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Modulation of Tactile Discrimination by Transcranial Magnetic Stimulation

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Abstract

Modulation of Tactile Discrimination by Transcranial Magnetic Stimulation

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Sensory features such as frequency of the vibrotactile stimulus are differently encoded in primary (S1) and secondary (S2) somatosensory cortices. Even though many human studies using functional magnetic resonance imaging (fMRI) or electrocorticography (ECoG) have found the general synchronization of brain activity or high frequency oscillatory activities associated with the vibrotactile perception, the activities of the multiple oscillatory bands in two somatosensory cortices and their functional roles still remain to be investigated. Therefore, in the current study, we aimed to demonstrate the effects of triple TMS pulses over S1 or S2 on tactile performance as well as on neural activity. In addition, we verified the different contribution of S1 and S2 to processing the frequency of vibrotactile stimulus.

In two alternative forced choice task, 53 healthy participants were asked to determine whether the deviant stimulus has a higher ratio of low (32 Hz) or high (350 Hz) frequency relative to the standard stimulus. The deviant stimulus was pseudo-randomly chosen from 7 different combinations of low and high frequency (99:1, 75:25, 60:40, 50:50, 40:60, 25:75 and 1:99) and the standard stimulus was 50:50 (X:Y means the ratio of low frequency to high frequency). At the same moment of the deviant stimulus presentation, the TMS was applied over a scalp site corresponding to contralateral S1 or contralateral S2 in each session. Further, neural activities were recorded for 25 participants with concurrent TMS-EEG system during the whole task.

Behaviorally, the effects of the triple TMS pulses are different depending on the frequency ratio of the tactile stimulus. TMS had no changes or improved the performance discriminating the low-frequency dominant stimulus whereas it significantly decreased the accuracy of discriminating the high-frequency dominant stimulus. The modulations of TMS over S2 were greater than that of TMS over S1 as high-frequency ratio increased. In terms of neural activities, reduction in delta band (1 ~ 3 Hz) was observed in common after TMS over S1 and S2, but it was more apparent in S2 stimulation. Additionally, TMS to S2 inhibited the activity of theta bands (4 ~ 7 Hz). Taken together, our results demonstrate that the triple TMS pulses can influence the perception during the discrimination task by modulating the certain neural activities, and human secondary somatosensory cortex is more influential in perceiving the high frequency of the vibrotactile stimulus.

Keyword : Transcranial magnetic stimulation (TMS), Electroencephalography (EEG), Primary somatosensory cortex (S1), Secondary somatosensory cortex (S2), Tactile discrimination.

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Contents

1. Introduction

1.1. Study Background

Providing information about the external environment, touch is indispensable in our life. It might affect survival directly, interacting with the motor control. Recently, in a tactile domain, the neuro-modulation has been actively studied not only to investigate a mechanism underlying sensory-related function but also to restore sensation for patients who have lost it.

When the tactile information is transmitted from mechanoreceptors over the body surface (Delmas et al., 2011), the sensory features such as frequency, duration and amplitude are represented differently onto somatosensory cortex. Studies of single unit recording in nonhuman primates and rats found that the specific frequency selectively excites the Meissner (RA) or Pacinian (PC) afferent fibers at the peripheral nerve ending, giving rise to different cortical encoding such as neurons' firing rates. (Talbot et al., 1968, Salinas et al., 2000, Luna et al., 2005) The development of techniques including functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electrocorticography (ECoG) and electroencephalography (EEG) boosted the human studies in the tactile domain. For instance, fMRI enabled the detail studies of the perceived representation in somatosensory-related cortices including the pre-central gyrus, anterior insula, posterior parietal cortex and posterior cingulate as well as the contralateral S1 and the bilateral S2. (McGlone et al., 2002, Soros et al., 2007, Chen et al., 2008) In addition, the MEG and ECoG studies addressed that the activity in low−gamma (30 ~ 50 Hz) and high−gamma (50 ~ 140 Hz) power over the contralateral somatosensory cortex is closely correlated to the sensory perception. (Prueckl el al., 2015, Ryun el al., 2017) However, most human studies have focused on measuring the general synchronization of brain activity or high frequency oscillatory activities. Therefore, the activities of the multiple oscillatory bands during the tactile perception still remain to be investigated.

Both primary and secondary somatosensory cortices mainly engage in processing the sensory information together. The early primary somatosensory responses to tactile stimulus are followed by longer contralateral secondary somatosensory responses. The temporally different responses might continue up to 250 ms after the onset of tactile presentation. (Simoes et al., 2003, Cheng et al., 2015, Ryun et al., 2017) In terms of the vibrotactile stimulus, the patterns of two cortical responses are different according to the frequency. Previous studies with fMRI and ECoG suggested that the S2 is more specialized in processing the high frequency compared to the S1. (Maldjian et al., 1998, Chung et al., 2013, Ryun el al., 2017) These studies can be considered a first step towards a deeper understanding of S1 and S2.

Brain stimulation to cerebral cortex has been used for multiple purposes. For example, an invasive cortical stimulation has been applied to treat the neurological disorders as well as to investigate the spatial and temporal organization of the neural systems supporting a certain behavior. In spite of the benefits in spatial and temporal efficacy, it is hardly feasible for most people because of possible surgery risks and side effects. For this reason, non-invasive stimulation such as transcranial magnetic stimulation (TMS) or transcranial electrical stimulation (tES) has been widely used as an alternative tool. The TMS has good spatial and temporal resolution to focally target a cortical area and it can induce intense intracortical currents. (Walsh and Cowey, 2000, Bolognini and Ro, 2010, Song et al., 2011) Accordingly, it has been actively studied by establishing its adjustable protocols. In the tactile area, the TMS effects are dependent on the protocols such as the number of the pulse train, pulse width or amplitude. For instance, supra-threshold single pulse disrupts the perception by generating a new artificial sensation. (Cohen et al., 1991, Seyal et al., 1997, McKay et al., 2003, Hannula et al., 2005, Meehan et al., 2008) Paired pulses lead to better or worse performance depending on the inter-stimulus interval (ISI). (Oliveri et al., 2000, Koch et al., 2006) In the previous studies, the duration of non-repetitive TMS was mostly shorter than that of somatosensory evoked responses. Lengthening the duration of TMS application by increasing the number of pulses might influence the TMS' s effects. Therefore, a study using multiple pulse trains had been required to better understand the TMS. Furthermore, few studies showed the TMS-evoked brain responses through the fMRI, suggesting that the desynchronization of the stimulated sensory cortex was accompanied with disruption of the perception. (Case et al., 2017) However, because of methodological limitations of TMS-EEG, modulations in oscillatory activity after TMS have been scarcely studied.

1.2. Purpose of Research

The current study aimed to demonstrate the effects of TMS over primary somatosensory cortex or secondary somatosensory cortex on neural oscillatory activity as well as on tactile performance. Moreover, it verified the different contribution of S1 and S2 to processing the frequency by addressing the disparity of TMS-induced modulations in two somatosensory cortices. As far as we know, no prior studies have examined the effects of non-repetitive TMS with multiple pulse trains which are concurrently applied for a whole period of somatosensory evoked response. Consequently, this study was carried out using the triple pulses of TMS.

2. Materials and Methods

2.1. Participants

53 healthy volunteers participated in this vibrotactile discrimination task. (26 men, 27 women, mean age = 23.78± 3.16, 52 righted-handed, 1 left-handed) None had a history of neurological or psychiatric illness. The protocol was approved by the Seoul National University Institutional Review Board (SNU-IRB), and all participants gave written informed consent. Also, we acquired EEG data from 25 participants (14 men, 11 women) performing the task. 3 participants were excluded from the final analysis because of their poor behavioral performance and/or unintended noise and artifacts in EEG data.

