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# **A causal involvement of the left supramarginal gyrus during the retention of musical pitches**

Nora K. Schaal<sup>1,2</sup>, Victoria J. Williamson<sup>3,4</sup>, Maria Kelly<sup>2</sup>, Neil G. Muggleton<sup>2,5,6</sup>, Bettina Pollok<sup>7</sup>,  
Vanessa Krause<sup>7</sup>, Michael J. Banissy<sup>2,6</sup>

1. Department of Experimental Psychology, Heinrich-Heine-University, 40225 Düsseldorf, Germany
2. Department of Psychology, Goldsmiths, University of London, SE14 6NW, London, UK
3. Lucerne University of Applied Sciences and Arts, 6003 Lucerne, Switzerland
4. Department of Music, University of Sheffield, S3 7RA, Sheffield, UK
5. Brain and Behavior Laboratory, Institute of Cognitive Neuroscience, National Central University, Jhongli 320, Taiwan
6. Institute of Cognitive Neuroscience, University College London, London, UK
7. Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

Running Head: Left SMG and pitch memory

## Corresponding Author:

Nora K. Schaal  
Heinrich-Heine-University Düsseldorf  
Department of Experimental Psychology  
Universitätsstraße 1  
40225 Düsseldorf  
Telephone: +49 211 81 13863  
Fax: +49 211 81 13490  
Email: [nora.schaal@uni-duesseldorf.de](mailto:nora.schaal@uni-duesseldorf.de)

## **Abstract**

Brain stimulation studies have previously demonstrated a causal link between general pitch memory processes and activity within the left supramarginal gyrus (SMG). Building on this evidence, the present study tested the impact of left SMG stimulation on two distinct pitch memory phases, retention and encoding. Repetitive transcranial magnetic stimulation (rTMS) was employed during the retention stage (Experiment 1) and the encoding phase (Experiment 2) of a pitch recognition task. Stimulation was applied on a trial-by-trial basis over the left SMG (target site) or the Vertex (control site). A block without TMS was also completed. In Experiment 1, rTMS over the left SMG during pitch retention lead to significantly increased reaction times compared to control conditions. In Experiment 2 no rTMS modulation effects were found during encoding. Experiment 3 was conducted as a control for non-specific stimulation effects; no effects were found when rTMS was applied over the left SMG at the two different time points during a perceptual task. Taken together, these findings highlight a phase-specific involvement of the left SMG only for the retention phase of pitch memory, thereby indicating that the left SMG is involved in the maintenance of pitch information.

Keywords:

Pitch memory, transcranial magnetic stimulation, retention, left supramarginal gyrus

## **1. Introduction**

Functional brain imaging studies of pitch memory have revealed the involvement of a complex neural system in parietal, temporal and frontal areas (e.g. Koelsch et al., 2009). One area that is consistent across studies is activation in the left supramarginal gyrus (SMG) (Gaab et al., 2003; Ellis et al., 2013). Recently, studies using transcranial direct current stimulation (tDCS) have implied that the left SMG is causally involved in pitch memory processes (Vines et al., 2006; Schaal et al., 2013). Suppressing left SMG function using cathodal tDCS leads to a deterioration in pitch recognition ability (Vines et al., 2006), while increasing left SMG excitability with anodal tDCS results in a facilitation of pitch memory (Schaal et al., 2013). In combination, these studies provide evidence that left SMG activity is important for the output of pitch memory, but the exact role of the left SMG in the pitch memory process remains unknown.

Another issue with previous work is that tDCS provides a relatively large window in which cortical excitability within a brain region can be modulated. In this regard, it is not clear whether the left SMG plays a causal role throughout the pitch memory process or in specific phases. Two major time-specific phases of pitch memory are of interest to the present study: encoding and retention. In the encoding phase, new pitch information is perceived and the tones are encoded in relative relationships with each other, whereas in the retention interval this same information is maintained and rehearsed. Schulze et al. (2011) showed that encoding and retention in auditory memory rely on dissociable brain activations.

Transcranial magnetic stimulation (TMS) is a method better suited for investigating a phase-specific involvement of the left SMG in pitch memory. This method enables a spatially and temporally precise modulation of neural mechanisms on a trial-by-trial basis (Walsh & Cowey, 2000). For example, 5Hz repetitive TMS (rTMS) over the precuneus has been shown to interfere with a visual working memory task differently when applied in the retention interval or during the re-presentation of the recognition probe (Luber et al., 2007). This

finding demonstrates the effective use of TMS for interfering with the time-specific stages of a memory process.

