Exploring the Contributions of the Supplementary Eye Field to Subliminal Inhibition Using Double-Pulse Transcranial Magnetic Stimulation

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Abstract: It is widely accepted that the supplementary eye fields (SEF) are involved in the control of voluntary eye movements. However, recent evidence suggests that SEF may also be important for unconscious and involuntary motor processes. Indeed, Sumner et al. ([2007]: *Neuron* 54:697–711) showed that patients with micro-lesions of the SEF demonstrated an absence of subliminal inhibition as evoked by masked-prime stimuli. Here, we used double-pulse transcranial magnetic stimulation (TMS) in healthy volunteers to investigate the role of SEF in subliminal priming. We applied double-pulse TMS at two time windows in a masked-prime task: the first during an early phase, 20–70 ms after the onset of the mask but before target presentation, during which subliminal inhibition is present; and the second during a late phase, 20–70 ms after target onset, during which the saccade is being prepared. We found no effect of TMS with the early time window of stimulation, whereas a reduction in the benefit of an incompatible subliminal prime stimulus was found when SEF TMS was applied at the late time window. These findings suggest that there is a role for SEF related to the effects of subliminal primes on eye movements, but the results do not support a role in inhibiting the primed tendency. *Hum Brain Mapp* 38:339–351, 2017. © 2016 Wiley Periodicals, Inc.

Key words: supplementary eye field; transcranial magnetic stimulation; negative compatibility effect; subliminal inhibition; unconscious

INTRODUCTION

Nonconscious information has been shown to influence cognitive processing and behavior [see Ansorge et al., 2014; Dehaene and Changeux, 2011; Soto and Silvanto, 2014; van Gaal et al., 2012 for reviews]. The nonconscious effects are often studied using masked-prime tasks, in which sensory stimuli making up the prime, are rendered invisible by the presentation of a nearby (in space or time) second object, the mask [Breitmeyer and Ögmen, 2006]. A visible target stimulus is processed more efficiently when preceded by a related and fully masked prime than when preceded by an unrelated prime [Eimer and Schlaghecken, 2003; Forster and Davis, 1983; Marcel, 1983].

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This phenomenon, often referred to as subliminal priming, has been demonstrated to occur at various levels, such as at semantic analysis [e.g., Kouider and Dehaene, 2007], working memory [e.g., Soto and Silvanto, 2014], and action selection [see Sumner and Husain, 2008; van Gaal et al., 2012 for reviews]. The subliminal priming effect is assumed to arise from automatic processing induced by the masked prime [Dehaene et al., 1998; Klapp, 2015; Sumner and Husain, 2008]. Potentially consistent with this, neuroimaging results have shown brain activation in several cortical areas evoked by the masked prime [Brooks et al., 2012; Dutta et al., 2014; van Gaal et al., 2010]. On one hand, the subliminal priming facilitates responses to familiar stimuli, thus helping to reduce cognitive load and benefiting performance [Eimer, 1995; Neumann, 1990; Soto and Silvanto, 2014]. On the other hand, there is a need to adjust the subliminal priming to allow flexible behavior when facing the ever-changing world [Eimer and Schlaghecken, 2003; McBride et al., 2012; Rushworth, 2008; van Gaal et al., 2012].

An example showing the adjustability of subliminal priming has been illustrated by Eimer and Schlaghecken [1998, 2003]. In a series of studies, they showed that it is possible for subliminal priming to have opposite effects. When the interval between prime and target was short, a typical priming effect was observed, with motor responses made faster when the prime and target indicated the same direction (compatible trials) than when they indicated opposite directions (incompatible trials). In contrast, when the interval between the prime and the target was increased to over 100 ms, the typical priming effect was reversed. Incompatible trials now lead to faster responses than compatible trials (negative compatibility effect, NCE). In addition, the lateralized readiness potential (LRP), an indicator of hand-specific movement preparation was also affected by prime-target compatibility [Eimer, 1995; Eimer and Schlaghecken, 1998]. The LRP waveform initially showed sub-threshold activation in the direction corresponding to the prime, but was immediately followed by a deflection in the opposite direction, suggesting an inhibition of the prime induced sub-threshold activation [Eimer and Schlaghecken, 1998; Eimer et al., 2002]. Further study has associated the shape and size of this LRP deflection with reaction time, suggesting that it might be directly related to the NCE [Seiss et al., 2014]. Therefore, the NCE has been used as an index for the subliminal inhibition, which is triggered to suppress the prime induced sub-threshold activation [Bowman et al., 2006; Boy et al., 2010c; Eimer and Schlaghecken, 2003; Sumner and Brandwood, 2008].

