0.000011$, $d = 1.04$).

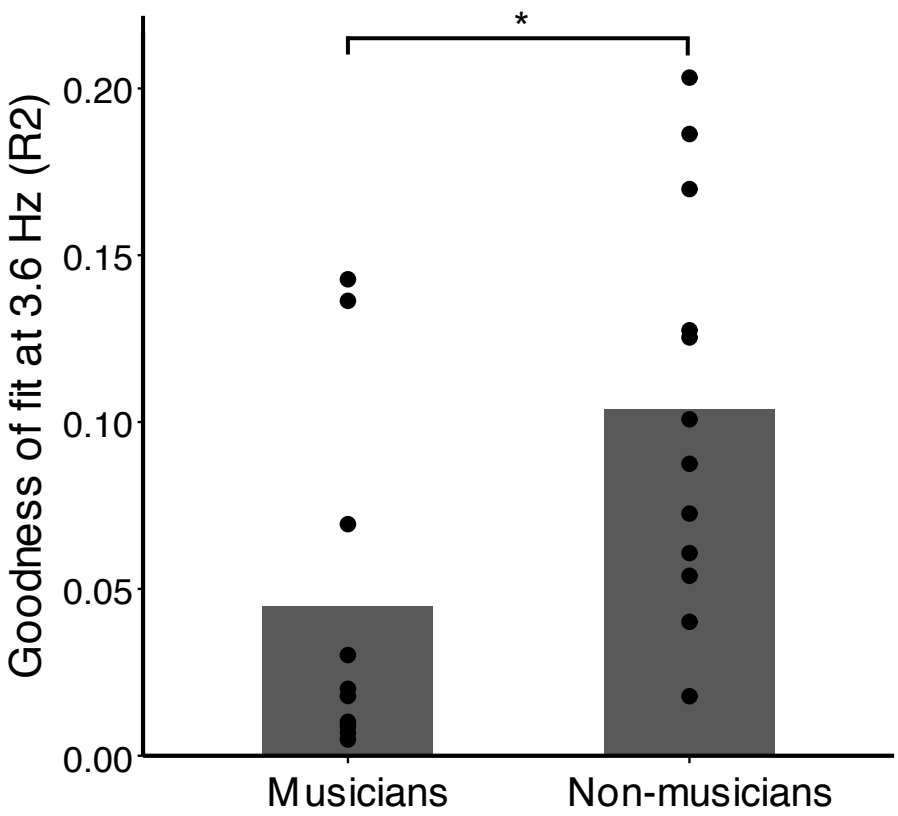


Figure 9: Influence of musicianship on goodness of fit at 3.6 Hz. Error bars indicate standard error. The two groups were significantly different ($p < 0.05$).

Chapter 4

4 Discussion

The aim of the present study was to determine whether motor excitability fluctuates periodically when humans listen to and generate an isochronous sequence, and to characterize these fluctuations if they were present. Contrary to our hypothesis, we did not find sufficient evidence for periodic fluctuations in motor excitability. Specifically, using a permutation test, we found that excitability fluctuations at the stimulus frequency were not statistically significant. Importantly, however, we found distinct and prominent peaks in the curve-fitting frequency spectra, including one at the stimulus frequency. While these peaks were not statistically significant, they may represent a real signal in otherwise noisy data. Thus, part of the discussion is dedicated to exploring potential interpretations of these peaks.

Our secondary hypothesis was that motor excitability would fluctuate at a higher magnitude during internal generation than passive listening. We investigated this by comparing the amplitude of fit (the amplitude of the best-fitting cosine function) across the audible and silent portions of the isochronous sequence. We found no difference between the amplitudes of fit, suggesting that the magnitude of fluctuation was comparable across internal generation and listening. Lastly, we found no correlation between our measures of interest (goodness of fit and amplitude of fit at stimulus frequency) and performance on the tapping task.

