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### Brain mechanisms of unconscious cognitive control

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## **6. Pre-SMA grey-matter density predicts individual differences in action selection in the face of conscious and unconscious response conflict**

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### **Abstract**

The pre-supplementary motor area (pre-SMA) is considered key in contributing to voluntary action selection during response conflict. Here we test whether individual differences in the ability to select appropriate actions in the face of strong (conscious) and weak (virtually unconscious) distracting alternatives are related to individual variability in pre-SMA anatomy. To this end, we scanned 58 participants with structural magnetic resonance imaging who performed a masked priming task in which conflicting response tendencies were elicited either consciously (through primes that were weakly masked) or virtually unconsciously (strongly masked primes). Whole-brain voxel-based morphometry revealed that individual differences in pre-SMA density predict subjects' ability to voluntarily select the correct action in the face of conflict, irrespective of the awareness-level of conflict-inducing stimuli. These results link structural anatomy to individual differences in cognitive control ability, and provide support for the role of the pre-SMA in the flexible adjustment of ongoing behavior by inhibiting irrelevant action plans. Furthermore, these results suggest that flexible and voluntary behavior requires efficiently dealing with competing motor plans, including those that are activated automatically and unconsciously.

### **Introduction**

To optimize our behavior, we must overcome conflicting information in the environment and rapidly select contextually relevant information to achieve our goals. In the lab, this phenomenon has been studied with various "conflict tasks", such as the Stroop, the Simon or the Eriksen flanker task. In these tasks, one response is activated through rapid and direct capture from salient but task-irrelevant stimulus features, and must be subsequently overcome by another, more deliberate response. For example, in the flanker task, participants have to respond as quickly as possible to the direction of a target arrow and ignore flanking distracting arrows. When the target and flankers are incongruent (pointing in opposite directions) responses are generally slowed down compared to congruent trials (target and flankers point in the same direction). Several lines of consistent evidence suggest that the human medial frontal cortex (MFC), and the pre-supplementary motor area (pre-SMA) in particular, is of crucial importance for selecting the appropriate action in such situations of response conflict (Botvinick et al., 2001;

Forstmann et al., 2008; Mostofsky & Simmonds, 2008; Nachev, Kennard, & Husain, 2008; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007).

The aim of the present study was to investigate the link between brain function and brain structure and to test whether individual differences in the ability to select the appropriate action during response conflict are related to structural differences in the pre-SMA. Furthermore, we were interested in the relation between overcoming response conflict and the level of awareness of conflict. In daily life, people are overwhelmed with visual information from which they have to select the relevant information to guide their behavior. Although a large part of this information probably remains unnoticed (i.e. unconscious), it might still influence our behavior, as evidenced by many subliminal priming (e.g. Dehaene et al., 1998; Vorberg et al., 2003) and attentional blindness studies (Mack, 2003; Most, Scholl, Clifford, & Simons, 2005). Recent evidence is somewhat contradicting in whether the human MFC is important for action selection in the face of unconscious conflict (Dehaene et al., 2003; Mayr, 2004; Praamstra & Seiss, 2005; Sumner et al., 2007; Ursu, Clark, Aizenstein, Stenger, & Carter, 2009). In fact, the prefrontal cortex has been assumed to be strongly associated with consciousness (Dehaene & Naccache, 2001; Rees et al., 2002) and even free will (e.g. Brass & Haggard, 2007; Haggard, 2008; Lau et al., 2004) and tends not to become involved in unconscious operations. However recently, we and others have shown that even high-level prefrontal cognitive control processes, such as response inhibition (van Gaal et al., 2008; van Gaal et al., 2009) and task-switching (Lau & Passingham, 2007) can be initiated by unconscious (masked) stimuli.

Here we used voxel based morphometry (VBM) to characterize the brain areas important for action selection in the face of strong (conscious) and weak (virtually unconscious) response conflict. To this end, fifty-eight participants performed a masked priming task in which awareness of conflict-inducing stimuli was manipulated (Figure 6.1a). Participants were required to perform a speeded two-choice response to a target arrow that was preceded by a smaller arrow, the so-called prime. Because the prime fitted within the contour of the target, the target functioned as a (metacontrast) mask. Under this specific circumstance, participants are generally not aware of the prime when it is presented very briefly, whereas it is clearly visible when presented slightly longer (Breitmeyer, 1984; Kunde, 2003). However, a prime that cannot be perceived is still be processed, as evidenced by faster response times and fewer errors when the prime and target are congruent than when they are incongruent (Kunde, 2003; Vorberg et al., 2003), referred to here as the *correspondence effect*. The magnitude of the correspondence effect is

determined by the strength of response activation induced by the prime (stronger activation of the incongruent action leads to greater interference) and the efficiency of the inhibition of this activation (stronger inhibition reduces interference (Ridderinkhof, 2002)) and reflects the efficiency of an individual to overcome response conflict.

