

Bilateral basal ganglia activity in verbal working memory

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ABSTRACT

Although the cortical substrates of verbal working memory are reasonably well understood, less is known about the relative contribution of subcortical structures to verbal working memory. Therefore, in addition to elaboration of a model of verbal working memory by including a specific focus on basal ganglia, the purpose of this study also was to examine potential differences in neural function across the complete process of verbal working memory, from encoding through retrieval. Functional magnetic resonance imaging was used to observe regions of brain activation in neurologically normal participants during a task of verbal working memory. The expected frontal-parietal network was found to be active over the course of the verbal working memory task. The encoding portion of the task engaged left inferior frontal regions and bilateral caudate and thalamus. Bilateral medial thalamus and posterior cingulate regions were engaged during the maintenance phase of the task. Retrieval activated the left inferior frontal sulcus and posterior parietal/occipital regions. Findings are considered in light of current models of verbal working memory and subcortical structures.

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1. Introduction

The neural substrates of verbal working memory include parietal cortices, thought to play a role in phonological processing and storage, and frontal cortices, thought to subserve articulatory processes including vocal, or subvocal, rehearsal (Buchsbaum, Padmanabhan, & Berman, 2010; Paulesu, Frith, & Frackowiak, 1993; Schweickert & Boruff, 1986). Over the past several years, increasing attention has been given to further elucidation of the role of the frontal lobes such that Broca's area is appreciated both for articulatory/phono-motor processing (i.e., pars opercularis), as well as for semantic processing (i.e., pars triangularis; Paulesu et al., 1997). These findings, when considered in the context of electrophysiological studies that document relationships between medial frontal and lateral frontal regions (Abdullaev & Posner, 1998), begin to reveal a rich and broad network that supports the complex processes of verbal working memory. Many structures in this verbal working memory network also are involved in verbal processing. Motivated by this literature, along with the well-established structural connections between frontal and subcortical

structures (e.g., Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000), we endeavored to use functional magnetic resonance imaging (fMRI) to examine neural activity in frontal-subcortical circuits in neurologically healthy adults during rest and as they completed a task of verbal working memory.

Despite considerable debate on the importance of the basal ganglia for language, the current consensus is that lesions of the basal ganglia *alone* do not cause aphasia either acutely (Hillis et al., 2002) or chronically (Copland, Chenery, & Murdoch, 2000). Yet, these subcortical structures do have a role in more complex language functions (Copland et al., 2000; Hillis et al., 2002; Snijders, Petersson, & Hagoort, 2010). It is equally clear that basal ganglia lesions and disease affect performance on verbal tasks that are more challenging than those found on the typical aphasia battery, including producing multiple interpretations for ambiguous sentences, generating sentences, interpreting figurative language, and giving synonyms, antonyms, or definitions for words (Copland et al., 2000). Deficits understanding complex syntactic structures also have been noted in basal ganglia disease (Grossman, 1999; Grossman et al., 2003; Lee, Grossman, Morris, Stern, & Hurtig, 2003), and Lee and colleagues (1999) showed that limited resources for strategic attention and impaired processing speed contribute to syntactic deficits in Parkinson's disease.

The basal ganglia do have a clear and direct role in motor function. They serve to enhance desired motor behaviors and to

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suppress or inhibit undesired motor behaviors (Mink, 1996; Penney & Young, 1986). Recent research has suggested that this “enhance/suppress” function of the basal ganglia is easily applied to the broad domain of cognition (see Crosson, Benjamin, & Levy, 2007 for review). These subcortical structures influence the efficiency and accuracy of working memory and language, including semantic processing. Specifically, there is literature to suggest that the basal ganglia facilitate language generation by increasing focus on the intended lexical target and inhibiting focus on associated, but non-intended, targets (Crosson et al., 2003). This literature, while not addressing verbal working memory specifically, is relevant because of the overlap in language and verbal working memory networks. For example, when asked to think of fruits that are red and grow on trees, the items strawberry, raspberry, and apple might be elicited. However, while strawberries and raspberries are red fruits, they do not grow on trees. The focus on these associated red fruits needs to be inhibited so that the target “apple” is enhanced. In fact, dorsal caudate activity during tasks of language generation, but not during generation of non-lexical/non-meaningful utterances, has been taken as evidence of the role of the caudate in access and retrieval of words from pre-existing lexical stores (Crosson et al., 2003). These data encourage us to consider not just the basal ganglia in a broad manner, but specifically caudate nucleus activity during verbal working memory.