2.2. Vibrotactile stimuli and transcranial magnetic stimulation

We designed a pin-point stimulator consisting of a piezoelectric actuator and a plastic pin (2 mm in diameter) to deliver the sinusoidal vibrotactile stimuli. The stimulator was encased in a plastic box to avoid electrical artifact and sound. It was capable of delivering vibrotactile stimuli in the frequency range of 1 to 500 Hz. The deflection amplitude was determined by the input voltage. Prior to the behavioral task, we set two stimuli with fixed frequency and amplitude. One stimulus with 32 Hz and 100 μm and another stimulus with 350 Hz and 50 μm were defined as low-frequency stimulus and high-frequency stimulus respectively in the current study. Based on our prior behavioral experiment that matched the amplitude to the frequency in order to elicit similar intensity of the sensation, the amplitude was fixed. Two fixed frequencies were chosen each from flutter range (< 50 Hz) and vibration range (> 100 Hz). Seven tactile stimuli presented for discrimination were composed of the different ratio of the low and high-frequency stimuli and their ratio were 99:1, 75:25, 60:40, 50:50, 40:60, 25:75 and 1:99. ('X:Y' expresses the proportional relationship of low-frequency stimulus (X) to high-frequency stimulus (Y).)

Additionally, transcranial magnetic stimulation (TMS) was applied during the tactile presentation. It was given using a MagPro X100 magnetic stimulator (MagVenture, Denmark) through a figure-of-eight shaped coil. The stimulation was made up of triple pulses with a pulse width of 20 ms and inter-pulse interval of 50 ms. And it was conveyed 50 ms after the onset of the presentation of the deviant tactile stimulus because there is a time delay when the somatosensory cortex encodes incoming tactile information from the mechanoreceptor. Moreover, the TMS' s intensity was determined in individuals by 80% of motor threshold which is the minimum strength to evoke motor-evoked potential in at least 50% of trials. Finally, TMS was tangentially placed over the scalp overlying the primary somatosensory cortex or secondary somatosensory cortex in each session and it was only applied at stimulation trials.

A custom-made code (MATLAB version 2018a; Mathworks, Natick, MA) not only controlled the vibrotactile stimulator and TMS device but also collected the participants' responses. To lessen a delay in operating multiple devices, a NI9264 analog output device (National Instruments, U.S.A) which is also referred to as DAQ was used.

2.3. Localization of primary and secondary somatosensory cortices

Since brain volume and cortical surface area were individually different, it is important to localize S1 and S2 accurately. The finger area of S1 was identified by asking a participant to detect an artificial sensation in the right finger when a single TMS pulse was given onto contralateral hemisphere. Unlike S1, stimulating S2 doesn't elicit any sensation. Therefore, we first localized S2 through invasive brain mapping in an epilepsy patient and obtained S2's coordinates. Using the coordinates, individual brain image and neuro-navigation system, the scalp corresponding to the S2 was marked and targeted by TMS.

2.4. Behavioral experiments

The behavioral experiment was designed as a two-alternative forced choice task. During the experiment, participants were comfortably seated in a chair with the right hand on the vibrotactile stimulator and left hand on the laptop. Two vibrotactile stimuli, a deviant stimulus and a standard stimulus, were sequentially presented onto a tip of the right index finger. The deviant stimulus was pseudo-randomly chosen from the seven tactile stimuli described above and the standard stimulus was always 50:50. TMS was applied only during the presentation of the deviant stimulus. Two consecutive tactile stimuli lasted for 500 ms each, separated by an inter-stimulus interval of 2.5 seconds. In the task, the participants were instructed to decide whether the deviant stimulus has a higher ratio of low or high frequency relative to the standard stimulus by pressing keys on the laptop and to respond as fast and accurate as possible. S1 and S2 sessions had 420 trials each; 60 trials for each deviant stimulus. During a session, half of the total trials was defined as a sham condition while another half was considered as a TMS condition. To minimize any changes in sound between sham and stimulation, the white-noise was played and earplugs were inserted in the ear canal during the whole task. Moreover, fake TMS sound we recorded in prior was played during the sham to mimic the click sound from the TMS coil. Before the task, all participants were trained until they obtained accuracy over 70% under the sham condition.

2.5. Behavioral analysis

For the discrimination task, the accuracy, response, and reaction time (RT) were assessed in a total of 840 trials for each participant (420 trials/session). In every condition, percent of accuracy (correct responses) was averaged across the participants for each deviant stimulus. And percent change after stimulation was obtained by subtracting the accuracy in sham from that in stimulation. In addition, the proportion of the responses that the participants chose the deviant stimulus as a higher frequency was plotted as a function of the real high frequency ratio.

As mentioned above, the time taken to make a response was recorded. In some trials, participants were asked to pause the response while we fixed their postures. Subsequently, the time that does not correspond to the actual response time was included in the collected RT. Any data points which are away from 3 standard deviations were therefore classified as the outlier and excluded from the final analysis. The RT was averaged across the participants in sham and stimulation.

Statistical analysis of the data was performed using paired t-test within and across the sessions. All analyses used SPSS23 (IBM, Armonk, NY) and MATLAB 2018a (Mathworks, Natick, MA). The level of significance was fixed at $P \leq 0.05$.

2.6. EEG recording and analysis

EEG was recorded with a sampling rate of 2000 Hz using a 64-channel active electrode system (Neuroscan, Australia). We started recording when all electrodes' impedances were under 8.2 kOhms. EEG cap was compatible with the TMS so that the EEG data were acquired simultaneously with the TMS application. The deblocking system of the EEG temporarily suspended the acquisition for 230 ms after the TMS onset to eliminate large induced artifact. The missing period was later reconstructed using a spline interpolation to a continuous signal. In addition, connecting to the analog output, the EEG system recorded the time of all vibrotactile stimulus onset and offset and exported it as an event file required for extracting data epochs.

EEG analysis was performed using EEGlab and custom Matlab code. Preprocessing included rejection of noisy channels, interpolation of the deblocking period, common average referencing, down-sampling to 400 Hz, and high- (0.5 Hz) and low-pass (100 Hz) filtering. The continuous recordings were segmented into epochs from 1000 ms before the first stimulus onset to 1000 ms after the second stimulus onset. The epoch trials which had greater amplitudes than 80 mV were rejected. To analyze signals in time-frequency map, we applied continuous Morlet wavelet transform to the epoched data. The transformed data were then squared and normalized by the mean and standard deviation of a baseline period (from −0.7 sec to −0.3 sec of the first stimulus onset).

To test for differences between sham and stimulation and to compare the impacts of S1 TMS and S2 TMS, we computed paired t-tests or Wilcoxon test for normalized power in each oscillatory band during a period of retaining memory of the first perception (Memory retention period) and of the second perception.

3. Results

3.1. Effects of TMS on behavioral performance

Percent accuracy of the discrimination task

We examined accuracy (correct responses) in percentage for 50 subjects performing the behavioral task. Three subjects whose overall accuracy was below the chance level (50%) were excluded from the analysis. In sham condition, the subjects correctly discriminated 75.07 ± 6.83% (mean ± standard deviation) and 76.12 ± 6.66% of total trials for S1 and S2 sessions. There is no significant difference between S1 sham and S2 sham ($p = 0.22$). In the presence of S1 TMS and S2 TMS, the accuracy decreased to 69 ± 7.72% and to 66 ± 9.74% respectively. Each stimulation significantly reduced the overall accuracy relative to sham ($p < 0.001$) (Fig. 2A). A paired t−test revealed a significant difference in changes of overall accuracy between S1 TMS and S2 TMS ($p < 0.03$) (Fig. 2B).

Mean accuracy was then obtained for each deviant stimulus (99:1, 75:25, 60:40, 40:60, 25:75 and 1:99) under all conditions. (Table 1, Fig. 3A and B) Compared to S1 sham, S1 TMS significantly increased or decreased the accuracy across the deviant stimuli of 60:40 ($t = -3.07$, $p = 0.003$), 40:60 ($t = 4.45$, $p < 0.001$), 25:75 ($t = 5.83$, $p < 0.001$) and 1:99 ($t = 6.30$, $p < 0.001$). There were also significant differences across the stimuli of 60:40 ($t = -2.57$, $p = 0.01$), 40:60 ($t = 6.64$, $p < 0.001$), 25:75 (t

= 7.53, $p < 0.001$) and 1:99 ($t = 8.13$, $p < 0.001$) after S2 TMS.

