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Sequential inhibitory control processes assessed through simultaneous EEG–fMRI

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ABSTRACT

Inhibitory response control has been extensively investigated in both electrophysiological (ERP) and hemodynamic (fMRI) studies. However, very few multimodal results address the coupling of these inhibition markers. In fMRI, response inhibition has been most consistently linked to activation of the anterior insula and inferior frontal cortex (IFC), often also the anterior cingulate cortex (ACC). ERP work has established increased N2 and P3 amplitudes during NoGo compared to Go conditions in most studies. Previous simultaneous EEG–fMRI imaging reported association of the N2/P3 complex with activation of areas like the anterior midcingulate cortex (aMCC) and anterior insula. In this study we investigated inhibitory control in 23 healthy young adults (mean age = 24.7, n = 17 for EEG during fMRI) using a combined Flanker/NoGo task during simultaneous EEG and fMRI recording. Separate fMRI and ERP analysis yielded higher activation in the anterior insula, IFG and ACC as well as increased N2 and P3 amplitudes during NoGo trials in accordance with the literature. Combined analysis modelling sequential N2 and P3 effects through joint parametric modulation revealed correlation of higher N2 amplitude with deactivation in parts of the default mode network (DMN) and the cingulate motor area (CMA) as well as correlation of higher central P3 amplitude with activation of the left anterior insula, IFG and posterior cingulate. The EEG–fMRI results resolve the localizations of these sequential activations. They suggest a general role for allocation of attentional resources and motor inhibition for N2 and link memory recollection and internal reflection to P3 amplitude, in addition to previously described response inhibition as reflected by the anterior insula.

Introduction

Inhibitory control has been a prominent topic in neuroimaging (as reviewed by Swick et al. (2011)) and has been defined to include the ability to suppress actions that are inappropriate in a certain context and that interfere with goal-driven behaviour (Aron, 2007). The concept of inhibitory control has been investigated in numerous studies using a variety of cognitive tasks and neuroimaging methods. However, only few studies have focused on the combination of more than one imaging modality.

The most commonly used tasks to investigate inhibitory control are Go/Nogo, stop signal and conflict tasks. During Go/NoGo tasks, subjects are usually asked to respond to one type of stimulus, while withholding their response to another type of stimulus. Withholding a response following NoGo stimuli is more difficult when Go trials are frequent. Go/NoGo and stop signal tasks have frequently been treated interchangeably (Aron et al., 2004). Conflict- or interference tasks (as e.g. the Stroop task) have also been used extensively by neuroscientists to assess inhibitory control. These kinds of tasks require subjects to discriminate between task relevant and task irrelevant stimuli or stimulus dimensions and, in turn, inhibit the reaction to the task irrelevant aspects. Critics have suggested that many of the experimental effects

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observed during conflict correspond to the facilitated processing of task relevant stimuli rather than to active inhibition (Aron, 2007; Egner and Hirsch, 2005). However, for the common flanker task, where a central target stimulus is usually surrounded by other, irrelevant stimuli which are either compatible, neutral, or incompatible with the target stimulus or response (Eriksen and Eriksen, 1974), cortical motor inhibition appears to play an important role (Klein et al., 2013).

The signal of the electroencephalogram (EEG) is directly related to electric neuronal activity and shows a high temporal resolution within the millisecond range, while its spatial precision depends on restrictive assumptions or is limited to imprecise, blurred localizations of the distributed cortical and sometimes subcortical regions involved in cognitive processes (Pascual-Marqui et al., 2009). EEG studies have provided a large database on highly time-resolved neurophysiologic processes during response inhibition in Go/NoGo and stop signal tasks (see review by Huster et al. (2013)). The most prominent findings are enhanced inhibitory or conflict-related components of the event-related potentials (ERPs) during NoGo or Stop trials (the NoGo N2 and the NoGo P3).

The N2 is a negative potential increased in frontocentral regions during NoGo compared to Go trials (Review by Folstein and Van Petten (2008)). This association between the amplitude of the NoGo N2 and successful response inhibition has also been reported by Falkenstein et al. (1999). However, the N2 is also increased by conflict processing without inhibition (e.g.Randall and Smith (2011)), and therefore not specific for inhibitory processes.

In contrast, the subsequent NoGo P3 seems to be more consistently linked to response inhibition (Bekker et al., 2004; Bruin et al., 2001; Donkers and van Boxtel, 2004), and is characterized by a frontocentral positivity which has been extensively demonstrated in healthy adults (Bokura et al., 2001; Bruin et al., 2001; Fallgatter et al., 1997; Pfefferbaum et al., 1985). The NoGo P3 is increased in participants responding fast when compared to slow responders (Smith et al., 2006). Some other studies found that the amplitude of the NoGo P3 is increased in relation to the level of response preparation (Bekker et al., 2004; Bruin et al., 2001; Smith et al., 2007).

