Spatiotemporal characterization of response inhibition

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ABSTRACT

Despite an extensive literature on the neural substrates of response inhibition, when and where this process occurs in the brain remain unclear. The present study aimed to shed light on this issue by exploiting the high temporal resolution of the event-related potentials (ERPs) and recent advances in source localization. Temporo-spatial principal component analysis was employed to define more precisely the two ERP components most often associated with response inhibition (i.e., frontocentral N2 and frontocentral P3), as well as to improve the accuracy of source localization. In addition, participants (N = 40) performed a modified Go/ Nogo task composed of three types of stimuli (frequent-Go, infrequent-Go, and infrequent-Nogo), which allowed us to dissociate neural activity associated with response inhibition from that related to novelty processing by directly contrasting nogo and go trials matched with respect to frequency of occurrence. Scalp ERP data indicated that the frontocentral P3, but not the frontocentral N2, showed larger amplitudes for infrequent-Nogo than for infrequent-Go trials. Source localization data parallel the results obtained at the scalp level: only P3-related activity showed differences between infrequent-Nogo and infrequent-Go trials. This increased activation was observed predominantly in the presupplementary motor area (preSMA). Present results suggest that the frontocentral P3 and the preSMA play a core role in response inhibition. The findings of this study substantiate and complement previous results obtained by hemodynamic procedures.

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Introduction

Response inhibition, defined as the ability to suppress unwanted thoughts and actions, is crucial for successful adaptive behavior. Indeed, impaired response inhibition is thought to be a central feature of several neurological diseases and psychiatric disorders, including Hungtington's disease (Beste et al., 2008), obsessive–compulsive disorder (Bannon et al., 2002), borderline personality disorder (Ruchsow et al., 2008) and attention-deficit/hyperactivity disorder (Tamm et al., 2004). The Go/Nogo task is perhaps the most commonly used paradigm to study response inhibition in the laboratory setting. This paradigm involves the execution and inhibition of a motor response, triggered by a go and nogo stimulus, respectively. Many more go than nogo stimuli are generally presented in order to set up a pre-potent response tendency, thereby increasing the mobilization of inhibitory resources to withhold the response to nogo stimuli. However, using this traditional design, inhibitory processing is difficult to disentangle from and may be confound with processes related to detection of novelty such as stimulus-driven attention, since nogo stimuli elicit both types of cognitive processing. A modified version of the Go/Nogo task controlling for the oddball effect of

infrequent nogo stimuli is therefore necessary to define more precisely the behavioral and neural mechanisms supporting response inhibition (Chikazoe et al., 2009a; Smith et al., 2008; Tamm et al., 2004).

Given their precise temporal resolution that allows neural processes to be tracked in milliseconds, the timing of brain mechanisms underlying response inhibition has been extensively examined using scalp-recorded event-related potentials (ERPs). Indeed, the successful suppression of a pre-potent response is known to be characterized by involving rapid (early latency onset) and brief (short duration) neural processes, some of the most important occurring within the first second after nogo stimulus presentation (Bokura et al., 2001; Falkenstein et al., 1999; Kiefer et al., 1998; Kok et al., 2004). Specifically, two frontocentral ERP components have been consistently associated with response inhibition: N2 (200–400 ms) and P3 (300–600 ms). This conclusion has been reached based on the fact that both components have shown increased amplitude to nogo compared to go stimuli during different inhibitory paradigms, being the stop-signal and Go/Nogo tasks the most prominent. Nevertheless, the precise functional significance of these two components remains unclear. Either or both components could reflect the inhibition process per se, but also processes that occur just prior or even subsequent to inhibition itself, such as stimulus-driven attention, detection of response conflict or evaluation of the outcome of inhibition. Importantly, it should be noted that both frontocentral N2 and P3 have shown to be very sensitive to stimulus frequency and novelty (Bruin and Wijers,

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2002; Daffner et al., 2000; Duncan-Johnson and Donchin, 1977; Folstein and Van Petten, 2008; Friedman et al., 2001; Tarbi et al., 2011). Thus, frontocentral N2 and P3 amplitudes elicited by nogo stimuli during traditional Go/Nogo tasks might be reflecting, at least in part, cognitive processing associated with the presentation of rare infrequent stimuli (such as mismatch detection and stimulus-driven attention). Disentangling the contribution of this oddball effect in the generation of frontocentral Nogo-N2 and Nogo-P3 is thus needed to examine the specific association of each component with response inhibition.

The findings on the timing of response inhibition (*when* inhibition occurs) have been complemented by data on its anatomical substrates (*where* inhibition occurs). ERP source localization and especially functional magnetic resonance imaging (fMRI) studies indicate that response inhibition is subserved by a brain network distributed across multiple cortical and subcortical regions, including dorsolateral prefrontal cortex (dlPFC), inferior frontal cortex (IFC), dorsal anterior cingulate cortex (dACC), presupplementary motor area (preSMA), inferior parietal cortex and basal ganglia (Aaron and Poldrack, 2006; Chikazoe et al., 2007; Horn et al., 2003; Li et al., 2006, 2008a; Liddle et al., 2001; Mostofsky et al., 2003; Rubia et al., 2001; Simmonds et al., 2008; Swick et al., 2011). Such widespread activation pattern raises the question of whether these regions support other processes not strictly circumscribed to inhibition per se that are also involved in inhibitory paradigms such as the go/nogo or the stop-signal tasks. Indeed, some of these structures, including the inferior parietal lobe and IFC, are known to play a significant role in the rapid processing of novel, rare or significant events (Kiehl et al., 2001; Kiehl et al., 2005; Strobel et al., 2008; see also Corbetta et al., 2008). Interestingly, some recent fMRI studies have examined the neural basis of response inhibition using inhibitory paradigms that controls for this novelty processing (Chikazoe et al., 2009a; Sharp et al., 2010). Chikazoe et al. (2009a) observed a functional dissociation within the IFC, which distinguishes a posterior region preferentially related to inhibition and an inferior frontal junction region primarily associated with novelty processing. By contrast, Sharp et al. (2010) found that preSMA, but not the IFC, was specifically linked to response inhibition. Further research employing other techniques that complement the hemodynamic data obtained by these fMRI studies may be useful to clarify which regions of the brain are specifically involved in response inhibition.

