

Prefrontal and parietal contributions to refreshing: An rTMS study

Brian T. Miller,^{a,*} Timothy Verstynen,^{a,b} Marcia K. Johnson,^c and Mark D'Esposito^{a,b}

^aHelen Wills Neuroscience Institute, University of California, 132 Barker Hall, MC #3190, Berkeley, CA 94720-3190, USA

^bPsychology Department, University of California, Berkeley, USA

^cDepartment of Psychology, Yale University, USA

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Refreshing is a basic reflective component process that can serve to prolong activation of task-relevant information. Neuroimaging work has shown that left middle frontal gyrus (MFG) and supramarginal gyrus (SMG) are selectively engaged during refreshing. Functional MRI (fMRI), however, is not able to determine if these regions are necessary for refreshing. In this experiment, we utilize repetitive transcranial magnetic stimulation (rTMS) to assess the behavioral effect of functionally deactivating these regions. We report a selective slowing of response times (RTs) to refresh words following MFG stimulation, consistent with a role of lateral prefrontal cortex (PFC) in top-down control mechanisms necessary for refreshing. In contrast, SMG stimulation slowed participants in both refreshing and repeating words, indicating a more general role of SMG in verbal processing.

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Introduction

Refreshing (e.g., Johnson, 1992; Johnson and Hirst, 1993) is a reflective component process that is engaged and executed immediately (i.e., within 100s of milliseconds) to increase and/or prolong activation of information that would otherwise quickly become less available (e.g., Sperling, 1960). The target can be a just-experienced thought or percept, but in any case, refreshing is an instance of reflective (as opposed to perceptual) attention by which top-down control is exerted so that an active representation of information no longer in the environment is foregrounded. Refreshing is a basic component of many complex cognitive tasks. For example, refreshing may help keep agendas active (i.e., goals, subgoals, contexts, attentional templates, rules); keep potentially relevant information active during comprehension or problem solving; and bridge between a thought and its expression, or between intention and action. Importantly, a refresh signal serves as a minimal maintenance operation since it targets active representa-

tions that are decaying in either iconic/echoic memory or in working memory as part of a multi-representation rehearsal loop. Refreshing can be conceptually distinguished from other mnemonic control processes like retrieval and reactivation which target latent, nonactive representations in long-term memory.

In a typical refresh study (e.g., Johnson et al., 2002), items such as single unrelated words are presented briefly and participants are told simply to read aloud each word as it appears. Some words are seen once (*read* condition), some words are presented twice in succession (*repeat* condition), and other words are followed by a dot cue (●) that signals participants to think of the just-preceding item and say it again (*refresh* condition). The typical behavioral finding is that participants take longer to refresh a just-seen word than to read a word once or to read it a second time. In addition, refreshing generally improves long-term memory (LTM) for items compared to seeing the item just once or even seeing it twice (but see, Johnson et al., 2003, Experiment 1, for an interesting counter-example).

As reviewed by Johnson et al. (2005), a number of neuroimaging studies consistently have shown refresh-related activity within left dorsolateral PFC (especially in the MFG) that varies somewhat depending on what is refreshed (e.g., words, locations, pictures of people or places). MFG also showed greater activation for items that were subsequently quickly recognized on a LTM test vs. those that were missed (Raye et al., 2002). There typically is refresh-related activity in more posterior regions such as parietal cortex as well (especially around SMG/LPi; e.g., Johnson et al., 2003; Raye et al., 2002).

Disruptions to the refresh process have also been demonstrated. For example, older adults are disproportionately slower than young adults to refresh compared to reading words shown once or words that are repeated, and older adults do not reap the same benefit to LTM as young adults (Johnson et al., 2002). Emotion can also disrupt refreshing. Johnson et al. (2005, Experiment 6; see also Johnson et al., 2006) varied whether participants were cued to read again or to refresh an emotional or a neutral word from a set of three words they had just read. All other things being equal, in processing a set of mixed emotional and neutral words, attention should be drawn to the more salient emotional item (*mental rubbernecking*), making it harder to refresh a less salient neutral word. This is exactly what they found. Furthermore, it appears to be a PFC component of

* Corresponding author. Fax: +1 510 642 3192.

