Direct evidence for a prefrontal contribution to the control of proactive interference in verbal working memory

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Controlling the effects of proactive interference (PI), the deleterious effect of prior mental activity on current memory representations, is believed to be a key function of the prefrontal cortex. This view is supported by neuroimaging evidence for a correlation between the longer reaction times caused by high PI conditions of a working memory task and increased activity in left inferior frontal gyrus (IFG) of the prefrontal cortex. An alternative that has never been ruled out, however, is that this left IFG effect may merely reflect sensitivity to such nonspecific factors as difficulty and/or time on task. To resolve this confound, we applied the interference methodology of repetitive transcranial magnetic stimulation (rTMS) to the left IFG and two control regions while subjects performed delayed letter recognition. rTMS was guided with high-resolution magnetic resonance images and was time-locked to the onset of the memory probe. The effect of rTMS, a disruption of accuracy restricted to high-PI probes, was specific to the left IFG. These results demonstrate that unpredictable, phasic disruption of the left IFG selectively disrupts control of responses to high-conflict verbal working memory probes, and they conclusively reject nonspecific alternative accounts.

cognitive control | inferior frontal gyrus | transcranial magnetic stimulation

The left inferior frontal gyrus (IFG) of the prefrontal cortex is central to many theoretical accounts of cognitive control, including retrieval of semantic knowledge (1), selection among competing alternatives (2), reactive control (3), and the control of the effects of proactive interference (PI) in working memory (4). PI, the deleterious effect of previously remembered information on current memory representations, is widely seen as a critical factor in forgetting, and therefore capacity, in working memory (5–7). Thus, understanding the control of PI in working memory has implications for understanding the cognitive and neural bases of a remarkable breadth of cognitive functions and "real-world" outcome measures, from general fluid intelligence, to reading ability, to standardized test performance, to income and socioeconomic status, to personality traits, that are predicted by working memory capacity (8–10).

One influential experimental paradigm for the investigation of PI is the "recent probes" variant of the classic item-recognition task (Fig. 1), which controls the level of PI by varying whether or not an invalid memory probe matches an item from the preceding trial. The PI produced by such "recent negative" (RN) probes manifests as costs in reaction time (RT), and, less reliably, in accuracy. This PI derives from the presumed conflict of processing the probe's high level of familiarity vs. its absence from the current trial's memory set. The neuroimaging correlate of these effects is an increase of signal in the left IFG that is time-locked to the onset of the memory probe. It has been interpreted as evidence for prefrontal cortex-based control of PI (reviewed in ref. 4) [as have analogous results found in the same region, with different tasks, as evidence for inhibition (11), selection (2), or reactive control (3)]. These theoretical claims, however, rest almost entirely on the correlational inference afforded by neuroimaging data. An alternative account of the neuroimaging results that does not invoke a control process is the possibility that the more difficult high-PI trials require additional time on task from probe evaluation processes (e.g., memory retrieval and/or decision processes), which produces a "duty cycle" effect in regions supporting these processes[§]. (Indeed, a fundamental assumption about neuroimaging-behavior relations would be violated if trials with longer RTs, regardless of the cause, didn't produce greater signal somewhere in the brain.)

The neuropsychological evidence marshaled to date is also unable to rule out the duty-cycle alternative. Most notably, a case study showed that a patient with a lesion of left Brodmann's area 45 of the left IFG displayed selective, disproportionate impairment on high-PI trials (13). Similarly, neurologically healthy older adults revealed a disproportionate impairment on high-PI trials, coupled with weak left IFG neuroimaging effects (14). Although these results have been interpreted as evidence for a role for left IFG in the control of PI, they could also have come about if the experimental groups encoded information less effectively. By this latter account, performance would be expected to decline differentially on the objectively more difficult high-PI trials, and left IFG's contribution to the selective deficit on high-PI trials would be related to encoding (a function well established for this region; ref. 15), rather than conflict resolution, inhibition, or some other PI-resolving process[¶].

The present experiments were designed to adjudicate conclusively between the cognitive control and the duty-cycle accounts of the working memory PI effect in the left IFG. They would do so by applying a technique that affords precise experimental control of the time period during which brain function is disrupted, repetitive transcranial magnetic stimulation (rTMS), thereby enabling one to explore the causal contribution of a

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Abbreviations: IFG, inferior frontal gyrus; M1, primary motor cortex; NN, nonrecent negative; NP, nonrecent positive; PCG, postcentral gyrus; PI, proactive interference; RC, response-level conflict; RN, recent negative; RP, recent positive; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area.

