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State dependency of inhibitory control performance: an electrical neuroimaging study

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Abstract

Behavioral and brain responses to stimuli not only depend on their physical features but also on the individuals' neurocognitive states before stimuli onsets. While the influence of pre-stimulus fluctuations in brain activity on low-level perceptive processes is well established, the state dependency of high-order executive processes remains unclear. Using a classical inhibitory control Go/NoGo task, we examined whether and how fluctuations in the brain activity during the period preceding the stimuli triggering inhibition influenced inhibitory control performance. Seventeen participants completed the Go/NoGo task while 64-channel electroencephalogram was recorded. We compared the event-related potentials preceding the onset of the NoGo stimuli associated with inhibition failures false alarms (FA) vs. successful inhibition correct rejections (CR) with data-driven statistical analyses of global measures of the topography and strength of the scalp electric field. Distributed electrical source estimations were used to localize the origin of the event-related potentials modulations. We observed differences in the global field power of the event-related potentials (FA > CR) without concomitant topographic modulations over the 40 ms period immediately preceding NoGo stimuli. This result indicates that the same brain networks were engaged in the two conditions, but more strongly before FA than CR. Source estimations revealed that this effect followed from a higher activity before FA than CR within bilateral inferior frontal gyri and the right inferior parietal lobule. These findings suggest that uncontrolled quantitative variations in pre-stimulus activity within attentional and control brain networks influence inhibition performance. The present data thereby demonstrate the state dependency of cognitive processes of up to high-order executive levels.

Introduction

Behavioral and brain responses to stimuli not only depend on the physical features of the stimuli but also on the neurocognitive state of the subject at stimulus onset. So far, the literature on the state dependency of cognitive processes focused mostly on how exogenous factors, such as task instructions or cueing, modulate the processing of forthcoming stimuli (Otten *et al.*, 2006; Smith *et al.*, 2006; Jaffard *et al.*, 2008; Aron, 2011; Sallard *et al.*, 2014). However, growing evidence indicate that endogenous modulations of pre-stimulus activity, driven for example by spontaneous fluctuations in attention, might also modulate stimuli processing and performance (Ress *et al.*, 2000; Mohr *et al.*, 2005; Fox *et al.*, 2006; Pourtois *et al.*, 2006; Fox & Raichle, 2007; Britz *et al.*, 2009, 2011; Britz & Michel, 2010). While these studies indicate that endogenous brain activity influences performance during low-level perceptual tasks, whether such effects also contribute to higher order executive processes – and notably inhibitory control – remains unclear.

In an Eriksen Flanker interference task, Eichele *et al.* (2010) observed a sustained negative event-related potential (ERP) component starting from 200 to 300 ms before the onset of inaccurately processed stimuli that was absent before accurate trials. A corresponding effect was found in another interference task by Britz & Michel (2010), who showed decreases in the activity within the dorsolateral frontoparietal cortices during the 100 ms preceding errors but not correct color stroop trials. These findings suggest that behavioral outcomes during interference tasks might depend both on how participants manage the conflict induced by the stimuli, and on the brain states preceding the stimuli onsets. In motor inhibitory control tasks, cues predicting the occurrence of inhibition stimuli (NoGo) have been shown to modulate the activity of inhibition-related prefrontal brain areas [the inferior frontal gyrus (IFG) and pre-supplementary motor area], which in turn facilitated subsequent response suppression (Aron, 2011 for a review; Swann *et al.*, 2012).

Based on evidence for (i) endogenous fluctuations effects on behavior in pre-stimuli brain activity during low-level sensory-cognitive processing, and (ii) exogenous modulations effects of pre-stimulus brain state during executive processes, we hypothesized that the performance at higher order tasks such as inhibitory control Go/

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NoGo paradigms would at least partly depend on uncontrolled variations in pre-stimulus activity.

