

A Rational Account of Memory Predicts Left Prefrontal Activation during Controlled Retrieval

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What is the role of the left prefrontal cortex in the controlled retrieval of learned information? We present a theory of declarative retrieval that posits that the amount of control exerted by this region during retrieval is inversely proportional to 1) the frequency and recency of previous experiences with the retrieved memory and 2) the associative strength between the current context and the retrieved memory. This theory is rational in the sense that it claims that declarative retrieval is highly sensitive to the statistical regularities in the environment. We demonstrate how our theory produces precise predictions of response time and neural activity during recall and test these predictions in an experiment that manipulates the frequency of previous experiences and the associative strength to the retrieval cues. Our findings suggest that the control process performed by the left prefrontal cortex directly reflects the demands of the environment on memory.

Keywords: associative strength, cognitive modeling, competition, left inferior frontal gyrus

Introduction

Controlled access to learned information is essential for the adaptive, flexible behavior that is the hallmark of human cognition. The ease with which information is accessed is dependent upon both the frequency with which the information is encountered in the environment and the relevance of the information to the current context (Anderson and Schooler 1991). The left prefrontal cortex has been implicated in this effortful retrieval process since the landmark positron emission tomography studies of Petersen et al. (1988, 1989). In the years since then, this region has been repeatedly implicated in the controlled retrieval of semantic and episodic information (Tulving et al. 1994; Buckner 1996; Buckner et al. 1998; Nolde et al. 1998; Cabeza and Nyberg 2000; Buckner and Wheeler 2001; Wagner et al. 2001; Gold and Buckner 2002; Velanova et al. 2003; Wheeler and Buckner 2003). Although it is generally accepted that this region is somehow critical to the retrieval process, substantial debate has surrounded the specific role that this region plays in the retrieval of semantic information (Thompson-Schill et al. 1997, 1998, 1999; Wagner et al. 2001; Badre and Wagner 2002; Martin and Byrne 2006; Martin and Cheng 2006; Thompson-Schill and Botvinick 2006). The task that stimulated the most controversy was the verb generation paradigm, in which participants provided appropriate verbs for nouns that were strongly associated with either one (low selection, e.g., APPLE-EAT) or multiple (high selection, e.g., DOOR-OPEN/CLOSE) verbs (Thompson-Schill et al. 1997). Out of this debate sprung 2 competing accounts of the role of the left prefrontal cortex in retrieval. On the one side, Thompson-Schill et al. (1997, 1998, 1999) provided evidence in support of

the selection hypothesis. According to the selection hypothesis, this region is not involved in the retrieval attempt per se but rather the selection of information among competing alternatives (e.g., OPEN vs. CLOSE). On the other side, Wagner et al. (2001; Badre and Wagner 2002) and later Martin and Cheng (2006) argued that the data of Thompson-Schill et al. (1997) could be explained in terms of associative strength rather than selection (the controlled retrieval hypothesis). According to Wagner et al., the left prefrontal region was responsible for controlled retrieval of information, and selection among competing alternatives is just one factor that influences this process. Martin and Cheng compared the stimuli of Thompson-Schill et al. (1997) with verb norms and found that associative strength was confounded with selection in the verb generation task. For example, APPLE was more strongly associated to EAT than DOOR was to either OPEN or CLOSE. In addition, Martin and Cheng found that associative strength accounted for the majority of the behavioral effect in the verb generation task in a variation of the paradigm in which associative strength and selection were isolated.

In a recent reply to Martin and Cheng (2006), Thompson-Schill and Botvinick (2006) claimed that the perennial debate rested upon a false dichotomy between associative strength and selection and proposed one mechanism to unite these 2 processes in a Bayesian “competition model” in the tradition of Usher and McClelland (2001). This model relied crucially on the strength of cue-response associations (e.g., APPLE-EAT) as well as inhibitory connections between competing responses (e.g., OPEN vs. CLOSE). This apparent end to the debate between the selection hypothesis and the controlled retrieval hypothesis has heightened the demand for parsimonious models of the role of the left prefrontal cortex in retrieval. In response to Thompson-Schill and Botvinick (2006), Martin and Byrne (2006) proposed a model that explained the same range of data without the necessity of a true competitive mechanism (i.e., direct inhibition between responses). According to Martin and Byrne, the results of Martin and Chen could be explained solely by the spread of activation across associative connections between cue and response. Martin and Byrne claimed that their model should be preferred to the competition model on the basis of parsimony.

In the style of Martin and Byrne (2006), we propose a framework for understanding the left prefrontal cortex that accounts for a variety of retrieval phenomena without proposing a direct inhibitory mechanism. This framework, first proposed in Anderson et al. (2003), is an extension of the adaptive control of thought-rational (ACT-R) cognitive architecture (Anderson 2007) and maps modules in ACT-R onto regions of the brain. Specifically, ACT-R proposes a general

retrieval module that is responsible for maintaining control over the retrieval process during semantic and episodic retrieval and maps this module onto the left prefrontal cortex. The amount of time this module must exert control is precisely determined by the availability of the memory as calculated by its activation value, which is the sum of the base-level activation of the memory (i.e., the amount of previous experience) and the spreading activation from the cues (i.e., the context).

A handful of studies have already made some progress in characterizing this model of left prefrontal activity. For example, activity in this region increases as the number of math fact retrievals required to solve an algebra problem increases (Anderson et al. 2003; Qin et al. 2003, 2004; Danker and Anderson 2007). In addition, a paired associate paradigm that manipulated the number of associations, or fan (Anderson 1974), of the retrieval cue found that both response time and prefrontal activity increase as a function of fan (Sohn et al. 2003, 2005). Within the ACT-R architecture, the fan effect is explained much in the same way as Martin and Byrne explained effects in the verb generation paradigm: by a reduction in associative strength between the cue and each associate as the number of associates is increased (Anderson and Reder 1999). Although the fan task is technically an episodic memory paradigm, it bears some semblance to the verb generation paradigm. The primary difference between the 2 paradigms is that the number of competing associations is experimentally manipulated in the fan paradigm and selected from among preexisting associations in the verb generation paradigm. We believe the fan paradigm is a better choice for studying precise theories of left prefrontal cortex because of the lack of preexisting confounding factors.

In the following paper, we present our model of left prefrontal cortex activity along with an experiment that demonstrates the sensitivity of this model to a pair of theoretically orthogonal task manipulations. We adopt a recall paradigm in which both the fan of the retrieval cues and the number of times each stimulus is repeated are manipulated—allowing for the investigation of the independent effects of current context and previous experience on activity in the left prefrontal cortex. Our model proposes that prefrontal activity is determined by a single activation value that is a sum of both factors.

We will now briefly sketch out our model of declarative memory. Human declarative memory is a vast store capable of powerful parallel processing. Given the appropriate cue (e.g., “What is your mother’s maiden name?”), we are capable of quickly singling out the corresponding fact from a vast warehouse of information. Although declarative memory can seem both infinitely large and extraordinarily efficient, it also has limited resources and must prioritize some facts over others. ACT-R, the latest instantiation of Anderson’s ACT theory, is at its heart a Bayesian theory of declarative memory that was inspired by the rational analysis of Anderson and Schooler (1991). The theory is rational in the sense that it claims that declarative memory is highly sensitive to the statistical regularities in the environment. In ACT-R, the speed and success with which a fact is retrieved from memory is determined by the usefulness and relevance of said fact and is affected by such factors as recency, frequency, and context. That is, those memories that are most likely to be needed are also the easiest to retrieve. According to Anderson (2007), declarative memory provides “moment by moment, the most appropriate window into our past” (p. 91).

