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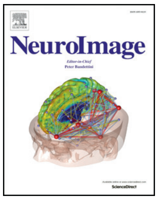

Spatiotemporal brain mapping during preparation, perception, and action

Francesco Di Russo [a,b,*], Giuliana Lucci [b], Valentina Sulpizio [b], Marika Berchicci [a], Donatella Spinelli [a,b], Sabrina Pitzalis [a,b], Gaspare Galati [b,c]

[a] *Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Rome 00135, Italy*
[b] *IRCCS Santa Lucia Foundation, Rome 00179, Italy*
[c] *Department of Psychology, University of Rome "La Sapienza", Rome 00185, Italy*

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ABSTRACT

Deciding whether to act or not to act is a fundamental cognitive function. To avoid incorrect responses, both reactive and proactive modes of control have been postulated. Little is known, however, regarding the brain implementation of proactive mechanisms, which are deployed prior to an actual need to inhibit a response. Via a combination of electrophysiological and neuroimaging measures (recorded in 21 and 16 participants, respectively), we describe the brain localization and timing of neural activity that underlies the anticipatory proactive mechanism. From these results, we conclude that proactive control originates in the inferior Frontal gyrus, is established well before stimulus perception, and is released concomitantly with stimulus appearance. Stimulus perception triggers early activity in the anterior insula and intraparietal cortex contralateral to the responding hand; these areas likely mediate the transition from perception to action. The neural activities leading to the decision to act or not to act are described in the framework of a three-stage model that includes perception, action, and anticipatory functions taking place well before stimulus onset.

1. Introduction

Most life situations require the selection of the right timing for acting, or the ability to refrain from inappropriate actions. Motor control is crucial for intelligent behavior and enables the suppression of compelling, inopportune, stimulus-driven responses. Most studies have examined reactive inhibition, that is, the blocking response that occurs after stimulus discrimination when no motor response is needed. However, based on seminal observations (Whitely and Blankfort, 1933), the existence of another form of control that occurs *prior* to stimulus onset (biasing the subject to not-respond, i.e., proactive inhibition) has been proposed primarily through studies using cue-probe or go/no-go paradigms (for a review, Aron, 2011).

Relevant to the issue of proactive inhibition, an event-related functional magnetic resonance (fMRI) study (Jaffard et al., 2008) postulated that the prefrontal cortex (PFC) and the inferior parietal cortex may be responsible for proactive inhibition, and the primary (M1), the supplementary motor cortex (SMA), and the putamen are likely the target sites of this inhibition; however, the low temporal resolution of fMRI did not enable to evaluate the temporal dynamic of the observed activities. The involvement of the PFC well before stimulus onset and before the typical SMA activity associated with movement preparation was shown by some electrophysiological studies of our group using discriminative reaction task with go/no-go paradigm; this PFC pre-stimulus activity increased as a function of age, was positively correlated with the response time (RT), and likely represented age-related increments of inhibitory control that compensate for general cognitive decline (Berchicci et al., 2012). Links between pre-stimulus PFC activity and behavioral characteristics such as response speed, accuracy or false alarms has also been found in other studies using a similar task (Perri et al., 2014, 2015a,2015b). These data reinforce the idea that the PFC is the neural basis of proactive inhibitory control (Bogacz et al., 2010). In support to the existence of an interplay of proactive and reactive inhibitory control mechanisms during cognitive tasks, see Chikazoe et al., 2009; Sætrevik et al., 2013.

Despite proposals that proactive control should be a critical component of the response inhibition system (Criaud et al., 2012), current models of inhibitory control are predominately based on studies that have investigated reactive mechanisms. Two main factors may have masked the detection of proactive control: first, in neuroimaging studies, proactive inhibition does not emerge in standard contrasts such as no-go versus go trials because it is present in both conditions (i.e., both when motor execution or inhibition is required) (Criaud and Boulinguez, 2013; Jaffard et al., 2007; Swick et al., 2011); second, many event-related potential (ERP) (and event-related fMRI) studies have used the pre-stimulus period as a baseline to measure stimulus-

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[*] Corresponding author at: Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Rome 00135, Italy.
E-mail address: francesco.dirusso@uniroma4.it (F. Di Russo).

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related activity, which makes it problematic to examine the activity that precedes stimulus onset and thus overlaps with the baseline period (Raichle and Snyder, 2007). Our knowledge about pre-stimulus anticipatory activities is mostly based on electrophysiological studies of the contingent negative variation (CNV), which is typically recorded when the preparation for an imperative stimulus (S2) is induced by a warning stimulus (S1). The CNV can be described as a gradually rising negative wave that precedes the S2 and has a maximal amplitude at the Cz electrode (Walter et al., 1964). The early phase of the CNV reflects attention, expectancy, stimulus processing, and categorical description, while the late phase of the CNV has been also related to the motor preparation for the action required by the imperative stimulus (Rohrbaugh et al., 1980; van Boxtel and Böcker, 2004). The main cortical sources of the CNV are reported to be located within the medial frontal lobe; however, when the S1 conveys specific information about the features of the S2, additional posterior sensory and fronto-parietal (including the dorsolateral prefrontal cortex; DLPFC) networks may contribute to the CNV (Gómez et al., 2003, 2007; van Boxtel and Böcker, 2004). The CNV paradigm has enabled the investigation of cortical anticipatory activities in a variety of tasks; however, a limited number of CNV studies have employed go/no-go tasks, but these did not focus on proactive control mechanisms (for a review, see van Boxtel and Böcker, 2004). Another anticipatory brain wave is the stimulus preceding negativity (SPN), which is a sustained negativity over parietal and frontal cortex during the waiting period for a feedback stimulus after a time estimation task (e.g., Hillyard, 1973; Brunia and Damen, 1988).

