Context-dependent switching between proactive and reactive working memory control mechanisms in the right inferior frontal gyrus

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A B S T R A C T

A critical feature of higher cognitive functioning is the capacity to flexibly tailor information processing and behaviors to current situational demands. Recent neurocognitive models have been postulated to account for the dynamic nature of human executive processing by invoking two dissociable cognitive control modes, proactive and reactive control. These may involve partially overlapping, but temporally distinct neural implementation in the prefrontal cortex. Prior brain imaging studies exploring proactive control have mainly used tasks requiring only information about single-items to be retained over unfilled delays. Whether proactive control can also be utilized to facilitate performance in more complex working memory tasks, in which concurrent processing of intervening items and updating is mandatory during contextual cue maintenance remains an open question. To examine this issue and to elucidate the extent to which overlapping neural substrates underlie proactive and reactive control we used fMRI and a modified verbal 3-back paradigm with embedded cues predictive of high-interference trials. This task requires context information to be retained over multiple intervening trials. We found that performance improved with item-specific cues predicting forthcoming lures despite increased working memory load. Temporal dynamics of activation in the right inferior frontal gyrus suggest flexible switching between proactive and reactive control in a context-dependent fashion, with greater sustained responses elicited in the 3-back task involving context maintenance of cue information and greater transient responses elicited in the 3-back task absent of cues.

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Introduction

Attaining behavioral goals require executive control mechanisms important for selecting task-relevant information and suppressing task-irrelevant information. A large body of cognitive and neuroscience research has focused on defining the variety of subprocesses by which executive control guides behavior, and the brain structures upon which these functions depend. Core regions involved in executive control constitute the lateral PFC, the anterior cingulate cortex (ACC), basal ganglia and brainstem neuromodulatory systems (e.g. Duncan and Owen, 2000; Marklund et al., 2007; Nyberg et al., 2003). However, the specific functional contribution of these regions and their interactive role in the coordination of cognitive processes still remains to be well characterized. In a recent theoretical framework, the dual mechanisms of control (DMC) model, Braver and co-workers have proposed two dissociable but complementary control modes, referred to as proactive and reactive control, to account for the dynamic nature of human executive processing (e.g. Braver et al., 2007, 2009). According to DMC a fundamental distinction among diverse executive functions can be inferred from the temporal signature of their neural implementation in task-relevant circuitry.

Proactive control mechanisms reflect tonic preparatory processes that rely on active maintenance of goal-relevant context information, exerting their mitigating effect on behavioral conflict/interference in a pre-stimulus manner or across entire task blocks. This “early selection” mode is associated with sustained neural activity and appears to be obligatorily triggered by cue-induced expectation of changes (i.e., augmentation) in processing demand on the next trial(s) (e.g., cued task-set switching) but may in principle carry any context information conveying a facilitatory bias on future response selection. By contrast, reactive control mechanisms operate on a trial-to-trial basis and remain dormant until ‘online’ detection of conflict triggers this “late correction” mode associated with episodic retrieval or reactivation of context and transient neural activity (Braver and West, 2008).

Because of the great expenditure of neural resources invested to maintain a tonic mode of preparatory attention, proactive control is conjectured to be mainly deployed in situations defined by high expectancy...
with respect to need for PFC-mediated executive processing to overcome impending conflict (Braver et al., 2007). In keeping with this notion, a recent study manipulating interference expectancy during a working memory task, demonstrated an expectancy-dependent shift from transient probe-related activity to sustained preparatory activity in the left lateral PFC regions (Burgess and Braver, 2010). Proactive control may also be engaged in situations when there are large behavioral consequences or motivational benefits for accurate performance (e.g. Jimura et al., 2010; Locke and Braver, 2004).

The less resource-demanding reactive control mode is preferred in situations where it is difficult to foresee conflict and when available resources are running low (e.g., in elderly relative to young adults) (Paxton et al., 2008) for individuals low in working memory capacity (Burgess and Braver, 2010), and when task demands reach or surpass the limits of working memory capacity (Speer et al., 2003). In a similar vein, another theoretical model of executive control, proposed by Kane and colleagues (e.g. Kane et al., 2004), suggests that active maintenance of task relevant goals (proactive control) becomes crucial primarily when demands on overcoming interference are high, but only to the degree that individuals are endowed with high working memory capacity, and interference can be anticipated. Otherwise, they posit that reactive-like inhibitory processes need to be engaged to overcome trial-specific interference. For consistency we will be referring to these two control strategies as proactive and reactive executive control.

