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RESEARCH NOTE

Supplementary motor area activations in unconscious inhibition of voluntary action

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Abstract It is widely accepted that regions within the dorsal medial frontal cortex are involved in the control of voluntary action. However, recent evidence suggests that a subset of these regions may also be important for unconscious and involuntary motor processes. Indeed, Sumner et al. (Neuron 54:697–711, 2007) showed that two patients with micro-lesions of the supplementary motor area (SMA) and supplementary eye field (SEF) demonstrated an absence of unconscious inhibition as evoked by masked-prime stimuli, while pre-SMA damage had no such effect. Here, we employ fMRI and a similar masked-prime task to test whether SMA and pre-SMA are similarly dissociated in healthy volunteers. Reaction times (RT) revealed that responses to compatible trials were slower than those to incompatible trials (negative compatibility effect, NCE), indicating automatic inhibition in every participant. BOLD signals in the SMA were modulated by prime compatibility, showing greater signal for compatible trials, but there was no change in pre-SMA. There was also no modulation in the hand motor cortex (HMC). These findings imply that the SMA is involved in automatic suppression of manual motor plans.

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Introduction

There is substantial evidence that regions within the dorsal medial frontal cortex such as the supplementary motor area (SMA), the supplementary eye field (SEF), and the pre-SMA are crucial for the regulation voluntary actions. For instance, in the macaque, deficits in simple and sequential self-initiated movements are observed when SMA or pre-SMA is temporarily inactivated or lesioned (Shima and Tanji 1998; Nakamura et al. 1999). However, evidence from two human patients with small lesions of the SMA and SEF suggests that these regions also play a key role in involuntary non-conscious sensorimotor processes (Sumner et al. 2007). Thus, there may be no clear distinction in the brain between regions involved in voluntary and involuntary processes. Rather, the medial supplementary motor areas could be part of a network where condition–action associations are instantiated into actual motor plans, whether in a conscious voluntary setting or a non-conscious automatic one (Nachev et al. 2008). This would be consistent with the fact that simply viewing objects can automatically prime manual responses normally used to grasp such an object (Tucker and Ellis 2004) and such activations appear to occur in the SMA (Grèzes and Decety 2002).

Sumner et al. (2007) tested their patients using a widely known masked-prime task, developed by Eimer and Schlaghecken (2003, 1998) in which subliminal priming can be either positive or negative depending on the delay

between prime and target. This reversal of priming is known as the negative compatibility effect (NCE) and is thought to index an automatic inhibitory mechanism that is triggered by the mask and suppresses the partial response activation caused by the primes (Jaskowski 2008a, b; Boy et al. 2008; Boy and Sumner 2010). In the patients, the reversed priming was absent in the oculomotor domain in JR (who has a SEF lesion) and in both oculomotor and manual domains in CB (who had a lesion of SMA that also probably extended into SEF). Interestingly, however, a patient with a much larger lesion of pre-SMA showed entirely normal results, suggesting there may be critical distinction between the roles of SMA and pre-SMA during automatic priming and inhibition. However, the strength of evidence from elderly patients in masked priming tasks has been put in doubt by a finding that even healthy elderly participants can show reduced or absent reversed priming effects (Schlaghecken and Maylor 2005). Very recently, the NCE has been related to the SMA in another way. Boy et al. (in press) used magnetic resonance spectroscopy and found that the regional concentration of the GABA (gamma amino-butyric acid) neurotransmitter in SMA was robustly correlated with the magnitude of the NCE.

Here, we turn to BOLD-fMRI with young healthy participants to test the distinction between SMA and pre-SMA with respect to non-conscious inhibition. Previously, Aron et al. (2003) found that regions of the basal ganglia were modulated during reversed priming, but they did not report any cortical activation. It would not be surprising if the cortical BOLD response was entirely insensitive to the subtle activation and inhibition evoked by subliminal stimuli, but nevertheless we hoped to detect modulation with a region-of-interest (ROI) approach.

Methods

Participants

Ten participants (2 women; age 27–34) from Cardiff University participated. All reported having normal or corrected-to-normal vision and were right-handed.