As mentioned briefly above, in ACT-R, the availability of a fact in memory is represented by its activation value. The activation value of a fact reflects both its inherent strength, or base-level activation, and its strength of association to cues in the current context, or spreading activation. This relationship is formally expressed in the activation equation,

$$A_i = B_i + \sum_{j \in C} W_j S_{ji},$$

where A_i is the activation of fact i , B_i is the base-level activation of fact i , C is the context which is defined as the set of retrieval cues j , W_j is the attentional weighting given to retrieval cue j , and S_{ji} is the strength of association between retrieval cue j and fact i . As developed in detail in Anderson and Lebiere (1998), the base-level activation and strengths of association change with experience so that activation directly reflects the log odds that a memory will be needed in the next moment of time. Here, we will briefly review the aspects of these quantities relevant to the experiment that we will describe.

The base-level activation B_i will reflect both the recency and frequency of fact i and is determined by the number of presentations n of fact i and the time since the first presentation L according to the base-level learning equation,

$$B_i = \ln\left(\frac{n}{1-d}\right) - d \ln(L),$$

where d represents the decay rate of facts in memory. As the number of presentations n increases, so does the ease with which the fact is retrieved (i.e., its activation value), producing the power law of practice. In addition, as the time since the first presentation L increases, the activation value of the fact decreases, producing the power law of forgetting.

As for the spreading activation component of the activation equation (W_j and S_{ji}), W_j can be set to W/n , where n is the number of sources of activation. This assumes an equal attentional weight provided to each retrieval cue and a maximum attentional weight, W . S_{ji} represents the probability with which retrieval cue j predicts fact i and can be calculated with the associative strength equation,

$$S_{ji} = S - \ln(\text{fan}_j),$$

where S is the maximum associative strength and fan_j is the number of associations of cue j . Essentially, associative strength is spread equally among each of the associates such that as the number of associates increases, the spreading activation to each decreases. From a rational perspective, the degree to which a cue predicts a fact decreases as the number of associated facts increases.

The activation value A_i of fact i determines the time T_i that it takes ACT-R’s retrieval module to retrieve said fact from declarative memory according to the retrieval time equation,

$$T_i = F e^{-A_i},$$

where F is a latency scaling parameter. According to our theory of the left prefrontal cortex, this equation determines the amount of time this region must exert control over the retrieval process and the amount of metabolic activity in this region will be proportional to T_i and inversely proportional to A_i . The parameters that will most affect activity in this region

are the same parameters that will most affect the activation value of the memory according to the activation equation—specifically, the fan of the retrieval cues fan_j via its impact on spreading activation and the number of repetitions n via its impact on base-level activation. (The time since the first presentation L also impacts the base-level activation, but this will not be addressed further in this paper because it is held constant across conditions in our experiment.) In the following experiment, participants must indicate an appropriate Object in a Subject-Verb-Object phrase (e.g., “Farmer Greets Dentist”) given the Subject and Verb as cues (i.e., “Farmer Greets?”). We manipulate the fan of the Subject and Verb cues such that they both either have 1 association (fan-1 condition) or 2 associations (fan-2 condition). We also manipulated the number of repetitions of each stimulus such that each stimulus appears either once (low-repetition condition) or twice (high-repetition condition) per block. We investigate the effects of these factors on response time and activity in left prefrontal cortex during cued recall.

Materials and Methods

Participants

Twenty-one right-handed participants (9 female, 12 male; ages 18–27; mean age 21.3) completed 2 sessions each. All participants were given informed consent in accordance with Carnegie Mellon University and University of Pittsburgh guidelines. Two participants were excluded from further analysis, 1 because of abnormalities in the structural scan and 1 because of large fluctuations in the blood oxygen level-dependent (BOLD) signal.

Stimuli and Design

Participants performed 2 test sessions, each consisting of 8 blocks of 24 trials, that were no more than 1 week apart and were identical except they used entirely different stimulus sets. The first session was a training session outside of the scanner and was intended to familiarize participants with the procedure. The second session was done in the scanner. All data presented are from the scanning session.

The design was 2×2 factorial with 4 conditions and 2 major factors: fan (1 or 2) and repetition (low or high). Stimuli for each session were 16 unique phrases in the form Subject-Verb-Object (e.g., Farmer Greets Dentist). Each Subject-Verb pairing was unique as a combination and therefore entirely predictive of the Object. However, in 8 of the phrases, the subject and verb were both unique to that phrase (fan-1), and in 8 of the phrases, the subject and verb each appeared in a different phrase (fan-2). For example, if one of the phrases in the fan-2 condition was “Farmer Greets Dentist,” there might also be the 2 phrases “Farmer Visits Camper” and “Doctor Greets Baker,” such that the subject and verb each appeared in an additional phrase but not the same one. There were only 4 possible objects, and they started with the letters A (Agent), B (Baker), C (Camper), and D (Dentist), which were mapped onto unique fingers on the response glove. In addition, 8 of the pairs were shown only once in a block (low repetition) and 8 were shown twice (high repetition), resulting in the 24 trials in each block.

Procedure

The structure of an experimental trial is presented in Figure 1. Each trial began with the presentation of a 2-word phrase consisting of a Subject-Verb pairing for 6 s. Participants had to indicate 1 of 4 possible objects to complete a unique Subject-Verb-Object phrase by clicking an appropriate finger on the response glove. If the object indicated was incorrect, the correct response was presented on screen for 6 s. Because there was no initial training on the stimuli, this feedback was the only information made available for learning the appropriate phrases. Next, a warning (–) was presented on screen for 1 s followed by 8 s of a 1-back task. In this task, a set of 3-letter words

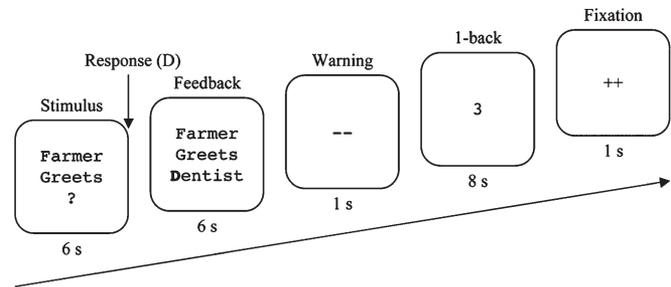


Figure 1. The structure of an experimental trial. The feedback stage only appears on error trials.

was presented randomly and the participant responded with a thumb press whenever a word was repeated. The purpose of the 1-back was to bring neural activity down to baseline. This has been effective in previous studies by our group (e.g., Anderson et al., forthcoming). Finally, a fixation (++) was presented for 1 s to indicate that the next trial was about to begin.

Functional Magnetic Resonance Imaging Procedure and Preprocessing

Event-related functional magnetic resonance imaging data were collected using a gradient echoplanar image acquisition on a Siemens 3T Allegra Scanner. The imaging parameters were time repetition = 2000 ms, time echo = 30 ms, flip angle = 79° , field of view = 200 mm, matrix size = 64×64 , slice thickness = 3.2 mm, slice gap = 0 mm, and 34 axial slices per scan with the anterior commissure-posterior commissure (AC-PC) on the 11th slice from the bottom. Correct trials lasted 8 scans and incorrect trials lasted 11 scans. Anatomical scans were acquired by using a standard T_2 -weighted pulse sequence, with 34 slices and the AC-PC on the 11th slice from the bottom.

Preprocessing of the functional imaging data included 6-parameter rigid-body motion correction using automated image registration (AIR, Woods et al. 1992). Images were coregistered to a common reference anatomical magnetic resonance imaging scan by means of the 12-parameter AIR algorithm (Woods et al. 1998) and smoothed with a 6-mm full-width half-maximum 3-dimensional Gaussian filter.