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§Evidence for a comparable sensitivity of neuroimaging signal from the left IFG to recent positive (RP) probes would be incompatible with this differential-difficulty account. However, the only study with which we are familiar that has reported differential sensitivity of the left IFG to RP probes reported this effect to be significantly smaller than the analogous effect for RN probes (12).

¶Note that ref. 13 also found no correlation between general working memory performance and PI effects when looking across the entire sample from that study, which included neurologically healthy young and elderly subjects, frontal lesion control subjects, and the left IFG-lesioned case. Although one might expect an encoding deficit to manifest itself as a common source of variance between these two measures, this need not be the case if the putative encoding problem interacted in a nonlinear fashion with performance, such that it only affected performance on the most difficult trials.

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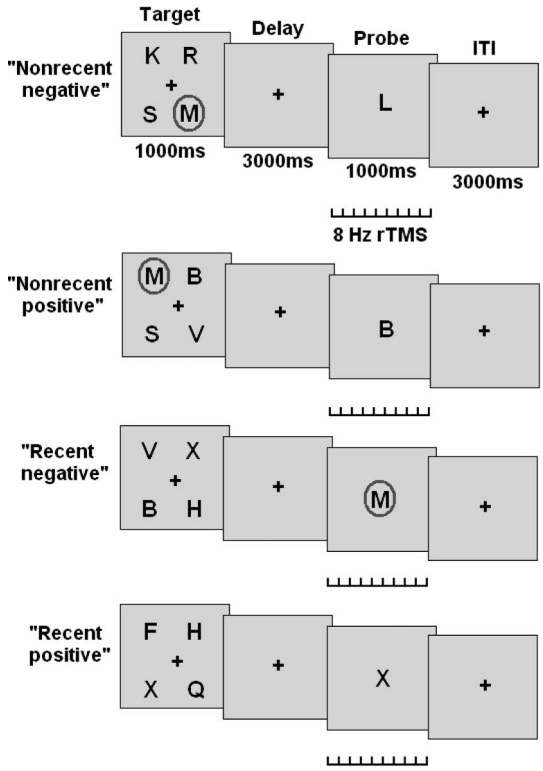

Fig. 1. An illustration of four consecutive trials of the delayed item-recognition task. The task crossed the factors of probe validity (positive, negative) with probe recency (nonrecent, recent). For clarity, items related to the RN probe are circled. Orthogonal to these factors was rTMS (present, absent), which was randomized across trials, and delivered in 8-Hz, 10-pulse trains with onset coincident with probe onset. Subjects were instructed to indicate the validity of each probe, as quickly and accurately as possible, via a button press.

specific brain area to task performance (16). The cognitive control model predicted that rTMS applied over the left IFG, time-locked to memory probe presentation, would selectively affect performance on high PI item-recognition trials (i.e., those with RN probes), compared with probes that did not invoke the need for PI resolution, and compared with interleaved trials without rTMS. The duty-cycle alternative, in contrast, predicted an effect of rTMS on all probe types. rTMS of control regions, including the leg area of primary somatosensory cortex, located in left postcentral gyrus (PCG; selected because it is assumed not to have a direct involvement in working memory or some undefined effect of inducing current in cortex), would control for possible regionally nonspecific effects of rTMS (caused by, e.g., acoustic noise and/or sensation of stimulation). The hand area of the primary motor cortex (M1) would control for effects of stimulation on motor processes. For subjects 7–12, stimulation was applied over the left supplementary motor area (SMA), instead of the right M1 (see Fig. 2 for illustration of stimulation sites). For this site, subjects also performed item recognition in which the probe repeated on half of the trials, and on half of these repetition trials the validity of the probe was reversed. These latter probes were expected to produce response-level conflict (RC). The logic of including this task was to find another type of conflict-resolution trial that would not be differentially sensitive to rTMS of the left IFG but that would be sensitive to rTMS of a different frontal brain region, in this case, the SMA (17). This approach would provide a double dissociation of function that would strengthen the case for the control-of-PI account of the left IFG.