E-mail address: btmiller@berkeley.edu (B.T. Miller).

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the refresh circuit that is selectively disrupted by aging (Johnson et al., 2004) and by emotion (Johnson et al., 2005). The parietal component has not shown such disruptions in previous studies. Given the nature of these disruptions in concert with the fMRI findings, it is our hypothesis that TMS over the PFC will have a disproportionate disruption of refresh performance compared to TMS over the SMG.

To test these hypotheses, we use low-frequency repetitive transcranial magnetic stimulation (rTMS) to directly assess the necessity of MFG vs. SMG activity for successful refreshing. Low-frequency rTMS protocols have been shown to transiently inhibit neural activity in cortex for an extended window following administration allowing for the assessment of off-line behavioral performance (e.g., Kosslyn et al., 1999; for a discussion, see Robertson et al., 2003). Although the direct mechanism of this inhibition is still unknown, physiology evidence suggests that the effects of this disruption extend beyond the time-period of stimulation (Robertson et al., 2003). In this set of experiments, this low-frequency off-line administration offers a distinct advantage over single-pulse fMRI protocols given the absence of clear temporal hypotheses about regional involvement and confounds caused by pulse-induced eye blinks during the reading paradigm. In order to test the specificity of TMS-induced behavioral effects to regions actively engaged in the cognitive operations, we also ran a control group with the same TMS protocol over the right motor cortex to rule out generalized effects of TMS on behavior. By functionally deactivating relevant regions during a refresh task with TMS, we can gain converging evidence on the relative functional importance of the prefrontal and parietal components of the refresh circuit.

Materials and methods

Participants

Three participant groups, composed of right-handed undergraduate students, were recruited from the campus of the University of California, Berkeley. The middle frontal gyrus (MFG) group had 9 participants (4 females, M age=21.2 years) and the supramarginal gyrus (SMG) group had 9 participants (3 females, M age=21 years). A third group of 9 control participants (3 females, M age=21.4) were stimulated over the right motor cortex to test for any generalized effects of TMS on performance. All participants received TMS stimulation to the site of interest along with a sham procedure to the same region, as described below. The procedure was approved by the Institutional Review Board of UCB and all participants gave informed consent. Given an upper-range on number of total pulses per participant per subject set by the IRB, we ran independent groups to increase the number of trials for each condition (and hence statistical power) as well as to limit any potential practice effects or re-exposure effects within individuals across multiple sessions or days. All participants received monetary compensation for their participation.

Behavioral procedure

All participants were seated 31 centimeters away from a 17" CRT monitor on which stimuli were presented centrally. Vocal response times (RTs) were recorded via a microphone and registered using an EPRIME voice trigger box (Psychology Software Tools, Inc.), with 1 ms temporal resolution. Responses were monitored by the experimenter for accuracy (errors in mispronouncing words or

refreshing were rare and occurred on less than 0.5% of the trials); RTs less than 100 ms were assumed to be spurious triggers of the voice key and were discarded before analysis (1.5% of total responses).

Stimuli were common 1 to 3 syllable words taken from those used by Johnson et al. (2002), each presented for a 2 s duration with a 1 s interval (i.e., ITI) between words (total trial length=3 s). Half of the words were presented in lower-case font and half in upper-case font. Following Johnson et al. (2002), participants were instructed to read each word aloud as quickly and accurately as possible. Sometimes the same word would appear again (referred to as *Repeat* trials). Other times, instead of a word, an asterisk cue (*) appeared and the participants were instructed to think of, and say again, the just-previous word (referred to as *Refresh* trials). In each TMS stimulation or sham block, there were 36 Repeat and 36 Refresh trials, randomly intermixed with 36 additional filler words that participants merely read so as to attenuate any anticipatory rehearsal (total block length=9 min). RTs to critical items (repeated word or asterisk cue) were recorded. Following each block of behavioral trials, a 5 min break was taken to allow for wash-out of the TMS effect before the next stimulation block.

