TIP-OF-THE-TONGUE STATES IN AGING: EVIDENCE FROM BEHAVIORAL AND NEUROIMAGING STUDIES

By

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SIGNED: Jasmeet Kaur Pannu
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DEDICATION

I dedicate this work to my mother and grandmother, who have paved the way for me to accomplish my career goals. I could not have made it without your love, encouragement, and sacrifice.
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ABSTRACT

Metamemory is defined as the knowledge about one’s memory capabilities and about strategies that can aid memory (Shimamura, 1994). One particularly intriguing type of metamemory judgment is a tip-of-the-tongue experience, which refers to a strong feeling that a target word, though presently not recalled, is known and on the verge of being produced. Older adults report more TOT experiences than young adults. However, there is great variability among older adults in performance on memory and executive function tasks, and it is unknown whether subsets of older adults experience more TOT states. Additionally, the neural correlates of successful retrieval, TOTs, and unsuccessful retrieval in aging have not been studied. In the studies reported here, the relationship between frontal and medial temporal neuropsychological factor scores (see Glisky et al., 1995) and performance on metamemory tasks was examined. Importantly, this was the first study to examine the neural correlates of tip-of-the-tongue experiences in older adults. In an event-related fMRI design, participants viewed famous and novel faces and were asked to respond regarding successful retrieval, unsuccessful retrieval, or tip-of-the-tongue experiences. Results show that, as a group, older adults had activation in the medial prefrontal cortex and anterior cingulate during tip-of-the-tongue states, consistent with similar studies in young adults (Maril et al., 2001; Pannu et al., 2004, Schnyer et al., 2005). Additionally, activations in lateral prefrontal cortex and medial temporal areas during the task varied systematically with frontal and temporal lobe factor scores. These results provide evidence for differences in neural activation between groups of healthy
older adults characterized on the basis of neuropsychological performance, and shed light on the neural underpinnings of the tip-of-the-tongue states in aging.
CHAPTER 1
INTRODUCTION

A tip-of-the-tongue (TOT) state is characterized by a strong feeling that a target item (e.g., a word), although not presently recallable, is nonetheless known and on the verge of being recalled (Schwartz, 2002). This definition, although accurate, fails to convey the subjective experience of frustration that is often accompanied by a TOT feeling. William James captures the essence of what it is like to experience a TOT state most elegantly in the following passage:

Suppose we try to recall a forgotten name. The state of our consciousness is peculiar. There is a gap therein; but no mere gap. It is a gap that is intensely active. A sort of wraith of the name is in it, beckoning us in a given direction, making us at moments tingle with the sense of our closeness and then letting us sink back without the longed-for term. If wrong names are proposed to us, this singularly definite gap acts immediately so as to negate them. They do not fit the mould. And the gap of one word does not feel like the gap of another, all empty of content as both might seem necessarily to be when described as gaps. (p. 251).

William James’ observations resonate with the results from experimental studies investigating the nature of the TOT phenomenon. Subjects in these studies report a majority of their TOT experiences are accompanied by emotion (Schwartz, 1999) and that words that are semantically related to the TOT word are easily rejected as not being the right word (Schwartz, 2002). In addition, studies show that having a TOT experience is quite commonplace—on average, people experience a TOT state least once a week, and older adults experience at least twice that (Burke, MacKay, Worthley, & Wade, 1991). Older adults typically report that they experience more TOTs as they age, particularly in the retrieval of proper names (Schwartz, 2002). As Cohen and Faulkner
note (1986), the retrieval of proper names was “singled out by many of the elderly
respondents as the most noticeable and most frustrating change in cognitive ability” (pg.
50). Experimental studies corroborate older adults’ phenomenological reports. A number
of studies document that TOT frequency increases with age (Dahlgren, 1998; Heine, et
al., 1999), and that more TOTs are experienced for proper nouns than abstract words or
object names (Burke et al., 1991). To explain this phenomenon, the decrement hypothesis
proposes that older adults experience more TOTs due to impairment in retrieval processes
during aging (Schwartz, 2002; Schwartz & Frazier, 2005). However, it is unclear whether
increased TOTs for proper names are attributable to pathological aging (e.g., mild
cognitive impairment or a dementing illness), or whether they are simply a byproduct of
healthy aging. Additionally, the neural changes that occur in aging that might explain
increased TOTs and fewer successful retrievals are poorly understood. Given that
unsuccessful retrieval with a concomitant TOT experience is one of the most robust and
frustrating experiences that adults report during the aging process, and that older adults
typically agonize about the integrity of their memories as a result of increased TOTs, it is
important to understand the neural changes that occur in the retrieval process in aging.