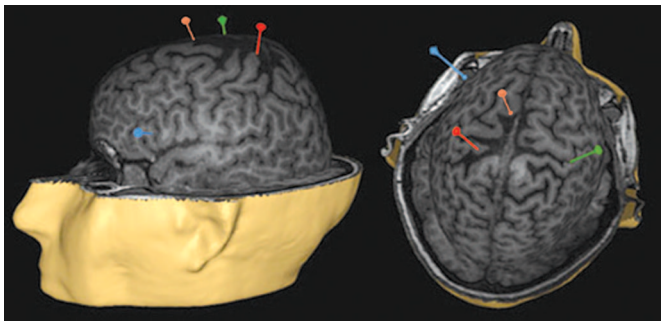

Fig. 2. Illustration of stimulation sites, from a representative subject, as displayed by the NBS system. (*Left*) A view of the left hemisphere, in which the blue marker represents the left IFG stimulation site, red marker is the right M1 site, green marker is the left PCG site, and the orange marker is the left SMA. (*Right*) The same brain as though looking down from above. The right hemisphere appears on the right side of the image. The cortex has been ''peeled'' to the depth that best displays the stimulation regions.

Results

Recent Probes Task. Trials were blocked by brain region (left IFG, left PCG, right M1 for subjects 1–6; left IFG, left PCG, and left SMA for subjects 7–12), order was counterbalanced across subjects, and the experimental factor of rTMS (present, absent) was varied randomly, orthogonal to the factors of probe validity (positive, negative) and probe recency (recent, nonrecent). We first tested for a replication of the standard PI effect on the rTMS-absent data. ANOVA of the RT data, with the factors of region, validity, and recency revealed a significant interaction of recency × validity [$F(1,11) = 9.38$; $P < 0.05$], carried primarily by the fact that subjects took longer to respond to RN than to nonrecent negative (NN) probes [$t(11) = 2.55$; $P < 0.05$; all *t*s in this report are two-tailed, unless otherwise noted], the standard PI effect. ANOVA of the rTMS-absent accuracy data also revealed a recency × validity [$F(1,11) = 10.01$; $P < 0.01$] interaction [with region × recency missing significance at $F(1,11) = 3.24$; $P = 0.10$], with a pairwise comparison confirming that the PI effect was also reliable in the accuracy data [$t(11) = -2.50$; $P < 0.05$].

Turning now to the full data set (Fig. 3), we did not find evidence for prefrontal cortex-based control of PI in our analyses of RT data, so we report only results from accuracy data. rTMS selectively impaired the accuracy of responses only when it was applied to the left IFG. This observation was borne out in a reliable three-way interaction of rTMS × region × recency [$F(1,11) = 9.91$; $P < 0.01$] {and borderline three-way interactions of rTMS × region × validity [$F(1,11) = 3.99$; $P = 0.07$] and of rTMS × validity × recency [$F(1,11) = 4.24$; $P = 0.06$]}. We followed up on these interactions with contrasts evaluating the effect of rTMS at the left IFG on each probe type. In a manner analogous to the ANOVAs, these were computed relative to the comparable effect of rTMS on the PCG with the contrast $[(\text{probe}_{\text{leftIFG,rTMSoff}} - \text{probe}_{\text{leftIFG,rTMSon}}) - (\text{probe}_{\text{PCG,rTMSoff}} - \text{probe}_{\text{PCG,rTMSon}})]$[‖]. rTMS of the left IFG reliably disrupted accuracy for RN [$t(11) = 4.63$; $P < 0.001$], but not NN [$t(11) = 0.00$; not significant), RP [$t(11) = 0.26$; not significant], or nonrecent positive (NP) [$t(11) = 1.29$; not significant] probes.

Inspection of Fig. 3 raises the question of whether the selective effect of rTMS on RN probes was disproportionately driven by

[‖]The importance of including the control is made evident by considering the NN probes. In the left IFG, rTMS had the effect of lowering NN accuracy from 93.8% to 90.2% correct, a simple pairwise difference that approached significance with $t(11) = 1.66$. But because this effect is almost identical to what one sees for NN probes in the PCG, it is clear that it cannot be interpreted as anything other than a regionally nonspecific effect of rTMS on task performance.

