Prefrontal Control of Familiarity and Recollection in Working Memory

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Abstract

■ Left inferior frontal gyrus (IFG) is a critical neural substrate for the resolution of proactive interference (PI) in working memory. We hypothesized that left IFG achieves this by controlling the influence of familiarity- versus recollection-based information about memory probes. Consistent with this idea, we observed evidence for an *early* (200 msec)-peaking signal corresponding to memory probe familiarity and a *late* (500 msec)-resolving signal corresponding to full accrual of trial-related contextual ("recollection-based") information. Next, we applied brief trains of repetitive transcranial magnetic stimulation (rTMS) time locked to these mnemonic signals, to left IFG and to a control region. Only early rTMS of left IFG produced a modulation of the false alarm rate for high-PI probes. Additionally, the magnitude of this effect was predicted by individual differences in susceptibility to PI. These results suggest that left IFG-based control may bias the influence of familiarity- and recollection-based signals on recognition decisions. ■

INTRODUCTION

Proactive interference (PI) can be manipulated during item recognition when recent, but no longer relevant, items compete with currently relevant memory representations. It is generally assumed that PI arises because the familiarity of such "recent negative" (RN) memory probes conflicts with information specific to that trial's context (Jonides & Nee, 2006). Lesion (Thompson-Schill et al., 2002) and repetitive transcranial magnetic stimulation (rTMS; Feredoes, Tononi, & Postle, 2006) studies have shown that left inferior frontal gyrus (IFG) is a critical substrate for the control of PI, and rTMS and functional magnetic resonance imaging (Feredoes et al., 2006; D'Esposito, Postle, Jonides, & Smith, 1999) have isolated this region's involvement to the memory probe (i.e., response) period of the task. The underlying mechanisms by which left IFG achieves the control of PI, however, are poorly understood.

The present investigation was motivated by observed similarities between "recency" in the working memory PI literature and "familiarity" in the long-term memory literature. Specifically, it has been suggested that the two sources of information—familiarity- and recollection-based—that have been proposed to influence recognition from long-term memory (Yonelinas, 2002) may also influence working memory (e.g., Goethe & Oberauer, 2008; Oztekin & McElree, 2007). Behavioral studies using a response-deadline (or speed–accuracy tradeoff) procedure, an approach that can provide an estimate of the time course of information accrual, show that elevated levels of PI correspond with an increase in false alarms on trials requiring early responses (Goethe & Oberauer, 2008; Oztekin & McElree, 2007). The time course of these effects is critical because the long-term memory literature has established that familiarity is a fast signal, processed earlier than recollection (Diana, Reder, Arndt, & Park, 2006; Yonelinas, 2002; Hintzman & Curran, 1994). Oztekin and McElree (2007) concluded that the build-up of PI might result in fast familiarity-dependent assessments being deemphasized as a source of information guiding the evaluation of memory probes.

In the present study, we applied a response-deadline procedure to a "recent probes" task design (Monsell, 1978), reasoning that RN probes would trigger both a (relatively fast) familiarity signal and a (relatively slow) recollection signal. Thus, we predicted that RN probes would produce an elevated false alarm rate at the shortest response lags due to the influence of the misleading familiarity signal. At longer lags, however, we expected that the accrual of a sufficient amount of recollection-based information would bring the false alarm rate back down to the same level as that of "nonrecent negative" (NN) probes (i.e., probes corresponding to items that had appeared on neither the current nor either of the two preceding trials). Assuming the confirmation of this prediction, the next step would be to use this information to assess, with rTMS, evidence for each of two classes of models of mechanisms by which left IFG may control PI.

One class of model of left IFG-based control emphasizes the operation of *selection*. By this account, left IFG's critical function is one of selecting from among competing sources of mnemonic information (e.g., familiarity-based vs. recollection-based; see Badre & Wagner, 2007). [Note that response-based selection has been ruled out as a

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function of left IFG (Feredoes et al., 2006; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003).] Importantly, the putative selection operation would necessarily be engaged only after a sufficient amount of recollection-related information has been retrieved. These models have the appeal of making contact with selection accounts of left IFG function in non-working-memory behaviors (e.g., Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Moreover, Badre and Wagner (2007) have suggested that the same post-retrieval selection processes recruited to resolve PI in long-term memory are also engaged in working memory.