Before the start of the session, participants were given practice with 10–15 trials. During this practice period only, the voice trigger terminated each trial when it detected the participant's voice. This was meant to provide participants with feedback on the volume of their response that was necessary to trigger the voice key.

rTMS stimulation

Subject-specific location of coil placement was determined using an MRI image-guided stereotaxic system (Rogue-Research Inc.) and individual high-resolution T1-weighted MRI images of each participant. This system displays the position of the TMS coil on the 3D MRI image with 2-mm precision. For the MFG group, a target location was identified on the left MFG, directly above the ascending ramus of the inferior frontal gyrus. For participants in the SMG group, a target location was identified on the posterior bank of the left SMG, just caudal of the Sylvian fissure. Both of these regions were selected based on brain regions shown to be engaged during refreshing in a previous fMRI study (Raye et al., 2002). The control region in the right motor cortex group was identified functionally by targeting the location in the right hemisphere over which pulses led to the movement of each individual's left dorsal interosseus muscle of the hand.

Transcranial magnetic stimulation (TMS) was conducted with a 70 mm, figure-8 NeoPulse stimulator and iron-cored coil (NeoTonus Inc.). Before the session, participants were stimulated over left primary motor cortex. Stimulation level was adjusted to determine the minimum intensity needed to induce a visible twitch of the first dorsal interosseus muscle of the right hand in 5 out of 10 pulses. This stimulation intensity was determined to be the motor threshold. During the session, participants were then stimulated over either the left MFG or left SMG or the right motor cortex at a 45° angle relative to the scalp with an intensity set at 115% of this motor threshold (average stimulator output: MFG: 52% M.S.O., SMG: 51% M.S.O.). The average scalp to cortex distance across the two areas was 12.4 mm for the MFG group and 11.7 for the SMG group. These distance measures were not significantly different across groups ($p>0.30$). Stimulation lasted for 10 min with an inter-pulse frequency of 1 Hz. This method has been shown to transiently attenuate activity of the underlying cortex (for review, see Robertson et al., 2003). One run of behavioral testing immediately followed the

stimulation period. Following the behavioral testing, participants then underwent sham procedures over the same site as a within-subject control. This stimulation was performed at the same 115% motor threshold intensity. This sham stimulation was aimed at providing a within-subject control of performance by being the same temporal duration as real rTMS and also mimicking the auditory click accompanying the stimulation. During this time, the TMS coil was rotated 90° away from the scalp, resulting in no stimulation of the underlying cortex. A second run of behavioral testing followed.

MRI parameters

A Varian 4T Unity INOVA scanner was used to collect high-resolution, anatomical images of each participant in the MFG and SMG groups. These images consisted of T1-weighted scans that were acquired using a FLASH pulse sequence (91 slices, Matrix size=91 × 109, Thickness=2 mm). Each participant's structural image was used to identify a target scalp location for rTMS by frameless stereotaxy (see above).

Results

Response times for the MFG, SMG, and Motor control groups are shown in Fig. 1. An ANOVA that included the between subject factor of Group (MFG, SMG, Motor) and repeated factors of Condition (Refresh, Repeat) and TMS (Stimulation, Sham) resulted in a main effect of Condition ($F[1,24]=91.25$, $MSe=1560$, $p=0.001$), and two interactions: TMS × Group ($F[1,24]=5.37$, $p=0.01$) and TMS × Condition ($F[1,24]=5.92$, $MSe=580$, $p=0.02$). Response times were longer in the Refresh (606 ms) than Repeat conditions (533 ms). The TMS × Group interaction reflected the fact that stimulation increased response times in the MFG group and SMG group, but decreased response times slightly in the Motor group. When the Motor Control group was analyzed separately, there was only a main effect of Condition (Refresh > Repeat, $F[1,8]=17.4$, $MSe=2264$, $p=0.003$). Since stimulation had no significant effect in this group, it is not considered further.

