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Interference resolution in the left inferior frontal gyrus

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## ABSTRACT

Functional neuroimaging work has mapped interference resolution processing to left inferior frontal regions for both verbal working memory and a variety of semantic processing tasks. The similarity of the identified regions from these different task domains suggests the existence of a common, general-purpose interference resolution mechanism. The current research specifically tests this idea. Twenty-two subjects completed both a verb generation task and a verbal working memory task while neural activity was measured using functional magnetic resonance imaging. In the verb generation task, participants generated a verb in response to a visually presented noun. On high-interference trials, the nouns had many verb associates (e.g., Ball → “Kick”, “Throw”, “Bounce”, etc.) while low-interference trials had few strong verb associates (e.g., Scissors → “Cut”). In the verbal working memory task, participants retained a small set of letters for a few seconds, then responded “yes” or “no” via button press if a single-letter probe matched one of the currently memorized letters. High-interference probes were not members of the current target set but were members of recent target sets. High interference trials on both tasks were associated with left inferior frontal activity, and the patterns of left frontal activity in each task strongly overlapped. The results indicate that an elemental component of executive processing used in a variety of task contexts can be mapped to a portion of the left inferior frontal gyrus.

It is widely accepted that the human frontal lobes, and the prefrontal cortex (PFC) in particular, are largely responsible for mediating a class of functions collectively referred to as “executive processes”. Executive processes are not directly involved in sensory processing or motor-act production, but rather in the control or strategic use of these lower level processes. Executive processes are a crucial component of high-level cognition, playing a central role in such systems as working memory (Baddeley, 1996; Collette et al., 1999; Morris & Jones, 1990). Despite the importance of executive processing, a lack of an accepted taxonomy of executive functions poses a major obstacle for characterizing the organization of human PFC.

Recent work on two very different tasks, one a working memory task, and the other a semantic retrieval task, suggests that they may share a cognitive operation which resolves interference by selecting among competing representations. Evidence from independent studies of each task has linked their selection requirements to an area of ventrolateral prefrontal cortex, in the left inferior frontal gyrus (IFG). In the present investigation our goal was to obtain further evidence that the selection/interference resolution processes entailed in these tasks share a neural substrate, using fMRI to identify the neural correlates of each task within the same individuals. If these tasks do not recruit overlapping regions of cortex, the hypothesis that they entail a common executive function would be challenged. Alternatively, identifying a neural substrate that is common to both tasks is consistent with the hypothesis that these tasks invoke a common executive process, and would be progress towards clarifying the neural organization of executive function. What follows is an overview of the tasks under

investigation and a summary of the existing evidence linking their selection demands to the IFG.

Recently, there has been increased interest in examining proactive interference in verbal working memory using a modified item recognition task as first used by Monsell (1978). In the version of the task used by Jonides et al (1998) participants are required to briefly retain a set of four letters in memory, and then respond to a probe letter that on half of the trials matches one of the members of the current test set (positive probes) and on half of the trials does not (negative probes). In a high-recency condition, half of the negative probes were members of the test set on the immediately preceding trial; in a low recency condition, no negative probe was a member of the preceding test set. Jonides et al. found an interference effect of about 50ms on reaction times of high-recency negative probes. PET measurements indicated significantly more activation in left Brodmann's area (BA) 45, located in the left IFG, in the high-recency condition compared to the low-recency condition. This was the only significantly different neural activation between the two conditions.

Furthermore, left IFG activity is not only correlated with, but appears to be necessary for, proper interference resolution. Older participants showed a disproportionately larger interference effect on high recency negative trials in verbal working memory, and also lacked activation in left BA45, suggesting that full recruitment of this area may be necessary for proper resolution of interference (Jonides, et al., 2000). This interpretation is corroborated by evidence from a patient with an acquired lesion which included left BA45 who showed abnormally large interference

effects on high-recency trials (Thompson-Schill, et al., 2002), while frontal patients with lesions sparing this area showed normal interference effects.