A second class of model emphasizes a role for left IFG in *familiarity processing*. These derive support from investigations from the long-term memory literature suggesting that left IFG might be particularly important in the processing of familiarity. In one, activity in prefrontal regions, including left IFG, was found to correlate significantly with variation in a probe's familiarity, but a different set of brain regions was found to be sensitive to recollection (Yonelinas, Otten, Shaw, & Rugg, 2005; but see also Dobbins, Rice, Wagner, & Schacter, 2003). Another study on patients with left or right prefrontal lesions showed that lesions of left hemisphere (which included IFG) selectively impaired familiarity-based recognition from long-term memory (Duarte, Ranganath, & Knight, 2005). Two familiarity-based accounts of left IFG's contribution to the control of PI in working memory are that this region may serve to tag mnemonic information as being familiarity based, or that it may weight mnemonic information so as to de-emphasize familiarity.

To assess these two classes of models, we would target left IFG with short rTMS trains timed to coincide with when the fast familiarity signal dominated (*early* rTMS), or after recollection-based information had accrued (*late* rTMS). Familiarity-processing models predicted that early rTMS would modulate the false alarm rate specifically for RN probes. Such an effect of early rTMS would not constitute evidence for selection models, however, because heavy demands on selection would only develop as a sufficient amount of recollection-based information had accrued (Badre, Poldrack, Pare-Blagoev, Insler, & Wagner, 2005). An effect of late rTMS, however, would provide evidence for a postretrieval selection mechanism. We also included a third rTMS condition (*full*: rTMS delivered throughout the probe period) to permit replication of our previous results (Feredoes et al., 2006). Interleaved between these three stimulation conditions were rTMS-absent trials. Our predictions about the effects of rTMS on behavior were as follows: The effect of rTMS of left IFG would be apparent relative to control-site stimulation; the pattern of results for early rTMS (consistent with familiarity-processing models) or late rTMS (consistent with selection models) would be qualitatively similar to that produced by full rTMS; and the effects of both of these (early or late rTMS, and full rTMS) would be similar to the results of our previous rTMS study of this task (Feredoes et al., 2006). (Note that because familiarity and selection accounts of left IFG function are not mutually exclusive, it was also possible that both early and late rTMS would influence performance.)

In parallel to the questions of mechanism summarized in the previous paragraph, we also sought with this study to extend our understanding of the anatomical specificity of the effects of rTMS of left IFG. Although previous neuroimaging studies have localized the "RN effect" to left IFG (e.g., D'Esposito et al., 1999), the sensitivity of adjacent middle frontal gyrus (MFG) to PI remains unclear. Therefore, whereas the Feredoes et al. (2006) rTMS study had used control sites whose involvement in working memory is assumed to be minimal—the leg area of primary somatosensory cortex of postcentral gyrus (left hemisphere) and the hand area of primary motor cortex (M1; right hemisphere)—in the present study we targeted left MFG as a control site.

In many previous studies, the effect of rTMS has been presumed to be disruptive, such as when rTMS of right dorsolateral PFC delivered simultaneously with a memory probe lowers accuracy of recognition from long-term memory (Rossi et al., 2001), or when delay-period rTMS of left posterior peri-sylvian cortex impairs recognition from working memory (Feredoes, Tononi, & Postle, 2007). It is important to emphasize, however, that our previous study of PI in working memory (Feredoes et al., 2006) did not produce a straightforward rTMS-induced disruption of behavior. Rather, rTMS of left IFG produced a differential effect on responses to high-PI RN probes relative to the effect of rTMS of two cortical control sites. The specific pattern was a modest decline in accuracy to RN probes produced by rTMS of left IFG, coupled with a marked improvement in accuracy to RN probes produced by rTMS of the control regions. This pattern was observed independently for two separate control-site brain regions. That rTMS does not necessarily have a disruptive effect on cognitive performance is consistent with recent observations that the nature of its effects can depend on the state of the targeted cortex at the time of stimulation (Hamidi, Tononi, & Postle, 2009; Silvanto & Muggleton, 2008a, 2008b), and that sometimes rTMS can improve performance (e.g., Hamidi et al., 2009; Kahn et al., 2005).

METHODS

Subjects

The 20 right-handed participants (11 men, mean age = 24.1 years, SD = 4.38) had no psychiatric or neurological disorders, as assessed by a structured diagnostic screening interview administered by a psychiatrist or a clinical psychologist. All subjects gave written informed consent and the experiment was approved by the local institutional review board.