Apparatus

Stimulus presentation was performed by a PC-controlled Cambridge Research Systems (CRS) Visage® connected to a Canon SX60 LCOS video-projector, coupled to a Navitar SST300 zoom converter lens. Stimuli were back-projected onto a screen placed behind the participant's head in the scanner and viewed through a mirror mounted on the head coil. Stimulus presentation was synchronized with the screen refresh rate of 60 Hz, and timings were controlled and measured by the CRS clock and thus not subject to the errors produced by normal PC operating systems. Manual responses were collected using a Lumitouch® response pad (Lightwave Medical Industries, Burnaby, BC, Canada).

Behavioral masked priming task

Participants had to respond to leftward or rightward pointing arrow targets as quickly as possible by pressing a left- or right-hand button. The arrow stimuli, $\gg$ or $\ll$ (1° by 1.5°), were displayed within 0.5° of fixation for 96 ms (See Fig. 1a). Before each target arrow stimulus, there occurred a prime arrow and a mask. The prime was either identical to the target arrow stimulus (compatible) or it was the opposite arrow stimulus (incompatible). The prime was presented for only 33 ms and appeared in the same vicinity as the target, but not in an identical location on any trial. The mask following the prime (size 3° × 3°) was constructed of 35 randomly orientated lines, excluding any orientation closer than ±5° to the ±60° oblique lines contained in the prime. A new mask was constructed on each trial but appeared always in the same location, centered on fixation. We chose to exclude from the masks the orientations close to those of the prime and target stimuli to limit the contribution of mask-induced priming to the NCE (Sumner 2008). We set the mask-target stimulus-onset asynchrony (SOA) at 150 ms.

There were also trials in which the targets did not appear, and the participants were simply instructed not to press any button when this occurred. 'prime-mask' trials were identical to the standard 'Experimental' trials described above, but without a target. In 'Baseline' trials, the prime was also absent, being replaced by a neutral ++ stimulus (see Fig. 1a). Thus, there were seven different kinds of trial in total: left prime-left target; right prime-right target; left prime-right target; right prime-left target; left prime-no target; right prime-no target; neutral prime-no target (baseline condition). All trials contained a mask stimulus. The seven types of trial were presented in a random order, in an event-related fMRI design. There were 98 trials per fMRI run and three runs per subject.

Prime identification task

In order to test whether the participants could discriminate the primes, following the masked priming runs, there was a block of 76 trials of the prime-mask type (performed in the scanner, but without scanning) and the participants' task was to guess the identity of the prime (forced-choice). In order to minimize the potential influence of non-conscious motor priming on the prime identification response, participants were instructed to make their responses after a short delay rather than in a speeded manner (e.g., see