In addition to studies based on the CNV and other pre-stimulus ERPs (e.g., Everling et al., 1997, 1998), cortical anticipatory mechanisms have been investigated in a growing number of studies that have linked pre-stimulus EEG oscillatory activity with behavioral performance, either in terms of perceptual accuracy or reaction times (e.g., Busch et al., 2009; Mathewson et al., 2009; Drewes and Van Rullen, 2011; Bompas et al., 2015; in the monkey, see Zhang et al., 2008). However, in these studies as well, there was not a specific emphasis on evaluating proactive control.

To advance the study of proactive control, the present study investigated the spatiotemporal dynamics of cortical activities taking place in a wide time window using a go/no-go task performance that involved the discrimination of stimulus category and, according to this information responding as fast as possible, or refraining from responding while avoiding false alarms. To this aim, we combined the high temporal resolution of event-related potentials (ERPs) with the high spatial resolution of event-related functional magnetic resonance imaging (fMRI) to evaluate the temporal dynamics of neural activity in the different brain areas activated on go and no-go trials. As a control condition, we used a simple response task (SRT) where no stimulus discrimination was needed, and there was no risk of false alarms. To obtain a spatiotemporal model of the involved brain activities, the ERP data were seeded to the fMRI activations to allow the measurement of the time course for each brain area. This method can be designated as fMRI-informed EEG analysis because it aims to reduce the spatial EEG inverse problem by guiding electromagnetic source imaging with anatomical constraints obtained from fMRI (Di Russo and Pitzalis, 2013; Huster et al., 2012). Therefore, the present combined ERP/fMRI study offers a novel description of the neural substrates and the temporal dynamics of brain activations "before" and "in the course of" perceptual decision and action.

2. Materials and methods

2.1. Participants

Twenty-one participants volunteered for the ERP experiment (10 females, mean age 26.7 years, SD = 6.2). Structural MRI and fMRI scanning were executed in an age- and gender-matched sub-group of 16 volunteers (eight females, mean age 26.0 years, SD = 4.4), which participated in both the ERP and fMRI experiments.

All participants were healthy having no history of neurological, psychiatric, or chronic somatic problems. The participants did not take medication during the experimental sessions and had normal or corrected-to-normal vision. All participants were right-handed (average handedness score: +0.87; SD: 0.12 on the Edinburgh Handedness Inventory; Oldfield, 1971). Consent was obtained from all participants according to the Declaration of Helsinki after being approved by the Santa Lucia Foundation Ethical Committee.

2.2. Stimuli and task

The fixation point was a cross (0.15 × 0.15° of visual angle) in the center of the computer monitor, which never disappeared. Square configurations consisting of vertical and horizontal bars and subtending 4° × 4° were presented for 250 ms on a dark grey background (Fig. 1a). Each recording was initiated with the white fixation cross that lasted 2750–4250 ms (inter-trial interval). The entire trial duration varied from 5250 to 6750 ms (mean 6000 ms, SD = 536). The trials of the go/no-go task initiated with the fixation cross color changing to green for 250 ms (called instruction cue, or cue). After a long interval (2000 ms), one of the four visual patterns was displayed for 250 ms. Also "relax" trials were included as a control condition for evaluating the cue-related orienting and perceptual brain activity (this condition was especially useful for the analysis of fMRI data); relax trials initiated with the fixation cross color changing to red for 250 ms (instruction cue); in this case, the participants were informed that no stimulus would be presented after the red cross (Fig. 1b). Additionally, null trials were inserted in the paradigm, in which nothing appeared except for the fixation cross that remained on the screen for other 5250–6750 ms.

In the go/no-go tasks, participants performed a discriminative response task (DRT) where two configurations were defined as targets and two configurations were defined as non-targets. The participants had to press a button with their right hand as fast as possible when a target appeared on the screen (go stimuli; $p = 0.5$) and withhold a response when a non-target appeared (no-go stimuli; $p = 0.5$). The four configurations were randomly displayed with equal probability ($p = 0.25$). We chose to use a 50% go/no-go because it has several advantages: first, it produces maximum uncertainty regarding the stimulus probability minimizing differences in response conflict between event types (Lavric et al., 2004); second, the number of go and no-go trials is comparable, which eliminates distributional discrepancy and enables a clearer comparison between the two conditions; third, the equiprobability of go and no-go stimuli allows excluding that some of the observed ERP differences between the go and the no-go brain activity could be due to the different frequencies of the stimuli ("relative novelty" or "oddball effect") rather than other processes. Many ERP studies (Bekker et al., 2005; Bruin and Wijers, 2002; Eimer, 1993; Falkenstein et al., 1995; Jodo and Kayama, 1992; Lavric et al., 2004; Verleger and Berg, 1991) and also some fMRI studies (Lauren et al., 2005; Watanabe et al., 2002) have used this 50% paradigm, although studies using larger percentage of go stimuli are much more frequent (Swick et al., 2011 for a review of fMRI experiments). The order of presentation of go and no-go stimuli and trial types were randomized within the run. The duration of each run was 6′12″, including 18 go, and 18 no-go trials, as well as 18 relax and 8 null trials.

In the ERP experiment, which required a high number of repetitions to obtain reliable data, sixteen runs were executed (with interleaved pauses). One short warm-up run (3′) preceded the experiment. The session duration was approximately 2 h. In the fMRI experiment, eight runs were executed (with interleaved pauses). One warm-up run preceded the experiment. The session duration was approximately 1 h.

2.3. Analysis of behavioral data

The median response time (RT) for correct trials was calculated at individual level, while we considered the mean value at group level.

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