

Unity and diversity of tonic and phasic executive control components in episodic and working memory

P. Marklund,^{a,e,*} P. Fransson,^b R. Cabeza,^c A. Larsson,^d M. Ingvar,^b and L. Nyberg^{d,e}

^aDepartment of Psychology, Umeå University, Sweden

^bCognitive Neurophysiology Research Group, Department of Clinical Neuroscience, Karolinska Institute, Sweden

^cCenter for Cognitive Neuroscience, Duke University, USA

^dDepartment of Radiation Sciences, Radiation Physics, Umeå University, Sweden

^eDepartment of Integrative Medical Biology, Physiology Section, Umeå University, Sweden

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The present study aimed to delineate the extent to which unitary executive functions might be shared across the separate domains of episodic and working memory. A mixed blocked/event-related functional magnetic resonance imaging (fMRI) design was employed to assess sustained (tonic control) and transient (phasic control) brain responses arising from incrementing executive demand (source versus item episodic memory – vis-à-vis – two-back versus one-back working memory) using load-dependent activation overlaps as indices of common components. Although an extensive portion of the regional load effects constituted differential control modulations in both sustained and transient responses, commonalities were also found implicating a subset of executive core mechanisms consistent with unitary or domain general control. ‘Unitary’ control modulations were temporally dissociated into (1) shared tonic components involving medial and lateral prefrontal cortex, striatum, cerebellum and superior parietal cortex, assumed to govern enhanced top-down context processing, monitoring and sustained attention throughout task periods and (2) stimulus-synchronous phasic components encompassing posterior intraparietal sulcus, hypothesized to support dynamic shifting of the ‘focus of attention’ among internal representations. Taken together, these results converge with theoretical models advocating both unity and diversity among executive control processes. © 2007 Elsevier Inc. All rights reserved.

Introduction

A question of central importance to the understanding of higher order cognition concerns the nature of executive control and its neural implementation in the brain. Although much studied, the concept of *executive function* or cognitive control remains elusive. There is however an emerging consensus in the literature for the

need to fractionate the early conception of a unitary ‘central executive’ (Baddeley and Hitch, 1974) and recent models have posited a view of executive functions as a conglomerate of largely independent, but constantly interacting control processes such as interference resolution, attention-shifting, updating, refreshing and inhibition (Johnson, 1992; Baddeley, 1996; Fuster, 1997; Smith and Jonides, 1999; Miyake et al., 2000; Friedman and Miyake, 2004). Common to such models is that the postulated executive subprocesses are considered (at least implicitly) to be domain general in the sense that they can come into play in a broad range of distinct cognitive domains (e.g., attention, working memory, long-term memory) (e.g., Baddeley, 1996). By this view, the engagement of a particular executive function (e.g., inhibition) within any one cognitive task is simply a matter of the degree to which load is exercised on the operations ascribed to that control mechanism and should extend to any cognitive challenge that incorporates sufficient control requirements of the same kind.

Recently, functional brain imaging studies have revealed considerable overlap in the frontal activity elicited in tasks indexing working memory and episodic memory processes (Braver et al., 2001; Cabeza et al., 2002; Nyberg et al., 2002, 2003; Ranganath et al., 2003). This pattern may reflect common executive control processes tapped into by episodic and working memory tasks (Wagner, 1999, 2002). However, such an interpretation is limited by the fact that most previous cross-functional investigations merely used a single task for respective cognitive domain whereby activation overlaps were assessed relative to a common low-level baseline. Nonetheless, these studies, although inconclusive regarding the precise functional contributions of common frontal activations, strongly indicate a set of key frontal regions to play a generic role across these two major cognitive domains.

Given the assumption of domain generality posited for different executive functions and their alleged implementation in the prefrontal cortex (PFC), we conjecture that episodic and working memory (partially) draw on the *same* cognitive and neural mechanisms to comply with increased executive task demands indepen-

* Corresponding author. Department of Psychology, Umeå University, S-901 87 Umeå, Sweden. Fax: +46 90 7866695.

E-mail address: Petter.Marklund@psy.umu.se (P. Marklund).

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dently manipulated within each domain. To this end, the main purpose of the present functional magnetic resonance imaging (fMRI) study was to examine whether the patterns of brain activity induced by increasing executive requirements within the domains of episodic and working memory involve overlapping neural systems. Although fundamental to models of executive functions, this issue has to the best of our knowledge not been addressed in previous functional imaging studies.

To manipulate executive demands in the episodic memory domain, we contrasted source and item memory, which are considered to vary with respect to their reliance on controlled processing during retrieval (Yonelinas, 2002). Specifically, prior to scanning, subjects were shown two different study lists. In the subsequent item memory task, subjects were instructed to decide whether each presented item had been part of *any* of the two study lists. In the source memory task, they had to respond positively only if an item had been part of a specific study list (e.g., LIST 1). Previous studies have shown that source memory relative to item memory yields greater activity in several frontal regions (Nolde et al., 1998a; Henson et al., 1999; Rugg et al., 1999; Dobbins et al., 2002; Lundstrom et al., 2003), which can be related to increased demands on systematic retrieval control operations (Nolde et al., 1998b; Johnson and Raye, 2000; Cabeza et al., 2003), including monitoring (Henson et al., 2005) and cue specification processes (Fletcher et al., 1998) during source judgments, all of which conceivably depend on inhibitory and/or selection mechanisms.

To manipulate executive demands in working memory, we used two versions of the *n*-back paradigm, one-back and two-back (Cohen et al., 1994), which may be construed as ‘short-term’ source memory tasks. A number of previous studies have reported frontal and parietal activity increases during two-back relative to one-back task performance as well as parametric variations of *n* (Braver et al., 1997; Cohen et al., 1997; Jonides et al., 1997; Ragland et al., 2002), which presumably reflects the augmented load on control processes devoted to holding item and temporal information in working memory, and transient ‘updating’ of maintained representations (Smith and Jonides, 1999). Updating during the two-back task constitutes several subcomponents that become more critical or added relative to one-back, such as temporal coding and eliminating selective information from working memory (Morris and Jones, 1990; Jonides et al., 1997; Postle et al., 2001). Inhibition, monitoring and selection processes should be crucial for the updating function and for keeping track of item order, but also in the implementation of interference resolution during source judgments involving recent context-irrelevant items (e.g., items presented “three-back” in the two-back task) (Jonides et al., 1998; D’Esposito et al., 1999; Badre and Wagner, 2005).

Incrementing the executive requirements in the context of *n*-back paradigms and episodic retrieval tasks have been shown to modulate activity in similar PFC areas that could implicate the shared recruitment of domain general executive control mechanisms (e.g., inhibition and/or selection). The present within-study manipulation allowed us to more formally address this issue by directly comparing the activation patterns associated with increased executive demands within the domains of working and episodic memory.