The present study attempted to better characterize the neural bases and dynamics of response inhibition by exploiting the high temporal resolution of the ERPs and recent advances in source localization. Concretely, a two-step approach analysis was devised. First, temporo-spatial principal component analysis (PCA) was employed to detect and quantify those ERP components related to response inhibition (i.e., frontocentral N2 and frontocentral P3). PCA is a data-driven method which has shown to be a powerful approach to isolate ERP components across time course (temporal PCA) and scalp recording sites (spatial PCA). The main advantage of PCA over traditional methods of analyzing ERP data is that presents each component free of the influences of adjacent or latent components, thus disentangling the overlapping of different electrical potentials that represent functionally distinct processes. For instance, PCA has been previously used to separate the late positive components elicited in oddball attention tasks, including the anteriorly distributed novelty-P3 and the posterior target-P3 (Simons et al., 2001; Spencer et al., 2001). In the second step, exact low resolution brain electromagnetic tomography (eLORETA; Pascual-Marqui, 2007; Pascual-Marqui et al., 2011) was performed on N2 and P3, as defined by temporal PCA, to identify which brain regions are specifically involved in each process. The use of PCA factors instead of raw voltages enabled us to improve the accuracy of these source localization analyses (Carretié et al., 2004; Dien, 2010; Dien et al., 2003). Furthermore, a modified Go/Nogo task that controls for the confounding effects of the low frequency appearance

of nogo stimuli was employed, as previously recommended (Chikazoe et al., 2009a). Thus, by using this task design in conjunction with temporo-spatial PCA, we were able to examine more precisely whether frontocentral N2 and/or frontocentral P3 are related to response inhibition, as well as to elucidate the cortical regions that specifically mediate this process.

Methods

Participants

Forty healthy right-handed subjects (25 females), with an age range of 20–35 years (mean = 21.72; S.D. = 2.62), took part in this experiment. All participants reported normal or corrected-to-normal visual acuity and had no history of neurological or psychiatric disorders. The study was approved by the Research Ethics Committee of the Universidad Autónoma de Madrid, and all subjects provided informed consent.

Stimuli and procedure

Stimuli consisted of three capital letters ("N", "M" and "W") presented in Arial font. These letters were coloured in yellow so they clearly highlighted from the black background on which they were superimposed. Angle of vision for all letters was 5.16° (height).

Participants were placed in an electrically shielded, sound-attenuated and video-monitored room. They were instructed to press a button with the thumb of their right hand, as fast and accurate as possible, whenever the letters "M" or "N" were presented, and to withhold pressing when the letter presented was "W". They were asked to look continuously at the center of the screen in order to control eye-movement interference. The Go/Nogo task consisted of a single block of 300 trials. Each trial began with the presentation of the letter (400 ms), followed by a black screen (700 or 900 ms), so that the resulting onset asynchrony (SOA) was 1100 or 1300 ms (Fig. 1). Both letter and fixation cross were superimposed at the center of the black background. The letters "M" (infrequent-Go) and "W" (infrequent-Nogo) were presented with the same probability of occurrence (20%) in order to equalize both types of trials with respect to novelty/oddball processing. The letter "N" (frequent-Go) was presented in the rest of trials (i.e., 60%) to increase the subjects' tendency to respond. The three types of trials (frequent-Go, infrequent-Go, and infrequent-Nogo) were presented in semi-random order (i.e., avoiding the consecutive presentation of two infrequent-trials). Infrequent-Nogo trials could be preceded by one to seven Go trials (frequent or infrequent).

Before the beginning of the experiment, subjects completed a practice block of 12 trials (4 infrequent-Nogo) to ensure task instruction understanding. The task was programmed using Inquisit Millisecond software (Millisecond Software, Seattle, WA) and presented through a RGB projector on a backprojection screen.

Recording

Behavioral performance was recorded through a two-button keypad whose electrical output was continuously digitized at a sampling rate of 840 Hz. Electroencephalographic (EEG) activity was recorded using an electrode cap (ElectroCap International) with tin electrodes. Thirty electrodes were placed at the scalp following a homogeneous distribution. All scalp electrodes were referenced to the nosetip. Electrooculographic (EOG) data were recorded supra- and infraorbitally (vertical EOG), as well as from the left versus right orbital rim (horizontal EOG). An online bandpass filter of 0.3 to 40 Hz was applied. Recordings were continuously digitized at a sampling rate of 360 Hz throughout the recording session. The continuous recording was divided into 1000-ms epochs for each trial, beginning 200 ms
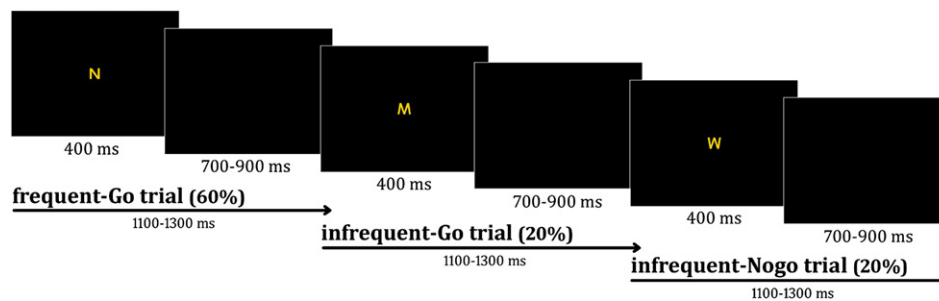
Fig. 1. Schematic illustration of the modified Go/Nogo task. An animation reproducing several trials of this Go/Nogo task as well as their temporal characteristics can be seen at http://www.uam.es/CEACO/sup/modGoNogo.html.

before stimulus onset. Trials in which participants responded erroneously or did not respond were a priori eliminated (an ad hoc analysis was performed to compare between successful and failed inhibitions; detailed description and results of this analysis can be found in Supplementary material 2). Ocular artefacts were removed using Independent Component Analysis (ICA; Jung et al., 2000), as implemented in Fieldtrip (http://fieldtrip.fcdonders.nl: Oostenveld et al., 2011). Following the ICA-based correction, a careful visual inspection of the EEG data was conducted. If any further artifact was present, the corresponding trial was discarded. To maintain a good signal-to-noise ratio, a lower limit of 25 artifact-free correct trials per subject per condition was set (Cohen and Polich, 1997; Duncan et al., 2009).