4.1 Prominent peaks in frequency spectra

Our analysis indicated that excitability fluctuations at the stimulus frequency were not statistically significant. Notably, we ensured that meaningful changes in motor excitability could be detected using our apparatus by collecting MEPs during rest and while participants imagined moving the target muscle. Congruent with previous studies, we found that MEP amplitudes were indeed significantly higher during motor imagery than rest, indicating that the overall setup was adequate to detect motor excitability

changes, and supporting that the other excitability-related findings are credible (Kasai et al., 1997, Tomassino et al., 2008).

The lack of evidence for periodic fluctuations in motor excitability, while not a direct contradiction, stands in contrast to the findings of previous research, which suggests the presence of such fluctuations (Fujioka et al., 2012). The previous study found evidence of modulations in beta band activity in time with isochronous sequences. However, the relationship between beta band activity and motor excitability is unclear and more research into that relationship is needed to reconcile the results of the two studies. Alternatively, the lack of statistical significance in our study could be due to noise. While acknowledging the validity of statistical significance, we feel it is important to address the consistent presence of three peaks in the frequency spectra, one of which occurs at the stimulus frequency. The argument for the potential legitimacy of these peaks is rooted in the high level of noise in the data. In the present study, due to the constraints of the experiment design and available technology, participants were only stimulated once per trial. In addition, because of testing limitations brough about by COVID-19 lockdown, only 22 participants were tested, and no follow-up studies were possible. Previous research shows that a variety of factors can affect motor excitability (e.g. postural demands or properties of sound being heard; Tokuno et al., 2009; Michaelis et al., 2014). Thus, while a signal that reflects excitability in time with the tone sequence should be detectable across trials, we would also expect a variable amount of noise in the measurement of each data point from neural phenomena during a given trial. Due to the noisy nature of the data and the exploratory nature of this study, it may be worthwhile to discuss the properties of the statistically non-significant peaks in the frequency spectra.

Three prominent peaks appear consistently across the analysis of the excitability time course as a whole, and in separate analyses of the audible and silent halves separately. These peaks occur at roughly the following frequencies: 1 – 1.2 Hz, 2.25 – 2.5 Hz, and 3.45 – 3.8 Hz (herein referred to as $P_{1.2}$, $P_{2.5}$, and $P_{3.6}$ respectively). $P_{1.2}$ is the earliest peak and may be a harmonic frequency of 2.5 Hz, the stimulus frequency. $P_{2.5}$ is the most compelling of these peaks as it occurs at the stimulus frequency. Interestingly, this peak occurs at a lower frequency (2.25 Hz) in the audible-only spectrum. If $P_{2.5}$ does

correspond to a real fluctuation present in motor excitability, this shift to a lower frequency could indicate some feature of auditory-motor interactions in the brain. Also of note is that $P_{2.5}$ is the most prominent peak in only the silent portion. Since the prominence of a peak in this data corresponds to the goodness of fit, this finding may suggest that oscillations at the stimulus frequency are greater during internal generation than during listening. This could suggest that the motor system is more involved in maintaining an internal representation of the tone sequence during silence than while listening to it.

$P_{3.6}$ is the most prominent of the peaks in 2 of the 3 spectra (in the third, silence-only spectrum, P3.6 is only marginally smaller than $P_{2.5}$). Similar to $P_{2.5}$, this peak occurs at its earliest (3.45 Hz) in the audible-only spectrum. $P_{3.6}$ is not a harmonic or half-harmonic of the stimulus frequency, or of $P_{2.5}$ when it occurs outside of the stimulus frequency. Due to its prominence in all of the spectra, we think this peak may correspond to an oscillatory process that is related to perceiving regularity. We also found that non-musicians had significantly higher $P_{3.6}$ values than musicians, which may be relevant to investigating this peak further. Finally, it is possible that this value arises from the equipment or apparatus used to record the MEPs (e.g., some type of electrical noise). However, since the observed peaks are analyzed in a way that is time-locked to the stimulus, it is difficult to speculate about what type of apparatus issues could arise that would give rise to a periodicity that was systematically related to the stimulus. Thus, any explanation of $P_{3.6}$ at this point is speculative and more data are needed to form a meaningful hypothesis.