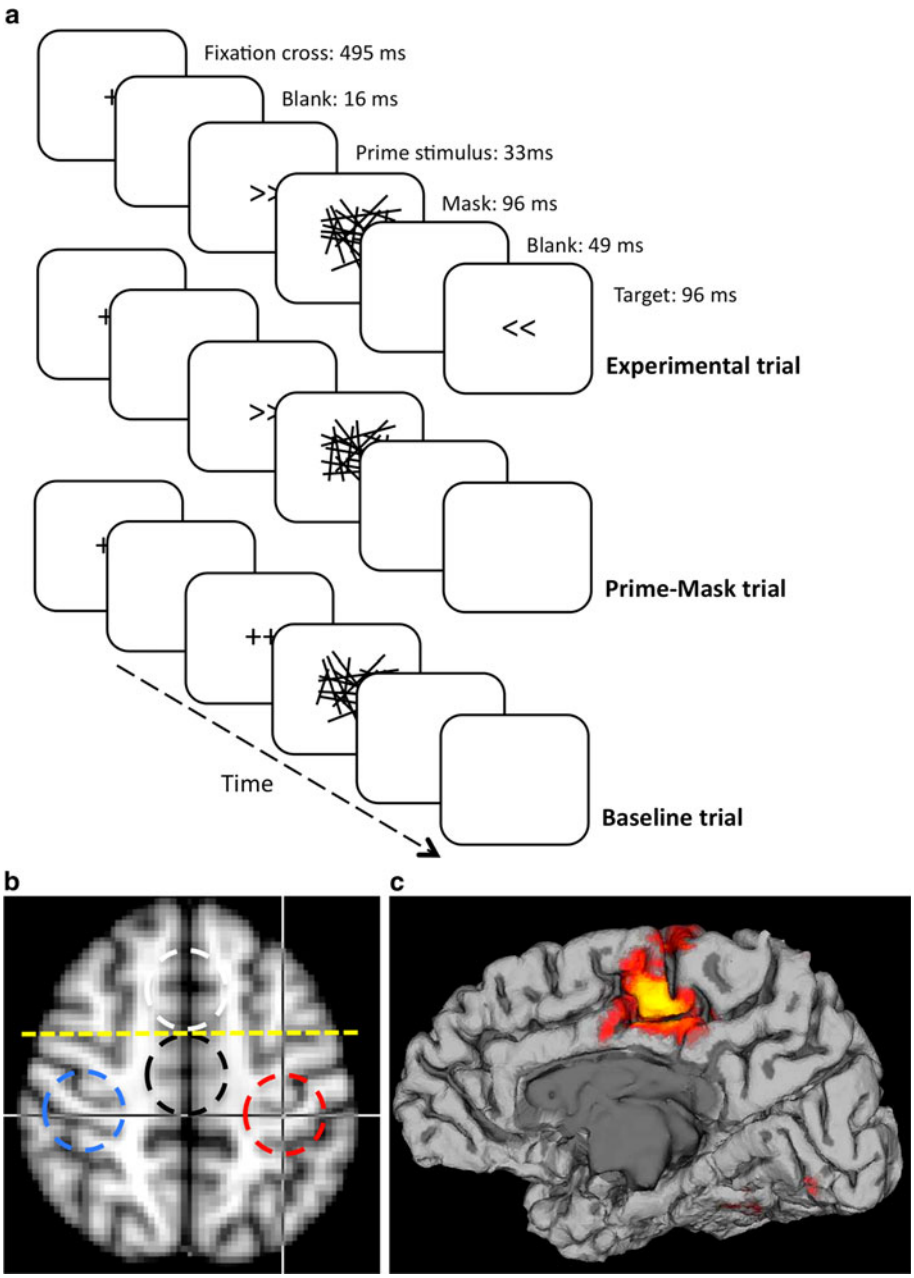

Fig. 1 **a** Illustration of the stimulus sequence (and relevant timings) for 'Experimental' trials, 'Prime-Mask' trials, and 'Baseline' trials. The experimental trial shown is incompatible (prime and target differ). **b** Definition of SMA, pre-SMA ROIs, left- and right-hand motor cortices ROI on a template brain (respectively *black*, *white*, *blue*, and *red circles*). In *yellow*, the VAC line is a landmark for the separation between the 2 premotor regions. **c** Medio-sagital view of the finger tapping versus rest BOLD contrast obtained in one subject in the SMA localiser task (thresholded using clusters determined by $Z > 2.3$ and corrected cluster significance threshold of $P < 0.05$)

Schlaghecken and Eimer 2002; Boy et al. 2008; Boy and Sumner 2010).

MRI data acquisition

For each participant, the experiment consisted of three fMRI runs for the masked priming task, one run for the SMA functional localiser, and an anatomical scan. There was also a behavioral run for prime identification, which took place within the scanner, but without MRI data acquisition. We employed a 3T GE scanner with a standard head-coil. The masked priming runs used a rapid event-related design with a random order for the seven different possible trials. Each run consisted of 98 trials and lasted 6 mn 38 s. fMRI data were acquired using a rapid gradient echo EPI sequence taking 26 oblique-axial slices at 3 mm isotropic voxel resolution and 265 T2*-weighted volumes (TR = 1500 ms, TE = 35 ms, 90° flip angle, acquisition matrix = 64 × 64). For the SMA localiser, we used a standard boxcar fMRI protocol with 15 s of sequential finger tapping (repetition of sequential opposition of each finger with the thumb) and 15 s of rest. The EPI parameters were the same as above. For the anatomical scan, we obtained a 3D FSPGR (Fast spoiled gradient echo) image with 1 mm isotropic voxel resolution (matrix: 256 × 256 × 176, flip angle 20°).

MRI data analysis

The data from the masked-prime runs were processed using FSL-Feat (Smith et al. 2004), modeling the 6 trial types that contained primes, and using the 'Baseline' trials as the implicit baseline. Only runs showing a behavioral NCE were kept in the analysis (73% of the total number of runs). We calculated contrasts for compatible versus incompatible and for 'prime-mask' versus baseline, but unsurprisingly for subliminal stimuli, there was nothing significant with whole brain correction. To test for effects in the SMA and pre-SMA, we defined regions of interest using anatomical landmarks and the results from the SMA localizer.