This subliminal inhibition underlying the NCE reflects the flexible character of subliminal priming that it is adjustable when an early automatic activation is subsequently unsuitable in a changed context [Eimer and Schlaghecken, 2003; McBride et al., 2012; Sumner and Husain, 2008]. However, the neural sources underlying the

NCE are still unclear. Neuroimaging studies have shown that the NCE is associated with activity change in the supplementary motor area (SMA) [Boy et al., 2010a,b; Krüger et al., 2013] as well as in the caudate and thalamus [Aron et al., 2003; D'Ostilio et al., 2012]. However, due to subliminal processing activation often being subtle, as well as the limited temporal resolution in current MRI-based neuroimaging techniques, it has proven difficult to distinguish between activity changes related to subliminal inhibition and those related to voluntary action selection [Boy et al., 2010b; Sumner et al., 2007]. Meanwhile, lesion studies have demonstrated the absence of subliminal inhibition in patients with medial frontal micro-lesions [Sumner et al., 2007]. Sumner et al. [2007] observed normal NCEs in healthy people and control patients with lateral premotor or pre-SMA damage. In contrast, two patients with SMA and supplementary eye field (SEF) lesions showed an absence of a NCE in manual or oculomotor responses corresponding to the function of the injured region. The individual with lesion damage to both the SMA and SEF showed an absence of a NCE for both manual and oculomotor responses while the other patient, whose lesion was small and restricted to the SEF, showed such an absence only for oculomotor responses. These findings suggest that the SMA/SEF region is involved in subliminal inhibition [Sumner et al., 2007]. Furthermore, the fact that subliminal inhibition is effector-specific implies that the inhibition occurs within the neural system unique to the specific effector [Eimer et al., 2002].

The SEF has been identified as part of the cortical network controlling eye movements [Schlag and Schlag-Rey, 1985, 1987]. Schlag and Schlag-Rey observed that electrical stimulation of this region in the monkey evoked saccades, and that neurons within the SEF exhibited changes in activity time-locked to visual stimuli and saccades [Schlag and Schlag-Rey, 1985, 1987]. Although the change of neuronal activity in the SEF is insufficient to directly initiate or cancel a saccade [Schall et al., 2002; Stuphorn et al., 2000], the changes in activity in this area have been associated with diverse cognitive variables during saccades, such as object-centered representations [Olson and Gettner, 1995], conditional rule learning [Chen and Wise, 1995; Olson and Gettner 2002], and monitoring response conflict, error, or reward [Roesch & Olson, 2003; Stuphorn et al., 2000; Stuphorn, Brown, & Schall, 2010]. These findings suggest that the function of the SEF is supervisory control of saccade preparation based on the context or task demand.

Here, we applied transcranial magnetic stimulation (TMS) to young healthy participants to test the hypothesis that oculomotor subliminal inhibition occurs in undamaged SEF. TMS is a technique to stimulate the brain activity non-invasively and can be used to draw causal links between brain regions and specific behaviors [Banissy and Muggleton, 2013; Silvanto et al., 2007, Silvanto et al., 2008; Silvanto and Pascual-Leone, 2012; Walsh and Cowey,

2000]. A single magnetic pulse is very brief (less than 1 ms) and can have functional effects lasting for tens of milliseconds [Barker, 1999; Miniussi et al., 2012]. We exploited the temporal resolution of TMS to test the function of SEF during the time course of the masked-prime task. We followed the conventional design of the masked-prime task, using centrally presented arrows as the prime and a target that instructed the direction of saccades [Eimer and Schlaghecken, 1998]. In addition, we included trials with neutral primes, which indicated an action of fixating that was consistent with the explicit requirements of the task during the presentation of the masked prime, that is, fixating in the center until the appearance of the target. It is, thus, assumed that the oculomotor system should be free from subliminal inhibition in neutral trials as the neutral prime does not indicate any direction and hence should not induce sub-threshold activation or subsequent inhibition. However, subliminal inhibition in trials with directional arrows as the primes is assumed to occur during the sufficiently long time interval between the prime and target regardless of the identity of the later target [Praagstra and Seiss, 2005; Seiss et al., 2014]. Therefore, we applied double-pulse TMS at two time windows (Fig. 1) [Juan and Walsh, 2003]. One time window was early, 20–70 ms after the onset of the mask but, importantly, before target presentation. This early time window is assumed to be during the period of subliminal inhibition in trials with arrow primes but not in trials with neutral primes. If the SEF is engaged in the inhibition of the primed tendency, applying TMS at the early time window would interfere with this subliminal processing. As a result, this would mean the magnitude of the NCE would be modulated by the SEF-TMS at the early time window, while the saccade latency in the neutral trials would not be affected by the SEF-TMS for the same time period. The other time window was later, 20–70 ms after target onset, during which the imperative target was presented, and a corresponding saccade would be expected to be being preparing. If the SEF is engaged only in voluntary saccades, applying TMS at the late time window may interfere with the saccade preparation. Consequently, if this is the case, the TMS at the late time window would be expected to modulate saccade latency, particularly in the neutral trials, but not affect the NCE.

In addition, we included sham stimulation and frontal eye fields (FEF) TMS as control conditions. The results of sham stimulation allow us to determine if there are non-specific effects of the lateralized auditory stimulus during the TMS pulses [Lisanby et al., 2001]. Our reasons for also adding FEF as a control condition in the present study are as follows. First, both SEF and FEF are known to be important cortical eye fields that are involved in eye movement control [for reviews see McDowell et al., 2008; Paus, 1996; Schall and Boucher, 2007]. In addition, the FEF has been reported to be involved in visual priming [Bichot and Schall, 2002; Lane et al., 2012]. Thirdly, neurons in the

FEF show visual activity in response to masked stimuli which are without effect on behavioral performance [Thompson and Schall, 1999]. Therefore, we examined the distinction between SEF and FEF with respect to oculomotor subliminal inhibition. These results would be a necessary complement to knowledge related to oculomotor control.

