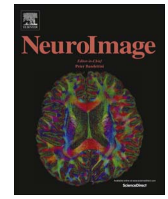
NeuroImage 148 (2017) 390–402

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage



Hemispheric asymmetries in the transition from action preparation to execution

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A R T I C L E I N F O

Keywords:
fMRI
EEG
Perceptual-decision
Prefrontal cortex
Go/No-Go

A B S T R A C T

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 origi-

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http://dx.doi.org/10.1016/j.neuroimage.2017.01.009
Received 23 November 2016; Accepted 5 January 2017
Available online 06 January 2017
1053-8119/

nates 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 intraparietal 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; Bozzacchi et al., 2012, 2015) 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