The mean percent changes after S1 TMS for 99:1, 75:25, 60:40, 40:60, 25:75 and 1:99 were −0.53%, 2.40%, 8.33%, −15.60%, −17.07% and −16.40% while the changes after S2 TMS were −1.20%, 1.47%, 8.47%, −20.47%, −23.27% and −23.73%. It showed that S2 TMS leads to greater attenuation of the performance at stimuli of 25:75 ($p = 0.01$) and 1:99 ($p = 0.008$) (Fig. 3C).

Psychometric function

Having quantified the participants' responses as a function of the high frequency ratio in the deviant stimulus, we proceeded to determine how TMS influences the discrimination task. (Fig. 4A and B) In sham conditions, subjects were more likely to respond that deviant stimulus has higher high-frequency ratio than standard does (50:50) as the real high frequency ratio increases. Interestingly, TMS reduced participants' likelihood of reporting it for all deviant stimuli except 99:1. There is a general trend that the TMS's impacts became stronger with increasing the high frequency ratio. Once again, as shown in the accuracy results, S2 TMS suppressed the proportion of the responses more than S1 TMS.

Response time

Both S1 sham and S1 TMS resulted in a response time of 0.91 sec. And the time taken for S2 sham and S2 TMS was 0.97 sec and 0.99 sec respectively. Neither S1 TMS nor S2 TMS identified a significant change in response time.

3.2. Effects of TMS on neural activity

Responses during sham condition

EEG was recorded from volunteers (n = 25) performing the same behavioral task. One subject' s data was not included in the final analysis due to severe artifacts. We first considered oscillatory EEG activity during first perception (0 ~ 0.5 sec), memory retention interval (0.5 ~ 3 sec) and second perception (3 ~ 3.5 sec) over S1 and S2 in time−frequency domain. Fig. 5A and Fig. 6A show that increases in delta (1 ~ 3 Hz) and theta (4 ~ 7 Hz) power bands were evident during two sequential tactile stimulus presentation. A prominent increase in alpha band (8 ~ 13 Hz) was also observed during memory retention. But the neural activities in delta, theta and alpha bands didn' t represent a parametric effect of the frequency ratio in each tactile stimulus.

Responses over primary somatosensory area during S1 TMS

Fig. 5A and Fig. 5B show a time−frequency map in S1 sham and S1 TMS condition respectively at the primary somatosensory area. The spectrum was normalized with delta power to compare the oscillatory activity between S1 sham and S1 TMS. The delta band power during retention interval and second perception statistically decreased after S1 TMS for all tactile stimuli (Fig. 5C). However, the decrease was not correlated with the frequency ratio or behavioral changes. In addition, TMS didn’t evoke any statistical changes in other bands including theta, alpha and beta (15 ~ 30 Hz) relative to sham.

Responses over secondary somatosensory area during S2 TMS

Through Fig. 6A and 6B, we demonstrated two clearly different response patterns of S2 sham and S2 TMS at the secondary somatosensory cortex. Fig. 6C and 6D show how a normalized power in the delta and theta bands varied across all tactile stimuli during retention and second perception periods. The delta band power was significantly lower after S2 TMS was given. Contrary to results of S1, there was a trend that S2 TMS decreased activity in theta band during retention and second perception period. However, the modulations of oscillatory activity didn’t reflect a function of high frequency ratio or changes in behavioral responses.

Difference in responses between TMS S1 and TMS S2

In terms of delta band showing the most prominent changes on both TMS sites, S2 TMS significantly more attenuated the evoked delta power relative to S1 TMS during the memory retention ($p < 0.001$) and second perception ($p = 0.002$) (Fig. 7).

4. Discussion

4.1. Summary

To our knowledge, this is the first study reporting the effects of triple transcranial magnetic stimulation (TMS) pulses over primary somatosensory cortex (S1) or secondary somatosensory cortex (S2) on performance as well as on neural activity. TMS to S1 or S2 selectively modulated the behavioral performance depending on the frequency ratio of the vibrotactile stimulus. Our EEG data showed TMS−induced modulations in oscillatory activity during periods of memory retention and second stimulus perception. To be specific, TMS to S1 decreased the activity in delta band while TMS to S2 inhibited the activities in the delta and theta bands. The decrease in power bands, however, neither reflected the ratio of the high or low frequency nor be correlated with % change in accuracy. In addition, it is clear from these behavioral and neural measures that effects of S2 TMS are far bigger than those of S1 TMS.

4.2. TMS induces behavioral and neural modulations.

In recent years, the effects of TMS have been increasingly studied in the tactile domain but they are still debatable. Most previous studies applying TMS to related sensory cortex showed either improvement or disruption of the tactile performance according to TMS protocol. The present study demonstrated the impacts of TMS on the behavioral measure, defined as the subjects' accuracy of discriminating two tactile stimuli. TMS was able not only to enhance the performance but also to deteriorate it. The impacts depended on whether the deviant stimulus is low-frequency or high-frequency dominant. In other words, TMS decreased participants' likelihood of perceiving the deviant stimulus as higher frequency-stimulus. This result might be explained by two hypotheses; 1) TMS facilitates the perception of low frequency or 2) TMS inhibits the perception of high frequency. In our EEG finding, the delta power was reduced in all periods after TMS regardless of the stimulated site. It is consistent with previous fMRI's finding that TMS reduced tactile responsiveness, entailing desynchronization of the somatosensory area. (Case et al., 2017) Further, the reduction in the delta power suggests how TMS affects the behavioral performance. Several previous reports about the delta band on sensory cortices have supported the idea that successful sensory perception is attributed to the increase of the delta power. (Başar-Eroglu et al., 1992, Yasuda et al., 2005, Schroeder and Lakatos, 2009) Ultimately, we can note that TMS modulates the performance by inhibiting the perception of the high frequency.

The EEG results demonstrated that triple pulses are sufficient to drive changes in neural activity of the brain. At a single cell level of non-human primates and rodents, TMS causes patterns of responses that could be activated or suppressed for each inhibitory or excitatory neuron but temporally diverse between the neurons.

(Mueller JK et al., 2014, Farzan F et al., 2016, Li B et al., 2017) The change of neuronal activities may decrease in power across nearly all frequencies on evoked Local Field Potentials (LFPs) (Pasley BN et al.,2005), and generate a series of time-locked peaks on EEG including the N15, P30, N45 and N100 that are known to reflect the cortical excitation or inhibition. (Hill AT et al., 2016) Hence, in terms of neuronal mechanism, TMS alters task-related neural activity by exciting or inhibiting the neurons and it consequently modulates the tactile perception. Additional studies will have to be carried out to examine the changes in neuronal activity evoked by the cortical stimulation at human single cell recording.

The TMS-induced neural activity might be associated with high cognitive functions such as working memory, comparison, or perceptual decision-making of somatosensory cortex. (Luna et al., 2005, Harris et al., 2002, Romo et al., 2002, Tame and Holmes., 2016) However, TMS' s effects should have been consistent across all deviant stimuli if it disrupted the other cognitive functions. Moreover, in our EEG results, TMS didn' t cause significant modulations of the alpha and beta bands which are thought to represent a tactile working memory and selective attention respectively in human sensory cortex. (Spitzer and Blankenburg, 2011, Pomper, 2015) Further, for both S1 TMS and S2 TMS, there was no significant difference in response time between sham and stimulation. Considering that many prior studies used the response time as a measure of memory or decision−making, (MacLeod and Nelson, 1984, Weidemann and Kahana, 2016) we propose that the TMS−induced behavioral modulation was not primarily resulted from the intervention in memory or perceptual decision making.

4.3. The impacts of S2 TMS are more evident than those of S1 TMS.

Multiple oscillatory activities play in communication as large−scale brain networks. Recently, cross−frequency coupling which links the activities at different frequencies has been received, suggesting a strong correlation between theta and gamma power (Canolty and Knight, 2010, Lisman and Jensen, 2013). In the present study, we particularly observed a reduction in theta band (4 ~ 7 Hz) on S2 after S2 TMS. It implies that TMS notably modulates the gamma power in S2 during the discrimination task. In contrast, no significant difference in the theta band was observed between S1 sham and S1 TMS. Therefore, this finding is in line with the previous result that gamma activity is quickly attenuated in S1 whereas it increases in S2 with increasing stimulus frequencies in vibration range. (Ryun et al., 2017) Moreover, as compared to the effects of TMS over S1, those of TMS over S2 induced greater behavioral and neural modulations. In particular, the disparity was the most prominent in behavioral performance when high frequency was dominant in the deviant stimulus. It suggests that TMS S2 more interferes with processing the high frequency. Hence, the current study verifies that the secondary somatosensory cortex mainly plays a role in processing the high frequency of the vibrotactile stimulus.