Here, we used rTMS to examine the causal role of the left SMG at different time-specific stages of the pitch memory process (retention and encoding), by adopting a similar phase-specific stimulation design to Luber et al. (2007). In Experiment 1, we examined the role of the left SMG in the retention phase of pitch memory. In Experiment 2, we focused on the encoding phase. In both experiments, participants completed a pitch memory recognition task, where they heard two six-tone long pitch sequences and judged whether they were the same or different (a protocol adapted from Williamson & Stewart, 2010). Participants completed this task under three stimulation condition: rTMS over the left SMG; rTMS over the Vertex (active control site); no TMS. The onset of stimulation was varied between each experiment with rTMS being applied either during the retention phase (after hearing the first sequence) or during the encoding phase (while hearing the first sequence). Finally, a control experiment was conducted to test for non-specific disruption effects of rTMS. In Experiment 3, participants completed a perceptual task while rTMS was applied over the left SMG at the two time points used in Experiments 1 and 2. In summary, the only disruptive effect was found for rTMS over the left SMG during the retention phase of a pitch memory task. This finding indicates that the left SMG is causally involved in the ongoing maintenance of pitch information in memory.

## **2. Experiment 1 and 2**

## 2.1 Experiment 1 and 2 Methods

### *2.1.1 Participants*

27 participants took part with a mean age of 27.22 years (S.D.  $\pm$  6.51, range 18-38 years). 13 (seven female) subjects participated in Experiment 1, and 14 (eight female) in Experiment 2. Participants were all non-musicians (less than two years of musical training in the past, not playing an instrument at present) and right-handed (see Table 1 for demographical details). The study was approved by the ethics committee of Goldsmiths, University of London and participants gave informed written consent.

To evaluate musical training, the Musical Training Dimension from the Goldsmiths Musical Sophistication Index (Gold-MSI, Müllensiefen et al., 2014) was used. This Gold MSI dimension is comprised of 7 items that assess an individual's musical training and practice habits. The participant is asked to rank the items on a seven-point agreement scale, giving a possible score range of between 7 and 49 points. The mean score from our sample was 10.9 points, confirming that they had little or no musical training in the past.

### *2.1.2 Materials*

A pitch memory recognition task was created, modeled on the pitch memory span task (Williamson and Stewart, 2010) that was used in one of our previous brain stimulation studies (Schaal et al., 2013). The task parameters were adjusted to match the TMS parameters.

80 pairs of six tone long pitch sequences were created. In 40 trials the two sequences were the same (same tones in identical order) and 40 were different (same tones in both sequences but in the latter sequence two tones were in reversed order). All sequences were created from a pool of 10 triangle-waveform tones (equally tempered, whole tone steps) with fundamental pitches ranging from 262 Hz (C4) to 741 Hz (F#5). Tones were 350 ms long, with a 150 ms pause at the end of each tone, so in total each sequence was 3 seconds long.

In order to create the pitch sequences, the tones were randomly sampled with the restriction that beginning and end tones were counterbalanced. There were no direct repetitions of a tone and adjacent tones were at least two whole tones apart. In the different trials, we counterbalanced for the position of the two reversed tones as well as the size of their tone interval.

Each trial consisted of two sequences (either same or different) with an inter-sequence interval of 3 seconds. The sequence length of six tones was chosen as previous studies have shown that non-musicians have a mean capacity score of six tones on the related pitch memory span task (Williamson & Stewart, 2010; Schaal et al., 2013). A pilot study with 12 participants confirmed that sequences were at the desired level of difficulty (Mean: 74.5 % correct).

As three blocks were required for the TMS procedure, three blocks of 24 trials (12 same, 12 different) were created, leaving 8 trials for a practice block. The three blocks were matched for difficulty based on the results of the first pilot test. A second pilot test was then conducted, with 10 novel participants who completed the blocks in counterbalanced order and confirmed that all three blocks were of equal difficulty (mean scores: 71.3%, 74.5%, 70.0%).

