Preparation for integration: the role of anterior prefrontal cortex in working memory

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The execution of complex working memory tasks often requires various cognitive control operations on stored content. Here we focus on the integration operation – defined as merging the outcome of subtask processing with additional information actively maintained before and during subtask execution. In prior work, we identified the anterior prefrontal cortex as critical for integration during mental arithmetic. Here we replicate and extend these results in an adapted mental arithmetic task that enabled examination of the detailed temporal dynamics of the anterior prefrontal activation. We find that this region is involved in the preparation for integration, possibly by ensuring that goal-relevant information is maintained in an accessible form, while at the same time protected from subtask interference. *NeuroReport* 19:15–19 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Working memory (WM) is a primary cognitive construct that allows temporary storage and manipulation of task relevant information [1]. Much work in neuroscience has examined the neural mechanisms that enable WM storage [2–4]. More recent studies have focused on the specific control processes that operate on the contents of WM, such as manipulation or transformation of stored information in accordance with task demands [5].

In this study we focus on the control operation of integration, defined as a process that combines the results of subtask processing with other information that is already stored in WM. Integration within WM frequently occurs in many cognitive tasks. The mental arithmetic domain provides clear examples. For example, to compute '3+' followed by '(6×4)', requires that the first piece of information '3+' be retained in WM whereas the intermediate result from the second piece of information is computed (6×4=24). Thus, integration does not just require the insertion of stored content into another representation, but also the maintenance during a period of subtask processing [6].

In an earlier neuroimaging study, we examined brain activation during performance of similar arithmetic problems that either did or did not involve integration [7]. We found that the integration demand selectively activated a region of the left anterior prefrontal cortex (Brodmann Area 46/10), consistently with previous work implicating the anterior prefrontal cortex in control operations during WM (for a review see Ref. [8]).

In this study, we extend these findings in a new task and subject sample, in order to investigate in detail the temporal dynamics of activity within left anterior prefrontal cortex during integration. In our earlier study [7], we found that anterior prefrontal cortex activity increased well in advance of the actual integration step. This anticipatory effect suggested that anterior prefrontal cortex may be more directly involved in the preparation for integration, rather than in mediating integration operations per se. The earlier study, however, was not designed specifically to address this issue: in fact, across all trials the integration step occurred on the last step of the math problem, leading to high temporal predictability regarding integration demands. It is possible that the anticipatory activity observed in the anterior prefrontal cortex reflected a nonspecific temporal prediction rather than specific preparation for upcoming integration. Furthermore, because the mental arithmetic task finished following integration, it was not possible to disentangle postintegration reduction of activation from a more general activity reduction associated with the end of trial. A final drawback of the earlier study was that, because of technical limitations, it was not possible to determine performance accuracy on scanned participants (although in a separate behavioral study more than 90% accuracy was observed in all conditions), and therefore activation levels and dynamics might have been influenced by confounding effects on error trials.

This study addresses these limitations of the previous one, by: (i) randomly varying the time-step of integration within the mental arithmetic problem across trials, so that the temporal demands of integration could not be predicted by the participants, and enabling better differentiation of preintegration, integration, and postintegration activity within the anterior prefrontal cortex; and (ii) restricting imaging analyses to correct trials only, so as to remove any accuracy confounds. Additionally, by maintaining continuity in some aspects of the experimental design, this study enabled a strong test of activation replication in anterior prefrontal cortex relative to Ref. [7].

Materials and methods

Participants

Sixteen neurologically intact right-handed individuals (five women and 11 men, mean age=21.3, age range=18–29) gave informed consent and were compensated $25/h to participate in this study.

Task

Trials started with a visually presented single digit as the first frame (PRE-LOAD). Next, a five-step mental arithmetic problem was sequentially presented in a frame-by-frame manner. Each of the five steps of the problem (which we designate as MATH-1 to MATH-5) consisted of a single digit and mathematical operator. Participants indicated when they were finished with each step of the computation with a button-press response. In the two subsequent steps, participants verbally reported the problem answer (REP-MATH) and then the PRE-LOAD (REP-PREOAD), or depending on the condition, merely said 'zero' in either of these steps. Four task conditions were performed (see Fig. 1 for description): integration (INT), segregation (SG), math only (MO), and recall only (RO). The INT condition was further divided into three trial types (IN2, IN3, and IN4) that varied according to when in the trial integration occurred.