Furthermore, a critical issue in this context is whether the neural consequences of greater executive control would be preferentially evoked at the (top-down) tonic ‘task set’ level, or during phasic stimulus-related item processing (Huettel et al., 2004). A control

effect at the task level could be induced by the added requirements to selectively attend and differentially respond to the items presented two-item back (two-back) or the items that had been part of a specific study list (source memory). Such incrementing demand for prolonged selective attention to task-relevant internal representations requires “the maintenance of a processing bias” (Wager and Smith, 2003), which at the neural level might translate into an elevated tonic top-down signal that persists throughout the task period (i.e., not specifically tied to stimulus-synchronous processing of individual items). Alternatively, the increased executive demands could primarily yield transient signal increases associated with executive control operations that are recruited on a trial-by-trial basis to comply with the presumably larger number of computations or more complex item processing required in the high-load conditions. Such transient effects may reflect executive processes that come into play in tasks that require more “active” search, retrieval and selection from memory, irrespective of whether the information to be retrieved is held online in working memory or stored in long-term memory (Moscovitch and Wincour, 2002; Petrides, 2002; Buckner, 2003). To examine the temporal dynamics of the fMRI BOLD signal with respect to sustained and transient responses, we used a mixed blocked/event-related design (Laurenti et al., 2003; Donaldson, 2004). This design allowed us to investigate the degree to which our manipulations of executive load would yield sustained control effects evoked throughout the task period versus transient stimulus-synchronous control effects. Of main interest was whether sustained and/or transient signal increases in response to increased executive demands would be common for episodic and working memory.

Methods

Subjects

Sixteen (8 male/8 female) healthy young adults (age range: 24–37) volunteered to participate in the study. All subjects were right-handed and had normal or corrected-to-normal visual acuity. The study was approved by the ethics committee at the University Hospital of Northern Sweden.

Task procedures

Prior to entering the scanner, subjects were seated in a secluded room and instructed to memorize a list of 16 words (LIST 1). Once more, after the subjects had been placed in the scanner they were instructed to memorize a new list of 16 words (LIST 2). Each word item was presented for 2 s, with an interval of 1 s between items. The study lists were presented twice successively and word order was randomized between presentations. No scanning was performed during word encoding. Subsequently, in the scanning sessions, BOLD signal changes were measured during two different types of episodic memory tasks, and two working memory tasks. All four task conditions were included in each of four sessions, in a pseudorandomized order that was balanced over sessions such that every task condition followed each other task condition equally often. Hence, altogether each four task conditions were performed four times. For all tasks identical stimuli in the form of single words was used. Stimuli were presented in white font on a black background. Each session began by the presentation of a small circle centered on a screen for 21 s prompting the beginning of a “resting” block. The subjects were instructed to relax while gazing

at the circle until a task cue (2.5 s) appeared which prompted the task to be performed. In addition to starting and ending each session, such “resting” blocks of 21 s were also interspersed between the task blocks. The task blocks lasted for 63 s, encompassing 8 stimulus items presented for 2.5 s with varying inter-trial intervals (ITIs) (see the Imaging analysis section). During the ITIs a centered fixation cross hair was presented. Each of the four sessions lasted for approximately 6 min (357 s). Subjects were instructed that response speed and accuracy were equally important.

Experimental tasks

Two episodic tasks were used: yes/no item memory and yes/no source memory (Yonelinas, 2002). In the former low-load task, single words (items) were presented and subjects were instructed to respond by pressing one of two keys with their left hand: “yes” if they thought the word was “old”, i.e., part of *either* of the two lists (LIST 1 and LIST 2); “no” if the word was “new”. The task cue for this condition read “RECOGNITION”. In contrast, the high-load source memory task required subjects to classify each presented word as to belonging to one *specific* list or not. Thus, subjects responded “yes” only if a word was identified as a member of the list indicated by the visual prompt initiating the task. This prompt read LIST 1 or LIST 2 (study lists were targets equally often). As two of the presented items corresponded to memorized words in the non-specified list, these, as well as new words, required subjects to generate a “no” response.

To manipulate executive demands for working memory, we varied n in the context of a verbal n -back paradigm, in which subjects are required to decide whether each presented word is identical to the word presented n items earlier (Kirchner, 1958). If the words matched, they responded by pressing a “yes” key of a response pad, if not they pressed a “no” key, corresponding to the response procedures in the episodic tasks. We used one-back and two-back tasks to index low-load and high-load demand, respectively. Task cues for respective task read “1-BACK” and “2-BACK”. For the two-back task, the first of the four task blocks always contained a “lure” item that were repeated within the same block, although not at the “target” position in the sequence (e.g., items presented three- or four-back).

The item-type ratio in all tasks were 3/8 for trials requiring a “yes” response (and 5/8 for trials requiring a “no” response). This disproportionate relation between items was due to the particular nature of the two-back task. Word items used in the experiment were repeated only in case of memory “match” or to introduce interference in source memory (corresponding to match with items of non-target list) and two-back (corresponding to match with items presented $n > 2$ items back).

fMRI data acquisition

Data were collected on a 1.5-T Philips Intera scanner (Philips Medical Systems, Netherlands). Functional T2*-weighted images were obtained with a single-shot gradient echo EPI sequence used for BOLD imaging. The sequence had the following parameters: echo time, 50 ms; repetition time, 3000 ms (33 slices acquired); flip angle, 90°; field of view, 22×22 cm, 64×64 matrix and 4.4 mm slice thickness. To eliminate signals arising from progressive saturation, five dummy scans were performed prior to the image acquisition. The word stimuli, ITI cross hair and “resting” circle were projected on the centre of a semitransparent

screen that the subjects viewed through a tilted mirror attached to the head coil. Behavioral performance (i.e., accuracy data and response time (RT) data) was handled by a PC running E-Prime 1.1 (Psychology Software Tools, Inc.). Prior to functional imaging, high-resolution T1- and T2-weighted structural images were acquired.

Behavioral analyses

In addition to recording behavioral measures for analyses of response accuracy and RT, subjective ratings of task difficulty in terms of mental effort were obtained after the scanning session. The subjects were asked to rate the effort associated with each task on a scale ranging from 1 (very low effort) to 5 (very high effort). These indices were analyzed to assess whether the manipulations of executive demands in episodic and working memory were subjectively experienced as representing increased effort of equal magnitude.