Data analysis

Behavioral analysis

Percentage error rates (both omissions and commissions: no responses in Go trials and button presses in Nogo trials, respectively) and mean reaction times (RTs) were analyzed. Univariate repeated-measures ANOVAs on each behavioral measure were carried out using Trial type (three levels: frequent-Go, infrequent-Go, infrequent-Nogo) as a factor. The Greenhouse–Geisser (GG) epsilon correction was applied to adjust the degrees of freedom of the F ratios where necessary, and post hoc comparisons were also made in order to determine the significance of pair-wise contrasts applying the Bonferroni procedure (alpha < 0.05). Effect sizes were computed using the partial eta-square (η^2_p) method. In addition, Pearson correlation coefficients were used to examine the relationship between behavioral measures.

Scalp ERP analysis

With the aim of reliably testing whether N2 and P3 were present in the ERPs, components explaining most of the ERP variance in the temporal domain were detected and quantified through a covariance-matrix-based temporal principal component analysis (tPCA). This technique has been recommended since the exclusive use of traditional visual inspection of grand averages and voltage computation may lead to several types of misinterpretation (Chapman and McCrary, 1995; Dien and Frishkoff, 2005). The main advantage of tPCA over traditional procedures based on visual inspection of recordings and on 'temporal windows of interest' is that it presents each ERP component separately and with its 'clean' shape, extracting and quantifying it free of the influences of adjacent or subjacent components. Indeed, the waveform recorded at a site on the head over a period of several hundreds of milliseconds represents a complex superposition of different overlapping electrical potentials. Such recordings can stymie visual inspection. In brief, tPCA computes the covariance between all ERP time points, which tends to be high between those time points involved in the same component, and low between those belonging to different components. The solution is therefore a set of independent factors made up of highly covarying time points, which ideally correspond to ERP components. *Temporal factor score*, the tPCA-derived parameter in which extracted temporal factors may be quantified, is linearly

related to amplitude. Similarly to previous studies, the decision on the number of components to select was based on the scree test (Cattell, 1966). Extracted components were submitted to promax rotation, as recently recommended (Dien, 2010; Dien et al., 2007). As explained in detail later, the presence of N2 and P3 was confirmed.

Once quantified in temporal terms, N2 and P3 temporal factor scores were submitted to spatial PCA (sPCA) in order to decompose the N2 and P3 topography at the scalp level into their main spatial regions. Thus, while temporal PCA "separates" ERP components along time, spatial PCA (sPCA) separates ERP components along space, each spatial factor ideally reflecting one of the concurrent neural processes underlying each temporal factor. This spatial decomposition is an advisable strategy prior to statistical contrasts, since ERP components frequently behave differently in some scalp areas than they do in others (e.g. they present opposite polarity or react differently to experimental manipulations). Basically, each region or spatial factor is formed with the scalp points where recordings tend to covary. As a result, the shape of the sPCA-configured regions is functionally based, and scarcely resembles the shape of the geometrically configured regions defined by traditional procedures. Remarkably, each spatial factor can be also quantified through the *spatial factor score*, a single parameter that reflects the amplitude of the whole spatial factor. The decision on the number of spatial factors to select was also based on the scree test, and extracted factors were submitted to promax rotation.

Finally, univariate repeated-measures ANOVAs were performed on N2 and P3 spatial factor scores using Trial type (three levels: frequent-Go, infrequent-Go, and infrequent-Nogo) as a factor. GG epsilon correction and Bonferroni post hoc comparisons (alpha < 0.05) were also applied, as previously described. Comparisons especially relevant to our purposes were those contrasting infrequent conditions (i.e., infrequent-Go vs. infrequent-Nogo) for the frontocentral N2 and frontocentral P3. Also in this case, effect sizes were determined by using the η^2_p method.

Source localization analysis

In order to three-dimensionally locate the cortical regions that were specifically involved in response inhibition, exact low-resolution brain electromagnetic tomography (eLORETA) was applied to N2 and P3, as defined by tPCA. eLORETA is a 3D, discrete linear solution for the EEG inverse problem (Pascual-Marqui, 2007; Pascual-Marqui et al., 2011). Although solutions provided by EEG-based source-location algorithms should be interpreted with caution due to their potential error margins, LORETA solutions have shown good correspondence with those provided by hemodynamic procedures such as fMRI and PET in the same tasks (including the go/nogo paradigm: Chiu et al., 2008) when at least 25 scalp electrodes are employed (e.g., Dierks et al., 2000; Mulert et al., 2004; Pascual-Marqui, 2002; Pizzagalli et al., 2003). Furthermore, the use of tPCA-derived factor scores instead of direct voltages (which leads to more accurate source-localization analyses: Carretié et al., 2004; Dien et al., 2003; Dien, 2010) and the relatively large sample size employed in the present study ($N = 40$), contribute to reducing

this error margin. In its current version, eLORETA computes the standardized current density at each of 6239 voxels in the cortical gray matter and the hippocampus of the digitized Montreal Neurological Institute (MNI) standard brain.

Concretely, three-dimensional current–density estimates for the N2 and P3 temporal factor scores were computed for each participant and each experimental condition. Subsequently, the voxel-based whole-brain eLORETA-images (6239 voxels at a spatial resolution of 5 mm) were compared between infrequent conditions (infrequent-Nogo vs. infrequent-Go) for N2 and P3 temporal factor scores using the non-parametric mapping (SnPM) tool, as implemented in the sLORETA/eLORETA software package (http://www.uzh.ch/keyinst/loreta.htm). As explained by Nichols and Holmes (2002), the non-parametric methodology inherently avoids multiple comparison-derived problems and does not require any assumption of Gaussianity. Voxels that showed significant differences between infrequent conditions (p < 0.01, two-tailed, corrected) were located in anatomical regions and Brodmann areas (BAs).