It is hypothesized that two sources of information are potentially used to produce a response in this interference version of the item recognition task (*IVIR task*): 1) familiarity of the probe, and 2) an explicit contextual or temporal tag that marks a probe item as belonging to a list (such as proposed by Monsell, 1978). For positive probes or for low recency negative probes, these two types of information are concordant with each other. In contrast, on high recency negative probes, familiarity would be relatively high but the probe would not be “tagged” for the current list. These probes would require inhibition of the potentially misleading familiarity information. We have proposed that left BA45 is recruited to meet the increased selection demands and resolve the interference produced by this conflicting information (e.g., Nelson et al., 2003).

A strong parallel can be drawn between the hypothesized function of the left IFG in interference resolution in working memory and a hypothesized function of the same area in semantic memory retrieval. Thompson-Schill et al. (1997) specifically varied the amount of “selection” (and thus interference) required in three different semantic tasks, two of which commonly activate inferior frontal regions in neuroimaging experiments (verb generation and object classification) and one type of task which does not (noun comparison). The authors reported greater activation in left IFG for high-selection versus low-selection versions of all three tasks. The authors proposed that “activation of the left IFG during semantic tasks is the result not of semantic retrieval *per se*, but of the need to select some relevant feature of semantic knowledge from a set of competing alternatives.” (p. 14792). An increased interference effect was found in another study

with a group of patients with left IFG lesions (Thompson-Schill, et al., 1998). Control patients whose lesions did not include left IFG did not show an exaggerated interference effect.

The strong similarity between the interference resolution processes proposed suggests that the tasks of Jonides et al. and Thompson-Schill et al. may be tapping a common executive processing component. If these two otherwise highly divergent tasks also recruited a common neural substrate specific to high-interference trials, this would provide powerful converging evidence for mapping a specific executive process to the shared cortical region. The reported activations associated with high-interference conditions were very similar and overlapping, although the peak activations straddled the borders of Brodmann's area 45 (Jonides, et al 1998) and Brodmann's area 44 (Thompson-Schill, et al. 1997). The similar anatomical locations of the activations from these two tasks should be interpreted with caution, however. The findings are from two different groups of participants measured with two different imaging techniques (PET vs. functional MRI), so the overlapping but non-identical activations may arise from distinct but adjacent cortical regions. Likewise, work from frontal-lesion patients has yet to reveal whether or not these two effects can dissociate.

In the present study, we examine the patterns of activation associated with interference resolution in a verbal working memory task and also a verb-generation task in a group of participants who performed both tasks during a single fMRI session. This approach provides a sensitive measure of the degree of overlap between the respective patterns of activation, and potentially allows mapping a particular executive processing component shared by both tasks to a specific region of frontal cortex.

## MATERIALS AND METHODS

### *Participants*

The participants were 22 young adults (18-30 years old, 12 female). Participants were recruited from the University of Michigan community through newspaper and posted advertisements. All participants were right-handed and had no history of neurological or psychiatric illness. None of the participants was taking medication or had a medical condition that could affect blood-oxygen levels (e.g. high blood pressure). All participants gave informed consent, and the study was approved by the University of Michigan Institutional Review board. All were native English speakers and had normal vision or wore contact lenses. Seventeen of these participants comprised the population of study of an earlier report on the verbal working memory task (Nelson, et al., 2003).

### *Tasks and Stimuli.*

Participants performed six total experimental blocks. Blocks 1 and 4 were verb generation, while the remainder were item recognition. After initial instruction, participants also received a 10-trial practice session of the item recognition task and a full block of the verb generation task before entering the scanner.

Item recognition with interference (IVIR): Participants performed 192 trials of the item recognition task, divided into four runs of 48 trials each. Trials were pseudorandomized within each run, and half the participants received runs 1 and 2 of the pseudorandom list first, and half received runs 3 and 4 first.

