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Title: Hemispheric Asymmetries in the Transition from Action Preparation to Execution

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Abstract: Flexible and adaptive behaviors require the ability to contextually stop inappropriate actions and select the right one as quickly as possible. Recently, it has been proposed that three brain regions, two prefrontal, i.e., the inferior frontal gyrus (iFg) and the anterior insula (aIns) and one parietal, the anterior intraparietal sulcus (aIPs), play an important role in several processing phases of perceptual decision tasks, especially in the preparation, perception and action phases, respectively. However, little is known about hemispheric differences in the activation of these three areas during the transition from perception to action. Many studies have examined how people prepare to stop upcoming responses through both proactive and reactive inhibitory control. Although inhibitory control has been associated with activity in the right prefrontal cortices (PFC), we have previously reported that, during a discriminative response task performed with the right hand, we observed: 1) a bilateral activity in the iFg during the preparation phase, and 2) a left dominant activity in the aIns and aIPs during the transition from perception to action, in the so-called stimulus-response mapping. To clarify the hemispheric dominance of these processes, we combined high temporal resolution of event-related potentials (ERPs) and high spatial resolution of event-related functional magnetic resonance imaging (fMRI) while participants performed a discriminative response task (DRT) and a simple response task (SRT) using their non-dominant left hand. We confirmed that proactive inhibitory control originates in the iFg: its activity started one second before the stimulus onset and was released concomitantly to the stimulus appearance. Most importantly, we confirmed the presence of a bilateral iFg activity that seems to reflect a bilateral proactive control rather than right-hemisphere dominance or a stronger control of the hemisphere contralateral to the responding hand. Further, we observed a stronger activation of the left aIns and a right-lateralized activation of the aIPs reflecting left-hemisphere dominance for stimulus-response mapping finalized to response execution and a contralateral-hand parietal premotor activity, respectively.

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Opposed Reviewers:

Rome, November 23, 2016

Dear Prof. Siebner,

Please find enclosed our manuscript entitled "***Hemispheric Asymmetries in the Transition from Action Preparation to Execution***" by Valentina Sulpizio, Giuliana Lucci, Marika Berchicci, Gaspare Galati, Sabrina Pitzalis and Francesco Di Russo, which we wish to resubmit to ***NeuroImage***.

Please note that, as you suggested, this is a resubmission of the previously rejected paper, NIMG-16-1553. We feel that all the reviewers' concerns, that made impossible to publish the work at first time, have been now fully addressed.

We have extensively revised the manuscript in accordance with the Reviewers' requests. We also substantially re-arranged several sections of the manuscript to avoid overlap with our previous works.

According to the suggestion of Reviewer 1, we re-arranged part of the introduction by formulating more specific hypotheses and by adding more information about what we expected from both fMRI and EEG data. We computed the motor-related potentials in the SRT and DRT-go conditions on C3 and C4 electrodes, and then calculated the lateralized readiness potential (LRP). According with the Reviewer's suggestion, we improved the discussion on the functional relevance of the ERP findings and their relationship with fMRI data, without lengthening it too to avoid any overlap and repetition with respect to the previous study (Di Russo et al., 2016).

As requested by Reviewer 2, we added bootstrap statistics to compare the fMRI-informed source waveforms of the present and the previous study. We also describe the No-go P3 anteriorization, better explain how the P3 is represented in the present model and clarify several details about the task parameters.

There are so many other relatively minor changes that are impossible to summarize here. All changes are evidenced in the text, and explained below, where we include point-by-point responses to the Reviewers' comments.

Overall we feel that the manuscript is much improved and we thank the reviewers for their helpful comments.

Thank you for considering this work for publication in ***NeuroImage***.

Sincerely yours,

Valentina Sulpizio, Ph.D.

P.S.: None of the material has been published or is under consideration elsewhere. The study was approved by the local ethics committee, and was performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki after obtaining informed consent from each participant. We declare no conflicts of interest.

Reviewers' comments:

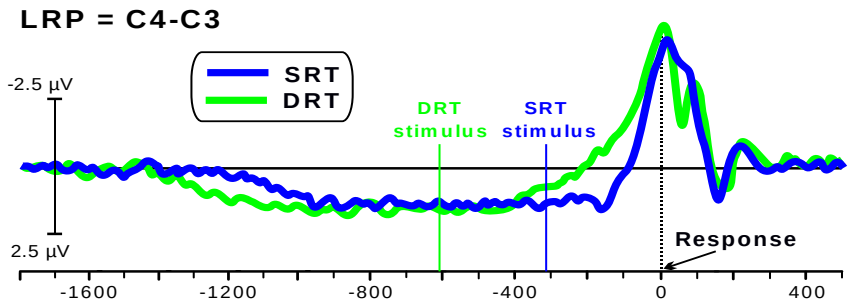
Reviewer #1: The manuscript by Sulpizio et al. presents a study on the modulation of action selection processes by hemispheric asymmetries. In particular, the authors focus on preparatory processes in action execution. The authors use fMRI and EEG methods, though not simultaneously, to investigate this topic. The topic is very interesting, especially because the question why inferior frontal regions involved during inhibitory processes in the preparatory period of the response are right-lateralized has not been answered. I think that this is a timely study on an interesting topic and the analyses of the data seem sound. However, I have several major concerns that need to be addressed.

1. In the introduction I am missing clear hypotheses about the to be expected effects. The introduction is a bit vague concerning the expected effects. When stating the hypotheses the authors should also be more precise about when effects are expected in the fMRI and EEG data.

Authors' reply: We thank the Reviewer for the comments. We agree with the Reviewer that the introduction was a bit vague concerning the expected effects. In the revised manuscript, we extended this part (p. 4, lines 25-34; p. 5 1-3; 9-20) to better explain what we expected from both fMRI and EEG data. The discussion has been modified accordingly (p. 19, lines 23-33; p. 20 lines 2-5 and 7-14).

2. What I am missing is analysis of the movement-related potentials. The authors present data on the "Bereitschaftspotential". However I think that regarding the involvement of the SMA and adjacent regions in the motor cortex seen in the fMRI data it is worth examining the processes related to the activation of the right hemisphere and inhibition of the left hemisphere. It would be interesting to see in how far the inhibition of the hemisphere that is not active but likely inhibited during responding the active hemisphere are modulated across tasks and how this relates to the fMRI data. These analyses are possible even though only 1-handed responses were required. The authors may refer to work by Taniguchi et al. 2001 (Exp Brain Res) how to analyze these aspects (see also: Beste et al. 2009 Exp Neurol; Burle et al. 2015 Int J Psychophysiol).

Authors' reply: To reply to the Reviewer concern, we computed the motor-related potentials in the SRT and DRT-go conditions on C3 and C4 electrodes, and then calculated the lateralized readiness potential (LRP). As depicted in the figure below (now Figure 4 of the revised manuscript), the results in the SRT showed that before responding the negativity was larger over the ipsilateral than the contralateral motor area up to 100 ms before the key-press. Afterwards, the contralateral hemisphere was more active than the ipsilateral, with a peak concomitant to the response onset. In the DRT, the contralateral hemisphere became more active 100 ms earlier than the SRT (about 200 ms before the key-press). The LRP shows that the motor inhibition is both initiated and released earlier in the DRT than in the SRT.



Further, the fMRI data (see Figure 2) showed the following findings: 1) the absence of an

ipsilateral M1 activation in both tasks (SRT and DRT), 2) larger activation of the contralateral CMA in the SRT (and a similar tendency for the DRT), 3) larger activation of the ipsilateral SMA in the DRT No-go condition (and a similar tendency for the go condition). If we combine LRP and fMRI data, we could conclude that the inhibition of right (not responding) hand, indexed by the early LRP, may be associated to the activity of the left (ipsilateral) SMA, supporting the role of the SMA in the inhibitory action control (Bonini et al. 2014, Science). We cited the suggested works. We added all these information in the revised manuscript (see the method section at p. 10 lines 30-33; p. 1 lines 1-4; see the results section at p. 15 lines 16-29; see the discussion at p. 21 lines 1-17).

3. The discussion is well organized, but in my opinion the fMRI data and EEG need a more coherent discussion and both data needs to more integrated. Especially the results of the ERP analysis are currently lacking a good discussion within the broader literature on the functional relevance of the ERPs investigated.

Authors' reply: Thank you for appreciating the good organization of the discussion. However, as suggested by the reviewer, we tried to uncover the reasoning behind fMRI and EEG data interpretation in the discussion session (see pages 19-22). We also improved the discussion on the functional relevance of the ERP findings and their relationship with fMRI data, without lengthening it too to avoid any overlap and repetition with respect to the previous study (Di Russo et al., 2016).

4. Generally, the added value of combining fMRI data and EEG data does not become clear in the discussion. The discussion strongly focuses on the fMRI data and the EEG data only plays a minor role. Depending on the outcomes of the additional analysis requested in my point 2, the discussion needs to re-written (at least in parts).

Authors' reply: As suggested, we amended the discussion including comments about the additional analysis requested.

Reviewer #2: In each trial, participants saw a white fixation cross for 3.5 s which then might change color for 2.25 s, becoming either green (in 58% of trials) or red or remaining white (in 29% and 13% of trials). The green cross was followed by one of four large line patterns (of size 4°x4°). With two of these four stimuli, participants had to press a key with their left hand ("go"). With the other two stimuli they had to do nothing ("no-go"). Thus, with each trial lasting about 6 s and go trials having a probability of (58%/2 = 29%), participants had to press the key about three times per minute.
The task was done twice, once in the fMRI scanner and once in the ERP lab. The authors imported the major regions of fMRI activation (averaged across participants) as fixed dipole locations to the BESA program, modeled ERP grand-average waveforms as being composed by these dipoles and, thereby, obtained an estimate of the time courses of activation of the fMRI sources in terms of ERP components.
This had been done by the authors before (published in NeuroImage 2016, 126:1-14) Specific to the present study is the requirement to respond with the left-hand, such that results may be compared to their previous study with right-hand responses.

Major comments:

1) The major topic of this paper is the comparison between response hands. One wonders why there is not any statistical test between the present left-hand and the previously published right-hand responses. I understand that the fMRI-informed dipole waveforms cannot be statistically tested because they describe the grand means only. Can a bootstrapping procedure be applied for statistical testing?

Authors' reply: As suggested, in the revised version of the manuscript we added bootstrap statistics to compare the fMRI-informed source waveforms of the present and the previous study (see ERP based time-course of the fMRI activations in results section, page 16-17).

2) The basic ERP signature of go/no-go tasks is the fronto-central no-go P3. To detail, go-P3 and no-go P3 are often equally large at Pz (when both have 50% probability) but no-go P3s are larger at fronto-central sites. Where do we find this well-replicated phenomenon in the present data?
One might argue that the task is not so much a go/no-go task but rather a usual oddball task where participants do nothing most of the time (here: in 71% of trials) and sometimes make a response (here: in 29% of trials). If so, the P3 evoked by no-go stimuli should be much smaller than the P3 evoked by go targets. Figure 3 shows that this is clearly not the case: P3s are equally large in go and no-go trials. Thus, participants apparently treated the task as a 50/50 task, following the green fixation cross. Why is there no no-go P3 then? In the absence of no-go P3, what psychological processes are measured in this task?

Authors' reply: We thank the reviewer for pointing out this issue. We agree that looking at the P3 amplitudes we can actually tell that the participants treated the task as a 50/50 task, following the green fixation cross. In the previous version of the manuscript, we generalized the P3 description stating that it peaked at Cz in all conditions. To be more precise, the P3 peaked at Cz for the SRT and for the No-go trials, but at CPz for go trials. The No-go P3 anteriorization was actually present and now we describe it in the result section (page 15).