Results

Behavioral data

Percentage error rates and mean RTs for each type of trial are shown in Table 1. Univariate repeated-measures ANOVAs on both behavioral measures were performed, as previously described. With respect to percentage error rates, a significant main effect of Trial type was observed ($F(2,78) = 176.7$, $p < 0.001$, $\eta^2_p = 0.82$). Post hoc tests showed that percentage error rates were higher for infrequent-Nogo trials (i.e., commission errors) than for frequent- and infrequent-Go trials (omission errors). In addition, omission errors were greater for infrequent-Go than for frequent-Go trials. With respect to mean RTs, a significant main effect of Trial type was also found ($F(2,78) = 87.7$, $p < 0.001$, $\eta^2_p = 0.69$). Post hoc tests showed that incorrect responses to Nogo cues (i.e., commission errors) were shorter than correct responses to Go cues (both infrequent and frequent). Likewise, correct responses to infrequent-Go cues were longer than to correct responses to frequent-Go cues. Pearson correlation coefficients showed a negative relationship between commission errors and RTs of correct responses to Go stimuli (frequent-Go: $r = -0.56$, $p < 0.001$; infrequent-Go: $r = -0.61$, $p < 0.001$), indicating that subjects who responded faster made more commission errors.

Scalp ERP data

Fig. 2 shows a selection of grand averages once the baseline value (prestimulus recording) had been subtracted from each ERP. These grand averages correspond to the frontocentral scalp area, where the relevant components (frontocentral N2 and frontocentral P3) are clearly visible. As a consequence of the application of the tPCA, seven components were extracted from the ERPs (Fig. 3). Factor peak latency and topography characteristics associate Factor 4 (from 213 to 369 ms; peaking at 277 ms) with the wave labeled N2 in grand averages and Factor 1 (from 320 to 713 ms; peaking at 433 ms) with that labeled P3. These labels will be employed hereafter to make the results easier to understand. As shown in Fig. 4, the sPCAs subsequently
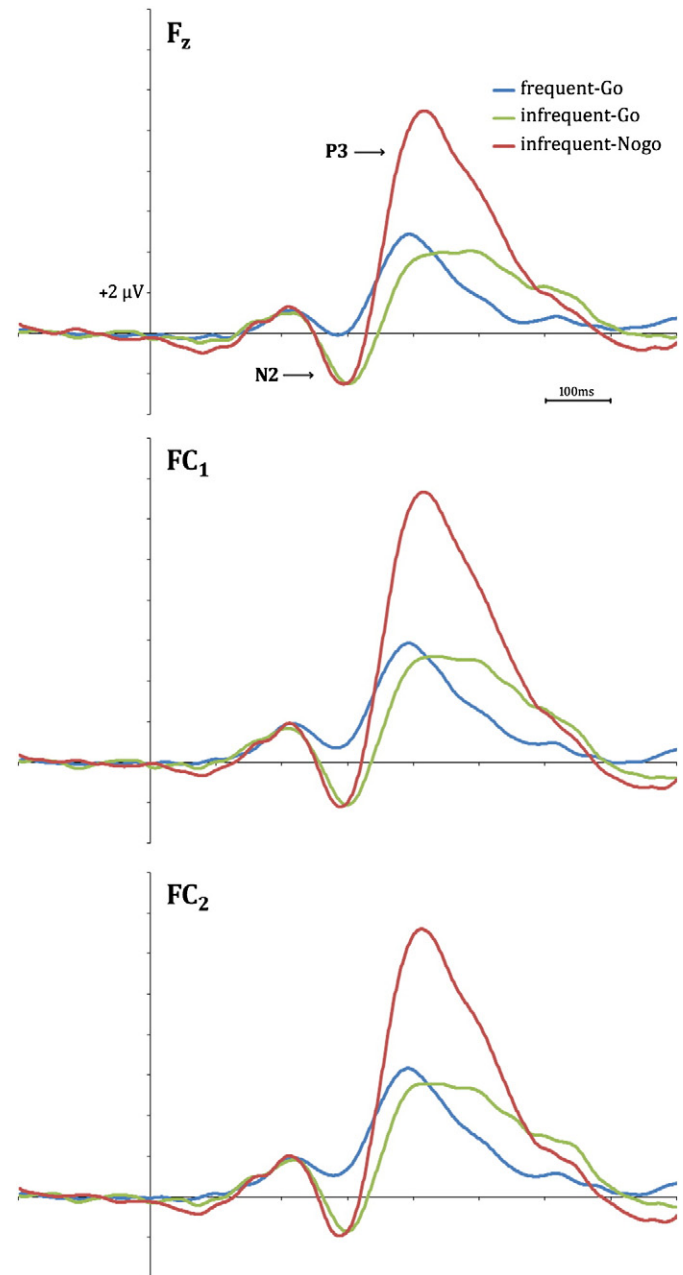

Fig. 2. Grand averages at frontocentral scalp sites, where the relevant ERP components (frontocentral N2 and frontocentral P3) were clearly visible.

applied to temporal factor scores extracted two spatial factors for both N2 and P3: one frontocentral and other parietooccipital.

As explained above, our analyses focused on frontocentral N2 and frontocentral P3 because they have been consistently implicated in response inhibition. Specifically, univariate repeated-measures ANOVAs on spatial factor scores (directly related to amplitudes, as previously indicated) were performed using Trial type as a factor. A significant effect of Trial type was found in both frontocentral N2 and frontocentral P3 ($F(2,78) = 24.43$, $p < 0.001$, $\eta^2_p = 0.38$, and $F(2,78) = 55.5$, $p < 0.001$, $\eta^2_p = 0.59$, respectively). Bonferroni post hoc comparisons indicated that frontocentral P3 amplitudes were larger for infrequent-Nogo trials than for infrequent-Go trials. By contrast, frontocentral N2 amplitudes were similar for infrequent-Nogo trials than for infrequent-Go trials. Post hoc comparisons also showed that both frontocentral N2 and frontocentral P3 amplitudes were larger for infrequent-Go and infrequent-Nogo than for frequent-Go trials.

Table 1
Means and standard deviations (in parentheses) of reaction times (RTs) and percentage error rates for each type of trial (frequent-Go, infrequent-Go, infrequent-Nogo).