4.4. Application of the triple TMS pulses

TMS has been applied to therapy or to investigate the functional mapping for decades. This study provided evidence that the triple TMS pulses can selectively modulate the brain function by inhibiting certain neural activity, and it subsequently leads to behavioral change. It sheds light on possible application of TMS which would be practically used with very few side effects, to derive intended human behaviors. In addition, expanding the TMS target over the cortical areas, we might alter the several functions such as perception of other sensory modalities, movement, memory, attention or cognitive decision. To develop the TMS as more powerful tool modulating the certain behaviors as intended, the protocols and corresponding neural mechanism should be actively investigated.

4.5. Limitations and further study

Conducting the behavioral task with concurrent TMS−EEG, we were able to examine the impacts of TMS on neural activity as well as on performance. However, our investigation of TMS−EEG is limited in some aspects. First, the EEG recording was not able to capture the high frequency spectra above the beta band (> 30 Hz). Even though the high gamma band is an important spectrum in encoding the vibrotactile stimulus onto two sensory cortical areas (Ryun et al., 2017, Rossiter et al., 2013), the current finding was restricted to low frequency oscillatory. It, however, brings a better insight of low frequency oscillatory activities which have been rarely analyzed in the previous studies. Secondly, despite using the deblocking system, the TMS-evoked artifacts persisted for about 400 ms. Therefore, we could not examine the oscillatory activities in the period of the first perception which had been expected to have the most evident changes by TMS.

Because of the variability of cortical anatomy, MRI-guided neuronavigation was required to target S2 area in the current study. However, obtaining an MRI image for all participants was not feasible. For subjects with no MRI images, we localized the S2 area based on MRI-group average coordinates, not taking account of individual differences. It might cause placement of TMS coil on different cortical areas across the subjects.

The TMS might affect the extended neural networks during the discrimination task rather than it solely had an impact on the stimulated area. Future studies are necessary to examine the neural modulations over the broader cortical areas such as prefrontal or parietal cortex, and to answer how the sensory information evolves in time and across multiple processes of the discrimination; perception, working memory, comparison and perceptual decision making.

4.6. Conclusion

The triple pulses of transcranial magnetic stimulation (TMS) to primary somatosensory cortex (S1) or secondary somatosensory cortex (S2) affect tactile discrimination on behavioral and neural responses. The TMS selectively modulates the performance by inhibiting the perception of the high frequency. Additionally, the S2 is more influential in processing the high frequency. However, a better understanding of the neuronal mechanisms underlying the somatosensory perception remains a challenge.

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List of Table

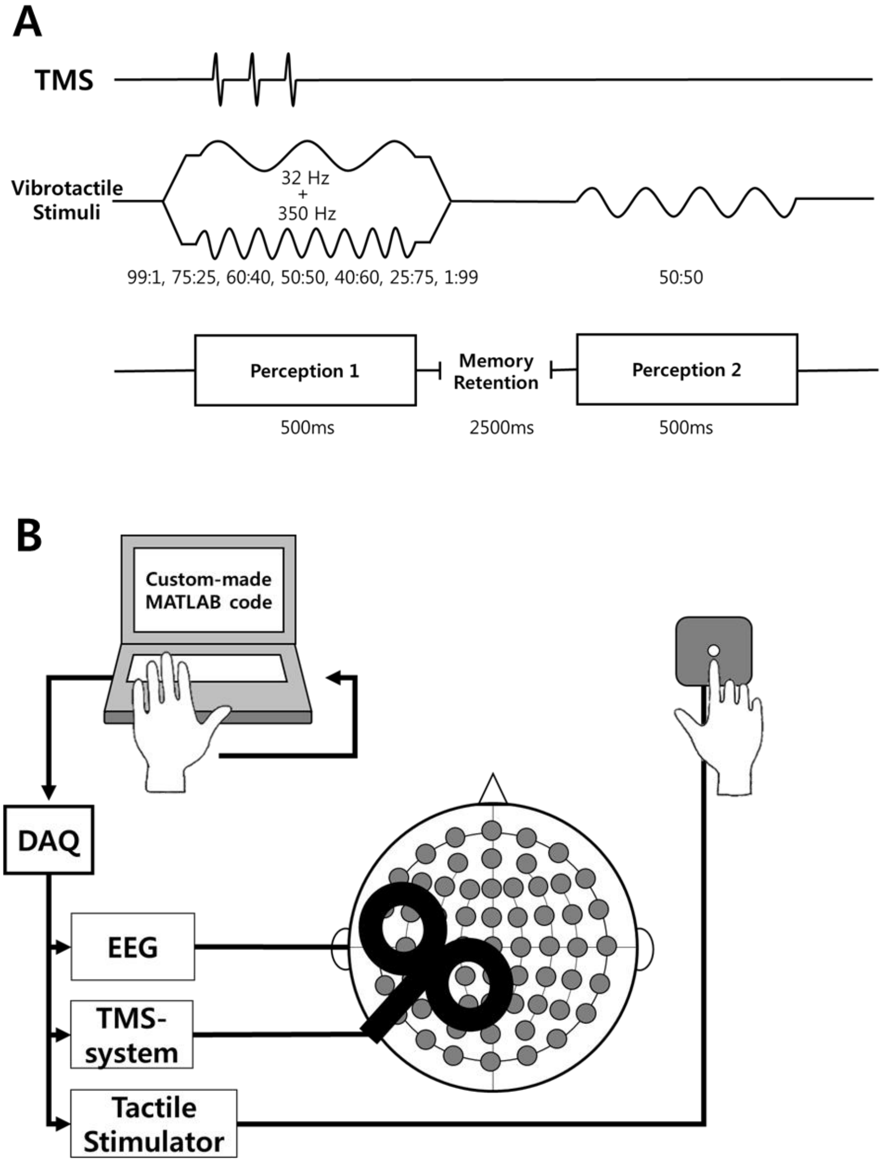
Table 1.

		Deviant Stimulus											
		99:1		75:25		60:40		40:60		25:75		1:99	
TMS over S1	**Sham**	93.13	(8.79)	78.80	(12.84)	63.33	(9.38)	60.93	(9.11)	72.47	(12.70)	82.87	(13.43)
	Stimulation	92.60	(13.89)	81.20	(16.48)	71.67	(18.25)	45.33	(21.77)	55.40	(20.86)	66.47	(19.79)
	Change	-.53	(11.01)	2.40	(14.52)	8.33	(18.77)	-15.60	(25.03)	-17.07	(20.20)	-16.40	(18.32)
TMS over S2	**Sham**	91.20	(9.52)	78.80	(12.30)	62.47	(10.81)	61.80	(9.69)	76.07	(10.18)	85.27	(10.65)
	Stimulation	90.00	(15.69)	80.27	(18.03)	70.93	(22.11)	41.33	(22.67)	52.80	(23.43)	61.54	(23.79)
	Change	-1.20	(12.65)	1.47	(17.96)	8.47	(23.86)	-20.47	(21.66)	-23.27	(22.36)	-23.73	(20.73)

Summary of mean accuracy (standard deviation) across 6 different deviant stimuli during TMS over S1 and over S2. Percent changes in accuracy were calculated each for S1 stimulation and S2 stimulation by subtracting the accuracy of the sham condition from that of the stimulation condition.

List of Figures

Figure 1.



