

of a working memory task, which places high demand on interference control by repeating items frequently from one trial to the next (Persson et al., 2007). More specifically, subjects completed two blocks of a verb generation task, a pretest and a post-test block, with either a recent probes task or item recognition without recent probes intervening. The verb generation task included nouns with many verb associates, the so-called “many” or high interference condition, and nouns with few verb associates, the “few” or (low interference) condition of verb generation. We found that average RT in the “many” condition was significantly increased at post-testing when a recent probes task intervened. In addition, we found the fatigue effects were specific: Behavioral performance was unaffected when interference control was minimally required by the intervening working memory task and when the intervening task relied on a different executive processes (i.e., response inhibition). In an additional experiment in which we replaced the pretest and post-test verb generation task with an episodic memory task featuring proactive interference (so that, like recent probes, it also required interference control), a similar episodic memory impairment in interference control was observed because of the intervening recent probes task.

Although the precise cognitive operations shared by these high interference conditions remain to be specified (see Persson et al., 2007, for a discussion), these observations of selective “negative” transfer between specific tasks is consistent with the proposal that some component operations are shared. Critically, recent imaging work provides converging evidence for shared components by demonstrating that the engagement of interference control in the recent probes task and during verb generation activates an overlapping region in left inferior frontal gyrus (IFG; cf. Atkins & Reuter-Lorenz, 2011; Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009; Jonides & Nee, 2006; Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997), suggesting that process-specific fatigue effects on behavior may be because of the depletion affecting this common neural resource.

Nevertheless, despite behavioral demonstrations of resource depletion, the neural correlates of this phenomenon are largely unknown. In one relevant study, Richeson et al. (2003) found that individuals with high racial bias showed greater activation in right dorsolateral PFC during simulated interracial interactions, presumably reflecting their need for more cognitive control. These individuals also showed greater behavioral interference on a subsequent Stroop task. Moreover, the magnitude of right dorsolateral PFC activity during the race task predicted Stroop performance, implying that dorsolateral PFC resources were depleted by the control demands of the prior task. This important result implicates shared cognitive control resources in the depleting interracial task and the (depleted) subsequent Stroop task; however, the recruitment of this common resource by both tasks was not directly demonstrated. Furthermore, it is not yet known

how the recruitment of a cognitive control process differs in the normal (i.e., baseline) and the depleted state. Therefore, despite the consequences that fatigue of executive control might have in everyday life, the neural basis for these effects is currently unknown.

Here we investigate the neural underpinnings of interference control depletion in a pre/post continuous acquisition fMRI design using the same tasks for which we have previously demonstrated strong and selective behavioral effects of process-specific fatigue (Persson et al., 2007): working memory with recent probes and verb generation. We replicate our finding that performing a high interference working memory task impairs the ability to control interference during verb generation while leaving low interference verb generation unimpaired. Furthermore, by obtaining fMRI measurements before, during, and after working memory blocks with recent probes, we demonstrate the recruitment of shared resources in the depleting and depleted tasks and characterize the effect of resource depletion on neural activation. By including a control group that performs the verb generation before and after a minimally depleting task, we can measure the effects of repeated task performance in the absence of process-specific fatigue. Also, by obtaining imaging measurements for both the depleting and the depleted tasks, we can identify regions of overlap between the two tasks and examine their role in depletion effects. Indeed, past behavioral and imaging results predict that fatigue-induced deficits in interference control should be associated with altered activation in left IFG. This study was designed to test this hypothesis.

In the current study, we compared the magnitude of semantic interference during the verb generation task, before and after the performance of a depleting item recognition task. Semantic interference in verb generation was measured by the RT difference between the “many” and “few” conditions (see Methods). The “resource depletion” group also performed a high interference item recognition task intended to deplete interference control, which would adversely affect the subsequent verb generation task. Their item recognition task included a high proportion of negative trials (requiring a “no” response) in which the probe was a member of the memory set on the preceding one or two trials. These so-called “recent probes” trials evoke proactive interference leading to slower, more error-prone responses than trials with non-recent probes. A second group of participants, the control group, performed the verb generation task before and after a low interference version of item recognition that did not include recent probes and where the depletion effects on the control of semantic interference were expected to be minimal. We refer to the blocks of working memory task as the “fatigue blocks.”

We provide new brain imaging evidence that depletion-induced performance decrements in resolving interference during the verb generation task are associated with reduced BOLD signal in task-relevant circuitry,

including left IFG and other sites associated with cognitive control. Depletion-related changes in activation magnitude correlated with behavioral changes, suggesting that decreased recruitment of task-relevant regions, including left IFG, contributes to impaired interference control. Moreover, we document the recruitment of additional sites in the opposite hemisphere following depletion.

METHODS

Participants

Thirty-two young adults (24 men; age range = 18–30 years) were recruited from the Umeå University community through posted advertisements. All participants were right-handed native Swedish speakers who reported no existing neurological or psychiatric illness. Vision was normal or corrected to near normal using MRI compatible glasses or contact lenses. All participants gave informed consent to participate in the study. The investigation was approved by the ethics committee in Stockholm.

Procedure

Participants were randomly assigned to one of two groups: one performed a high interference version of the recent probes item recognition task (resource depletion group), and the other group performed a low interference version of the item recognition task without recent probes (control group; Figure 1A). Participants first completed a health screen over the telephone to ensure their suitability for the study. The fMRI scanning took place at the MRI research facility where participants were given task instructions and completed practice versions of each of the tasks before the start of the scanning protocol. Also, the *n*-back working memory task was administered subsequent to the scanning protocol and a standardized intelligence test (Ravens Standard Progressive Matrices) was administered in a separate behavioral session. Importantly, there were no group differences on either Ravens SPM [$t(29) = 0.31, p = .76$] or performance on the *n*-back task [correct responses: $F(1, 29) = 0.43, p = .519$; RT: $F(1, 29) = 1.53, p = .23$].

fMRI Tasks

Item Recognition

During the fatigue blocks, the control group and the depletion group performed different versions of an item recognition task, each of which had 144 trials (Figure 1A). In both versions, participants must retain a memory set of four items for several seconds and then respond to a recognition probe indicating whether or not it was a member of the set. At the start of a trial, four lowercase letters (consonants only, excluding lower-