METHOD

Participants

Twenty-one participants (12 males, 20–27-year old) were included. Participants were naïve to the purpose of the experiments. All participants had normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. Participants were screened for medical contraindications against receiving repetitive TMS [Rossi et al., 2009; Wasserman, 1998] and provided informed consent to participate prior to taking part in the experiment. They received monetary payment for their participation. The study was approved by the Institutional Review Board of the Chang-Gung Memorial Hospital, Taoyuan, Taiwan.

Apparatus

Stimuli and trials were created using SR Research Experimental Builder 1.10.165 and presented on a 19-in. color cathode ray tube monitor (ViewSonic Professional Series P95f+) at a vertical refresh rate of 100 Hz. Eye positions were recorded by the EyeLink 1000 tracker (SR Research) every 1 ms (1,000 Hz). A chin rest was used to maintain a fixed distance of 85 cm from the monitor while restricting head movements, and to ensure participants' eye height was at the same level as the center of the display screen.

Stimuli, Design, and General Procedure

The stimuli were stylistically consistent with those used by Eimer and Schlaghecken [1998] (Experiment 1), all of which were presented in black on a white background. The stimulus arrangement and trial sequence are illustrated in Figure 1. The trial began with a fixation screen which contained a small fixation cross (+) ($0.38^\circ \times 0.38^\circ$) in the center of the screen for 500 ms. This was followed by a blank screen for 300 ms and then a prime screen for 20 ms. The prime was presented in the center of the screen and consisted of either a leftward (<) arrow, a rightward (>) arrow, or a "+" sign, all of which were 0.8° by 0.8° in size. After the prime screen, a mask screen was immediately presented. This was constructed from all three of the prime stimuli superimposed on top of one another and was presented for 100 ms. A 50 ms blank screen followed the mask, with the target subsequently presented for 100 ms. The target, placed in the center of the screen, was

A. The masked-prime task with a long prime-target interval **B. SEF** **C. FEF** **Figure 1.**

(A) Illustration of the trial sequence in a mask-prime task. In the present study, we adopt a long time interval between a prime and a target (150 ms) as we are interested in the NCE. All of the possible types of prime are shown, but only one is presented (randomly) per trial in the formal task. The target was either a left- or right-pointing arrow. Participants were required to maintain their fixation at the center of the screen until the target screen was displayed. They were then required to make a saccade to the lateral circle in the direction indicated

by the target as soon as it was presented. The two circles making the target landing points of saccades were constantly present on the screen throughout the entire task (they are not plotted here to simplify the figure). The times for application of double-pulse TMS are indicated in the figure with lightning symbols. The early time window was 20–70 ms after the onset of the mask and the late time window was 20–70 ms after onset of target. (B) Target of the TMS stimulation for the right SEF and (C) the right FEF. [Color figure can be viewed at wileyonlinelibrary.com.]

either a leftward or rightward arrow of the same sized as the prime arrows and required a saccade response to be made in the indicated direction. The time interval between prime offset and the onset of the target was 150 ms which can be categorized as a long prime-target interval for investigating the NCE in this study. Throughout the whole trial, two circles, each with a diameter of 0.5° and at a horizontal distance of 10° from the center of the screen, were displayed and these served as the landing points for the

leftward or rightward saccades. The two circles disappeared 400 ms after saccade execution. For simplicity, these circles are not shown in every screen in Figure 1. There was a 1,000 ms blank screen between trials.

Although our participants did not perform a prime detection task to check the effectiveness of the masking effect, previous studies have demonstrated that a 20 ms duration of priming resulted in discrimination performance below chance level (50%) in various types of

masked-prime tasks even after practice [e.g., D'Ostilio et al., 2012; Eimer and Schlaghecken, 1998, Experiment 3; Schlaghecken and Sisman, 2006; Sumner et al. 2006, Experiment 2; Wildegger et al., 2015, Experiment 1]. Therefore, we are confident that a short prime duration (20 ms) and a relevant mask would ensure effective masking and avoid intentional control over masked priming.

The experiment included four sessions of testing for each participant with each session at least 7 days apart. The first session was always used to find the participant's TMS motor threshold and to localize the FEF functionally. In the other three sessions, participants performed the masked prime task with TMS delivered over the FEF, SEF, or with sham stimulation. The order of these three experimental sessions was counterbalanced across participants. In each experimental session, participants performed one practice block of 96 trials, which was followed by one experimental block of 216 trials. Only the data from the experimental blocks were used for analysis.

Every experimental block was further divided into six cycles of three mini-blocks. The three mini blocks consisted of blocks of trials with early TMS (applied at 20 ms and 70 ms after the mask onset), late TMS (applied at 20 ms and 70 ms after the target onset), and no TMS. The order of the TMS conditions was fixed for each participant but counterbalanced across all participants. There were 12 trials in each mini-block, making a total of 72 trials for each TMS condition. A mini-block included six types of trials: (1) a leftward target with a compatible (i.e., leftward) prime; (2) a rightward target with a compatible prime; (3) a leftward target with an incompatible (i.e., rightward) prime; (4) a rightward target with an incompatible prime; (5) a leftward target with a neutral prime (i.e., "+"); and (6) a rightward target with a neutral prime. The number of each trial type was the same and the order was randomized within each mini-block.