### *2.1.3 TMS protocol*

TMS was applied by a figure of eight shaped coil (70 mm diameter) using a Magstim Super Rapid Stimulator (Magstim Co., UK). The Stimulator was set to 60% intensity of the maximum stimulator output as this level has been shown to be the average intensity for individual motor thresholds in previous studies (e.g. Pitcher et al., 2008; Tseng et al., 2010). rTMS was applied for every trial and a rTMS train lasted 3 seconds at 5 Hz (15 pulses). The coil was placed either over the targeted area, the left SMG or the vertex. The vertex was included as a control site in order to control non-specific effects such as tactile and auditory sensations. The left SMG was located using CP3 of the 10-20 system for electrode placement,

which has been shown to be a reliable method to identify this brain region (Mottaghy et al, 2002; Schaal et al., in press). The vertex was identified as the middle of the head, by measuring the point equidistant between the inion and nasion as well as the left and right intertragal notches.

The coil was placed above the stimulation site (left SMG or vertex) throughout the trials and the correct localization was checked constantly between trials. On every trial (24 trials per block; two blocks with active stimulation) 3 second long rTMS was applied in the retention interval (starting as soon as the first sequence finished playing and ending with the onset of the second sequence; Experiment 1) or encoding interval (rTMS is triggered with the onset and duration of the first sequence; Experiment 2) of the trial.

#### *2.1.4 Procedure*

Experiments 1 and 2 used a within-subject design. The order of blocks (block 1, 2 and 3) as well as the order of stimulation (no TMS, rTMS over the left SMG and rTMS over the Vertex) were counterbalanced.

To begin with the participants completed the practice phase of the pitch recognition task. In every trial two six-tone long sequences were played through speakers at a comfortable listening level and the participant indicated by button press whether the sequences were the same or different. They were instructed to use their index and middle finger of their right hand to press “1” for same and “2” for different. Participants heard a burst of pink noise after each trial to minimize carry over effects (Figure 1 details the exact procedure). Instructions were given on screen and participants were asked to respond as accurately and quickly as possible. After completing the practice phase, the two stimulation sites, the left SMG and the Vertex, were marked on the participant’s scalp. Finally, before beginning the experiment, one test trial of 3 seconds of 5 Hz rTMS was applied to each site of stimulation, in order to check that the

participant was fine with the experience of rTMS. The participants all reported that the perceptual sensations for both stimulation sites were the same.

Participants were instructed to concentrate on the sequences they heard and to ignore the TMS pulses as far as possible. Instructions were given on screen, the coil was placed according to the stimulation condition and the first block began, containing 24 trials. After completing one block (with a short pause in the middle to exchange coils), a five minute break was taken before starting the next block. After participants completed all three blocks, they filled in the Musical Training questionnaire. In Experiment 1 rTMS was applied during the retention phase of each trial and in Experiment 2 rTMS was applied during encoding phase of the first pitch sequence.

## 2.2 Experiment 1 and 2 Results

Median reaction times for correct trials were calculated, as well as percent correct and  $d'$  scores for the analysis of accuracy. The data from percent correct and the  $d'$  score analysis revealed the same pattern, so only the analysis from the more sensitive measure of  $d'$  scores are reported in the following results section.

For the statistical analysis, three outliers were excluded from the sample. One participant had reaction times more than four standard deviations above the group mean and two participants had accuracy scores below chance in at least one block, indicating that they did not meet the task demands.

### *2.2.1 Reaction Time Analyses*

For Experiment 1, a repeated measure ANOVA was conducted with *stimulation condition* (rTMS over left SMG vs rTMS over Vertex vs no TMS) as the within-subject factor and reaction times as the dependent variable. This analysis revealed a main effect of *stimulation condition* [ $F_{(2, 22)} = 6.50, p = .006, \eta_p^2 = .371$ ]. Contrasts revealed that the reaction

times obtained during rTMS over the left SMG were significantly slower than reaction times when rTMS was over the Vertex [ $F_{(1, 11)} = 21.66, p = .001, \eta_p^2 = .663$ ] and also significantly slower than no TMS performance [ $F_{(1, 11)} = 5.10, p = .045, \eta_p^2 = .317$ ]. In sum, the results indicated that stimulation over the left SMG significantly disrupted the reaction times for the retention phase of pitch memory (Figure 1).