3) There is not any information about model adequacy. In Methods (p.10 bottom) we read that residual variance and residual orthogonality was quantified, but I could not find any results.
What appears grossly inadequate in Figure 5 is that the large P3 is not modeled by any dipole. How come? This suggests that there was considerable residual variance. Is this a consequence of the authors' fMRI quantification (boxcar convolved with hemodynamic function; unfortunately, I am not an expert on this). Or is this a consequence of the authors' specific procedure in dipole modeling: How would things change if they started modeling with the P3 component rather than with the pre-stimulus interval?

Authors' reply: We thank the reviewer for noticing the missing information about the models adequacy in the results section that now we added on page 17. Regarding the P3 source, we already stated in the previous version of the manuscript that the P3 "resulted to be associated to multiple brain areas, from the sum of activities in parietal and frontal pre-motor areas and in motor and somatosensory areas, including the combined positive activities in the aIns, the aIPs and in the SMA+CMA" (Page 16). However, following the reviewer suggestion and considering that our sequential approach may underestimate late activity as the P3, we adjunctively fit all orientations around the P3 resulting in a much clear model. In the discussion we now better explain how the P3 is represented in the present model (pages 20-21).

4) It is not clear from the description in Methods whether the task parameters were exactly the same in fMRI and ERP. Strict parallelism of measurement, of course, is of utmost importance to the analytic procedure used by the authors. To detail: "Stimuli and task were the same [as] used in the fMRI experiment" (p.9, l.3). What about timing? Was there also a 3.5 s delay between trials? Were there also relax trials? Were there also null trials? Were the relax trials subtracted from the active trials for ERP analysis, too? (Otherwise there would be remnants of the cue-evoked potentials at the beginning of the analyzed epoch, 1500 ms before the stimuli). And was all this exactly identical to the experiment on right-handers in the NeuroImage 2016 paper?
From scrutinizing the 2016 paper, I get the impression that the answer on all these questions might be positive. This should be more clearly indicated in the present paper.

Authors' reply: We apologize for the lack of clarity. In the revised manuscript, we now clarify that the task parameters were exactly the same in fMRI and ERP experiments (page 9), and identical to the NeuroImage paper (page 5). As showed in the NeuroImage, 2016 paper (Figure 6), the cue-evoked potentials terminated about 700 ms after the cue that is 1550 ms before the stimulus (50 ms before the baseline). We now specify on page 10 that the baseline was selected during an interval with flat ERP activity.

Minor comments:

P.4, l.1 and l.5: Papers from 2008 should not be called "recent" any more.
Authors' reply: Done

P.6: "Each trial started with the white fixation cross that changed color" should read for clarity (as I understand the description and Figure 1) "A white fixation cross was present throughout. Each trial started with a change of color of this fixation cross".
Authors' reply: We rewrote the sentence as suggested

Last sentence of this paragraph: Isn't this an intertrial interval rather than an interstimulus interval (to include the null trials)?
Authors' reply: Term corrected

P.6, "including 18 target" and "including 36 target": I would suggest to insert "each" for clarity: "each including".
Authors' reply: Done

P.9, "active sensors": Electrode material should be indicated.
Authors' reply: We added that the sensors were made of non-polarizable sintered Ag/AgCl electrodes

P.9: "were initially referenced to the left mastoid": I could not find any indication about the final reference.
Authors' reply: We added that ERP initially referenced to the left mastoid were then re-referenced to average-reference (p.10).

P.9: "Trials with artifacts ... were automatically excluded": Please indicate the quantitative criteria.
Authors' reply: We now add that trials with artifacts exceeding an amplitude of ±60 μV were rejected.

P.9, 8th line from bottom: "was also guided". Why "also"? Shouldn't this "also" better be omitted?
Authors' reply: "also" is now omitted.

P.10-11: The separate description of BESA and ERP-fMRI combination is not entirely convincing. I suggest that this should be integrated. It reads now like the authors would have performed BESA dipole analysis first and then abandoned that enterprise in favor of using fMRI activations as seeds.
Authors' reply: As suggested, those two parts are now integrated.

P.11 bottom: F(1,15) = 4,47 cannot have p=0.52. Probably p=0.052 is meant. And since this is nearly p<.0.05, a description of this tendency should be given.
Authors' reply: We corrected the typo and explained that the RTs in the ERP session were 11% shorter than in the fMRI session (p. 13).

P.11 bottom: This description should also be given because 637 ms is extremely slow for a go/no-go task. Is this due to the difficult discrimination between patterns? (I do not think so, because then there should be more errors). Or is this due to the participants' presumably low motor activation, with only three responses required per minute? Is this a reason for the missing no-go P3?
Authors' reply: We now stated that this quite slow RT is likely due to the long interval between responses, which was about 20 s (p. 13).

P.13: I do not know why the authors call this pre-stimulus negativity a BP. This is a potential developing between cue (fixation cross turning green) and imperative stimulus, therefore by convention and general agreement a CNV.
Authors' reply: We now specified that similarities and differences of the pN and BP pre-stimulus components and the CNV components were fully described in the previous Neuroimage paper (Di Russo et al. 2016). However, present pre-stimulus negativities are independent by the presence of the cue, being present in uncued task too (p-14).

P.13 bottom: Why did P3 peak at Cz for go trials? Should we call the possible irregularity of the present data not an absence of no-go P3 but an absence of go-P3? Why are these P3s so equal? May I ask you a very stupid question: Perhaps you confounded the codes of patterns 1, 2, 3, 4 such that, say, 1 and 3 were "go" and 2 and 4 were "no-go" but you pooled 1and 2 to be "go" and 3 and 4 to be "no-go"?
Authors' reply: We thank the Reviewer for the suggestion. We made a double check, but the patter codes were correctly pooled. However, as responded to point 2, the Go-P3 actually peaked at CPz and the scalp distribution of the No-Go P3 was more anterior (p-15).

P.14: F-values should be indicated with an "=" sign rather than a "<" sign (except "F < 1" in line 2).
Authors' reply: We corrected the typos (see p. 15), except when the F refers to the ANOVAs on several components as:" The P1, pN1, N1, pP1 and N2 did not differ in amplitude between conditions ($F_{2,30}$<1.35, ns)".

Language:
Abstract, l.3&4: There is no reason to write "frontal", "insula", and "intraparietal" with capital letters.
Abstract, l.3&4: The "i.e." (twice) are unnecessary.

Abstract, l.8, l.9 and twice in l.18: The authors tend to use "the" where it should better be omitted, which is often the case before compound nouns.
Likewise on p.3, l.7 and l.10, l.11, l.12 (twice) and many times throughout the manuscript.
P.3, l.12: "inferior parietal activity" should obviously read here "inferior parietal cortex".
P.3, l.12: "Several evidence support" should read "Several pieces of evidence support"
P.4, l.8 from bottom: "underlies" should here read "underlines"
P.5, l.4 of "Subjects": "normal (or corrected to normal vision)" should read "normal (or corrected to normal) vision"
P.6 bottom: "trials' presentation" should read "trial presentation".
P.9: "eye1" should read "eye".
P.9: "reduced throughout the ... algorithm" should read "reduced through the ... algorithm"
P.12, 3rd line from bottom in middle §: "significant higher activity" should probably read "significantly higher activity".
P.13, 5th line from bottom ("In the SRT ..."): The syntax of this sentence is irregular.
P.14: "activities showed in Table 1" should read "activities shown in Table 1"
P.14, next line: "have been made" should read "were made". (It was a decision taken at one point in the past).
P.15, top line: "somatosensorial" should read "somatosensory"
P.17, l.6: "no-dominant" should read "non-dominant"
P.17, twice: "evidences" is not used in English.
P.17 middle: "Thalamus" should be written in lower case.
P.19 middle: "setting the system in a 'no-go' modality" might perhaps better read "setting the system to a 'no-go' mode"
P.27, legend of Figure 1: "stimuli sequence" should read "stimulus sequence"
Table 2: The F values should have decimal points rather than commas
Table 3: same
Authors' reply: All the language issues were corrected accordingly.

*7. Manuscript
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Hemispheric Asymmetries in the Transition from Action Preparation to Execution

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Keywords: fMRI; EEG; perceptual-decision; prefrontal cortex; Go/No-Go

Abstract

Flexible and adaptive behavior requires the ability to contextually stop inappropriate actions and select the right one as quickly as possible. Recently, it has been proposed that three brain regions, i.e., the inferior frontal gyrus (iFg), the anterior insula (aIns), and the anterior intraparietal sulcus (aIPs), play an important role in several processing phases of perceptual decision tasks, especially in the preparation, perception and action phases, respectively. However, little is known about hemispheric differences in the activation of these three areas during the transition from perception to action. Many studies have examined how people prepare to stop upcoming responses through both proactive and reactive inhibitory control. Although inhibitory control has been associated with activity in the right prefrontal cortex (PFC), we have previously reported that, during a discriminative response task performed with the right hand, we observed: 1) a bilateral activity in the iFg during the preparation phase, and 2) a left dominant activity in the aIns and aIPs during the transition from perception to action, i.e., the so-called stimulus-response mapping. To clarify the hemispheric dominance of these processes, we combined the high temporal resolution of event-related potentials (ERPs) with the high spatial resolution of event-related functional magnetic resonance imaging (fMRI) while participants performed a discriminative response task (DRT) and a simple response task (SRT) using their non-dominant left hand. We confirmed that proactive inhibitory control originates in the iFg: its activity started one second before the stimulus onset and was released concomitantly to the stimulus appearance. Most importantly, we confirmed the presence of a bilateral iFg activity that seems to reflect a bilateral proactive control rather than a right-hemisphere dominance or a stronger control of the hemisphere contralateral to the responding hand. Further, we observed a stronger activation of the left aIns and a right-lateralized activation of the aIPs reflecting left-hemisphere dominance for stimulus-response mapping finalized to response execution and a contralateral-hand parietal premotor activity, respectively.

Introduction

A fundamental aspect of flexible and adaptive behavior is the ability to contextually stop inappropriate actions. Inhibitory control is a key executive function that allows people to adjust performance in accordance to the goal of motor actions. From a cognitive point of view, successful inhibitory control can be achieved through both proactive and reactive control (Jaffard et al., 2008; Aron, 2011). Proactive control is conceptualized as the maintenance of goal-relevant information in order to prepare the cognitive system for upcoming events. In contrast, reactive control reflects the engagement of control processes only at stimulus onset, via reactivation of previously stored information. From a neural point of view, the inhibitory function is proposed to depend on a specific fronto-basal circuit in which the prefrontal cortex (PFC) and the sub-thalamic nucleus would play a special role in blocking response execution by suppressing thalamo-cortical output. Proactive inhibition, in particular, has been associated with activity in the inferior prefrontal cortex and the inferior parietal cortex (Jaffard et al., 2008). Several pieces of evidence support the idea that the inferior prefrontal cortex is critical for inhibiting response tendencies and for behavioral and attentional control (Aron et al., 2004). Recently, combining event-related potentials (ERPs) and event-related functional magnetic resonance imaging (fMRI), we confirmed that, during a discriminative response (Go/No-Go) task, proactive control originates bilaterally in the pars opercularis of the inferior frontal gyrus (iFg): its activity is set-up well before stimulus perception and is released (in Go trials) concomitantly to stimulus appearance (Di Russo et al., 2016). Moreover, we observed that stimulus perception triggers early activity both in the anterior insula (aIns) and in the anterior intra-parietal sulcus (aIPs) contralateral to the responding hand. In line with previous findings (Heekeren et al., 2008), we proposed that these areas likely mediate the transition from perception to action (stimulus-response (S-R) mapping). In particular, both the aIPs and the aIns may accumulate sensory-motor evidence necessary to reach a decision and only after that, the aIns may trigger the appropriate motor response.