A recent report by McNab and Klingberg (2008) puts forth a hypothesized role of the basal ganglia during a visuo-spatial working memory task. These authors found putamen and globus pallidus activity in neurologically normal subjects during the time immediately before presentation of the “to-be-remembered” visuo-spatial stimuli. They attributed this basal ganglia activity to “filtering” of irrelevant or distracting information. While this activity was positively correlated with performance on the visuo-spatial working memory task, the conclusions drawn must be considered in light of the known roles and neuroanatomic connectivity of the putamen and globus pallidus. Specifically, afferents to the putamen include the somatosensory and motor cortices (Alexander et al., 1986), and the putamen is efferent to the globus pallidus. Consistent with the enhance-suppress contribution of the basal ganglia, these authors concluded that the putamen and globus pallidus activity was due to an active filtering of irrelevant material, thereby allowing an unencumbered focus on the relevant material. However, because of the rich motor connectivity at the core of this circuit, one wonders if aspects of the findings were not influenced by the timing parameters of the paradigm and behavioral response of the subjects. A verbally based working memory paradigm would allow examination of the role of basal ganglia structures and, by virtue of being language based, would be hypothesized to engage the caudate preferentially to the putamen and globus pallidus. We hypothesized that a verbal working memory paradigm would elicit activity in the medial frontal cortex, caudate nucleus, thalamus, and lateral frontal cortices of the language dominant hemisphere.

The elegant work of Inase and colleagues (1999), documents that the pre-supplementary motor area (pre-SMA) of one hemisphere provides input bilaterally to the caudate, putamen, and subthalamic nucleus. Specifically, left pre-SMA is involved in verbal working memory (Crosson et al., 1999; Mecklinger, Bosch, Gruenewald, Bentin, & von Cramon, 2000) and projects bilaterally to the basal ganglia (Inase et al., 1999). Given bilateral projections from pre-SMA to the basal ganglia, it is likely that bilateral basal ganglia activity would be seen in verbal working memory tasks that involve pre-SMA. As a related example, bilateral basal ganglia activity has accompanied left pre-SMA activity during word production (Crosson et al., 2003). Therefore, we developed hypotheses about right hemisphere subcortical activation. Specifically, we expected that a verbal working memory task would produce right caudate

and thalamic activity, although to a lesser extent than the left hemisphere homologues. Further, we did not expect right frontal activity to be present to the same extent as left frontal activity.

Over the recent past, much attention has been given to patterns of synchronization present in low frequency spontaneous neural activity (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007); these patterns of signal coherence are thought to represent dynamic functional networks (Fox et al., 2005). In fact, brain regions with similar functionality tend to be correlated in their spontaneous BOLD activity (Fox & Raichle, 2007). Consistency between functional and spontaneous/resting state patterns of activation would buttress our conclusions about the role of bilateral subcortical regions within a broadly distributed network for verbal working memory. Therefore, in addition to recording the blood oxygen level dependent (BOLD) signal during execution of a verbal working memory task, recordings were made during a resting state as well. Specifically, we hypothesized that if the bilateral subcortical regions are intrinsic nodes in the verbal working memory network, they should show significant resting state signal correlation with brain areas typically reported in verbal working memory studies.

2. Method

2.1. Participants

Fourteen neurologically normal, right-handed female subjects participated in this study. All were English speakers and ranged from 18 to 28 years of age ($M = 21.6$ years, $SD = 2.59$ years), with between 12 and 18 years of education ($M = 12.9$ years, $SD = 1.86$ years). Potential volunteers were excluded if they had a history of major psychiatric disturbance, substance abuse, or neurological injury, including loss of consciousness greater than five minutes, stroke, and neurodegenerative illness. All participants gave informed consent in accordance with the guidelines established by the Emory University Institutional Review Board and the Atlanta Veterans Affairs Medical Center Research and Development Committee.

2.2. Experimental task

A semantic relatedness paradigm was used. Participants were shown word pairs and were instructed to indicate, using a button press, if there was a semantic relationship between the words in each pair. Word pairings were presented one at a time on a computer screen. Word pairings remained constant across participants (e.g., river always was paired with brook). The order of word pair presentation varied randomly across participants. The focus on semantics was maintained in an effort to mimic use of verbal working memory in every day conversation. In other words, as one engages in conversation, verbal working memory holds the store of salient conversational topics while suppressing potentially related but less immediately relevant topics.

The experimental task included both verbal working memory and control trials presented in a pseudorandom order across five runs, each containing 14 trials. This produced 35 verbal working memory trials and 35 control trials over the course of the experiment. For a verbal working memory trial, the first slide depicted a single lexical target. Participants were instructed to read and remember this “target word” with the knowledge that sometime later they would be shown a second word, referred to here as the “decision word”. Upon seeing the decision word, participants initiated a button press indicating whether the target and decision words were semantically related. The time in-between presentation of the target and decision words was filled with additional slides, referred to here as “distractor slides”. Each distractor slide

presented two words. Participants were asked to make a semantic relatedness judgment for each of these distractor word pairs. The purpose of the distractor slides was to prevent rehearsal of the target word during the interval between the target and decision slide. This model, designed to prevent rehearsal, is believed to more accurately reflect real life conversations during which participants, engaged in active listening, are not ending simultaneously in rehearsal of “just-said” information. Further, the experimental design employed in this study allows one to parse brain activity during encoding vs. maintenance/retrieval. A single verbal working memory trial is depicted in Fig. 1.