Imaging analysis

Functional imaging data were pre-processed in a number of steps prior to statistical analyses using the SPM2 software package (Wellcome Department of Cognitive Neurology, London, UK) on Matlab 6.5.1 (Mathworks Inc., Sherborn, MA). All image volumes were first corrected for variability in slice timing acquisition. Image realignment to the first volume was then performed using a truncated sinc interpolation. The image volumes were then normalized to an approximate Talairach space (Talairach and Tournoux, 1988) as defined by the SPM2 T1-weighted MNI template and finally smoothed with an isotropic 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

In mixed blocked/event-related designs the regressors modelling item-related responses will invariably exhibit some correlation with their corresponding epoch-related regressor. A high degree of correlation indicates a low parameter estimation efficiency (Otten et al., 2002; Visscher et al., 2003). In the present study, we sought to de-correlate the item and epoch regressors by introducing a jittering of the intervals between consecutive stimuli within each task block. The stimulus onset asynchronicity (SOA) was pseudorandomized between 2.5 and 25 s according to an approximate Poisson distribution (i.e., for approximately 60 % of the items, the SOA was 2.5 s, for 30 % of the items, the SOA was 20 s and only for a minority of items, the SOA was 22.5 (9 %) or 25 (1 %) s long), such that the correlation between item and epoch-related regressors did not exceed 0.6. This degree of correlation allows a reasonably efficient estimation of item- and epoch-related activity, while at the same time not compromising the test properties. Given that ITIs were of unpredictable length and that the majority of ITIs were very short, we believe that the risk for initiating ‘off task’ mental activities rather than maintaining a state of advance preparation for the next item was kept to a minimum even though the longest ITIs were of similar duration as the “resting” periods between task blocks. Importantly, the latter also differed with respect to the symbol displayed at the screen in order to make sure that subjects did not confuse the two such that they expected a stimulus occurrence during “resting” blocks.

Sustained and transient effects were separately modelled in the framework of the general linear model (GLM) (Friston et al., 1995) as implemented in SPM2. Item-related transient responses were modelled as regressors containing delta functions representing onsets of the stimuli whereas epoch-related sustained responses were modelled with a boxcar function (Friston et al., 1998b). In the

main analysis, both regressor types were convolved with a canonical hemodynamic response function (HRF) as implemented in SPM2.

Applying the general linear model to the data resulted in least square estimates of all regressors on a subject-specific level averaged across the four sessions. Effects of interest were calculated as linear combinations of the individual regressors and stored as subject-specific contrast images. All statistical inferences were based on contrast images (statistical parametrical maps, SPMs) from sixteen subjects that were entered into a second-level model (one sample *t*-tests) for each effect of interest, yielding a random effects analysis (Holmes and Friston, 1998).

SPMs were generated for both sustained and transient neural activity changes in all task conditions. The critical contrasts involved high- versus low-load conditions for episodic and working memory, respectively. Statistically significant BOLD signal changes were identified for each high- versus low-load contrast (i.e., two-back versus one-back for working memory, and source versus item memory for episodic memory) in terms of both sustained and transient effects. For the transient effects different item response-types (i.e., hits, misses, correct rejections and false alarms) were collapsed within each task condition and analyzed together. For each main effect, statistical significance was thresholded at $p < 0.001$ uncorrected. The degree of regional overlap between working and episodic memory in the context of different temporal profiles of control-modulated neural responses was assessed by employing separate intersection analyses for the sustained and transient load effects. Specifically, overlapping BOLD response increases were indexed by first submitting each of the two (high versus low) load contrasts from each individual subject to a repeated-measures ANOVA (within subjects). This procedure allowed each pair of executive load main effects (working memory vis-à-vis episodic memory for sustained and transient effects, respectively) to be interrogated for commonalities using a conjunction analysis, thresholded at $p < 0.001$ uncorrected, with a cluster extent of at least 10 contiguous voxels (testing the conjunction null hypothesis) (Nichols et al., 2005). We applied a masking procedure to make sure that the obtained measures of load-dependent increases were not attributable to a significantly reduced response in the low-load condition relative to baseline, whereas the response in corresponding high-load condition might not differ from baseline. Hence, to certify that load effects were associated with positive BOLD signal changes in respective high-load condition each SPM resulting from a high- to low-load contrast was inclusively masked with the SPM yielded from subtracting the resting baseline from corresponding high-load condition, thresholded at $p < 0.05$, uncorrected.

Additionally, we conducted a brain-behavioral analysis to examine the relationship between regions showing common load effects and RT differences associated with increased executive demand in respective domain. The correlation between load-dependent increases in RT (low-load average RT subtracted from high-load average RT for each individual) and regional load effect (average beta value difference between high and low task for each individual in respective domain) was calculated to obtain indices of the way effort/global difficulty might contribute to the results.

Additional 'validation' analysis

A critical issue regarding the separation of sustained and transient brain activity in mixed designs concerns the adequacy by which the item-related BOLD impulse response is modelled. It has been demonstrated that insufficient modelling of item-related

responses may cause misattribution of 'true' transient effects to the sustained effects (Visscher et al., 2003). In order to evaluate whether such confounds might have affected the present results in any significant way we conducted an additional analysis to specifically explore the likelihood of "impurity" in the sustained effects. The reason for modelling the item-related BOLD signal with a canonical HRF alone in the main analysis was to optimize the sensitivity (i.e., the probability of detecting load-dependent increases in sustained and transient responses, respectively) rather than optimizing estimation efficiency.

The validation analysis was performed using partial derivatives of the canonical HRF, with respect to onset time (temporal derivative) and peak duration (dispersion derivative) (Friston et al., 1998a), which have been shown to capture significant variability related to item responses that do not fit the canonical model (Henson et al., 2001). Applying the canonical HRF combined with its partial derivatives cover almost exclusively the additional variability in item responses that is accommodated by utilizing basis sets of delta functions that have no a priori assumptions regarding the shape of the hemodynamic response (i.e., the finite impulse response or FIR approach) as shown by Henson et al. (2001). In a first step, we created a tripartite set of item-related activation maps for each of the two load contrasts, modelling the BOLD response by the canonical HRF, and its temporal and dispersion derivative, respectively, as implemented in SPM2. Subsequently, the peak coordinates from the conjunction of sustained load effects (main analysis) were interrogated for transient load effects in the activation maps yielded by respective derivative. We examined potentially confounding transient effects for episodic and working memory separately since a misapplied effect in any one domain might result in spurious commonalities. It is assumed that this additional analysis should provide a reliable basis for identification of tentative contamination within the pattern of common sustained increases revealed in the main analysis. The statistical threshold was set to $p < 0.005$ uncorrected. Importantly, any region revealed to show transient effects by this procedure might still remain perfectly valid as regards their alleged sustained effect. In order to further delineate the risk for confounding effects the actual temporal profile(s) accommodating select regions were investigated, allowing inspection of the BOLD time course associated with the different tasks.

Results

Behavioral performance

The results from the working memory tasks showed a slightly lower accuracy [$t(15)=0.49$ ($p > 0.7$)] in the two-back task [$M=0.95$, $SD=0.05$] than in the one-back task [$M=0.96$, $SD=0.04$], whereas the RT was significantly slower [$t(15)=2.81$ ($p < 0.02$)] in the two-back task [$M=1001$ ms, $SD=106$] than in the one-back task [$M=920$ ms, $SD=99$]. Importantly, the two-back task was rated as significantly more difficult than the one-back task [$M=2.7$ (0.6) versus $M=1.2$ (0.4), $t(15)=12.33$ ($p < 0.001$)]. The results from the episodic memory tasks showed that accuracy was significantly lower [$t(15)=4.23$ ($p < 0.001$)] in the source task [$M=0.79$, $SD=0.14$] than in the item task [$M=0.90$, $SD=0.07$], and that the RT was slower, but not significantly so [$t(15)=1.00$ ($p > 0.4$)], in the source task [$M=1224$ ms, $SD=143$] than in the item task [$M=1189$ ms, $SD=143$]. Also, the source task was rated as significantly more difficult than the item task [$M=3.2$ (1.4)

versus $M=2.1$ (1.0), $t(15)=4.89$ ($p<0.001$]). Collectively, these results show that the manipulation of executive demands was effective for both episodic and working memory.