To address this question, we reanalyzed data from a visual Go/NoGo task in which the occurrence of inhibition NoGo stimuli was unpredictable (Hartmann *et al.*, 2015) and we compared the electrical neuroimaging activity during the period immediately preceding the presentation of NoGo trials associated with successful (correct rejections) or unsuccessful inhibition (false alarms). We hypothesized that as compared to false alarms, correct rejections would be associated with an endogenous pre-activation of the inhibitory control fronto-striatal brain networks.

Materials and methods

Participants

Twenty-two right-handed healthy adult males participated in the study. All had normal or corrected to normal vision and no history of neurological or psychiatric illness. They all provided written consent. The study was approved by our local ethics committee and conforms to the World Medical Association Declaration of Helsinki. Five subjects were excluded from the analyses for the following reasons: artifactual electroencephalogram (EEG) recording ($n = 3$), improper calibration phase ($n = 1$; see the Procedure section) and part of the response was performed with the left hand ($n = 1$). Seventeen participants (mean age \pm SD: 25.0 ± 4.7) were thus eventually included in the analyses.

Stimuli and task

The procedures and tasks are detailed in Hartmann *et al.* (2015), we thus provide only the essential information here.

The participants performed a Go/NoGo task. Visual stimuli were presented at the center of the screen with a black background. Stimuli consisted of six different letters (A, E, M, O, S or T) in six different colors (blue, cyan, green, red, white or yellow). In a given block, NoGo stimuli were either all letters of a given color or all colors of a given letter (total of 12 different NoGo stimuli); Go trials were all the remaining stimuli. A total of 36 different stimuli were used according to the possible letter-color combination. Participants had to press as quickly as possible with their right index finger on a response box in response to Go stimuli, while withholding their responses to NoGo stimuli.

Procedure

Participants sat in a quiet booth. Stimulus delivery and response recording were controlled with E-prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA).

The Go/NoGo paradigm consisted in 12 blocks of 60 trials (30 Go; 30 NoGo) separated by 2 min breaks. A calibration phase of 12 trials (6 Go; 6 NoGo) preceded each blocks. During the calibration phase, the mean response time (RT) to Go stimuli was calculated. This mean RT was used to determinate the response time threshold (RTt) computed as 90% of the mean RT to the Go stimuli. During the experimental phase, a feedback ‘too late!’ was presented if the RT was above the RTt.

Each trial started with the presentation of a gray fixation cross during a time range of 1500–1900 ms, followed by the stimuli (500 ms) and a response window (Fig. 1). Independently of the response time threshold determined during the calibration phase, the response window terminated as soon as the participant responded,

but had a minimal and a maximal duration of 250 and 1000 ms, respectively. Then, the participants received a feedback on their performance for 500 ms: a happy smiley icon after Fast Hits (response after a Go stimulus with a $RT < RTt$) and Correct Rejections (no response after a NoGo stimulus); a ‘Too late!’ feedback for Slow Hits, i.e. with a $RT > RTt$; and an unhappy smiley after Misses (no response after a Go stimulus) and False Alarms (response after a NoGo trial).

The NoGo criteria (specific letter or color) were pseudorandomized for each block (i.e. for each participant, all blocks had a different NoGo stimulus) and counterbalanced between participants (i.e. the order of the NoGo stimuli was different for each participant).

Electrophysiological recordings and data pre-processing

Electroencephalogram (EEG) was recorded with a 64-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands) at a sampling rate of 1024 Hz. Offline preprocessing and statistical analyses of the ERPs were conducted using the Cartool freeware programmed by Denis Brunet (<http://www.fbmlab.com/cartool-software>), the STEN toolbox developed by Jean-François Knebel (<http://www.unil.ch/line/home/menuinst/about-the-line/software-analysis-tools.html>), and the RAGU toolbox (Koenig *et al.*, 2011).