The requirements on PFC-mediated executive control needed to guide behavior are not only upregulated by the presence of task-irrelevant information competing with task-relevant information, but also to the extent that concurrent task-relevant processing impinges upon shared limited executive resources. Prior investigations aimed at elucidating the neural mechanisms of proactive control employed rather unchallenging tasks in this respect, such as cued-task switching (Braver et al., 2003; Ruge et al., 2009), AX-CPT (Paxton et al., 2008), and the recent probes task (Burgess and Braver, 2010). In these tasks, the executive load imposed on preparatory attention via context maintenance is rather small. For example, in the AX-CPT, only information about the most recently encountered item (whether ‘X’ or not ‘X’) must be retained over unfilled delays to guide upcoming responses.

The extent to which the same type of proactive control mechanisms can be utilized to anticipate and prepare for interference or conflict resolution, and ultimately, facilitate performance, when task demands are more stringent and entail other executive processes besides context maintenance that likely compete for the same neurocognitive resources, remains to be determined. In light of the prediction from DMC that lateral PFC regions in a domain-general common executive network should be capable of mediating such explicit cues also increase the burden on working memory, a total number of 224 words were partitioned into 16 task blocks (8 cued-interference and 8 uncued task blocks). Each word was presented for 2000 ms in a sequential order, with a uniform distribution of jittered interstimulus intervals at 500, 2500, 5000, and 7500 ms. The total time for performing the task was 18 min. Participants pressed the left button as quickly and accurately as possible when a word matched the one presented three words earlier, and the right button if the word had not been presented three words earlier. Thirty-six of the words matched the earlier item (target trials), and 188 did not (non-target trials). Here we use an interference version of the task (see also Derrfuss et al., 2004; Gray et al., 2003), in which target trials were intermixed with different kinds of non-target trials. On three quarters of the non-target trials the word presented matched the word two or four trials previously; thus, increased familiarity of a word due to its recent exposure (and hence increased demands for interference resolution). These non-target words were classified as lures. On the remaining non-target trials, the word presented was not a lure (i.e. an item not previously presented).

Importantly, we used two variants of this task (Fig. 1); a standard verbal 3-back task that was used for assessing reactive control, and a modified “cued” interference version that was designed to encourage participants’ use of a proactive strategy. This was done by embedding item-specific contextual cues (i.e. lure words were tagged with a “2” or “4” during their initial presentation) to disclose 2- and 4-back high interference probes in advance. For all other stimuli, both target items and never repeated lures, were tagged with an uninformative “0”. This enables advance preparation using proactive control for a negative response on high-interference trials (i.e. 2- and 4-back lures). Such preparation was not possible in the uncued N-back condition where an uninformative “0” was presented, and participants need to engage in reactive control mechanisms in order to resolve interference from the familiar, but not task-relevant stimuli. Using a hybrid fMRI-protocol with jittered stimulus presentation allowed us to tease apart, and directly compare sustained and transient (stimulus-
synchronous) neural activity elicited during cued and uncued 3-back task blocks. In consideration of our subtle experimental manipulation, and the rather small number of items assigned to different trial types, we mirrored the jittering of the stimulus intervals and trial sequences within each block across task conditions. This removes the risk that particular trial types (e.g., lures) occur in variable processing context between task conditions. Experimental tasks were presented using E-Prime 2.0 (Psychology Software Tools, Pittsburgh) and responses were collected using a scanner compatible 5-button response box.

**Image acquisition**

The study was carried out on a Philips 3.0 Tesla high-speed echo-planar imaging device using a quadrature headcoil. For functional scanning, the following parameters were used: repetition time: 1512 ms (31 slices acquired), echo time: 30 ms, flip angle: 70°, field of view: 22×22 cm, 64×64 matrix and 4.65 mm slice thickness. To avoid signals arising from progressive saturation, ten dummy scans were performed prior to image acquisition. Structural high-resolution T1 images were also acquired: a 3D turbo planar imaging device using a quadrature headcoil. For functional scans, the field of view: 24×24 cm, 170 sagittal slices with a slice thickness of 1 mm were acquired in 336×332 matrices and reconstructed to 800×800 matrices. All images were sent to a PC and converted to Analyze format.