The SMA localizer data were analyzed using the standard protocol in FSL-Feat for boxcar designs, with a simple contrast of finger tapping versus rest, to determine the location where the BOLD signal (Z-value) peaked in medial frontal cortex (see example in Fig. 1c). This allowed us to create a 32 mm spherical ROI mask centered on the inter-hemispheric fissure and comprising all the 10 individual SMA activation BOLD-peaks (see Fig. 1b, ROI centered at MNI = 0.0, −16.0, 50). Unfortunately, there is no such agreed functional localiser for pre-SMA, so we created another 32 mm diameter pre-SMA ROI rostral to the VAC (vertical to the anterior commissure) line (see Fig. 1b, ROI centered at MNI = 0.0, 16.0, 50.0). Note that there was no overlap between the two medial ROIs. Anatomically, the SMA is generally defined as the area of medial frontal cortex in the superior frontal gyrus lying dorsal to the cingulate sulcus, rostral to the primary motor cortex, and caudal to the VAC line (Picard and Strick 1996, 2001). SMA is distinct from the pre-SMA, which lies rostral to it, in its pattern of connectivity (Johansen-Berg et al. 2004; Kim et al. 2009), but in an anatomical image (in which connectivity cannot be assessed), the usual division is taken to be the VAC line (Rizzolatti et al. 1996).

In addition, two other ROIs were placed over the right- and left-hand motor cortices—HMC, MNI coordinates: ± 34.0, −29.0, 50.0, see Caulo et al. (2007)—and three ROIs were also chosen in the basal ganglia (Putamen, Caudate, and Thalamus). These three latter were automatically defined using the MNI structural atlas (Mazziotta et al. 2001).

Having defined the ROIs, we extracted the median value of the distribution for the top 20% of activated voxels for each trial type in the masked priming runs (i.e., upwards from the 80th percentile), following the method of Mitsis et al. (2008). Doing so, rather than taking the averaged BOLD signal over all the voxels in the ROI, is expected to enhance the sensitivity to changes in functional signal by excluding voxels whose signal level is less likely to be meaningful.

Results

Prime identification

Forced-choice responses in the prime identification block did not differ from 50% (mean correct identification = 48.6 ± 5.17%; 95% confidence interval, one-sample T test toward a norm of 50%; $T(9) = 1.1$, P = ns). Binomial tests for each subject showed that only 2 subjects (subject 4 and 9) had forced-choice prime identification data significantly different from 50% (35%, $P < .011$ and 63%, $P < .037$). However, it is important to note that these two participants were not outliers and showed NCE (respectively, −11 and −19 ms).

Behavioral masked-prime compatibility effect (see Fig. 2a)

To investigate the BOLD correlate of the behavioral negative compatibility effect (NCE), we wished to examine BOLD signal only in runs that showed a NCE. We therefore tested the compatibility effect in each block with a student t test. Twenty-two of a total of 30 runs (73%) showed a significant NCE ($P < 0.05$, 1 tailed), ranging between −11 and −40.5 ms (the mean RT for correct incompatible trials was 424 ms and for compatible trials was 447 ms).

fMRI results (see Fig. 2b, c)

For the SMA ROI, the percentage of signal change was greater for compatible than for incompatible trials, whatever the hand used for the response (two-tailed T test, Left hand: $t(9) = 3.1$, $P < .01$; Right hand: $T(9) > 2.32$, $P < .04$). Conversely, the pre-SMA ROI did not show any sign of this distinctive pattern (two-tailed T test, both Ts < 1.26, P = ns). Thus, there appears to be a distinction between the involvement of SMA and pre-SMA in this masked priming task. We also tested ROIs in both right and left HMC, which are expected to be active in this manual task. There was no notable effect of prime compatibility (two-tailed T tests, both Ts < 1.32, Ps = ns), but the expected laterality is evident: more activity in the left-hand motor cortex (HMC) for right-hand responses and vice versa (two-tailed T tests, Right responses: $T(9) > 3.6$, $P < .005$, Left responses: $T(9) > 4.6$, $P < .002$). Similarly, no effect of prime compatibility was found in the basal ganglia (two-tailed T test: caudate nuclei: both Ts < 0.95; thalami: both Ts < 0.96 and putamen nuclei: both $T(9) < 1.4$, Ps = ns).