First, NoGo trials were sorted according to their associated behavioral outcome (correct rejection: CR condition; or false alarm: FA condition). Second, the number of FA and CR trials for each block was matched to ensure that differences in signal-to-noise ratio across conditions did not confound the statistical comparisons. As there were more CR than FA, we considered the CR until their number matched the number of FA, and then ignored the remaining CR. This procedure was applied for each block separately. For example, if in a block there were 10 FA and 15 CR, then all the FA but only the first 10 CR of this block were included. A 0.18–40 Hz band-pass filter was then applied on the raw EEG data and epoch window from 150 ms pre-stimulus to 500 ms post-stimulus onset were extracted. Epochs with a maximal voltage exceeding $80 \mu\text{V}$ for at least one electrode were automatically rejected. This procedure resulted in the inclusion of 52 ± 28 epochs (mean: 5.2% rejection) for the CR condition and 50 ± 29 epochs (mean: 8.3% rejection) for the FA condition. The number of trials included between the two conditions did not differ statistically ($P = 0.16$). The remaining epochs were then averaged separately for the CR and FA conditions, and artifactual electrodes were interpolated using 3D spline (mean: 0.6% of interpolated electrodes; Perrin *et al.*, 1987). The ERPs were not baseline corrected.

Behavioral data analysis

To examine the influence of the preceding trial type and outcome on the NoGo performance, a $2 \times 2 \times 2$ repeated measure ANOVA with the factors Performance (CR; FA), Preceding stimulus (Go; NoGo), and Preceding accuracy (correct; incorrect) was computed using SPSS statistical software (Version 22.0; IBM Corp., Armonk, NY). Correct responses to the preceding trial were either Fast Hits ($RT < RTt$) to Go trials or CR to NoGo trials, and incorrect responses were Slow Hits ($RT > RTt$) and no-responses to Go trials (Miss), or FA to NoGo trials. As we were only interested in the influence of the preceding trials on the upcoming response, we considered only the interaction terms involving the ‘Performance’ factor (Performance \times Preceding stimulus; Performance \times Preceding accuracy; Performance \times Preceding stimulus \times Preceding accuracy) at an alpha threshold of 0.05.

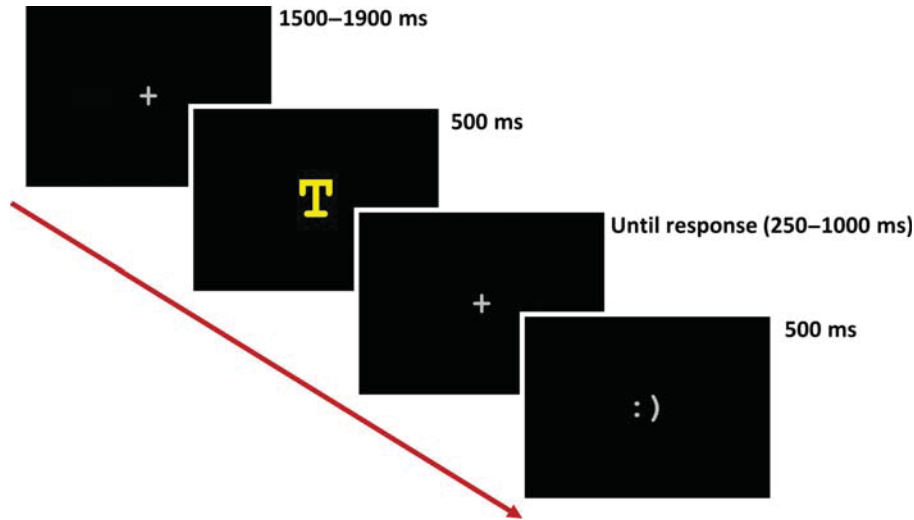


FIG. 1. Go/NoGo task. Participants were instructed to respond as fast as possible to a set of stimuli (the Go) while withholding their response to another set of stimuli (NoGo). A feedback was provided on response speed and accuracy.