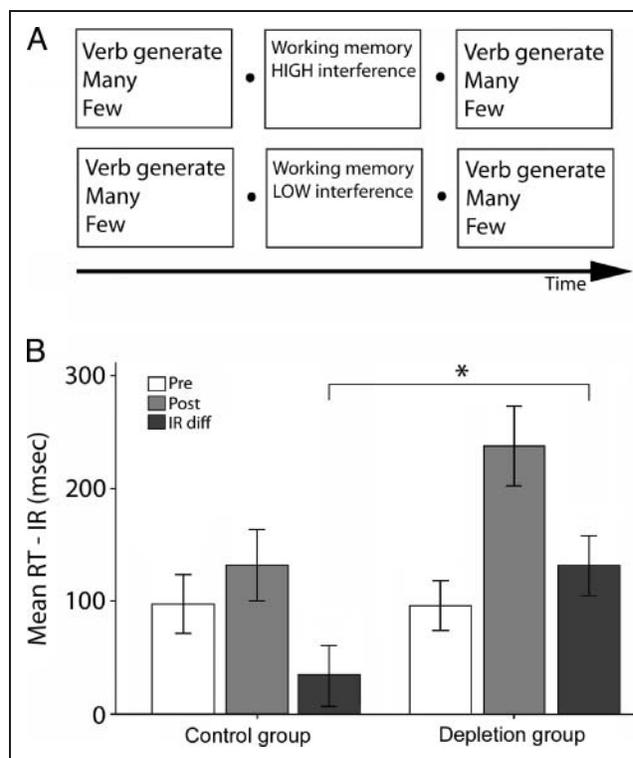


Figure 1. (A) Schematic depiction of the behavioral protocol. Participants were randomly assigned to one of two groups: one performed a high interference version of the recent probes working memory task (resource depletion group), and the other group performed a low interference version of the working memory task without recent probes (control group). From left to right, the task administered before the fatigue session (verb generation with high [many] and low [few] interference trials), the fatiguing working memory task (high/low), and the verb generation task administered after the fatigue session with high (many) and low (few) interference trials. (B) Mean many–few difference scores (RT), as a function of group (resource depletion/control), and time (before/after the fatigue session). Error bars depict the SEM.

case “L”) and a central fixation cross were presented in a square pattern for 1500 msec. After a 3000-msec delay, a 1500-msec probe appeared, 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 (72 ITIs of 1.5 sec, 36 ITIs of 3 sec, 18 ITIs of 4.5 sec, 12 ITIs of 6 sec, 3 ITIs of 7.5 sec, and 3 ITIs of 9 sec). Participants never received more than two positive or two negative trials in a row. For all RT analyses, participants’ medians were used to minimize the effect of extreme values. Critically, for the control group, all negative probes were nonrecent, meaning that the probe letter had not appeared in the current memory set nor in the sets on the preceding one or two trials.

Item Recognition with Recent Probes

The depletion group performed an item recognition task with the same parameters described above with one exception. Two thirds of the negative trials were recent probes. These trials contained probes that were not members of the memory set on current trial but that had been in the immediately preceding or the previous two target sets. These recent negative probes require subjects to overcome the familiarity because of the probe's recency to generate a correct negative response. Longer RTs and higher error rates are typically associated with the need to resolve interference on these trials. Therefore, the difference between RT to recent and non-recent probe trials indicates the magnitude of proactive interference. Trials were pseudorandomized (truly random trial orders were not feasible to maintain the proper relations between each trial's probes and previous probes and targets).

Verb Generation Task

Both groups performed the verb generation task before and after the fatigue blocks. In this task, participants were asked to generate silently a verb related to a visually presented noun. All nouns were in Swedish. For each of the nouns, the participants responded by pressing a button with their right index finger when they had generated a verb. Participants first practiced with experimenter supervision while saying the generated verb out loud. However, they generated the verb silently while in the scanner. In the condition with high interference 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 interference condition (the "few" condition), items were nouns with few associated responses or with a clear dominant response (e.g., scissors—cut). In this task, interference was measured by subtracting the RTs for low interference trials from the RTs for high interference trials (i.e., many vs. few). These scores are referred to as many–few difference scores. The RT difference between the many and few verb generation conditions provides a measure of semantic interference. Again, for all RT analyses, participants' medians were used to minimize the effect of extreme values. Although no verbal responses were made in this version of the task, previous data from our laboratory show that the interference effect is similar for verbal (RTs recorded using a voice key) and silent responses, paired-sample $t(14) = 1.92$, ns , and that subjects generate verbs covertly in accordance with task instructions. Covert fluency tasks have previously been implemented successfully to study verbal fluency using fMRI (Hirshorn & Thompson-Schill, 2006; Persson et al., 2004; Schlösser et al., 1998). A baseline (rest) task was also included. Four nouns were presented in each 16 sec block (except for baseline), and each word was presented for 3.5 sec with a 0.5-sec ITI. Each of two runs

(pre- and post-fatigue blocks) included 8 many, 8 few, and 4 baseline blocks.

Image Acquisition

The study was carried out on a Philips 3.0-T high-speed EPI device using a quadrature headcoil. For functional scanning, the following parameters were used: repetition time = 1512 msec (31 slices acquired), echo time = 30 msec, flip angle = 70°, field of view = 22 × 22 cm, 64 × 64 matrix, and 4.65 mm slice thickness. To avoid signals arising from progressive saturation, 10 dummy scans were performed before image acquisition. Structural high-resolution T1 images were also acquired: a 3-D turbo field-echo sequence was used with the following parameters: repetition time = 10.5 msec, echo time = 5 msec, flip angle = 8°, and field of view = 24 × 24 cm. One hundred seventy sagittal slices with a slice thickness of 1 mm were acquired in 336 × 332 matrices and reconstructed to 800 × 800 matrices. All images were sent to a PC and converted to Analyze format.

Data Analysis

Functional images were preprocessed and analyzed using SPM8 (Wellcome Department of Imaging Science, Functional Imaging Laboratory) implemented in Matlab 7.6 (Mathworks, Inc., Natick, MA). After correcting for differences in slice timing within each image volume, all images were realigned to the first image volume acquired, normalized to standard anatomic space defined by the MNI atlas (SPM8), and spatially smoothed using a 8.0-mm FWHM Gaussian filter kernel.

Blocked (verb generation) and event-related (item-recognition task) effects were separately modeled in the framework of the general linear model as implemented by SPM8. Event-related transient responses were modeled as regressors containing delta functions representing onsets of the stimuli, whereas blocked sustained responses were modeled with a boxcar function. All regressors of interest were convolved with the hemodynamic response function. Covariates of no interest included the six realignment parameters, which accounted for motion artifacts. Single-subject statistical contrasts were set up using the general linear model, and group data were analyzed in a random-effects model that differentiated between the resource depletion and control groups. Statistical parametric maps were generated using t statistics to identify regions activated according to the model.