The task used in the control trials was designed to replicate the visual, motor, lexical, and semantic processing involved in the experimental condition, without requiring verbal working memory activation. Therefore, in the control trials, the target and decision words were presented together on the final slide of the trial. A single control trial is also depicted in Fig. 1.

The timing parameters were identical for both the verbal working memory and control trials. Specifically, slides 1–4 were presented for 2 s each, and slide 5 was shown for 4 s. These parameters were established through pilot testing in the first author's lab and were chosen to allow sufficient time for the button-press response and to elicit satisfactory task performance. A 10-s blank screen intertrial interval was used to allow hemodynamic response recovery.

Presentation[®] software (<http://www.neurobs.com>) was used for both stimulus delivery and behavioral response recording. The visual stimuli were presented on a back-projection screen, and button-press responses were collected on a fiber optic button box (Current Designs, www.curdes.com). Participants were instructed to remain motionless throughout the imaging session and foam padding was used to minimize head motion.

2.3. Image acquisition

Anatomical, functional, and resting state data were acquired in the course of a single scanning session. All imaging was performed on a 3T Siemens Trio scanner (Siemens, Germany). Anatomic images were obtained using a T1 weighted MPRAGE sequence (2.6 s TR; 3.02 ms TE; 8° flip angle; 256 × 224 × 192 matrix; 1 mm thickness; 192 sagittal slices).

Functional images were obtained using six EPI-BOLD scans with 308 volume measurements in each (1 s TR; 30 ms TE; 60° flip angle; 64 × 64 matrix; 220 mm FOV; 5 mm thickness; 16 axial slices without gap). During the first of these six runs, participants were instructed to gaze at a fixation cross and remain motionless, thereby allowing functional acquisition of resting state data. For the remaining five runs, participants engaged in the experimental task.

2.4. Image preprocessing

AFNI (Cox, 1996) was used to perform the imaging data analysis. Data preprocessing included slice timing correction (to compensate for slice dependent acquisition time shift), multiple scan/run concatenation, rigid body volume registration (to correct small head motions during the scan) and 5 mm FWHM Gaussian blur.

2.5. Experimental task image analysis

Individual subject BOLD signal time courses were submitted to a deconvolution analysis using the onset of the verbal working memory and control trials as the input vectors to estimate the impulse response functions (IRF); this analysis included 21 time points (i.e., 20 s). Subsequently, brain activations associated with verbal working memory were identified by contrasting the integration (the summation of IRF intensity at all the 21 time points) of these two IRFs through a general linear test. After transforming the resulting contrast maps spatially into the Talairach space (Talairach & Tournoux, 1988) and statistically to z-scores, group average of brain activations across all individuals was generated. Finally, a $p < 0.05/\text{voxel}$ plus 1653 mm³ cluster threshold ($p < 0.01$ overall) was applied to control for multi-comparisons.

The experimental task can be parsed into three component phases: encoding (during presentation of the “target word”/slide 1), maintenance (during the “distractor slides”/slides 2–4), and retrieval (at presentation of the “decision word”/slide 5). In an effort to examine potential differences in brain activation across these phases of the experimental task, a multiple linear regression analysis was employed. Six regressors were used to model the verbal working memory-encoding, verbal working memory-maintenance, verbal working memory-retrieval, control-encoding, control-maintenance, and the control-retrieval conditions, respectively. These regressors were generated by convolving the stimulus event function with an ideal hemodynamic response function previously published in the literature ($y = t8.6e^{-t/0.547}$; where y = signal intensity and T = time after stimulus in sec.; Cohen, 1997). To account for data variations introduced by subject head motion, the 6 dimensional (3 translation and 3 rotation) head motion parameters were included in the multiple regression as the “baseline regressors”. For each individual subject, the regression coefficients were compared (using general linear tests) between the verbal working memory and control conditions for the three experimental task phases (encoding, maintenance, and retrieval) and the corresponding contrast maps were generated. These contrast maps were z score and Talairach transformed and averaged across all the subjects. A $p < 0.01/\text{voxel}$ plus 690 mm³ cluster threshold ($p < 0.01$ overall) was applied as well.