Electrophysiological data analysis

Event-related potentials

Paired *t*-tests were computed between the FA and CR conditions for each peri-stimulus time point at each electrode to determine periods showing differences in ERP amplitude. To correct for temporal autocorrelation, we considered only the differences lasting more than 20 ms (21 time-frames) at an alpha threshold of 0.05 (Guthrie & Buchwald, 1991). However, while the time-frame wise, electrode-wise analyses of the ERP provide a highly sensitive measure of whether the two conditions differ statistically, the timing and location of results of such analyses are dependent on the choice of the reference electrode and are thus subject to experimenter biases (Tzovara *et al.*, 2012 for discussion). Moreover, such analyses are very limited in terms of their neurophysiological interpretability. To circumvent this issue, we conducted the global analyses of the strength and shape of electric field potentials at the scalp described in the next section.

Global field power and Global Map Dissimilarity

We analyzed modulations in the global field power (GFP) and in the topography of the ERPs between our two experimental conditions. These global measures of field potentials are independent of the choice of the reference electrode and allow identifying whether ERP modulations follow from changes in the strength and/or in the configuration of the active brain networks across experimental conditions (e.g. Murray *et al.*, 2008; Michel & Murray, 2012; Tzovara *et al.*, 2012).

The GFP is calculated as the spatial standard deviation of all electrodes voltages at a given time frame (Lehmann & Skrandies, 1980; Koenig & Melie-Garcia, 2010; Koenig *et al.*, 2011), with higher values indicating on average a stronger potential across the electrode montage. Modulations in the ERP topography were assessed using the Global Map Dissimilarity index (GMD). GMD is calculated as the root mean square of the difference between GFP-normalized voltage potentials across the electrode montage. As differences in topography necessarily follow from differences in the configuration of the underlying intracranial generators, GMD can be interpreted as change in the brain networks engaged across experimental

conditions (Lehmann & Skrandies, 1980; Tzovara *et al.*, 2012). Importantly, because the GMD calculation is based on strength-normalized voltage potentials, its result is independent on GFP modulations; the GFP and GMD analyses are thus orthogonal measures.

A bootstrapping procedure was used to statistically compare the GFP and GMD values across conditions: The GMD and GFP values between the FA and CR conditions were compared at each time point with an empirical distribution based on randomly reassigning each participant's data to either of the two conditions (5000 permutations per data point; see details in Koenig *et al.*, 2011). For both GFP and GMD analyses, the threshold for statistical significance was set at $P < 0.01$. A correction for temporal autocorrelation was applied by considering only significant differences lasting more than 20 ms (i.e. 21 time frames; Guthrie & Buchwald, 1991).

Electrical source estimations

Electrical source estimations were analyzed over the time periods showing a significant GMD and/or GFP ERP difference between the FA and CR conditions. Source estimations of individual ERP for each participant and each experimental condition were calculated using a LAURA (local autoregressive average) distributed linear inverse solution (Grave de Peralta Menendez *et al.*, 2001, 2004). The solution space was calculated on a realistic head model composed of 3005 nodes selected from a $6 \times 6 \times 6$ mm grid of voxels equally distributed within the gray matter of the average brain of the Montreal Neurological Institute (MNI). To increase the signal-to-noise ratio, the source estimations were first averaged over the period of interest. The output of the source estimation, namely the current density at each solution node, was then compared between the two conditions with paired *t*-tests. A correction for multiple comparisons was applied by considering only clusters with a *P*-value < 0.01 in a minimum of 14 contiguous nodes (K_E).

Results

Behavioral results

There was on average $15.8 \pm 9.5\%$ (mean \pm SD) of false alarms (FA) to NoGo trials.

The $2 \times 2 \times 2$ ANOVA with factors Performance (CR; FA) \times Preceding stimulus (Go; NoGo) \times Preceding accuracy (correct; incorrect) showed (considering the interaction terms of interest, i.e. involving the Performance factor; Fig. 2), a Performance \times Preceding stimulus interaction driven by more FA than CR after Go trials ($F_{1,16} = 15.284, P = 0.001; \eta_p^2 = 0.49$).