**Data analysis**

Functional images were pre-processed and analyzed using SPM5 (Wellcome Department of Imaging Science, Functional Imaging Laboratory) implemented in Matlab 7.6 (Mathworks Inc., MA, US). After correcting for differences in slice timing within each image volume, all images were realigned to the first image volume acquired, normalized to standard anatomic space defined by the MNI atlas (SPM5), resampled to a voxel size of 2×2×2 mm, and spatially smoothed using a Gaussian kernel of 8×8×8 mm. Temporal autocorrelations within a session were corrected using an AR(1) model. All reported activations are in MNI space.

Event-related effects were modeled in the framework of the general linear model (GLM) as implemented in SPM5. For individual subject analyses, and event-related transient responses, a fixed effects event-related design was implemented using multiple linear regression time series analyses to determine the location and extent of brain activations associated with different trial types. In order to estimate event-related activation for different trial types, separate regressors for cue trials, targets, lures, and non-target non-lure trials were included in the GLM, for the cued and uncued conditions respectively. For the estimation of sustained activation, regressors were included that coded for cued and uncued task blocks. Hemodynamic responses for estimating transient activation were modeled using the SPM canonical HRF (two gamma functions) with temporal derivative (TD) and dispersion derivative terms (e.g., Friston et al., 1998). Sustained (blocked) responses were modeled as a box-car function, and convolved with the canonical hemodynamic response function (HRF). Single-subject statistical contrasts were set up using the general linear model, and group data were analyzed in a random-effects model. For the sustained regressors, statistical parametric maps were generated using t statistics to identify regions activated according to the model. In order to explore the effects for sustained activation in cued and uncued task blocks, the BOLD signal was extracted and plotted for the regions that showed stronger sustained activation in the cued compared to the uncued task blocks. For event-related regressors, we constructed an F-contrast to test for the difference in brain activation between cued and uncued probes. The resulting SPM-F maps identified voxels in which linear combinations of the three basis functions resulted in estimated responses significantly different between the conditions of interest. Since the F-contrast does not differentiate between positive and negative loadings (i.e., whether differences relate to activations or deactivations), plots of BOLD signal change were used to characterize whether the pattern of activation constitutes enhanced activation in the comparison of cued versus uncued trials, respectively.

Given our a-priori interest in regions previously identified as potentially contributing to proactive and reactive control mechanisms (e.g., Braver and Barch, 2006; Braver et al., 2007), we restricted our follow-up analyses to these particular regions. These regions included the PFC, the MTL, the striatum, and the midbrain. For all analyses an uncorrected threshold of $P = 0.001$ was initially applied for each contrast of interest and only clusters that had a cluster-level corrected $P = 0.05$ were reported. Cluster extent threshold was obtained from the CorrClusTh.m program (Thomas Nichols; http://www.sph.umich.edu/~nichols/JohnsGems5.html) which reports the statistically appropriate size threshold for identifying cluster-level corrected regions at an alpha level of $P = 0.05$ based on the number of voxels in the data, smoothness of the data, and uncorrected threshold used (i.e. $P = 0.001$).

The Marsbar toolbox (http://marsbar.sourceforge.net/) was used to create ROIs and to extract each ROI’s mean BOLD parameter estimate value for each condition within each subject. The parameter estimates were then used for plotting the results in SPSS, as well as for performing brain–behavior correlations. ROIs were functionally defined on the voxels that showed peak activations in the comparison of (i) the f-contrast for sustained responses in the cued condition compared to the uncued condition, or (ii) the F-contrast showing differential transient activation between the reactive and proactive conditions. Only regions that were identified a-priori (see above) were included in the ROI analyses, and further explored. Each region was created by including activated voxels ($P < 0.001$, uncorrected) within a 10-mm sphere around the peak voxel corresponding to regions...
with a proposed role in proactive and reactive executive control processes derived from the literature (see above). Each ROI contained a minimum of 30 contiguous voxels. Peak coordinates are presented in Table 1 (coordinates in bold are those used to define the ROIs) and corresponding regions in Figs. 3–5. For each ROI, effect sizes (% signal change) for the different conditions were then extracted and averaged, and time-courses were plotted for event-related responses.