TMS Parameters and Site Localization

Double-pulse TMS was delivered using a Magstim 200 Super Rapid Stimulator and a 50-mm figure-of-eight coil. To take into account the individual differences in cortical electrical conductivity and excitability, the stimulation intensity was set at 110% of the participant's motor threshold. Individual participant's motor threshold was measured by stimulating the right motor cortex and set at the lowest stimulation intensity of TMS that could induce a visible twitch in the resting contralateral hand in 5 of 10 trials [Schutter and van Honk, 2006]. The average motor threshold across participants was 66% of the machine output.

To determine the appropriate time window for TMS, we executed a pilot experiment with 11 subjects, with SEF TMS applied at the mask onset with a pulse train of 20 Hz frequency to fully cover the entire interval between mask and target. Our pilot data showed that SEF TMS facilitated overall saccade latency but did not cause any modulation of the NCE. We, therefore, selected the early time window

according to previous studies that showed the timing of processing of visual stimuli was early in FEF, with TMS pulses delivered at 40 and 80 ms following stimulus onset disrupting performance [Juan et al., 2008; O'Shea et al., 2004; Silvanto et al., 2006; Taylor et al., 2007b]. Furthermore, the timing data relating to responding to visual stimuli in FEF and SEF neurons has shown responses at around 60 ms and 80 ms, respectively [Pouget et al., 2005]. Although species differences should not be dismissed, and there is little additional data about the timing of human SEF involvement in visual processing, it seems reasonable to assume the available timing information provides a good guideline for the current study.

The site for right FEF stimulation was located using a simple saccade task during which 10 Hz TMS was delivered for 500 ms over candidate sites anterior to the hand motor area in the right hemisphere [Muggleton et al., 2003; Ro et al., 2002]. The site that resulted in the longest saccade latencies was marked, and the anatomical position was then located by co-registering the head of each participant with their individual high-resolution magnetic resonance imaging scans using the Brainsight system (Rogue Research, Montreal, Canada) so that the same site could be accurately relocated in subsequent test sessions.

The right SEF was located by moving 3 cm rostrally and 0.5 cm laterally of the vertex [Liu et al., 2011; Nyffeler et al., 2008]. The stimulating coil was oriented parallel to the midline with the handle pointing toward the back of the head for the SEF, whereas the coil was oriented at a 45-degree angle to the midline with the handle pointing in the posterior direction for the FEF and the dorsal motor area.

During the sham stimulation session, the coil was positioned at the same location as for right SEF stimulation, but was angled off the head such that only one wing of the coil touched the scalp. The degree of angulation from the plane tangential to the scalp was 90 degrees [Lisanby et al., 2001].

Data Analysis

Saccades were automatically identified by the EyeLink system according to acceleration and amplitude criteria (minimum speed 30°/s, minimum acceleration 8,000°/s², and minimum amplitude 1°) so that eye drifts or small eye movements were not erroneously categorized as saccades. Correct responses were defined as saccades in the same direction as the target arrow and within 2° of the landing point. Only the first saccade made on a trial was analyzed. Saccade latency (RT) was defined as the time interval between target onset and initiation of a saccade. Saccade latencies below 100 ms (0.43% of the total trials) or above 600 ms (0.08%) were considered anticipations or lapses, respectively, and were excluded from analysis. Accuracy and mean RTs of correct responses were calculated for each condition. The conventional indexes of NCE were also calculated by subtracting the mean saccade latencies on the compatible trials from those on the incompatible

trials. Two participants were excluded from the analysis because their accuracy fell below 30% in some conditions. Data from one other participant was not included in the analysis due to a lack of any NCE.

Several analyses were run to investigate the effects of magnetic stimulation on the NCEs, RTs, and response accuracy. For the first step, the conventional index of NCE (incompatible RTs minus compatible RTs) was entered into a 3 (session [SEF, FEF, sham]) $\times$ 3 (timing of stimulation [early, late, no]) $\times$ 2 (response direction [left, right]) repeated measures analyses of variance. Second, the TMS effects on saccade latencies were computed by calculating the change in saccade latencies following TMS during the early or late time window, relative to the saccade latencies under conditions without stimulation. These computations were also performed for response accuracy. These changes in RTs and accuracy were then separately entered into 3 (session [SEF, FEF, sham]) $\times$ 3 (prime type [compatible, incompatible, neutral]) $\times$ 2 (response direction [left, right]) repeated measures analyses of variance for early and late TMS. Significant main effects and interactions were further analyzed with follow-up one-way repeated measures analyses of variance and post hoc Fisher's tests. Significance was set at $P < 0.05$.

RESULTS

Negative Compatibility Effect

There was no overall effect of either session or timing of stimulation (both $F_s < 2$), but there was a significant interaction between session and timing of stimulation, $F(4, 68) = 2.77$, $P = 0.034$, $\eta^2 = 0.14$. One source of this interaction was that the simple main effect of timing was significant on the SEF session ($F(2, 34) = 4.67$, $P = 0.016$, $\eta^2 = 0.22$) but not significant for either the FEF or the sham session (all $F_s < 2$). For SEF stimulation, the negative priming effect was smaller in trials with stimulation applied in the late time window, compared to the early time window ($P = 0.033$) or without stimulation ($P = 0.020$) (Fig. 2).