For Experiment 2, the same repeated measure ANOVA was conducted. Unlike Experiment 1, there was no main effect of *stimulation condition* for reaction times [ $F_{(2, 22)} = 1.33, p = .285, \eta_p^2 = .108$ ]. When applying rTMS during encoding of the pitch sequence in the memory process, no differences were found (Figure 1).

Finally, a post-hoc analysis across the two experiments was conducted. A mixed ANOVA on reaction times with *stimulation condition* as the within-subject factor and *experiment* (Experiment 1 vs Experiment 2) as the between-subject factor, revealed a significant *stimulation condition\*experiment* interaction [ $F_{2, 44} = 6.83, p = .003, \eta_p^2 = .237$ ], confirming the differential involvement of the left SMG during the retention and encoding phases of pitch memory.

### 2.2.2 Accuracy Analyses

For Experiments 1 and 2, two separate repeated measure ANOVAs were conducted with *stimulation condition* (3) as the within-subject factor and accuracy measured by  $d'$ . No significant differences were found in Experiment 1 [ $F_{(2, 22)} = .68, p = .519, \eta_p^2 = .058$ ] or Experiment 2 [ $F_{(2, 22)} = .19, p = .832, \eta_p^2 = .017$ ] (Figure 2).

## **3. Experiment 3**

The findings from Experiment 1 and 2 suggest a phase-specific disruption by modulation of the left SMG during the retention but not encoding phase of pitch memory. However, it remained possible that this effect may be due to a non-specific modulation of motor performance. The left SMG has been reported to be involved in the process of motor attention (Rushworth et al., 2001) and, given the spatial distance between the left SMG and the motor cortex, one might posit that the results of Experiment 1 could result from an interference with motor responses. To address this possibility, we conducted a control experiment in which rTMS was applied either late (reflecting the timing of the stimulation during retention) or early (timing of the encoding interference) while participants completed a perceptual task (“is the last tone higher or lower than the second to last tone?”) in which memory demands were minimal.

### 3.1 Experiment 3 Methods

#### *3.1.1 Participants*

Twelve participants (seven female) with a mean age of 23.92 years (S.D.  $\pm$  2.19, range 20-27 years) took part in Experiment 3. They were all non-musicians (less than two years of musical training in the past, not playing an instrument at present) with a mean of 0.58 years of musical training and a mean Gold-MSI score of 10.5 (table 1, see section 2.1.1 for information about the Gold-MSI questionnaire). The ethics committee of the Medical Department of the Heinrich-Heine-University in Düsseldorf approved this study and participants gave informed written consent.

#### *3.1.2 Materials*

The same six-tone long sequences were used. Experiment 3 also consisted of three experimental blocks and a practice block. Only the second sequence of every sequence pair was used for the perceptual task in Experiment 3. The three blocks (24 trials each) all consisted of 12 trials where the last tone compared to the second to last tone was higher and 12 trials where it was lower.

### 3.1.3 TMS protocol

The TMS parameters were the same as those reported in Experiment 1 and 2. The timeline for the TMS application was identical even though in Experiment 3 no first sequence was played. The 3 seconds long rTMS trains were either applied 3 seconds before the tone sequence (*late* condition) or 6 seconds before the tone sequence (*early* condition). A block without rTMS was also included. Stimulation was applied over the left SMG.

### 3.1.4. Procedure

Participants completed three blocks of the perceptual task as part of the within subject design. The order of blocks (block 1, 2 and 3) as well as the order of stimulation (no TMS, *late* rTMS over the left SMG and *early* rTMS over the left SMG) were counterbalanced.

Before the experiment, participants completed a practice block of the perception task. After a 6 second long pause (in which rTMS was applied at two different time points in the experimental blocks) a six-tone sequence was played and participants were asked to judge whether the last tone was higher or lower than the second to last tone. As in the first two experiments, participants were asked to give their response as accurately and quickly as possible using their index and middle finger of their right hand and the keys “1” for “lower” and “2” for “higher. Participants heard a burst of pink noise between every trial to minimize carry-over effects.

After the practice block, the location corresponding to the left SMG was marked on the participants scalp and a test train of TMS was applied over the left SMG in order to make participants familiar with the sensation of the stimulation before starting the actual task and to ensure that they were fine with TMS.