**Results**

**Behavioral data**

The first sets of analyses demonstrate increased response-time (RT) in 2- and 4-back lures across cued and uncued conditions compared to new words (paired-samples t-test \((t(28)) = 4.02, P < 0.001\)). This shows that participants were slower on trials that involved interference resolution processes required for successful inhibition of proponent responses to familiar, but inappropriate words compared to non-familiar words. Next, two independent repeated-measure ANOVAs were performed on the RTs and accuracy respectively. In particular, we hypothesized that participants could use the information about upcoming interference in a proactive manner that would result in faster RTs and higher accuracy. First, the (cueing condition [cued/uncued] × trial type [target/lure/non-lure]) repeated-measures ANOVA on RTs showed a significant main effect of cueing condition \((F(1, 29)) = 6.76, P < 0.05, \eta^2_g = 0.19\) suggesting that RTs differed between the cued and uncued conditions across trial types. Also, the main effect of trial type \((F(1, 29)) = 12.5, P < 0.005, \eta^2_g = 0.31\), and the interaction \((F(1, 29)) = 14.4, P < 0.005, \eta^2_g = 0.34\) was significant. Planned comparisons showed that the difference between targets in the cued and uncued conditions did not differ significantly (mean RTs: cued target = 1100 ms, uncued target = 1123 ms; \(P > 0.05\)) while the RTs for non-lures in the cued were longer that in the uncued condition (mean RTs: cued non-lures = 1107 ms, uncued non-lures = 1055 ms; \(F(1) = 19.4, P < 0.005, \eta^2_g = 0.31\)). Importantly, RTs for probes in the cued condition were significantly faster compared to the non-cued condition (mean RTs: cued probe = 1129 ms, uncued probe = 1303 ms; \(F(1) = 29.2, P < 0.001, \eta^2_g = 0.51\)). This effect was significant for both 2- and 4-back lures. Interestingly, the comparison of RTs for non-lures and RTs in which participants could predict the presence of an upcoming lure (high interference) trial (cued probes) showed no statistical difference \((F(1) = 0.895, P = 0.378)\) suggesting that the use of this information could reverse the negative effect arising from the need to inhibit familiar and task-irrelevant responses. Also, across cuing conditions, individuals responded faster for targets compared to probes (mean RTs: targets = 1107 ms, probes = 1216 ms; \(F(1) = 11.8, P < 0.005, \eta^2_g = 0.29\)) and for non-lures compared to probes (mean RTs: non-lures = 1081 ms, probes = 1216 ms; \(F(1) = 37.9, P < 0.001, \eta^2_g = 0.57\)), while the difference between targets and non-lures was non-significant \((P > 0.05)\). Second, the (cuing condition [cued/uncued] × trial type [target/lure/non-lure]) repeated-measures ANOVA on accuracy showed a significant main effect of cueing condition \((F(1, 29)) = 6.25, P < 0.05, \eta^2_g = 0.18\) suggesting that also accuracy differed between the cued and uncued conditions across trial types. Also, the main effect of trial type \((F(1, 29)) = 42.8, P < 0.001, \eta^2_g = 0.60\), and the interaction \((F(1, 29)) = 9.08, P < 0.001, \eta^2_g = 0.24\) was significant. Planned comparisons showed that neither targets nor non-lures differed significantly between the cued and uncued conditions (mean proportion correct: cued target = 72%, uncued target = 68%; cued non-lures = 92%, uncued non-lures = 94%, both \(Ps > 0.05\)). However, and importantly, accuracy for probes in the cued condition was significantly higher compared to that in the non-cued condition (mean proportion correct: cued probe = 78%, uncued probe = 67%, \(F(1) = 18.3, P < 0.001, \eta^2_g = 0.39\)). Also, across cuing conditions, no significant difference was observed for targets compared to probes (mean proportion correct: targets = 71%, probes = 73%, \(P < 0.05\)), while the difference between targets and non-lures (mean proportion correct: non-lures = 93%, \(F(1) = 85.8, P < 0.001, \eta^2_g = 0.75\), along with the difference between non-lures and probes \((F(1) = 78.3, P < 0.001, \eta^2_g = 0.73)\) was significant. Together this suggests that participants were able to effectively use the information about upcoming 2- and 4-back lures in the proactive condition.