The hemispheric lateralization during the preparation-perception-action cycle remains an open issue. The iFg activation, consistently linked to response inhibition (Swick et al., 2011), has been proposed to be right-lateralized (e.g. Aron et al., 2014). Right frontal dominance for inhibitory motor control has become a commonly accepted view, although the results supporting this observation are not consistent. For example, a number of fMRI and lesion studies on response inhibition failed to observe a right iFg involvement (Drewe et al., 1975; Garavan et al., 2003; Godefroy and Rousseaux, 1996; Langenecker and Nielson, 2003; Li et al., 2006; Mostofsky et al., 2003, Picton et al., 2007; Ramautar et al., 2006; Wager et al., 2005; Watanabe et al., 2002).

Moreover, Swick and colleagues (2008) have demonstrated that not only the right, but also the left iFg is critical in suppressing the response of simple letter stimuli in a Go/No-Go task. Patients with lateral PFC lesions, including the left posterior iFg and the frontal opercular regions, made more commission errors than controls, particularly when the response inhibition was harder due to the presence of only 10% of No-Go trials. More importantly, a meta-analysis by Simmons et al. (2008) classified the Go/No-Go tasks as either simple (the No-Go stimulus was always the same) or complex (the No-Go stimulus changed depending on context), revealing that the right dorsolateral PFC was activated in complex tasks only, i.e., where the working memory demands are high. Thus, although the right iFg activation was emphasized by some studies to be critical to response inhibition (for review see Aron et al., 2014), it is not a universal finding. Rather, right-lateralized iFg activity has been observed only for complex Go/No-Go tasks, suggesting that this region is recruited under conditions in which working memory is necessary for response inhibition. Accordingly, we have recently reported a bilateral activity in the iFg during the preparation phase (preceding stimulus presentation) of a simple Go/No-Go task (Di Russo et al., 2016). In this study, after the stimulus appearance and concomitantly to the sensorial processing in visual areas, we also observed a stronger recruitment of left aIns and an exclusive left activation of the aIPs, related to right handed responses.

However, the aim of the abovementioned study was to describe brain activity as a function of time within preparation, perception and execution phases, and testing hemispheric differences was out of our aims. Left-lateralized (i.e., contralateral) activation has been previously observed in both aIns and aIPs. With respect to the aIns, a simultaneous ERP–fMRI study (Baumeister et al., 2014) showed its activation during No-Go trials. Coherently with this result a recent meta-analysis including studies in which right-handed participants responded with their dominant hand (Swick et al., 2011), showed that the left aIns is the most reliably activated region during response inhibition. Moreover, several other fMRI (e.g., Boehler et al., 2010) and clinical (Swick et al., 2008) pieces of evidence (detailed in the discussion) point to the involvement of the left aIns in general cognitive control functions and in the response inhibition preceding response execution independently of the hand used to perform the task. With respect to the aIPs, we previously observed that right-handed responses elicited contralateral activation in the anterior segment of the IPs (Di Russo et al., 2016), probably corresponding to the putative human homologue of monkey area AIP. This region is specialized for hand movements, as pointing and grasping (e.g. Culham and Valyear, 2006; Galati et al., 2011), toward the contralateral space. Some authors proposed that the activity in this parietal region is strictly related to the kinematics of the specific contralateral hand movement (van Schie and Bekkering, 2007; Ondobaka et al., 2014), while others (Rice et al., 2006; Grafton and

Hamilton, 2007; Tunik et al., 2007, 2008; Bozzacchi et al., 2012, 2014) suggested that it is more related to the representation of the meaning and the intention of an action, regardless of the specific hand movement performed for its accomplishment.

Here we investigate whether the contralateral activations, as observed in previous studies, are related either to right-hand responses or to hemispheric specialization. To shed light on the hemispheric dominance of proactive control and S-R mapping, we explicitly tested the effect of the responding hand in a Go/No-Go task. To this aim, we used exactly the same task as in Di Russo et al. (2016), but participants were instructed to respond by pressing a button with their non-dominant left hand. By changing the responding hand, we first aimed at confirming the bilateral preparatory iFg activity found in our previous study (Di Russo et al., 2016); accordingly, we hypothesized that the ERP-based time-course of the fMRI-based iFg activation starts before the stimulus onset and is released concomitantly to stimulus appearance, confirming its inhibitory role in proactive control. Second, we aimed at verifying whether the lateralized aIns and aIPs activities are related to: 1) the responding hand or 2) the hemispheric dominance for sensory-motor control of response execution. In the former case, we would conclude that the involvement of these two regions is effector-dependent and more related to the kinematic of the action (i.e., mechanical features of the key press hand movement to be performed). In the latter case, we would conclude that they have a broader representation of action, likely playing a role in the general cognitive control function and in the action meaning representation, respectively.

Moreover, since the identification of the proactive inhibitory control requires the use of an unbiased control condition performed in an independent block of trials in which the anticipatory locking of response triggering mechanisms is not required (Criaud et al., 2012), we used an appropriate control condition, i.e., a simple reaction task (SRT) in which stimulus discrimination was not required. In Di Russo et al. (2016) we suggested that proactive control is larger in discriminative response tasks (DRT) than in SRT, even if in that study our suggestions were based on a direct comparison between the two tasks based only on EEG data. In the present study, by directly comparing also fMRI data during DRT and SRT, we sought to isolate the effect of proactive inhibitory control to confirm the proper interpretation of the neural mechanisms underlying the numerous cognitive functions usually tested using cue–target protocols (e.g., attention, decision-making, executive control).

Methods

Subjects

Sixteen volunteers (seven females, mean age 25 yrs, s.d. 2.8) participated in the fMRI and ERP experiments. All participants were healthy and without a history of neurological, psychiatric, or chronic somatic problems. The participants were taking no medication during the experimental sessions and had normal (or corrected-to-normal) vision. All participants were fully right-handed (Edinburgh handedness inventory; Oldfield, 1971). Consent was obtained from all participants according to the Declaration of Helsinki after approval by the Santa Lucia Foundation Ethical Committee.

fMRI Experiment

Materials and Task

Participants laid on their back in the scanner and their left hand positioned palm down on a push button board so that the index finger could move freely. Each acquisition scan started with the fixation cross (0.15°x0.15° of visual angle) in the center of the screen, which never disappeared. Square patterns made by vertical and horizontal bars subtending 4°x4° were presented for 250 ms on a dark grey background (Figure 1). The four patterns were displayed in a random sequence with equal probability (p=0.25).

In separate runs, the participants performed two tasks: a simple response task (SRT) and a discriminative response task (DRT). In the SRT, the participants had to press a button with their left hand as quickly as possible when any of the four configurations appeared on the screen (Go stimuli; p=1). In the DRT, two configurations were defined as targets (Go stimuli; p=0.5), and two configurations were defined as non-targets (No-Go stimuli; p=0.5). The participants had to press a button with their left hand when a Go stimulus appeared on the screen and withhold the response when a No-Go stimulus appeared. The equal proportion of Go and No-Go stimuli was adopted because it corresponds to the highest uncertainty regarding stimulus probability and it further facilitates comparison between conditions.

A white fixation cross was present throughout. Each trial started with a color change of this fixation cross, becoming either green or red and remaining for 2250 ms. If the fixation cross became green, after 2250 ms from the color changing, one of the four patterns was presented and remained on the screen for 250 ms. If the fixation cross became red, the participants were informed that after 2250

ms no pattern would be presented. This latter condition, also known as "Relax", was used as control condition for evaluating the cue-related orienting and perceptual brain activity. As a low-level baseline, we also included "null" trials, where the fixation-cross remained white for 2250 ms and no pattern was presented. The inter-trial interval (ITI) varied between 2750 and 4250 ms (mean 3500 ms, standard deviation (SD) 536 ms).

Each subject completed six functional acquisition scans for the DRT, including 18 target and 18 non-target trials, plus 18 Relax trials and 8 null trials. They also completed three functional acquisition scans for the SRT, each including 36 target trials, plus 18 Relax trials and 8 null trials. Each scan lasted 6'20", and within each scan, the order of trial presentation was randomized. The order of the scans was counterbalanced across participants.

--- Insert Figure 1 about here---

Apparatus and procedures

Images were acquired using a 3 T Siemens Allegra MR system (Siemens Medical systems, Erlangen, Germany) operating at the Neuroimaging Laboratory, Foundation Santa Lucia, using a standard head coil. Stimuli were generated by a control computer located outside the MR room, running in-house software (Galati et al., 2008) implemented in MATLAB (The MathWorks Inc., Natick, MA, USA). An LCD video projector with customized lens was used to project visual stimuli to a back projection screen mounted inside the MR tube and visible through a mirror mounted inside the head coil. Presentation timing was controlled and triggered by the acquisition of fMRI images. Responses were given through push buttons connected to the control computer via optic fibers.

Echo-planar functional MR images (TR = 2 s, TE = 30 ms, flip angle = 70 deg, 64 × 64 image matrix, 3 × 3 mm in-plane resolution, 30 slices, 4.5 mm slice thickness with no gap, interleaved excitation order) were acquired in the AC–PC plane using blood-oxygenation level-dependent imaging (Kwong et al. 1992). From the superior convexity, sampling included all the cerebral cortex, excluding only the ventral portion of the cerebellum. A three-dimensional high resolution anatomical image was also acquired for each subject (Siemens MPRAGE sequence, TR = 2 s, TE = 4.38 ms, flip angle = 8 deg, 512 × 512 image matrix, 0.5 × 0.5 mm in-plane resolution, 176 contiguous 1 mm thick sagittal slices). The first four volumes of each scan were discarded to

achieve steady-state T1 weighting, and the experimental task started at the beginning of the fifth image.

Image processing and analysis

Images were preprocessed and analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Functional time series were temporally corrected for slice timing, spatially corrected for head movements, spatially normalized to the MNI152 standard stereotaxic space (final voxel size: 3 mm × 3 mm × 3 mm), and spatially smoothed with a three dimensional Gaussian filter (6 mm full-width-half-maximum). The time series of functional MR images obtained from each participant were then analyzed separately, on a voxel-by-voxel basis, using the general linear model (GLM) as implemented in SPM12. Low-frequency confounds with a period above 128 s were removed through a temporal high-pass filter. Serial correlations were estimated with a restricted maximum likelihood (ReML) algorithm, and ReML estimates were then used to whiten the data.

Neural responses during each trial were modeled as box-car functions spanning the whole time interval from the beginning of the trial to the presentation of the stimulus (2250 ms). This represented an ideally constant and sustained neural activity level, allowing to capture sustained pre-stimulus activity as showed by ERP data. Box-car functions were then convolved with a canonical hemodynamic response function and used as predictors in the GLM, with separate predictors for each trial type (SRT, DRT/Go, DRT/No-Go). Omissions and false alarms were modeled separately and then excluded from further analyses. DRT and SRT were studied in separate scans, but the comparison between the two tasks was possible by using an independent and common control condition (Relax trials) and a low-level baseline (null trials) in all scans.

Parameter estimated images from each participant and condition entered a group analysis where subjects were treated as a random effect. Here we looked at brain regions more implicated in at least one experimental condition (SRT, DRT/Go and DRT/No-Go) as compared to the control condition (Relax trials). The resulting map of the F statistic was thresholded at $p < 0.01$, corrected for multiple comparisons based on family-wise error (FWE), with a cluster size >20 voxels.

For each subject and region, we computed a regional estimate of the amplitude of the hemodynamic response in each experimental condition by entering a spatial average (across all voxels in the region) of the pre-processed time series into the individual GLMs.

Finally, the regional hemodynamic responses were analyzed by means of one-way ANOVAs with condition (SRT, DRT/Go and DRT/No-Go) as factor. To test hemispheric lateralization, we also included the hemisphere as a factor in the analysis, and the resulting 3x2 ANOVA was conducted on the brain regions activated bilaterally by the whole-brain contrast. For both ANOVAs, post-hoc comparisons were conducted using Bonferroni correction.