The Marsbar toolbox (marsbar.sourceforge.net/) was used to create functional ROIs including all suprathreshold voxels within a significant cluster derived from the SPM results at the group level ($p < .001$, uncorrected and cluster corrected at $p < .05$). Each ROI contained a minimum of 30 contiguous voxels. Marsbar was also used to extract each

ROI's mean parameter estimate value across all voxels contained in each cluster for high and low interference conditions in the verb generation task for each participant. The parameter estimates were then used for plotting the results in SPSS, as well as for performing brain-behavior correlations. The ROIs are depicted in Figures 3 and 4.

RESULTS

Behavioral Data

The first sets of analyses demonstrate the successful replication of semantic interference in the verb generation task for both groups and proactive interference in the recent probes task for the depletion group. Consistent with previous observations, covert generation of verbs in response to nouns with many associates takes longer than in response to nouns with one or few dominant associates (Nelson et al., 2009; Persson et al., 2007; Thompson-Schill et al., 1997): The average median RT was significantly slower in the many (high interference) condition compared with the few (low interference) condition, $F(1, 29) = 84.4, p < .001, \eta_p^2 = 0.74$. This effect was significant both before (pre) and after (post) the fatigue blocks (i.e., the item recognition task; pre: $F(1, 29) = 33.8, p < .001, \eta_p^2 = 0.54$; post: $F(1, 29) = 53.5, p < .001, \eta_p^2 = 0.65$). For the recent probes item recognition task and also consistent with previous findings (Nelson et al., 2009; Nee, Jonides, & Berman, 2007; Persson et al., 2007), RT analyses confirmed the presence of proactive interference in the depletion group. A one-way repeated-measures ANOVA on RT to recent negative trials (median RT = 953.2) compared with nonrecent negative trials (median RT = 884.4) was significant, $F(1, 14) = 8.88, p = .01, \eta_p^2 = 0.39$, indicating that participants were slower on recent negative trials. Accuracy on the item recognition task was consistently high (greater than 90%) and did not differ reliably between groups or trial types.

To explicitly test the notion that resource depletion is specific to the depletion group only and primarily affects high interference trials, we performed two complementary sets of analyses. The resource depletion hypothesis predicts that the magnitude of interference during verb generation before and after the item recognition task will depend on the extent to which these tasks engage the same executive processes (here interference control). Accordingly, the depletion group who performed the item recognition task with recent probes should show a reduced ability to resolve interference after the fatigue blocks compared with the low interference group who performed an item recognition task that placed minimal demands on interference control. The first analysis tested this prediction by comparing the many-few RT difference in the verb generation task for the two groups (depletion vs. control group) before and after (pre; post) the fatigue blocks (Figure 1B). There was a main effect of Time, $F(1, 14) = 9.41, p = .01, \eta_p^2 = 0.25$, suggesting an overall in-

crease in interference after the fatigue blocks. This main effect was modified by a Group \times Time interaction that approached significance, $F(1, 28) = 8.88, p = .07, \eta_p^2 = 0.11$; as predicted, the increase in interference was significantly greater in the depletion group [$t(15) = 1.86, p < .05$, one tailed] compared with the control group. Planned comparisons of the many-few difference scores showed that these scores increased from before to after the fatigue blocks for the depletion group [$t(15) = 2.97, p < .05$], but not for the control group [$t(15) = 1.08, p = .30$]. Importantly, there was no Group difference in the many-few difference scores before the fatigue blocks [$F(1, 29) = 0.03, p = .97$]. The second analysis, which was important for assessing the specificity of these effects, tested whether the fatigue effect (demonstrated as increased interference scores between pre- and post-testing) also was because of a specific reduction in performance (i.e., increased RT) on high interference trials only after the fatigue block session (post-testing) specifically for the depletion group. Such an effect would indicate that the resource depletion group had selectively reduced performance on high interference trials, with minimal effect on low interference trials. First, using a Group (resource depletion/control) \times Condition (high/low interference) \times Time (pre/post-fatigue blocks) ANOVA on the RTs we found that the three-way interaction approached significance, $F(1, 29) = 3.46, p = .073, \eta_p^2 = 0.11$, suggesting specific Group \times Condition \times Time effects, consistent with the analysis of difference scores. These results were followed up by paired comparisons on the pretesting scores showing that the groups did not differ on either high (many) interference, $F(1, 29) = 2.81, p = .16$, or low (few) interference, $F(1, 29) = 1.98, p = .18$, trials, thus establishing that the groups performed equally well before the fatigue blocks. Next, using paired comparisons on the post-testing scores, we found a reliable difference on high interference trials, $F(1, 29) = 3.85, p < .05$, whereas the Group difference was nonsignificant for low interference trials, $F(1, 29) = .942, p = .340$. Together, these analyses indicate that the fatigue effect was specific to high interference (many) trials in the resource depletion group.

Also, we performed additional analyses to examine whether these effects were related to (1) individual differences in performance on the item recognition task and (2) whether individual differences in the magnitude of fatigue were related to general intelligence (Gf) as measured by Ravens SPM. First, in a partial correlation analysis, we investigated the relationship between performance (RT) on high interference trials in the recent probes task and the amount of fatigue in the verb generation task while also controlling for performance on low interference trials (i.e., baseline performance) by including this measure as a covariate. We found no evidence of a direct relationship between the performance (RT) on high interference trials in the recent probes task and the amount of fatigue in the verb generation task (as assessed by the difference in RT between the "many" [high

interference] and “few” [no interference] trials pre- to post-fatigue; $r < 0.3$). Second, no relationship was found between the magnitude of the behavioral depletion effect (again, assessed by the difference in RTs between the “many” [high interference] and “few” [low interference] trials pre- to postdepletion) and performance on Ravens SPM ($r < 0.3$), suggesting no direct relationship between general intelligence and sensitivity to the fatigue manipulation. However, we found a significant positive correlation between performance on high interference trials in the item recognition task (resource depletion group; $r = .61, p < .05$) and Ravens, when controlling for performance on low interference trials. This result is in line with previous findings of a relationship between measures of general intelligence (gF) and working memory performance (Conway, Kane, & Engle, 2003).

In summary, these behavioral results reveal a reduced ability to resolve interference during verb generation following a verbal working memory task that placed high demands on interference control. This effect was specific to the depletion group. This behavioral result suggests the high interference condition of the working memory, and verb generation tasks are mediated by a common, resource-limited cognitive control mechanism that can be selectively depleted.