Response Deadline Task Procedure

Stimuli were drawn from the 20 consonant letters of the alphabet (excluding Y). For the response-deadline task,

each trial began with the 1000-msec presentation of four letters around a central fixation cross, followed by a 3000-msec unfilled delay period during which subjects were instructed to retain a memory of the target letters. At the end of the delay period, the probe was presented centrally for a variable duration (100, 200, 300, 500, 800, or 1200 msec, order randomized). Probe offset was followed immediately by a cue ("*****") prompting a button-press response within 350 msec to indicate if the probe was a "match" (right-hand button press) or a "nonmatch" (left-hand button press) of an item from that trial's target set. The response cue stayed on screen for 1000 msec and was followed by a 3000-msec intertrial interval. Reponses with a latency of less than 100 msec or more than 350 msec were discarded from further analyses (Hintzman & Curran, 1994). Prior to the experiment, subjects practiced on the task until a minimum of 75% of responses occurred within the response window for all lags. During each intertrial interval, feedback was given indicating the subject's RT from the previous trial, accompanied by a warning message if the response occurred outside of the required window. After each block, a summary of performance was displayed showing mean RT as well as the number of responses that were acceptable, too fast, or too slow, and subjects were encouraged to improve or maintain performance throughout the remaining blocks.

The behavioral session was performed across twelve 24-trial blocks. Within each block, presented in a pseudorandomized order, there were an equal number of four different probe types, which were achieved by crossing probe recency with probe validity: nonrecent positive (NP) and NN probes did not match any target items from the two preceding trials; recent positive (RP) probes matched a target item from the current trial and the previous trial; RN probes matched a target item from the two preceding trials.

Repetitive Transcranial Magnetic Stimulation

rTMS was delivered with a Magstim Standard Rapid magnetic stimulator fit with a 70-mm figure-eight air-cooled stimulating coil (Magstim Co., Whitland, Wales, UK). Subjects were seated comfortably in a chair with head stabilized to prevent movement. Localization of the stimulating coil was accomplished via infrared-based frameless stereotaxy (eXimia Navigated Brain Stimulation; Nexstim, Helsinki, Finland), which permitted real-time targeting of cortical structures via visualization of a 3-D reconstruction of the subject's high-resolution T1-weighted scan.

For each subject, resting motor threshold was determined as the intensity at which single pulses applied over the hand area of right primary motor cortex produced a visible muscle twitch in 5 out of 10 consecutive trials, and rTMS was applied at 110% of this value, corrected for scalp–cortex distance (Stokes et al., 2005). The coil was oriented with the handle pointing in a posterior direction with respect to the subject's head so as to induce a current in the posterior-to-anterior direction.

rTMS Procedure

rTMS was applied over pars triangularis of left IFG, defined as the portion rostral to the ascending ramus and dorsal to the horizontal ramus of the sylvian fissure (Damasio, 1995), and over left MFG, identified as the middle of the gyrus, halfway between frontal pole and precentral sulcus (BA 9/46). Twelve subjects received rTMS over left IFG and left MFG, the order of which was counterbalanced across subjects, whereas the remainder received rTMS only over left IFG. MFG served to control for the nonspecific effects of rTMS, including the acoustic and tactile artifacts, and any effects arising from applying high-frequency rTMS to the cortex. [Note that in the present study we did not employ sham stimulation as a control condition. Instead, in addition to the MFG control site, the additional probe types (NP, RP, NN) served to control for any nonspecific effects of rTMS and experimental design.] Targeting was performed using each subject's high-resolution anatomical magnetic resonance image (Figure 1).

The procedure for the delayed item-recognition task performed during the rTMS session was the same as described above, with the exception that the memory probe appeared centrally for 1000 msec on all trials. Responses made within 6000 msec from probe onset were recorded. (Note that there was no variable response deadline for the rTMS session.) The offset of the probe was followed by a 5000-msec intertrial interval. The rTMS experiment was performed across eight sequential 24-trial blocks per