Control modulation of transient fMRI activity

Working memory

Transient BOLD signal increases during item-related processes of the two-back compared with the one-back task were observed in several frontal and parietal regions, including left dorsolateral PFC (DLPFC), anterior cingulate cortex (ACC), orbitofrontal PFC, bilateral superior parietal areas near the intraparietal sulcus (IPS) and medial precuneus. Other sites showing transient load effects included the left caudate nucleus, the hippocampus and the bilateral lingual gyrus (data not shown).

Episodic memory

Regions associated with robust transient BOLD signal increases during source memory relative to item memory were found in DLPFC and ventrolateral PFC of the right hemisphere and bilateral pre-supplementary motor areas. Additional sites associated with transient load effects were primarily located in the right hemisphere, including posterior IPS, precuneus, anterior temporal pole and posterior parahippocampal gyrus (data not shown).

Overlap

A direct comparison of the transient effects associated with the high- versus low-load contrasts for episodic and working memory, respectively, revealed no overlap in frontal areas. Overlapping transient increases were found in a right posterior area along the IPS in the posterior precuneus/occipital lobe (Brodmann's area [BA] 7/19; MNI peak coordinate in conjunction, $x=34$, $y=-74$, $z=28$; $t=8.30$, 91 voxels; corresponding t values for respective contrast entering the conjunction, working memory load [WM], $t=8.30$; episodic memory load [EM], $t=8.42$). Common transient effects were also demonstrated in the right lingual gyrus, near the calcarine sulcus (BA 17/18; peak, $x=8$, $y=-80$, $z=-6$; $t=5.56$, 26

voxels; WM, $t=5.56$; EM, $t=6.25$), the right fusiform gyrus, near the anterior occipital sulcus (BA 19/37; peak, $x=30$, $y=-72$, $z=-8$; $t=5.50$, 29 voxels; WM, $t=5.50$; EM, $t=5.70$), as well as the brain stem, in the topographical vicinity of the locus ceruleus (peak, $x=-2$, $y=-36$, $z=-34$; $t=5.16$, 26 voxels; WM, $t=5.16$; EM, $t=5.32$) (see Fig. 1).

Control modulation of sustained fMRI activity

Working memory

The two-back relative to the one-back task showed the greatest sustained BOLD response increases in the left superior frontal gyrus, right premotor cortex, bilateral inferior parietal cortex and a right superior parietal area, as well as the left cerebellum (data not shown).

Episodic memory

The direct comparison of source memory relative to item memory revealed prominent sustained BOLD signal increases in bilateral superior frontal regions, right anterior IPS/precuneus, the striatum and several subregions of the cerebellum (data not shown).

Overlap

A direct comparison of the sustained patterns evoked in each high- versus low-load contrast revealed common sustained increases in a set of widely distributed regions including the right superior parietal cortex (BA 7; peak, $x=40$, $y=-68$, $z=52$; $t=5.54$, 54 voxels; WM, $t=8.30$; EM, $t=8.42$), the left DLPFC (BA 46/9; peak, $x=-46$, $y=30$, $z=30$; $t=4.26$, 10 voxels; WM, $t=5.47$; EM, $t=4.26$), the medial frontal cortex/dorsal ACC (BA 32/8; peak, $x=-4$, $y=28$, $z=46$; $t=4.75$, 19 voxels; WM, $t=5.08$; EM, $t=4.75$), the right caudate nucleus (peak, $x=16$, $y=-6$, $z=18$; $t=4.71$, 26 voxels; WM, $t=5.03$; EM, $t=4.71$) and the bilateral regions in the cerebellum (peaks, $x=-14$, $y=-78$, $z=-28$; $t=5.05$, 19 voxels; WM, $t=5.05$; EM, $t=5.46$, and $x=8$, $y=-72$, $z=-24$; $t=5.03$, 12 voxels; WM, $t=5.09$; EM, $t=5.03$) (see Fig. 2). An illustration of

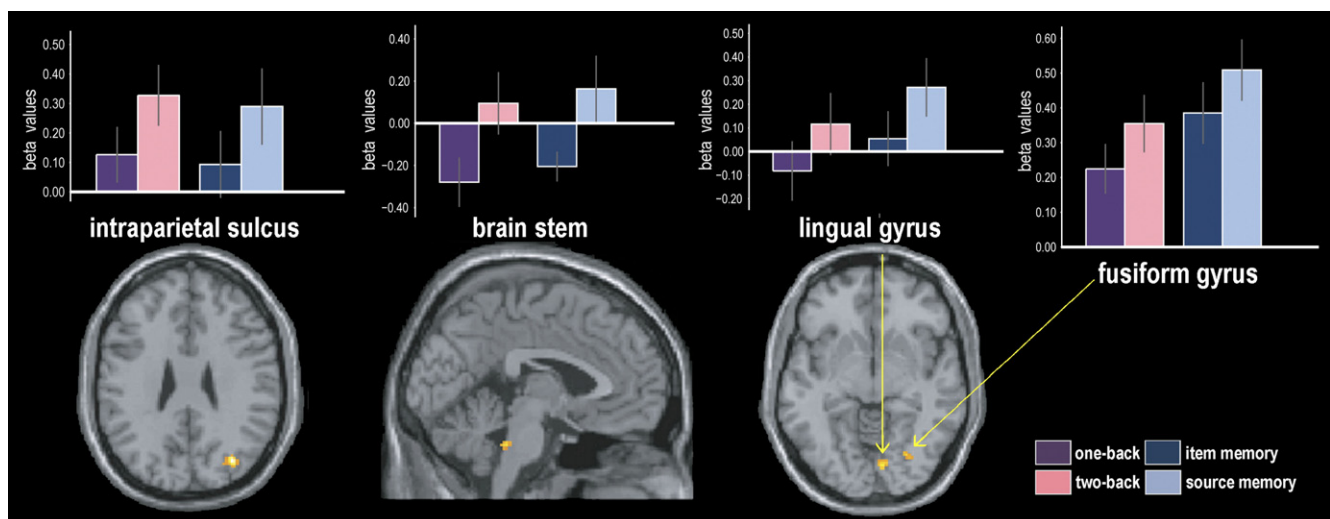


Fig. 1. Common transient BOLD response increases based on a conjunction analysis of respective high relative to low-load comparison. Overlapping transient effects are mapped on to transverse or sagittal sections of a canonical brain (for MNI coordinates, see the Results section). The conjunction analysis is thresholded at $p<0.001$ uncorrected, with an extent threshold of 10 contiguous voxels. Mean beta values (and standard error) over subjects are plotted for individual tasks in each brain region showing domain general increases in transient activity as a function of load (for MNI coordinates, see the Results section).