The Performance \times Preceding accuracy interaction revealed no difference in the number of positive feedback (after Fast Hits and Correct Rejections) vs. negative feedback (after Slow Hits, Misses, and False Alarms) at the trial preceding the FA and CR conditions ($F_{1,16} = 0.491, P = 0.493$), suggesting that differences in the performance to the trial preceding our trials of interest unlikely accounted for our pattern of results.

Electrophysiological results

Event-related potentials

Figure 3A depicts the ERP waveforms at one exemplar electrode (Pz). Significant pre-stimulus periods of ERP modulations ($P < 0.05, > 10\%$ of the electrodes) manifested from -141 to -111 ms and from -57 to $+9$ ms (Fig. 3B).

Global electric field analyses

The global field power analyses revealed a significant difference ($P < 0.01; > 20$ ms) between the FA and CR conditions from -38 to -8 ms pre-stimulus onset driven by a higher GFP in the FA than in the CR condition (Figs. 3C and D).

Global map dissimilarity analyses revealed a period of significant topographic modulations ($P < 0.01; > 20$ ms) between the FA and CR conditions from 295 to 471 ms post-stimulus onset (Fig. 3D). This control analysis of post-stimulus differences indicates that the sensitivity of our ERP analyses was appropriate to detect effects related to obvious differences induced by the elicitation vs. inhibition of the motor response in the CR vs. FA condition, respectively.

Electrical source estimations

Based on the global ERP analyses, the -38 to -8 ms interval was identified as the period of the pre-stimulus ERP modulation of interest. Difference in the electrical source estimation was computed over this time period and revealed higher activity ($P < 0.01; K_E = 14$)

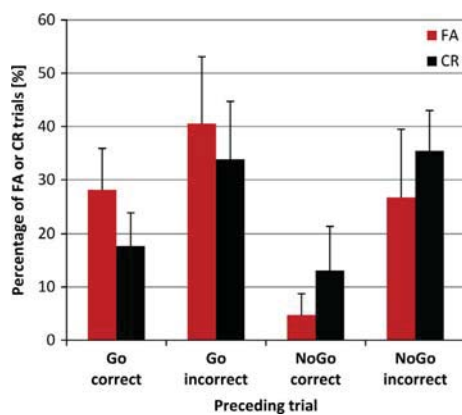


Fig. 2. Analysis of the trials preceding successful (correct rejections) and failed NoGo trials (false alarms) during the Go/NoGo task. FAs were preceded more frequently by Go than NoGo trials, and corresponding number of Go or NoGo trials preceded CRs. CR, Correct Rejection; FA, False Alarm.

during the FA than the CR condition within the bilateral inferior frontal gyrus (IFG) and the right inferior parietal lobule (rIPL; Fig. 3E).

Discussion

Pre-stimulus brain states differed before unpredictable NoGo stimuli in a classical inhibitory control Go/NoGo task depending on whether the motor response to these stimuli was correctly inhibited or not. The global field power (GFP) of the ERP was stronger before false alarms (FA) than correct rejections (CR) during the 40 ms preceding the onset of the NoGo stimuli. This modulation followed from a stronger activity within right frontoparietal areas before FA than CR.

The pre-stimulus GFP modulation we observed manifested without concomitant change in the ERP topography. This pattern of result can be interpreted as a change in the response strength of statistically indistinguishable configurations of intracranial generators (Lehmann & Skrandies, 1980; Tzovara *et al.*, 2012). Quantitative variations in the state of a specific brain network, rather than the engagement of different networks, thus influenced behavioral outcomes during the inhibitory control task. The statistical analyses of the electrical source estimations indicated that this effect followed from a higher activity within bilateral inferior frontal gyri (IFG) and the right inferior parietal lobule (rIPL) before FA than CR.