**fMRI data**

First, in order to specify regions showing sustained activity during proactive compared to reactive processes, we contrasted blocks in which participants were given cue information on upcoming 2- and 4-back lures, with standard 3-back task blocks where no such information was presented. Importantly, this contrast included both 2- and 4-back lures and activation was collapsed across trial types. For this

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**Table 1**

<table>
<thead>
<tr>
<th>Anatomical localization</th>
<th>BA x</th>
<th>y</th>
<th>z</th>
<th>mm³</th>
<th>Z</th>
</tr>
</thead>
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<tr>
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<td>34</td>
<td>−36</td>
<td>−2</td>
<td>1720</td>
<td>4.51</td>
</tr>
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<td>−8</td>
<td>1984</td>
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<tr>
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<td>1960</td>
<td>4.14</td>
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<tr>
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<td>860</td>
<td>4.12</td>
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<tr>
<td>L caudate nucleus</td>
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<td>−12</td>
<td>20</td>
<td>782</td>
<td>4.10</td>
</tr>
<tr>
<td>L posterior cingulate cortex</td>
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<td>−30</td>
<td>28</td>
<td>1912</td>
<td>4.10</td>
</tr>
<tr>
<td>L inferior frontal gyrus</td>
<td>45/46</td>
<td>−52</td>
<td>28</td>
<td>1554</td>
<td>4.01</td>
</tr>
<tr>
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<td>14</td>
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<tr>
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<td>48</td>
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<td>3.74</td>
</tr>
<tr>
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<tr>
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<td>−4</td>
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<tr>
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<td>40</td>
<td>−22</td>
<td>−480</td>
<td>3.57</td>
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</table>

L, left; R, right; BA, Brodmann’s area; x, y, z, stereotactic coordinates. The regions in bold were selected for ROI analyses. All reported regions survived an uncorrected threshold of \(P < 0.001\) (FWE cluster corrected at \(P < 0.05\)).
and all subsequent analyses an uncorrected threshold of $P = 0.001$ (cluster corrected at 0.05) was applied for each contrast of interest (see Methods section). This contrast revealed activation in the right middle PFC ($x, y, z = 46, 34, 30$), right inferior frontal gyrus ($x, y, z = 40, 26, 4$) and the brainstem ($x, y, z = -4, -12, -28$). These activations are presented in Fig. 3. The reverse contrast (sustained activation in uncued vs. cued conditions) revealed one significant activation in the right precentral gyrus (motor cortex; $x, y, z = 64 - 634$).

Second, for the transient effect, each of the different trial types was modeled separately, but given the small number of trials for the event-related analyses, all trial types were collapsed to increase power of detecting differential transient activation between the two task conditions. These results are reported in Table 1. Regions showing significant activation differences between uncued and cued task conditions included the inferior frontal gyrus, medial temporal lobe (hippocampus), middle temporal gyrus, caudate nucleus, posterior cingulate cortex, insula, and the lingual gyrus (Table 1). Critically, given our interest in proactive and reactive executive control mechanisms involved specifically in resolving interference in high conflict situations (i.e., on lure trials), in a second step we made a follow-up analysis focusing exclusively on differential transient activity between cued and uncued lures within regions identified in the initial event-related analyses. We focused on a set of 7 regions-of-interests (ROIs) all of which have been observed in prior literature to be functionally involved in domain-general executive control and interference resolution. All subsequent analyses for transient activation centered on these regions. Since results from $F$-tests are bidirectional, and given the suggested possibility that a given region can be involved in both proactive and reactive interference resolution processes, but at separate time-points, we addressed this issue by investigating the time-courses for transient BOLD signal on lures exclusively in regions revealed in the initial event-related analysis comprising all trial types. This analysis makes it possible to identify regions that showed stronger activation in the uncued condition compared to the cued condition, and the reverse. Also, this analysis might help reveal the neural overlap between proactive and reactive processes. We hypothesize that proactive control mechanisms would show early peak activation, while reactive processes demonstrate a later peak reflecting the longer time for initiating and bringing on-line necessary processes for resolving interference when no information is given to prepare for high-conflict trials. While no such pattern was observed overall, the right caudate nucleus and the right IFG which showed stronger activation in the cued condition compared to the uncued condition, the activation also peaked earlier for trials in which a proactive strategy could be used while a later peak was observed for trials in the uncued condition (Fig. 5). Together this provides evidence suggesting that regions involved in executive control are capable of dynamically shifting between proactive and reactive control modes depending on the task at hand.