Results

Behavioral

The proportion correct over blocks by condition is presented in Figure 2A. It can be seen that accuracy improved rapidly over the first few blocks and that high-repetition stimuli are remembered more accurately than low-repetition stimuli throughout the session, but this effect appears to attenuate over blocks. Furthermore, it appears that fan-1 stimuli are remembered better than fan-2 stimuli but not in the early blocks (1 and 2). In order to test these observations, we performed a 2-fan \times 2-repetition \times 8-block repeated-measures analysis of variance (ANOVA) with proportion correct as the dependent measure. The main effects of block ($F_{7,18} = 158$, mean squared error (MSE) = 0.03, $P < 0.001$), fan ($F_{1,18} = 13$, MSE = 0.07, $P < 0.005$), and repetition ($F_{1,18} = 47$, MSE = 0.07, $P < 0.001$) were highly significant, confirming the patterns apparent in Figure 2A. In addition, there was a significant interaction between block and repetition ($F_{7,126} = 3.8$, MSE = 0.03, $P < 0.001$), indicating that the effect of repetition decreased over blocks. The interaction between block and fan was only marginally significant ($F_{7,126} = 1.78$, MSE = 0.02, $P < 0.10$). There was no significant interaction between fan and repetition ($F_{1,18} = 1.1$, MSE = 0.10, $P > 0.10$).

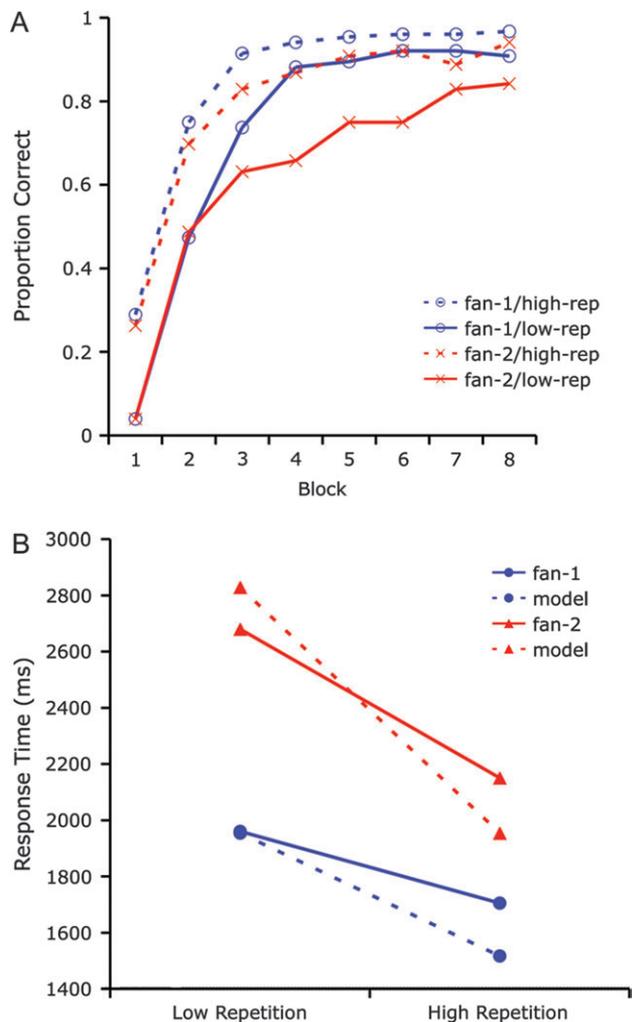


Figure 2. (A) The proportion correct by condition and block. (B) The mean response times for correct trials by condition for blocks 3–8 along with model predictions.

The mean response times for correct trials are presented by condition in Figure 2B. Dotted lines represent model predictions and can be ignored for the time being. Trials from the first 2 blocks were excluded from analysis due to the paucity of correct trials during these blocks. Participants take longer to respond to fan-2 stimuli compared with fan-1 stimuli. In addition, they take longer to respond to low repetition compared with high-repetition items. The combination of these effects appears to be superadditive, with the effect of fan being larger in the low-repetition condition. In order to confirm these observations, we performed a 2-fan \times 2-repetition repeated-measures ANOVA with mean response time as the dependent measure. There were strong main effects of both fan ($F_{1,18} = 59$, $MSE = 102983$, $P < 0.001$) and repetition ($F_{1,18} = 24$, $MSE = 126353$, $P < 0.001$). In addition, there was a significant interaction between fan and repetition ($F_{1,18} = 5.3$, $MSE = 78062$, $P < 0.05$), confirming the superadditivity of these 2 factors.

Imaging: Predefined

We used the same predefined left prefrontal that has been used extensively in previous imaging studies by our group (e.g., Anderson et al. 2003). This prefrontal region is centered at

Talairach coordinates $x = -40$, $y = 21$, $z = 21$ and contains parts of Brodmann areas 45 and 46 around the inferior frontal sulcus (see Figure 3A). We also included a prefrontal region defined using the regions of interest reported in Thompson-Schill et al. (1997). We will refer to this region as TS97-prefrontal. This region neighbors our prefrontal region and is centered at $x = -44$, $y = 9$, $z = 30$ (see Fig. 3D), which is the mean location of the prefrontal regions reported to be sensitive to selection in the verb generation (region at $x = -49$, $y = 8$, $z = 30$), classification ($x = -38$, $y = 15$, $z = 30$), and comparison ($x = -45$, $y = 4$, $z = 30$) tasks of Thompson-Schill et al. (1997). A third prefrontal region, defined from an experiment by Dobbins and Wagner (2005), is a more anterior region that Badre and Wagner (forthcoming) contrast with Thompson-Schill's competition region. This region, which we will refer to as ant-prefrontal, lies anterior and ventral to the other 2 prefrontal regions (Brodmann area 47) and is centered at $x = -45$, $y = 29$, $z = 0$ (see Fig. 3G). We used several other predefined regions that have been established in previous studies by our group (Anderson et al. 2003). A predefined parietal region is centered at $x = -23$, $y = -64$, $z = 34$ and includes parts of Brodmann areas 7, 39, and 40 at the border of the intraparietal sulcus (see Fig. 4A). A motor region is centered at $x = -37$, $y = -25$, $z = 47$ and includes parts of Brodmann areas 2 and 4 around the central sulcus (see Fig. 4D). We also included a fusiform region centered at $x = -42$, $y = -60$, $z = -8$ that was identified for its role in visual processing in a recent study by our group (Anderson et al. 2007). This fusiform region includes part of Brodmann area 37 (see Fig. 4G). Each region is approximately 16 mm wide, 16 mm long, and 13 mm high ($5 \times 5 \times 4$ voxels), except the fusiform region, which is 10 mm high (3 voxels). All analyses on imaging data were performed on correct trials only, and data from the first 2 blocks were excluded entirely due to the paucity of correct trials. In addition, trials with low MR (below 200 in our scanner) or scan-to-scan fluctuations in the BOLD signal exceeding 5% were excluded from analysis. We conducted separate 2-fan \times 2-repetition \times 8-scan repeated-measures ANOVAs on each of these 6 regions, where the dependent measure is calculated as the percent BOLD signal change relative to baseline on the first scan. We were particularly interested in fan \times scan and repetition \times scan interactions, as they indicate a differential rise in the BOLD response across conditions. To deal with the nonindependence of scans, we applied the lower bound correction to these interactions.