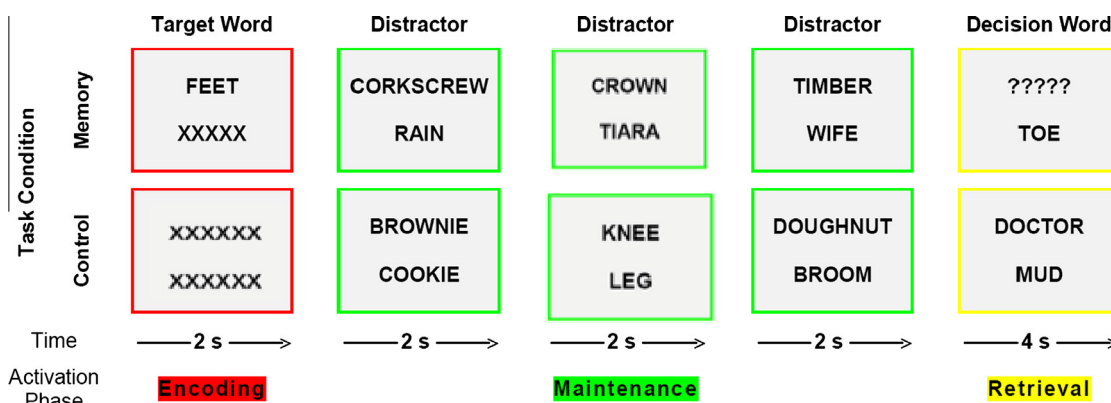


Fig. 1. Diagram of the experimental task, showing a single verbal working memory trial and a single control trial. Each trial lasted 12 s for both task conditions (control and memory) and was separated from the subsequent trial by a 10-s blank screen. Color-coding indicates the phases delineated for the functional task activation analysis.

2.6. Resting state analysis

The images were preprocessed with slice timing correction, rigid body registration, temporal band-pass filtering ($0.009 < f < 0.08$; to extract low frequency signal fluctuation), and 5 mm full width at half-maximum (FWHM) Gaussian spatial smoothing. High-resolution anatomical images for each individual were segmented into white matter, gray matter, and cerebral spinal fluid (CSF). Because resting state functional connectivity measurements are based on distant gray matter region correlations (Damoiseaux et al., 2006; Lowe, Mock, & Sorenson, 1998; Nir, Hasson, Levy, Yeshurun, & Malach, 2006), spurious signal variations were removed. This was accomplished through multiple linear regression analysis including the white matter signal, CSF signal, whole brain average signal, and the 6 parameters of rigid body head motion (L/R, A/P, I/S shifts, and pitch, roll, and yaw rotations).

The BOLD time course of the seed region was extracted from the averaged low frequency signal from the medial prefrontal area. Consistent with our hypotheses and past literature, this area was chosen as the seed region because it was activated during the verbal working memory trials of the experimental task. A medial brain seeding area was chosen to ensure that no hemisphere bias was introduced in the final resting connectivity map. This region was centered in Brodmann's areas 32 and 8 (Talairach centroid coordinates: 0, −18.7, 40.6 with a total volume of 17888 mm³ and full extent of left to right activation from −11 mm to 11 mm). Cross-correlations between this ideal reference waveform and the time series from all other brain voxels were calculated. In order to average across subjects, correlation coefficients matrices for each subject were converted to an equivalent $N(0,1)$ deviate (or z-scores) and then transformed into the Talairach space. Voxel-wise and cluster threshold applied to the final group mean result was $p < 0.01/\text{voxel}$ and 690 mm³ ($p < 0.01/\text{overall}$).

3. Results

3.1. Task analysis

For all participants, there was a high level of performance accuracy for both the verbal working memory and control trials. On average, participants responded correctly to the decision slide 94% of the time in the verbal working memory condition ($SD = 5.9\%$), and 97% of the time in the control condition ($SD = 2.6\%$). A two-way paired-samples t -test reveals that there is a trend for the accuracy to be greater on the decision slide in the control condition (no memory component) when compared to the verbal working memory condition ($t = -2.13$, $p = 0.053$). There is no difference in latency to respond to the decision slide between the verbal working memory and control conditions ($p = 0.36$). Performance was comparable for the distractor slides across task conditions, with 96% accuracy during the verbal working memory condition ($SD = 6.5\%$) and 95% accuracy during the control condition ($SD = 4.9\%$; $t = 1.59$, $p = 0.14$). There is no difference in latency to respond to the distractor slides between conditions ($p = 0.78$). The consistency of task performance and latency to respond between the verbal working memory and control tasks indicates that participants were equally engaged across tasks.

3.2. Image analysis

Global comparisons of the verbal working memory vs. the control task revealed distributed activation throughout a rich cortical network associated with verbal working memory. Specifically, as can be seen in Fig. 2, bilateral frontal and parietal cortices were activated by the verbal working memory associated task. Further,

there is clear activation bilaterally within subcortical areas including caudate and thalamus. These robust global findings supported the initial hypotheses of bilateral subcortical activity in verbal working memory. Further, these findings reinforced the need to deconstruct the experimental task to understand better the component processes of verbal working memory.