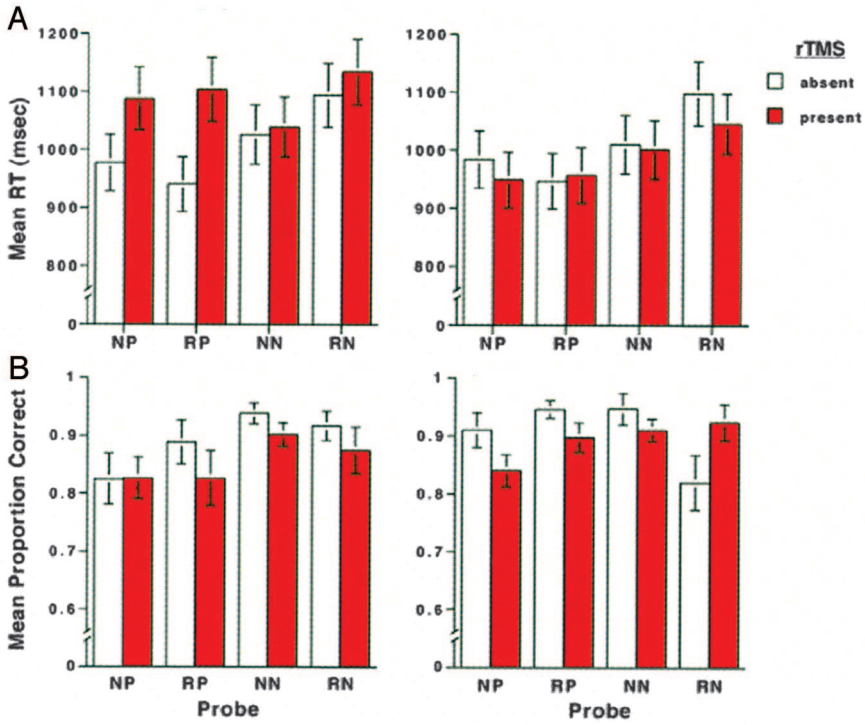

Fig. 3. Aggregated results for the recent probes task. (*Left*) Left IFG. (*Right*) Left PCG. (*A*) Results for RT data. Error bars indicate +/− SEM. (*B*) Results for accuracy data. Error bars indicate +/− SEM.

the relatively low accuracy on $RN_{rTMSoff}$ trials from the PCG. There are several reasons to believe that this observation does not compromise our interpretation of these results. The first is simply that the randomization of trials and counterbalancing of regions across subjects rules out the possibility that this pattern reflects order effects, or some other methodological confound. A second is the fact that this pattern was highly reliable across subjects. Indeed, Fig. 4 illustrates that the disruptive effect of left IFG rTMS on RN probes ($probe_{rTMSoff} - probe_{rTMSon}$) was greater than or equal to the PCG effect in all but 1 of 12 subjects. {And this effect differed significantly from the analogous effect for NN [$t(11) = 3.21$; $P < 0.01$] and NP [$t(11) = 3.31$; $P < 0.01$] probes, and marginally for RP probes [$t(11) = 2.05$; $P = 0.065$].} A third reason is that the pattern of higher RN accuracy for rTMS-on than rTMS-off trials was also seen in M1 (for RN probes only) in subjects 1–6 [mean accuracy $RN_{rTMSoff} = 0.86$ (SEM = 0.08); mean $RN_{rTMSon} = 0.93$ (SEM = 0.04)]. Together, these reasons support two assertions about our results. The first is that the pattern of superior RN performance on rTMS-on than on rTMS-off trials was seen in all regions except the left IFG, giving credence to the likelihood that it was "real". (Although our design does not permit us to identify definitively the factors behind this pattern in our results, we consider some possibilities below.) The second is that they are consistent with the control account, in that RN accuracy was differentially sensitive to rTMS of the left IFG.