The simple main effect of session was significant only when stimulation was applied during the late time window ($F(2, 34) = 3.51$, $P = 0.041$, $\eta^2 = 0.17$) but not for the early time window or no TMS trials (all $F_s < 1$). Post hoc tests indicated that the negative compatibility effect with late TMS over SEF was significantly different (lower) than sham stimulation ($P = 0.034$), demonstrating this late-SEF elicited reduction of negative compatibility effect was not due to a non-specific effect of TMS.

There was a significant main effect of stimulus direction, $F(1, 17) = 6.98$, $P = 0.017$, $\eta^2 = 0.29$, with the negative compatibility effect was more negative for rightward ($M = -45$ ms, $SE = 3.84$) than for leftward responses ($M = -38$ ms, $SE = 3.16$). All interactions between response direction and other factors were not significant (all $F_s < 2$), indicating this rightward enhancement in negative compatibility effect was an overall effect.

Figure 2.

The NCE amplitudes for the three sessions (SEF, FEF and sham stimulation), and the three time windows (No TMS, early TMS, and late TMS). The NCE was observed in all three sessions. The SEF TMS reduced the magnitude of NCE. Error bars represent the 95% within-subjects confidence intervals. * $P < 0.05$. [Color figure can be viewed at wileyonlinelibrary.com.]

Changes in Saccade Latency and Accuracy by TMS at the Early Time Window

Repeated measures analyses of variance revealed no main effect of session, prime type, or direction for the early-TMS trials (all $F_s < 2$). All interactions were non-significant except for the interaction between session and prime type, $F(4, 68) = 3.56$, $P = 0.011$, $\eta^2 = 0.17$. Follow-up analysis of this interaction revealed that sham stimulation led to a pronounced decrease in incompatible RTs compared to neutral RTs ($P = 0.013$), but difference between incompatible and compatible RTs was not significant ($P = 0.128$). In contrast, SEF-TMS decreased neutral RTs significantly more than compatible ($P = 0.041$) but not incompatible ($P = 0.103$) RTs. Similarly, FEF-TMS also tended to decrease neutral RTs more than compatible ($P = 0.084$) and incompatible ($P = 0.066$) RTs (Fig. 3A).

For responses accuracy, repeated measures analyses of variance revealed only a significant effect of prime type, $F(2, 34) = 4.83$, $P = 0.014$, $\eta^2 = 0.22$, with lower accuracy responses for compatible trials than incompatible ($P = 0.036$) and neutral ($P = 0.033$) trials when collapsed across the three sessions. Although Figure 3B shows that the sham stimulation seemed to decrease accuracy on compatible trials more than FEF and SEF, the interaction between session and prime type was not significant. Session, direction main effect, or interactions among the three factors were also found to not be significant (all $F_s < 2$).

Changes in Saccade Latency and Accuracy by TMS at the Late Time Window

The analysis of late-TMS induced change in saccade latencies yielded a significant main effect of session, $F(2,$

Figure 3.

Early TMS induced changes in **(A)** saccade latencies and **(B)** accuracy for TMS over the three sites (SEF, FEF, and sham), plotted separately for incompatible (red), neutral (green), and compatible (purple) trials. These changes RTs were calculated by subtracting RTs in trials without TMS from RTs in trials with early TMS. The computations of early TMS effects were also performed for response accuracy. The error bars indicate 95% within subjects CI. * $P < 0.05$. [Color figure can be viewed at wileyonlinelibrary.com.]

34) = 6.79, $P = 0.003$, $\eta^2 = 0.285$, and a significant interaction between session and prime type, $F(4, 68) = 5.14$, $P = 0.001$, $\eta^2 = 0.232$, with a non-significant main effect of prime type, $F(2, 34) = 2.65$, $P = 0.085$, $\eta^2 = 0.14$. These indicate that the effects of late-TMS on responses to the three types of primes were different dependent on where the late-TMS was applied. This interaction between session and prime type was further analyzed with data collapsed across both response directions (Fig. 4A) as neither main effect of direction nor interactions between direction and other factors was significant (all $F_s < 2$).

The increase in saccade latencies by stimulation over SEF was longest for incompatible trials (15.8 ms), compared with neutral ($P = 0.007$) and compatible ($P = 0.020$) trials (simple main effect of prime type under SEF session:

$F(2, 34) = 5.61$, $P = 0.008$, $\eta^2 = 0.25$). The increase in neutral RTs was approximately twice as large as the increase in compatible RTs (8.9 vs. 4.6 ms), but this difference did not approach statistical significance ($P = 0.195$).

When the late-TMS was applied over the FEF, the changes in saccade latencies were also significantly different among the three prime types ($F(2, 34) = 4.43$, $P = 0.020$, $\eta^2 = 0.21$). Post hoc tests show that the increase of incompatible RTs was comparable to that on compatible RTs ($P = 0.306$) but was significantly larger than the change on neutral RTs ($P = 0.015$).

In blocks with sham stimulation, the late-TMS induced changes were comparable across the three prime types ($F(2, 34) = 1.70$, $P = 0.198$, $\eta^2 = 0.09$).

Figure 4.

Late TMS induced changes in **(A)** saccade latencies and **(B)** accuracy over the three sites (SEF, FEF, and sham), plotted separately for incompatible (red), neutral (green), and compatible (purple) trials. These changes in RTs were calculated by subtracting RTs in trials without TMS from RTs in trials with late TMS. The computations of late TMS effects were also performed for response accuracy. The error bars indicate 95% within subjects CI. * $P < 0.05$. [Color figure can be viewed at wileyonlinelibrary.com.]