task-related sustained time courses in the DLPFC region is depicted in Fig. 3a. The validation analysis substantiated the main results by showing that the majority of regions associated with sustained increases were not additionally related to transient increases when taking into account temporal and dispersion derivatives of the canonical HRF. Only three regions yielded findings indicative of such confounding, all of which were associated with the dispersion derivative ($p < 0.005$, uncorrected). Potential misattribution of transient effects to sustained effects was implicated in the left cerebellum in association with episodic memory ($t = 3.26$, $p < 0.003$). No transient cerebellar effect was seen for working memory ($p = 0.31$). The right superior parietal cortex showed a significant load effect for episodic memory ($t = 2.94$, $p < 0.005$) and a strong trend in the same direction for

working memory ($t = 2.51$, $p = 0.0051$), which taken together suggest that this area might equally well be characterized in terms of a transient load effect. In the right caudate nucleus a transient load effect was seen for episodic memory ($t = 2.96$, $p < 0.005$), whereas for working memory there was a non-significant trend towards a transient effect ($t = 2.51$, $p < 0.02$). Inspecting the item-related time courses of the neural activity elicited in the caudate nucleus in respective task indicates that it might still be correctly referred to as exhibiting a common sustained load effect, with an additional transient effect signified by a peak of greater width (see Fig. 3b). For the item-related time courses displayed in Fig. 3b, other regressors were not corrected for. This approach yields a crude approximation of the relative magnitude of sustained responses in the caudate nucleus (at the time of stimulus onset) for

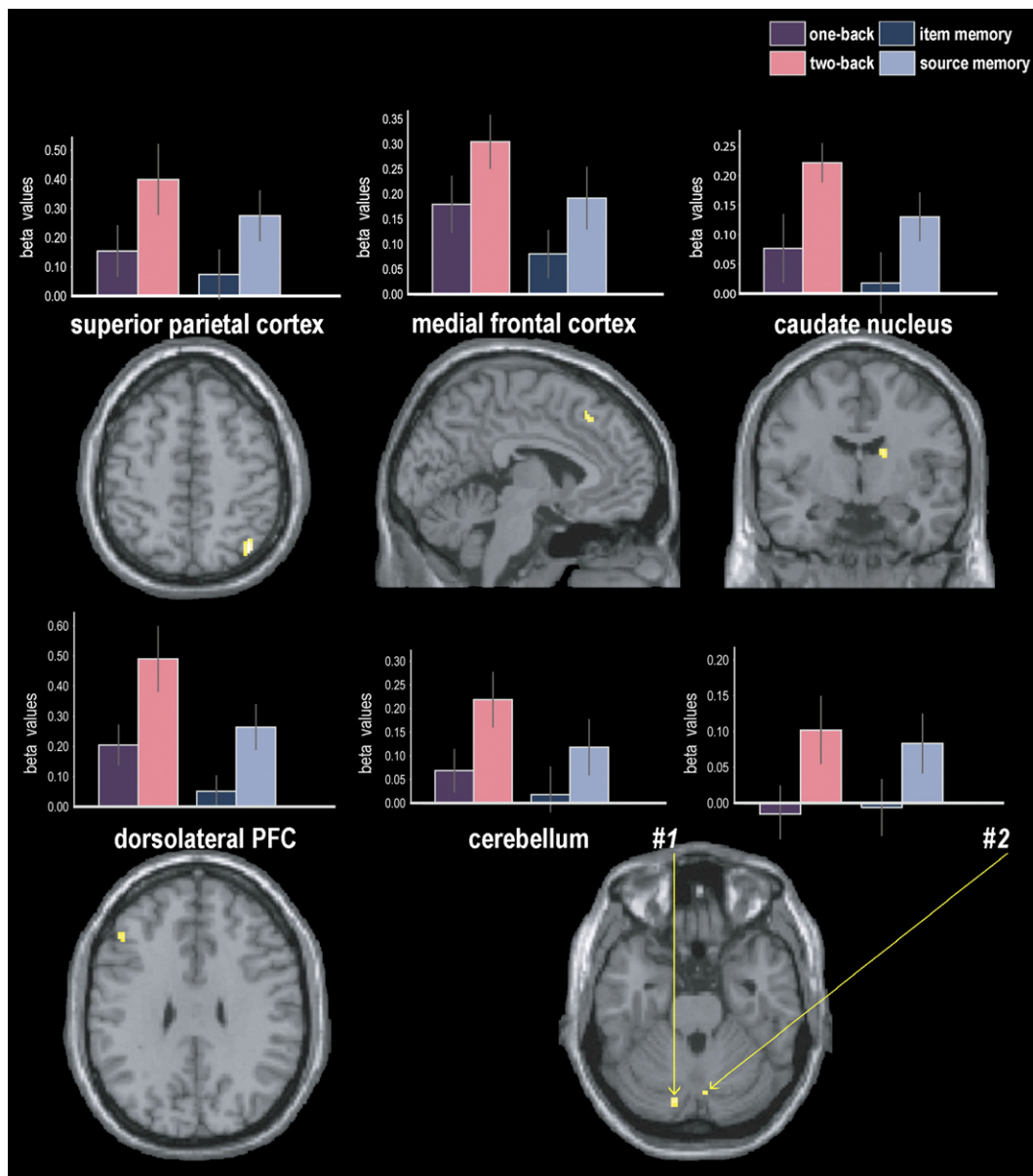


Fig. 2. Common sustained BOLD response increases based on a conjunction analysis of respective high relative to low-load comparison. Overlapping sustained effects are mapped on to transverse, coronal or sagittal sections of a canonical brain (for MNI coordinates, see the Results section). The conjunction analysis is thresholded at $p < 0.001$ uncorrected, with an extent threshold of 10 contiguous voxels. Mean beta values (and standard error) over subjects are plotted for individual tasks in each brain region showing domain general increases in sustained activity as a function of load (for MNI coordinates, see the Results section).