Our main interest was in the effects of TMS stimulation of MFG and SMG areas. An ANOVA including the MFG and SMG groups resulted in a significant Group × Condition × TMS interaction ($F[1,16]=4.25$, $p=0.05$). The MFG and SMG groups were analyzed separately to clarify this interaction. As can be seen in Fig. 1 (top panel), in the MFG group, Refresh trials (584 ms) were slower than Repeat trials (502 ms) ($F[1,8]=98.8$, $MSe=614$, $p<0.0001$). Importantly, there was a significant Stimulation × Condition interaction ($F[1,8]=14.80$, $MSe=307.3$, $p=0.005$) because participants were slower after TMS stimulation to MFG than sham selectively for Refresh trials ($t[8]=3.42$, $p<0.05$) but not for Repeat trials ($p>0.50$).

As can be seen in the middle panel of Fig. 1, for the SMG group, Refresh trials (600 ms) were slower than Repeat trials (526 ms) ($F[1,8]=24.14$, $MSe=1800$, $p=0.001$). There was also a main effect of TMS ($F[1,8]=17.40$, $MSe=616$, $p=0.003$) and the TMS × Condition interaction was not significant ($p>0.20$); performance was slower after TMS stimulation (579 ms) than after sham (546 ms) in both types of trials.

Behavioral control group

Participants in both the MFG and SMG stimulation groups tended to be slower after stimulation than sham, which raises the

possibility that the effect of stimulation was confounded by a practice effect. That is to say, perhaps all participants got faster in the second block, which was always the sham procedure, because of a practice effect that disproportionately improved performance on the more difficult refresh trials. While this is not likely to be the case given that the MFG group did not get faster on the repeat trials and that the SMG group had a condition-independent decrease in RTs (and the Motor Control group did not show faster responses on the second, sham block), we tested this by running a behavioral control. In the behavioral control group, participants ($N=11$, 4 females, M age=19 years) were drawn from the same general population as those in the stimulation groups. During the behavioral session, control participants simply remained seated for 10 min between the two blocks of behavioral trials to match the temporal parameters of the stimulation groups' procedure.

In this nonstimulation control group, there was a significant main effect of condition on RTs ($F[1,10]=32.5$, $MSe=1803$, $p<0.001$), such that responses on Refresh trials (615 ms) were slower than Repeat trials (542 ms). Importantly, there was not a decrease in RTs across blocks ($F[1,10]<1$, $p>0.90$). In fact, more than half of the control group showed slower RTs in the second block. There also was no Block × Condition interaction. An analysis of these sham results in a mixed ANOVA including sham trials from the MFG, SMG, and motor control groups revealed no significant condition × group interactions ($F[1,31]=0.280$, $p>0.83$). This highlights the lack of any systematic differences across groups that could artificially lead to the TMS effects reported.

Discussion

Although refreshing is a simple reflective operation, it requires the coordinated interaction of a number of neural systems. Previous fMRI investigations (e.g., Raye et al., 2002; Johnson et al., 2004) highlighted two main regions of this refresh circuit – left MFG and SMG – which showed greater responses to refreshed words relative to repeated words. Since fMRI measures are inherently correlational, however, they cannot elucidate the causal role of these regions in refreshing. Moreover, fMRI responses cannot reveal the differential contributions of two neural systems that are similarly engaged in response to a cognitive manipulation. The current experiment extends our understanding of mnemonic function by employing a low-frequency rTMS protocol (see Pascual-Leone et al., 2000) to provide direct evidence regarding the functional roles of left prefrontal and parietal cortices in refreshing.

We found that TMS stimulation to the MFG group caused a refresh-selective slowing of RTs following stimulation whereas stimulation to the SMG caused slowing nonselectively on both trial types. The presence of a Group by Condition by TMS interaction is consistent with different contributions of these two regions to refreshing. The TMS by Condition interaction in the MFG group indicates that this region is necessary for refreshing but not for operations engaged in both task conditions (e.g., general verbal processing, vocal response preparation, etc.). One plausible contribution of left dorsolateral PFC is that it provides a top-down signal to posterior regions that biases processing in favor of the now relevant word representation (e.g., Raye et al., 2007). When an incoming sensory stimulus (i.e., the asterisk) indicates that a previously presented stimulus is important for behavior, the PFC could be the source of the top-down signals to posterior areas that foreground and strengthen the decaying sensory trace. This role of the PFC as the source of top-down signals in the refresh circuit is