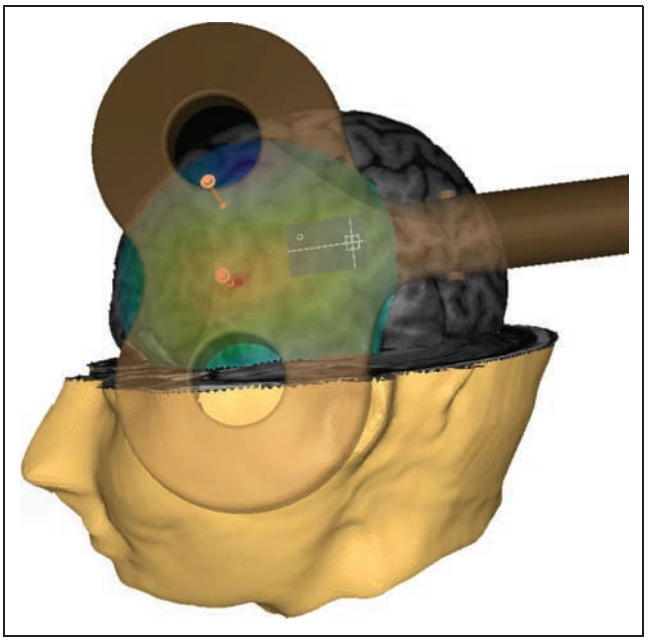

Figure 1. Example from a representative subject of left IFG and left MFG rTMS targets, with the figure-eight stimulating coil projected over left IFG.

stimulation site. Orthogonal to the factor of probe type was that of rTMS condition—*none* (rTMS absent), *early* (3 pulses, 0–250 msec from probe onset), *late* (3 pulses, 500–750 msec from probe onset), and *full* (10 pulses, 0–1250 msec from probe onset)—which was also randomized within each block (yielding 6 trials per condition per block; 48 trials per condition per stimulation site). Thus, the full rTMS condition was a replication of the procedure from Feredoes et al. (2006), with the exception that in the present study the control stimulation site was located over left MFG instead of over left postcentral gyrus.

Magnetic Resonance Imaging

Whole-brain T1-weighted images (128 sagittal slices, acquired with a 512 × 512 × 256 matrix within a 512-mm^2 field of view), used to guide rTMS, were acquired with a 3-T scanner (GE Signa VH/I).

RESULTS

Response Deadline Behavioral Session

The response-deadline results from all 20 subjects revealed that the false alarm rate to RN probes increased between the 100 msec and 200 msec lags, and was numerically higher than for NN probes at all lags (Figure 2). Importantly for the timing of the rTMS conditions, the peak of the RN function ranged between the 100 and 300 msec lags across all subjects. (The mean RTs within the 100–350 msec latency window for each probe type for each lag are reported in Table 1.) Repeated measures ANOVAs, with the factors of probe recency (recent, nonrecent), probe validity (valid, invalid), and lag (100, 200, 300, 500, 800, 1200 msec) revealed reliable main effects of recency [$F(1, 19) = 43.81, p < .001$], validity [$F(1, 19) = 363.24, p < .001$], and lag [$F(5, 95) = 3.69, p < .01$]; reliable two-way interactions of Recency × Validity [$F(1, 19) = 9.56, p < .01$], Validity × Lag [$F(5, 95) = 42.17, p < .001$], and Recency × Lag [$F(5, 95) = 4.22, p < .01$]; and a reliable three-way interaction [$F(5, 95) = 3.25, p < .01$].

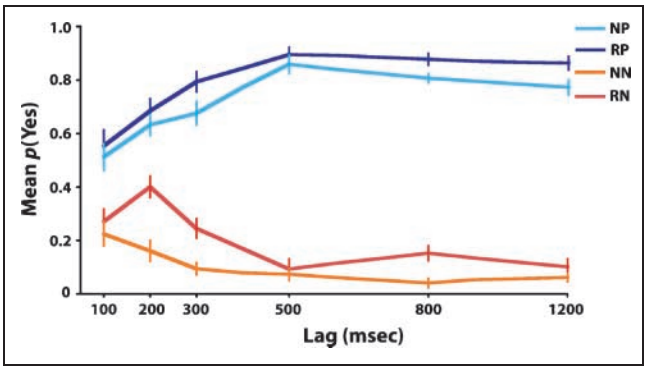

Figure 2. Results from the response-deadline task ($n = 20$), plotting mean probability of a *yes* response as a function of the stimulus onset asynchrony ("Lag") between probe onset and response-cue onset.

Table 1. Mean RTs (msec) as a Function of Lag for the Behavioral-only Response Deadline Task Procedure

	Lag					
Probe	*100*	*200*	*300*	*500*	*800*	*1200*
NP	296.15	262.20	234.95	228.59	227.14	219.89
RP	278.49	257.33	235.17	224.71	223.73	225.22
NN	285.59	264.42	251.45	225.64	224.20	219.47
RN	295.31	268.66	252.81	224.41	222.74	222.02

These are for trials in which subjects responded between 100 and 350 msec following onset of the response cue.