A future study could address whether the different peaks are indeed related to motor system excitability in response to the stimuli, or from the equipment itself, by using a design that replicates the present study but with a different stimulus tempo. Equipment-related noise should stay at a constant frequency regardless of stimulus tempo, whereas peaks to stimulus-related motor excitability changes should shift with stimulus tempo. By assessing how the motor excitability frequency spectra change with increasing and decreasing stimulus tempo, it can be determined whether $P_{3.6}$ (and the other peaks) are tempo-dependent or not. Based on the current study, the prediction would be that $P_{1.2}$ and

$P_{2.5}$ would shift with stimulus tempo, but that, as $P_{3.6}$ is unrelated to stimulus tempo in the current study, it might remain the same across stimulus tempos.

4.2 Magnitude and phase of fluctuation

The magnitude of fluctuations, as indexed by amplitude of fit, was similar across the audible and silent portions of the sequence. This is contrary to the hypothesis that magnitude of fluctuations would be higher during internal generation than listening. This hypothesis was based on previous work (Teselink et al., 2017), which found that amplitude of fit was higher at the beat rate than unrelated rates when people listened to complex metrical rhythms. In comparison to simple metrical rhythms, complex rhythms elicit a weaker sense of beat and thus require more engagement from the listener to maintain the beat percept. Thus, we had hypothesized that greater engagement of the motor system would be apparent in the greater magnitude of fluctuations during internal generation. However, the results suggest that either the motor system was not more engaged during internal generation or that greater engagement of the motor system may not translate to a greater magnitude of fluctuation, but instead, may translate to greater prominence of goodness-of-fit peaks, as the engagement could increase the ratio of signal to noise.

The phase of fluctuation varied widely across individuals with no evidence of phase concentration. While we did not directly hypothesize about phase relationships, the assumption implicit in our primary hypothesis was that phase relative to the stimulus would align across individuals. Specifically, we expected that excitability would be higher at the beat position and lower between beats across people. The lack of phase concentration in the presence of oscillatory activity is inconsistent with previous research, which reported higher motor excitability at beat positions compared to random positions (Cameron et al., 2012). Several key differences may account for this inconsistency. First, previous work recorded from lower leg muscles whereas we recorded from a hand muscle. While we expect motor excitability changes to be measurable at multiple effector sites, perhaps it is easier to detect in larger muscles or muscles that are often used to keep

time in music, such as the lower leg muscles (e.g., tapping your feet or dancing). Additionally, previous work used metrical rhythms containing a strong beat, which could be utilizing a distinct mechanism from the one underlying detection of regularity in isochrony. In fact, many of the studies that implicate the motor system in perceiving regularity use metrical rhythms (Grahn & Brett, 2007; Chen et al., 2008; Grahn, 2009). Moderately complex rhythmic stimuli may increase involvement of the motor system. This is supported by behavioural work that shows medium rhythmic complexity increase feelings of wanting to move (Witek et al., 2014). An increased desire to move may translate to a more robust and more detectable response at the motor cortex.

We did not find evidence of correlations between goodness of fit and tapping performance or amplitude of fit and tapping performance. As expected, participants tapped more consistently (i.e., with less variable taps) during synchronization than during continuation. However, despite these expected findings, there was no relationship between synchronization or continuation performance and the excitability measures used in this study. This suggests that tapping performance may not be linearly related to motor excitability fluctuations. While this is a surprising finding, it may be that performance is related to features of motor excitability changes that we didn't measure (e.g., rate of excitability decay following a peak, time between excitability minima and maxima etc.). Alternatively, perhaps differences in performance cannot be reliably detected via MEPs induced by TMS at the level of the primary motor cortex. For instance, timing information could be encoded in upstream regions such as the SMA and communicated with the motor cortex temporally. In this case, the signal being sent to the motor cortex would be identical for two performers, but this signal would arrive at the motor cortex at a different time (relative to the tone or beat) for each performer. Thus, patterns of excitability fluctuations could be identical across a good and bad performer, but the timing of the signal and the related behavioural output could differ. Lastly, it's possible that motor excitability is modulated in distinct ways across groups of people. For instance, a previous study found that excitability was maximally modulated close to peoples' spontaneous motor tempo (the tempo that individuals naturally produce when asked to tap 'at a rate that is most comfortable for them'). Moreover, the direction of this modulation (whether their excitability increased or decreased) differed for two subgroups

within the participant pool (Michaelis et al., 2014). That is, one group's excitability increased close to their spontaneous motor tempo while another group's excitability decreased closer to their tempo. These findings suggest that patterns of motor excitability differ across people, which could explain the lack of correlation between behaviour and excitability measures in the present study.