Behavioral measures

Each task frame was presented for a maximum of 2000 ms, or until the button-press response was made (for slow or absent responses, the task advanced to the next frame, and reaction time was not recorded). The frame stimulus-onset asynchrony was 2500 ms, allowing for a minimum of 500 ms interstimulus interval. Thus, total trial duration was 20.0 s (2.5 s/frame × 8 frames/trial). Intertrial intervals were randomly jittered (between 0 and 7500 ms in 2500 ms steps), to better estimate the event-related hemodynamic response.

Functional magnetic resonance imaging

Whole-brain images were acquired on a Siemens 3 Tesla head-only (Allegra System, Erlangen, Germany) with a standard circularly polarized head coil. Both structural and functional images were acquired for each participant. High-resolution structural images (1.25 × 1 × 1 mm) were acquired using a magnetization-prepared rapid gradient echo imaging T1-weighted sequence (TR=9.7 ms, TE=4 ms, flip=12°, TI=300 ms) [9]. Functional images were acquired using an asymmetric spin-echo echo-planar sequence (TR=2500 ms, TE=25 ms, flip=90°), sensitive to blood oxygen level-dependent magnetic susceptibility. Each volume contained 40, 3.75-mm thick slices (in-plane resolution 3.75 × 3.75 mm). Each task condition was performed in individual scanning runs consisting of 24 trials, separated by a short rest break (six runs total, three INT, and one each of SG, MO, RO; 247 scans/run; 10.5-min duration/run).

Participants viewed visual stimuli projected on a screen through a mirror attached to the head coil. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button Box (New Micros, Dallas, Texas, USA) was used to record participants' behavioral performance. Verbal responses were recorded in the scanner and coded for accuracy off-line.