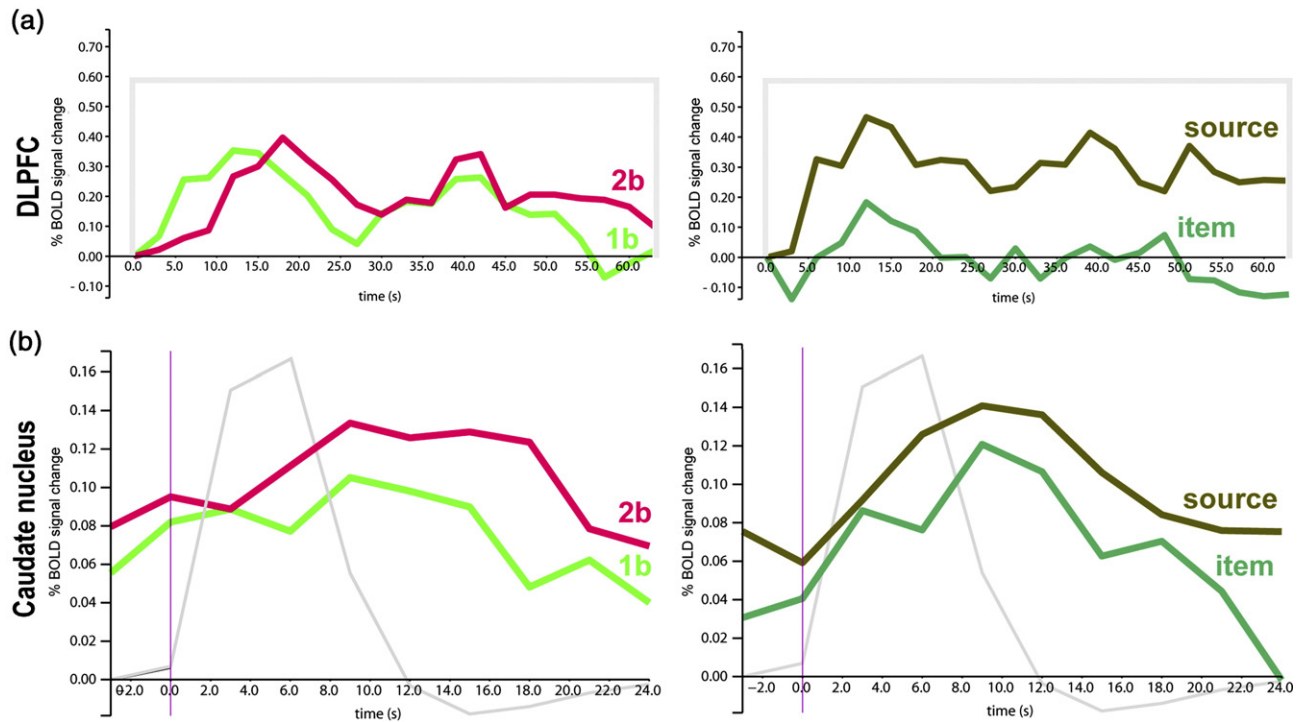


Fig. 3. (a) Average sustained time courses across task blocks are displayed for the left DLPFC region. (b) Average item-related time courses are depicted for the right caudate nucleus (with the canonical HRF displayed in grey).

each task, in addition to concurrent item-related transient increases. However, for these three regions some caution is in place regarding functional interpretations related to tonic control components.

Brain-behavior correlation analysis

It was found that none of the regions showed a significant correlation for these brain-behavior indices in either domain. For the majority of regions, the correlation was even below $R^2=0.05$. These results would argue against an interpretation of the reported common load effects in terms of brain responses evoked by increased effort *per se*. Instead this null finding provides support for domain general executive control as the critical factor giving rise to the present fMRI findings.

Discussion

Increased executive demands were found to be associated with robust neural effects in multiple brain regions. For the working memory *n*-back manipulation, sustained and transient increases were noted in several regions, notably within dorsal frontal cortex (cf. Cohen et al., 1997). Sustained and transient frontal activity increases were also evoked by the executive load manipulation in episodic memory (cf. Velanova et al., 2003). In addition, several posterior and subcortical areas were modulated with increased executive demand in each domain. These findings, together with the pattern of behavioral results, suggest that the manipulations of executive demands were effective.

Of central interest was the assessment of overlap in regions responsive to executive demands for working and episodic memory. We did not observe any significant overlap for transient brain activity in frontal regions, indicating that the stimulus-

synchronous processing demands that were induced or further enhanced by incrementing executive load were mediated by differential frontal circuitry in respective domain.¹ This is consistent with evidence from neuropsychological focal lesion studies on frontal patients which indicate that different frontal regions are responsible for different executive functions (Stuss et al., 2002).

Phasic executive control components

The most pronounced effect among regions demonstrating common enhanced transient activity was seen in the right posterior parietal cortex (at the caudal end of the IPS near the transverse occipital sulci and precuneus; BA 7/19). Although generally associated with different aspects of visual attention (Wojciulik and Kanwisher, 1999), several lines of evidence converge on a fundamental role for posterior parietal cortex in (sensory-independent components of) executive control. For example, a positron emission tomography (PET) study that attempted to isolate executive processes from working memory storage found that 'on-line' manipulation of items, in the absence of storage

¹ It is important to note that the present analyses of item-related BOLD responses were based on *all* trial types collapsed for each task condition. Hence, common transient increases in the context of high relative to low-load conditions are preferably related to the awareness/expectancy that the processing of each item *may* require proactive interference resolution (or other control processes) and should not be taken to reflect the relatively few trials that necessitated the factual realization of certain executive control processes. The inclusion of sufficient items to isolate the neural processes underlying trials explicitly requiring the implementation of interference resolution mechanisms would potentially have allowed us to identify overlapping transient increases in frontal circuitry previously reported in the literature (Badre and Wagner, 2005).

demands, was associated with robust activation in bilateral regions of IPS (BA 7) (Collette et al., 1999). Furthermore, a recent PET study that examined brain activity across multiple tasks ascribed preferentially to either of three executive functions, updating, shifting and inhibition (after subtracting from each an appropriate control task), revealed a common recruitment of bilateral areas in the posterior parietal cortex (including right IPS) for all tasks (Collette et al., 2005). In terms of specific executive functions, the relative contribution of IPS was found to be biased toward shifting and inhibition (Collette et al., 2005). Converging evidence in support of a generic role of IPS in executive control comes from a meta-analysis on 60 working memory imaging studies (Wager and Smith, 2003). The meta-analysis revealed a right-hemispheric area in the anatomical proximity of our transient parietal activation to be the only region (together with its left-hemispheric homologue) to exhibit a material-independent effect of executive demand across all executive functions indexed; manipulation, updating and temporal order memory (Wager and Smith, 2003). Taken together, these findings strongly indicate that previously reported load effects in posterior parietal areas in working memory *n*-back and item-recognition paradigms (e.g., Braver et al., 1997; Ravizza et al., 2004) could relate to manipulation/executive control processes, rather than to storage or a more general attention component.

Of special interest to the present finding might be the association of IPS with temporal order processing (Wager and Smith, 2003). Several imaging studies have found activity in the right IPS during digit comparison and other number processing tasks (e.g., Chochon et al., 1999) and damage to the right IPS causes a highly selective impairment in the ability to make use of temporal order and other types of quantitative information for judgments (Dehaene and Cohen, 1997). A PET study of episodic memory that compared brain activity during temporal-order retrieval relative to item retrieval (Cabeza et al., 1997) and an event-related fMRI study that compared high versus low demand for temporal-order retrieval (Konishi et al., 2002) found parietal activity increases very similar to the present foci. Consistent with these findings, the parietal cortex has also been associated with orienting attention to temporal dimensions (Coull and Nobre, 1998). These results point to the possibility that IPS plays a critical role in processing and coding of order information and temporal relations (Petrides, 1994). In the present experiment, specification of temporal context/order information should be a critical aspect during source judgments in high load, but not low-load conditions, regardless of whether information is to be retrieved from working or episodic memory stores. Toward this end, inhibitory control processes/selective attention promotes internal shifting between active representations in the service of filtering out or updating relevant input for source monitoring. This process presumably ensues until a sufficient temporal discrimination can be reached upon for a context-appropriate response to be made. Specifically, phasic interactions between these executive processes would provide dynamic top-down guidance in the context of all items eliciting immediate and strong “familiarity” signals. Two-back and source memory share the feature that item familiarity promotes a prepotent veridical response tendency, requiring inhibitory mechanisms to hold or override potentially erroneous responding, while internal shifting between context or item information might be carried out for verification purposes. This would be consistent with the key association between IPS and inhibition/shifting implicated in the study by Collette et al. (2005). In line with this reasoning, a recent study comparing brain activity for multiple