Imaging Data

First, to specify regions involved in interference control during verb generation, we contrasted the many relative to few verb generation conditions before the item recognition task. This contrast was identical for both subject groups. For this and all subsequent analyses (unless specifically noted) an uncorrected threshold of $p = .001$ was

initially applied for each contrast of interest and only clusters that had a family-wise error (FWE) corrected cluster-level $p < .05$ are reported. Cluster extent threshold was obtained from the CorrClusTh.m program (Thomas Nichols; www.sph.umich.edu/~nichols/JohnsGems5.html), which reports the statistically appropriate size threshold for identifying cluster-level (FWE) corrected clusters at an alpha level of $p = .05$ based on the number of voxels in the data, smoothness of the data, and uncorrected threshold used (i.e., $p = .001$). Critically, regions from this contrast were also expected to show changes in activity associated with depletion and thus served as ROIs in a subsequent hypothesis-driven test of depletion-induced activity changes assessed in a Time \times Group interaction (see below). This many–few contrast indicated significant activation in several expected regions, including the left IFG, cerebellum, ACC, and the striatum (Table 1). Note that this method of selecting ROIs has the advantage of identifying regions that are task-relevant before the fatigue blocks (cf. Kelly & Garavan, 2005).

The second step was to identify the regions involved in the control of interference in working memory to test our specific hypothesis regarding the contribution of left IFG to a common interference control process. We therefore compared recent probe trials to nonrecent probe trials in the resource depletion group. Note that the interference contrasts in the verb generation task were based on data from all subjects ($n = 30$), whereas only half the subjects (the resource depletion group; $n = 15$) performed the recent probes task. This contrast revealed greater activation in the left IFG (Figure 2B) for high compared with low interference trials (see also Table 2 for a full set of results from this comparison).

An additional conjunction analysis contrasting high interference and low interference conditions for both

Table 1. Brain Regions Activated during Verb Generation

Contrast	Region	Side	<i>x</i>	<i>y</i>	<i>z</i>	BA	<i>t</i>	Size (mm ³)
Many–Few	Superior PFC	L	–8	16	50	8	5.47	3328
	Striatum	L	–8	4	–4		4.52	1056
	PCC	L	–16	–52	8	30	4.14	568
	IFG	L	–40	26	2	45	4.09	452
	MTL	R	38	–32	–14		4.04	192
	Temporal pole	L	–50	6	–22	38	4.01	600
	Insula	L	–38	16	2		3.88	248
	ACC	L	–8	22	28	32	3.82	224
	PCC	R	16	–54	6	30	3.43	522
	Cerebellum	L	–18	–40	–26		3.29	296
Few–Many	No significant voxels						<i>t</i>	

These regions were selected based on peak coordinates reported from the pre-fatigue session and therefore acted as a priori regions in the analysis described in the paper.

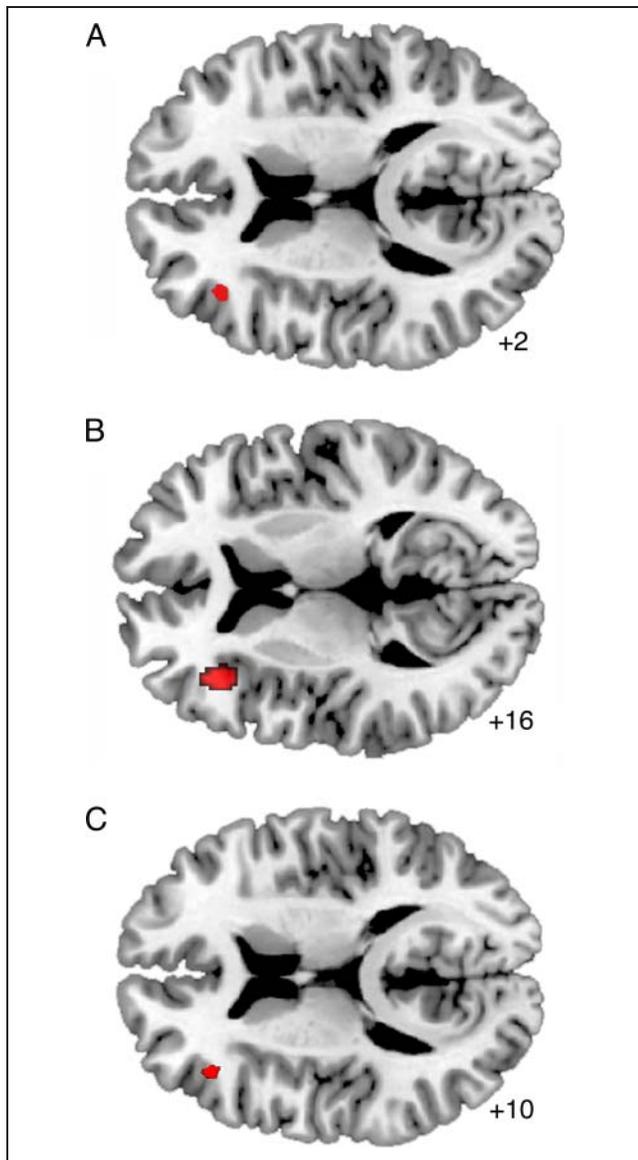


Figure 2. Transverse sections showing activation in the left IFG (thresholded at an uncorrected $p < .001$; cluster corrected at FWE $p < .05$) for (A) the verb generation interference resolution contrast (peak: $x, y, z = -40, 26, 2$) and (B) interference resolution in the recent probes task (peak: $x, y, z = -48, 34, 14$). (C) Results from the conjunction analysis showing activation for the interference control contrast common for both the verb generation and recent probes task (peak: $x, y, z = -42, 30, 10$; results from the conjunction analysis is thresholded at $.005$ uncorrected, cluster corrected at FWE $p < .05$).

verb generation and the recent probes tasks was used specifically to identify common activation associated with interference control across tasks. In particular, we wanted to test whether the IFG was commonly activated in the high versus low interference conditions in the verb generation task and the item recognition task. This conjunction analysis should only yield significant activations that are present in both original contrasts of the conjunction (Nichols, Brett, Andersson, Wager, & Poline, 2005). As this type of second level conjunction is relatively

susceptible to slight spatial variations of activity in the two contrasts and given our a priori hypothesis about a role for the IFG in interference control in these tasks, we opted for a slightly more liberal threshold at $p < .005$ uncorrected (cluster corrected at $p < .05$), for each of the original contrasts. Because the probability reported by such an analysis can pass a certain statistical threshold even if one of the contrasts would not be significant if tested alone, the results of the conjunction analysis were masked with the results of the individual t test for each of the two tasks testing for effects of high versus low interference at $p < .05$. This analysis showed that a region within the left IFG was commonly activated by the high interference condition in both the verb generation and the recent probes task ($x, y, z = -42, 30, 10$; cluster size = 384 mm^3 ; Figure 2C). This is in line with previous observations showing left IFG involvement for these tasks (e.g., Nelson et al., 2009; Persson et al., 2004; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003; Jonides et al., 2000; Thompson-Schill et al., 1997) along with overlapping left IFG activation using within-session task comparisons (Nelson et al., 2009).