Why was RN accuracy higher in the PCG and M1 with rTMS than without it? One possibility is that that the regionally nonspecific effect of rTMS on RN probes, as indexed by rTMS of the PCG and M1, may be to paradoxically improve performance on these trials, perhaps a result of their "naturally" low baseline (i.e., subjects had more room to improve with RN

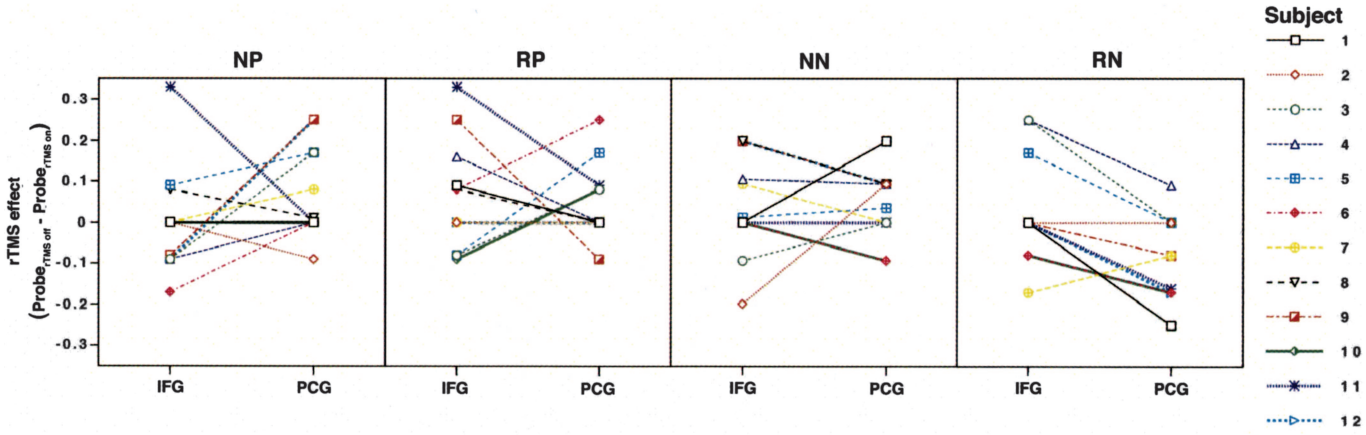

Fig. 4. Individual results comparing relative effects of rTMS on the left IFG versus left PCG rTMS, in the same subjects.

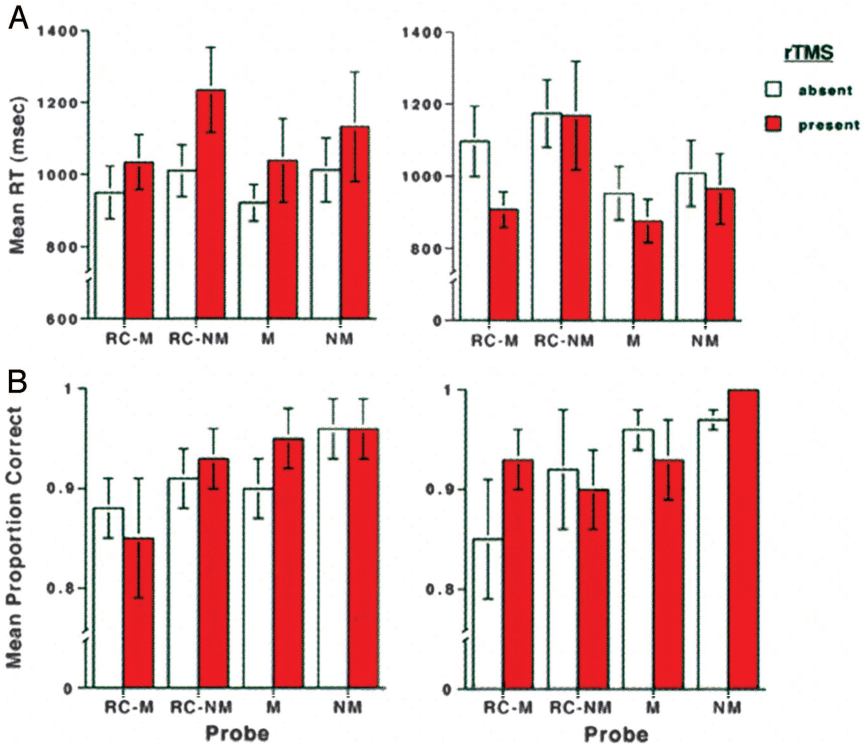

Fig. 5. Aggregated results for the RC task. (*Left*) The left IFG. (*Right*) The left SMA. (*A*) Results for RT data. Error bars indicate ± SEM. (*B*) Accuracy data. Error bars indicate ± SEM. RC-P, RC-positive probes; RC-N, RC-negative probes; P, positive probes; N, negative probes.