Additionally, follow-up analysis of the interactions for late-TMS induced changes described above also revealed a significant simple main effect of session for incompatible ($F(2, 34) = 10.26, P < 0.001, \eta^2 = 0.376$) and neutral primes ($F(2, 34) = 3.74, P = 0.034, \eta^2 = 0.38$) but not for compatible primes ($F(2, 34) = 0.89, P = 0.419, \eta^2 = 0.05$). For incompatible primes, the effects of late-TMS at both SEF and FEF were significantly different from the effect of sham stimulation (SEF vs. sham, $P = 0.002$; FEF vs. sham, $P = 0.005$). The effect with SEF-TMS tended to be larger than that of FEF-TMS ($P = 0.090$). With regard to neutral primes, the effects of late-SEF TMS showed a stronger increase than sham ($P = 0.027$) and FEF ($P = 0.023$) while changes in saccade latencies were comparable for FEF and sham stimulation ($P = 0.446$). Lastly, the effect on compatible trials by late-TMS were comparable across all three sites.

For responses accuracy after late-TMS, repeated measures analyses of variance results revealed no main effect of session, prime type, or response direction and showed no interaction among these factors (all $F_s < 2$) (Fig. 4B).

DISCUSSION

Previous studies have suggested an involvement of medial frontal cortex (including SEF) in the negative compatibility effect [Boy et al., 2010a, 2010b; Sumner et al., 2007]. It remains, however, an open question as to whether the functional role of medial frontal cortex is inhibiting the prime-induced activation or processing related to voluntary action. We applied double-pulse TMS over SEF at two different time windows to clarify the functional role of SEF in the Negative Compatibility Effect with a long interval masked-prime task. The early time window was an interval between prime and target, during which inhibition of prime-induced activation is assumed to be present [Eimer and Schlaghecken, 1998; Eimer et al., 2002; Jaśkowski et al., 2008; Seiss et al., 2014]. We, therefore, expected a modulation of the negative compatibility effect after the SEF TMS at the early time window if this subliminal inhibition of the oculomotor system occurs in SEF. Indeed, we found that the magnitude of the NCE was reduced after TMS stimulation of SEF, a result analogous to the results in the lesion study by Sumner et al., in which the NCE was absent in patients with specific lesions of SEF [Sumner et al., 2007]. However, this modulation of NCE in the present study occurred with SEF TMS only at late time window rather than at the expected early time window.

In addition, we found that SEF TMS delivered at the early time window shortened the saccade latencies in neutral trials. The neutral prime in the present study was a symbol “+” which was also used at the beginning of each trial to indicate the action of maintaining fixation at the center of the screen until the presentation of the imperative target. Therefore, trials with neutral primes are assumed to be free from subliminal inhibition as the

neutral prime does not indicate any direction and hence there is no pre-activation or subsequent inhibition. It is worth noting that FEF TMS at the early time window also shortened the saccade latencies in neutral trials. This facilitation is unlikely to be a consequence of a non-specific TMS effect because it was not found in the sham stimulation trials. Indeed, both FEF and SEF, with their direct projections to the subcortical oculomotor network, have neurons that show fixation-related activations [Bon and Lucchetti, 1992; Goldberg et al., 1986]. These fixation-related neurons change their signal related to the presence or absence of a fixation point [Goldberg et al., 1986; Sommer and Tehovnik, 1999; Tehovnik et al., 1999] and cause inhibition of saccade-related neurons, for example, through the SC [Munoz and Istvan 1998; Sommer & Wurtz, 2000]. It seems probable that TMS at the early time window in the present study interfered with fixation-related signals from these neurons in the FEF and SEF, which in turn weakened the suppression of subcortical saccade-related activity, consequently facilitating saccadic responses. Therefore, facilitation by SEF or FEF stimulation before target onset presumably reflects their preparatory roles in oculomotor control [Grosbras and Paus 2003; Nagel et al., 2008; Nyffeler et al 2004]. In summary, the TMS effect at the early time window suggests that the functional role of SEF during the period before target presentation appears to be more on preparation than on subliminally inhibiting the (directional) prime induced activation. Furthermore, the functional role of FEF seems to be similar to the SEF during this early time window.

In contrast, SEF TMS in the late time window reduced the negative compatibility effect and increased response times mainly for incompatible and neutral primes. The late time window was after the presentation of the imperative target, during which it is thought preparation of a saccade relative to the target is underway. Our results of an increased saccade latency due to SEF TMS at the late time window are consistent with previous studies which have shown disruptive effects of SEF TMS on saccade generation soon after the presentation of a target for saccade, such as slower saccade initiation [Nagel et al., 2008] or more poorly planned saccades [van Donkelaar et al., 2009], suggesting a functional role for SEF in saccade preparation. Furthermore, the results from the present study reveal an interesting pattern: saccade latencies were increased most on incompatible trials, showed an intermediate increase for neutral trials, and had the least increase on compatible trials as a result of TMS over SEF during the late time window (Fig. 4A). In fact, the relationship between inverse priming and target direction becomes apparent only after the presentation of the imperative target. In this case, a response to a target that is compatible with the prime has been subject to subliminal inhibition while a response to the target that is incompatible to the prime has been activated at a sub-threshold level [Aron et al 2003; Eimer and Schlaghecken 2003]. Therefore, given the unequal

interference caused by late SEF-TMS in these three types of trials, it is possible that saccade preparation in the SEF may interact with the sub-threshold activation, and then result in gaze in the correct direction. However, the actual inhibition or facilitation from subliminal priming in the present study appears not to be exerted by the SEF.