consistent with neurophysiology, neuroimaging, and neuropsychology evidence implicating it in the top-down control of sensory and mnemonic processes (for a review, see Miller and D’Esposito, 2005). Recent fMRI evidence that left dorsolateral PFC plays a role in processes involved in the representation of information during refreshing comes from a study showing left dorsolateral PFC activity when participants are signaled to refresh a previous item, but not when they are signaled to push a button (whereas anterior PFC is

recruited for both conditions, Raye et al., 2007) and from a study showing that refreshing results in modulation of activity in posterior representational areas (refreshing a scene produces activity in the parahippocampal place area, M.R. Johnson et al., 2007).

Johnson et al. (2002) hypothesized that refresh impairments in normal aging are due to an increase in frontal neuropathology (Raz, 2000) and a corresponding deficit in necessary top-down control in the refresh circuit. With the new evidence from this experiment,

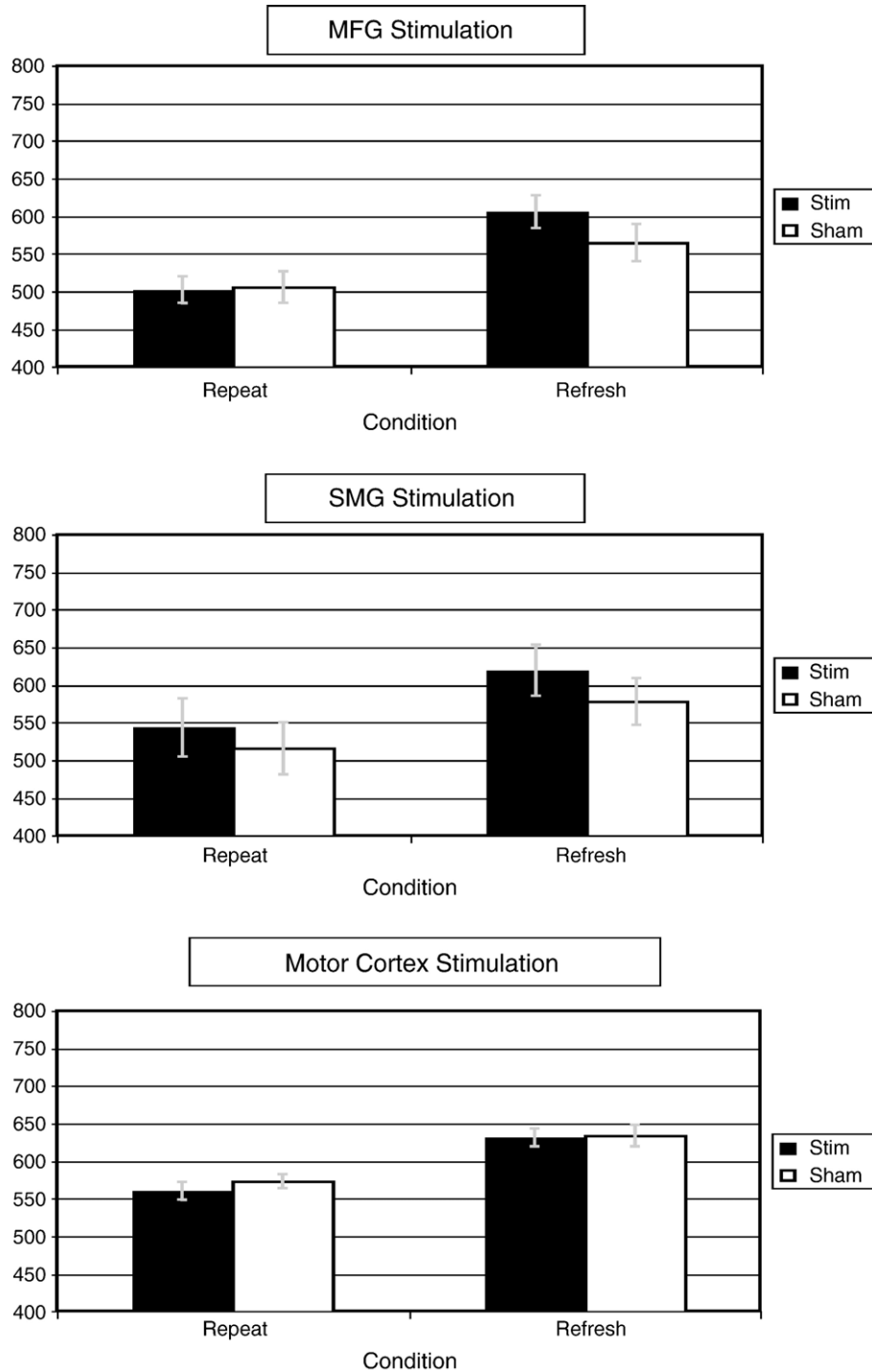


Fig. 1. Mean RT in repeat and refresh conditions (error bars are standard error of the mean) across TMS conditions. These results show stimulation effects in MFG and SMG after rTMS stimulation sham procedures and the absence of rTMS effects following Motor Cortex Stimulation.

there are now two lines of empirical support for this hypothesis. Johnson et al. (2002) reported that, relative to young adults, older adults demonstrated a disproportionate slowing of refresh latencies, and Johnson et al. (2004) reported age-related attenuation of refresh-related fMRI activity in left MFG. The present TMS findings provide further support that refresh deficits in normal aging are likely due to frontal disruption. By deactivating MFG in normal young controls, we report RT deficits that mimic the pattern of behavioral disruption found in normal older participants.

Johnson et al. (2005, 2002) have reported selective refresh-related left SMG activity, yet in the present experiment, the SMG participants showed a general slowing across both types of trials following TMS stimulation of this region. One possibility is that the SMG is not only involved in the refresh circuit, but is also involved in the repetition priming generally found for the repeat condition (faster RTs when a word is read immediately again, e.g., Johnson et al., 2002). Thus, one can disrupt refreshing by disrupting either the top-down prefrontal signal or the short-term representation in the SMG. Disrupting the short-term representation in the SMG will also disrupt repetition priming, accounting for