This more in depth examination of the neural substrates of working verbal was accomplished by conducting a multiple linear regression analysis based on the three phases of the task (encoding, maintaining, retrieving). As can be seen in Fig. 3, the encoding portion of the task produced activation in the left inferior frontal regions including Broca's area, in medial frontal cortices including pre-SMA, and bilaterally in the caudate nucleus and thalamus. Specifically, bilateral caudate activity, with right greater than left spatial extent, and bilateral thalamic activity, left greater than right spatial extent, were evident during encoding. There was modest activity seen in the right dorsolateral prefrontal cortex as well. The maintenance phase of the task engaged bilateral medial thalamus as well as posterior cingulate regions. The retrieval portion of the task engaged left IFS and posterior parietal/occipital regions. These results were subsequently validated by point-to-point comparisons of the IRF values between the verbal working memory and control conditions. As shown in Fig. 4, the caudate and thalamus had significant verbal working memory vs. control IRF difference in an earlier phase (around 6–7 s), but the major IRF difference in the medial thalamus area was shifted to a later time (around 8–9 s).

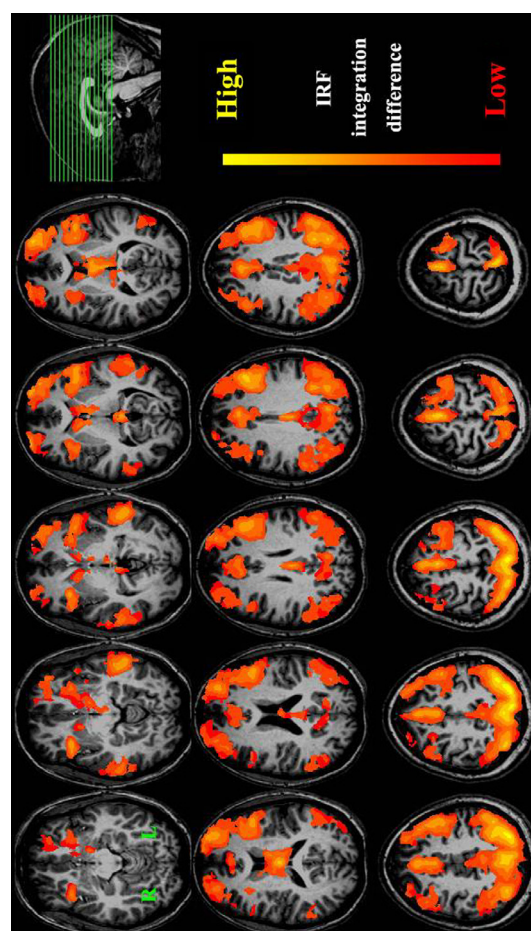


Fig. 2. The verbal working memory associated brain activations generated by the IRF integration comparison ($p < 0.05/\text{voxel}$ plus 1653 mm³ cluster threshold, $p < 0.01$ overall). Activations here are overlaid on one subject's anatomical image. Images are in radiographic space.

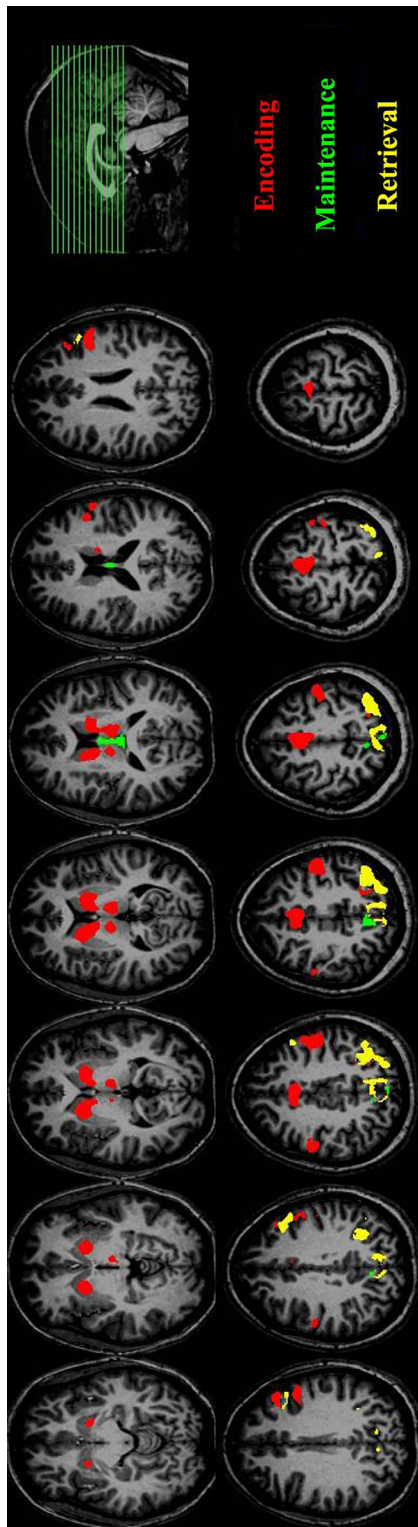


Fig. 3. Brain areas significantly involved in different memory phases. This map is a combination of the brain activations ($p < 0.01/\text{voxel}$ plus 690 mm^3 cluster, $p < 0.01/\text{overall}$) separately generated in the three-phases-based data analysis. Regional activations are labeled with words in the same color. (Figures are in radiologic convention).