One alternative interpretation of the current results could be that participants engage in strategic non-encoding (or directed forgetting) of 2- and 4-back cues in order to reduce familiarity with those stimuli at the probe period. In order to investigate this possibility, we performed additional control analyses. First, we compared activation for 2/4 cues with activation for 0 cues in the predefined ROIs. Increased,
regions survived an uncorrected threshold of \(P < 0.001\) (FWE cluster corrected at \(P < 0.05\)). All reported regions were then extracted for transient and sustained effects respectively.

The ROIs included the right and left IFG, right and left caudate nucleus, the brainstem, and the right and left medial temporal lobes. For each ROI, effect sizes (% signal change) for the different conditions were then extracted for transient and sustained effects respectively. For sustained activation, the BOLD signal was averaged across the loci where transient activation was signiﬁcantly greater for cued compared to uncued lure trials.

For further exploratory analyses, we also conducted brain–brain correlations between ROIs to investigate possible close interplay between critical control regions. The only signiﬁcant correlation was found between the lateral PFC regions and the caudate nucleus.

<table>
<thead>
<tr>
<th>Anatomical localization</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>mm(^3)</th>
<th>Z</th>
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</thead>
<tbody>
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<td>24</td>
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<td>732</td>
<td>3.91</td>
</tr>
</tbody>
</table>

L, left; R, right; BA, Brodmann’s area; x, y, z, stereotactic coordinates. All reported regions survived an uncorrected threshold of \(P < 0.001\) (FWE cluster corrected at \(P < 0.05\)).

Brain–behavior correlations

Do individual differences in activation correspond to individual differences in behavior? To examine the relationship between neural activation and behavior, we performed correlations between behavioral measures of executive control (reaction time and accuracy), and BOLD signal in functionally defined regions-of-interest (ROIs). ROIs were defined based on task-related activation in voxels showing signiﬁcant involvement in transient (uncued vs. cued and cued vs. uncued) and sustained (cued vs. uncued) contrasts (see Methods section). Peak coordinates correspond to regions displayed in Figs. 3–5. The ROIs included the right and left IFG, right and left caudate nucleus, the brainstem, and the right and left medial temporal lobes. For each ROI, effect sizes (% signal change) for the different conditions were then extracted for transient and sustained effects respectively. For sustained activation, the BOLD signal was averaged across the
task blocks, and for transient activation, the BOLD signal was averaged over 2–8 TRs (3–12 s).

Of primary interest was to investigate whether behavioral advantages from utilizing a proactive control strategy were associated with altered activation in regions differentially responsive to the cued condition. From this analysis we found that transient activation for cued lure trials in the right IFG (40 26 4) was positively correlated with cued lure RT. This suggests that less right IFG activation at the occurrence of the lure was associated with faster responses. The activity dynamics demonstrated within a region in the right IFG implicated a shift from reactive to proactive control when participants were given predictive cue information about upcoming high-interference trials. Right IFG has previously been strongly linked with response inhibition (e.g. Aron et al., 2003; Menon et al., 2001; Rubia et al., 2003), and more general attentional control processes mediating this and other executive function, such as working memory, response inhibition, and task switching (Derrfuss et al., 2004; Duncan and Owen, 2000; Hampshire et al., 2010; Miller and Cohen, 2001). This region has also been implicated in sustained attention, suggesting that tonic activation in cued task blocks, involves processes implicated in focusing attention to potentially upcoming lure trials and domain-general task-set maintenance (e.g. Marklund et al., 2007; Pardo et al., 1991). The present results extend on prior work demonstrating shifting activity dynamics within the same lateral PFC regions in low-load tasks (e.g. AX–CPT) absent of concurrent processing demands during context maintenance (Braver et al., 2009), by showing that the same type of context-dependent flexible utilization of proactive and reactive control within a single region can also be induced in high-load working memory tasks.