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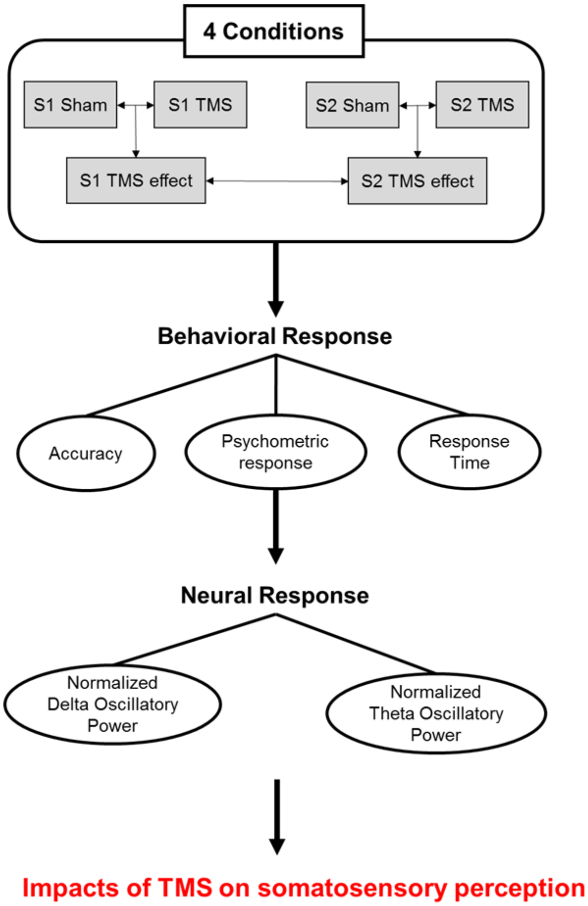
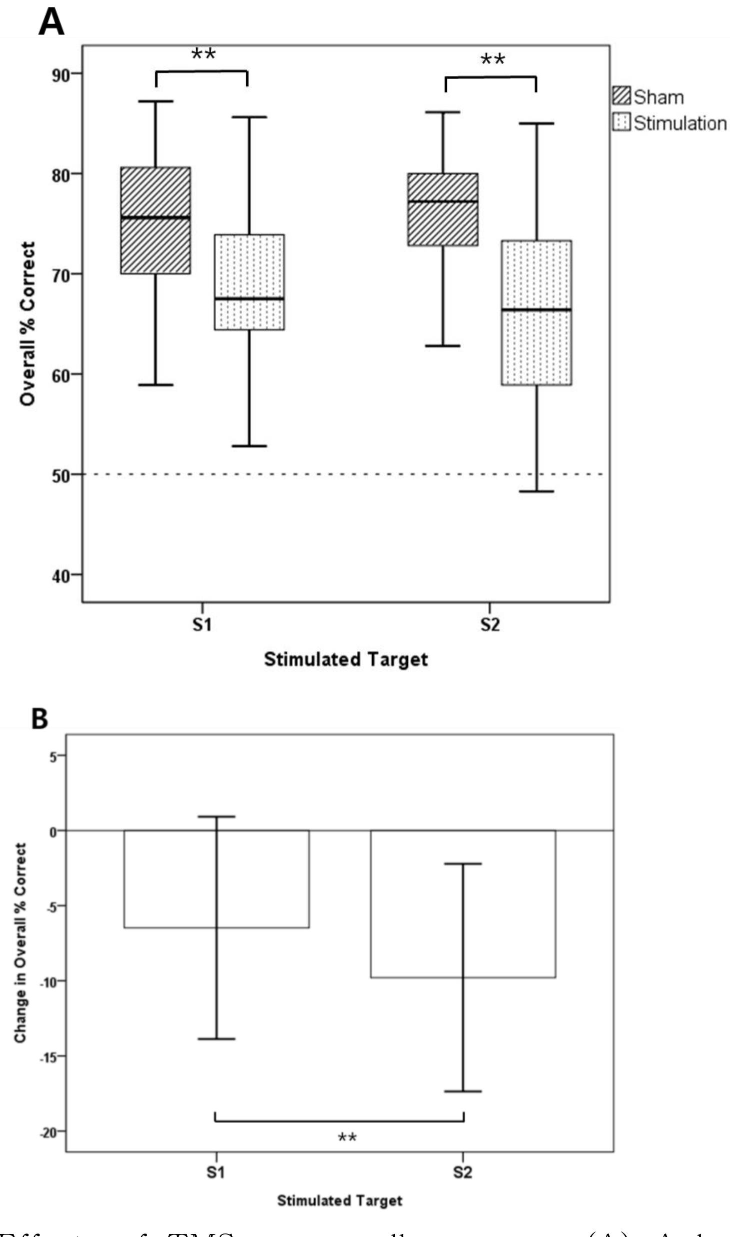


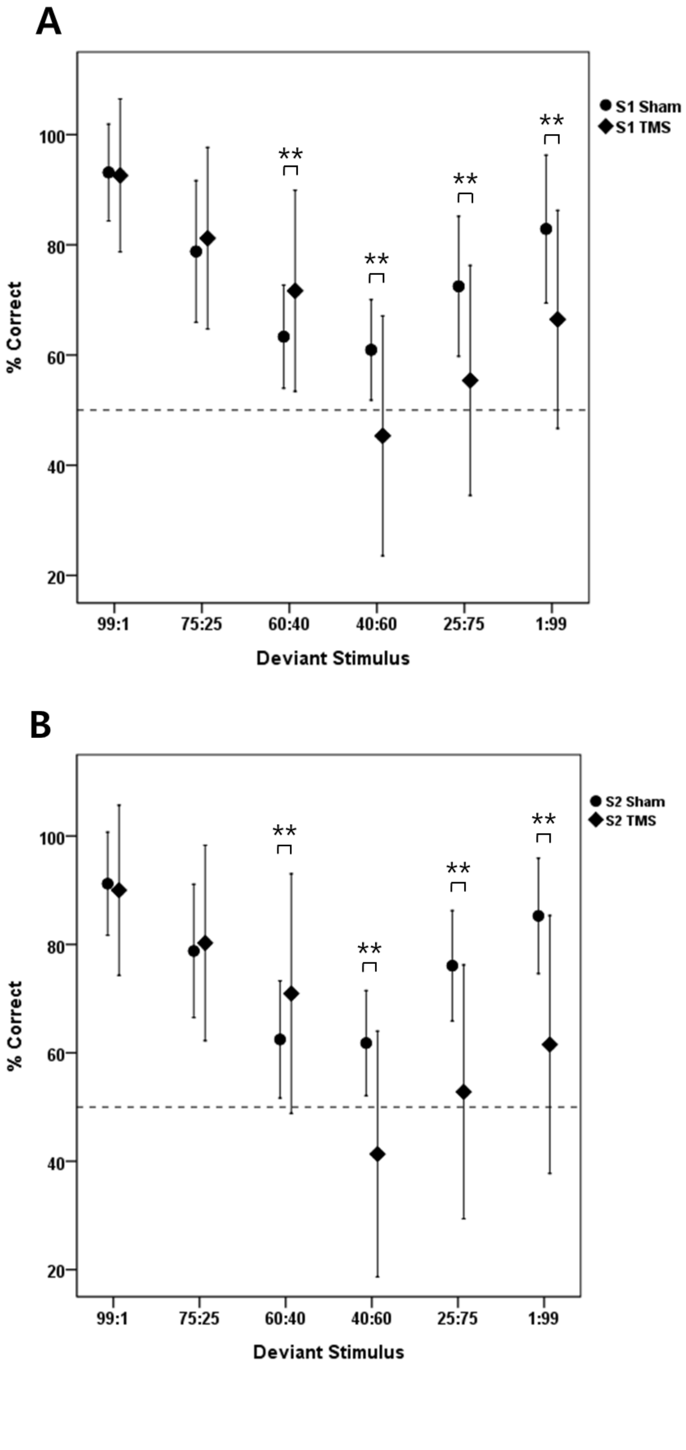
Two alternative forced choice task and schematic design of the experiment and analysis. (A) Two sequential vibrotactile stimuli, deviant stimulus and standard stimulus, were delivered to the right index finger. They lasted each for 500 ms, separated by 2500 ms. In trials of stimulation, TMS was applied only with the deviant stimulus. (B) A custom–made code in MATLAB controlled the EEG, TMS and tactile stimulator through the analog output (DAQ) and collected the participants' responses. (C) A workflow of analyzing the behavioral and neural measures.

Figure 2.