Together, these findings suggest that inhibition performance depends on fluctuations in the brain state immediately preceding the NoGo onset and that the strength of frontoparietal pre-stimulus activity is behaviorally relevant during Go/NoGo tasks.

The right IFG has been found to be involved in inhibitory control by myriads of functional neuroimaging (Garavan *et al.*, 1999; Rubia *et al.*, 2003; Aron & Poldrack, 2006; Aron, 2007) and lesion studies (Decary & Richer, 1995; Aron *et al.*, 2003; Rieger *et al.*, 2003; Floden & Stuss, 2006; Picton *et al.*, 2007). This region has been advanced to act as a 'general braking mechanism' (Aron *et al.*, 2014). The left IFG has also been involved in inhibitory control, but is thought to support inhibition mainly in difficult conditions (Swick *et al.*, 2008; Hirose *et al.*, 2012). The IPL has also been involved in response inhibition (Garavan *et al.*, 1999; Liddle *et al.*, 2001; Menon *et al.*, 2001; Rubia *et al.*, 2003) or response conflict resolution (Braver *et al.*, 2001; van Veen *et al.*, 2001), and is thought to mediate how attention is allocated to such tasks. Hampshire and colleagues (Hampshire *et al.*, 2010; Hampshire, 2015; Hampshire & Sharp, 2015) proposed that a frontoparietal network including the right IFG and IPL might contribute to inhibitory control by potentiating task-relevant processes such as the detection of the target stimuli or motor control, notably by modulating the allocation of attentional resources.

The direction of our effect (i.e. stronger frontoparietal activity before inhibition failure) may appear at odds with previous evidence associating better inhibition performance with higher stimulus-related or pre-stimulus frontoparietal activity (Aron, 2011 for a review). Performance improvement via the engagement of cue-induced proactive inhibitory control has indeed been associated with a pre-activation of inhibitory-related brain areas, such as the right IFG (Cai *et al.*, 2012; Duque *et al.*, 2012; Swann *et al.*, 2012; Berkman *et al.*, 2014).

Two non-exclusive hypotheses may account for the association between higher pre-stimulus frontoparietal activity and inhibition failure in this study: an over engagement of attentional resources and/or the pre-activation of unspecific inhibition-related neural ensembles.