4.3 Limitations

One major limitation of the present study is the poor signal to noise ratio. This limitation can be overcome in the future by increasing the resolution of the MEP time course. Due to time constraints (the experiment was close to two hours after setup, which was quite demanding for participants), this would be most easily accomplished by stimulating across a smaller number of intervals. The present study investigated the presence of motor excitability fluctuations over the span of 6 intervals. Future studies could focus on just the audible or just the silent intervals and double their resolution. Another potential method for improving the signal to noise ratio is to stimulate participants while they hold a certain level of contraction (for instance, 10% of maximum voluntary contraction), which may reduce noise in the MEPs. However, this method may have some limitations of its own since holding a contraction at a set level would require attention and visual processes (attending to the EMG feedback) that may interfere with the auditory task.

Another limitation of this study is the lack of monitoring of muscles other than the target muscle. While participants were instructed to not move during the task trials, they could have been automatically contracting certain muscles in time with the tone sequence. Contraction of other muscles could lead to changes in motor excitability and variable levels of contraction across participants could be a confound. In fact, even voluntary breathing has been shown to affect motor excitability (Li et al., 2011). One way to address this limitation is to place EMG electrodes on several muscles and compare participants' background EMG activity to their MEP amplitudes to determine whether they correlate.

In addition to the above limitations, the equipment and the protocol used also presented some technical challenges that should be addressed, where possible, in future studies.

While we used BrainSight software to mark the hotspot and tried to hold the coil steady through the experiment, there was no way to confirm the coil was on the same position on the scalp afterwards. We attempted to address this shortcoming by assessing whether MEP amplitudes changed over the course of the experiment (i.e., in chronological time) and determined that they did not. In the future, software where tracking of pulses is possible and the coil position is automatized (rather than a human holding it) would help with coil drift. Another challenging aspect to the protocol was the heating of the coil. Due to the lengthy run-time of the experiment, the coil would often start heating up. This limited our ability to stimulate at a higher than a particular stimulation intensity (approximately 60% of maximum intensity). Coils with cooling technology or the ability to switch out multiple coils would address this issue.

4.4 Summary

In summary, the present study did not find reliable evidence of periodic fluctuations in motor excitability in response to an isochronous sequence. Additionally, there was no evidence of a difference in the magnitude of excitability fluctuation between listening to and maintaining an internal representation of the sequence. Goodness of fit of the frequency spectra suggest the existence of peaks at the stimulus frequency, but also at two other frequencies. Due to the noisy measure used, these peaks (or some of them) may correspond to a real and meaningful signal and warrant further study.

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Appendix

Appendix A: Ethics approval

Western Research

Date: 14 June 2020

To: Dr. Jessica Grahn

Project ID: 103860

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

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 16/Jun/2020

Date Approval Issued: 14/Jun/2020

REB Approval Expiry Date: 24/Jun/2021

Dear Dr. Jessica Grahn,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Curriculum Vitae

Name:	Syed Raza
Post-secondary Education and Degrees:	Brock University (Neuroscience, Honours) St. Catharines, Ontario 2013-2018 B.Sc.
	The University of Western Ontario (Neuroscience) London, Ontario, Canada 2018-present M.Sc.
Honours and Awards:	NSERC Undergraduate Research Award 2017
	NSERC Canada Graduate Scholarship – Master's 2019-2020
Related Work Experience	Teaching Assistant The University of Western Ontario 2018-2020

Publications:

Reischl, S. A., **Raza, S. Z.,** Adkin, A. L., Patterson, J. T., Tokuno, C. D. (2019). Examining changes in corticospinal excitability and balance performance in response to social-comparative feedback. *Gait and Posture*, 73, 14-19.