For the areas that were involved in both encoding and retrieval, such as the left DLPFC, the significant IRF difference could be observed in both the early (around 6 s) and late (15 s) phases. Table 1 lists areas of activation across the three phases of the task along with cluster size of the activation.

The findings of coactivation in medial frontal and subcortical regions during verbal working memory were reinforced by the analyses of spontaneous activity during a resting state. Specifically, by taking the medial prefrontal activation as the seeding area, subcortical regions bilaterally showed close resting correlation with important nodes throughout the verbal working memory network. Functional connectivity maps are shown in Fig. 5.

4. Discussion

Findings from this study document clear activation of not only traditionally reported frontal/parietal regions seen in verbal working memory, but also of subcortical regions including the caudate and thalamus. Although others report findings from *verbal* working memory tasks, one novel aspect of this paper rests in the nature of the behavioral task: the task itself, and the experimental design, were structured to leverage the overlap in networks between lexical-semantic and verbal working memory tasks while parsing the encoding, maintenance, and retrieval components of verbal working memory. Specifically, the verbal material in this study actively engaged both lexical and semantic stores in a direct and meaningful way. It was not enough simply to read and remember a lexical unit, but participants also had to process the semantics of each lexical item encountered. The equivalent performances for response accuracy between the “decision” slides and the “distractor” slides suggests that participants did not use the distractor slide time simply to rehearse the “target” word but instead engaged effectively in the distractor task.

After semantic processing components were parsed from the verbal working memory components through comparison with the control task, the encoding phase of verbal working memory was associated with bilateral caudate and thalamic activity; the maintenance phase was associated with bilateral medial thalamic activity; the left dorsolateral prefrontal cortex was active during both encoding and retrieval phases. Resting state data confirm this frontal-subcortical model for a verbally mediated working memory task. The particular salience of bilateral caudate activation during the encoding portion of the task provokes additional consideration of this structure in terms of its role and function.

Working memory, by definition, is resource limited. It makes sense that the brain would engage in efforts to enhance working memory and facilitate the attention to, temporary storage of, and manipulation of the target material. Our findings, in conjunction with past work, point toward a model of basal ganglia function in verbal working memory that is focused on enhancement of the target and suppression of the distractors, with bilateral caudate activity seen during the encoding phase of the task.

Past research using fMRI to study language generation in healthy subjects has shown the expected left hemisphere activation (including the caudate nucleus) in addition to right caudate and putamen activity (Crosson et al., 2003). The interpretation of these data was that the left basal ganglia activity served to enhance the language processing of the dominant hemisphere, and right basal ganglia activity served to suppress potentially disruptive activation of the non-dominant right frontal cortex.

Though functional activation of basal ganglia in working memory tasks has been observed in other neuroimaging studies, less attention is traditionally paid to these regions when compared to the cortical activation. In fact, as shown recently by Chang and colleagues (Chang, Crottaz-Herbette, & Menon, 2007), the basal ganglia do play an important role in verbal working memory. The present activation results exhibited high consistency with those reported by Chang et al., which also showed verbal working memory load associated with basal ganglia activation in the encoding and maintenance phase. However, the multiple regression approach