We hypothesized that, if the pre-SMA has a direct role in actively resolving response conflict and deliberately selecting the appropriate action, regional grey-matter density in the pre-SMA should correlate with individual differences in the ability to resolve response conflict. More specifically, we expected to observe a negative correlation between pre-SMA grey-matter density and the correspondence effect across participants, since a better developed action selection system (greater pre-SMA grey-matter density) should lead to more efficient conflict resolution (thus a smaller correspondence effect). Furthermore, because we could calculate correspondence effects for weakly and strongly masked conditions separately, we were able to examine the relation between grey-matter anatomy and individual differences in the ability to overcome strong (conscious) and weak (virtually unconscious) conflict.

## **Method and Materials**

### *Participants*

Fifty-eight volunteers participated in the experiment for course credits or financial compensation. All procedures were executed in compliance with relevant laws and institutional guidelines and were approved by the local ethical committee. Subjects gave written informed consent before experimentation.

### *Design*

Participants came to the lab twice; for a scanning session and a behavioral session. In the behavioral session, participants participated in a battery of tests including the one described in the present paper. Participants performed a typical masked priming task, previously used to study response selection in the face of consciously and unconsciously presented distractors (Kunde, 2003). Stimuli were presented using Presentation (Neurobehavioral Systems, Albany, USA) against a white background at the centre of a 17-inch VGA monitor (frequency 70 Hz.). Participants viewed the monitor from a distance of approximately 90 cm, so that each cm subtended a visual angle of 0.64 degrees. A blue prime arrow (width 0.96°, height 0.64°) was presented for a short duration (14 ms) or a long duration (128 ms), followed by a blank interval (28 ms), and then by a target arrow (128 ms, width 2.20°, height 1.47°) that

instructed participants to respond as quickly and accurately as possible to its direction (see Figure 6.1a). Participants were instructed to ignore the primes that preceded the target. The prime was a smaller version of the target and fitted within the contour of the target. By manipulating prime duration the prime was either visible (on half of the occasions), or its visibility was sharply reduced (in the other half of the occasions). By this means, four conditions were created: 1) weakly masked incongruent trials, 2) weakly masked congruent trials, 3) strongly masked incongruent trials, and 4) strongly masked congruent trials. Participants performed four blocks, each containing 160 trials (40 per condition, pseudo-randomized). Total trial duration was 1400, 1500, 1600 or 1700 ms (equal frequency). Before the main experiment participants practiced the task briefly (32 trials).

Immediately after the final experimental block, participants performed a two-alternative forced-choice discrimination task on the primes (80 trials; 20 trials of each condition). Stimulus and trial timing was exactly the same as in the masked priming task, except that a pair of choices was presented left and right of fixation after each trial. Participants were asked to determine as accurately as possible whether a left-pointing or right-pointing prime was presented in the preceding trial. Before administering this task, participants were told that left and right pointing primes were presented equally frequently and were instructed to consider this in giving their response. Participants were also told that only accuracy was important in this task, not the speed of responding. Upon responding a new trial started.

#### *Behavioral data analyses*

For the RT analyses (masked priming task), RTs > 100 ms and < 1000 ms were included. Mean RTs from correct responses were entered into an ANOVA with within-subjects variable of prime-target correspondence (congruent vs. incongruent) and masking strength (weak vs. strong masking). Subsequently, paired two-tailed t-tests were performed for strongly masked and weakly masked trials separately. For the accuracy analyses, the same was done for the square root of response accuracy. Detection performance (percentage correct in the two-alternative forced-choice discrimination task) was tested for significance using a one-sample t-test (compared against 50%) evaluated at an alpha level of 0.05.

#### *VBM data acquisition procedure*

In a separate session, magnetic resonance images were acquired using a 3-T scanner (Philips, The Netherlands). We acquired two structural scans from each subject, which were averaged (T1 turbo field echo; 182 sagittal slices; FA 8°; TE 4.6 ms; TR

9.6 sec; slice thickness 1.2 mm; FOV 256\*256 mm; inplane voxel resolution 1\*1 mm). Data was analyzed with voxel-based morphometry (Good et al., 2001) carried out with FSL software (Smith et al., 2004). First, structural images were brain-extracted (Smith, 2002). Next, tissue-type segmentation was carried out using FAST4 (Zhang, Brady, & Smith, 2001). The resulting grey-matter partial volume images were then aligned to MNI152 standard space using the affine registration. The resulting images were averaged to create a study-specific template, to which the native grey-matter images were then non-linearly re-registered with a method that uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field (Ashburner & Friston, 2000). The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm.