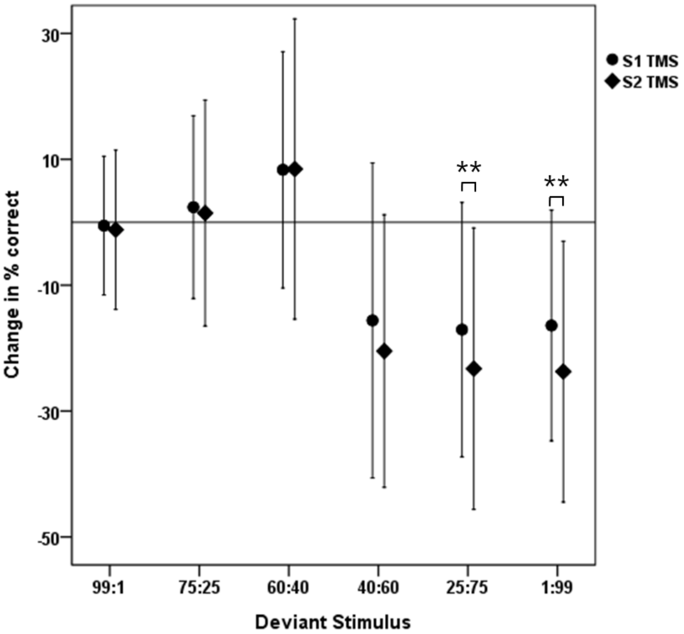


Effects of TMS on overall accuracy. (A) A boxplot for overall accuracy in percent. Diagonal lined bars indicate accuracy for sham and dotted bars indicate it for stimulation. A horizontal dashed line represents a chance level of the task (50%). (B) Mean changes in overall accuracy (± standard deviation) after TMS over S1 and S2. TMS over S2 more decreased the overall accuracy relative to TMS over S1. (**: $p < 0.05$)

Figure 3.

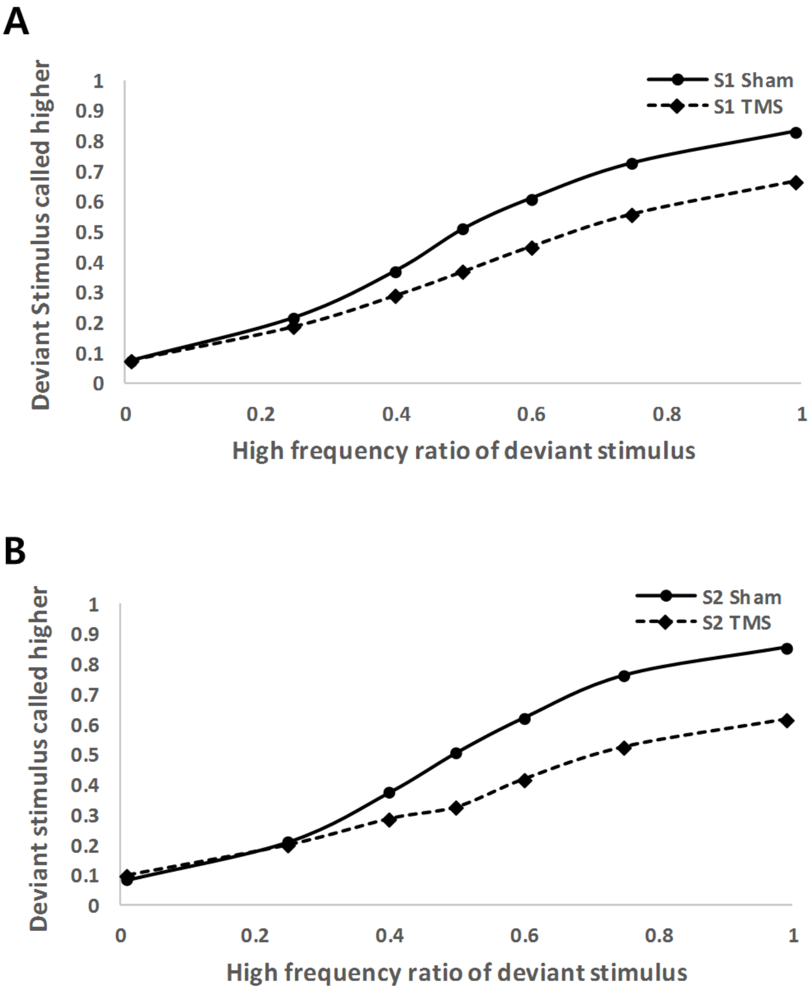

A
S1 Sham
S1 TMS
% Correct
Deviant Stimulus
99:1
75:25
60:40
40:60
25:75
1:99
B
S2 Sham
S2 TMS
% Correct
Deviant Stimulus

C



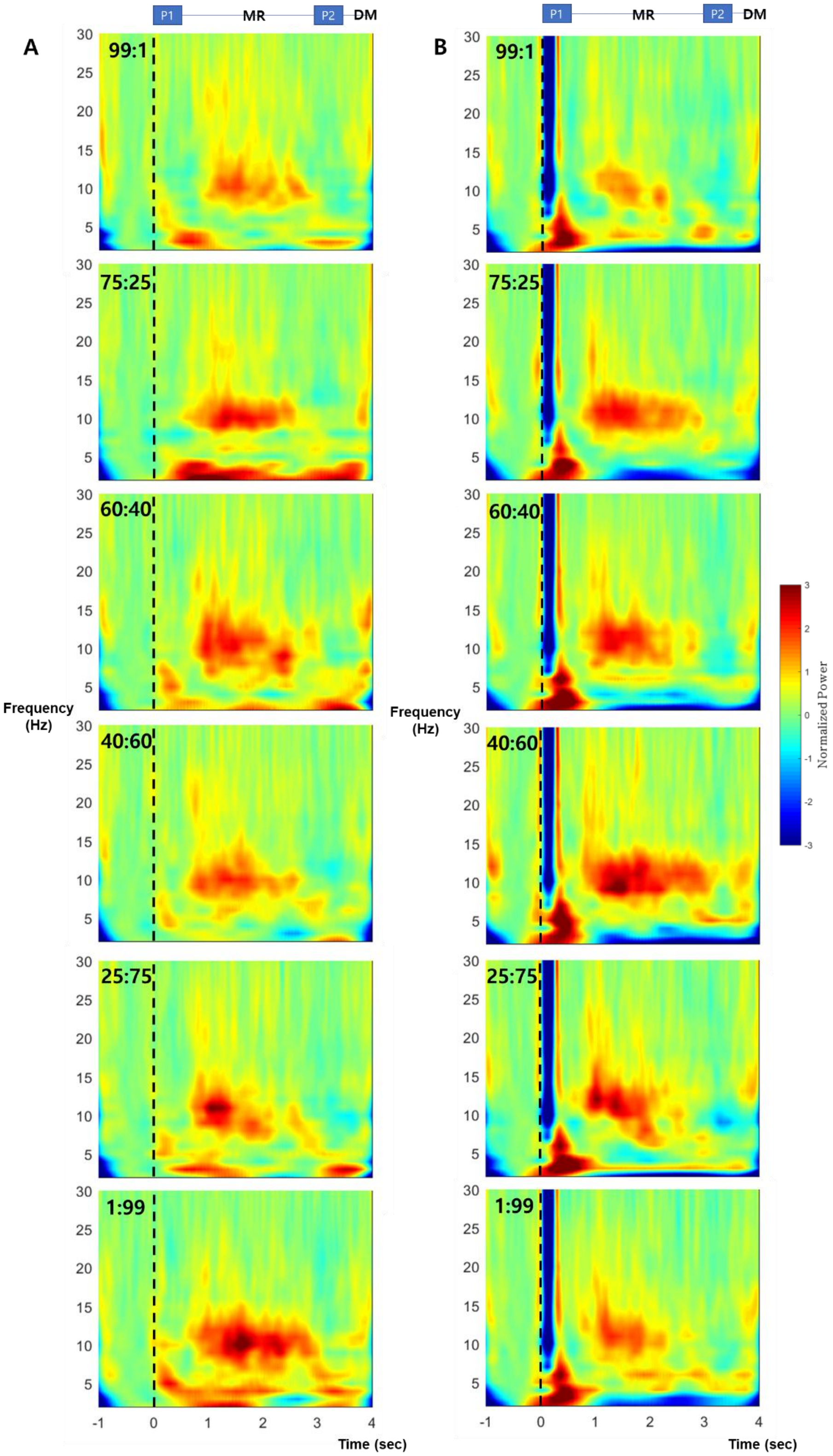
Mean percent accuracy (± standard deviation) and mean percent changes (± standard deviation) across 6 deviant stimuli. A horizontal dashed line indicates a chance level of the task (50%). (A) Effects of TMS over S1 on accuracy for each stimulus. TMS significantly improved or deteriorated the accuracy for stimuli of 60:40, 40:60, 25:75 and 1:99. (B) Effects of TMS over S2 on the accuracy for each stimulus. The trend was similar to the effects of TMS over S1 shown in (A). (C) Comparison of the TMS-induced changes between S1 TMS and S2 TMS. S2 TMS significantly decreased the accuracy more when the stimulus of 25:75 or 1:99 was delivered. (**: $p < 0.05$)

Figure 4.