Third, as in prior studies of the neural correlates of training (e.g., Erickson et al., 2007), we tested the impact of the fatigue manipulation by assessing the Group (depletion; control) \times Time (prefatigue; post-fatigue) interaction using the functionally defined, a priori ROIs from the many-few contrast obtained in the prefatigue verb generation block. To confirm that significant interaction effects were independent of differences before the fatigue manipulation, we established that the groups did not differ in interference-related prefatigue activation by running a series of one-way ANOVAs (all $F_s < 2$, see also Figure 3). The Group \times Time interaction thus indicates which task-relevant regions change differentially between two groups. Indeed, in a subset of the ROIs the Group \times Time interaction was significant, including the left IFG (pars triangularis), ACC, the striatum, and the cerebellum (Figure 3). To investigate the direction of these effects for each region, we plotted the signal for each group, pre- and post-fatigue blocks (Figure 3). We found that the interactions all resulted from a greater reduction in interference-related activity for the depletion group relative to the control group. The other regions did not show significant Group \times Time interactions. Furthermore, to test for reliable group differences after the fatigue blocks, we conducted a series of post hoc one-way ANOVAs on the post-fatigue parameter estimates to determine if the groups significantly differed as a function of the depletion manipulation. These analyses showed that all regions, except for the cerebellum, differed significantly in the post-fatigue session [left IFG: $F(1, 29) = 4.91, p < .05$; ACC: $F(1, 29) = 6.01, p < .01$; cerebellum: $F(1, 29) = 3.06, p = .08$; striatum: $F(1, 29) = 4.13, p < .05$]. More specifically, participants in the depletion group showed less interference-related activation in these regions after the fatigue blocks. These results suggest that, although the groups did not differ in the magnitude of activity in these

regions before the fatigue manipulation, they differed reliably after performing their respective tasks: the depletion group showed reduced interference-related activation during verb generation. Also, given our a priori hypotheses about depletion-related change in the left IFG (and similar to the behavioral analysis above), we examined the BOLD signal for many (high interference) and few (low interference) conditions separately for the left IFG using a Group (resource depletion/control) \times Condition (high/low interference) \times Time (pre/post-fatigue blocks) ANOVA. This analysis was included to explicitly address the question of process specificity by assessing whether resource depletion effects were restricted to changes in BOLD signal for high interference trials in the resource depletion group only. This analysis showed a reliable three-way interaction, $F(1, 29) = 4.59, p < .05, \eta_p^2 = 0.19$, suggesting specific Group \times Condition \times Time effects. Follow-up analyses using paired comparisons on the pre-fatigue BOLD data showed that the groups did not differ on either high interference, $F(1, 29) = .655, p = .43$, or low interference, $F(1, 29) = .001, p = .98$, trials. This analysis established that there was no Group difference in left IFG activation before the fatigue blocks. Next, we addressed the question of whether Group differences post-fatigue were specific to the high interference trials. Using paired comparisons on the post-testing scores, we found a reliable difference on high interference trials, $F(1, 29) = 5.71, p < .01$, whereas the Group difference was nonsignificant for low interference trials, $F(1, 29) = .338, p = .56$. Again, this suggests that the main finding of a reduced activation in left IFG for the resource depletion group was specific to the high interference condition.

The fourth set of analyses was more exploratory and sought to determine whether behavioral depletion effects were associated with change in any regions outside our predefined ROIs. Prior evidence from older adults indicates additional activation in right PFC regions during verb generation (Persson et al., 2004), so we were especially interested in possible interference-related activation increases in the right hemisphere. We therefore conducted a whole-brain voxel-wise analysis to determine whether interference-related activation changed as a function of the

depletion manipulation. We performed a between-group analysis on the post-fatigue verb generation blocks to investigate the presence of greater interference-related activation in the depletion group compared with the control group. We found that three right hemisphere regions—the IFG/anterior insula, the superior temporal gyrus, and the posterior insula—showed stronger activation in the depletion group compared with the control group (Figure 4). To ensure the direction of this effect and to reveal whether this change was an actual increase in activity or a reduction in a deactivation from the pre-fatigue session we plotted the signal from these areas for both the pre- and post-fatigue sessions (Figure 4). We conducted a series of post hoc one-way ANOVAs on the post-fatigue parameter estimates to determine if the groups significantly differed as a function of fatigue. These analyses showed that all regions differed significantly in the post-fatigue session [right IFG: $F(1, 29) = 8.29, p < .01$; STS: $F(1, 29) = 5.85, p < .05$; insula: $F(1, 29) = 6.77, p = .05$]. These results suggest that, although the groups did not differ in the magnitude of activity in these regions before the fatigue blocks, they reliably differed after the depletion manipulation.

Brain–Behavior Correlations

Our finding that task-relevant regions in the left IFG, ACC, cerebellum, and the striatum all demonstrate decreased interference-related activation in the high-interference group after the fatigue blocks suggest that they are modulated by depletion. If this is true, we should be able to show that individuals with greater performance decline following the fatigue blocks also show the strongest reduction in interference-related brain activation in these task-relevant regions. To investigate the relationship between brain activity and behavioral measures of depletion, we performed brain–behavior correlations. Because the goal of this study was to determine what neurofunctional changes may underlie behavioral indicators of cognitive fatigue and given that these effects should be primarily restricted to the resource depletion group, we performed the brain–behavior analyses for each group separately. The difference between

Table 2. Brain Regions Activated by the Recent Probes Task

Contrast	Region	Side	<i>x</i>	<i>y</i>	<i>z</i>	BA	<i>t</i>	Size (mm ³)
Recent > Nonrecent trials	Cerebellum	L	−42	−48	−20		9.36	4120
	Temporal pole	L	−32	−7	−23		7.62	2368
	Temporal pole	R	26	−6	−32	20/36	7.07	808
	IFG	L	−48	34	16	45	5.24	704
	MTL	L	−18	−22	−8		4.01	328
	IFG	L	−38	34	14	46	3.90	208
Nonrecent > Recent trials	Middle temporal	R	44	−30	−14	20/21	5.82	448
	Medial frontal	L	−12	48	10	11	3.92	320

Figure 3. Transverse sections depict activation in ROIs showing a significant Group \times Time interaction (left) for the many versus few contrast in the verb generation task. Bars (right) show average BOLD signal change as a function of group (resource depletion/control) and time (before/after the fatigue session). Error bars depict the *SEM*.