Finally, in FSL, a voxel-wise GLM analysis was performed using permutation-based non-parametric testing (10,000 iterations). The correspondence effect (mean RT incongruent trials - mean RT congruent trials) for the weakly masked as well as the strongly masked condition were both entered as covariates. We specified one contrast for positive and one for negative correlations for each condition (four contrasts in total). In a whole-brain omnibus ANOVA, statistical significance was determined using a voxel height threshold of  $p < 0.001$  and a cluster size of more than 10 contiguous statistically significant voxels. To analyze the strength of the correlations between grey-matter density and each covariate, rank-order correlations (Spearman) were conducted.

## **Results**

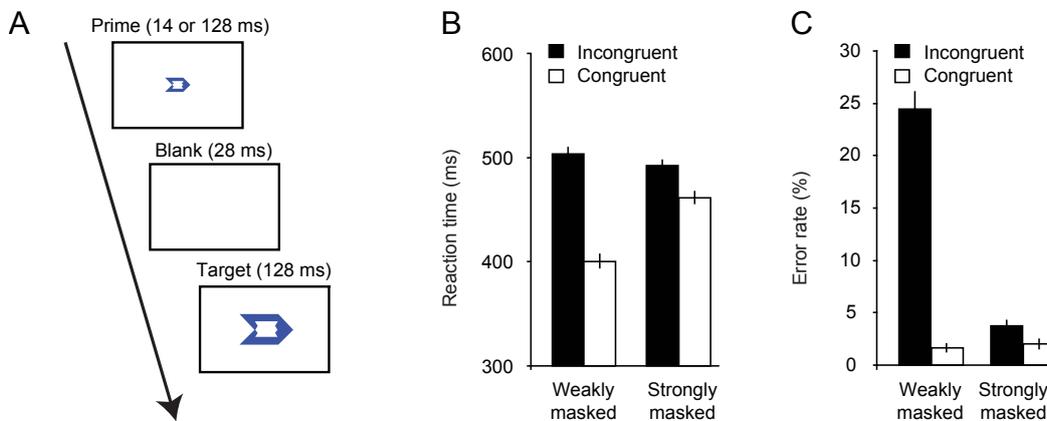
### *Behavioral results*

As expected, participants were significantly faster on congruent conditions than on incongruent conditions ( $F(1,57) = 513.91; p < 0.001$ ). This difference was significant in the weakly masked ( $t(57) = 21.63, p < 0.001$ ) as well as strongly masked conditions ( $t(57) = 16.16, p < 0.001$ , see Figure 6.1b), but was significantly larger for the weakly masked condition than for the strongly masked condition ( $F(1,57) = 297.04; p < 0.001$ ). Additionally, participants made more response errors on incongruent trials than congruent trials ( $F(1,57) = 194.47; p < 0.001$ ). Again this difference was reliable in the weakly masked ( $t(57) = 14.18, p < 0.001$ ) as well as strongly masked ( $t(57) = 6.14, p < 0.001$ ) conditions (see Figure 6.1c); but again, the magnitude of the correspondence effect reflected in error rates was significantly

larger for the weakly masked conditions than the strongly masked conditions ( $F(1,57) = 200.68, p < 0.001$ ).

### *Pre-SMA and action selection during conflict*

To extract the brain areas that are associated with response conflict per se, correlations with brain anatomy and the correspondence effects on both weakly and strongly masked conditions together were examined in the whole brain grey-matter volume (omnibus ANOVA). This whole-brain F-test revealed a significant cluster in the right pre-SMA (Figure 6.2a, 105 contiguous voxels with a  $p < 0.001$ ). We used this region as a mask to extract individual pre-SMA grey-matter values and correlated these values with the correspondence effect for both conditions across subjects. Consistent with our predictions, pre-SMA grey-matter density correlated negatively with the correspondence effect derived from the weakly masked conditions across individuals ( $\rho = -0.48, p < 0.001$ , see Figure 6.2b, upper left panel). Interestingly, grey-matter density in the pre-SMA correlated just as strongly with the correspondence effect derived from the strongly masked conditions ( $\rho = -0.46, p < 0.001$ , upper right panel).