The BOLD responses across conditions for the 6 predefined regions are presented in Figures 3 and 4. Figure 3B displays the BOLD response for our left prefrontal region. It can be seen that activity in this region increases with fan and decreases with repetition, exerting the least activity in the easiest condition (fan-1/high repetition, see Fig. 2) and the most activity in the hardest condition (fan-2/low repetition, see Fig. 2). In addition, the effects of these factors appear to be superadditive, with the most difficult condition showing a larger BOLD response than would be predicted by an additive model. That both manipulations affected this region is confirmed by a significant effects of fan ($F_{1,18} = 7.04$, $MSE = 0.07$, $P < 0.05$ for main effect; $F_{1,18} = 7.45$, $MSE = 0.05$, $P < 0.05$ for interaction with scan) and repetition ($F_{1,18} = 2.75$, $MSE = 0.07$, $P = 0.12$ for main effect; $F_{1,18} = 11.14$, $MSE = 0.07$, $P < 0.005$ for interaction with scan). A marginally significant interaction between fan and repetition provides some support for the superadditivity of these factors apparent in Figures 2B and 3B ($F_{1,18} = 3.38$,

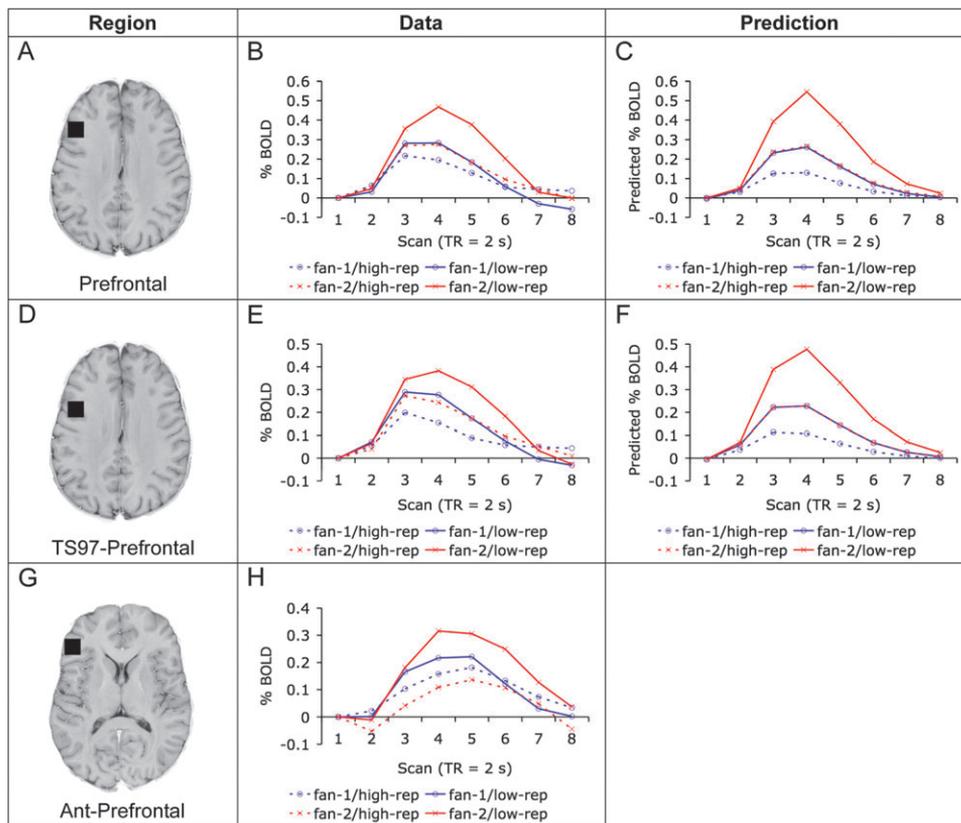


Figure 3. The BOLD responses and model predictions for the effects of fan and repetition in the predefined prefrontal (A–C), TS97-prefrontal (D–F), and anterior prefrontal (G–H) regions.

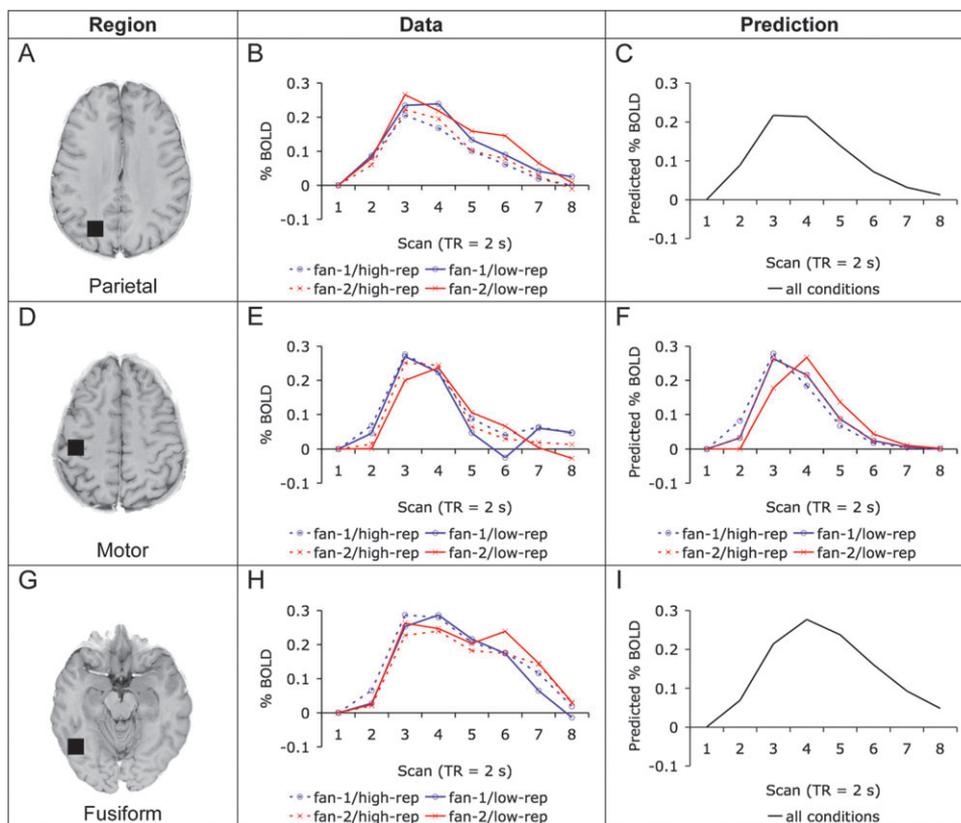


Figure 4. The BOLD responses and model predictions for the effects of fan and repetition in the predefined parietal (A–C), motor (D–F), and fusiform regions (G–I).

MSE = 0.06, $P < 0.10$), but the 3-way interaction with scan is not significant ($F_{1,18} = 1.47$, MSE = 0.06, $P > 0.10$).

Figure 3E displays the BOLD response from the TS97-prefrontal region. This region appears to respond to the task manipulations similarly to our other prefrontal region. Like our prefrontal region, this region shows significant effects of both fan ($F_{1,18} = 4.54$, MSE = 0.06, $P < 0.05$ for main effect; $F_{1,18} = 5.22$, MSE = 0.06, $P < 0.05$ for interaction with scan) and repetition ($F_{1,18} = 2.43$, MSE = 0.09, $P = 0.14$ for main effect; $F_{1,18} = 9.56$, MSE = 0.06, $P < 0.01$ for interaction with scan). However, the interaction between fan and repetition is not significant in this region ($F_{1,18} = 0.43$, MSE = 0.06, $P > 0.10$ for 2-way interaction; $F_{1,18} = 0.49$, MSE = 0.06, $P > 0.10$ for 3-way interaction with scan). We conducted a 2-region (prefrontal or TS97-prefrontal) \times 2-fan \times 2-repetition \times 8-scan repeated-measures ANOVA to see whether the effects in these 2 prefrontal regions differed significantly. There were no detectable differences between regions as could be detected by region \times fan ($F_{1,18} = 0.63$, MSE = 0.02, $P > 0.10$), region \times fan \times scan ($F_{1,18} = 0.74$, MSE = 0.01, $P > 0.10$), region \times repetition ($F_{1,18} = 0.02$, MSE = 0.02, $P > 0.10$), or region \times repetition \times scan ($F_{1,18} = 1.11$, MSE = 0.02, $P > 0.10$) interactions. Furthermore, there was no significant region \times fan \times repetition interaction ($F_{1,18} = 2.11$, MSE = 0.02, $P > 0.10$), indicating that the superadditivity did not differ significantly between regions.