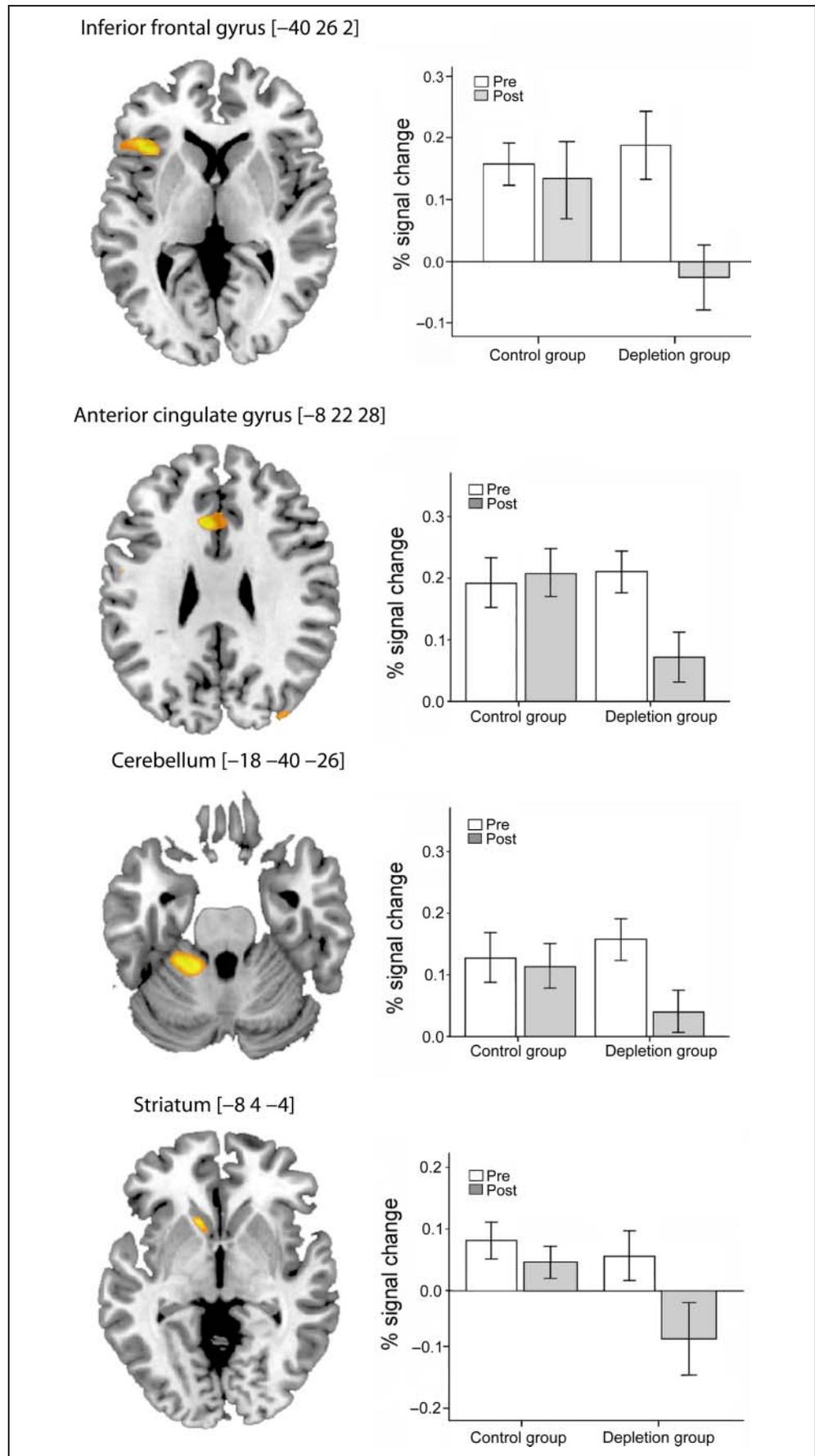
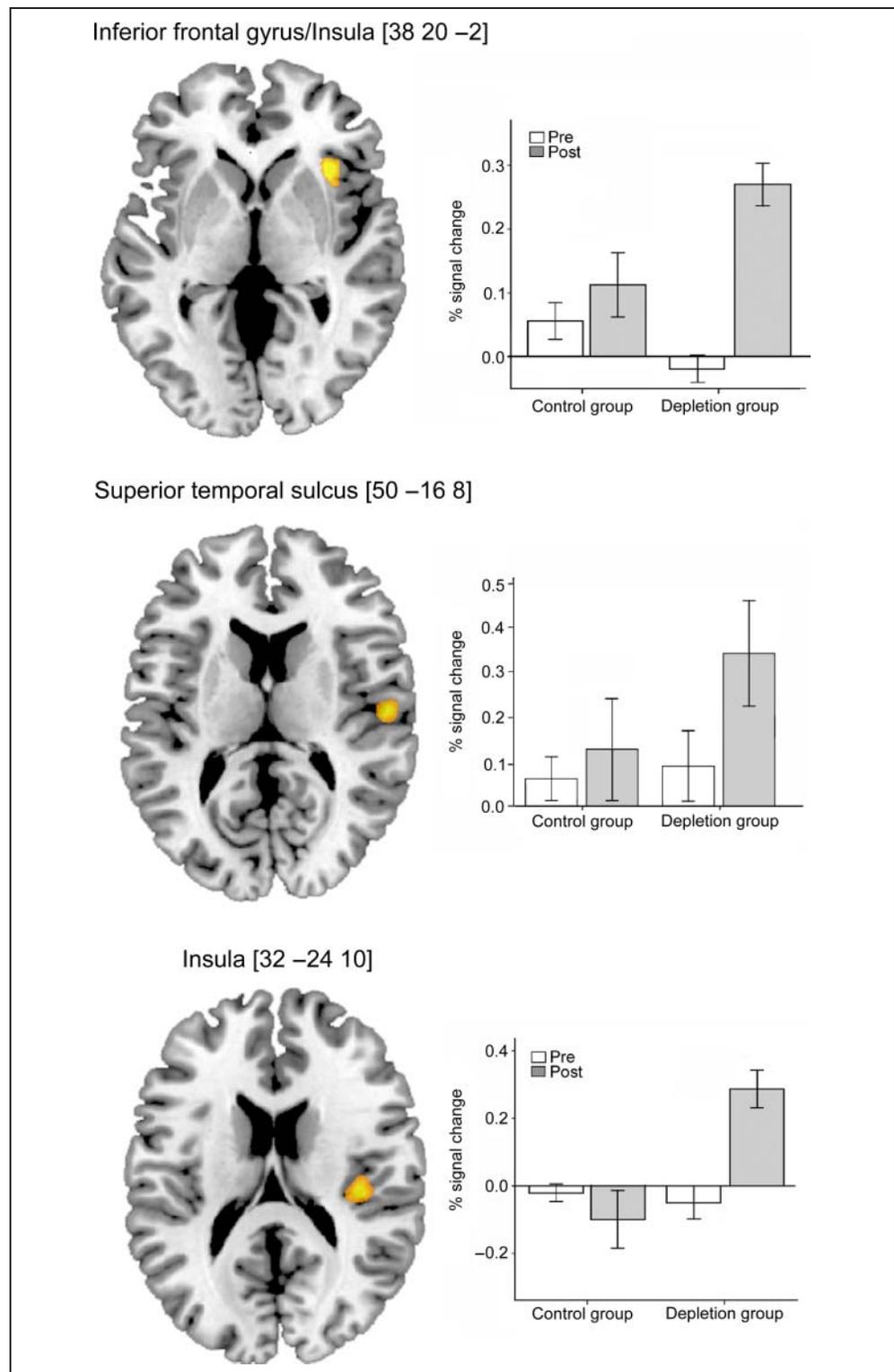