In addition, we saw that FEF TMS at late time window delayed saccade latencies only for incompatible trials and not for neutral trials, implying FEF involvement to a lesser extent or at a later time point compared to the SEF. Indeed, monkey single-unit recordings from the FEF and SEF may fit with this [Hanes et al., 1995]: movement neurons in both the FEF and SEF show presaccadic discharges before initiation of saccades and that are related to this saccade initiation. The beginning of this presaccadic discharge was generally seen earlier in SEF than in FEF presaccadic movement cells, which may be why our results showed more of an effect due to SEF TMS than due to FEF TMS for the late time window. Presaccadic activity might increase in parallel with subliminal priming and hence may start earliest in incompatible trials, and consequently be most disrupted. Nonetheless, further studies with more detailed temporal parameters of TMS are needed to elaborate on the temporal relationship among these cortical eye fields in a masked-prime paradigm.

Previous studies have suggested that the SEF controls eye movements in a proactive manner [Heinen et al., 2011; Nyffeler et al., 2008; Purcell et al., 2012; Sharika et al., 2013; Stuphorn et al., 2010]. For instance, in a go/nogo task, neurons in the SEF do not directly inhibit or initiate saccades, instead, they regulate saccade production based on the prior probability of trial types by biasing the balance between gaze-holding and gaze-shifting [Stuphorn et al., 2010]. Similarly, in an ocular baseball task, the action rule of whether to go changes with combinations of multiple stimuli rather than a single feature of one stimulus. Neurons in the SEF continuously interpret stimulus contingencies, signaling go or no go in compliance with the complex rule rather than simple motion per se [Heinen et al., 2011]. These results contradict the speculative role of SEF in subliminal inhibition that suggests SEF inhibition of the primed motor tendency always occurs regardless of type of the following action (target). Instead, in a way similar to a proactive control, our findings suggest that the functional role of SEF is dependent on the time course of subliminal inhibition. The SEF prevents an inappropriate response from undergoing subliminal processing when the target is still pending. Once the goal becomes clear, the SEF facilitates the initiation of an appropriate response.

The finding of SEF dependence on target processing is in agreement with other studies which have addressed the neuronal sources of the NCE [Boy et al., 2010b]. Boy et al. used fMRI and a similar masked-prime task involving manual responses. They found that BOLD signals in the SMA were modulated by prime compatibility, showing greater activation during compatible trials. More

importantly, these results required the existence of the target stimuli, with no change in SMA activity when the target stimuli were absent. The authors, thus, suggested that SMA activity is related to the interaction between subliminal inhibition and target processing rather than prime-mask interaction [Boy et al 2010b]. Therefore, our finding that the SEF is involved in the prime-target interaction adds one more piece of evidence to support that the role of SMA for NCE of manual responses is analogous to the role of SEF for oculomotor NCE [Sumner et al., 2007].

Additionally, we found a nonspecific effect of stimulation, with the negative compatibility effect enhanced for rightward responses. It is worth mentioning that the coil was always placed over the right hemisphere in the present study. Consequently, the somatosensory stimulation evoked by the device on the right side of the head may be distracting and bias attention to the right side. In fact, it has been demonstrated that the negative compatibility effect is enhanced by an exogenous attentional cue [Sumner et al., 2006]. Therefore, a tentative account of this ipsilateral enhancement of NCE is due to a lateralized cueing by TMS.

It is worth noting that the TMS effect of stimulation of SEF could be diffuse. It may also be argued that our TMS effect could be ascribed to modulation of neighboring structures such as the pre-SMA or SMA. Indeed, the pre-SMA has been shown to be involved in oculomotor [Hikosaka and Isoda, 2008; Isoda, 2005; Nachev et al., 2007] and inhibitory control [Chen et al., 2009; Duque et al., 2013; Hsu et al., 2011; Rushworth et al., 2002; Taylor et al., 2007a]. It is, thus, possible that our SEF TMS might have affected the pre-SMA. Fortunately, previous studies concerning the neural mechanisms of NCE provide clear functional dissociation between the SEF, pre-SMA, and SMA [Boy et al., 2010a,b,c; Sumner et al., 2007]. A patient with a lesion of pre-SMA showed a normal behavioral pattern of NCE for both ocular and manual responses, which is inconsistent with our present findings of reduced NCE by SEF TMS. Furthermore, activity changes during a long interval masked-prime task were not found in pre-SMA in a recent neuroimaging study [Boy et al., 2010a, 2010b, 2010c]. Hence, it is less possible that any modulation of NCE would be observed in our study if we had stimulated one of these brain areas that seem not to be involved during the masked-prime task. Furthermore, the NCE is suggested to be effector specific. For example, lesions in SMA result in deficits in NCE only for manual responses but not for oculomotor response [Sumner et al., 2007]. It is, thus, unlikely that there would be any modulation of saccadic NCE in our present study if we had stimulated at the SMA. We, therefore, think that it is plausible to infer the observed effect is due to an influence on the SEF, although an involvement of the pre-SMA cannot be ruled out.