The BOLD response for the anterior prefrontal region is displayed in Figure 3H. This region shows a different response profile from the other 2 prefrontal regions, consistent with the hypothesis of Badre and Wagner (forthcoming) that this region is functionally distinct from more posterior prefrontal regions. Like the other regions, this region appears to decrease activity with more repetitions. However, it appears to respond only weakly to fan, and the direction of the fan effect appears to depend on the number of repetitions (i.e., fan-2 is greater for low repetition, fan-1 is greater for high repetition). Consistent with these observations, this region shows a significant effect of repetition ($F_{1,18} = 5.46$, MSE = 0.09, $P < 0.05$ for main effect; $F_{1,18} = 6.14$, MSE = 0.06, $P < 0.05$ for interaction with scan) but not of fan ($F_{1,18} = 0.30$, MSE = 0.14, $P > 0.10$ for main effect; $F_{1,18} = 1.65$, MSE = 0.09, $P > 0.10$ for interaction with scan). Furthermore, there was a moderately significant interaction between repetition and fan ($F_{1,18} = 3.79$, MSE = 0.10, $P < 0.10$). The 3-way interaction with scan was not significant ($F_{1,18} = 1.36$, MSE = 0.07, $P > 0.10$). We conducted a 2-region (ant-prefrontal or TS97-prefrontal) \times 2-fan \times 2-repetition \times 8-scan repeated-measures ANOVA to see if this region differs significantly from the more posterior TS97-prefrontal region with regard to our task manipulations. There were no detectable differences between regions as could be detected by region \times fan ($F_{1,18} = 2.194$, MSE = 0.05, $P > 0.10$), region \times fan \times scan ($F_{1,18} = 2.84$, MSE = 0.04, $P > 0.10$), region \times repetition ($F_{1,18} = 0.47$, MSE = 0.06, $P > 0.10$), or region \times repetition \times scan ($F_{1,18} = 2.01$, MSE = 0.03, $P > 0.10$) interactions. However, it is worth noting that the region \times fan \times scan interaction is significant if the less conservative Greenhouse-Geisser correction is applied ($F_{3,13,56,39} = 2.19$, MSE = 0.05, $P < 0.05$). The region \times repetition \times fan ($F_{1,18} = 2.17$, MSE = 0.05, $P > 0.10$) and region \times repetition \times fan \times scan ($F_{1,18} = 0.70$, MSE = 0.03, $P > 0.10$) interactions were not significant.

The BOLD response for the left parietal region is displayed in Figure 4B. There is a weak tendency for activity in this region to be least in the fan-1/high-repetition condition and greatest

in the fan-2/low-repetition condition, indicating that it may be responding to task difficulty to some extent. However, this region did not show significant effects of fan ($F_{1,18} = 0.28$, MSE = 0.03, $P > 0.10$ for main effect; $F_{1,18} = 0.95$, MSE = 0.04, $P > 0.10$ for interaction) or repetition ($F_{1,18} = 2.74$, MSE = 0.05, $P > 0.10$ for main effect; $F_{1,18} = 1.13$, MSE = 0.04, $P > 0.10$ for interaction), indicating that these observations are not reliable. In addition, we conducted a 2-region (prefrontal or parietal) \times 2-fan \times 2-repetition \times 8-scan repeated-measures ANOVA to test the reliability of the difference between this region and our prefrontal region. That the effect of fan differed across regions was confirmed by significant region \times fan ($F_{1,18} = 12.60$, MSE = 0.01, $P < 0.005$) and region \times fan \times scan ($F_{1,18} = 7.72$, MSE = 0.02, $P < 0.05$) interactions. That the effect of repetition differed across regions was confirmed by a significant region \times repetition \times scan interaction ($F_{1,18} = 7.45$, MSE = 0.04, $P < 0.05$), although the interaction between repetition and region was not significant ($F_{1,18} = 0.08$, MSE = 0.03, $P > 0.10$).

Figure 4E shows the BOLD response for the left motor region. That this region responds is hardly surprising, given that participants respond to the task with their right hand. This region does not appear to show differential activity across conditions, besides showing a later peak in the conditions with longer response times, particularly the fan-2 conditions. This tendency is captured by a marginally significant fan \times scan interaction ($F_{1,18} = 3.69$, MSE = 0.05, $P < 0.10$). This region did not show a significant repetition \times scan interaction ($F_{1,18} = 0.38$, MSE = 0.04, $P > 0.10$) or significant main effects of fan ($F_{1,18} = 1.07$, MSE = 0.04, $P > 0.10$) or repetition ($F_{1,18} = 0.32$, MSE = 0.06, $P > 0.10$). The presence of the interaction in the absence of main effects supports the idea that the effects in this region can be explained by a shift in the response curve.

The BOLD response for the left fusiform region is shown in Figure 4H. This region does not seem to show differential activity across conditions and did not show effects of fan ($F_{1,18} = 0.00$, MSE = 0.03, $P > 0.10$ for main effect; $F_{1,18} = 0.82$, MSE = 0.05, $P > 0.10$ for interaction) or repetition ($F_{1,18} = 0.00$, MSE = 0.06, $P > 0.10$; $F_{1,18} = 0.82$, MSE = 0.05, $P > 0.10$).

Imaging: Exploratory

In this section, the results of the exploratory analyses will be reported. We selected regions of interest that showed significant fan \times scan or repetition \times scan interactions and consisted of at least 40 contiguous voxels at $P < 0.05$. The lower bound correction was applied to these interaction terms. Regions with significant interactions showed effects of fan or repetition that were dependent on scan (i.e., an effect that changes over time), and most of them could be characterized as having a differential rise or fall in the percent BOLD change across conditions relative to baseline at the first scan.

The regions showing significant fan \times scan interactions are displayed in Figure 5 along with the predefined regions and listed in Table 1 along with their sizes, locations, and areas under the curve (% BOLD) for the fan-1 and -2 conditions. Several regions showed positive-going responses that increased with fan, including a pre/postcentral region, a left middle/inferior frontal region, and a right insular region. The left middle/inferior frontal region overlaps substantially with our predefined prefrontal and TS97-prefrontal regions. This region appears to show an extremely small effect of fan (Table 1) but that is because it envelops several other functional regions

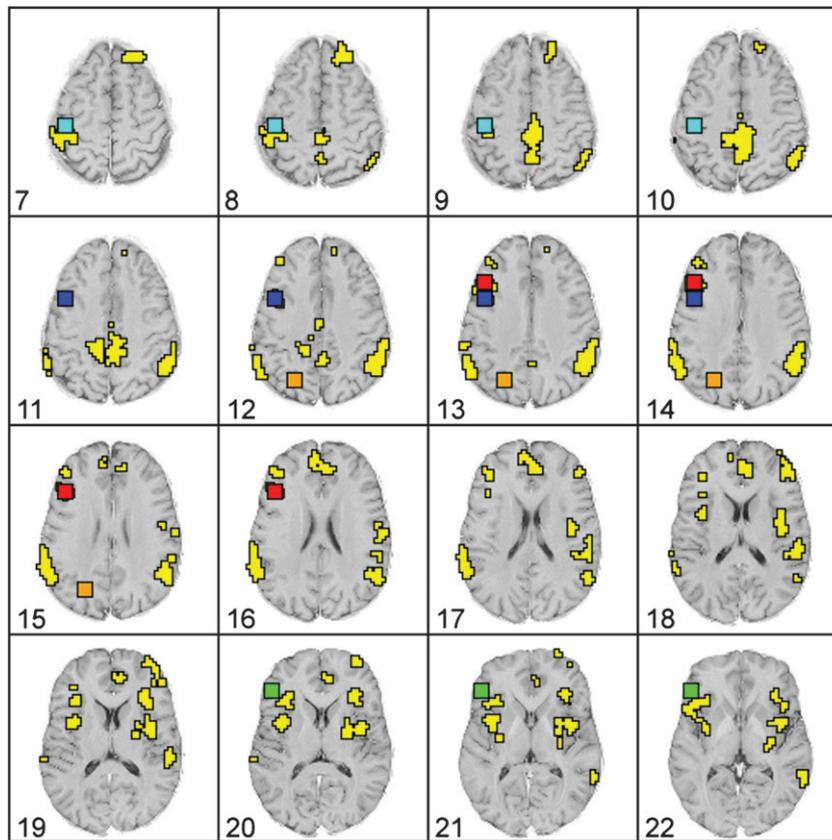


Figure 5. Exploratory regions showing fan effects. Exploratory regions are displayed in yellow, whereas predefined regions are shown in: prefrontal, red; TS97-prefrontal, blue; Ant-prefrontal, green; parietal, orange; and motor, cyan. The predefined fusiform region is not shown.

besides our predefined prefrontal regions. A particularly interesting contrast is between the anterior right insular region and the more posterior insular region. Even though they are neighbors, the anterior region shows a positive-going response that increased with fan, whereas the posterior region showed a positive-going response that decreased with fan. The majority of the remaining regions showed responses with large negative-going components that became more negative with increasing fan.