types of attention shifts (e.g., internal versus external) demonstrated IPS to be preferentially recruited for internal shifts (Wager et al., 2005). Assuming that part of right posterior parietal cortex participates in cognitively demanding tasks by imposing a context-appropriate ‘focus of attention’ capable of dynamically switching between mental space and the external world could explain findings from cross-functional fMRI studies yielding overlapping activity in IPS between tasks of verbal working memory and covert spatial attention (LaBar et al., 1999; Pessoa and Ungerleider, 2004).

Tonic executive control components

A more distributed pattern of common regional increases in response to executive load was noted for the sustained BOLD response, which involved left-hemispheric DLPFC, medial frontal cortex and right-hemispheric regions of the striatum and superior parietal cortex, as well as bilateral cerebellar regions. The medial frontal cortex and right superior parietal cortex are both generally ascribed to top-down attentional control processes that involve a tonic component, such as performance or conflict monitoring (Carter et al., 1998; Botvinick et al., 2001; Ullsperger and von Cramon, 2004) and sustained, focused and selective attentional orienting (Corbetta et al., 2000; Sarter et al., 2001), respectively.

Recruitment of the performance-monitoring function posited to rely on the ACC should be expected to up-regulate with increased executive demands, and this notion has received much indirect support from consistent findings of a strong positive relationship between ACC responses and task difficulty (Paus et al., 1998; Duncan and Owen, 2000; Fu et al., 2002) in both working memory (Barch et al., 1997) and attention domains (Corbetta et al., 1991). Notably, recent proposals suggest that greater medial frontal activity in the ACC may be preferentially associated with elevated arousal rather than working memory load *per se* (cf. Luu and Posner, 2003), and the dorsal ACC has been indicated as a key modulator of intrinsic arousal levels, thus mediating a context-appropriate bodily arousal state (Critchley et al., 2003). In healthy subjects, effortful cognitive processing engenders increases in general arousal, whereas in patients with lesions encompassing the medial frontal cortex this is not the case (Critchley et al., 2003), although they retain predominantly normal performance on executive and attentional tasks (Fellows and Farah, 2005; Baird et al., 2006). In a similar vein, the right-hemispheric parietal cortex has also been closely linked with tonic alertness (Sturm and Willmes, 2001).

Interestingly, the three other regions associated with domain general tonic control, the DLPFC, the striatum and the cerebellum, have recently been discussed together in the context of executive control (e.g., Casey, 2005) and their conjoint load-dependent sustained activation in the present study deserves special consideration. Theories attempting to characterize the functional significance of the basal ganglia and the cerebellum in terms that go beyond motor control have a very brief history. It is only during the last 10 years that a putative role in higher order functions has been attributed to these structures, and the precise nature of their involvement in cognitive operations remains unclear. Current views drawing on clinical and neuropsychological evidence (Owen et al., 1993; Rogers et al., 1998; Ravizza and Ivry, 2001; Ravizza and Ciranni, 2002) and anatomical connections (Alexander et al., 1990; Middleton and Strick, 1994; Saint-Cyr, 2003) implicate that the striatum (the caudate nucleus) and the cerebellum might

support prefrontal top-down mechanisms underlying control of task set and context processing. The common sustained activity increase in frontostriatal–cerebellar ‘circuitry’ may reflect a shared tonic executive component whose *modus operandi* is called upon to down-regulate processing dissonance among neurocomputational resources. By means of top-down biasing mechanisms, something akin to complementary ‘boosting’ and ‘insulation’ of context-relevant processing pathways (and mental representations) might sustain parsing of critical component processes from more salient, but irrelevant ones to secure accurate performance during executively demanding mental challenges. This would be achieved in a fashion analogous to increasing “signal-to-noise” ratio (with ‘noise’ denoting distracting elements, the attendance to which engenders task interference). Such a tonic top-down mechanism might tentatively represent a candidate neural substrate corresponding to the shared variance seen among nine executive tasks, selectively indexing either shifting, updating or inhibition, in a latent-variable analysis conducted by Miyake and colleagues (Miyake et al., 2000). This posited ‘unitary’ and multi-purpose control mechanism relates to the concept of *context processing* (Cohen and Servan-Schreiber, 1992; Miller, 2000; MacDonald et al., 2005) and might in the current experiment have been instigated to deal with the augmented need for selective attention among task-relevant representations retained ‘on-line’. During maintenance phases of the two-back task, immediately after updating the contents of working memory, an endogenous shift of focus to the item that was presented “two-back” may occur. Thus, the relevant item could be selectively attended to in anticipation of the next stimulus, while the most recently presented “one-back” item would be retained in the background of the temporary buffer until the next updating. Such a strategy might be beneficial with regard to processing efficiency and has recently been discussed in the context of *n*-back paradigms (Verhaeghen et al., 2004). In the source memory task, a similar mechanism of selective attention among internal representations may have been recruited to maintain and enforce the appropriate ‘retrieval orientation’ (Rugg and Wilding, 2000), thereby promoting advance biasing of item-related mnemonic processing in favor of information encoded in the relevant context and suppressing the irrelevant context. Furthermore, additional refreshing or updating of the currently non-prioritized context or item (entailing [inverse] relevance as far as being tagged ‘not appropriate’) might occasionally be necessary during demanding ITIs that could require more periodic signals. Thus preventing the decay of intentionally suppressed information might in case of failure have the counterintuitive effect of increasing the interference potential in subsequent encounters with the misplaced information. The neural implementation of the putative control processes implicated above could likely depend on the type of selective gating mechanism that has been ascribed to dynamic frontal-basal ganglia interactions (e.g., Frank et al., 2001).

A context processing interpretation of the common sustained effect evoked in left DLPFC (BA 46/9) and the concurrent sustained and/or transient effect in the caudate nucleus resonates well with many neurocomputational models of cognitive control and working memory in which dopaminergic modulations promote top-down biasing of relevant information processing and updating via frontostriatal circuitry (Cohen and Servan-Schreiber, 1992; Durstewitz et al., 1999; Braver and Barch, 2002; Durstewitz and Seamans, 2002; Ashby et al., 2005; Hazy et al., 2006). The co-activation of DLPFC and the striatum is consistent with extensive anatomic connections between the frontal lobes and basal ganglia,

including dense projections from DLPFC to the striatum (Alexander et al., 1990; Levitt et al., 2004). Moreover, it has been shown that the degree of maturation in frontostriatal projection fibres, presumably reflecting the integrity of functional connectivity between these areas, is correlated with task performance efficiency, and importantly this association apparently become stronger with increased executive task demands (Liston et al., 2005). Prior observations from human neuroimaging studies also corroborate a generic role of the striatum in executive control of memory processing by demonstrating conjoint activation of the caudate nucleus and PFC in association with working memory manipulation relative to item retrieval (Lewis et al., 2004) as well as accurate source memory retrieval (Cansino et al., 2002).