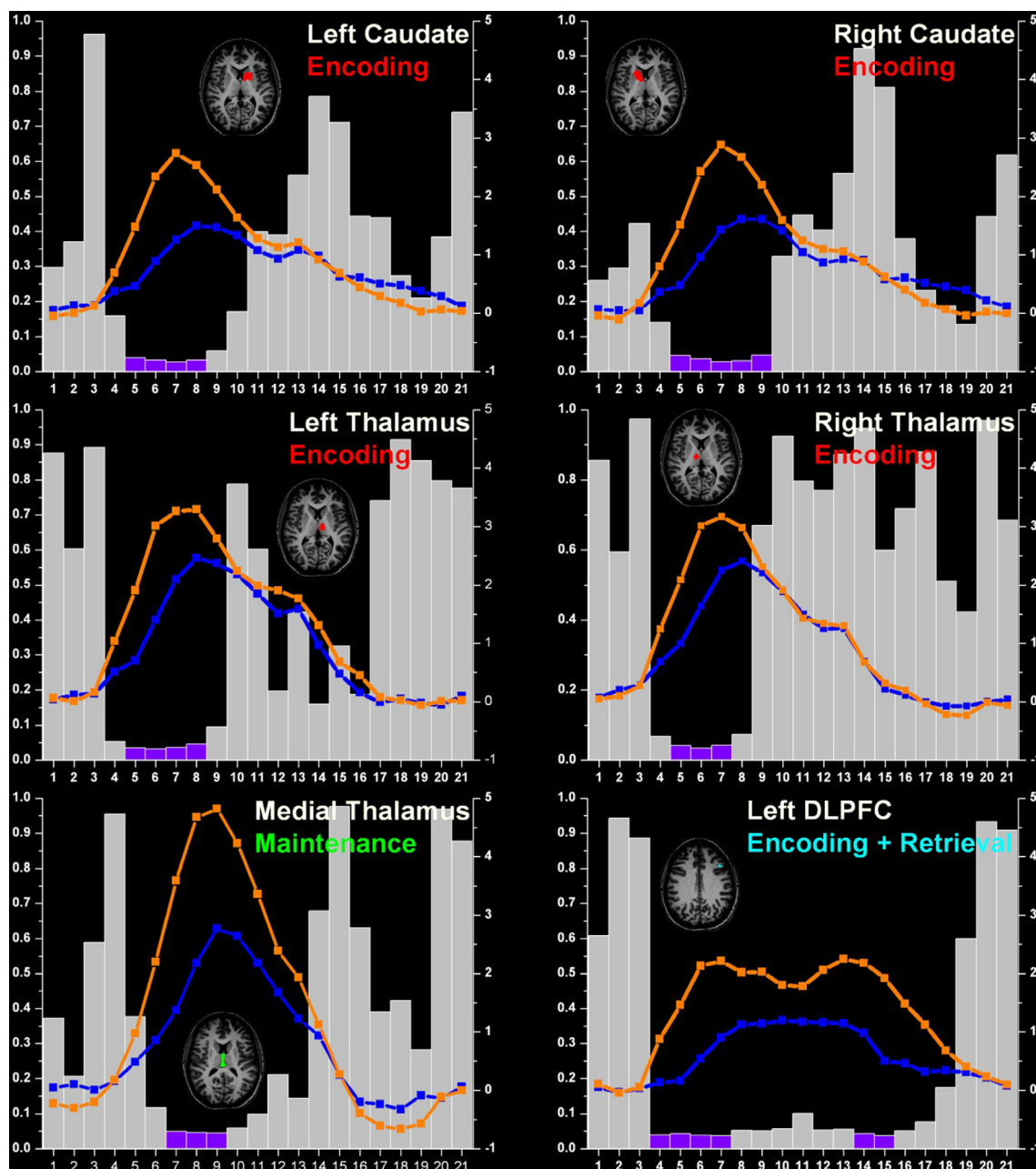


Fig. 4. The memory (orange curve) vs. control condition (blue curve) IRF comparison in bilateral caudate, thalamus, medial thalamus and left DLPFC areas. These areas are exactly the same regions shown in the Fig. 3. The horizontal axes represent the time in unit of TR (1TR = 1 s). The bar plots behind the curves indicate the p -value of the t -test comparison between the memory and control IRF points at that particular time. Significant ($p < 0.05$) bars are shown in violet and non-significant ones are shown in gray. The left and right vertical axes in each sub-graph respectively scale the p -value and the IRF curve. The experimental phase indicated in each graph is based on the standard impulse response generated for each of the three phases.

used in both studies does have limitations, as the mathematical model may not represent the real physiological signal properly. As shown in the report of Chang and colleagues, the maintenance signal was modeled as a positive response in the high load condition but a negative response in the low load condition. Though this model provides the best fit to the measured fMRI data, it is unlikely that the maintenance signal would change its polarity in real physiological response. We took additional precautions in the present study in interpretation of the multiple regression results by inspecting the point-to-point signal difference between the two experimental conditions, thereby ensuring that the signal to noise ratio was sufficient for the mathematical modeling.

The challenge in interpreting the current data is to relate the subcortical activity during encoding and maintenance to prevailing theories about subcortical functions. With respect to the motor system, one line of thinking suggests that the basal ganglia enhance selected actions and suppress competing ones (Mink, 1996). The idea has been applied to lexical semantic systems, suggesting that the basal ganglia enhance concepts needed to perform a task and suppress competing ones (Crosson et al., 2007). Enhancement of the presented lexical semantic information for verbal working memory while suppressing competing information could explain basal ganglia and anterior thalamic activity present during the encoding phase of lexical-semantic working memory

Table 1

Areas differentially activated during verbal working memory task.