Figure 4. Transverse sections depict activation (thresholded at an uncorrected $p < .001$; cluster corrected at FWE $p < .05$) where the resource depletion group shows stronger activation during verb generation (many–few) in the post-fatigue session compared with the control group (left). Bars (right) show average BOLD signal change as a function of group (resource depletion/control) and time (before/after the fatigue session). Error bars depict the *SEM*.



the pre- and post-fatigue parameter estimates from the ROIs obtained from the many–few verb generation contrast before the fatigue session (see above and Table 1) were correlated with the performance change in the many–few RTs difference between the pre- and post-fatigue session (i.e., magnitude of the behavioral depletion effect). From this analysis, we found that, in the resource depletion

group, two of the predefined regions, the left IFG and the cerebellum, showed a significant negative correlation between behavioral fatigue and change in BOLD activation (left IFG [-40 26 2]: $r = -.55$, $p < .05$; cerebellum [-18 -40 -26]: $r = .6$, $p < .05$; Figure 5). Thus, increased interference between pre- and post-fatigue sessions was correlated with reduced BOLD activation in these two regions.

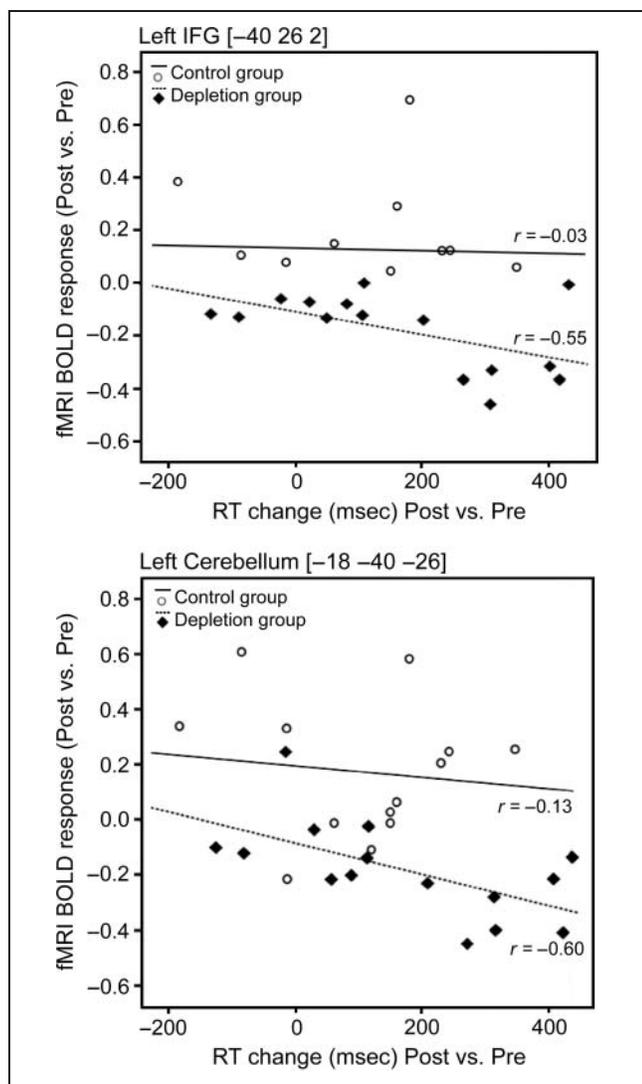


Figure 5. Scatter plots showing correlations between BOLD signal activation change (pre to post) and change in RT indexing fatigue (i.e., the performance change in the many–few RT difference between the pre- and post-fatigue session) in the left IFG (top) and the cerebellum (bottom). Correlations for each group (resource depletion and control) were tested separately. Significant negative correlations for the resource depletion group in the left IFG ($r = -.55$; $p < .05$) and the cerebellum ($r = -.6$; $p < .05$) suggest that reduced activation is associated with reduced performance in the resource depletion group. Brain–behavior correlations were not significant for the control group in either the left IFG ($r = -.03$; $p = .9$) or the cerebellum ($r = -.13$; $p = .68$).

For the control group, no significant brain–behavior correlations were found in either the left IFG ($r = -.03$; $p = .9$) or the cerebellum ($r = -.13$; $p = .68$; Figure 5). Also, a formal analysis examining group differences in brain–behavior correlations using the Fisher r -to- Z transformation showed that there were no significant differences between the groups (left IFG: Fischer $z = -1.38$, $p > .05$; cerebellum: Fischer $z = -1.30$, $p > .05$). Together, these results show that decreased recruitment of task-relevant regions, including left IFG, is related to impaired interference control.

DISCUSSION

The present results support the idea that the resources needed for interference control can be depleted with use. The resulting behavioral inefficiency is associated with alterations in the activity of a network of task-relevant regions measured with fMRI. Critically, left IFG, a region commonly activated during verb generation, together with the cerebellum, ACC, and the caudate showed reduced activation in the resource depletion group, who participated in a high-interference fatigue blocks, compared with the low-interference control group. Our results support recent observations of behavioral resource depletion of interference control and extend our understanding of this phenomenon by demonstrating robust modulation of brain responses associated with reduced efficiency to control interference. Moreover, the right IFG, which is not typically related to performance of these tasks in young adults, along with the STS and the insula showed increased activation in the resource depletion group compared with the control group. Possibly, increased interference-related activity in these regions is a consequence of reduced left hemisphere resources available for successful task performance. Also, direct brain–behavior correlations between the magnitude of behavioral fatigue and interference-related activation indicated a number of regions in which activation change was associated with performance change. In particular, individuals who demonstrated depletion-induced reduction in performance also showed reduced interference-related activation in left IFG.