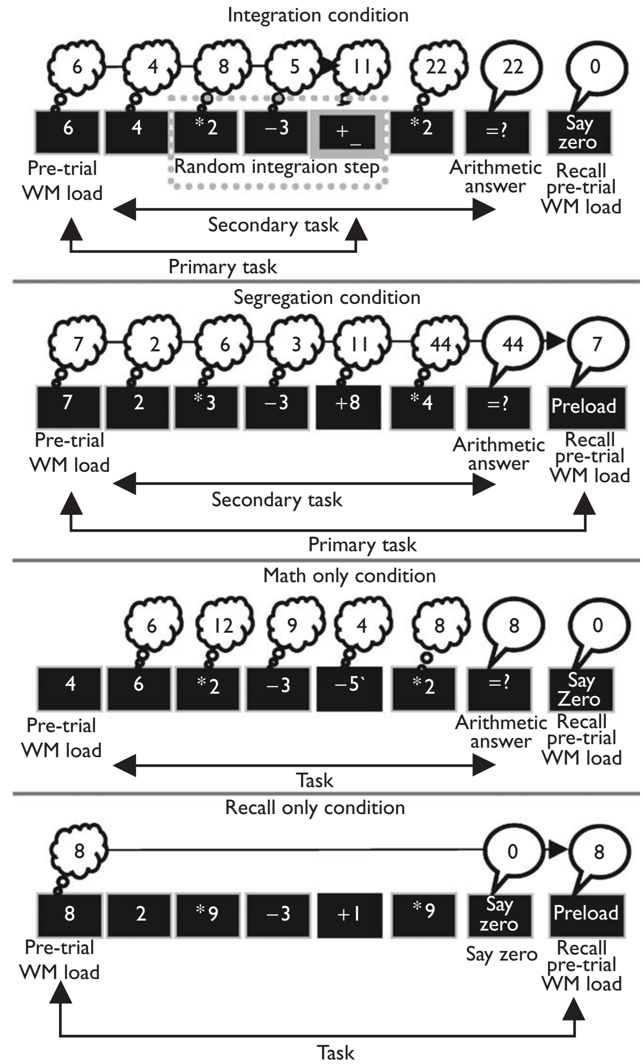

Fig. 1 Task design of the four different block conditions. During integration (INT), the preload had to be incorporated into the math problem unpredictably as part of the second, third, or fourth arithmetic frame (IN2, IN3, and IN4), as indicated with an underline bar. During segregation (SG), the preload digit had to be reported in the last trial step (REP-PRELOAD), but had not to be inserted into the math problem. During recall (RO), participants reported the preload, but did not have to compute the math problem. During math only (MO), the math problem had to be performed and the total reported at the REP-MATH step, but the preload did not have to be maintained or reported. To control for verbal responding, in the conditions where either the preload or math problem did not have to be reported, participants said 'zero' at the corresponding trial step.

Data analysis

Analysis of behavioral data were conducted via analyses of variance and *t*-tests on the accuracy and reaction time measures. Functional imaging data were preprocessed using standard procedures, and then a general-linear model approach [10] was used to estimate parameter values for the event-related responses. We identified integration-selective regions by comparing activation in the IN4 trials against the three other control conditions (IN4 trials most closely replicated the INT condition used in our earlier study [7]). Specifically, voxels were identified that simultaneously satisfied each of the following contrasts ($P<0.05$; see Ref. [7] for more details and justification of this analysis approach): (i) significantly greater activation during IN4 trials relative to the estimated activation during the intertrial interval (fixation); and (ii) significantly greater activation specifically in the IN4 trials compared to the entire block of each control condition (SG, MO, RO). The contrasts were applied to the estimated activation averaged across scan frames 4–7 of each trial, corresponding to the period of mental arithmetic processing and integration (MATH-1 to MATH-4), after accommodation of the approximate 5 s hemodynamic response lag.

Results

Behavioral results

Average mental arithmetic accuracy was very high (more than 90% correct trials), and was not significantly reduced by the presence of a WM preload in either the INT (90.6%) or SG conditions (92.7%) when compared with the MO baseline [91.7%; $F(2,15) <1$ for the effect of trial type]. Mental arithmetic demands did impair recall of the WM preload, with slightly lower accuracy found in SG (92.5%) compared with the RO baseline [100%; $F(2,15)=21.6$, $P<0.001$]. All trials with errors were excluded from analyses in the neuroimaging data.

Computation time effects during mental arithmetic processing closely replicated the pattern observed in our earlier study [7], including (i) slowing of reaction times with each successive step of the math problem (main effect of math frame, $P<0.001$); and (ii) additional slowing of reaction times with the presence of a secondary WM load in SG (main effect of condition, $P<0.001$). We further examined the specific effect of integration by averaging data in the INT condition according to three time windows (see Fig. 2): preintegration (IN2-MATH1, IN3-MATH2, IN4-MATH3), integration (IN2-MATH2, IN3-MATH3, IN4-MATH4), and postintegration (IN2-MATH3, IN3-MATH4, IN4-MATH5). Control periods were defined by averaging corresponding windows in the MO and SG conditions (preintegration: MATH-1 to MATH-3; integration: MATH-2 to MATH-4; postintegration: MATH-3 to MATH-5). This analysis revealed that during the preintegration period INT RTs were similar to (but slightly faster than) SG [$t(15)=-1.23$, $P=0.2$] and slower than MO [$t(15)=4.08$, $P<0.001$], while during the integration period INT RTs were slower than both SG [though not significantly, $t(15)=0.75$, $P=0.46$] and MO [$t(15)=5.62$, $P<0.0001$]. Conversely, in the postintegration period, INT RTs were faster than SG [$t(15)=-2.59$, $P<0.02$] and not significantly slower than MO [$t(15)=1.52$, $P=0.15$]. Together these results are consistent with the interpretation that, in the INT condition, cognitive demands are similar to SG in the preintegration period, increase during the integration period, and then decrease to be similar to MO in the postintegration period.