At the start of a trial, four lowercase letters (consonants only, excluding lowercase “L”) and a central fixation cross were presented in a square pattern for 1,500 ms. After a 3,000-ms delay, a 1,500-ms probe followed, which consisted of a single uppercase letter. On 50% of the trials, this probe was a member of the current trial’s set of four target letters (positive trials), and on 50% of the trials it was not (negative trials). Disregarding case, participants responded with a “yes” for a positive probe, with their right index finger, or with a “no” for a negative probe, with their right middle finger. A variable length inter-trial interval (ITI) followed (96 ITIs of 1.5 sec, 48 ITIs of 3 sec, 24 ITIs of 4.5 sec, 16 ITIs of 6 sec, 4 ITIs of 7.5 sec, and 4 ITIs of 9 sec). Participants never received more than two positive or two negative trials in a row.

The target sets were constructed so that each contained one letter in common with the preceding trial’s target set, but with no other letter in common with the previous two trials. The probe letter for positive trials was a member of the current target set, but was not a letter in common with either the preceding or subsequent trial’s target set. The probe for a non-familiar negative trial was a letter neither in the current target set nor the target set of the previous two trials.

In addition, there were three types of familiar trial: familiar, highly familiar, and response conflict trials. The probe for familiar negative trials was a letter in the immediately preceding target set. The probe for highly familiar negative trials was a letter in the previous two trials. The probe for response-conflict trials was a member of the previous target set, and was also a positive probe on the previous trial. For negative trials, each of four types of negative trials was represented equally. For the current analyses, we will group familiar and highly familiar trials and compare them to non-familiar trials.

Response conflict trials are excluded from subsequent analyses. For this report we do not consider the quantitative differences in activation between highly familiar and familiar trials, nor the qualitatively different activations arising from familiarity-based conflict and response-based conflict; instead see Nelson, et al. (2003).

Verb generation: In the generation task, participants were asked to generate a verb related to a visually presented noun. For each of the words, the participants' responded by pressing a button with their right index finger when they had generated a word.

Participants first practiced with experimenter supervision while saying the generated noun out loud, but generated the noun silently while in the scanner. In the condition with high selection demands (the "MANY" condition), items were nouns with many appropriate associated responses (e.g. BALL – THROW, KICK, BOUNCE etc.) without any clear dominant response. In the low selection condition (the "FEW" condition), items were nouns with few associated responses or with a clear dominant response (e.g. SCISSORS – CUT). Two control tasks were also included; (i) participants were asked to silently read words (nouns) that were presented visually for 4 s each and respond by pressing the response button (READ), and (ii) a low-level baseline (rest). Six nouns were presented in each block (except for baseline), and each word was presented for 4 s. The study was divided into two runs, each with 8 MANY, 8 FEW, 8 READ, and 4 Baseline blocks, (see Persson et al., under review, for more details).

*fMRI Methods*

Images were acquired using a 3T whole-body MRI scanner (General Electric) equipped with a standard quadrature headcoil. Functional T2\* blood oxygenation level-dependent (BOLD) images were acquired using a spiral sequence with 25 contiguous axial 5 mm slices [repetition time (TR) = 1500 ms, echo time (TE) = 25 ms, flip angle = 90°, and field of view (FOV) = 24 cm]. A T1-weighted gradient echo (GRE) anatomical image was also acquired by using the same FOV and slices as were used in the functional scans (TR = 275 ms, TE = 35 ms, and flip angle 90°). In addition, a 60-slice high resolution set of anatomical images was acquired by using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (TR = 35 ms, TE = 3 ms, flip angle = 35°, and FOV = 24 cm, 2.5 mm slice thickness). The T1 GRE images were acquired at the start of the scanning session, and the SPGR images were acquired at the end of the scanning session.

Experimental tasks were presented using E-Prime (Psychology Software Tools, Pittsburgh) and the IFIS 9.0 system (MRI Devices, Waukesha, WI) and responses were collected using a 10-button response pad. Head movement was minimized with foam padding, as well as a restraint that was strapped across the participants' foreheads.