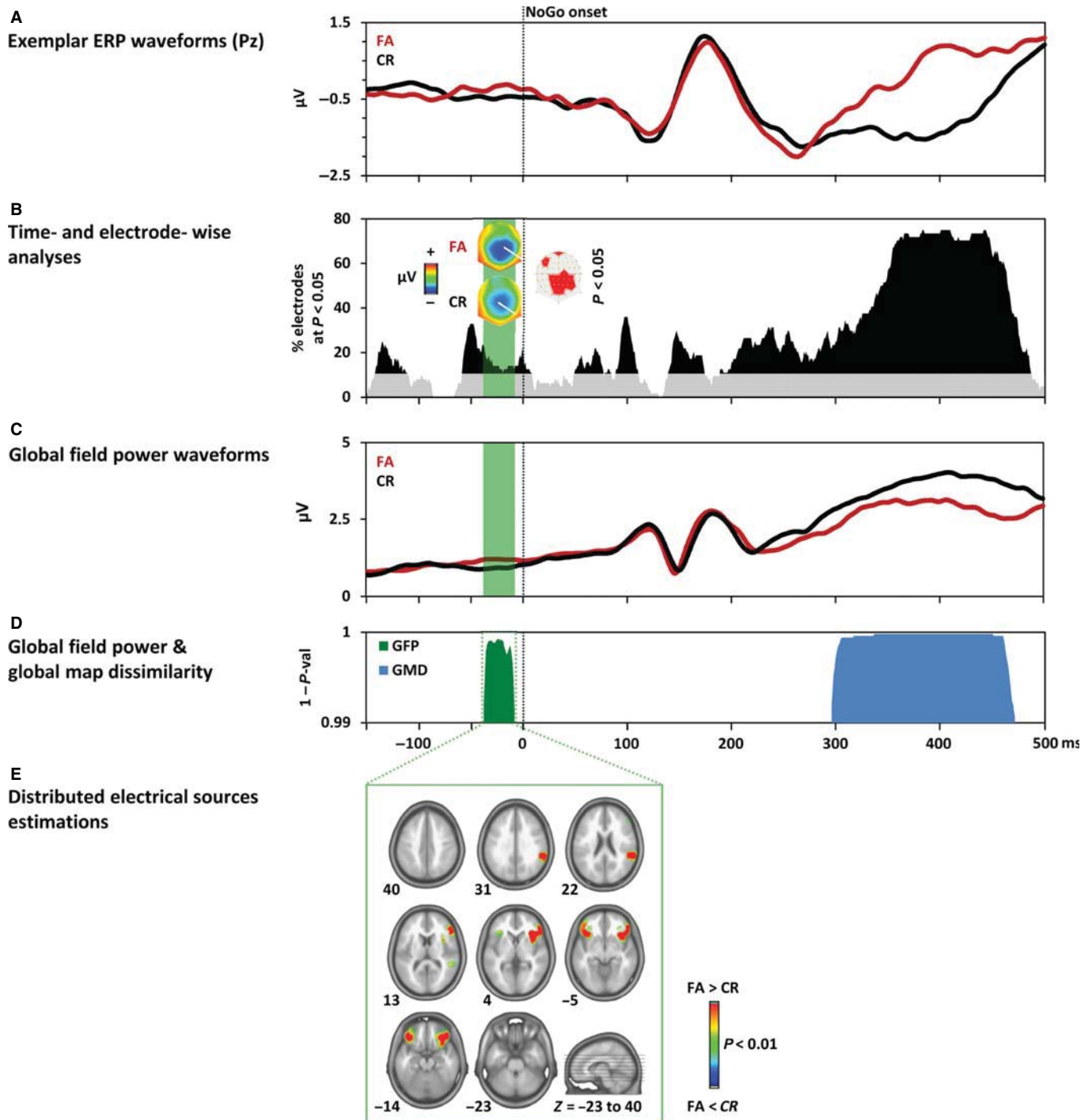


FIG. 3. Electrical Neuroimaging results. (A) Group-averaged event-related potential (ERP) at one exemplar electrode (Pz) for FA and CR. Zero millisecond corresponds to the onset of the NoGo stimuli. (B) Electrode-wise analyses of the ERPs. The graph depicts the percentage of electrodes showing a significant difference at each peri-stimulus time point and the map showing the electrodes where significant differences occurred, as well as ERP topography (nasion upward) for the FA (up) and the CR condition (bottom) over the period of significant global field power (GFP) modulation. (C) GFP waveforms for FA and CR conditions. (D) P -values of the FA vs. CR GFP (38–8 ms pre-stimulus onset) and global map dissimilarity contrast over periods of significant differences between the FA and CR conditions (295–471 ms post-stimulus onset; $P < 0.01$; > 20 ms). (E) Statistical analysis of the electrical source estimations over the period of significant pre-stimulus GFP difference between the FA and CR conditions ($P < 0.01$; $K_E = 14$). CR, Correct Rejection; FA, False Alarm; GFP, Global Field Power; GMD, Global Map Dissimilarity.

First, fluctuations of attention during the task might have led to an overengagement of parietal brain areas before NoGo trials (Kizilirmak *et al.*, 2015), in turn interfering with inhibition processes and impairing performance. Supporting this hypothesis,

several studies observed that increases in the activity of task-relevant brain areas during sustained attention correlated negatively with performance (Sadaghiani *et al.*, 2009; Wieser & Keil, 2011; Esterman *et al.*, 2014). For example, in an auditory detection task, Sadaghiani

et al. (2009) observed stronger activity in the dorsal attention network, including the IPL, preceding the onset of missed stimuli. Taken together, these results suggest that overengagement of attentional resources during our Go/NoGo task might have interfered with inhibition performance.