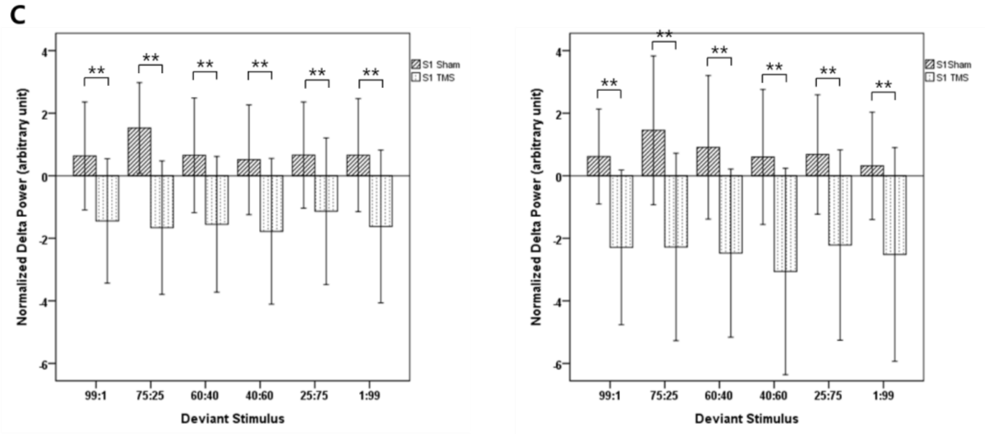


Psychometric performance under sham and TMS. (A) Proportion of responses that deviant stimulus is higher frequency than standard stimulus during sham and TMS over S1. A solid line represents responses with S1 sham; dashed one with S1 TMS. (B) Proportion of responses that the deviant stimulus is higher frequency than the standard stimulus during sham and TMS over S2. A solid line indicates responses for S2 sham while the dashed line indicates responses for S2 TMS.

Figure 5.

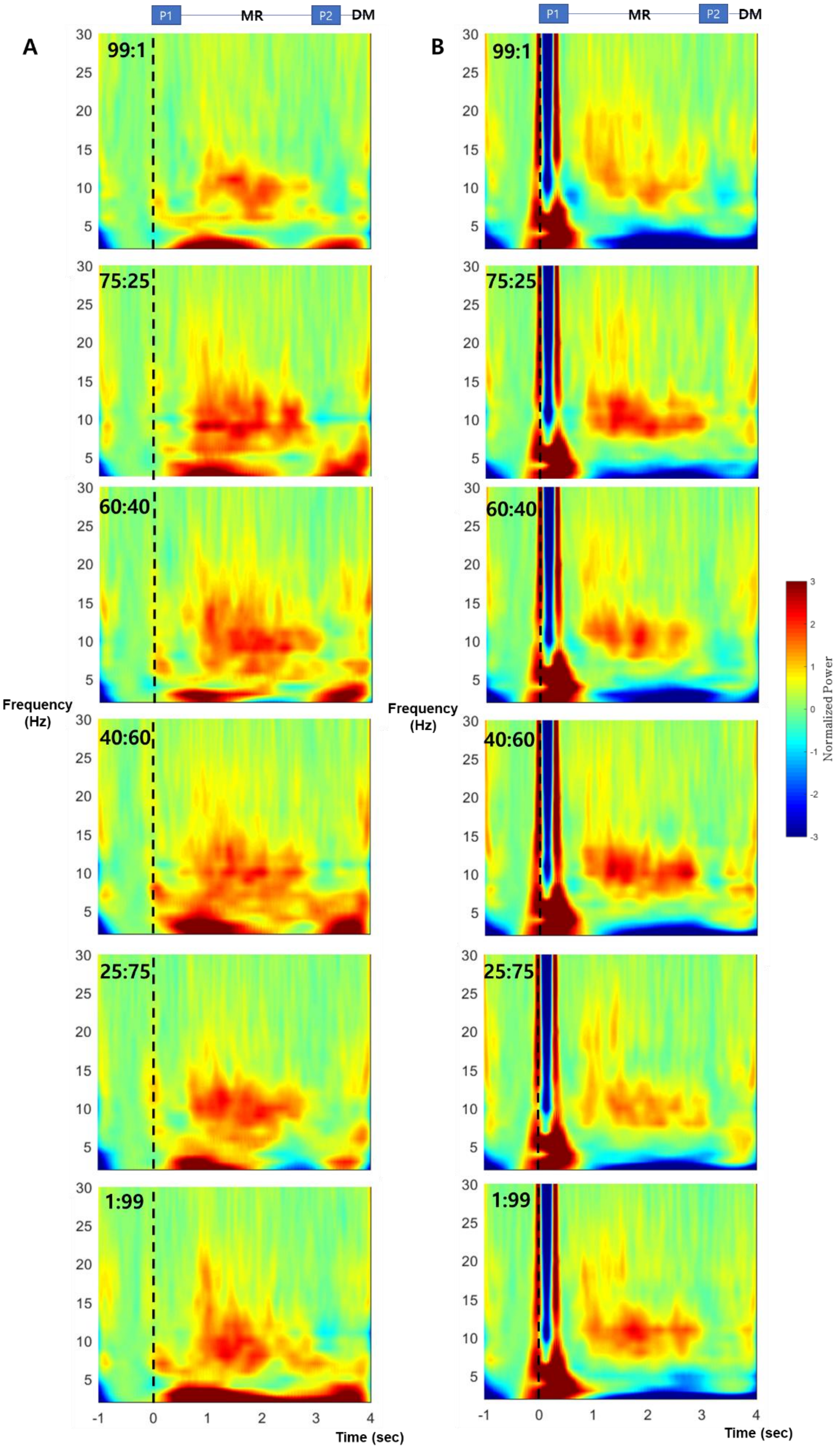


P1
MR
P2
DM
A
B
99:1
75:25
60:40
40:60
25:75
1:99
Frequency (Hz)
Time (sec)
Normalized Power



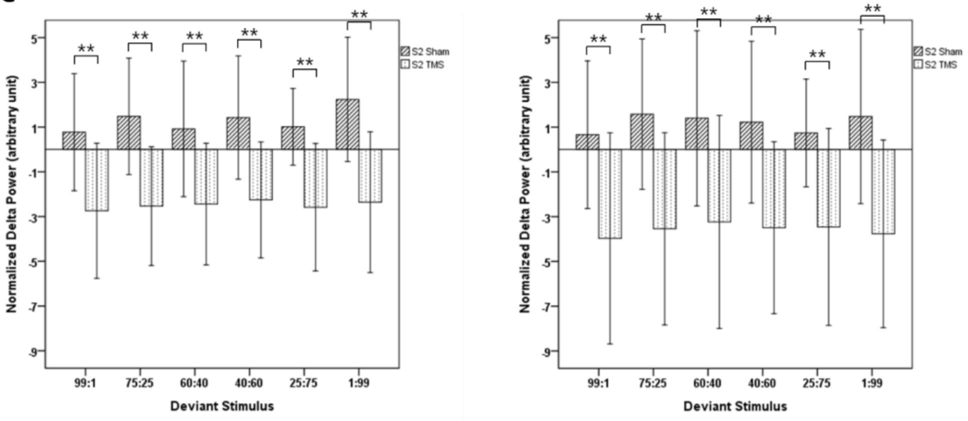
Effects of S1 TMS on oscillatory activities in S1 area. (A) Time−frequency representations showing increases of power in the delta, theta and alpha band during the discrimination task under S1 Sham. (B) Time−frequency representations during the task under S1 TMS. (C) Mean changes (± standard deviation) in normalized delta power during memory retention (left) and during second perception (right) after TMS. (**: $p < 0.05$) (P1: first perception, MR: memory retention, P2: second perception, DM: decision−making)

Figure 6.