For the Eriksen flanker task (Eriksen and Eriksen, 1974), incompatible arrays, where the reaction to the flanking stimuli has to be inhibited, lead to a frontocentral increase of the N2 amplitude when compared to compatible arrays (incongruent vs. congruent condition). In contrast, there is almost no effect on the P3 positivity (Gehring et al., 1992; Kopp et al., 1996; van Veen and Carter, 2002). However, an increase in the latency of the P3 was reported in the incongruent condition (Ridderinkhof and van der Molen, 1995).

Both, N2 and P3 have been subject to intensive research in clinical populations. Differences in amplitude or anteriorization of the P3 can be detected e.g. in patients with ADHD and are interpreted as a representation of a persistent neurophysiological deficit, while results for NoGo-N2 are more heterogeneous showing no significant reduction of N2 amplitude in ADHD in many studies (Albrecht et al., 2012; Brandeis et al., 2002; Dhar et al., 2010; Doehnert et al., 2010; Fallgatter et al., 2004, 2005; Valko et al., 2009).

While EEG source localization allows high temporal resolution but in most cases only an approximate or blurred localization of inhibition- or conflict-related activity (Fallgatter et al., 1997; Strik et al., 1998), functional magnetic resonance imaging (fMRI) provides consistently high spatial resolution and enables a more precise localization of brain regions engaged during cognitive processes. However, the latter offers only low temporal precision, as the blood-dependent oxygen-level-dependent (BOLD) response is rather slow. Neuroimaging studies have investigated inhibitory control using a variety of tasks and contrasts, but the contrast of successfully inhibited NoGo trials compared to Go trials is most commonly reported. Various studies have yielded activation in areas such as the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) and inferior frontal cortex (IFC) for this contrast (Menon et al., 2001; Nee et al., 2007). Some studies also report activation in the lingual gyrus and caudate (Menon et al., 2001). However, a recent meta-analysis by Swick et al. (2011) found activation in the anterior insula to be largest and most significant. Further activation for NoGo compared to Go trials was found in the right middle frontal gyrus, right inferior parietal lobule/precuneus and left middle frontal cortex. The same meta-analysis also compared Go/NoGo to Stop signal tasks, and found overlapping activation in the right insula and superior frontal gyrus, while areas more activated during the Go/NoGo task comprised the right middle and superior frontal gyrus, as well as the right inferior parietal lobule and precuneus.

The multimodal approach of simultaneous EEG and fMRI recording integrates the advantages of both imaging modalities. Although important insights have been obtained by separate sequential recordings in the same subject (Halder et al., 2007; Vitacco et al., 2002), simultaneous recordings are needed to ensure the identical cognitive state and to capture spontaneous variation and trial-by-trial coupling of electrical and hemodynamic activity. The aim of integrating both imaging modalities is gaining both high spatial and temporal resolution in the same subject (Debener et al., 2005). Although a number of studies have used this approach, only one has so far investigated inhibitory control (Huster et al., 2011). Using cross-modal correlation and independent component analysis (ICA) to integrate ERP with fMRI data in a stop-signal task they found the stop-related N2/P3 complex to be correlated with activation in the rostral anterior midcingulate cortex (aMCC), pre SMA, anterior insula, putamen and globus pallidus, while the Go-related N2/P3 complex was associated with activation in the ventral anterior and posterior MCC, the left postcentral region, the SMA and deactivation in the occipital gyrus.

The present study combined fMRI and ERP measures to investigate spatio-temporal aspects of inhibitory control through single trial parametric modulation as suggested by previous EEG–fMRI studies (Benar et al., 2007; Eichele et al., 2005). In contrast to the previous study by Huster et al. (2011), the N2 and P3 were treated as separate components to model their successive, independent parametric modulations of the fMRI in order to gain new insights into the time course and the specific inhibitory characteristics of their BOLD correlates. Still, our EEG-informed fMRI analysis also represents an asymmetric approach to simultaneous EEG–fMRI integration, while fMRI-informed EEG source analysis, or symmetric multimodal data fusion represent alternative approaches as reviewed in Huster et al. (2012).

Material and Methods

Subjects

The full sample consisted of 23 right-handed healthy subjects (12 male, 11 female) aged between 20 and 35 years (M = 24.70, SD = 4.29). Due to technical difficulties and insufficient EEG-data quality, six subjects had to be excluded from EEG- and combined analyses. The EEG sample therefore consisted of 17 subjects (9 male, 8 female) aged between 20 and 35 years (M = 24.71, SD = 4.15).

All subjects gave written informed consent prior to their participation and had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University Heidelberg.

Experimental paradigm

In this Flanker/NoGo task (Blasi et al., 2006; Bunge et al., 2002; Meyer-Lindenberg et al., 2006) stimuli consisted of an array of five shapes including a central target arrow pointing either left or right, flanked by two shapes (arrows, squares or Xs) on each side. Subjects were instructed to press a button corresponding to the central arrow when the flankers were also arrows (congruent and incongruent conditions) or boxes (neutral condition), but not when they were Xs (NoGo condition). Flanking arrows were pointing either in the same (congruent) or opposite (incongruent) direction as the central arrow, thus allowing to investigate conflict processing and interference. A total of 145 stimuli (33 NoGo, 31 neutral, 40 incongruent, 41 congruent)