The regions showing significant repetition \times scan interactions are displayed in Figure 6 along with the predefined regions and listed in Table 2 along with their sizes, locations, and areas under the curve (% BOLD) for the low- and high-repetition conditions. The superior frontal and left middle/inferior frontal regions had positive-going responses that were weaker in the high-repetition condition. This left middle/inferior frontal region also overlaps with our predefined prefrontal and TS97-prefrontal regions. The medial frontal and middle temporal regions had negative-going responses that were weaker in the high-repetition condition.

Modeling

The ACT-R architecture is not only a theory of declarative memory but also a framework for creating models of cognitive tasks (Anderson 2007). ACT-R is instantiated as a group of cognitive and perceptual-motor modules that perform distinct cognitive operations and interact with each other through a central procedural system. These modules consist of the retrieval module discussed above as well as several other

Table 1

Results of fan \times scan exploratory analysis

Region of interest	Brodmann area(s)	Voxel count	Coordinates			Fan-1	Fan-2
			x	y	z		
Pre/postcentral gyrus	1–4	155	–40	–30	60	1.55	1.63
R. superior frontal	8	72	22	41	43	–0.40	–0.55
Paracentral lobule	5, 7	215	0	–32	48	0.23	–0.04
R. inferior parietal	40	329	53	–50	40	0.01	–0.26
L. inferior parietal	40	180	–53	–50	40	0.23	–0.01
L. middle/inferior frontal	9, 46	242	–44	20	25	0.69	0.73
R. middle/inferior frontal	10, 46	56	45	40	15	0.08	–0.06
L. middle/inferior frontal	10, 46	43	–42	41	20	0.56	0.57
Medial frontal gyrus	10, 46	91	0	50	15	–0.24	–0.59
R. insula	13	40	32	20	10	0.50	0.64
R. insula	13	41	35	–4	13	0.57	0.28
R. middle temporal	21, 22	58	59	–42	8	–0.34	–0.57

Note: R, right; L, left.

modules that will be discussed shortly. Although each of the modules provides precise timing predictions that contribute to the absolute response time (i.e., the intercept), the retrieval module is solely responsible for the differential response time predictions across conditions due to retrieval manipulations like fan and repetition.

In our model of this recall task, we propose encoding, retrieval, and response phases during which the model visually encodes the cue, retrieves the answer, and responds accordingly, respectively. The encoding phase is divided between a visual module, which attends to each of the retrieval cues, and

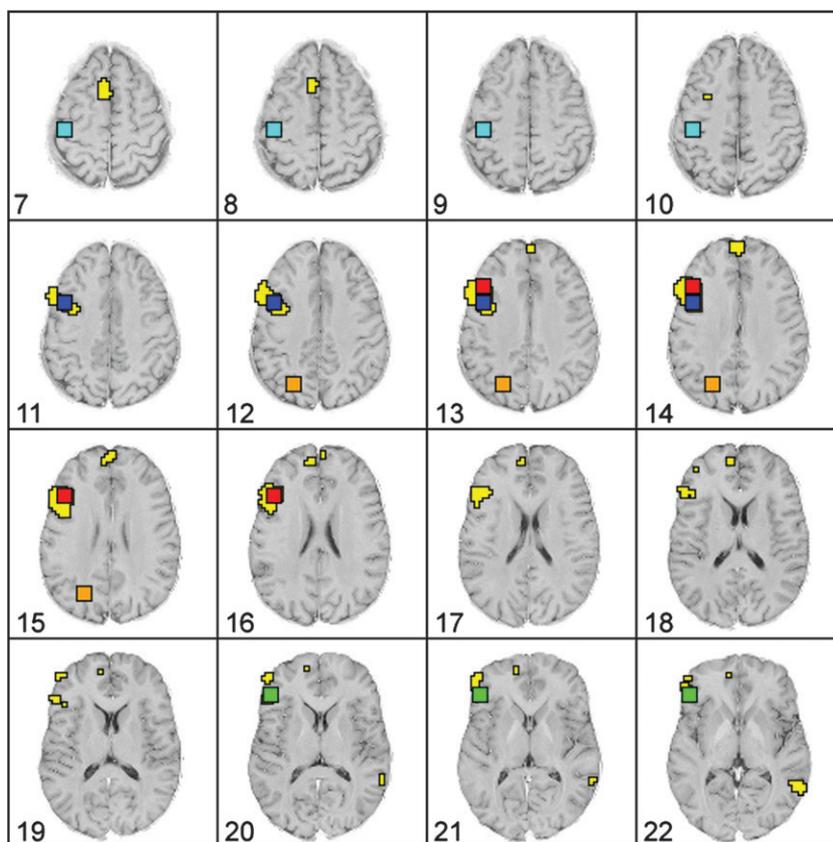


Figure 6. Exploratory regions showing repetition effects. Exploratory regions are displayed in yellow, whereas predefined regions are shown in: prefrontal, red; TS97-prefrontal, blue; Ant-prefrontal, green; parietal, orange; and motor, cyan. The predefined fusiform region is not shown.

the imaginal module, which encodes these cues into working memory. The retrieval is performed by the retrieval module discussed above, and the response is performed by a manual module responsible for controlling the hands. This model, along with the time for each operation derived from default ACT-R parameters, is depicted in Figure 7. In ACT-R, it takes 185 ms to attend to a visual object, 250 ms to modify an imaginal representation, and 160 ms to prepare a binary response. The response time for condition i , RT_i , is predicted to be the sum of the duration of all the other operations plus the retrieval time for that particular condition, T_i ,

$$RT_i = 1080 + T_i.$$

Like previous models of the fan effect (Anderson and Reder 1999; Sohn et al. 2003, 2005), this model attributes response time differences across conditions to differences in retrieval time. That is, the fan and repetition manipulations solely impact activity of the retrieval module. The retrieval time can be calculated using the standard ACT-R activation equations described above, and the end result has 1 free parameter, C , which reflects overall speed of retrieval (see Supplementary Material online for the derivation). The repetition manipulation impacts T_i via its effect on base-level activation, and the fan manipulation impacts T_i via its effect on spreading activation. The retrieval time predictions for each condition in terms of C are presented in Table 3. The response times predicted when C is estimated to be 874 ms are presented in Figure 2 along with the response time data. This value of C was calculated to minimize the deviation from the response time data. These

Table 2

Results of repetition \times scan exploratory analysis

Region of interest	Brodmann area(s)	Voxel count	Coordinates			Low repetition	High repetition
			x	y	z		
Superior frontal gyrus	6, 8	56	0	14	52	0.82	0.42
L. middle/inferior frontal	8, 9, 46	360	-46	20	25	1.05	0.70
Medial frontal gyrus	10	45	0	55	20	-1.19	-0.76
R. middle temporal	21, 39	42	58	-55	8	-0.90	-0.41

Note: R, right; L, left.

predictions represent a reasonable fit to the data ($r^2 = 0.96$). Although C is an estimated parameter, it is worth noting that the correlation tests a parameter-free prediction about the pattern of times in the 4 conditions. Estimating the C parameter just scales these predictions to match the magnitude of the data. For example, the model predicts that the time to respond to the fan-1/low-repetition condition will be the same as the time to respond to the fan-2/high-repetition condition. Although the data points for these 2 conditions are somewhat different in Figure 2B, the difference between them is not reliable ($t_{18} = -1.42$, $P > 0.10$). Furthermore, our model predicts the super-additive effects of fan and repetition apparent in Figure 2B.