ERP Experiment

Materials and Task

Participants were seated on an armchair with the left responding hand positioned palm down on a push button board. Visual stimuli were presented through a computer display at 114 cm. Stimuli, timing and tasks (including Relax and Null trials) were exactly as the same used in the fMRI experiment. Five runs of SRT and ten runs of DRT allowed to obtain 300 trials per task.

Electrophysiological recording and ERP analysis

EEGs were recorded via two 32-channel BrainAmp™ amplifiers (BrainProducts GmbH., Munich, Germany) using 64 active devices with non-polarizable sintered Ag/AgCl electrodes (ActiCap™) mounted according to the 10-10 International System that were initially referenced to the left mastoid and then re-referenced to average-reference. The EEGs were digitized at 250 Hz, amplified (bandpass of 0.01-80 Hz, with a 50 Hz notch filter) and stored for off-line averaging. Horizontal eye movements (electrooculogram, EOG) were monitored with a bipolar recording from electrodes at the left and right outer canthi. Blinks and vertical eye movements were recorded with electrodes below and above the left eye. Eye movement artifacts were reduced through the Gratton et al. (1983) algorithm, and then trials with artifacts were automatically excluded from averaging if amplitude was larger than ±60 μV.

The ERPs were averaged in epochs starting 1500 ms prior to stimulus onset and lasting 3000 ms. To further reduce high-frequency noise, the group-averaged ERPs were filtered (at 25 Hz) and sorted into three categories: 1) ERPs for Go stimuli in the DRT, 2) ERPs for No-Go stimuli in the DRT and 3) ERPs for Go stimuli in the SRT. Trials with RTs outside 100-1000 ms were discarded from further analysis. Amplitudes were measured with respect to the first 200 ms of the epoch. This baseline was taken after the cue-evoked potentials in a period of flat ERP activity. The pre-stimulus slow components, pN and BP, were calculated for each subject as the mean amplitude in the -800/0 ms interval. Post-stimulus components were calculated as peak amplitudes and latencies in the

following time windows (in ms): P1: 80–150; N1: 130–200; pP1: 100-200; P2: 180–300; N2: 180-350; pP2: 200-400 and P3: 300–700. The identification of components was guided by their polarity and topography as previously described (Di Russo et al., 2006, 2010, 2016; Di Russo and Spinelli, 2010). The selection of electrodes used for the analyses was based on the greatest activity for a given component at the group level and on the literature (i.e., P1, N1 and P2 at PO7 or PO8; N2 at Fz; BP and P3 at Cz). Pre-stimulus pN and post-stimulus (pP1 and pP2 were measured at Fpz (Berchicci et al., 2012; Di Russo et al., 2016).

For pre-stimulus components, two-level one-way ANOVA were used to compare SRT and DRT as a within-subjects factor (DRT Go and No-go condition were averaged). For post-stimulus components, data were submitted to separate three-level one-way ANOVAs with Condition (SRT vs DRT/Go vs. DRT/No-go) as a within-subjects factor. Post-hoc comparisons were conducted using Bonferroni correction. The overall alpha level was fixed at 0.05.

To examine both task effects and the processes related to the activation of the right hemisphere and inhibition of the left hemisphere during response trials, we analyzed the lateralized readiness potential (LRP) in the SRT and the DRT (see Coles, 1989; Beste et al. 2009; Burle et al. 2015; Taniguchi et al., 2001). To calculate the LRP, the motor-related cortical potentials (MRCP) were first obtained synchronizing the individual averaged ERPs on the response onset, then the electrodes overlying both contralateral and ipsilateral hand motor areas (C3 and C4, respectively) were selected to compute the LRP (LRP=C4-C3). A first sample t-test against zero on the LRP at any time point was used to detect significant lateralization, and a second t-test was used to find differences between conditions.

ERP-fMRI combination

Topographical mapping of scalp voltage and estimation of the time-course of dipolar sources of the ERP components in the grand-average waveforms were performed using Brain Electrical Source Analysis (BESA 2000 v.5.1.8; Megis Software GmbH, Gräfelfing, Germany). Analysis used a realistic approximation of the head, with the radius obtained from the average of the group of subjects (81 mm). The model quality was assessed with the residual variance (RV) expressed as the perceptual difference between the variance expressed by the ERP data and that expressed by the source model. In addition to the RV, the model quality was estimated by applying residual orthogonality tests (ROTs; e.g., Böcker et al., 1994). For more details on the BESA method, see Di Russo et al. 2016.

To obtain a spatiotemporal model of the involved brain activities, the ERP data were seeded on the fMRI activations to allow the measurement of the time-course of each brain area. This method, routinely used by our research group (e.g., Di Russo et al., 2001, 2005, 2006, 2007, 2012, 2016; Pitzalis et al., 2012, 2013; Di Russo and Pitzalis, 2013), can be defined 'fMRI-informed EEG analysis', because it aims at moderating the spatial EEG inverse problem by guiding electromagnetic source imaging using results obtained from fMRI (Huster at al., 2012). With this method, the source location is not estimated by BESA, but from the main fMRI data. Specifically, regions of interest were selected by clustering the fMRI spots, and the resulting coordinates (Table 1) were used to seed the sources. The source orientations were subsequently optimized to minimize the cross-talk and interactions between the sources. To select the interval and the order of the orientation optimization (crucial to define the time course of the source), we followed the timing and the scalp topography of the ERPs. Modeling followed a sequential approach according to which the dipoles that accounted for the earlier portions of the waveform were maintained in place as additional dipoles were added. Considering that this approach may underestimate late activities, such as the P3 component, we finally fit all orientations around the P3 peak. Thus, the number of dipoles chosen for these models corresponded to the major topographical features of the ERP waveforms. The rationale for this strategy was to use the fMRI information to solve the inverse problem of the ERP source localization. To test significant differences between the present source model and the one obtained in our previous study (right hand responding during the same tasks) (Di Russo et al., 2016), the bootstrap bias-corrected and adjusted (BCa) method was employed (Efron and Tibshirani, 1993) for any cortical area, using 95% confidence intervals for each differential source waveforms. The difference between the present and the previous experiment was considered significant if the confidence interval of the differential source waveform did not include zero.

Analysis of Behavioral Data

The median RTs for the correct trials were calculated in both fMRI and ERP experiment for SRT/Go and DRT/Go. The accuracy was measured by the percentage of omission errors (i.e., omitted responses in SRT and Go stimuli in DRT), and commission errors (i.e., responses to No-Go stimuli in the DRT). A couple of 2x2 ANOVA with Experiment (fMRI and ERP) and Task (SRT and DRT) were performed on RTs and omission errors. Commission errors were submitted to one-way ANOVA. Only trials associated with correct responses were included in all the subsequent analyses.

Results

Behavioral results

Statistical comparisons on RTs showed a significant main effect of Task ($F_{1,15}$=601, p<0.0001). The effect of Experiment ($F_{1,15}$=4.47, p=0.052) and the interaction ($F_{1,15}$<1, ns) were not significant, even though the RTs in the ERP session were 11% shorter than those in the fMRI session. The mean RTs in the SRT and DRT were 353 and 637 ms respectively. This quite slow RT is likely due to the long interval between responses, which was about 20 s. Analysis on accuracy yielded non-significant results. The overall omission rate was 1.1%. The rate of commission errors in DRT was 8.8%.

fMRI results

Figure 2A shows an "omnibus" F-contrast (any condition > Relax) revealing the involvement of a distributed network including the bilateral striate and extrastriate visual areas, the bilateral posterior intraparietal sulcus (pIPs), the bilateral supramarginal gyri (sMg), the right anterior intraparietal sulcus (aIPs), contralateral to the responding hand, the hand territory of the right primary motor and somatosensory areas (M1 and S1), and the bilateral supplementary and cingulate motor areas (SMA and CMA). Strong activations were also bilaterally found in the thalamus (Thal), in the anterior insula (aIns) and the adjacent pars opercularis of the inferior frontal gyrus (iFg). The anatomical location of local maxima (Talairach coordinates) in each of these brain regions is shown in Table 1.

We performed two separate analyses. First, we submitted the BOLD signal change estimated in each region activated by the "Omnibus" whole-brain contrast to a one-way ANOVA, with condition (SRT, DRT/Go, DRT/No-Go) as factor, to verify any task-related differences on brain activity. The statistical results of this first analysis revealed that some of the activated regions, such as the bilateral aIns and sMg, the right aIPs, M1/S1, Thal and SMA showed a significant higher activation in the SRT and DRT/Go trials as compared to the DRT/No-Go trials. In other regions, such as the bilateral CMA, the left SMA, the left Thal and the striate and extrastriate visual areas of the right hemisphere, we observed a stronger activation in the DRT/Go trials as compared to both SRT and DRT/No-Go trials. A greater activation in the DRT (both Go and No-Go trials) as compared to the SRT was instead observed in the left striate and extrastriate visual areas, in the bilateral pIPs and in the bilateral iFg. In this latter region, we further observed a significantly higher activity in the DRT/Go trials as compared to the SRT trials. Statistical results of this first analysis are also detailed in Table 2.

Second, to verify any hemispheric and task-related differences on brain activity, the BOLD signal change, estimated in each of the bilaterally activated cortical regions, was compared as a function of condition (SRT, DRT/Go, DRT/No-Go) and hemisphere (left: ipsilateral to the responding hand, right: contralateral the responding hand) (Figure 2B-C). Results of statistical analysis are also detailed in Table 3. A main effect of hemisphere was observed in the CMA and in the aIns (Figure 2A). In the former, this effect reflected a greater activation of the right hemisphere (contralateral to the responding hand) as compared to the left (ipsilateral to the responding hand) while in the latter it reflected the opposite pattern. A significant condition by hemisphere interaction was observed in both regions: in the CMA the interaction reflected a greater activation of the right hemisphere, as compared to the left hemisphere, but only in the SRT trials ($p=0.009$); in the aIns it depended on the higher activation of the left hemisphere, as compared to the right hemisphere, in both SRT and DRT/No-Go trials ($p<0.01$), even more, in DRT/Go trials ($p<0.0001$). Finally, we found a significant condition by hemisphere interaction in both SMA and Thal, indicating a greater activity of the left as compared to the right hemisphere in the DRT/No-Go trials in the former ($p=0.006$), and a greater activity of the right ($p<0.0001$) as compared to the left hemisphere in the SRT trials in the latter (Figure 2C).

--- Insert Figure 2 about here---

--- Insert Table 1 about here---

--- Insert Table 2 about here---

--- Insert Table 3 about here---

ERP results

Figure 3 shows the ERP waveforms for SRT (blue lines) and DRT (Go: green lines, No-Go: red lines) task from three representative scalp electrodes at medial prefrontal (Fpz), central (Cz) and lateral (RH) parieto-occipital (PO8) sites. Mean RTs of SRT and DRT/Go tasks are marked by vertical dashed lines. Zero on the time scale indicates stimulus onset. In DRT, the earliest pre-stimulus brain activity recorded on the scalp started with a slow rising negativity on prefrontal locations (corresponding to prefrontal negativity, pN) approximately 1050 ms before the stimulus onset. The pN component was comparable between Go and No-go DRT conditions and very small in SRT, where stimulus discrimination, and thus a 'cognitive preparation' was not required. The Bereitschaftspotential (BP) emerged at Cz approximately 1000 ms before the stimulus, and it was similar for all conditions, given that the requested motor activity (key pressing) is always the same. Similarities and differences between the pN and the BP pre-stimulus components and the contingent

negative variation (CNV) components were fully described in the Neuroimage paper (Di Russo et al. 2016). After the stimulus onset, the typical P1 and N1 visual components peaked at approximately 110 and 170 ms, respectively at PO8. An early prefrontal negativity peaked at 115 ms (pN1) followed by a positivity at 200 ms (pP1) in all conditions and an additional late prefrontal positivity peaked at 310 ms in the DRT/Go condition only (pP2). The N2 component peaked at 290 ms at Fz in the DRTs and was larger for the No-Go trials. In the SRT, the N2 peaked earlier at 240 ms at Cz and was also present a strong visual parieto-occipital P2, which was barely visible in DRTs (likely covered by the other components like the N2). For all conditions the P3 component peaked after the response emission, earlier for the SRT (435 ms) at Cz and later for the DRTs (620 ms at CPz and 625 ms at Cz for Go and No-Go trial, respectively). The P3 showed the typical Go/No-go anteriorization shifting the peak from the central-parietal to the central sites.