the slower response times after stimulation than sham in the repeat condition. Another possibility is that the SMG could perform a number of roles in the refresh circuit. Several reports have implicated this region in the storage and retrieval of verbal working memory representations (Jonides et al., 1998). These experiments focused on tasks with longer delay periods requiring rehearsal mechanisms, but it is possible that the SMG could also serve as an early, pre-rehearsal, buffer for recently presented verbal information. Recall that, in the refresh procedure, trials of each type are intermixed and thus participants do not know what kind of trial it is. It may be that at the shorter ISIs used in Johnson et al.'s usual fMRI procedure (400–500 ms), participants do not yet engage an explicit rehearsal mechanism, and thus SMG activity is selective to the refresh trials in which the PFC encourages the quick minimal foregrounding of the relevant representation. That is, under the short ISI conditions used in the fMRI studies, successful refreshing involves an early top-down signal from the MFG to the SMG that enhances the activation of behaviorally relevant representations before they decay from the storage buffer. At the slightly longer ISIs we used here (1 s), on the other hand, participants may have engaged an explicit rehearsal strategy on at least some trials in both conditions, leading to the nonselective effect in SMG across both trial types (see Fig. 3 of Raye et al., 2007). The SMG also is involved in more basic lexical or phonological processes – particularly in converting orthography into phonology (Moore and Price, 1999) – likely evoked during both repeat and refresh trials, and it may be this activity of SMG that we disrupted in the current study. Further experimentation will be necessary to tease apart the possible roles of the SMG across the conditions in this task.

In conclusion, previous fMRI evidence highlighted left MFG and SMG as critical nodes in a refresh circuit (Johnson et al., 2005; Raye et al., 2002) and the present study utilized low-frequency repetitive TMS to test for a causal role of these areas in refreshing. The selective slowing of RTs during refresh trials after MFG stimulation, with additional slowing of RTs during repeat trials after SMG stimulation, suggests that MFG is involved in top-down operations that guide refreshing while SMG is involved in general verbal processes engaged in both conditions. These data highlight a complementary role for TMS in testing the direct causal contribution of different neural systems that exhibit similar fMRI measures in response to a cognitive manipulation.