Participants then completed the three experimental blocks. The procedure was the same as that reported in Experiment 1 and 2, except that the task was perceptual in nature and not a memory task. Stimulation was applied according to the stimulation condition either *late* (3 seconds before the tone sequence) or *early* (6 seconds before the tone sequence) over the left SMG. After completing all three blocks, participants filled in the German version of the Gold-MSI questionnaire (Schaal et al., 2014).

## 3.2. Experiment 3 Results

### *3.2.1 Reaction Time Analysis*

The group mean reaction times for the block without stimulation were 440.54 ms (S.D.  $\pm$  186.09), for the early rTMS condition 448.67 ms (S.D.  $\pm$  191.91) and for the late rTMS condition 423.08 ms (S.D.  $\pm$ 207.65).

A repeated measure ANOVA with *stimulation condition* (late rTMS vs early rTMS vs no TMS) as the within subject factor and median reaction times as the dependent factor revealed no main effect of *stimulation condition* [ $F_{(2,22)} = .363, p = .699, \eta_p^2 = .032$ ]. rTMS over the left SMG at the late (reflecting the time point of the retention interval) or early (reflecting the encoding phase) time point did not affect reaction times during the perception task compared to no TMS.

### *3.2.2 Accuracy Analysis*

The mean  $d'$  scores, reflecting the accuracy performance, for the block without TMS were 1.60 (S.D.  $\pm 0.71$ ), for the early rTMS condition 1.55 (S.D.  $\pm 0.75$ ) and the late rTMS condition 1.30 (S.D.  $\pm 0.52$ ).

A repeated measures ANOVA with *stimulation condition* (3) as the within factor and  $d'$  scores was conducted and also showed no main effect of *stimulation condition* [ $F_{(2,22)} = 1.67, p = .21, \eta_p^2 = .132$ ]. The analysis showed no effects of stimulation condition on accuracy performance.

#### **4. Discussion**

This study sought to investigate the causal role of the left SMG across different time-specific stages of pitch memory processing. Using a non-invasive brain stimulation method (rTMS), we disrupted the pitch memory process during the retention (Experiment 1) and encoding (Experiment 2) phases of a recognition pitch memory paradigm. In both cases, stimulation over the left SMG was compared to performance without stimulation as well as stimulation over the Vertex (control site). The results showed that only rTMS over the left SMG during retention resulted in a significant increase in reaction times, therefore supporting the theory that the left SMG is causally involved in the ongoing maintenance of pitch information in memory. A third experiment confirmed that rTMS over the left SMG at the two stimulation time points of Experiment 1 and 2 (late and early) did not have an effect on motor responses to a perceptual task; thus our findings from Experiment 1 cannot be explained by a non-specific modulation of the motor cortex or motor attention. Taken together, our three experiments support the critical involvement of the left SMG during retention of pitch information in memory.

The increase in reaction times when rTMS was applied over the left SMG in the retention phase supports previous tDCS evidence showing that pitch memory can be modulated following anodal or cathodal stimulation over the left SMG (Vines et al., 2006; Schaal et al., 2013). Our findings extend this prior work by showing that modulating neural activity in the left SMG leads to a phase-specific shift in the retention, but not the encoding phase of the pitch memory processes. Several previous studies have postulated that the left SMG is involved in pitch memory retention (Sakurai et al., 1998; Gaab et al., 2003; Vines et al., 2006), but we provide the first casual evidence for the specific role of the left SMG in the ongoing maintenance of pitch traces as opposed to earlier encoding processes.

The present study is a step forwards in investigating neural distinctions of the auditory memory system for the different stages of memory processing (encoding, retention), a largely unexplored field. Previous non-invasive brain stimulation studies using tDCS have revealed causal relationships between targeted areas and pitch memory (Vines et al., 2006; Schaal et al., 2013) and pitch discrimination (Mathys et al., 2010), but few have used non-invasive brain stimulation to probe how different stages of processing may be influenced by cortical modulation. One rare TMS study on melodic pitch perception investigated the effect of off-line TMS (stimulation before the task) on melody discrimination and found significant modulation effects of 10Hz rTMS targeted over the right Heschl's Gyrus (Andoh & Zatorre, 2011), a region associated with melody perception (Zatorre & Belin, 2001). This finding, alongside the present study, corroborates the idea that TMS is an effective tool for investigating the causal involvement of brain areas in pitch processing.