--- Insert Figure 3 about here---

Statistical analysis showed that the pN was smaller (nearly absent) in SRT ($F_{1,15}$=132, p=0.0001) than DRT. The BP did not differ between conditions ($F_{1,15}$<1, ns). The P1, pN1, N1, pP1 and N2 did not differ in amplitude between conditions ($F_{2,30}$<1.35, ns). The P1, the N1 and the pP1 peak latency did not differ between conditions ($F_{2,30}$<1, ns). The N2 was significantly earlier ($F_{2,30}$=7.27, p=0.001) in SRT than in DRTs. The pP2 was larger ($F_{2,30}$=24.61, p=0.0001) in the DRT/Go condition than the DRT/No-Go and SRT, where it was not detectable. The P2 was larger ($F_{2,30}$=89.38, p=0.0001) in SRT than DRTs. The P3 in the SRT was earlier ($F_{2,30}$=76.19, p=0.0001) and smaller ($F_{2,30}$=11.53, p=0.005) than in the DRTs, which did not differ each other. Although the DRT trials were interleaved with Relax and Null trials (the response was required only in the 29% of trials), the lack of difference between Go and No-go P3 confirms that the present DRT can still be considered a Go/No-go task rather than an odd-ball task, wherein the go P3 is much larger than the No-go P3 (Lucci et al., 2016).

The LRP showed significant lateralization in favor of the ipsilateral hemisphere (motor inhibition) between -1110 and -160 ms before the response in the SRT (t_{15}>3.17, p<0.05) and between -1300 and -280 ms in the DRT (t_{15}>3.25, p<0.05). Significant lateralization in favor of the contralateral hemisphere (motor excitation) was present from -80 to 120 ms in the SRT (t_{15}>4.01, p<0.05) and from -110 to 125 ms in the DRT (t_{15}>3.51, p<0.05). A short peak of motor inhibition was present at about 175 ms after the response in both conditions (t_{15}>2.63, p<0.05). Comparison between conditions showed significant differences in the -1300/-1060 ms interval and in the -200/-80 ms

interval (t_{15}>4.37, p<0.05), indicating that motor inhibition was initiated and released earlier in the DRT than in the SRT (Figure 4).

Figure 5 shows the scalp topographies of four anterior ERP components showing statistically significant differences in the SRT, Go and No-Go conditions. Before the stimulus onset (top row: time interval -800/0 ms) the pN, present in the DRTs only, showed a medial fronto-polar distribution with a small contralateral prevalence. The BP was quite similar in the three conditions showing a fronto-central distribution, slightly contralateral to the responding hand. After the stimulus onset (bottom row: time interval 270/350 ms) the pP2 showed a bilateral distribution (red, positive activity) on prefrontal areas. The N2 showed a fronto-central distribution quite similar to the BP.

--- Insert Figure 5 about here---

ERP-fMRI combination

Association between ERP components and fMRI activation

According to how ERP data fit (see methods) the fMRI activities shown in Table 1 the following associations were made: the pN was associated with the activation in the bilateral iFg; the BP was associated with the fMRI activity in supplementary and cingulate motor areas (due to their vicinity, these two areas were well fit by a single source defined SMA+CMA); the P1, the N1 and the P2 components were associated with the fMRI activations in the bilateral striate and extrastriate areas; the N1 was also associated with activity of posterior intraparietal sulcus (pIPs) peaking at 175 and 240 ms; the prefrontal activities pN1, pP1 and pP2 were all associated with the activations in the aIns; the N1 and the P2 were also associated to activity contralateral (to the responding hand) in the anterior intraparietal sulcus (aIPs); the N2 component is actually explained by peak activity in the SMA+CMA before the response emission; the P3 resulted to be associated to multiple brain areas, from the sum of activities in parietal and frontal pre-motor areas and in motor and somatosensory areas, including the combined positive activities in the aIns, the aIPs and in the SMA+CMA (see next section for more details).

ERP based time-course of the fMRI activations

Figure 6 shows the ERP based time-courses of activity in the fMRI regions reported on Table 1 for both SRT and DRT conditions, separately for the two hemispheres.

Before stimulus onset, the main activities were observed bilaterally in both IFg and SMA+CMA. Specifically, the earliest brain activity was detected in the bilateral iFg for DRT; it started with a slow rising negativity at approximately 1100 ms prior to the stimulus onset. The iFg showed peak activity at 400 ms prior to the stimulus appearance, and then decreased up to 500 after it; note that the iFg activity is the only one that increased again after response emission or withholding. In both SRT and DRT, the SMA+CMA activities started approximately 1000 ms prior to the stimulus onset, slowly reached their negative peaks prior to the response and concomitantly to the N2 component, and, before returning to the baseline level, their activities were characterized by a positive peak concurrent to both the response emission and the peak amplitude of the P3 component. The bootstrap statistic with right hand data could not find significant difference between responding hands.

After the stimulus onset, the sequence of brain responses was substantially faster than before and involved three bilateral cortical sites (striate and extrastriate areas, anterior insula and pIPs) with multiple peak activities. Specifically, a sequence of four peak activities at 70, 110, 170 and 260 ms are present in bilateral striate and extrastriate areas, and two peak activities were recorded in the bilateral pIPs at 175 and 240 ms. The aIns showed two early peaks at 115 ms (pN1) and at 200 ms (pP1). These post-stimulus activities observed in visual, parietal and insular cortices were similar in SRT and DRT conditions. The bootstrap statistic with right hand data could not find significant difference between responding hands.

In later time intervals (i.e., just before and after the motor response), differences between conditions were identified in both signal strength and cortical sites. The SRT, DRT/Go and DRT/No-go activities started to diverge in the aIPs, found only in the right hemisphere, which showed an earlier peak at 180 ms for the SRT and at 280 ms for the DRT/Go. The later peak coincided to the P3 at 400 and 600 ms for the SRT and DRT, respectively. Given the exclusive contralateral localization of the aIPs, the bootstrap statistic with right hand data showed significant differences; however, if the time-course of the left and right aIPs is compared, the waves almost overlap showing no significant differences. Note that the right aIPs activity was absent in the case of No-Go stimuli. For the Go stimuli, the bilateral aIns activity quickly increased and showed a third peak at 360 ms (pP2); for the SRT and DRT No-go, the aIns did not show further activity. Finally, the M1+S1 activity, found exclusively in the right hemisphere as well, was only present in the SRT and DRT/Go trials concomitantly and after the response. These fMRI-seeded models were quite reliable, because explained most of the ERP variance in the -800/700 ms time interval. The RV was 5.9%, 6.5% and 6.7% for the SRT, Go and No-go trials, respectively. For ROT, no scalp electrodes

pointed to a significant residual signal, which indicated that there was no failure in any electrode associated with the model.

--- Insert Figure 6 about here---

Discussion

In the present study, we combined the high temporal resolution of ERPs with the high spatial resolution of event-related fMRI to investigate the neural substrates and the temporal dynamics during the preparation, perception and action phases of both discriminative and simple response tasks.

Hemisphere dominance or contralateral (hand-related) activity?

A first goal of this study was to highlight the brain network involved in the preparation-perception-action phases using left (non-dominant) hand movements, thus clarifying any hemispheric specialization underlying the transition from perception to action. In searching for a hemispheric preference on bilaterally-activated regions, we found task-related hemispheric differences in four cortical (aIns, aIPS, CMA, SMA) and one subcortical (thalamus) regions.

An important finding of this study is that we found hemispheric differences in the anterior insula (aIns). Specifically, we observed a stronger activation of the left than the right aIns in the DRT/Go trials at about 360 ms, as also showed by the ERP pP2 component results. Similarly, in our previous study we observed a stronger recruitment of the left aIns while participants performed the same task with their dominant right hand (Di Russo et al., 2016). We also confirmed this area as the main generator of the ERPs' pN1, pP1 and pP2 components peaking on frontopolar derivations between 100 ms post-stimulus and the response emission. Although we did not observe both task- and hemispheric-related differences in the activities related to the pN1 and the pP1 components, here we confirm previous studies reporting larger pP2 amplitude in the Go than No-Go trials (Di Russo et al., 2016; Berchicci et al., 2014; Perri et al., 2014), suggesting that its activity reflects the stimulus–response (S–R) mapping process finalized to response execution. This is in line with the idea that the aIns would be involved in triggering the motor response when enough action-related information is accumulated (Boettiger and D'Esposito, 2005). In a recent fMRI experiment using

conjunction analyses (Boehler et al., 2010), the left aIns was the only brain region that showed a significant correlation with stopping efficiency: greater activation in the left aIns was associated with shorter Stop-Signal RTs. Since the activity in the left aIns was associated with both stopping efficiency and overall accuracy in a Stop-Signal task, the authors concluded that this region might support a more general cognitive control function. In addition, patients with focal damage in the left aIns showed response inhibition deficits in Go/No-go tasks (Swick et al., 2008). Further, by comparing activations produced by Go/No-go and Stop-to-Signal tasks in the same subjects, Rubia et al. (2001) found different hemispheric dominance, with Go/No-go showing a greater left hemisphere involvement and Stop-to-Signal showing a greater right hemisphere involvement. A stronger activation of the left aIns was also observed when comparing No-go and Stop trials with "oddball" Go trials (McNab et al., 2008). Finally, Turkeltaub et al. (2002) reported a laterality effect of the aIns, showing an association between the left insula and the pre-response conflict, and between the right insula and the post-response processing. Moreover, in a recent EEG study employing a Go/No-go task similar to the present one, but requiring right hand response, Perri et al. (submitted) computed the source analysis of the ERP pP2 component and observed different hemispheric activities in the aIns. More specifically, the left aIns activity peaked just before the decision time, independently from the condition (target/non-target), whereas the right aIns showed a larger activity in case of target than non-target trials in the 250-650 ms time window, suggesting that the early accumulation of sensory evidence was followed by action monitoring after the response; this observation is also supported by the ERP study of Perri et al. (2015b) and the fMRI data of Ullsperger et al. (2010), which reported the contribution of the right aIns to the performance monitoring. Taken together, these pieces of evidence support present data on the involvement of the left aIns in the cognitive control function independently by the used hand. However, further studies should take into account the participants' handedness (no study, to our knowledge, has been conducted on left-handed participants) and/or the effect of using the dominant or the non-dominant hand in such inhibitory tasks.