Current findings showed that transient item-related increases in the right IFG were seen when no cue information was available (uncued 3-back task) relative to when cues tagged each item that were to be repeated in upcoming high-interference trials (cued 3-back task). The role of right IFG in reactive control processes demonstrated during the uncued 3-back task appeared to flexibly shift to a proactive or preparatory role during the cued 3-back task in which sustained activity increases were seen in a partially overlapping right IFG region. More specifically, the crossover pattern of activity dynamics in the right IFG, with greater sustained responses elicited in the 3-back task involving maintenance of contextual cue information and greater transient responses elicited in the 3-back task absent of cues corresponds to that predicted by DMC for a region with capacity to flexibly shift between the two forms of control mode. This suggests that the additional context information provided by cues enables tonic maintenance of preparatory response-biasing/inhibition signals during anticipation of an upcoming high-interference trial, which in turn reduces phasic inhibitory control demands during response selection. An alternative interpretation of the higher transient activation in the right IFG activity during the reactive condition would be that episodic retrieval operations are selectively engaged to reactivate contextual source information to guide response selection when no cue information is available, which concords with the co-occurrence of greater transient activation in the left hippocampus. The role of hippocampus during reactive control via episodic retrieval of context information is also in line with the DMC model (Braver, 2012).

The right lateralization of the IFG implicated as playing a unitary role in preparatory and reactive interference resolution deserves some commentary given prior research findings suggesting a crucial role of the left, rather than right, IFG in interference resolution (e.g. Badre et al., 2005; Nee et al., 2007; Nelson et al., 2009). A plausible explanation of the lack of a similarly dynamic effect in the left PFC may be that the left IFG is equally involved in context maintenance in the 3-back task regardless of whether predictive contextual cues are present or not. Thus, the same activity dynamics would be expected in both task conditions employed in the present study, with no modulation resulting as a function of trial-specific anticipation of interference/response conflict. The right IFG, on the other hand, has previously been associated with both preparation for response conflict resolution (e.g. in cued stop-signal paradigms), and the actual inhibition of prepotent response tendencies once they threaten to interfere with successful task performance (e.g. Chikazoe et al., 2009; Jahfari et al., 2010; Vink et al., 2005). Possibly, the response-biasing induced by cues; to suppress and overcome familiarity-based, but faulty, “yes”-responses to high-interference lures in favor of more
control-enforcing “no”-responses, may instantiate executive control processes corresponding to response inhibition, as well as the preparation thereof, rather than interference resolution per se.

While the current findings, along with previous observations support a role for right IFG in proactive interference control, recent results using electrocorticography measures during the stop-signal have demonstrated that the right IFG activates at the time of the response rather than earlier in the trial, and thus occurs too late to be considered proactive (Swann et al., 2012; see also Zandbelt et al., 2012 for similar findings using fMRI). Clearly, additional studies using different imaging techniques might help resolve these issues.

Consistent with predictions, the current findings give support to the notion that some PFC regions recruited in proactive control partially overlap with those engaged in reactive control, given that preparatory mechanisms are made feasible and permissible by task demands. The argument is that the same mechanism of interference control should be involved, regardless of whether pre-knowledge that allows for anticipatory coding of upcoming high-interference exists or not, the only difference being the temporal dynamics involved in the neurocognitive implementation. Our findings corroborate nicely with models dissociating early and late components of executive control (Aron, 2011; Banich et al., 2009; Braver et al., 2007, 2009; Kane et al., 2004; Velanova et al., 2003). These models dissociate between a late-acting, reactive, component involved in transient detection and resolution of interference on a trial-to-trial basis, and an early-acting, proactive, component involved in preparing for and anticipating interference before its occurrence. This later component might recruit active maintenance of goal-related representations in working memory. Importantly, here we show that these components can operate within the same brain regions, but at different stages of processing.

Regarding our finding of increased transient activation in the striatum during proactive compared to reactive probes, our results are in line with the suggestion that proactive and reactive control mechanisms can be dissociated in terms of the involvement of the dopamine (DA) system. Moreover, these results also corroborate findings suggesting that the right IFG, together with the striatum, is critically involved in reactive operations during response inhibition in stop-signal tasks (for a recent review, see Aron, 2011). Consistent with this possibility, there is evidence from the stop-signal task suggesting that there is a parametric increase of striatal activation the more stopping was anticipated (Vink et al., 2005, 2006; Zandbelt et al., 2011, 2012). Indeed, by inspecting the respective time-courses for transient BOLD signals in cued and uncued conditions, there is an apparent shift where cued trials show an early peak while uncued trials are associated with a late peak. More generally, current views based on clinical and neuroimaging evidence implicate that the striatum (the caudate nucleus) might support prefrontal top-down operations underlying control of task set and context processing (e.g. Zandbelt and Vink, 2010). This largely dopamine mediated interaction between PFC and striatal regions was further supported by a positive correlation between transient activation during reactive control in the left posterior DLPFC and the right caudate nucleus. Similarly, we found evidence for a positive correlation between transient activation in the right IFG and left caudate nucleus related to lures (indexing reactive control).