We hoped to further elucidate the exact nature of SMA's involvement by the inclusion of prime-mask trials, in which no targets appeared and no responses were made.

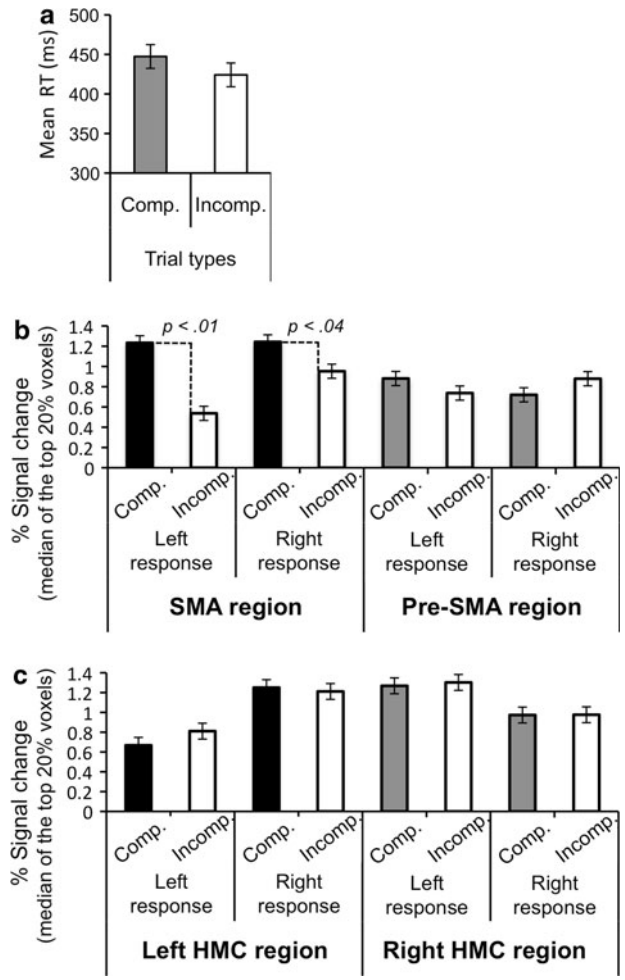

Fig. 2 **a** Behavioral data acquired during fMRI: correct mean reaction times are shown for compatible and incompatible trials (error *bars* are the within-subject normalized standard error). The NCE is the reduction in RT between compatible and incompatible primes. **b** Percentage of signal change in the top 20% voxels (median value) within the SMA and the pre-SMA ROIs for compatible and incompatible trials (error *bars* represent the within-subject normalized standard error). **c** Percentage of signal change in the top 20% voxels (median value) within the *right*- and *left*-hand motor cortex (HMC) ROIs for compatible and incompatible trials (error *bars* represent the within-subject normalized standard error)

Comparing these to the baseline condition would potentially reveal activity that was purely prime-induced without involving any interaction with target-related activity. However, we found no difference between prime-mask and baseline conditions in any of the ROIs, presumably because the processes evoked by only a small symbolic subliminal prime are too subtly different from those evoked by neutral primes to be detected with fMRI. It seems that the effects of our subliminal primes could only be detected with fMRI through their interaction with target-related activity in the SMA. Using a closely related paradigm, D'Ostilio and Garraux (2010) recently observed prime-evoked activity in the SMA. Interestingly, their prime and mask were followed by a NoGo stimulus, while ours were not. Possibly, the presence of a potential but un-used target stimulus in their experiment could have increased the overall cortical excitability, therefore strengthening the reaction to the prime and making BOLD signal changes detectable.