An additional novel result of this study is the exclusively contralateral activation of a region in the anterior intraparietal sulcus (aIPs) starting concomitantly to the activities of both the aIns and the striate/extrastriate areas, and lasting over right response emission for Go stimuli only. We previously identified the same activation patterns associated with Go trials exclusively in the left aIPs contralateral to the responding hand (Di Russo et al., 2016). This fMRI activity is a large lateral parietal cluster at the intersection between the horizontal and the ascending segment of the IPs (see Figure 2A). As mentioned in the introduction, this parietal cluster showed a consistent overlap with the putative human homologue of monkey area AIP described originally by Culham

and colleagues (Culham et al. 2003, 2006) and later also by our (Galati et al. 2011) and other groups (e.g., de Jong et al., 2001; Astafiev et al., 2003; Rice et al., 2006; Grafton and Hamilton, 2007; Tunik et al., 2007). This region is specialized for hand movements, as pointing and grasping actions (e.g. Culham and Valyear, 2006; Galati et al., 2011), toward the contralateral space and, as shown here, its activity is strictly related to the responding hand. The contralateral (hand-related) activity found here in this region reinforces the concept that the AIP function is strictly related to the kinematics of the movement and not to a broader representation of action (Fillimon et al., 2007). One possible implication for the present finding is that the aIPs activity likely represents the contralateral-hand parietal premotor activity, which supports "intentional" models of perceptual decisions (e.g., Cisek & Kalaska, 2010). Indeed, the AIP 'effector selectivity' represents a positive evidence for the notion that the human PPC subserves not only the deployment of general spatial attention, but also the early phases of action plans towards the external space (see Galati et al., 2011 for similar interpretations). According to the Heekeren et al.'s (2008) model, these results suggest that sensorimotor parietal areas are involved in accumulating and converting perceptual evidence into specific actions. The ERP-based data provided an accurate timing of the right aIPs activity, showing a biphasic activity only in response trials: an earlier negative peak at 180 ms and at 300 ms for the SRT and the DRT/go, respectively, and a later peak at 400 ms and at 600 ms for the SRT and the DRT/go, respectively, with this latter explaining part of the scalp recorded P3 component. This pattern of results is in line with the ERP findings reported in our previous studies in which participants performed both SRT and DRT EEG experiments responding with the right hand (Di Russo et al., 2016). Specifically, in both previous and present study, the activation of the aIPs is generated in the hemisphere contralateral to the responding hand.

In addition to the aIns and the aIPs, we found a condition by hemisphere interaction also in CMA, SMA and thalamus. In both CMA and thalamus, this effect depended on a greater activation of the right hemisphere during response trials (SRT and DRT/go), likely reflecting the contralateral hand-related control during motor response. In SMA, this result was due to a greater activation of the left hemisphere during the DRT task, which should speak in favor of a specific role of this area in visuo-motor discrimination. In particular, the hemispheric asymmetry of SMA during DRT/No-Go trials confirmed the SMA involvement in response selection and motor inhibition reported by several previous experiments (see the meta-analysis by Simmonds et al., 2008) and provided further support to the notion that left SMA plays a dominant role in right-handers (Babiloni et al., 2003) independently to the hand used to perform the task. Our finding further confirms that the activity of the SMA and the CMA is associated to the ERPs' preparatory BP component, but also to the N2 and the P3 component in both the SRT and the DRT. Although the cortical origin of the BP

component in the SMA and the CMA is a well-establish data (Di Russo et al., 2016; Cui et al., 2000; van Boxtel and Böcker, 2004), the source of the N2 component within the same brain regions is relatively innovative and corroborates recent evidence (Perri et al., 2014; 2015a,b; Di Russo et al., 2016; Berchicci et al., 2016). Indeed, these data confirm that the N2 component rather than representing an electrophysiological index of reactive response inhibition (e.g., Baumeister et al., 2014) or response-conflict monitoring (e.g., Nieuwenhuis et al., 2003), may reflect a premotor activation related to the BP component (e.g. Di Russo et al., 2016; Verleger et al., 2006).

With respect to the movement-related activations, the fMRI data (see Figure 2) showed also the following findings: 1) the absence of an ipsilateral M1 activation in both tasks (SRT and DRT), 2) larger activation of the contralateral CMA in the SRT (and a similar tendency for the DRT), 3) larger activation of the ipsilateral SMA in the DRT No-go condition (and a similar tendency for the go condition). If we combine LRP and fMRI data, we could conclude that the inhibition of right (not responding) hand, indexed by the early LRP, may be associated to the activity of the left (ipsilateral) SMA, supporting the role of the SMA in the inhibitory action control. Therefore, the ipsilateral inhibition seems to be more related to the SMA than the CMA and the M1 activity, supporting the more general role of the SMA in inhibitory action control (Bonini et al., 2014)

Present findings also confirm that the P3 complex is generated by multiple areas active concomitantly and following the response as task closure (Di Russo et al., 2016). These areas include at least, the SMA, the CMA and the pIPs, in addition to the aIns, the aIPs and the sensorimotor cortex, involved in case of response execution (see Figure 6). The P3 complex encompasses several components with different timing, topography and functional correlates, it is sensitive to a variety of global factors and experimental conditions (e.g., Berchicci et al., 2016), and present findings add important information on the neural origin and the cognitive processes that the P3 may reflect.

Here, and in our previous work (Di Russo et al., 2016), we observed a bilateral activation of the iFg regardless of the used hand, and these results deserve some comments. Previous studies reported different hemispheric dominance for motor response inhibition (Swick et al., 2008, Swick et al., 2009, Swick et al., 2011). One prominent hypothesis states that a dedicated neural module within the right iFg is specialized in supporting the motor response inhibition (Aron et al., 2014). Support to this view comes from several imaging studies showing the right iFg activation during inhibition of prepotent responses in both Go/No-go and Stop Signal tasks (Menon et al., 2001, van Boxtel et al., 2001, Aron et al., 2003a, Aron et al., 2003b, Rubia et al., 2003, Aron et al., 2004, Picton et al., 2007, Verbruggen and Logan, 2008). However, results from human lesion studies revealed the

critical role of the left iFg in suppressing prepotent responses to simple letter stimuli in a Go/No-go task (Swick et al., 2008). Furthermore, recent imaging studies from our (Di Russo et al., 2016) and other laboratories (Cai and Leung, 2009; Leung and Cai, 2007; Li et al., 2006) reported bilateral rather than unilateral iFg activation. The present results confirmed that the iFg is bilaterally activated during a Go/No-go task and suggested that its activity is not related to the responding hand. These findings are compatible with the idea that right-lateralized activations were found only for more complex designs which involved increasing number of stimulus–response associations (i.e., by using multiple Go and No-go cues) with increasing short-term/working memory demands (see Simmonds et al., 2008 for a recent meta-analysis).

Overall, we confirm that proactive inhibitory control (cognitive preparation) originates long before stimulus perception in the bilateral iFg, showing that its activity reflects a bilateral inhibitory control rather than a right-hemisphere dominance or an effector-related activity. The fMRI data are also supported by the ERP data, showing a slow rising negativity over bilateral prefrontal derivations, indexed by the pN component, beginning approximately 1 s before stimulus onset and reaching the baseline concomitantly to the response, before slowly rising again. Further, this activity was particularly pronounced in the DRT and almost absent in the SRT, supporting the iFg origin of the pN component and also the proactive cognitive control function played by the iFg. These data will be deeply discussed in the next session. After stimulus perception, we observed a stronger activation of the left anterior insula and an exclusive right activation of the anterior intraparietal sulcus developing concomitantly to the activity in visual areas. These results respectively reflect a left-hemisphere dominance of the aIns in the stimulus-response mapping process finalized to response execution and a contralateral (hand-related) activity in the aIPs.

Cognitive preparation and "no-go" mode in the DRT

A second goal of this study was to confirm with an fMRI study that the iFg activity observed in the DRT is specific to discriminative tasks. To this aim, we directly compared in both the ERP and fMRI studies the DRT (Go/No-go) with a simple response task (SRT) not requiring stimulus discrimination. In the fMRI experiment, we found an extended fronto-parietal and occipital network of cortical regions activated during both discriminative and simple response tasks. Bilateral aIns, right aIPs, right M1/S1, right SMA, and right Thal did not discriminate between SRT and DRT/Go, thus reflecting their general involvement in the motor response execution during either discrimination or simple detection. Bilateral CMA, left SMA, left Thal and right striate+extrastriate resulted to be more activated by the DRT/Go than SRT trials and, thus, these regions are specifically involved in the proactive control of motor response when discrimination is required.

Other regions, such as iFg, pIPs and left striate+extrastriate areas, were more activated during both DRT conditions (Go and No-go) as compared to the SRT. The activity of these regions is then related to the Go/No-go discrimination and response selection, a process that in turn requires both integration of perceptual evidence (striate+extrastriate and pIPs) and proactive inhibition (iFg).

These results are in line with our previous study, confirming the activation of certain brain areas during preparation, perception and action phases of cognition (Di Russo et al., 2016). As expected, we observed that proactive inhibitory control originates in the iFg and can be electrophysiologically identified with the pN component. Specifically, the iFg activity starts one second before the stimulus onset and seems to be released concomitantly to stimulus appearance. This result is in line with a recent theoretical framework that posits the prefrontal cortex as the dedicated neural module supporting the proactive inhibitory control (Aron, 2011; Aron et al., 2004). The iFg is involved in response inhibition tasks as Go/No-go tasks (Aron, 2011; Swick et al., 2008), and it is recruited regardless of whether the stimulus detection was followed by either inhibition or motor response (Hampshire et al., 2010). Recently, we proposed that the iFg exerts a cognitive control by setting the system in a "no-go" mode while preparing for the action. According to Aron (2011), the iFg activity may reflect a mechanism through which subjects put a "brake" on response tendencies when conflict is detected. Second, and more importantly, we clearly found such a proactive control in the iFg when discrimination was required, i.e., in the DRT, while it was almost absent in case of SRT. One potential explanation for the functional role of this proactive inhibition is to prevent incorrect responses, gating the mechanisms responsible for movement triggering as long as there is uncertainty about the movement itself (whether to act or not). Two lines of evidence from our laboratory motivate this interpretation. First, previous studies on older people revealed that, to reach the same accuracy level as younger people, older subjects prepared the action with greater anticipation and higher cost, as indexed by both anticipation and increased amplitude of the slow pre-motor pN activity in the iFg (Berchicci et al., 2012, 2013a). Second, when proactive control is absent, i.e., in the SRT task, such prefrontal control was absent in young adults (Berchicci et al., 2012; Di Russo et al., 2016), but it was well detectable in mid-aged participants, and very large (as much as in the DRT) in old participants (Berchicci et al., 2012, 2013b).

Conclusions

In conclusion, our study confirms and further extends previous data on the role of the brain areas involved in the preparation-perception-action phases. Before stimulus perception, the iFg anticipates the stimulus onset by putting the brain in a "no-go" mode, while stimulus perception triggers early activities in two brain areas (the aIns and the right aIPs), reflecting the accumulation

of sensory-motor evidence to decide whether an action is required. Most importantly, we reported evidence on the bilateral proactive control exerted by the iFg, rather than its hemispheric specialization, supporting that proactive control is not strictly linked to the necessary computations to trigger movement. Furthermore, we confirmed the role of the aIPs and aIns in perceptual categorization and in motor response planning, as we previously described (Di Russo et al., 2016). In addition, we reported here a stronger activation of the left than the right anterior insula and a right-lateralized activation of the anterior intraparietal sulcus and premotor cortex (CMA). These results reflect a left-hemisphere dominance of the anterior insula in mapping the stimulus-response association before response execution and a contralateral hand-related activity (reflecting kinematic features of the action) in the parietal-premotor cortex, respectively.

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Figure and table Legends

Figure 1. Schematic illustration of stimulus sequence in a) Go/No-Go trials and b) Relax trials employed in the fMRI and ERP experiments.

Figure 2. A. Regions activated by the omnibus F-contrast comparing DRT (Go and No-go) and SRT trials with Relax trials. Activations are rendered on reconstructions of the lateral and mesial/posterior surfaces (top and bottom panels, respectively) of the two cerebral hemispheres of the Conte69 atlas (Vann Essen et al., 2005). B-C. Plots show the percent BOLD signal change as a function of condition (SRT, DRT/Go and DRT/No-go) and hemisphere (LH: left hemisphere; RH: right hemisphere). *p<0,01; **p< 0.001.

Figure 3. ERP waveforms recorded on representative scalp electrodes for the SRT and DRT. The vertical dashed lines indicate the mean values of the RTs in the SRT and DRT.

Figure 4. Lateralized readiness potential (LRP) obtained subtracting the motor-related cortical potential (MRCP) at C4 electrode from that of C3.

Figure 5. Scalp topography of the anterior ERP components in the SRT and DRT conditions.