Images were corrected for slice time differences using a local 17-point sinc interpolation program (Oppenheim et al., 1999). Head movement was adjusted by using the Automated Image Registration (AIR) software (Woods et al., 1998). Subsequent preprocessing and analyses were done using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; [www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)). SPGR images were corrected from signal inhomogeneity using a toolbox developed by G. Glover and K. Christoff ([www-psych.stanford.edu/~kalina/SPM99/Tools/vol\\_homocor.html](http://www-psych.stanford.edu/~kalina/SPM99/Tools/vol_homocor.html)), and coregistered to the T1 images. The skull was removed from the SPGR images using the Brain Extraction Tool

from FSL (Smith, 2002), and normalized to a T1 template in the Montreal Neurological Institute (MNI) space. The same normalization procedure was used for the functional images. After spatial normalization, the functional images were smoothed using an 8-mm full width at half maximum Gaussian filter. All images were high-pass filtered and scaled to a global mean intensity of 100.

All subsequent analyses of the functional images were performed using the general linear model implemented in SPM99. For the verb generation task, all conditions (READ, FEW, and MANY) were modeled as a fixed response (box-car) waveform convolved with the hemodynamic response function (HRF). For the item recognition task, event-onset times for the probes of the five trial types (positive probes, and four kinds of negative probe types: non-familiar, familiar, highly familiar, and response-conflict) were convolved with the canonical hemodynamic response function. Statistical parametric maps (SPMs) were generated using t-statistics to identify regions activated according to the model. Statistical models were fit for each participant, and contrasts of interest were estimated. Group data were analyzed using a random-effects model.

The first two trials were omitted from each block to prevent artifacts of T1-equilibrium from contaminating contrasts. For each block these trials comprised one “positive” trial and one “negative, non-familiar” trial.

## RESULTS

### *Behavioral results.*

The behavioral results are summarized in Table 1. Most importantly, the expected interference effects were found for both tasks. In the item recognition task, participants

took 87ms longer to make a response, ( $t(21)=4.96$ , one-tailed  $P<.001$ ) and were 5.1% less accurate ( $t(21)=4.73$ , one-tailed  $P <.001$ ) on familiar negative probes than non-familiar negative probes. In the verb generation task, participants were 214ms slower ( $t(21) = 1.98$ , one-tailed  $P=.03$ ) to respond to noun probes with many alternative responses than noun probes with few alternative responses.

*Neuroimaging results:*

The blocked design of the verb generation task typically has greater statistical power than the event-related design used in the item recognition task; any lack of activation in the item recognition task compared to the verb generation task could be attributable to this statistical issue rather than cognitive differences between the tasks. To address this issue, we also present results from the item recognition task at an arbitrary low threshold of  $T = 3.0$  in addition to standard statistical tests.

Left inferior frontal gyrus analysis: Of greatest interest is the interference related activity in the left inferior frontal gyrus previously shown in tasks similar to the ones in this study. So, we first present an analysis restricted to the left IFG before considering other activations in a whole brain analysis. The entire left IFG was defined anatomically using the WFU-PickAtlas utility (Maldjian, et al. 2003). Localization of activations to specific Brodmann's Areas was achieved using the Talairach Daemon utility (cite) after converting the coordinates to Talairach space (using a transform developed by M. Brett, Medical Research Council Cognition and Brain Sciences Unit, Cambridge, U.K., which can be accessed at [www.mrcbu.cam.ac.uk/Umaging/mnispace.html](http://www.mrcbu.cam.ac.uk/Umaging/mnispace.html) ).

For the verb generation task, with an anatomically-based region of interest (ROI) analysis on the left IFG, a “Many” – “Few” contrast reveals a large cluster of activation (79 voxels, FWE  $p < .05$ ) with the peak activation ( $T = 4.41$ ) at  $x = -48.75$ ,  $y = 26.25$ ,  $z = 20$  (MNI coordinates) in Brodmann’s Area (BA) 45 and a secondary peak ( $T = 4.13$ ) at  $x = -45$ ,  $y = 22.5$ ,  $z = 0$ , in BA 47.