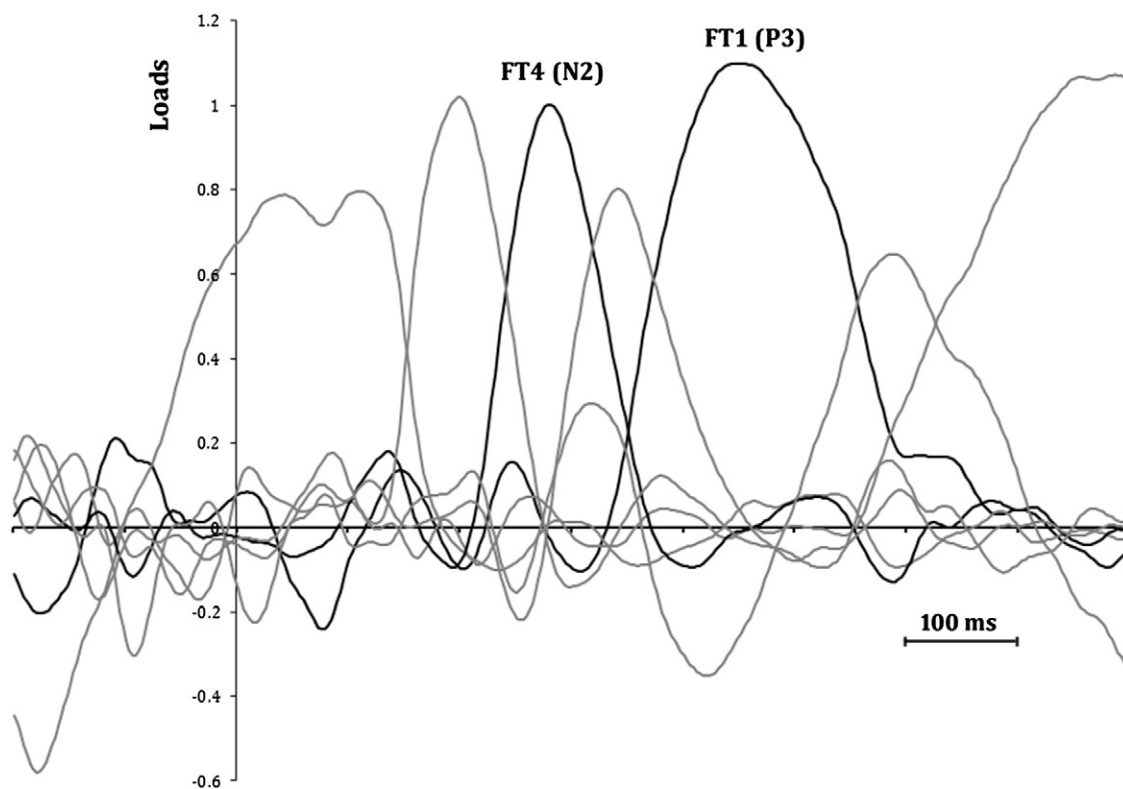|	Frequent-Go	Infrequent-Go	Infrequent-Nogo
RTs (ms)	317.46 (33.17)	363.41 (48.46)	302.60 (47.12)
Error rates (%)	0.57 (0.83)	2.43 (3.5)	30.79 (14.03)

Fig. 3. Temporal principal component analysis (tPCA): factor loadings after promax rotation. Temporal factors 4 (N2) and 2 (P3) are drawn in black.

Source localization data

To localize the cortical regions that were responsible for the experimental effects observed at the scalp level, three-dimensional current–density estimates for N2 and P3 (as defined by tPCA) were computed for each subject and each condition using the sLORETA/eLORETA software package. Subsequently, the voxel-based whole-brain eLORETA-images (6239 voxels at a spatial resolution of 5 mm) were compared between infrequent conditions using the SnPM toolbox of sLORETA/eLORETA. As illustrated in Fig. 5, greater P3-associated activation in the superior medial frontal cortex was found for infrequent-Nogo than for infrequent-Go trials (t = 3.98, two-tailed corrected p < 0.01). Specifically, this increased activation during the P3 time range was primarily observed in the left pre-SMA (BAs 6/8; peak MNI coordinates:

X = −10, Y = 15, Z = 65). By contrast, N2-related activation did not differ between infrequent-Nogo and infrequent-Go conditions in any cortical region (t = 3.73, two-tailed corrected p = 0.76).

Relationship between behavioral, scalp- and source-ERP data

To assess whether behavioral measures of performance were related to frontocentral Nogo-N2 or to frontocentral Nogo-P3, multiple regression analyses were conducted using the enter method. The dependent variable was the spatial factor scores (i.e., amplitudes) of frontocentral Nogo-N2 or Nogo-P3 and the independent or predictor variables were the Go/Nogo task performance measures (i.e., omission errors to infrequent-Go and frequent-Go stimuli, commission errors to infrequent-Nogo, correct RTs to frequent-Go and infrequent-Go, and incorrect RTs to infrequent-Nogo). Frontocentral Nogo-N2 did not show any relationship with behavioral performance. By contrast, frontocentral Nogo-P3 was negatively associated with mean correct RTs to frequent-Go stimuli (β = −0.34, two-tailed p < 0.05): subjects who responded more quickly to frequent-Go stimuli required larger frontocentral P3 amplitudes to successfully over-ride the motor response to infrequent-Nogo stimuli.

To test whether pre-SMA and behavior were also interrelated, the association between inhibition-related activation within the pre-SMA (dependent variable) and performance measures in the Go/Nogo task (independent variables) was analyzed via multiple regression analyses using the enter method. The pre-SMA region of interest (ROI) was defined functionally by selecting those voxels showing greater P3-related activity in the infrequent-Nogo vs. infrequent-Go contrast described above (61 voxels comprising BAs 6/8). Similar to the results obtained with frontocentral Nogo-P3 scalp amplitudes, inhibition-related activation in the pre-SMA was negatively correlated to mean correct RTs to frequent-Go stimuli (β = −0.48, two-tailed p < 0.01). Thus, subjects who responded more quickly to frequent-Go cues showed greater preSMA activation when they successfully withheld the response to infrequent-Nogo cues.
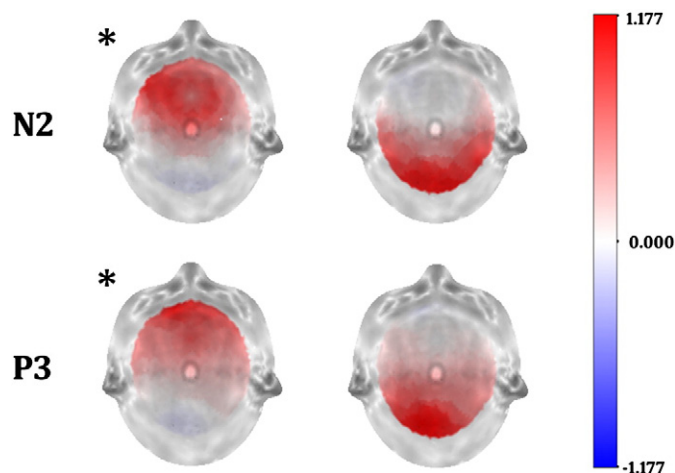