Neuroimaging results

The first analysis identified regions showing integration-selective effects. This analysis was consistent with our earlier study in revealing a region within left anterior prefrontal cortex (14 voxels; $x=-45$; $y=45$; $z=20$; BA46/10), which showed greater activation in all three integration trial types relative to each of the three control conditions (see Fig. 3). Additional regions were found in posterior prefrontal cortex and the right anterior cingulate cortex, which also replicated previous results (Table 1, coordinates in stereotaxic space [11]). To test more rigorously for whether the current results could be considered a true replication, we constructed a sphere of 12-mm radius from the centroid of the anterior prefrontal cortex region identified in the previous work ($x=-33$; $y=42$; $z=21$). Over 70% (10/14) of the voxels in the current anterior prefrontal cortex region were contained within this sphere, suggesting that the two regions are anatomically identical, after accounting for spatial variability across the two samples.

The second analysis examined the dynamics of integration-related activation within the anterior prefrontal cortex region of interest (ROI) as well as the other identified ROIs. Peri-event time courses were extracted for each ROI based on time-locking to the onset of integration demands (i.e. aligning to the integration frame, and examining prior and subsequent frames). We then examined event-related activation in these ROIs for the three integration trial types (IN2, IN3, IN4), using a quadratic contrast to estimate the event-related response in the 10-s (four scan) epoch locked to the integration step (see inset, Fig. 3). This analysis revealed a significant integration-locked event-related response in the left anterior prefrontal cortex ROI [$t(15)=2.2$, $P<0.05$], and no differences between trial types [$F(2,30) <1$]. When the other ROIs were tested, only three were found to show a similar pattern of effects (left posterior prefrontal cortex, left fusiform, and left anterior insula).

Discussion

In a previous fMRI investigation, we found that the left anterior prefrontal cortex was selectively engaged by integration demands during WM task performance [7]. The goal of this study was to both address important limitations of the earlier study and investigate the dynamics of integration-related activation. A critical finding was that left anterior prefrontal cortex activity was robustly

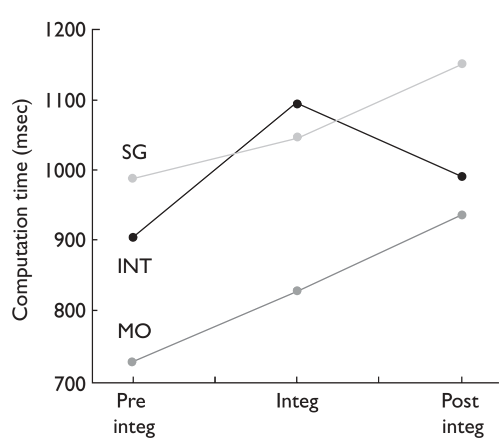

Fig. 2 Time required for computation in INT condition during the preintegration, integration and postintegration periods of the mental arithmetic problem, as compared with corresponding periods in the SG and MO control conditions. INT, integration; MO, math only; SG, segregation.

replicated using a different sample, task, and even MRI scanner (3T Allegra vs. 1.5T Vision in [7]). As was previously observed, this anterior prefrontal cortex region selectively increased in activity under integration conditions, but not during closely matched control conditions requiring WM maintenance and/or subtask processing but no demand for integration. A second critical finding was that this result was obtained even after controlling for potential effects of performance accuracy, by restricting neuroimaging analyses to only correctly performed trials. The third and most important new finding of this study was that the left anterior prefrontal cortex activation could be more strongly time-locked to integration demands. In particular, we confirmed that anterior prefrontal cortex activity increased during the preintegration period, peaked at the point of integration, and then decreased again during the postintegration period, independently of when integration occurred during the trial.

Still a number of potential interpretations exist regarding the functional role of anterior prefrontal cortex in integration and WM that are consistent with the current results (for a full list, see the discussion in Ref. [7]). When combined with the earlier study, the current results, however, seem to confirm more strongly a specific role for anterior prefrontal cortex in preparing for integration rather than in the integration computation per se. Specifically, the anterior prefrontal cortex (or at least a subregion) might serve to promote maintenance of previously stored WM content (in this case the preload information) in a specialized buffer during performance of a subtask, to keep the information in an active and accessible state that can facilitate rapid integration. After integration is completed, the specialized buffer is no longer necessary, which leads to deactivation of the anterior prefrontal cortex, even though subtask processing may still continue. A buffer for WM integration operations has been previously proposed in the literature, the so-called episodic buffer [1,12]. Previous accounts of the episodic buffer, however, have suggested that the integration operation itself is critical rather than preparation for integration. The role of preparation thus clearly differentiates our account.