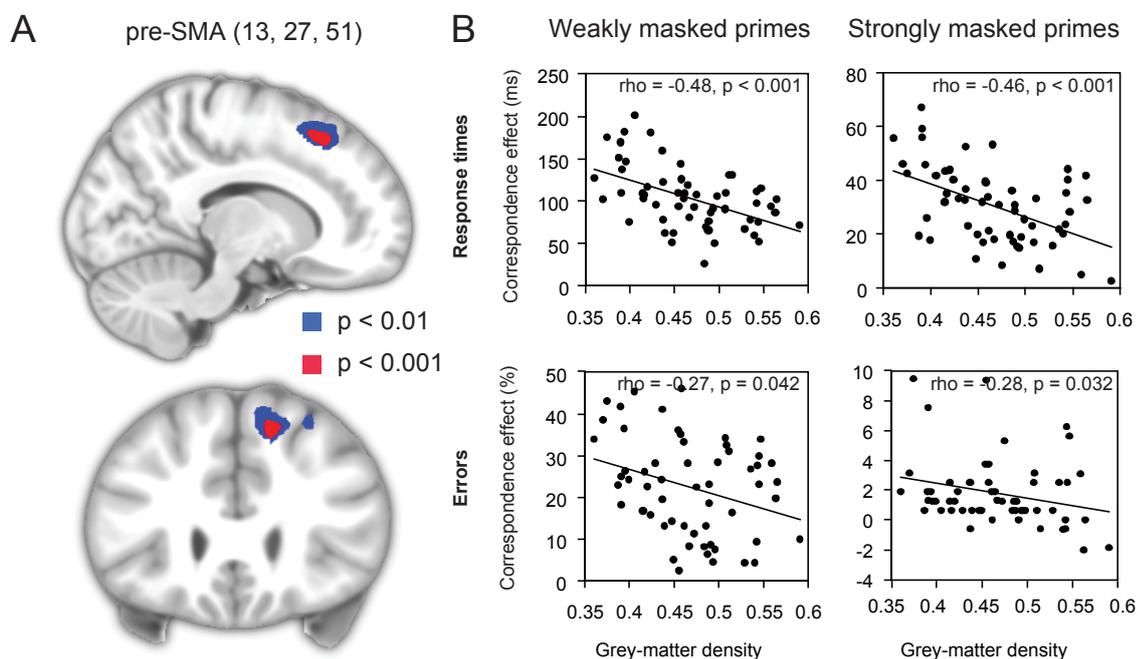


### **Figure 6.1 Experimental design and behavioral results**

a) The sequence of events in the masked priming experiment. The prime could either be congruent (pointing in the same direction) or incongruent to the target (pointing in the opposite direction). Prime visibility was manipulated by presenting the prime either briefly (14 ms) or longer (128 ms). b) Response times for congruent and incongruent trials for strongly and weakly masked conditions separately ( $\pm$  SEM). c) Error rates for congruent and incongruent trials for strongly and weakly masked conditions separately ( $\pm$  SEM).

To validate this finding, pre-SMA density values were correlated with a second, independent measure, namely the difference in the number of response errors on incongruent and congruent trials. Note that this measure was not entered as a

covariate in the initial whole-brain VBM analysis and therefore was not used to select the pre-SMA region. Pre-SMA density correlated negatively with error rates observed in the weakly ( $\rho = -0.27$ ,  $p = 0.042$ , see Figure 6.2b, lower left panel) as well as the strongly masked condition ( $\rho = -0.28$ ,  $p = 0.032$ , lower right panel). Pre-SMA structure was specifically related to individual differences in the ability to resolve conflict, since it did not correlate with other behavioural measures such as overall mean RT in the masked priming task or discrimination performance in the forced-choice discrimination task (largest  $\rho < 0.11$ , smallest  $p > 0.40$ , see also below).



**Figure 6.2 Pre-SMA and action selection in the face of conflict**

a) Pre-SMA grey-matter density correlated ( $p < 0.001$ , in red) with the ability to select the correct action in the face of response conflict, irrespective of the awareness-level of conflict-inducing primes. Also voxels at a more liberal threshold ( $p < 0.01$ , in blue) are shown to observe the extension of the significant pre-SMA cluster. MNI coordinates reflect the centre of gravity. b) Scatter plots for the correlation between pre-SMA grey-matter density values and the correspondence effect derived from the weakly masked (left panel) and strongly masked (right panel) conditions. RT effects (top); error effects (bottom).