Fig. 4. Spatial factors extracted for N2 and P3 through spatial principal component analysis (sPCA). Frontocentral N2 (74% explained variance of N2) and frontocentral P3 (85% explained variance of P3) are marked with an asterisk.
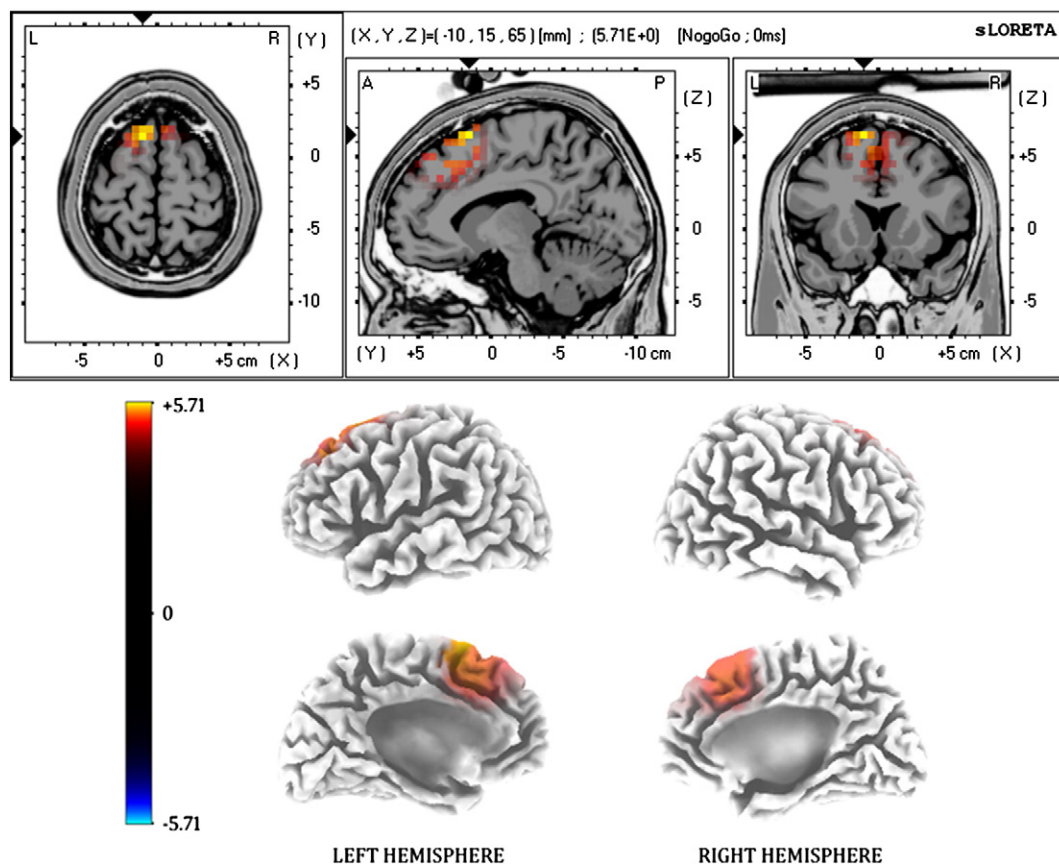
Fig. 5. Source localization analysis (eLORETA): increased P3-related activation during infrequent-Nogo relative to frequent-Go trials primarily observed in the preSMA (t = 3.98, two-tailed corrected p < 0.01). Color bar represents voxel t values.

These results seem to suggest that those participants exhibiting a stronger pre-potent response tendency (shorter RTs to frequent-stimuli) were also those that required greater mobilization of inhibitory resources to successfully over-ride the motor response. To test this hypothesis, we isolated ERP activity related to the response on frequent-Go trials and examined the relationship between this activity and inhibition-related measures (frontocentral Nogo-P3 amplitudes and inhibition-related preSMA activation). Activity specifically associated with frequent-Go stimuli was obtained by subtracting the ERPs to frequent-Go from the ERPs to infrequent-Go (Inline Supplementary Fig. S1). The difference waveforms exhibited a prominent positive deflection that was maximal at Cz and peaked around the mean RT of correct responses on frequent-Go trials (317 ms; see Table 1). Temporo-spatial PCA was then employed to detect and quantify, in a reliable manner, this positive ERP component associated with overt responses on frequent-Go trials, and source localization was also carried out to identify its neural substrates (see Supplementary material 1 for further details). A motor related-structure, the supplementary motor area (SMA), was identified as the generator of this component (peak MNI coordinates: X = −10, Y = −10, Z = 70; Inline Supplementary Fig. S1). Notably, positive relationships were found between this centrofrontal motor-related ERP component and frontocentral Nogo-P3 amplitudes as well as between this motor-related component and inhibition-related activation within the preSMA (r = 0.45, p < 0.01, and r = 0.55, p < 0.001, respectively).

Inline Supplementary Fig. S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.03.011.

Discussion

The current study attempted to determine the timing and location of neural activity supporting response inhibition using scalp-recorded ERPs in conjunction with recent source localization techniques. To this end, we used a modified Go/Nogo task composed of three kinds of stimuli (frequent-Go, infrequent-Go, and infrequent-Nogo), which allowed us to dissociate brain electrical activity related to response inhibition from that related to processing of infrequent stimuli by directly contrasting nogo and go trials matched with respect to frequency of occurrence (i.e., infrequent-Nogo vs. infrequent-Go).