Pairwise tests confirmed that the mean p(Yes) for RN probes differed from that of NN probes at lags of 200 msec [$t(19) = 5.82, p < .001$], 300 msec [$t(19) = 5.29, p < .001$], and 800 msec [$t(19) = 5.75, p < .001$] (all other ts < 2). (All paired t tests are two-tailed, unless specified otherwise.) The mean p(Yes) for RP probes was greater than for NP probes at the 300-msec lag [$t(19) = 2.29, p < .05$] (for all other lags, ts < 2.0).

We also noted considerable interindividual variability in the magnitude of the divergent functions of the probability to (incorrectly) endorse an RN versus an NN probe as a function of lag—that is, considerable interindividual variability in susceptibility to PI. We quantified this "behavioral familiarity effect" for each subject by computing the difference of the areas under the RN versus the NN curves from lag 100 msec to lag 300 msec, and used this measure for individual differences analyses of the rTMS data.

Repetitive TMS Session

These analyses were performed on the data of the 12 subjects who received rTMS over both IFG and MFG. We first analyzed the RT data of rTMS-absent trials to confirm replication of the standard PI effect: Collapsing these RT data across brain regions, subjects were, on average, slower by 64.5 msec ($SD = 73.4$ msec) on RN compared to NN probes [$t(11) = 3.04, p < .05$]. We next confirmed the replication of the finding that (full) rTMS of left IFG selectively impairs accuracy for RN relative to NN probes. As with Feredoes et al. (2006), full rTMS had no PI-related effects on the RT data (the mean RTs for all probe types, rTMS timings, and brain regions are reported in Table 2). ANOVA of the accuracy data, with the factors of brain region (left IFG, left MFG), probe recency (recent, nonrecent), probe validity (valid, invalid), and rTMS (present, absent), however, revealed reliable two-way interactions of Recency × Validity [$F(1, 11) = 9.18, p < .05$] and of Region × Recency [$F(1, 11) = 5.00, p < .05$], and reliable three-way interactions of Region × Recency × Validity [$F(1, 11) = 9.12, p < .05$] and of Region × Recency × rTMS [$F(1, 11) = 5.34, p < .05$] (all other Fs < 3.9). A targeted contrast confirmed the replication of the key finding from Feredoes et al., that (full) rTMS to left IFG selectively

Table 2. Mean RTs (msec) for the rTMS Experiment

		Brain Region	
Probe	*rTMS Timing*	*IFG*	*MFG*
NP	none	828.98	813.75
	early	854.18	842.03
	late	814.12	834.99
	full	857.92	877.43
RP	none	852.02	787.24
	early	814.48	818.30
	late	821.83	831.71
	full	825.86	916.39
NN	none	850.57	867.17
	early	895.42	868.34
	late	856.39	872.32
	full	854.21	860.44
RN	none	915.05	916.39
	early	897.40	891.14
	late	986.60	948.77
	full	933.79	930.79

No significant effects of rTMS on RTs were evident. In addition, these results show that, in all cases, late rTMS was given prior to subjects' response.

affects responses to high-conflict RN probes, by determining that $[(RN_{IFG,\ full\ rTMS\ absent} - RN_{IFG,\ full\ rTMS\ present}) - (NN_{IFG,\ full\ rTMS\ absent} - NN_{IFG,\ full\ rTMS\ present})]$ was significantly different from the analogous contrast for left MFG results [$t(11) = 2.26, p < .05$] (Figure 3). Note that decomposition of this effect into pairwise comparisons revealed, for rTMS of IFG, only a modest effect of rTMS lowering accuracy to RN probes [1.50%; $t(11) = 0.33$, *ns*], and a larger effect of rTMS increasing accuracy to NN probes [5.25%; $t(11) = 2.11, p = .06$]. For MFG, rTMS improved accuracy to RN probes [5.50%; $t(11) = 1.80, p = .10$] and slightly lowered accuracy to NN probes [1.25%; $t(11) = 0.64$, *ns*]. This pattern replicated that of Feredoes et al., with left MFG in the present study mimicking the previously reported effects of rTMS of two other control regions: left postcentral gyrus and right precentral gyrus.