Second, studies on training-induced plasticity in inhibitory control repeatedly showed that a decrease in right prefrontal activity supported inhibitory control improvement (Manuel *et al.*, 2013; Spierer *et al.*, 2013; Chavan *et al.*, 2015; Hartmann *et al.*, 2015). These authors advanced that with training, the neural units less relevant to the inhibition processes were excluded, leading to faster inhibition and thus improved performance. Accordingly, one could hypothesize that in this study, a similar phenomenon or variations in internal noise in the inhibition network (Faisal *et al.*, 2008) accounted for the positive effect on performance of the reduced frontoparietal activity before correct rejections.

The difference we observed within frontoparietal areas before successful vs. failed inhibition trials could be accounted for by fluctuations in the brain activity before NoGo onsets that were either spontaneous or influenced by the performance on the preceding trial.

On the one hand, increasing evidence suggests that spontaneous fluctuation of brain or cognitive states influence upcoming information processing and thus eventually performance (Ress *et al.*, 2000; Mohr *et al.*, 2005; Hesselmann *et al.*, 2008; Britz *et al.*, 2009, 2011; Britz & Michel, 2010). A wide array of phenomena ranging from non-conscious physiological activity (e.g. autoregulation of the cerebral vasculature) up to conscious mental processes (e.g. changes in vigilance) may lead to endogenous variations in neurocognitive brain states (Hesselmann *et al.*, 2008).

On the other hand, the preceding trial type may also explain pre-stimulus differences between FA and CR. The behavioral results indeed indicate that there were more Go before FA than before CR. Sequential (in) congruency effects might thus have confounded our results. However, in our study, the interstimulus interval varied randomly. As a consequence, since the analyses were time-locked to the stimuli associated with the CR or FA outcomes and the ERP averaging procedure reduces to zero all activity (and thus any statistical differences across conditions) not time-locked to our stimuli of interest, effects of the previous stimulus type unlikely confounded our pre-stimulus results. In addition, the timing and localization of our effect do not correspond to those of sequential congruency effects (around 200 ms post-stimulus onset within the anterior cingulate and the dorsolateral prefrontal cortices (e.g. Millner *et al.*, 2012), and if any general effect of the preceding stimulus type had survived the ERP averaging, it would have most likely manifested over all the pre-stimulus period and not over a restricted period of 40 ms before stimulus onset as in our results. That said, we investigated the correlation between the number of preceding Go and NoGo trials with our effect size, and found no link between the $\Delta(\text{FA}-\text{CR})$ activity in each of our three cluster of interest with the percentage of Go trials preceding FA minus the percentage of Go preceding CR ($r_{\text{IFG}} = -0.052$, $P = 0.840$; $r_{\text{IPL}} = 0.140$, $P = 0.593$; $r_{\text{IFG}} = 0.312$, $P = 0.224$), suggesting that there was no influence of the preceding trial type on our statistical contrast. As we did not have enough trials to analyze the ERP to the FA and CR separately for the different preceding trial type, we could not disentangle the precise effect of this factor in our data. Future studies are necessary to address this question.

To conclude, our results counterintuitively indicate that potentially uncontrolled overengagements of attentional and inhibition-related brain areas before inhibition stimuli may have detrimental effects on inhibitory control performance. The present data add to the current knowledge on the state dependency of cognitive processes by

demonstrating that cognitive processes up to high-order executive levels are influenced by pre-stimulus brain activity.

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Abbreviations

CR, Correct Rejection; ERP, Event-Related Potential; FA, False Alarm; GFP, Global Field Power; GMD, Global Map Dissimilarity; IFG, Inferior Frontal Gyrus; IPL, Inferior Parietal Lobule; RT, Response Time; RTt, Response Time threshold; SD, Standard Deviation.

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