Cognitive activity	Brain region	Talairach coordinates			Activation volume (mm ³)
		X	Y	Z	
Encoding	Left caudate	15.7	−6.0	6.3	3772
	Right caudate	−14.6	−7.4	6.4	4277
	Medial-frontal-cingulate (BA 6,32)	0.3	−3.7	47.6	5053
	Left middle frontal gyrus (BA 9)	40.3	−23.0	28.7	1054
	Left precentral gyrus (BA 6)	45.6	11.2	43.8	5073
	Right precentral gyrus (BA 6)	−49.3	9.0	38.5	862
	Left precuneus (BA 7)	26.6	55.9	42.1	849
	Left thalamus	8.9	15.1	9.1	1847
	Right thalamus	−9.2	14.2	10.3	753
	Medial precuneus	0.6	67.4	41.7	3413
Maintenance	Thalamus	−0.2	16.7	14.9	1127
Retrieval	Left middle frontal gyrus (BA 9)	42.4	−15.7	31.5	1308
	Medial precuneus (BA 7)	3.7	68.2	41.7	5280
	Left parietal (BA 7,39,40)	33.0	60.0	43.0	5380

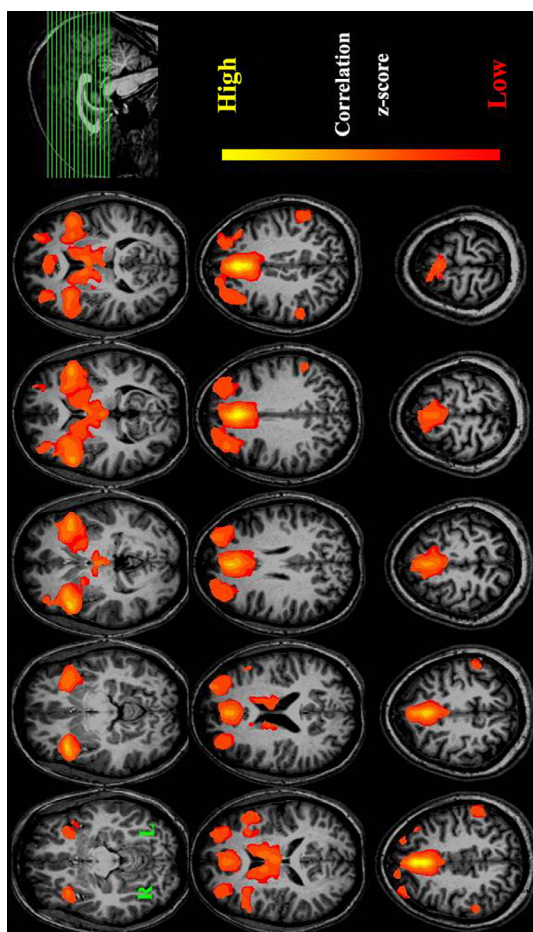


Fig. 5. The resting functional connectivity map ($p < 0.01/\text{voxel}$ plus 690 mm³ cluster, $p < 0.01/\text{overall}$) generated by seeding in the working memory activated medial prefrontal area. The underlay, left/right, and slice coverage information are the same as those in the Fig. 2.

in the current study. The anterior thalamic activity during encoding encompasses the ventral anterior nucleus, which is active along with the caudate nucleus in other lexical-semantic tasks. Hence, the caudate and anterior thalamic activity are most likely a part of the same system. Further, work is needed to address whether the enhancement-suppression schema of basal ganglia functions can be supported empirically with regard to lexical-semantic working memory.

An interesting difference at the thalamic level is the involvement of the medial thalamus in the maintenance phase of verbal working memory. It has been known for some time that the dorsal medial and midline thalamic nuclei are involved in primary memory (Gaffan & Parker, 2000; Crosson, 1992). The distractor task in the current study was designed to prevent rehearsal. We hypothesize that this aspect of the task necessitated the engagement of this component of the primary memory systems to maintain the presented concept in working memory. Again, future studies will be necessary to address this hypothesis. The retrieval task involved matching the current stimulus to the contents of verbal working memory. It appears that participants were dependent on the frontal-parietal system for this aspect of the task. For this region of the parietal lobes (BA 7, 30, and 40), involvement in verbal working memory was unique to retrieval.

In summary, once semantic processing and decision making are parsed from the semantic verbal working memory task, encoding elicited bilateral caudate and thalamic activity; the maintenance phase showed activation of the medial thalamus bilaterally, and the retrieval phase brought about activation in the left dorsolateral prefrontal cortex and parietal regions often seen in tasks of verbal working memory. It is interesting that the dorsolateral prefrontal activation is seen during encoding and retrieval but that the basal ganglia co-activate with the dorsolateral prefrontal regions only during encoding. In other words, increased dorsolateral prefrontal activity during *retrieval* is not linked to increased basal ganglia activity while bilateral basal ganglia activity co-occurs with dorsolateral prefrontal activity during encoding. Results of the current study have suggested two hypotheses regarding subcortical structures that require further testing: (1) the basal ganglia are involved in enhancing relevant and suppressing irrelevant information during encoding for verbal working memory, and (2) when a semantic processing task interferes with rehearsal, verbal working memory relies on structures involved in primary memory, the midline thalamic nuclei. Further assessment of these hypotheses will shed light on how subcortical structures contribute to verbal working memory systems.

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