Figure 6. ERP-based time-courses of the source activities obtained from the fMRI seeded dipoles for the SRT and DRT (Go and No-Go trials). Time zero corresponds to stimulus onset; the green dashed vertical line indicates the DRT response onset (mean RT). The left panel represents the left hemisphere (LH); the right panel refers to the right hemisphere (RH).

Table 1. Anatomical location of local maxima (Talairach coordinates) in brain regions activated during the whole-brain "Omnibus" contrast. LH: left hemisphere; RH: right hemisphere.

Table 2. Statistical results of the one-way ANOVA with condition (SRT, DRT/Go; DRT/No-go) as factor conducted in each brain region activated by the "Omnibus" contrast (see also Figure 2A). Significant Bonferroni-corrected comparisons are also reported. LH: left hemisphere; RH: right hemisphere. *p<0,05; **p< 0.001.

Table 3. Statistical results of the 3x2 ANOVA conducted on the brain regions activated bilaterally by the whole-brain "Omnibus" contrast. The BOLD signal change has been analyzed as a function of condition (SRT, DRT/Go and DRT/No-go trials) and hemisphere (left, right). * p<0.05; ** p<0.001.

8. Table

Local maxima		Coordinates		
		x	y	z
M1	RH	43	-13	48
S1	RH	48	-16	43
aIPs	RH	45	-25	38
CMA	LH	-8	20	34
	RH	9	20	34
SMA	LH	-2	-2	55
	RH	9	1	45
iFg	LH	-29	23	3
	RH	31	23	1
aIns	LH	-37	-3	9
	RH	40	0	10
sMg	LH	-58	-27	22
	RH	57	-19	20
pIPs	LH	-27	-49	42
	RH	34	-54	45
Extrastriate	LH	-30	-85	3
	RH	34	-86	5
Thal	LH	-11	-17	7
	RH	14	-20	7

8. Table

Region	Hemisphere	Condition	Bonferroni-corrected comparisons
M1/S1	RH	F (2.30)=60.93**	SRT> DRT/No-Go**; DRT/Go > DRT/No-Go**
aIPs	RH	F (2.30)=60.61**	SRT> DRT/No-Go**; DRT/Go > DRT/No-Go**
CMA	LH	F (2.30)=15.73**	DRT/Go > SRT*; DRT/Go > DRT/No-Go**
CMA	RH	F (2.30)=25.55**	DRT/Go > SRT**; DRT/Go > DRT/No-Go**
SMA	LH	F (2.30)=15.23**	DRT/Go > SRT*; DRT/Go > DRT/No-Go**
SMA	RH	F (2.30)=67.02**	SRT> DRT/No-Go**; DRT/Go > DRT/No-Go**
iFg	LH	F (2.30)=30.31**	DRT/Go> SRT**; DRT/No-Go > SRT*; DRT/Go > DRT/No-Go**
iFg	RH	F (2.30)=28.85**	DRT/Go> SRT**; DRT/No-Go > SRT*
aIns	LH	F (2.30)=38.67**	SRT> DRT/No-Go*; DRT/Go > DRT/No-Go**
aIns	RH	F (2.30)=34.83**	SRT> DRT/No-Go**; DRT/Go > DRT/No-Go**
pIPs	LH	F (2.30)=23.04**	DRT/Go> SRT**; DRT/No-Go > SRT*
pIPs	RH	F (2.30)=11.50**	DRT/Go> SRT*; DRT/No-Go > SRT*
sMg	LH	F (2.30)=37.22**	SRT> DRT/No-Go**; DRT/Go > DRT/No-Go**
sMg	RH	F (2.30)=52.82**	SRT> DRT/No-Go**; DRT/Go > DRT/No-Go**
Striate+Extrastriate	LH	F (2.30)=18.99**	DRT/Go> SRT**; DRT/No-Go > SRT*
Striate+Extrastriate	RH	F (2.30)=13.37**	DRT/Go > SRT**; DRT/Go > DRT/No-Go*
Thal	LH	F (2.30)=22.78**	DRT/Go > SRT*; DRT/Go > DRT/No-Go**
Thal	RH	F (2.30)=18.39**	SRT> DRT/No-Go*; DRT/Go > DRT/No-Go**

8. Table

Region	Main effect Condition	Main effect Hemisphere	Interaction
CMA	F (2.30)=22.60**	F (1.15)=5.00*	F (2.30)=0.03*
SMA	F (2.30)=38.26**	F (1.15)=2.49	F (2.30)=12.06**
iFg	F (2.30)=37.68**	F (1.15)=0.26	F (2.30)=3.24
aIns	F (2.30)=38.78**	F (1.15)=20.79*	F (2.30)=5.41*
pIPS	F (2.30)=21.49**	F (1.15)=0.49	F (2.30)=0.82
sMg	F (2.30)=54.16**	F (1.15)=1.09	F (2.30)=1.22
Striate+Extrastriate	F (2.30)=18.03**	F (1.15)=0.07	F (2.30)=4.00
Thal	F (2.30)=20.77**	F (1.15)=2.81	F (2.30)=12.00**

9. Figure

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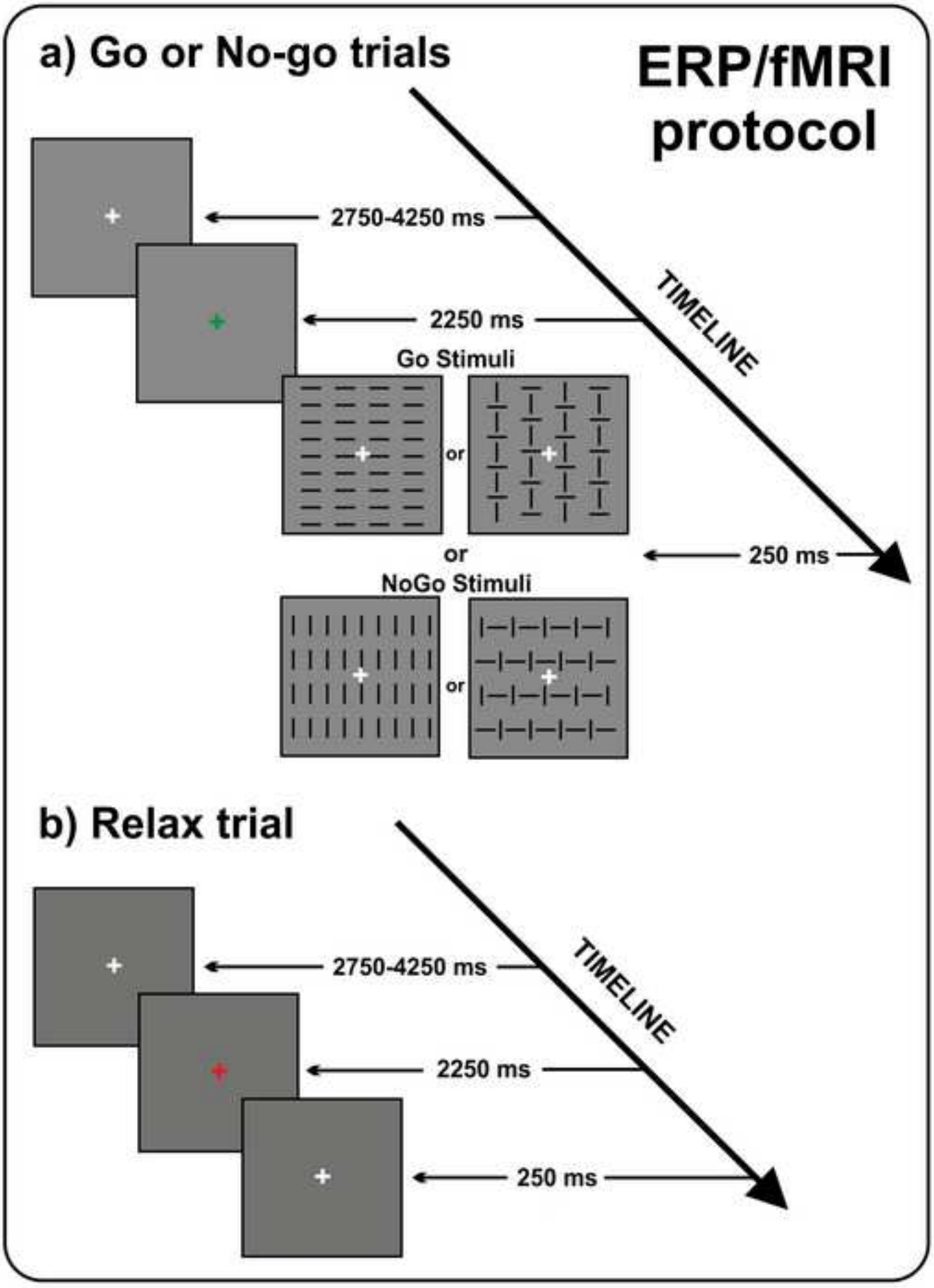

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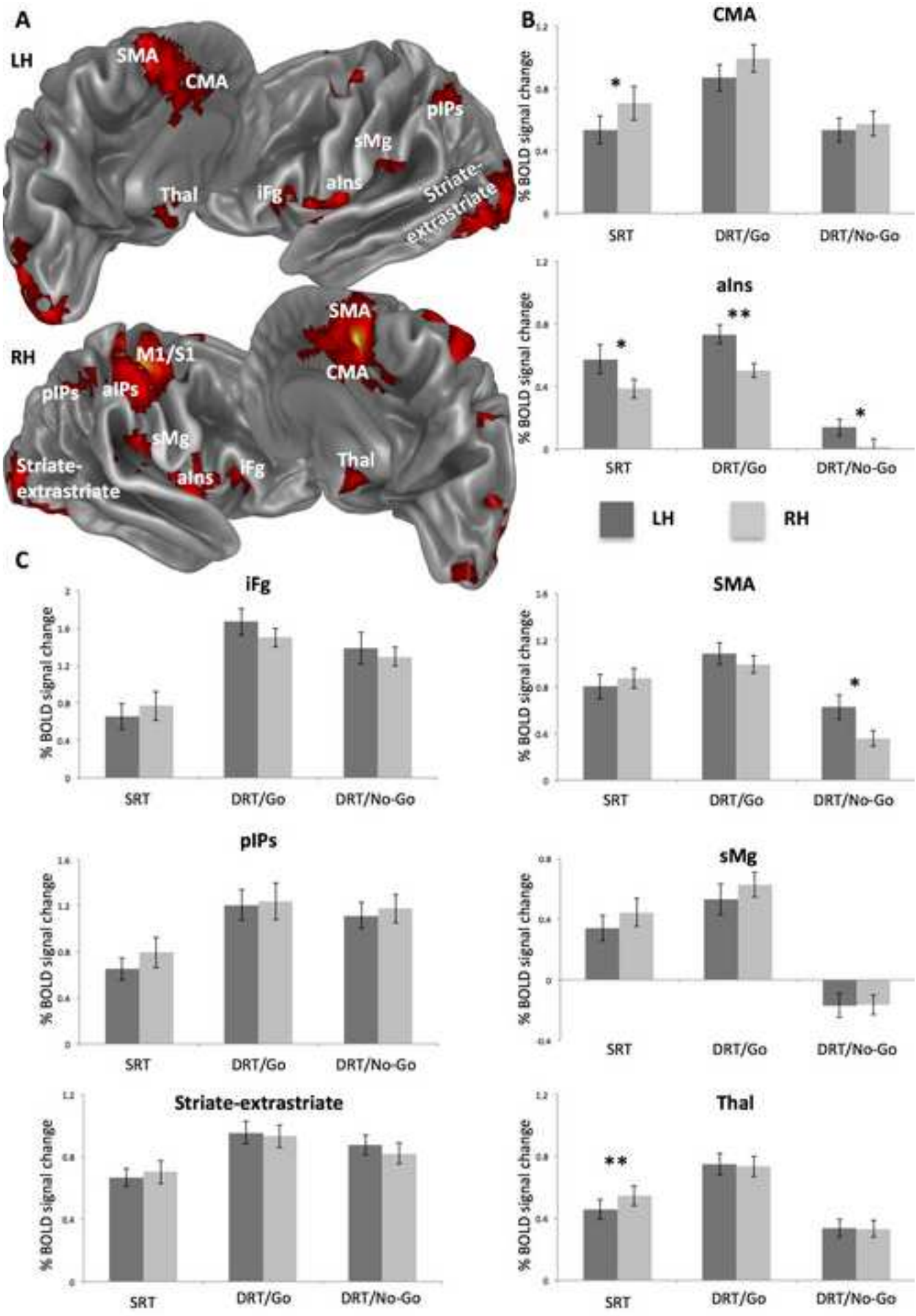