To test the predictions of the familiarity-processing and selection models of left IFG, we examined the effect of early versus late rTMS effects on RN probes, using the same contrast formula as above (Figure 3). Early rTMS had a significantly greater effect on RN probe accuracy when applied to left IFG as compared to left MFG [$t(11) = 3.18, p < .01$, one-tailed]. The same was not true, however, for late rTMS [$t(11) = 0.75$, *ns*, one-tailed], and these effects of early versus late rTMS differed significantly from each other [$t(11) = 2.19, p = .05$, one-tailed]. (See Table 3 for all pairwise comparisons, for each region separately.) Thus, the selective effect of early rTMS on high-conflict probes is consistent with a familiarity-processing, but not a selection, role for left IFG in the control of PI.

The same analyses, when performed on the accuracy data from positive probes, revealed no temporally specific effect: There was a trend toward a greater effect on RP versus NP probes of early rTMS over left IFG versus over left MFG [$t(11) = 1.9, p = .08$, one-tailed], a significant effect for late rTMS [$t(11) = 2.39, p < .05$, one-tailed], but these early versus late rTMS effects did not differ from each other [$t(11) = 1.03$, *ns*].

Individual Differences

The considerable variability of behavioral familiarity effect values across individuals afforded the opportunity to investigate whether one's susceptibility to PI could predict the magnitude of the effect of left IFG rTMS on the processing of RN probes. And because each subject's behavioral familiarity effect value could be regressed against early and late rTMS effects on accuracy, this approach also provided a second means by which to evaluate familiarity and selection accounts of left IFG function. To maximize the number of data points entered into the regression analysis, we included the data from the eight additional subjects who had received rTMS over left IFG but not left MFG.

Although the effect of early rTMS correlated positively with the size of the subject's behavioral familiarity effect ($r = .48, p < .05$; Figure 4A), the effect of late rTMS did not relate to the behavioral familiarity effect ($r = .06$, *ns*; Figure 4B). Moreover, this relation with early rTMS differed significantly from the relation of behavioral familiarity effect with late rTMS [comparison of correlated *r* values (Howell, 1982): $t(19) = 1.94, p < .05$].

To confirm that the left IFG rTMS effects did not merely show that poorer performers are more sensitive to rTMS,

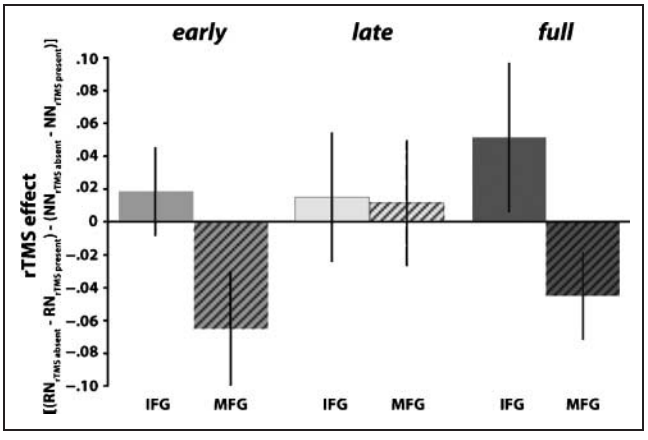

Figure 3. rTMS results for the targeted contrast. Early rTMS produced a significantly different effect on RN versus NN probes when applied over left IFG to that of left MFG. There was no significant effect of late rTMS on performance, whereas for full rTMS, there was a trend toward significance. Error bars indicate ±*SEM*.

Table 3. Pairwise Comparisons of Accuracy Data for RN and NN Probes, for $rTMS_{absent}$ versus $rTMS_{early}$ or $rTMS_{late}$ Trials, for Both IFG and MFG Stimulation

Region	*Probe*	*Contrast*	*Change in Accuracy (%)*	*t(11)*	*p*
IFG	RN	$rTMS_{absent}$ vs. $rTMS_{early}$	+1.42	0.61	.56
		$rTMS_{absent}$ vs. $rTMS_{late}$	+3.42	1.08	.30
	NN	$rTMS_{absent}$ vs. $rTMS_{early}$	+4.33	3.06	.02
		$rTMS_{absent}$ vs. $rTMS_{late}$	+5.17	1.78	.11
MFG	RN	$rTMS_{absent}$ vs. $rTMS_{early}$	+6.92	2.37	.04
		$rTMS_{absent}$ vs. $rTMS_{late}$	−1.00	0.78	.29
	NN	$rTMS_{absent}$ vs. $rTMS_{early}$	−2.08	1.19	.26
		$rTMS_{absent}$ vs. $rTMS_{late}$	−0.17	0.08	.94

All *t* tests are two-tailed.

we collapsed across the four probe types from left IFG to derive an index of overall performance—the d' measure from signal detection theory—then regressed this against the early left IFG rTMS effect. This analysis showed no relationship between the two ($r = -.24$, *ns*).