For the IVIR task, with an anatomically based region of interest (ROI) analysis on the left IFG, a familiar – non-familiar contrast revealed a small, 2 voxel activation with a peak activation at  $-48.75$ ,  $22.5$ ,  $20.0$ , (FWE  $p < .05$ , peak  $T = 4.13$ ) in BA 45; at a reduced threshold of  $t = 3.0$  the cluster size increased to 12 voxels, but no other additional clusters are revealed.

The activation from the item recognition task is entirely contained within the area defined by the many/few conflict activation from the verb generation task. Even at the low threshold of  $T = 3.0$ , no voxels were unique to the working memory interference-related activation. Also, the peak voxels of activation from each contrast are immediately adjacent to each other (see Figure 1).

Whole-brain analysis. Previous studies have revealed considerable selection-related activation outside of left IFG for the verb generation task, including medial frontal cortical areas, but there is little if any evidence for activation in the IVIR task outside of left IFG. To help determine if the hypothesized selection function is localizable to a single cortical area, or if it arises from a network of activations, we performed a whole-brain analysis for each task.

Results from a whole brain analysis of the verb generation Many – Few contrast (False detection rate [FDR; see Genovese, et al., 2002],  $p < .05$ ; all activations larger than 5 voxels) are shown in Table 2.

Using the same threshold did not reveal any activations in the familiarity contrast from the item recognition task. With an arbitrary low threshold of  $T=3.0$ , a cluster corresponding to the left IFG activation in the preceding region-of-interest analysis is revealed, as are weaker clusters in the caudate ( $x = -7.5, y = 0, z = 15$ , 12 voxels, peak  $T=3.52$ ) and medial frontal cortex (Brodmann's area 6,  $x = -3.75, y = 3.75, z = 60.0$ , 6 voxels, peak  $T=3.33$ ) and a single isolated voxel in white matter near the posterior cingulate ( $x = 3.75, y = -67.5, z = 15$ ; peak  $T=3.06$ ).

## DISCUSSION

The results show that the region of activation that is correlated with interference resolution in a verbal working memory task is superimposed on the cortical region that is recruited by increased selection demands in semantic retrieval. Although each region of activation derives from highly divergent task types, the high degree of overlapping cortical activity suggests that the two different contrasts were successful in isolating a shared selective process. This strategy of identifying overlapping cortical activations is similar to the strategy used by Thompson-Schill (1997) to isolate this specific process, except in that report the three tasks were all from the domain of semantic memory retrieval. The current results indicate that the neural process in the left inferior frontal gyrus found in the domain of semantic memory is not restricted to semantic memory, but

is the same process found in resolution of proactive interference in a verbal working memory task.

*Extra activation from verb generation task:*

The contrast for Many-Few from the Verb Generation task showed substantially more activation than the familiarity contrast from the IVIR task, including a larger swath of activation in left IFG that extends into area 47, as well as additional activations in other portions of the brain including medial frontal cortex. In contrast, for interference resolution in the verbal working memory task, there is only weak evidence for activation outside of left BA45 (in the caudate and medial frontal cortex). This extra activation in the verb generation task may be due in part to the greater statistical power of the experimental design; however, the statistical values for the peak activations in each task are not dramatically different (T values: 4.41 vs. 4.13).

Alternatively, the more focal activation of the IVIR contrast may be due to more effective isolation of the proposed cognitive process. First, the event related analysis model for the IVIR task was specific to probe activity, while the model for the verb generation task included activity from over the full course of multiple high-selection trials. Second, the several potential candidate representations evoked in the MANY condition of the verb generation task may have produced additional processing and selection demands. Finally, introspective reports by the current and past participants indicate differences between the tasks; while participants often report some conscious insight into the differences in generating responses for various nouns, participants seem to be generally unaware of the subtle trial-to-trial manipulations in the IVIR task. This

may indicate greater conscious, strategic processing in the verb generation task on high-interference trials.