Previous brain imaging studies using a cross-functional approach to investigate executive control and memory processes have typically noted common activation of the left DLPFC (BA 44/9/46) in direct comparisons of working memory and long-term memory (Cabeza et al., 2002; Nyberg et al., 2003) and across diverse executive functions such as inhibition, updating, shifting, interference control and task coordination (Derrfuss et al., 2004; Collette et al., 2005). However, the present study is the first to allow the examination of the relationship between domain generality *and* executive load-effects on DLPFC activity in terms of sustained and transient signal increases. Intriguingly, in a recent mixed blocked/event-related fMRI study, a closely corresponding focus in DLPFC [peak, $x=-44$, $y=16$, $z=26$] was found to exhibit transient item-related activity across two-back, episodic recognition and semantic classification, but no sustained activity (Marklund et al., 2007). An inspection of the present data set with respect to the transient main effect for each of the four memory tasks (relative to the ‘resting’ baseline) replicated the previous finding of Marklund et al. (2007) by showing a common item-related activity for all tasks [peak from a conjunction analysis, $x=-48$, $y=18$, $z=26$, $p<0.001$] bordering the reported sustained activity cluster in DLPFC. However, rather than postulating a concurrent role of the DLPFC in phasic component processes shared by diverse cognitive challenges (independent of task load) and tonic control processes uniquely exploited in situations of high executive load, it is hypothesized that the same underlying cognitive operation is responsible for both of these seemingly divergent neural processes. Cohen et al. (1997) have indicated that the segregation between executive control and working memory maintenance processes may not be as clear-cut as proposed by some authors (e.g., Teuber, 1955; Smith and Jonides, 1999) and posited that DLPFC contributions to active maintenance may entail transient control signals that help maintain representations stored in posterior cortices in an active state. They argued that “if the control signal were generated sufficiently often (and more so at higher levels of load), it might produce a pattern of sustained, load-sensitive activation within PFC as measured by fMRI” (Cohen et al., 1997, p. 606). In a similar vein, we propose that the apparently tonic control signal seen in DLPFC actually reflects transient ‘refreshing’ operations (Johnson, 1992; Raye et al., 2002; Johnson et al., 2003). A refreshing mechanism could be triggered periodically during the longer ITIs to promote internally generated cue signals biasing ‘on-line’ (context and item) representations in accord with current task priorities. This view receives support from findings of cue-related activity in a similar left DLPFC region (center of mass in Talairach coordinates: MacDonald et al., 2000 [$x=-41$, $y=18$, $z=28$], and Weissman et al., 2005 [$x=-41$, $y=18$, $z=30$]), which was assumed to reflect top-down biasing of

attention toward task-relevant items). However, it has been argued that the control process(es) carried out by the DLPFC, although contributing to the selection of task-relevant information, might operate on a more abstract representational basis than stimulus or item-related mnemonic information *per se* (e.g., Brass and von Cramon, 2004). This control might entail ‘prospective’ context-integrative codes subsuming the priorities and ‘means-end’ agenda by which relevant systems and ‘on-line’ representations are “tagged” to guide immediate or future behavior (Marklund and Nyberg, *in press*). In the current experiment, such implementation would determine task-relevant properties on the basis of prioritized versus non-prioritized temporal context (e.g., item “two-back” versus “three-back” or “one-back” and context “LIST 1” versus “LIST 2”) combined with the appropriate set of ‘if-then’ rules (Passingham, 1993). Hence, this putative higher order selection mechanism would act to specify and boost task-relevant representations and item-specific processing in an abstract context-integrative manner (Marklund and Nyberg, *in press*), both on a trial-by-trial basis (relatively independent of load) and by periodically refreshing the context during delay periods in tasks involving high executive requirements.

The cerebellum has been found to be activated in several imaging studies of working memory (Awh et al., 1996; Klingberg et al., 1996; Schumacher et al., 1996) and episodic memory (Buckner et al., 1998; Andreasen et al., 1999), and it has become increasingly clear that the functional contributions of the cerebellum is not limited to motor control (Schmahmann, 1996; Desmond and Fiez, 1998) but may extend to cognitive control. A general role of the cerebellum in attentional control has been proposed by some authors (Allen et al., 1997; Townsend et al., 1999; Gottwald et al., 2003). Cerebellar lesions are known to produce cognitive deficits linked to covert attention-shifting (Akshoomoff and Courchesne, 1992), with the most pronounced effects in speeded tasks requiring rapid switching of selective attention (Courchesne et al., 1994; Ravizza and Ivry, 2001). This inspired a functional account of the cerebellum in terms of a global preparatory role based on predictive mechanisms (Courchesne and Allen, 1997). According to this view, the cerebellum acts to ‘optimize’ the internal configuration of context-relevant neural computations in advance of task execution. The fact that cognitive performance is reduced, rather than abolished, following cerebellar damage, and selectively concerns effortful and speeded tasks of divided attention and working memory has been attributed to the disruption of this preparatory process (e.g., Courchesne and Allen, 1997). Similarly, the domain general enhancement of sustained activity with increased executive demands seen in the present study endorses a role of the cerebellum as a ‘supportive system’ promoting coordination of attention and anticipatory control in resource-demanding tasks.

Conclusions

The present manipulations of executive demand in episodic and working memory suggest a high degree of differential functional organization among recruited phasic and tonic executive control components as well as other non-executive task components. Nevertheless, the principle of domain generality (often implicitly ascribed to executive control functions) was also represented in the evoked brain patterns, implicating executive ‘core’ mechanisms subsumed by shared circuitry exhibiting

generic transient or sustained control modulation across domains. It was hypothesized that the transient right IPS activity might convey phasic inhibition/shifting of the ‘focus of attention’ in complex tasks that require a dynamical interface between stimulus and mnemonic information (e.g., source judgments) prior to response selection (e.g., Corbetta and Shulman, 2002). The sustained activity observed in a common frontostriatal–cerebellar ‘circuitry’ might reflect a unitary executive control mechanism (cf. Miyake et al., 2000) responsible for top-down biasing of context processing in resource-demanding tasks (e.g., Cohen and Servan-Schreiber, 1992; MacDonald et al., 2005). The extent to which the common load-sensitive regions generalize across a broader array of functional demands, beyond the memory domains investigated here, remains to be answered by empirical inquiry in the future. As such, our results provide empirical support for theoretical models of executive functions that posit both unity and diversity among executive control processes (Miyake et al., 2000), while explicating the usefulness of mixed designs as to dissociating temporal dynamics of the neural mechanisms underlying cognitive (control) processes.

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