DISCUSSION

The results described here provide novel insight about the role of left IFG in the cognitive control of recognition in working memory. After replicating the earlier finding that rTMS of this region produces a selective impairment in the control of PI (Feredoes et al., 2006), we tested two candidate explanations of the nature of this control: familiarity processing and selection. Critical to this test were the response-deadline results, which established that the influence of familiarity-based information is strongest at latencies of between 0 and 200 msec after probe onset, whereas the influence of contextual (i.e., "recollection-based") information is not maximal until after 500 msec. This timing information provided the basis for assessing these two accounts, because familiarity-processing accounts, which posit that left IFG acts to minimize the influence that familiarity-based information can have on the recognition decision, predicted left IFG involvement at short lags after probe onset. Postretrieval selection models, on the other hand, in positing a role in the recognition judgment that occurs only after enough context-related information about a probe has been recollected, predicted left IFG involvement at longer lags. Our results, in which rTMS delivered early, but not late, had a selective effect on accuracy for RN (i.e., high-conflict) probes, providing support for familiarity accounts. This outcome was echoed in the individual differences analysis, which indicated that a subject's susceptibility to PI, as assessed in a separate behavioral testing session, predicted the magnitude of the effect of early (but not late) rTMS of left IFG on the control of PI. (Note that although these results did not provide support for selection models, neither can they be construed as a decisive rejection. This is because the response-deadline data suggested that recollection-based information began to accrue as early as 100–200 msec after probe onset for some subjects. Thus, for some subjects, the recognition decision may have occurred before or soon after the onset of late rTMS trains.)

There are several hypothetical mechanisms that left IFG could influence for the processing of a familiarity-based signal, and thereby bias the influence of familiarity versus recollection in item recognition. One is that left IFG may control the relative weighting given to information conveyed about the familiarity of a memory probe, compared to recollection-based information. Support for this idea comes from a behavioral investigation of PI, in which increases in PI slowed retrieval speed, suggesting that as PI

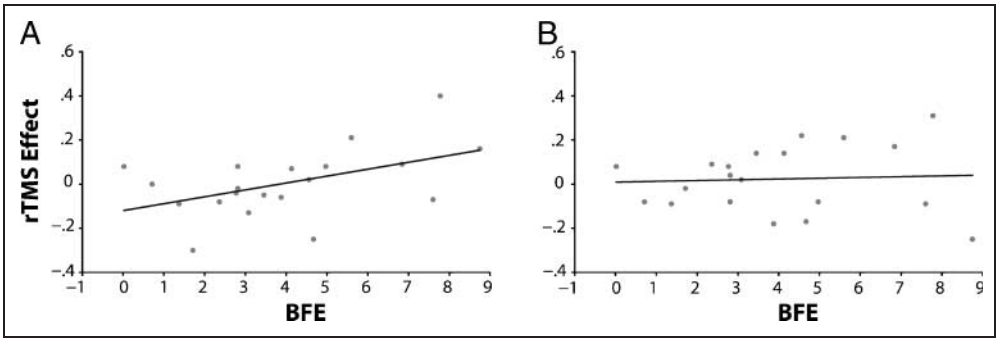

Figure 4. Results from the individual differences analysis. "rTMS effect" was calculated as: $[(RN_{IFG,\ rTMS\ absent} - RN_{IFG,\ rTMS\ present}) - (NN_{IFG,\ rTMS\ absent} - NN_{IFG,\ rTMS\ present})]$. (A) Early rTMS; (B) Late rTMS. BFE = behavioral familiarity effect.

builds up, fast assessments based on familiarity are downgraded (Oztekin & McElree, 2007). From this perspective, applying rTMS to left IFG may have disrupted the processes de-emphasizing the influence of familiarity on probe recognition, thereby increasing the probability of familiarity-based information being used to endorse RN probes. A second possibility is that left IFG may support the identification or "tagging" of memory-related signals, such that downstream decision mechanisms would be able to weight each source of recognition-related information. By this "source of activation ambiguity" account, rTMS may have its effect by disrupting the tagging process, which, in normal situations, would facilitate the discounting of familiarity-based information (for a similar account, see Diana et al., 2006). (Note that one might expect this latter account to predict a facilitatory effect of early rTMS on RP trials. But although results from the response-deadline data did show increased accuracy on RP compared to NP trials at the 300-msec lag, the rTMS results did not show a selective effect of early rTMS on RP probes. This outcome is more consistent with the hypothesized mechanism whereby familiarity is downgraded across the task rather than assessed on a probe-by-probe basis.)