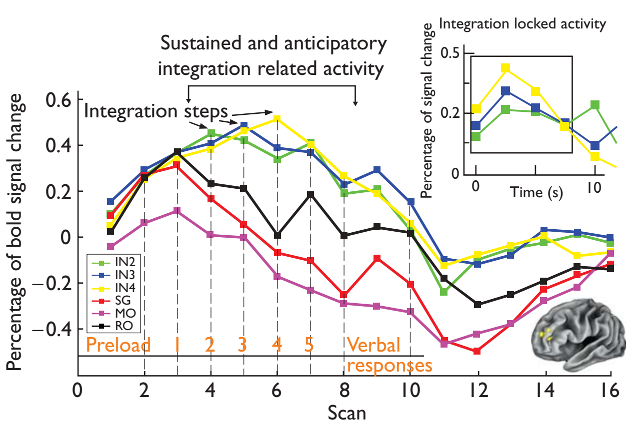

Fig. 3 Hemodynamic responses of left anterior prefrontal cortex region (depicted in the 3D brain) selectively increased during integration conditions, at both the time period of integration and in the preintegration period. The inset shows the event-related response of this region across the three different integration trial types (IN2, IN3, IN4) time-locked to the onset of integration demands.

The engagement of anterior prefrontal cortex during subtask-plus-integration conditions might specifically serve the function of preventing interference or conflict from ongoing unrelated subtask processing until needed. Interference or conflict effects may be detected within the anterior cingulate cortex, and subsequently lead to increased activation in anterior prefrontal cortex to reduce this interference, as would be consistent with theoretical accounts of a conflict-control loop between prefrontal and anterior cingulate cortex [13,14]. This study was not specifically designed to test the relationship between preparation for integration and interference effects, but the results are consistent with this account, particularly the coactivation of anterior cingulate cortex and left anterior prefrontal cortex which was both observed in the current results and in the earlier study [7]. More direct study of this issue is an important direction for future research.

Integration, as we have operationally defined it, appears at first to be a very subtle operation with its key requirement of insertion into WM contents, and of dependence upon subtask processing. This and earlier studies have examined the very specific and narrow domain of mental arithmetic. Yet careful consideration reveals that integration may be essential for the correct execution of many types of cognitive tasks, including logical and analogical reasoning [15,16], problem-solving [17,18], episodic memory [19], multimodal processing in perception [11], and semantic/syntactic analysis in language [6]. Whether these diverse task

Table 1 Brain regions relative to the IN4 trials against the three other control conditions (SG, MO, RO). Coordinates are in stereotaxic space [11]

Integration selective regions	Brodmann area	X	Y	Z	Size (mm^3)
Left anterior prefrontal	46/10	−45	45	20	378
Left dorsolateral prefrontal	9	−48	18	30	4914
Right dorsolateral prefrontal	9	42	33	33	1107
Right posterior prefrontal	9/44	42	12	36	1431
Left supplementary motor area	6	−18	6	63	2133
Left anterior insula	13/45	−39	18	0	297
Left anterior cingulate	32	−12	15	42	405
Right anterior cingulate	32	9	24	39	594
Right posterior cingulate	23	3	−33	27	756
Left precuneus	7	−24	−63	39	7911
Right inferior parietal lobule	40	39	−51	51	4617
Left fusiform gyrus	37	−39	−57	−9	216
Right parahippocampal gyrus	36	33	−21	−27	405
Right posterior insula	22	42	−27	−3	432
Right thalamus	—	9	−12	0	405

demands all require the engagement of a common neural mechanism for integration within anterior prefrontal cortex is a question for further investigation.

Conclusion

The study results support a functional role for the anterior prefrontal cortex in integration during WM. More importantly, the findings suggest that although integration demands are a necessary precondition for anterior prefrontal cortex engagement, activation of this region primarily occurs during integration preparation, potentially to maintain goal-relevant information in an accessible form while protected from interference.

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