For reactive conditions, one might also expect to find engagement of additional brain systems other than PFC associated with mediating performance. For example, if reactive control can be obtained by activation of long-term representations or episodic memories, involvement of hippocampal/medial temporal lobe (MTL) structures might be expected. Indeed, the observation of transient activation for reactive conditions suggests a role of the hippocampus in trials in which no cue about upcoming interference was present possibly reflecting a stronger need for retrieving source or context information in order to flag a lure trial as familiar. Thus, transient hippocampal activation for reactive trials might signify a more pronounced need for context retrieval in order to correctly reject the familiar lure trial. Possibly, top-down signals from the PFC might play a role in modulating hippocampal activation related to source memory/context retrieval. More generally, the present results support a role for a system including the striatum, the hippocampus and PFC in resolving interference for familiar 2- and 4-back lures at the moment of their presentation and accompanying conflict detection. The anatomical circuitry of the PFC, striatum and hippocampus is well-characterized (Alexander et al., 1986; Goldman-Rakic et al., 1984; Middleton and Strick, 1994; Rolls, 1994), but their temporal dynamics and involvement in interference resolution is less well-understood.

Our observation of sustained brainstem activation for cued task blocks is in line with previous studies on intrinsic alertness and vigilance that consistently have found brainstem activation associated with maintaining responsiveness in cognitive tasks (Langner et al., 2012; Paus et al., 1997; Perin et al., 2010; Sturm et al., 1999). It has been suggested that midbrain and brainstem structures are involved in arousal systems important for maintaining optimal efficiency of information processing. For example, it has been shown that decline in arousal over time in a vigilance task varied with activity in midbrain structures (Paus et al., 1997). Possibly, these alertness systems innervate, through release of neurotransmitters, cortical regions such as the PFC which modulate computational processes controlling the efficiency of executive control processes. Also, a recent study provided evidence for midbrain activation following cues allowing preparation for trials requiring response inhibition in the stop-signal task (Zandbelt et al., 2012). While we are aware that fMRI lacks the ability to localize specific brainstem and midbrain structures given its coarse spatial resolution, our data provides further evidence that brainstem structures are involved in neuromodulation contributing to maintaining proactive executive control processes.

Our findings showing that activation in regions involved in proactive control also correlated with behavioral performance suggest that decreased recruitment of task-relevant regions, including the right IFG, contributes to more efficient interference resolution by involving proactive control. Presumably, less effort was needed when responses were anticipated, and thus reducing the need for interference control during lure presentation. This is in line with numerous previous observations from PET and fMRI studies that have shown reduced activation in faster than in slower individuals (Haier et al., 1988; Kosslyn et al., 1996; Persson et al., 2004; Rypma and D’Esposito, 2000; Rypma and Prabhakaran, 2009; Rypma et al., 2006). For example, Kosslyn et al. (1996) have observed neural activity reductions for faster, compared to slower participants on a mental imagery task.

One caveat with the design of the present study, which is also shared by some other studies using mixed block/event-related designs, is that the maintenance of the cue information was required over the subsequent 2- and 4-back trials, but for the sustained regressor a boxcar was modeled across the entire block of trials. Possibly, the sustained activity regressor relies also on the non-modeled shorter duration activity, in addition to activity sustained over the entire task block.

We believe that our results constitute important insights into the temporal dynamics of brain function involved in executive control operations in working memory. Our results indicate behavioral performance gains when participants were given information about upcoming interference trials. When participants could utilize a proactive control strategy, increased sustained activation in brainstem and right PFC regions were observed together with transient responses in the striatum and left PFC. These observations suggest functional specificity for transient and sustained responses in proactive control in working memory. Transient increase in a partially overlapping right PFC regions was observed when no cue information about upcoming high interference trials was present (reactive control) suggesting flexible switching between proactive and reactive control in a context-dependent fashion. Moreover, correlations between transient activation in the right PFC during proactive control, and behavioral performance suggest that activation in this region has behavioral consequences.
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References