The involvement of the left SMG for the retention phase in memory has also been shown by Romero et al. (2006), who investigated the causal involvement of left parietal areas (Brodmann's areas 44 and 40, the latter is comparable with the location of the left SMG) for verbal short-term memory. They showed that rTMS, applied during the retention phase over the targeted areas (compared to the Vertex), affected phonological judgments. This finding is

also in accordance with other studies that have reported SMG activation during tonal and verbal rehearsal (Schulze et al., 2012) using fMRI, and which have demonstrated involvement of the SMG in phonological processing and reading tasks using TMS (Celsis et al., 1999; Hartwigsen et al., 2010; Stoeckel et al., 2009). In this context, one may suggest the left SMG plays a modality general role in auditory memory retention. It will be important for future studies to examine this directly.

There is some debate with regards to the lateralization of neural activity relating to pitch memory. Imm et al. (2008) applied single-pulse TMS at different time points (ranging between 250 ms and 800 ms after stimulus onset) over the dorsolateral prefrontal and inferior parietal regions. They found that during the pitch task reaction times increased when stimulation was applied over the *right* inferior parietal site for all time points and for the audio-verbal condition only single-pulse TMS at 450ms over the left inferior parietal cortex increased reaction times (Imm et al., 2008). These results contribute to the understanding of how specialized neural mechanisms may be involved in different auditory domains. But with reference to our study, it should be noted that the parietal site targeted by Imm et al., (2008) was more posterior to the SMG and also that the working memory task used by Imm et al., (2008) has different, more complex demands compared to the pitch memory tasks used in our study. The selective hemispheric involvement of the SMG in our results is more comparable to the pitch memory recognition tasks that have been shown to be left laterised (Gaab et al., 2003; Vines et al., 2006). Furthermore, a tDCS study from our laboratory (Schaal et al., in press) revealed that only cathodal stimulation over the left SMG but not the right SMG led to a deterioration of pitch memory performance.

A broader caveat related to TMS studies relates to the choice of active control site, which in our study was the Vertex (based on the common use of this region in visual and auditory domains; e.g. Romero et al., 2006; Pitcher et al., 2008; Andoh & Schlaug, 2013; Banissy et al., 2010). The choice of an active control sites is frequently contentious and there

is the possibility that the Vertex may produce less superficial scalp effects relative to left SMG stimulation. However, if superficial effects of TMS caused the slower reaction times reported in Experiment 1 then we would expect a similar effect in Experiment 2. As this was not the case, it is unlikely that the results reported in Experiment 1 are due to non-specific general effects of TMS. Additionally, we acknowledge that using the 10-20 system for electrode placement is not the most precise method to localise the left SMG. This method is commonly used for targeting brain areas in brain stimulation studies (e.g. Gallace et al., 2014; Imm et al., 2008; Schaal et al., in press) even though brain imaging guided targeting would be desirable in future studies to optimise the precision of TMS.

A further broader issue raised by our study relates to the constraints of the relative modest sample sizes used in TMS experiments. Moreover, here we tested 12-14 participants in each experiment, which is commensurate with the majority of TMS experiments in the literature. Although commensurate with other work, this does place limitations on the ability to detect small effects that may also be of theoretical interest. In this regard, it is worth mentioning that on a descriptive level our data hints at two interesting potential effects: firstly, in Experiment 1 the  $d'$  scores are also the lowest when stimulation was applied over the left SMG and secondly, the reaction times in Experiment 2 are decreased when rTMS was applied during encoding. It can be hypothesized that these potential effects, which would have strengthened our hypothesis, would reach significance if sample size and subsequently power would have been enlarged. It seems pertinent to note the issue about modest sample sizes in TMS experiments and to highlight this as an important area for wider consideration in the TMS community.

In conclusion the present study demonstrates a causal role for the left SMG in the retention phase of pitch memory. In doing so, the finding broadens our knowledge regarding the involvement of the left SMG in the pitch memory process: only rTMS during the retention phase of the pitch sequence recognition task, and not encoding, modulated performance. This

result confirms that the left SMG is selectively involved in the ongoing maintenance of pitch information in memory and offers avenues for future investigations on this topic.