Additionally, the whole-brain F-test revealed a significant cluster in the anterior part of the thalamus (25 voxels, MNI coordinates: 4, -1, 7), however, the pattern of results in this structure was less consistent than observed in the pre-SMA. Structural grey-matter density in the thalamus did not correlate significantly with the correspondence effect derived from the weakly masked conditions ( $\rho = 0.22$ ,  $p = 0.093$ ; if anything positively), but correlated negatively with the correspondence

effect derived from the strongly masked conditions ( $\rho = -0.30, p = 0.022$ ). The thalamus finding could not be validated since grey-matter density in this structure did not correlate with error rates in the weakly ( $\rho = -0.02, p = 0.905$ ) nor in the strongly masked condition ( $\rho = 0.03, p = 0.854$ ).

### *Prime visibility*

The two-alternative forced-choice discrimination task administered after the masked priming experiment revealed an overall percentage correct for weakly masked primes of 92.4% (SD = 12.1) vs. 59.4% (SD = 9.1) for strongly masked primes. Participants were significantly better at detecting weakly masked primes than strongly masked primes ( $t(57) = 17.6; p < 0.001$ ). Although prime visibility was low in the strongly masked condition, it was significantly above chance-level ( $t(57) = 7.88; p < 0.001$ ).

To test whether the reported pre-SMA effects are related to the visibility of strongly masked primes, we correlated the detection measure obtained in the two-alternative forced-choice discrimination task (percentage correct) with pre-SMA density values across participants. Both measures were not reliably correlated ( $\rho = 0.11, p = 0.423$ ). As an additional check, we only selected the one-third worst detection performers (mean detection performance = 49.9%) and computed the correlation between pre-SMA density and the correspondence effect derived from the strongly masked conditions. Across these 20 participants, this correlation was still robust and significant ( $\rho = -0.57, p = 0.009$ ); if anything the strength of the correlation even increased. These additional analyses suggest that the reported effects are not related to prime visibility.

## **Discussion**

We investigated whether structural differences in cortical grey-matter density could predict individual variation in the extent to which people are able to select the appropriate action in the face of distracting alternatives. Participants performed a masked priming task in which conflicting response tendencies were elicited either consciously (weakly masked primes) or virtually unconsciously (strongly masked primes). Consistent with our predictions, whole-brain VBM analysis revealed a strong negative correlation between pre-SMA density and the size of the RT correspondence effect (mean RT on incongruent trials – mean RT on congruent trials). Pre-SMA density also correlated with the size of the correspondence effect observed in the error rates. These negative correlations indicate that individuals with greater pre-SMA grey-matter density are better at selecting the appropriate

action in the face of response conflict than individuals with smaller pre-SMA grey-matter density. Interestingly, pre-SMA anatomy correlated with individual variability in the ability to select a deliberate response when conflict was triggered consciously as well as (virtually) unconsciously.

These present findings confirm and extend previous functional imaging studies (Forstmann et al., 2008; Nachev, Rees, Parton, Kennard, & Husain, 2005), lesion effects studies (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007; Picton et al., 2007), TMS effects studies (Kennerley, Sakai, & Rushworth, 2004; Taylor, Nobre, & Rushworth, 2007) and single-cell recording studies (Isoda & Hikosaka, 2007; Stuphorn & Schall, 2006) that provided support for a crucial role of the pre-SMA in resolving conflict by selecting task-relevant information while inhibiting task-irrelevant information. However, our results further extend these findings in two important ways. First, by linking structural, instead of functional, correlates to conflict resolution mechanisms in the pre-SMA, and second by showing that this mechanism is not related to the level of awareness of conflict-inducing stimuli.

The exact origin of structural differences in grey-matter is still a matter of debate and might be related to either innate predispositions or environmental factors, or both. Interestingly, recent VBM studies demonstrated rapid learning-dependent structural changes of the brains anatomy over the course of only a few weeks/months of juggling (Draganski et al., 2004; Driemeyer, Boyke, Gaser, Buchel, & May, 2008), extensive studying (Draganski et al., 2006) or mirror reading (Ilg et al., 2008). The precise nature of such grey-matter increase is still a matter of debate, but several mechanisms have been proposed, including a change in cell size of neurons or glial cells, changes in axonal structure and perhaps even neurogenesis (Gross, 2000; Ilg et al., 2008; May & Gaser, 2006; Trachtenberg et al., 2002). These results suggest that the brain can alter its shape quickly and that structural neuroplasticity plays a crucial role in adapting our behavior to environmental changes as well as learning. Future studies are required to further elucidate whether individual differences in pre-SMA structure are due to learning (some people might encounter more conflict than others), innate predispositions, or both.