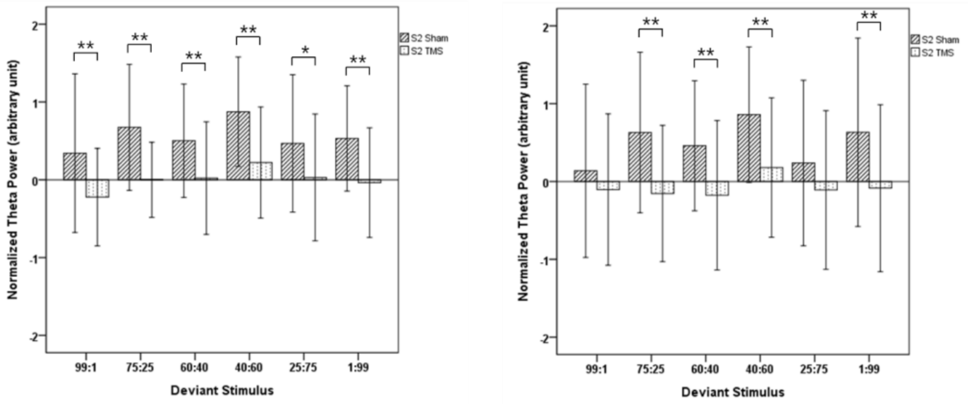


A
B
P1
MR
P2
DM
99:1
75:25
60:40
40:60
25:75
1:99
Frequency (Hz)
Time (sec)
Normalized Power

C

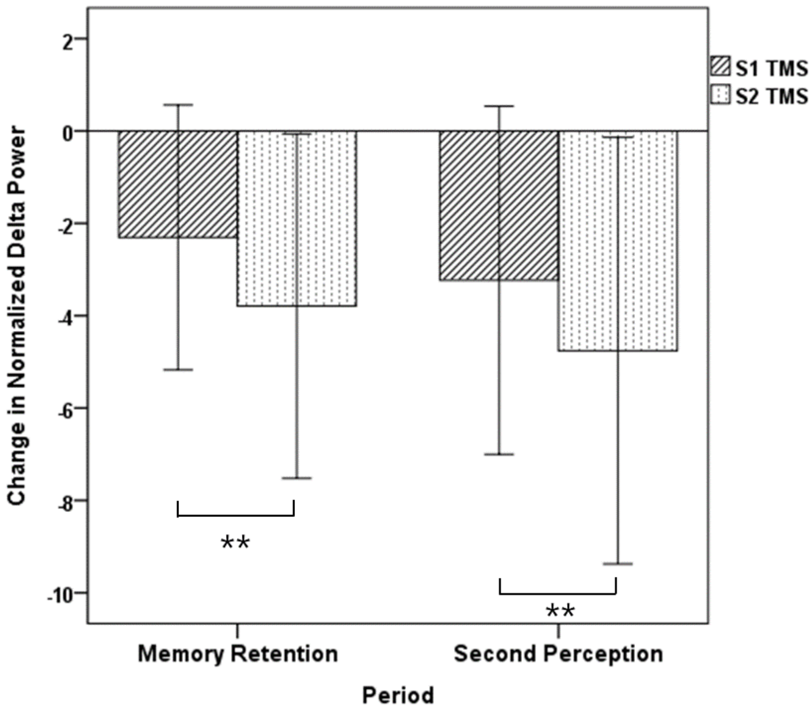


D



Effects of TMS over S2 on oscillatory activities in S2 area. (A) Time−frequency representations showing the increase of power in the delta, theta and alpha band during the discrimination task under S2 sham. (B) Time−frequency representations during the task under S2 TMS. (C) Mean changes (± standard deviation) in normalized delta power during memory retention (left) and during second perception (right) after TMS. (D) Mean changes (± standard deviation) in normalized theta power during memory retention (left) and during second perception (right) after TMS. (*: $p < 0.10$; **: $p < 0.05$) (P1: first perception, MR: memory retention, P2: second perception, DM: decision−making)

Figure 7.



Mean changes (± standard deviation) in normalized delta power during memory retention and second perception when TMS was applied over S1 or S2. S2 TMS significantly decreased the delta power relative to S1 TMS. (**: $p < 0.05$)

Abstract in Korean

주파수와 같은 진동 촉각 특성들은 신체 대부분에 퍼져 있는 수용기를 통해 들어와 뇌의 일차 체성 감각 피질(S1)과 이차 체성 감각 피질(S2)에 다르게 부호화된다. 인간을 대상으로 하는 많은 연구가 기능적 자기 공명 영상(fMRI) 또는 뇌파 검사(ECoG)를 이용하여 진동 촉감각 지각과 관련된 뇌의 활동이나 고주파 뇌파를 확인하였지만, 두 군데의 체성 감각 피질에서 나오는 다양한 주파수의 뇌파 활동들과 이것들의 기능적인 역할은 아직 정확하게 밝혀진 바가 없다. 그러므로 우리는 본 연구를 통해 경두개자기자극이 촉감을 구분하는 수행 능력과 관련 뇌파에 어떠한 영향을 미치는지 보고자 하였다. 더불어, 촉각 자극의 주파수를 인지하는 데 있어 S1과 S2의 역할이 어떻게 다른지를 확인하고자 하였다.

53명의 건강한 피험자들에게 저주파(32 Hz)와 고주파(350 Hz)가 다양한 비율로 혼합된 두 개의 촉각 자극을 주고, 이들의 주파수 비율을 구분하는 분별력 테스트를 진행하였다. 첫 번째로 제시되는 deviant stimulus는 서로 다른 비율로 섞인 7가지의 촉각 자극 (99:1, 75:25, 60:40, 50:50, 40:60, 25:75, 1:99) 중에 무작위로 선택되어 제시되었고, 그다음으로 standard stimulus가 항상 50:50의 비율로 제시되었다. (X:Y는 저주파(X)와 고주파(Y)의 비율을 뜻한다) Deviant stimulus가 제시되는 동안에 반대쪽의 S1 혹은 S2 위치에 경두개자기자극이 주어졌다. 또한, 25명의 피험자를 대상으로 TMS-EEG 시스템을 이용하여 분별력 실험을 진행하는 동안에 뇌 활동을 측정하였다.

행동 결과를 통해, 3번의 pulse로 이루어진 경두개자기자극의 효과가 촉각 자극이 가지는 주파수 비율에 따라 달라지는 것을 확인하였다. 저주파 비율이 우세할 때는 TMS의 효과가 없거나 정답률이 증가한 것에 반하여, 고주파 비율이 우세할 때는 TMS가 정답률을 유의미하게 낮추었다. 이때, TMS의 효과는 촉각 자극의 고주파 비율이 우세한 조건 안에서 S1를 자극했을 때보다 S2를 자극했을 때가 더 분명하였다. 뇌 활동 측면에서는 S1과 S2를 자극했을 때 델타 영역(1 ~ 3 Hz)이 공통으로 떨어지는 것을 보였으며, 마찬가지로 S2를 자극했을 때 더 감소하였다. 추가로, S2 자극 시 세타 영역(4 ~ 7 Hz)이 억제되었다. 이러한 결과들을 통해, 3번의 pulse로

이루어진 경두개자기자극이 특정 뇌파 활동을 변화시킴으로써 촉각 분별력 실험 동안 감각 지각 능력에 영향을 끼치는 것을 알아내었고, 나아가 이차 체성 감각 피질이 진동 촉각 자극의 고주파를 인지하는 데 있어 더 중요한 역할을 하는 것을 확인하였다.

주요어: 경두개자기자극, 뇌전도, 1차 체성감각피질, 2차 체성감각피질, 촉감각 분별력

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