Discussion

We have found modulation in the SMA during the subliminal inhibition task, but not in pre-SMA. This appears to be consistent with the data from patients with lesions in these areas reported by Sumner et al. (2007). They found that subliminal inhibition was absent in a patient with a micro-lesion of SMA (and absent in the oculomotor domain in a patient with a micro-lesion of SEF), but normal in a patient with a large lesion of pre-SMA. Overall, then, our results imply that in un-damaged brains, one of the roles of the SMA is to contribute to the automatic processes evoked by subliminal primes. Since the SMA is also known to contribute to voluntary control of actions (Picard and Strick 1997, 2003), there may be no clear separation between automatic and voluntary processes in the brain. Accordingly, we can consider non-conscious partial activations of movement plans as useful and intrinsic components of voluntary behavior, facilitating actions by "pre-activating" motor cortices (Neumann and Klotz 1994; Leuthold and Kopp 1998; Tucker and Ellis 2004). Likewise, the subliminal and automatic inhibitory mechanism can also be considered an intrinsic component of voluntary behavior, suppressing partially primed actions to allow alternative actions to occur (Bowman et al. 2006; Eimer and Schlaghecken 1998; Klapp and Hinkley 2002; Schlaghecken and Eimer 2002, 2006; Sumner and Husain 2008).

However, the data do not straightforwardly fit the simplest possibility that the measured SMA activation is elicited by the prime. In this case, we would have expected activity for the prime-mask trials, and not necessarily have expected modulation by the compatibility of prime-mask-target trials (after all primes occur in both). Instead, the relationship between prime identity and target identity modulated the BOLD signal, which should not be surprising given that we assume SMA is involved in responses to the target as well as any response to the subliminal primes. Let us then consider in turn how our data might be interpreted according to the various theories of the NCE.

Some authors have suggested that the NCE could have a perceptual locus, either due to habituation to the features in the prime (Huber et al. 2008) or attentional suppression of those features (Sohrabi et al. 2005). In these theories, the NCE occurs because the perceptual processing of the target signal is somehow hampered on compatible trials. It is not obvious why this would cause greater activity in SMA

(unless due to the extra demands of making a motor response to weaker perceptual information). However, there is now strong behavioral evidence for a motor or sensori-motor explanation of the NCE, rather than a purely perceptual one (Boy and Sumner 2010), so we do not consider the perceptual explanations further here. Boy et al. found that when the mapping between stimuli and responses was suddenly reversed, the NCE also reversed and became a PCE for a number of trials, before re-establishing itself as an NCE as the new motor mappings were learnt. Since nothing about the stimuli had changed during this period, a purely perceptual account cannot explain these results. Rather, they indicate that the old motor responses continued to be primed and inhibited for a while after the reversal.

A second category of explanation for the NCE, known as 'object updating', 'active mask', or 'mask-induced priming', suggests that it does not require any inhibitory mechanism (Lleras and Enns 2004; Lleras and Enns 2005; Lleras and Enns 2006). Instead perceptual interactions between the rapid prime stimulus and longer mask stimulus promote the salience of features in the mask that were not in the prime. These salient features in the mask then cause motor priming opposite to that expected from the prime. Such a prime-mask interaction relies on a similar principle to the perceptual theories mentioned above—that the visual system generally favors new stimuli over old. However, the key difference in this theory is that compatible trials are slowed not through a perceptual deficit in target processing, but through motor priming opposite to the required response. In this case, the extra activation in SMA might arise through the need to overcome this opposite priming. However, the mask-induced priming class of theory has received extensive behavioral testing, and the consensus appears to be that it can account for the NCE when certain types of mask are used, but it does not account for the NCE in the type of paradigm we employed here, in which the mask is not composed of features of the possible targets (Sumner 2008; Schlaghecken and Eimer 2006; Klapp and Hinkley 2002; Klapp 2005; Jaskowski 2008a, b).

The third category of explanation supposes that the NCE is due to rapid motor inhibition of the primed response, as outlined in the introduction. Originally, it was supposed that such inhibition was triggered by the motor priming itself if it was not corroborated by conscious perceptual evidence (e.g., Bowman et al. 2006; Eimer and Schlaghecken 1998; 2002; Klapp and Hinkley 2002; Schlaghecken and Eimer 2006; Schlaghecken et al. 2006b). In other words, subliminal inhibition occurred precisely because the primes were subliminal (Eimer and Schlaghecken 2002). Later, it was discovered that it was not crucial for the primes to be invisible (Schlaghecken and Eimer 2006; Jaskowski 2008a, b; Verleger et al. 2004; Jaskowski and Przekoracka-Krawczyk 2005; Schlaghecken et al. 2006a), and instead the mask stimulus appears to play a critical role in triggering inhibition directly, rather than just indirectly through making the prime invisible (e.g., Boy et al. 2008; Jaskowski et al. 2007; Lleras and Enns 2006). Thus, the theory consistent with most current evidence (though not all see e.g., Sumner and Brandwood 2008) is that the NCE is caused by rapid motor inhibition of the subliminally primed response, and this inhibition is triggered automatically by the occurrence of a second stimulus (the mask) immediately after the prime. Either way, the inhibition is thought to be initiated before the identity of the target is known, and if this is the case, it should not differ between compatible and incompatible trials. The BOLD modulation we measure in SMA must therefore result from an interaction between the inhibition and the response required to the target. This would also be consistent with the lack of BOLD response in trials with prime and mask but no target.