We previously developed a methodology for mapping activity in the imaginal, retrieval, manual, and visual modules onto activity in our predefined parietal, prefrontal, motor, and fusiform regions, respectively (Anderson et al. 2003; Anderson 2007). This technique allows us to make predictions about brain activations based on ACT-R models of cognitive tasks. The

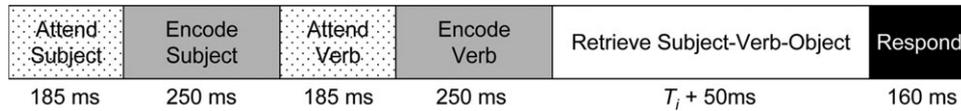


Figure 7. Model of the recall task, with time accounted for by visual (dotted), imaginal (gray), retrieval (white), and manual (black) module operations. The variability in response time across conditions is entirely caused by differences in the retrieval time, T_i .

Table 3
Estimated retrieval times for each condition, T_i

	Low repetition	High repetition
Fan-1	C	$C/2$
Fan-2	$2C$	C

major assumption of this technique is that whenever a module is performing a cognitive operation, the corresponding region is metabolically active. The technique involves convolving a demand function that has a value of 1 whenever the module is active and a value of 0 otherwise with a hemodynamic function corresponding to the shape of the BOLD response. The hemodynamic function we have adopted is the standard gamma function, which has been used by several other researchers to represent the BOLD response (Boynton et al. 1996; Cohen 1997; Dale and Buckner 1997; Glover 1999). When a module is engaged, it will elicit a BOLD response t time units later according to the function

$$H(t) = N(a, s) m \left(\frac{t}{s} \right)^a e^{-t/s},$$

where m determines the magnitude of the response, a determines the shape of the response, and s determines the time scale. $N(a, s)$ is a normalizing constant and is equal to $1/(s \times a!)$. This function reaches a peak at $a \times s$. The BOLD response accumulates whenever a region is engaged according to the engagement function $f(t)$, thus the cumulative BOLD response in a particular region can be calculated by convolving the engagement function with the BOLD function

$$B(t) = \int_0^t f(x) H(t-x) dx,$$

We used these principles to predict activity in our predefined regions using engagement functions from the model in Figure 7. To reiterate, the visual module was engaged during “attend” operations, the imaginal module during “encode” operations, the retrieval module during the “retrieve” operation, and the manual module during the “respond” operation. In addition to our standard mappings, we also mapped activity in the retrieval module onto the TS97-prefrontal region. We do not currently have a module in ACT-R to map onto the ant-prefrontal region. The values of m , a , and s were calculated to minimize the degree of mismatch against the noise in the data according to the following chi-square statistic:

$$\chi^2 = \frac{\sum_i (\hat{X}_i - \bar{X}_i)^2}{S_X^2},$$

where the denominator is estimated from the interaction term between condition and participants. The least squares predictions for each region are displayed alongside the data in

Figure 3. The best fitting parameters for the BOLD function in each of these regions are presented in Table 4 along with correlations and chi-square statistics to determine the goodness of fit of the model predictions to the data. The correlations are calculated across all 32 data points (4 condition \times 8 scan), and the chi-square statistic has 29 degrees of freedom, calculated as 32 minus the 3 parameters estimated for the BOLD function. This results in chi-square values greater than 42 representing significant deviations from the data ($P < 0.05$).

All 5 regions correlate well with the predictions of the model, and none of the model predictions deviate significantly from the data. This suggests that our model of the task accounts well for the neural as well as response time data. It is worth noting that the model only predicts differences across conditions for the prefrontal (Fig. 3C), TS97-prefrontal (Fig. 3F), and motor regions (Fig. 4F). In the case of the prefrontal regions, this is because of the differential engagement in different conditions. In the case of the motor region, this is because of the shift in response times across conditions. The predictions for the parietal and fusiform regions are identical across conditions.

It is notable that our prefrontal region elicits roughly equivalent BOLD responses for the fan-1/low-repetition condition and the fan-2/high-repetition condition (see Fig. 3B). This is a parameter-free prediction of the ACT-R activation equations (see Table 3). The model also predicts the super-additive effects of fan and repetition on activity in this region. Whereas this interaction is only marginally significant in the ANOVA performed on this region, a 1-tailed contrast looking for this superadditivity in the interaction between fan and repetition is significant ($t_{18} = 1.83$, $P < 0.05$). Our prefrontal region fits the retrieval module better than the TS97-prefrontal region. This is hardly surprising considering that the exact location of our region has been refined over many studies while the TS97-prefrontal region represents the results of only one. The motor region shows the predicted shift in peak from the fan-1 to the fan-2 condition (see Fig. 4E,F). The parietal (Fig. 4C) and fusiform (Fig. 4J) regions both seem to match well with the model predictions, but there may be some variability in these regions across conditions unaccounted for by our admittedly simple model. For example, repetition of items and increasing fan both result in certain words being presented more often, which could prime encoding such that fan-2 and high-repetition items have an encoding advantage, but there is little evidence for this in the data. Overall, our model produces more than sufficient fits to the BOLD responses in our predefined regions and appears to account particularly well for the behavior of our predefined prefrontal and TS97-prefrontal regions.

Discussion

In this paper, we have described our rational theory of the left prefrontal cortex and provided an empirical study supporting

Table 4

Parameters estimated and fits to the BOLD response

	Prefrontal/ retrieval	TS97-prefrontal/ retrieval	Parietal/ imaginal	Motor/ manual	Fusiform/ visual
Magnitude (<i>m</i>)	1.90	1.81	3.91	11.53	13.42
Exponent (<i>a</i>)	4.41	3.57	4.07	4.27	4.33
Scale (<i>s</i>)	1.10	1.30	1.31	0.86	1.55
Correlation (<i>r</i> ²)	0.93	0.91	0.92	0.92	0.88
Chi square	35.92	40.03	24.88	24.90	33.38

our theory. According to our theory, which is an extension of Anderson's (2007) ACT-R theory, the amount of metabolic activity in prefrontal cortex during retrieval is precisely determined by the accessibility of the retrieved fact (i.e., its activation value). This activation value is a summation of base-level activation (i.e., previous experience) and spreading activation (i.e., current context). Memories with lower activation values are retrieved more slowly and require more control than memories with higher activation values. We claim that it is the left prefrontal region that is responsible for exerting control over the retrieval process, and therefore, the hemodynamic response in this region during retrieval should be negatively correlated with the activation value of the retrieved memory. We found substantial evidence for this theory by showing that activity in prefrontal cortex increases as a function of manipulations that affect both base-level activation (repetition) and spreading activation (fan). That is, the amount of activity exerted by left prefrontal cortex decreases as 1) the previous experience with the memory increases and 2) the strength of the association with the context increases. This is consistent with previous studies showing that left prefrontal cortex responds to the frequency of previous experiences (Velanova et al. 2003; Wheeler and Buckner 2003) as well as number of associations (Thompson-Schill et al. 1997, 1999; Sohn et al. 2003, 2005). Not only did our theory predict that these manipulations would affect activity in this region but also it provided precise predictions of the effect sizes that matched the data well. It made the prediction that increasing the fan of both items in a pair from 1 to 2 would have the same impact on left prefrontal activity as halving the number of presentations of the pair, and this prediction bore out in the data. It also predicted the superadditive effects of fan and repetition on response time and prefrontal activity that is apparent in the data.