#### *Medial frontal cortex and unconscious conflict resolution*

These results extend the sparse and somewhat contradicting evidence obtained in recent functional imaging studies that looked into how the brain overcomes the interference of unconscious information in conflicting situations. Dehaene and colleagues (2003) measured behavioral and brain imaging correlates of response conflict induced by conscious and subliminal primes in a masked priming paradigm.

Although they observed a typical masked priming effect in behavior (for conscious as well as unconscious primes), fMRI revealed that the anterior cingulate cortex (ACC) responded more strongly to incongruent primes than to congruent primes, but only when primes were presented consciously. Therefore, the authors concluded that the ACC was only responsive to consciously experienced conflict, but not to unconscious conflict. However, recently, others have demonstrated that the ACC is responsive to conflict induced by unnoticed (“unconscious”) sequence violations of an implicitly learned rule (Ursu, Clark, Aizenstein, Stenger, & Carter, 2009) and “unnoticed” response errors (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein et al., 2007; Nieuwenhuis et al., 2001).

Instead of studying the immediate effects of unconscious conflict-inducing stimuli, Wolbers and colleagues (2006) studied the strategic control over interfering unconscious information using fMRI. To this end, they varied the number of congruent and incongruent trials in a masked priming block. Behaviorally, strategic effects consisted of longer RTs and fewer errors across incongruent blocks (containing more incongruent trials than congruent trials) compared to congruent blocks (containing fewer incongruent trials than congruent trials), indicative of a changed speed/accuracy balance according to the number of unconsciously presented distractors. The pre-SMA was more active during incongruent than congruent blocks and psychophysiological interaction analyses demonstrated a tight coupling between the pre-SMA and both the putamen and the lateral occipital complex (LOC) on incongruent blocks. The authors concluded that the pre-SMA might have an overarching role in controlling the processing of unconscious primes by modulating perceptual analysis (LOC) and response selection (putamen) during conflict. Although such strategic effects differ slightly from the immediate control operations studied here, the results nicely converge on the role of the pre-SMA in selecting relevant information over irrelevant unconscious distractors. However, here we show that individual differences in structural, instead of functional, properties of the pre-SMA predict individual differences in the ability to overcome (virtually) unconscious response conflict.

Behavioral studies have demonstrated that masked primes initially facilitate responses (as observed here), but somewhat later, when the delay between prime and target is increased (> 100 ms), are followed by inhibition of these responses (Eimer & Schlaghecken, 1998). Although the exact cause of this effect is controversial (Lleras & Enns, 2004; Verleger, Jaskowski, Aydemir, van der Lubbe, & Groen, 2004), it seems that it is (at least partly) caused by an automatic and unconscious process of self-inhibition (Klapp, 2005; Schlaghecken & Eimer, 2006). Recently Sumner and

colleagues (2007) showed that a patient with a highly specific SMA lesion did not show automatic inhibition of unconscious primes in a manual version of a masked priming task. Interestingly, a patient with a large lesion including the pre-SMA still showed normal automatic inhibition effects, which suggests that the pre-SMA is not necessary for such automatic (unconscious) forms of motor inhibition. In combination with the present results, this suggests that the supplementary motor areas (SMA/pre-SMA) have a key role in voluntary action selection by suppressing irrelevant or premature response tendencies that have been primed unconsciously. However, both areas might contribute differently to this process, which is in line with recent theoretical accounts that have proposed that the SMA is primarily involved in automatic (unconscious) forms of motor control, whereas the pre-SMA might be crucial for more complex higher-level control processes that are experienced as difficult and voluntary (Botvinick, Cohen, & Carter, 2004; Lau et al., 2004; Rushworth, Hadland, Paus, & Sipila, 2002).

### *Conclusion*

We report that individual differences in the ability to select the correct action in the face of distracting alternatives are accompanied by structural differences in pre-SMA grey-matter anatomy. Thereby, these results link structural anatomy to cognitive control ability, and extend recent functional imaging and electrophysiological evidence for the role of the pre-SMA in the adjustment of ongoing behavior by selecting appropriate actions in the face of conflicting response tendencies. Furthermore, these results suggest that the pre-SMA is important for flexible and voluntary behavior, which requires efficiently dealing with several competing action plans, including those that are activated automatically and unconsciously.