A significant body of research highlights a role for the left IFG in resolving interference between competing representations during verb generation (Crescentini, Shallice, & Macaluso, 2010; Nelson et al., 2009; Persson et al., 2004; Thompson-Schill et al., 1997) and other tasks with related cognitive demands (Nee, Wager, et al., 2007). Here we extend this body of research by showing that the activation in this region associated with verb generation can be modulated by prior engagement in a working memory task involving overlapping cognitive and neural components. The striatum and cerebellum, which also showed reduced activation related to depletion of interference control, have been consistently activated along with left IFG, in similar executive task conditions (Nelson et al., 2009; Stoodley & Schmahmann, 2009; Badre & Wagner, 2007; Bellebaum & Daum, 2007; Jonides & Nee, 2006; O’Reilly, 2006; Lewis, Dove, Robbins, Barker, & Owen, 2004; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Thompson-Schill et al., 1997), and are considered components of executive control circuitry. Thus, fatigue-induced impairment of interference control in the verb generation task may be due to reduced activation in this network. Although the present results suggest it is possible to deplete resources associated with a specific executive process, interference control, the exact mechanisms of fatigue remain to be specified (see also Persson et al., 2007, for a discussion).

Several regions also showed increased activation following the fatigue blocks. We speculate that this upregulation is a consequence of reduced resources available for successful task performance. Our findings, however, cannot resolve the question of whether increased activation in right IFG in the depletion group might indicate some attempt to compensate for diminished resources, or it may be a neural expression of the behavioral decrement in interference control because of resource depletion. The present results cannot adjudicate between these possibilities. Although there is little known about the relationship between cognitive and neural efficiency (Rypma et al., 2006), these results suggest that brain activation associated with reduced performance may be related to both decreased activation in task-specific regions and increased activation in task-atypical areas, such as the right IFG.

A parallel to this pattern of redistributed activation has been demonstrated in the aging literature (Persson et al., 2004, 2006; Rajah & D'Esposito, 2005; Reuter-Lorenz, 2002), where both reduced activation of typical and overactivation of atypical (often prefrontal) regions often is found for older adults compared with young adults. For example, using the verb generation task, we previously demonstrated that older adults showed activation in the right IFG whereas young adults did not (Persson et al., 2004). Although reduced activations may be related to reductions in cognitive performance, age-related increases in brain activity may constitute a form of functional reorganization, which occurs as a compensatory response initiated by age-related changes (Reuter-Lorenz & Cappell, 2008). The current results may represent an analogue of cognitive aging whereby transient cognitive decline is induced in young adults; dynamic interhemispheric interactions modulate processing efficiency and resource availability. A similar pattern of results has also recently been demonstrated in women diagnosed with breast cancer who also show a left-to-right shift in activation in association with reduced efficiency of interference control (Cimprich et al., 2009).

Although the blocked design used in the current study does not make it possible to dissociate between transient and sustained executive components, the effect of resource depletion on these two diverse processes deserve some comment. This is particularly interesting given recent theories of executive control as composed of two dissociable but complementary control modes, proactive and reactive control (e.g., Braver, 2012; Marklund & Persson, 2012; Braver, Gray, & Burgess, 2007). This model might provide a plausible explanation of our findings of reduced activation in left IFG, ACC, and the striatum along with increased activation in right lateralized regions including the right IFG and the right insula associated with resource depletion. Possibly, these results might indicate a shift from primarily proactive (sustained) mechanisms operating when resources availability is sufficient for maintaining a proactive strategy to a predominantly re-

active (transient) item-by-item control strategy when resources are reduced following depletion. Indeed, this is in line with suggestions that proactive control is metabolically costly and thus is used only when cognitive resources are high (Braver et al., 2007). Also, recent studies have related left IFG activation with proactive interference control operations (e.g., Burgess & Braver, 2010). Thus, when cognitive resources become limited following the fatigue session, participants may engage predominantly reactive mechanisms for interference control, reducing the involvement of left IFG in the task. Because this idea could not be directly tested in the current data, additional research is required to test this interpretation.

Our findings also relate to and have implications for recent observations of changes in resting state dynamics, following engagement in an effortful task. For example, it has been shown that endogenous brain dynamics can be altered several minutes following completion of an effortful task (Barnes, Bullmore, & Suckling, 2009; Pyka et al., 2009). Although such alterations may relate to task-induced fatigue, it has also been suggested that dynamic modulations reflect a beneficial adaptation to recent experiences (Stevens, Buckner, & Schacter, 2010). Regardless, one general implication may be the importance of considering within-session effects on BOLD dynamics when conducting and analyzing fMRI experiments.

Although the physiological and molecular underpinnings of process-specific fatigue remain to be fully characterized, we believe that our results provide an important first step in specifying a mechanistic account of resource depletion at the level of brain activation dynamics. To speculate about the present results, a possible account for reduced brain activation in the task-specific network could be that greater metabolic demand is placed on these regions in response to increased requirements for interference control. Consequently, higher demand on an interference control circuitry might lead to increased glucose requirements in the resource depletion group and thus reduced brain activation during subsequent verb generation requiring interference control. In support of this hypothesis, albeit at a more general level, reduced glucose metabolism in frontal cortex and striatum has been demonstrated in patients with multiple sclerosis suffering from a more generalized form of mental fatigue (Roelcke et al., 1997). Likewise, alterations in glucose levels have been associated with alterations in higher cognitive functions, including decision-making, self-control, and memory (Smith, Riby, Eekelen, & Foster, 2011; Masicampo & Baumeister, 2008; however, see Kurzban, 2010; Wang & Dvorak, 2010). Another possible mechanism is disruption of glutamate transport, which has been hypothesized to have a role in mental fatigue in patients suffering from stroke or brain trauma (Rönnbäck & Hansson, 2004). Although these explanations have been proposed to account for more global cognitive fatigue, similar mechanisms might be involved in task-induced interference control depletion demonstrated by the current results. In this respect, the present paradigm

may serve as a model task with which to analyze the basic mechanisms of fatigue.

In conclusion, the current data provide initial insights into the neural correlates of fatigue of interference control. Our results indicate that depletion-induced performance decrements are associated with reduced BOLD signal in task-relevant circuitry, including prefrontal and striatal regions associated with cognitive control. We also demonstrate that recruitment of additional sites in the opposite hemisphere is associated with depletion, which may indicate adjustments in control mechanisms and/or attempted compensation for deficient resource supplies. As a first demonstration of depletion-induced modulation of an executive control function, our findings suggest the need for future research into temporal brain dynamics across executive control components. Although future studies will determine the extent to which the present results generalize across practice regimens, cognitive domains, and brain regions, our findings demonstrate the value of fMRI for investigating interactions between tasks that share operations. Certainly, a neurally specified mechanism of use-related fatigue of interference control may contribute fundamentally to theoretical models of how control processes are modulated in the service of task performance.

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