Although the precise nature of left IFG-based control remains to be determined, either of the mechanisms summarized here would be consistent with the view that the same, or overlapping sets of processes may control conflict in recognition from long-term as well as from working memory. Indeed, they are consistent with the view that the control process(es) under investigation here may not be specialized for working memory, but rather, may be engaged by conflict in many contexts. We have already discussed how left IFG has been shown to be sensitive to PI in long-term memory (Badre & Wagner, 2005). In affective neuroscience, IFG has been implicated, along with amygdala, in controlling the effects of emotional distraction on working memory performance (Dolcos, Kragel, Wang, & McCarthy, 2006). Within clinical neuroscience, studies of confabulation, the pathological fabrication of memories to compensate for amnesic gaps, have identified a "feeling of rightness" that predicts confabulation, and whose electrophysiological correlates (A. Gilboa, personal communication) suggest a correspondence with those of familiarity-based signals that have been described in more traditional studies of recognition from long-term memory (Curran, 2000). One framework that might accommodate these disparate findings is that of dual modes of control, which implicate left IFG in a network that implements "reactive" cognitive control (Braver, Gray, & Burgess, 2007). Although the present study included measures of neither fluid intelligence nor brain activity, our finding of a positive correlation of the behavioral familiarity effect with the effect of early rTMS of left IFG fits with the idea that this region may be preferentially recruited by individuals who are more susceptible to PI. For example, individuals with lower working memory spans (Mecklinger, Weber, Gunter, & Engle, 2003) or lower general fluid intelligence (Braver et al., 2007) show greater PI effects, as well as greater high-interference probe-related activity in left posteroventral PFC.

Three distinctive features of our results are their anatomical, behavioral, and temporal specificity. Considering firstly anatomy, rTMS had different effects on left IFG versus left MFG. This is consistent with the known effective functional resolution of TMS, which can be as small as approximately 1 cm (Walsh & Rushworth, 1999). In one noteworthy example, rTMS of cortical sites, separated by an estimated 2.5 cm, has dissociated linguistic functions of the anterior versus posterior left IFG (Gough, Nobre, & Devlin, 2005). Nonetheless, it is also well established that the effects of TMS are not only local but also influence regions that are distal to, but connected with, the targeted region of cortex (reviewed, e.g., in Walsh & Rushworth, 1999). Thus, our results are best construed in terms of a functionally connected network of which posterior left IFG is a node.

Turning to behavioral specificity, the effects of both full and early rTMS to left MFG, but not left IFG, were to improve accuracy to RN probes. This seemingly paradoxical result replicates our earlier findings with two other control areas (left postcentral gyrus and right M1; Feredoes et al., 2006) and highlights the importance of including a control region in rTMS studies, by illustrating that one cannot know a priori what might be the anatomically nonspecific effect of rTMS for a given behavior. For short-term item recognition, these results indicate that an anatomically nonspecific effect of 10 Hz rTMS is to improve accuracy to RN probes. From this, we can speculate that the seemingly "null" effect of rTMS of left IFG may arise from coincident cancellation of the anatomically nonspecific effect with an opposing effect that is specific to IFG. However, a more definitive account will require simultaneous measurement (with, e.g., EEG) of the task-specific physiological effects of rTMS.

Turning finally to the temporal specificity of our results, we suspect that this reflects the temporal dynamics of the fast familiarity signal, rather than a generalizeable feature of the functions of left IFG. For example, Kahn et al. (2005) have demonstrated that TMS of left (and right) posterior IFG delivered 380 msec after word onset, but not earlier or later, influences encoding into long-term memory. Similarly, the critical timing of left IFG involvement in other functions, such as phonological processing (e.g., Gough et al., 2005) and selection (e.g., Thompson-Schill et al., 1997), is likely to reflect process- and task-specific factors.

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