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## Legends

### **Table 1**

Demographical details of participants for Experiments 1, 2 and 3

### **Figure 1**

Timing of a single trial for Experiments 1 and 2. In Experiment 1, 5 Hz rTMS was applied during the retention period and in Experiment 2, rTMS was applied during encoding of the first sequence.

### **Figure 2**

**A** Bargraphs representing the median reaction time scores for all three blocks for Experiment 1 (left) and Experiment 2 (right). rTMS over the left SMG during the retention period (experiment 1) lead to a significant increase in reaction times. No modulating effects could be found when applying rTMS during encoding (experiment 2). The error bars represent SEM.  
\*\*  $p = .002$ , \*  $p = .046$

**B** Bargraphs representing the accuracy scores ( $d'$ ) for all three blocks for Experiment 1 (left) and Experiment 2 (right). No significant effects of stimulation condition were seen. The error bars represent SEM.

**Table 1**

	N	Age	Gold-MSI-Score	Musical Training
Experiment 1	13 (7f/6m)	26.2 years	12.2	0.77 years
Experiment 2	14 (8f/6m)	28.2 years	9.5	0.32 years
Experiment 3	12 (7f/5m)	23.9 years	10.5	0.58 years

Figure 1

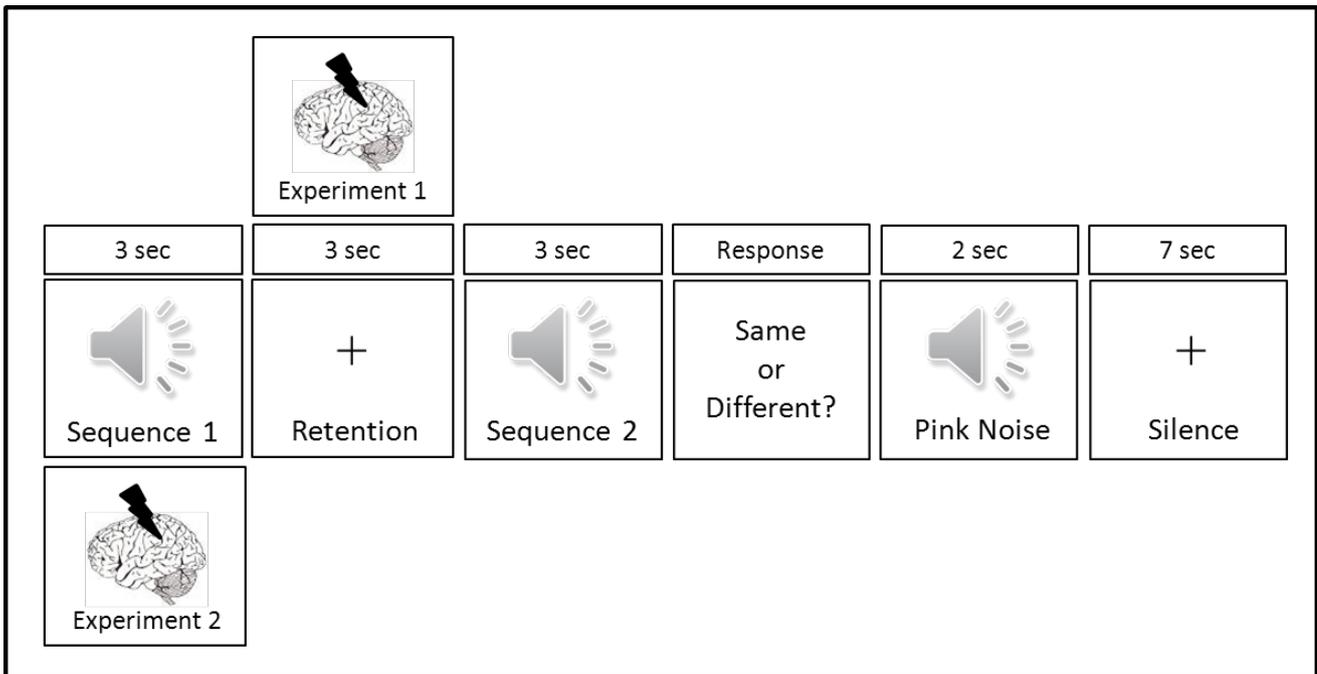


Figure 2