probes than with the other three probe types). A second, which is not incompatible with the first, is that rTMS to the left IFG (and only the left IFG) may have residual "potentiating" effects that produce improved baseline performance on RN trials. {If this were true, however, one would expect to see performance on rTMS-off trials improve as a function block, but neither visual inspection of the data nor a test for linear trends [$F(1,11) = 0.01$; not significant] supported this.} A third is that the motoric functions of M1, and of regions proximal to the PCG, interact with some feature of RN probes (e.g., the PI) such that rTMS produces facilitation, rather than, disruption, of performance.

A separate analysis performed on the data from subjects 7–12 indicated that rTMS of SMA (normalized by rTMS of the PCG) did not differentially affect performance with RN vs. NN probes in either the RT [$t(5) = -1.36$; not significant] or the accuracy [$t(5) = 0.99$; not significant] data.

RC Task. Analyses of the RC task revealed no differential effects on the RC of rTMS applied to the left IFG, but there was an effect when rTMS was applied to the left SMA. Thus, they yielded the completion of a conceptual double dissociation with the PI data, in that they showed a pattern of sensitivity to rTMS that was opposite to the pattern seen with PI (sensitive to rTMS to the left IFG but not to the SMA). We qualify this as a "conceptual" double dissociation because the critical effect with the RC task was borne out in the RT data, rather than in the accuracy data. This finding was expected based on prior work with this task (17). Omnibus ANOVA of the RT data with the factors of the brain region (left IFG, left SMA), rTMS (present, absent), RC (present, absent), and validity (positive, negative) revealed a main effect of RC [$F(1,5) = 18.93$; $P < 0.01$], a marginally significant two-way interaction of region × rTMS [$F(1,5) = 4.35$; $P < 0.09$], and a marginally significant three-way interaction of region × RC × validity [$F(1,5) = 4.25$; $P < 0.09$] (all other Fs < 3.04; not significant). Omnibus ANOVA of the accuracy data revealed only a main effect of validity [$F(1,5) = 450.47$; $P < 0.0001$] (all other Fs <2.85; not significant). Inspection of Fig. 5 suggests that the effects of rTMS on SMA, to decrease RT and a more complex pattern in the accuracy data, were generally in the opposite direction as the effects on the left IFG. Our test of the hypothesis that rTMS to the two regions would have differential effects on RC was limited to positive probes, because subjects appeared to be trading speed for accuracy with negative RC probes during left IFG blocks. (That is, for these probes rTMS had the effect of slowing performance but increasing accuracy.) For positive RC probes, rTMS to the SMA had the effect of speeding responses and making them more accurate. These trends were in the opposite direction in the left IFG, effects that failed to achieve significance in the accuracy data [$t(5) = 1.65$; not significant] but that approached it in the RT data [$t(5) = 2.48$; $P = 0.056$, one-tailed]. Although a complete understanding of the effects of rTMS of the SMA on RC will require a full study that includes a cortical control area, the present results suggest that rTMS to the SMA has the effect of minimizing the cost to performance of RC. With negative RC probes, for example, rTMS reduced RT to a level comparable to negative RC-absent probes and also increased accuracy to a level comparable to negative RC-absent probes. Thus, it may be that rTMS to the SMA had the effect of disrupting the detection and/or processing of RC (functions ascribed to this region; refs. 17 and 18), such that negative probes with RC present were processed like negative probes without RC.

Discussion

The results from our experiment are consistent with the control account of the PI effect in the left IFG and rule out the duty-cycle alternative. These results afford the strongest possible inference that the cognitive control of high-conflict conditions in verbal working memory depends on the function of the left IFG. The rejection of the duty-cycle account of left IFG neuroimaging

effects is particularly convincing because the effects were restricted to accuracy, whereas the premise of the duty-cycle alternative is that longer time on task is responsible for the stronger neuroimaging signal in the left IFG. At a mechanistic level, the fact that rTMS of the left IFG increases false alarms to RN probes suggests an important role for this region in processes that resolve the conflict between the RN probe's high level of familiarity vs. its validity. This, in turn, suggests that the process(es) disrupted by rTMS in the present experiment may share similarities with processes invoked in dual-process models of recognition from long-term memory (e.g., ref. 19). Further theoretical and empirical work will be necessary to evaluate this possibility and determine whether the present results generalize to other putative examples of left IFG-dependent control (e.g., retrieval, selection, reactive control; refs. 1–3).