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References

- Johnson, M.K., 1992. MEM: mechanisms of recollection. *J. Cogn. Neurosci.* 4, 268–280.
- Johnson, M.K., Hirst, W., 1993. MEM: memory subsystems as processes. In: Collins, A.F., Gathercole, S.E., Conway, M.A., Morris, P.E. (Eds.), *Theories of Memory*. Erlbaum, Mahwah, NJ.
- Johnson, M.K., Reeder, J.A., Raye, C.L., Mitchell, K.J., 2002. Second thoughts versus second looks: an age-related deficit in reflectively refreshing just-active information. *Psychol. Sci.* 13, 64–67.
- Johnson, M.K., Raye, C.L., Mitchell, K.J., Greene, E.J., Anderson, A.W., 2003. fMRI evidence for an organization of prefrontal cortex by both type of process and type of information. *Cereb. Cortex* 13, 265–273.
- Johnson, M.K., Mitchell, K.J., Raye, C.L., Greene, E.J., 2004. An age-related deficit in prefrontal cortical function associated with refreshing information. *Psychol. Sci.* 15, 127–132.
- Johnson, M.K., Raye, C.L., Mitchell, K.J., Greene, E.J., Cunningham, W.A., Sanislow, C.A., 2005. Using fMRI to investigate a component process of reflection: prefrontal correlates of *refreshing* a just-activated representation. *Cogn. Affect. Behav. Neurosci.* 5 (3), 339–361.
- Johnson, M.K., Mitchell, K.J., Raye, C.L., McGuire, J.T., Sanislow, C.A., 2006. Mental rubbernecking to negative information depends on task context. *Psychon. Bull.* 13, 614–618.
- Johnson, M.R.J., Mitchell, K.J., Raye, C.L., D'Esposito, M., Johnson, M.K., 2007. A brief thought can modulate activity in extrastriate visual areas: top-down effects of refreshing just-seen visual stimuli. *NeuroImage* 37, 290–299.
- Jonides, J., Schumacher, E.H., Smith, E.E., Koeppe, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., Willis, C.R., 1998. The role of parietal cortex in verbal working memory. *J. Neurosci.* 18 (13), 5026–5034.
- Kosslyn, S.M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J.P., Thompson, W.L., Ganis, G., Sukel, K.E., Alpert, M.N., 1999. The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science* 284 (5411), 167–170.
- Miller, B.T., D'Esposito, M., 2005. Searching for “the top” in top-down control. *Neuron* 48 (4), 535–538.
- Moore, C.J., Price, C.J., 1999. Three distinct ventral occipitotemporal regions for reading and object naming. *NeuroImage* 10 (2), 181–192.
- Pascual-Leone, A., Walsh, V., Rothwell, J., 2000. Transcranial magnetic stimulation in cognitive neuroscience: virtual lesion, chronometry, and functional connectivity. *Curr. Opin. Neurobiol.* 10 (2), 232–237.
- Raye, C.L., Johnson, M.K., Mitchell, K.J., Reeder, J.A., Greene, E.J., 2002. Neuroimaging a single thought: dorsolateral PFC activity associated with refreshing just-activated information. *NeuroImage* 15 (2), 447–453.
- Raye, C.L., Johnson, M.K., Mitchell, K.J., Greene, E.J., 2007. Refreshing: A minimal executive function, 43: 135–145.
- Raz, N., 2000. Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In: Craik, F.I.M., Salthouse, T.A. (Eds.), *Handbook of Aging and Cognition*, 2nd ed. Erlbaum, Mahwah, NJ, pp. 1–90.
- Robertson, E.M., Theoret, H., Pascual-Leone, A., 2003. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. *J. Cogn. Neurosci.* 15 (7), 948–960.
- Sperling, G., 1960. The information available in brief visual presentations. *Psychol. Monogr.* 74, 1–29.