At first sight, it may appear that a discrepancy has emerged between the current data and the data from the lesion patients in Sumner et al. (2007), which pointed to SMA as the source of automatic inhibition rather than emphasizing an interaction between inhibition and target response. However, these possibilities can happily coexist. If there is both prime-related inhibition and target-related activity in the SMA, then the BOLD signal is much more likely to be sensitive to modulation of the latter than to the very subtle processing and inhibition of subliminal primes alone. However, a lesion approach will be more sensitive to an initial defect in prime-initiated processes, because they are a prerequisite for modulation of target activity to occur. Additionally, it is interesting to note that some aspects of the patient data did imply an unusual interaction between inhibition and response planning. One patient had an asymmetric priming effect, and this cannot be accounted for by an asymmetric loss of inhibition (see supplementary material in Sumner et al. 2007), but it could be explained if disruption to the inhibitory process interacted asymmetrically with the response to the target.

Lastly, we must consider whether BOLD modulation is a side effect of the behavioral RT difference between compatible and incompatible trials. It is common to many fMRI studies that where there are BOLD differences, there are also behavioral differences, such as RT. The aim is always to relate the BOLD differences to the same functional factors that produced the behavioral differences, but they might also be a side effect of the behavioral differences—in this case that the compatible responses were longer in the planning, allowing more time for BOLD signal to emerge. We believe three considerations taken together make this latter explanation implausible: (1) the RT difference is only about 20 ms, which is a small fraction of the time taken to plan the response ($\sim$200 ms,

taking into account the overall RT and the likely perceptual signal delays and motor output delays); (2) the longer RT of compatible trials did not create extra BOLD response in motor cortex, where we might expect activity to be tied more closely to response execution; and (3) most importantly, many other paradigms that show longer RT in one condition than another do not activate SMA (e.g., Botvinick et al. 2001; Wager et al. 2005; Egner 2007).

Past research has related automatic motor inhibition to modulation of neural activity in the basal ganglia rather than the medial frontal cortex, specifically deactivation of the caudate and thalamus. Additionally, reduced or variable NCEs have been reported in patients with Parkinson's or Huntington's disease (Aron et al. 2003; Seiss and Praamstra 2004), although a later study reported no difference in the inhibitory pattern between Parkinson's disease patients and controls (Seiss and Praamstra 2006). However, Aron et al. used different types of trial and different comparisons from those reported here; they employed two different SOAs between mask and target (zero, which produced a positive priming effect, and 150 ms, which produced an NCE). They then analyzed the interaction between prime type (arrow vs. neutral) and SOA. Given the differences between the studies and the fact that the BOLD response is generally not very sensitive to these kinds of subliminal processes, we cannot draw strong conclusions from a comparison of the two studies. Overall, it is likely that the basal ganglia do interact with the SMA during the inhibitory process and response to the target, via cortico-striato-thalamic connections (Lehericy et al. 2004; Aron et al. 2003) but their precise role remains unknown, especially given the normal behavioral results from Parkinson's patients (Seiss and Praamstra 2006).

The role of the primary motor cortex also remains unknown. The HMC must be involved in the response to the targets, and thus the manifestation of any behavioral difference between compatible and incompatible primes, but here we found no modulation of the HMC bold response by priming. Consistent with this, Schlaghecken et al. (2003) have reported no modulation of the NCE by slow frequency repetitive transcranial magnetic stimulation of the hand motor cortices.

Conclusion

We have found that the generation of the behavioral negative compatibility effect, indicating automatic inhibition, is accompanied by BOLD modulation in SMA but not in the neighboring pre-SMA or in the motor cortex. Taken together with patient data (Sumner et al. 2007), this finding implies that SMA is involved in the non-conscious motor inhibition processes elicited by subliminal primes.

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