Materials and Methods

Subjects. The 12 right-handed adults (6 males, 6 females, mean age = 22.91 years; SD = 3.63) had no psychiatric or neurologic disorders, assessed by a structured psychiatric diagnostic screening interview (MINI; ref. 20), and a mood assessment (HAM-D; ref. 21), administered by a psychiatrist. All subjects gave written informed consent, and the experiment was approved by University of Wisconsin institutional review board.

Behavioral Tasks. Each trial began with the 1,000-ms presentation of four letters around a central fixation cross, followed by a 3,000-ms unfilled delay period during which subjects were instructed to retain a memory of the target letters. In all rTMS sessions the memory probe then appeared centrally for 1,000 ms, and subjects were instructed to indicate as quickly and accurately as possible whether the probe was a "match" (subjects 1–6: right index finger button press; subjects 7–12 and for experiment 2: right hand button press) or a "nonmatch" (subjects 1–6: right thumb button press; subjects 7–12: left hand button press) of an item from that trial's target set. Responses made within 3,000 ms of probe onset were recorded. The offset of the probe was followed by a 5,000-ms intertrial interval.

MRI. Whole-brain T1-weighted images (128 sagittal slices, acquired with a $512 \times 512 \times 256$ matrix within a 512-mm^2 field of view) were acquired with a 3T scanner (Signa VH/I, GE, Milwaukee, WI).

rTMS. rTMS was delivered with a Super Rapid magnetic stimulator fit with a 70-mm figure-8 air-cooled stimulating coil (Magstim, Whitland, Wales). Subjects were seated comfortably in a chair with head stabilization to prevent movement. Localization of the stimulating coil was accomplished by infrared-based frameless stereotaxy (eXimia Navigated Brain Stimulation, Nexstim, Helsinki, Finland). For each subject resting motor threshold was determined as the intensity at which single pulses applied over the hand area of right M1 produced a visible muscle twitch in 5 of 10 consecutive trials. At each stimulation site, 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.

Experimental Procedure. For subjects 1–6, the experiment was performed across 12 blocks of 24 trials, with four sequential blocks performed at each brain region. Each block presented an equal number of the four probe types in a pseudorandomized order that was constrained by the following: NP and NN probes did not match any target items from the two preceding trials; RP probes matched a target item from the current trial and the previous trial; and RN probes matched a target item from the two preceding trials (Fig. 1). Orthogonal to the factor of probe type was that of rTMS, the presence or absence of which was equiprobable and determined according to a randomized order, with the constraint that each probe type experienced an equal number of rTMS-present and rTMS-absent trials. For subjects 7–12, the number of blocks performed was increased to include two RC blocks each for the left IFG and left SMA stimulation sites. RC was produced by probes that repeated the identity of the probe from the preceding trial, but required the opposite response. Rather than design this task as a full factorial, we maximized the number of RC observations with the following design: from 30 trials, 24 were entered into a 2×2 that crossed validity with repetition, and in which all repeated probes featured RC; the remaining 6 trials featured repeating probes without RC (3 positive, 3 negative).

For subjects 1–6, three cortical sites were selected on each subject's MRI for rTMS (Fig. 2): the left IFG, right M1, and left PCG. The left IFG (Brodmann's area 45) corresponded to the pars triangularis of the IFG, defined as the portion rostral to the ascending ramus and dorsal to the horizontal ramus of the sylvian fissure (22). The location of right M1 was confirmed through the motor threshold procedure described above. For subjects 7–12, the left SMA replaced the right M1 stimulation site to demonstrate a conceptual double dissociation of function between frontal areas associated with PI vs. RC. This region was located on each subject's high-resolution MRI based on anatomical descriptions provided by refs. 17 and 23. The order of rTMS application to these sites was counterbalanced across subjects. rTMS was administered during a 1,250-ms period, its onset time-locked to the onset of the memory probe, at a rate of 8 Hz and at an intensity of 110% of motor threshold (mean = 63.58% of maximum stimulator output, SD = 5.76, uncorrected for scalp-cortex distance).

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