Subliminal inhibition has been assumed to be an inhibitory mechanism in motor control [Eimer and Schlaghecken, 1998, 2003], and thus, we followed previous studies in using an arrow in the center as the prime and as the target stimuli

to avoid confounds with spatial orienting. Similarly, spatial orienting has been shown to result in a biphasic pattern of facilitation and inhibition on reaction times or detection performance [Jonides, 1981; Posner, 1980]. When attention is firstly oriented to a peripheral visual cue there is a facilitation of detection of targets that soon occur at that location. If attention is then shifted away from the cued location, for example, back to the fixation point, there is slower processing related to the originally cued location than for other areas of the visual field, termed inhibition of return (IOR) [Posner and Cohen, 1984; for review, see Klein, 2000]. IOR appears to be similar to the NCE at first glance due to its biphasic pattern, with changes from facilitation to inhibition dependent on the length of the interval between the cue/prime and the target. A comprehensive comparison between IOR and NCE is beyond the scope of this article. However, we can highlight a seemingly critical differences between IOR and NCE. IOR seems to occur only when attention is captured exogenously [Godijn et al., 2004; Posner and Cohen, 1984] whereas the NCE is not always found for stimuli presented in the periphery [Schlaghecken and Eimer, 2000]. Nonetheless, it is still under debate whether mechanisms underlying the IOR and NCE are the same or dissimilar. Mulckhuyse and Theeuwes [2010], Mele et al. [2008], or Hermens et al. [2010] all offer a more detailed discussion.

So far, we have interpreted our findings only from the motor inhibition perspective. However, recent studies assume that the NCE can be both perceptual and motor in origin [Boy and Sumner, 2010; McBride et al., 2012], although it is still a controversial issue about which factors determine the relative contribution between perceptual and motor sources [Jaśkowski and Verleger, 2007; Jaśkowski and Przekoracka-Krawczyk, 2005; Sumner, 2008]. For instance, mask construction has been viewed as a primary factor to determine the source of the NCE [Lleras and Enns, 2004]. Lleras and Enns argued that objects updating in visual perception also explains the NCE when the mask contains prime-like features (e.g., a relevant mask, such as the mask stimuli used in the present study, that is constructed by superimposing the possible prime stimuli). The object-updating hypothesis assumes that the visual system favors new stimuli over old. The rapid succession of the prime and prime-like mask, thus, increases the salience of elements in the mask that were not presented in the preceding prime. These salient elements in the mask then cause motor priming opposite to that has been elicited by the preceding prime. Therefore, the observed NCE is actually the positive priming effect that is caused by the updated scene of the prime and mask [Lleras and Enns, 2004, 2006; Verleger et al., 2004].

Following the framework of the objects-updating hypothesis, an alternative explanation of our result is that the SEF was not involved in the perceptual updating of prime and mask and the subsequent priming. Nonetheless our main finding that the SEF TMS at late time window delayed the incompatible trials still indicates dependence of role of SEF on target processing related to oculomotor control.

On the other hand, some researchers have put emphasis on the strength of association between prime stimuli and motor responses [Klapp, 2015; Liu and Wang, 2014]. Klapp argued that masked priming is possible only when the stimuli-and-response (S-R) association has been established. In other words, a stimulus has been firmly connected to a specific action and can induce this specific action without conscious mediation [Klapp, 2015]. Arrow stimuli are examples that have been closely associated with directional responses in our real world. Indeed, Eimer and Schlaghecken [1998] (Experiment 1A) have used arrow stimuli as prime and target in their pioneering study that first reported the NCE. However, the mask stimulus used in their study was constructed by superimposing the prime arrows, which have been criticized for interacting with the prime to produce positive priming of the alternative response [Lleras and Enns, 2004]. Eimer and Schlaghecken further examined this possibility by replacing the arrow targets with letter targets while the prime and mask remained unchanged. According to the object-updating hypothesis the negative priming should have been still observed because it was caused by perceptual interaction between the prime and mask. However, they found that the negative priming was eliminated when the masked primes were arrows but the target stimuli were letters [Eimer and Schlaghecken, 1998] (Experiment 1B), suggesting that masked priming is not possible owing to lack of automatic association between responses to letter targets and arrow prime stimuli [Klapp, 2015].

Liu and Wang [2014] used numerical stimuli as primes as well as both relevant and irrelevant mask stimuli of similar masking effectiveness to test whether the strength of S-R association modulates the NCE. The required responses to specific numbers were arbitrarily set. Therefore, the association between the number stimuli and motor responses was weak at the beginning of the experimental periods. They found that the perceptual priming dominated with the relevant mask only when the S-R association was weak, that is, at the beginning of the experimental period. Furthermore, the motor priming dominated and play major part in the NCE in the later stage after the S-R association was reinforced by practice [Liu and Wang, 2014].

In summary, in our study the main interest was the role of SEF in subliminal processing. Although it may be that the relevant mask modulated the relative contribution of perceptual and motor sources to the NCE, our main finding is unaffected by the perceptual perspective. That is, the involvement of SEF in the masked-prime task is dependent on the presence of a target. Moreover, SEF mediates information not only from target but also from priming to control motor activity in a goal-directed manner.

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