Scalp ERP data revealed that only the frontocentral P3 exhibited larger amplitudes for infrequent-Nogo than for infrequent-Go trials. These results therefore suggest that the frontocentral P3 plays a key role in response inhibition. This conclusion receives additional support from several lines of evidence. First, the frontocentral P3 has been shown to be greater not only for manual inhibition (Smith et al., 2008), but also for inhibition of spoken (Etchell et al., 2011) and covert (silent counting) responses (Bruin and Wijers, 2002; Smith et al., 2008). Second, larger frontocentral P3 amplitudes to successful compared to failed inhibitions have been observed during the stop-signal task (Dimoska et al., 2006; Kok et al., 2004), another inhibitory paradigm that measures the ability to suppress a response that has been already initiated (see Verbruggen and Logan, 2008). As can be seen in Supplementary material 2, the same result has been found in the present study using a modified version of the Go/Nogo task. Third, the frontocentral P3 (but not the frontocentral N2) has been shown to be modulated by response priming (Bruin et al., 2001; Smith et al., 2007). Four, an enhanced frontocentral P3 to stimuli requiring response inhibition (nogo/stop) has been observed regardless of whether they were frequently or infrequently presented (Donkers and van Boxtel, 2004; Enriquez-Geppert et al., 2010). The latter finding is in consonance with our data and suggests that the frontocentral P3 elicited by go/nogo cannot be solely explained in terms of probability of occurrence of nogo stimuli. It should be emphasized, however, that the results of the present study highlight the importance of

controlling for the contribution of oddball frequency effects in the generation of the frontocentral Nogo-P3 in order to examine the electrophysiological activity specifically related to response inhibition.

An important question to be discussed is the timing of the frontocentral Nogo-P3. In the current study, this component reached its maximum amplitude at 433 ms after nogo stimulus onset. Thus, it peaked at about 70 ms later than the mean RT of correct responses on infrequent-Go trials (see Table 1), which were the trials more closely matched to infrequent-Nogo both in terms of frequency of occurrence and visual features. Assuming that response inhibition and response execution occur at the same timing, the peak latency of the frontocentral Nogo-P3 seems to be too late for representing the inhibitory process itself. Alternatively, it may primarily correspond to a process associated with the termination of response inhibition such as the evaluation of the inhibitory process or its outcome, an idea previously advanced by some authors (Bruin et al., 2001; Roche et al., 2005). Therefore, from this perspective, the frontocentral Nogo-P3 might reflect response-related, evaluative processing stages (Huster et al., 2012). It should be noted, however, that the frontocentral Nogo-P3 (and thereby the underlying process generating this component) started before the mean RT of correct responses on infrequent-Go trials. Specifically, its onset was 320 ms following the nogo stimulus onset (i.e., 40 ms earlier than the overt response on infrequent-Go trials). Considering this, it would be also possible that the frontocentral Nogo-P3 was related to the inhibitory process itself. Although the exact functional significance of the frontocentral Nogo-P3 seems to remain a matter of future research, present results and current evidence on this issue strongly support that this component plays a critical role in response inhibition, being the ERP component most closely linked to this process.

Notably, there were no significant differences between frontocentral N2 amplitudes evoked by infrequent-Nogo and infrequent-Go stimuli. However, frontocentral N2 amplitudes were larger to infrequent (both Go and Nogo) than to frequent stimuli. Therefore, frontocentral N2 showed increased amplitudes to low-frequency stimuli regardless of whether these stimuli were associated with generating or withholding a response. These results provide further evidence that the frontocentral N2 elicited in the Go/Nogo tasks does not reflect the inhibitory process per se (Donkers and van Boxtel, 2004; Enriquez-Geppert et al., 2010; Nieuwenhuis et al., 2003), contrary to early interpretations of this component (Jodo and Kayama, 1992; Kopp et al., 1996). Current findings indicate that frontocentral N2 represents a process that occurs just prior to the moment of response onset irrespective of the output required (response inhibition or response execution). One possibility is that frontocentral N2 indexes conflict (at the stimulus level rather than at the response level) arising from differences in the relative frequency of stimuli (Nieuwenhuis et al., 2003; Wendt et al., 2007). From this perspective, a greater degree of conflict was present in the case of low versus high frequency events, whereas there was no differential conflict between stimuli matched in terms of frequency of occurrence. Another possibility is that frontocentral N2 represents the detection of visual mismatch between the frequent-go visual template and infrequent stimuli (in our experiment, go or nogo) (Daffner et al., 2000; Folstein and Van Petten, 2008). Indeed, there is a growing literature indicating that, at least, part of the frontocentral N2 elicited in the traditional Go/Nogo task as well as in other inhibitory paradigms is associated with bottom-up processes such as the automatic detection of novelty or mismatch (Helenius et al., 2010; Kropotov and Ponomarev, 2009; Kropotov et al., 2011; see also Folstein and Van Petten, 2008). Present findings cannot rule out any of these interpretations. Thereby, additional studies are needed to clarify the functional role of frontocentral N2 in inhibitory paradigms such as the go/nogo or stop-signal tasks.

Source localization data revealed greater activation for infrequent-Nogo than infrequent-Go trials during the P3 time range. Specifically, this increased activation was primarily found in the preSMA. By contrast, we did not find any region that showed significantly greater activation for infrequent-Nogo than for infrequent-Go trials during the N2 time range. These findings therefore parallel the results obtained at the scalp level: only brain electrical activity associated with P3 showed differences between nogo and go trials matched with respect to frequency of occurrence. Because this activation was strictly restricted to P3 through the use of temporal PCA and considering that oddball frequency confounds were removed, our findings suggest that preSMA plays a specific and important role in response inhibition. Remarkably, recent studies using hemodynamic procedures have observed inhibition-related activity in the preSMA even after controlling for the confounding effects of the low frequency appearance of nogo/ stop stimuli (Chikazoe et al., 2009a; Sharp et al., 2010). Present results therefore substantiate and complement these fMRI findings by delineating the particular processing stage at which the activity of the preSMA occurs (starting at 320 ms after nogo stimulus onset and continue for about 400 ms: P3 time range).