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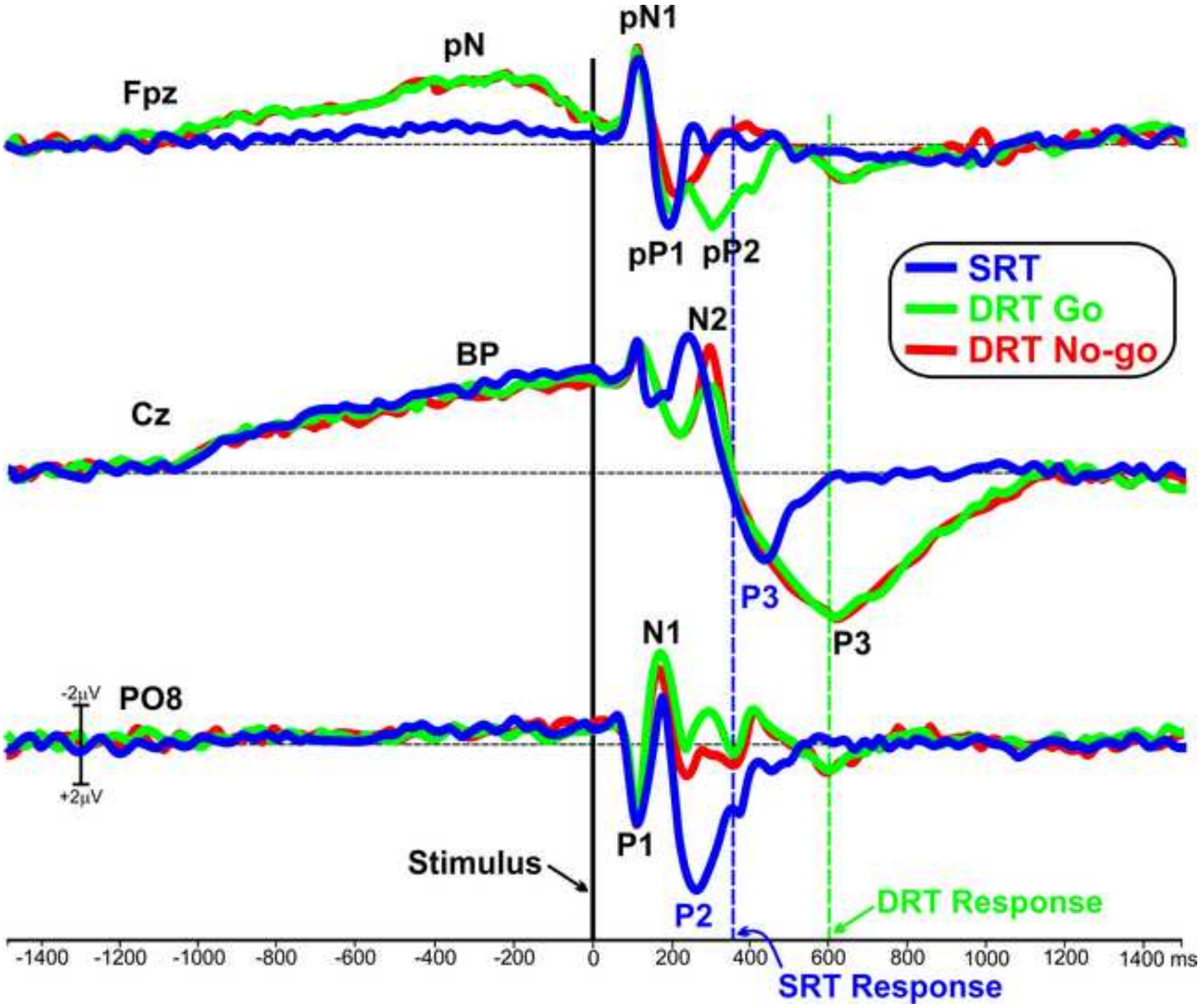

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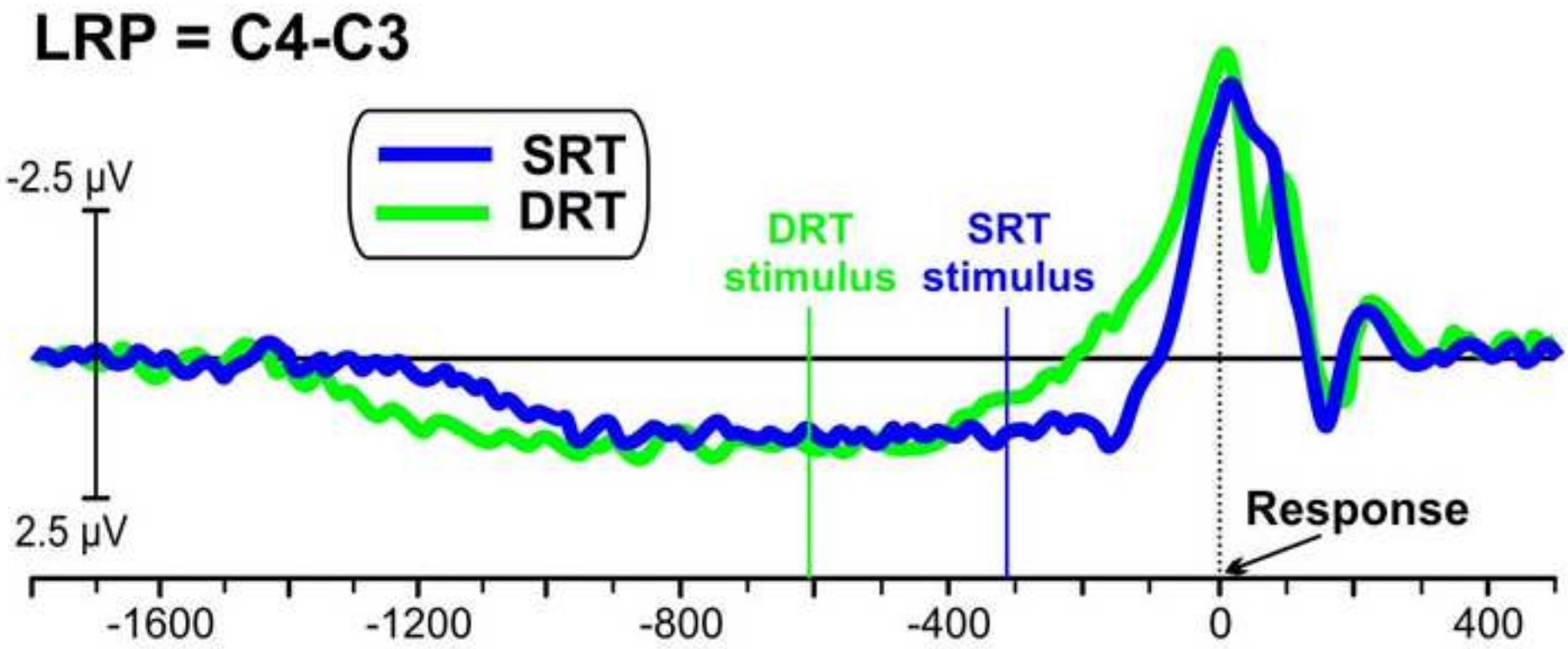

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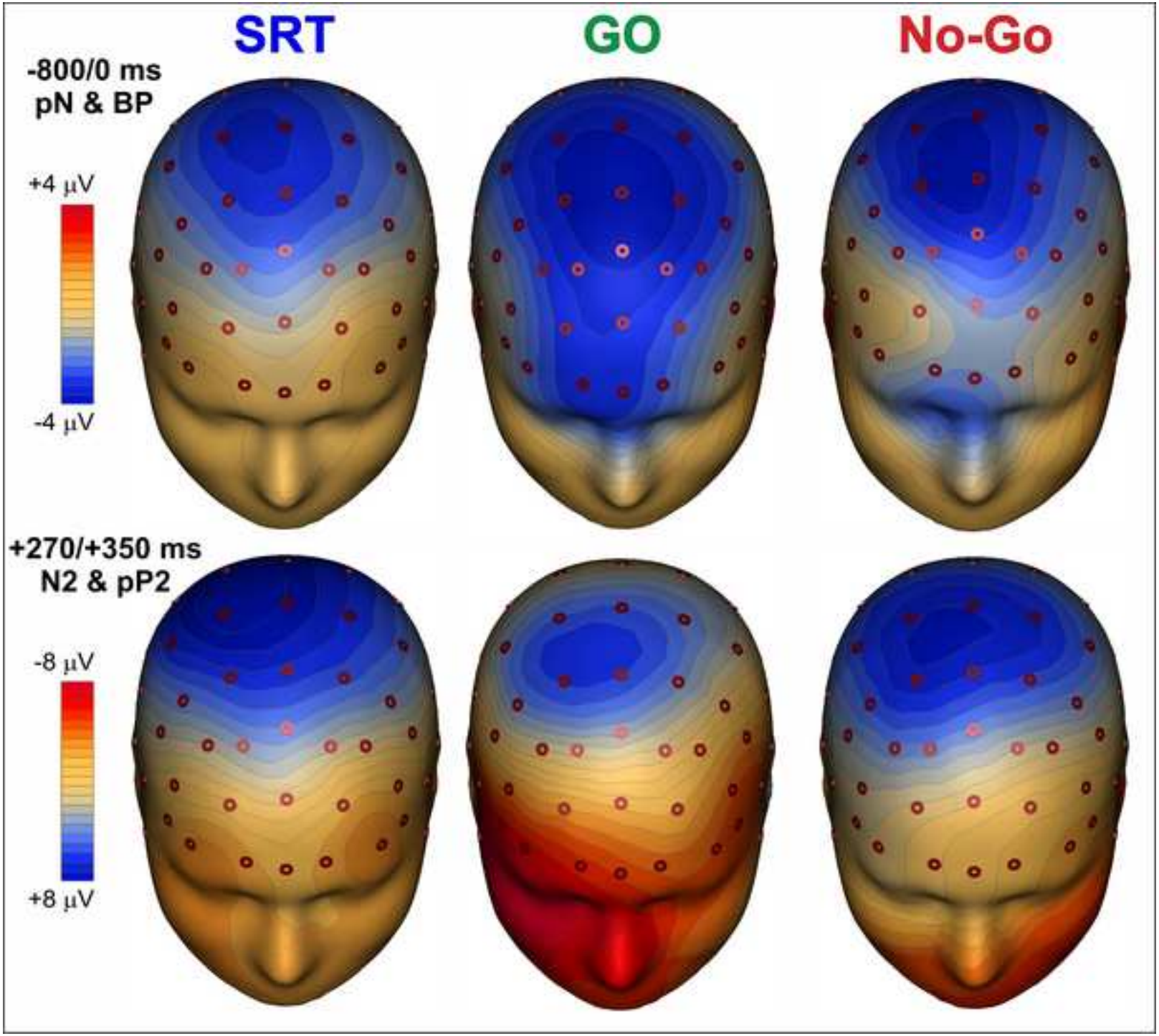

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