We have demonstrated that our theory is sufficiently precise to predict the activation of prefrontal cortex in response to 2 theoretically orthogonal manipulations of retrieval difficulty. It is important to understand the relationship between our computational theory of prefrontal cortex and existing theories in the literature. In essence, our theory is akin to that put forth by Wagner et al. (2001; Badre and Wagner, 2002). According to Wagner et al., left prefrontal cortex is engaged whenever retrieval of semantic information is nonautomatic (i.e., whenever control must be exerted over the retrieval process). Wheeler and Buckner (2003) make a similar proposal about this region in episodic retrieval. The idea is that activity in this region will be affected by any manipulation that alters the amount of control that must be exerted during the retrieval process, including frequency and associative strength. Wagner et al. describe this region as providing a "bias mechanism" that facilitates the retrieval process. In our activation equations, we

provide a precise mathematical description of this biasing signal. That is, our theory posits that the left prefrontal region maintains activation of the memory cues during controlled retrieval, leading to activation of relevant concepts in declarative memory and eventually the selection of the most active memory.

Our theory shares the Bayesian origins of the competition model put forth by Thompson-Schill and Botvinick (2006). Activation in ACT-R is intended to compute the log posterior odds that a memory will be needed in a certain context. If we let *M* denote the event that a memory is needed and *C* denote the current context, then the activation equation mirrors the following Bayesian equation:

$$\log\text{-posterior-odds}(M|C) = \log\text{-prior-odds}(M) + \text{likelihood-ratio}(C|M),$$

where the log-prior-odds corresponds to the base-level component of our activation equations and the likelihood ratio corresponds to the associative strength component. The spreading activation essentially scales up the base-level activation according to the relevant context. This is similar to Thompson-Schill and Botvinick's competition model except that their model does not include base-level activation. That is, our model accounts for the recency and frequency of items in a way that is not currently implemented in Thompson and Botvinick's admittedly succinct and demonstrative model. As ACT-R predicts, fan and repetition can equally impact activation of the left prefrontal cortex because both factors determine the amount of time that control must be exerted over the retrieval process. It is worth emphasizing that a competitive model like Thompson-Schill and Botvinick's could be easily modified to account for recency and frequency in its competitive mechanism. In this case, we believe it would differ from our own account only in its emphasis on competition rather than associative strength (see below).

As is reflected in its name, competition is at the heart of Thompson-Schill and Botvinick's (2006) model. In Bayesian terms, competition corresponds to the likelihood ratio and can be seen as a selection process among activated alternatives. The context *C* can be conceived of consisting of a set of cues *j*. Making the naive Bayes assumption of independence of information sources, this is expanded in ACT-R into a sum of likelihood ratios $\log[\text{likelihood}(j|M)]$, where

$$\log[\text{likelihood}(j|M)] = \log \left[\frac{p(j|M)}{p(j|\bar{M})} \right],$$

which are equal to the S_{ji} in the activation equation. Anderson (1990) argues that this can be approximated by $\log[p(M|j)] - \log[p(j)]$. If all memories are equally associated with a concept likely given *j* as in this fan experiment, $p(M|j) = 1/\text{fan}_j$, and we get the associative strength equation by setting $S = -\log[p(j)]$.

This formulation makes clear that what is important for associative strength is not the overall frequency of a pair (that is reflected in the base-level activation) but the probability of one member of the pair *M* given the other as a cue *j*. We agree with Thompson-Schill and Botvinick's (2006) assertion that the distinction between associative strength and competition is illusory and that "any manipulation of associative strength must also be a manipulation of competition" (p. 407). In our model, like that of Martin and Byrne (2006), competition between associates is only implemented via the effect of competitors on associative strength. If a cue *j* is only associated with *M*, then

the associative strength between them is high, and if j has many associates, associative strength between the cue and any one of them is low. The latter situation can be conceived of as a condition of high competition. However, as this Bayesian formulation makes clear, whether we think of this in terms of associative strength or competition is just a matter of whether we think of the same statistical glass as half full (associative strength adding to the log odds) or half empty (competition subtracting from the log odds).

A complication for our account of the left prefrontal cortex is the recent empirical evidence that distinct prefrontal regions exert control over retrieval and selection processes (Badre et al 2005; Gold et al. 2006; Dobbins and Wagner 2005; Badre and Wagner, forthcoming). Badre and Wagner (forthcoming) propose a 2-process theory of prefrontal cortex, in which an anterior prefrontal region is responsible for controlled retrieval of semantic information and a more posterior region is involved in postretrieval selection among competitors. We compared the TS97-prefrontal region originally associated with selection with a more anterior prefrontal region. The differences in the response profiles of these 2 regions garners some support for the 2-process theory. That the anterior region did not respond to our selection manipulation (fan) is consistent with the idea that this region is not affected by competition. The presence of both repetition and fan effects in the more posterior regions would concur with a competitive theory of these regions that was expanded to account for recency and frequency, as mentioned briefly above with respect to Thompson-Schill and Botvinick's (2006) model. In this sense, our data seem to be consistent with the current 2-process theory of retrieval. However, although our data are roughly in line with the 2-process theory, the mathematical details of our framework make it difficult to reconcile our perspective with the 2-process theory. As outlined above, a rational account of prefrontal function necessarily equates associative strength and competition. In fact, the primary manipulation of associative strength is the addition of competitors (fan). According to Badre and Wagner, the experimental manipulations that most typify the processes performed by the anterior and posterior prefrontal regions are "strength of association between cues and target knowledge" and "number of retrieved competitors," respectively. Thus, they are proposing a dissociation between 2 processes that are equivalent from our perspective. We believe reconciling the 2-process theory with our own should be a catalyst for future research. It might benefit the 2-process theory to define the processes performed by these 2 regions in a way that acknowledges the relationship between associative strength and competition. On the other hand, our own framework would greatly benefit from a computational theory of the process performed by the anterior prefrontal region.

Like the theories discussed above, the ACT-R theory of the left prefrontal cortex in retrieval is based on evidence from studies of semantic memory (Anderson et al 2003; Qin et al. 2003, 2004). However, the declarative memory system in ACT-R is a general theory of retrieval in prefrontal cortex that fits into the ACT-R cognitive architecture (Anderson 2007), and because of this it has substantially more breadth than the semantic memory theories discussed in this paper. We believe this breadth confers on ACT-R 2 advantages over other theories. First, its scope extends beyond semantic memory and can inform memory tasks that, like the experiment presented here, are more episodic in nature. We have

presented evidence here that the same left prefrontal region that spurred years of discussion in the semantic memory literature also responds to manipulations of retrieval difficulty in episodic memory paradigms, but we are not the first to make this connection (Velanova et al. 2003; Wheeler and Buckner 2003; Badre and Wagner, forthcoming). If there was any doubt that our model is describing this region, we have also shown that a region of interest based on the original Thompson-Schill et al. (1997) study also responds to our manipulations.

Second, the retrieval module in ACT-R interacts with an extensive architecture of other modules, which allows for precise response time predictions across a variety of tasks as well as predictions about which other brain regions are invoked in which tasks. In this paper, we discussed the visual, imaginal, and manual modules, which attend the cues, encode the cues, and respond, respectively (see Fig. 7). By using the default ACT-R timing parameters for these modules, we were able to make precise response time predictions for this task as well as predict the amount of neural activity in the associated brain regions. Of these modules, only the manual/motor module predicted differential activity in its corresponding brain region across conditions, and this was simply a shift in response corresponding with the response time. The imaginal/parietal and visual/fusiform modules predicted no differences in activity across conditions, and this leads to reasonable fits to the data. That our imaginal/parietal region did not respond to our task manipulations is theoretically interesting, given that activity in this region is typically difficult to isolate from activity in our prefrontal region in symbolic manipulation tasks (for a discussion of this issue, see Danker and Anderson 2007).

We have demonstrated the accuracy of our model of left prefrontal cortex with an empirical study and have argued that it offers more than the previous models of this region. We have also shown that it fits in a framework that can account for activity in several other regions, although the model of left prefrontal cortex is by far the most developed. There is increasing evidence of multiple, distinct regions in left inferior prefrontal cortex that perform different roles in the retrieval process (Gold and Buckner 2002; Velanova et al. 2003; Badre et al. 2005; Gold et al. 2006; Badre and Wagner, forthcoming). We believe we have captured the role of one of these regions whose behavior can be precisely explained by the rational analysis of human declarative memory.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

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Notes

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