Our finding that the preSMA is critically involved in response inhibition receives further support from other lines of evidence. First, human lesion studies suggest that damage of the superior medial frontal lobe, particularly the preSMA, leads to the impaired ability of patients to inhibit their responses (Floden and Stuss, 2006; Picton et al., 2007). In the same line, a recent investigation has found that transcranial magnetic stimulation delivered over the preSMA disrupts the ability of healthy subjects to appropriately inhibit pre-potent responses, their ability to execute responses not being affected (Chen et al., 2009). Second, preSMA hemodynamic activation has been shown under a variety of inhibitory paradigms, including the go/ nogo, stop-signal, anti-saccade and anti-pointing tasks, which required not only motor response inhibition but also the suppression of spoken and oculomotor responses (Li et al., 2006; Mostofsky et al., 2003; Rubia et al., 2001; Simmonds et al., 2008; Swick et al., 2011; Xue et al., 2008). Third, preSMA has been identified as a core region mediating response inhibition by comparing subjects with short and long stop-signal reaction time (SSRT). Specifically, greater preSMA activity was observed in individuals with short as compared to those with long SSRT (Li et al., 2006, 2008a). The SSRT is an estimation of the latency of the inhibitory process in a stop-signal task according to a horse-race model (see Verbruggen and Logan, 2008 for further details), so it is assumed that faster SSRT's reflect more efficient response inhibition. The crucial role of the preSMA in the implementation of efficiency of inhibitory control has been confirmed on the basis of a within-subject analysis (Chao et al., 2009). Finally, strong evidence from anatomical connectivity studies indicates that the preSMA sends projections to the subthalamic nucleus (STN) and striatum (King et al., 2012), two subcortical regions critical for inhibitory control of behavior (Aaron and Poldrack, 2006; Li et al., 2008b). Interestingly, recent data have even shown a functional connectivity between the preSMA and the basal ganglia (primarily, the caudate head) during resting-state and stop-signal performance (Duann et al., 2009; Zhang et al., 2012). Taken together, these findings pinpoint the preSMA as a crucial region for inhibitory control that probably mediates this process through its direct connections with the STN and especially with the caudate nucleus.

The functional dissociation between the SMA (implicated in motor response execution) and preSMA (involved in response inhibition) observed here is consistent with previous evidence from anatomical, functional and connectivity studies (Nachev et al., 2008; Picard and Strick, 2001; Zhang et al., 2012). Commonly, the vertical commissure anterior line (y = 0) serves as an anatomical landmark to distinguish between these two regions of the medial superior frontal cortex (Picard and Strick, 1996). Whereas the SMA has strong connections with the primary motor cortex and spinal cord, the pre-SMA does not. Instead, the pre-SMA, but not the SMA, has substantial connections with the prefrontal cortex and caudate (Nachev et al., 2008; Picard and Strick, 2001; see also Zhang et al., 2012). These patterns

of connectivity support the key roles of SMA and preSMA in movement planning/execution and inhibitory control, respectively. Recently, on the basis of functional and connectivity evidence, a further distinction has been made between anterior and posterior regions of the preSMA. The anterior portion of the preSMA seems to be the core region involved in response inhibition, whereas the posterior preSMA (in conjunction with the SMA) would be more related to conflict- and error-related processing (Ide and Li, 2011; Li et al., 2006, 2008c). This functional differentiation was also found in our supplementary analysis comparing successful versus failed inhibitions. Specifically, results from this analysis revealed that the SMA was associated with error-related activity (N2 evoked during failed inhibitions), whereas the preSMA was related to inhibition-related activity (P3 elicited during successful inhibitions; for further discussion of these and other results of this analysis, see Supplementary material 2).

The behavioral performance in the modified Go/Nogo task and its relationship with brain functional measures also revealed noteworthy findings. Subjects were slower to respond and made more omission errors to infrequent-Go relative to frequent-Go stimuli. These differences appear to reflect that processing of infrequent stimuli is more difficult and requires greater cognitive resources than processing of frequent stimuli. Again, these results underline the importance of controlling for oddball effect in studies of response inhibition that use go/nogo and stop-signal tasks. In addition, the fact that subjects made a large number of commission errors (also called false alarms) confirmed that our modified Go/Nogo task was effective in increasing the tendency to respond and thereby making it difficult to withhold responding to infrequent nogo stimuli. Interestingly, our data also showed an association between behavioral performance and brain electrical activity during the modified Go/Nogo task. Concretely, we found that participants who responded more quickly to frequent-Go stimuli revealed higher frontocentral P3 amplitudes and stronger preSMA activation to successfully over-ride the motor response to infrequent-Nogo stimuli. These results seemed to indicate that those participants exhibiting a stronger pre-potent response tendency were also those that revealed greater activation of inhibitory resources to successfully withhold responding to infrequent-Nogo cues. This hypothesis was supported by the findings of positive correlations between motor-related electrophysiological activity observed during frequent-Go trials (as mentioned above, this activity was generated in the SMA) and frontocentral Nogo-P3 amplitudes/inhibition-related preSMA activation. Thus, it seems that impulsive subjects (defined here as those who responded faster; these participants also made more commission errors; see behavioral results) activated inhibition-related mechanisms to a greater extent in order to counteract a stronger pre-potent response tendency. Although one could expect that impulsive subjects should show a reduce activation of inhibitory mechanisms (Logan et al., 1997; Tamm et al., 2004), present results correspond well with some earlier findings obtained in non-clinical samples (Dimoska and Johnstone, 2007; Horn et al., 2003). For example, Dimoska and Johnstone (2007) found larger frontocentral P3 amplitudes in high- in comparison to low-impulsive individuals during successful inhibitions. Therefore, present results add further evidence on the crucial role of frontocentral Nogo-P3 and preSMA in response inhibition (Albert et al., 2010; Chao et al., 2009; Li et al, 2006), being especially important when a strongly pre-potent response tendency must be overridden.

To conclude, the findings reported here suggest that the frontocentral P3 and the preSMA are critically involved in response inhibition. Importantly, present results could have implications for the understanding of neurological and psychiatric disorders characterized by impairments of response inhibition, such as attention-deficit hyperactivity disorder and obsessive–compulsive disorder. The marked attenuation of the frontocentral N2 typically observed in these patients during inhibitory paradigms has been often interpreted as

reflecting a deficit in the inhibitory process itself (Kim et al., 2006; Yong-Liang et al., 2000). However, on the basis of current results and evidence from other works discussed here, only alterations related to the frontocentral P3 (and once controlling for oddball frequency confounds) might reflect impairments related to response inhibition. By capitalizing on fine temporal resolution of the ERPs and the recent advances in source localization, the results of this research shed light on the spatiotemporal characterization of response inhibition. Future electrophysiological studies exploring the influence of preparatory processes on response inhibition (Chikazoe et al., 2009b; Garavan et al., 2002) as well as post-response processing (Garavan et al., 2002; Li et al., 2008b) will be important to extend present findings.

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Conflict of interests

The authors declare no conflict of interest.

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