*Left BA45 activation in episodic encoding.*

Activation of Brodmann's Area 45 in the left hemisphere is also found in other cognitive domains; in particular, episodic encoding is often associated with left BA45 activation. Area 45 activation found in episodic encoding tasks may reflect retrieval of relevant semantic information for deeply encoding a target. For example, left IFG activations during episodic encoding are stronger during "deep" encoding using semantic judgments of test items (Kapur, et al., 1996; Otten et al., 2001; Baker, et al., 2001). Results from Reynolds, et al. (2004) demonstrate that episodic encoding-related left IFG activity is higher on task conditions that increase semantic selection demands yet result in lower subsequent recognition accuracy, suggesting the mechanisms are not related to successful episodic encoding *per se*, but rather are related to selection of semantic information. It is therefore plausible that left IFG activation present in many episodic memory tasks reflects the same process isolated in the current report.

*Organization of Prefrontal cortex function:*

The current results suggest that a discrete component of executive processing can be localized to a specific area of cortex within left IFG (with weak indications of a small network also involving the caudate and a portion of medial PFC). These results support a localizationist view of prefrontal cortex, or a hybrid localizationist-network view of PFC function (such as Duncan and Owen, 2000). Each component task used was verbally-based, so the current results do not address the content-specificity of this process directly; however, results analogous to the verbal interference effect from the current study have

been found using face stimuli (Brandon, et al., 2003), so a test of the content specificity of this process is feasible.

The current results show interference resolution related activation for both tasks in left IFG; previously, right IFG has been proposed as a site of inhibitory processing (Aron, et al. 2004). The right hemisphere IFG has been implicated in dealing with tasks such as response inhibition (Konishi, et al. 1998, 1999; Rubia, et al. 2003; Aron et al. 2003) and task-set switching (Konishi, et al. 1999; Aron et al., in press). Exploring the relation between these two similar systems could provide further clarification of their respective roles and status within a developing taxonomy of executive functions.

Further research to clarify the boundary conditions for recruitment of the left IFG process discussed in this paper holds the potential to specify a basic executive processing component, and by contrast to better define the role of other, closely related frontal subsystems.

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Table 1

Item Recognition	<u>Yes</u>	<u>No</u>	
		Non-familiar	Familiar
Reaction Time	834 ms	840	926
(Standard error)	(33.7)	(35.0)	(40.3)
Accuracy	91.6 %	97.9	92.9
(s.e.)	(1.47)	(0.80)	(1.40)
Verb Generation	<u>Read</u>	<u>Generate</u>	
		Few	Many
Reaction Time	694 ms	1180	1394
(s.e.)	(74.3)	(70.5)	(85.3)

TABLE 2

Verb Generation interference (FDR &lt; .05; all clusters &gt; 5 voxels)

MNI coordinates	Label	Size in voxels
Lateral Frontal		
-49 26 20	Left BA45	152
-45 23 0	<i>Left BA47</i>	<i>(sub-peak)</i>
-26 15 60	Left BA6	11
-30 56 20	Left BA10	6
-38 -4 60	Left BA6	5
Medial Frontal		
-4 8 60	Left BA6	37
-4 26 50	<i>Left BA8</i>	<i>(sub-peak)</i>
Temporal		
-53 -56 -5	Left BA37	15
Cerebellum		
0 -60 0	Medial vermis	22

Figure 1. Activity in left inferior frontal gyrus in the verb generation interference resolution contrast (light blue) with a family wise error of  $p < .05$  with a left inferior frontal gyrus region of interest analysis, and the item recognition conflict condition (dark blue) at a lower threshold of  $t=3.0$  (at FEW of  $p < .05$  a small region near the peak was also active). Activity is projected onto an inflated brain surface, with the relevant portion fully flattened in the inset. The small dark dot marks the peak activation for the verb generation conflict contrast; the small light dot marks the peak activation for the verb generation conflict contrast. Projections prepared using CARET software (cite).

FIGURE 1