TOT experiences are encompassed within the broader framework of
metamemory. Metamemory is the defined as the knowledge about one’s memory
capabilities and about strategies that can aid memory (Shimamura, 1994). Performance
on metamemory tasks, which typically require the subject to make judgments regarding
the accuracy of their memory, is thought to rely critically on frontal lobe function (Pannu
& Kaszniak, 2005). After reviewing the literature regarding neurological populations and
metamemory performance, Pannu and Kaszniak concluded that patients with various neurological conditions (e.g., Korsakoff’s syndrome, multiple sclerosis, epilepsy) had metamemory impairments if they also demonstrated poor performance on measures of executive function and/or showed evidence of frontal lobe structural damage. The critical mechanism underlying accurate judgments of memory that is dependent upon frontal function is proposed to involve monitoring, verification, and decision-making processes (Pannu, Kaszniak, & Rapcsak, 2005; Rapcsak et al., 1999; Schnyer, Nicholls, & Verfaellie 2005). For instance, Pannu et al. (2005) reported that patients with frontal lobe damage were less accurate in their retrospective confidence metamemory judgments than healthy control subjects, but only for items for which there was a weak memory trace present (e.g., a less-familiar celebrity), and not when the memory trace was strong (e.g., a very famous face). Pannu et al. proposed that when subjects are presented with items that elicit a vague sense of familiarity, greater monitoring and verification are required in order to make an accurate judgment regarding the item. By contrast, less monitoring is required when items are well-known and tied to specific information, or when there is no familiarity for the item at all (e.g., novel faces).

Two prominent theories regarding the basis of TOT and feeling-of-knowing (FOK; a type of judgment that is thought to be similar to a tip-of-the-tongue) judgments are the cue familiarity account (Reder & Ritter, 1992), and the accessibility account (Koriat, 1993). Although these two proposals suggest that FOK and TOT judgments are based on differing processes, they are not mutually exclusive (see Koriat & Levy-Sadot, 2001). The cue familiarity hypothesis states that these judgments of memory arise from
the level of familiarity of the cue. For example, if a person is shown a picture of a famous face and asked to retrieve the name, the magnitude of the TOT or FOK is related to how familiar the face is to the subject. The accessibility account, however, states that unsuccessful retrieval attempts of the target word are accompanied by the retrieval of partial clues, such as fragments of the target, semantic, and episodic attributes, and that the partial clues give rise to a subjective feeling that the target is known and can be recalled or recognized in the future. As an example, consider the situation in which a person is asked to recall the name of the actor Russell Crowe, after being shown his picture. If the name is not successfully retrieved, the person may generate letters in the name (e.g., “I know it starts with an R”) or may generate other names within the same genre, (i.e., leading men), that could be alternatives (e.g., Mel Gibson, Bruce Willis, Harrison Ford). The retrieval of these partial clues give rise to a TOT, and the monitoring process is recruited for sorting these responses and verifying whether they represent the sought-after target. The subject may then decide that none of these names is the correct one, and if the TOT is resolved, he/she will remember the name. One important objective of the study reported here is to examine the neural correlates of retrieval from memory, and specifically, whether the activation associated with successful recall differs from activation associated with partial retrieval during a TOT state.

This study represents the first to examine the neural correlates of FOK and TOT states in older adults. There have been a handful of studies examining the neural correlates of metamemory in young adults. The findings generally implicate the anterior cingulate gyrus and medial prefrontal cortex as areas underlying metamemory judgments.
The first published study that investigated TOT judgments was conducted by Maril, Wagner, and Schacter (2001) and involved eliciting tip-of-the-tongue judgments for general knowledge information. In this study, participants viewed semantic cue pairs (e.g., Iraq + capital), and were instructed to recall the answer (i.e., Baghdad). Participants made “know,” “TOT,” or “don’t know” judgments in response to their level of recall. The results, which were direct contrasts between the TOT and know and don’t know conditions, indicated that the right middle frontal (Brodmann’s area [BA] 9) and anterior cingulate cortex (BA 32/24) were activated differentially in the TOT condition. In another study conducted by the same group (Maril, Simons, Mitchell, Schwartz, & Schacter, 2003) participants engaged in an episodic memory task involving the encoding and retrieval of word pairs. After studying the word pairs, subjects were instructed to recall one word of the pair after the cue was provided. Subjects made “know,” “feeling-of-knowing,” or “don’t know” responses. The primary finding in this study was that a graded activation pattern was observed, such that the greatest activation in frontal and parietal regions was associated with successful recall, an intermediate level of activation in feeling-of-knowing states, and the least amount of activation was observed in don’t know states. The authors suggest that the results could in part reflect partial access to the information, supporting the accessibility account (see Koriat & Levy-Sadot, 2001).

In a study by Schnyer, Nicholls, & Verfaellie (2005), the role of the ventromedial prefrontal cortex in metamemory judgments was examined using structural equations modeling. In their study, participants viewed sentences at study and then again at test, with the last word of the sentence missing. While undergoing fMRI, subjects attempted to
recall the last word of the sentence and made either a “know,” “feeling-of-knowing,” or “don’t know” judgments. The feeling-of-knowing judgments were further divided into 25% chance, 50% chance, and 75% chance, reflecting the likelihood of future recall. Results showed that multiple areas, including medial and lateral frontal cortex, hippocampus and parahippocampal gyrus, and the middle temporal gyrus were activated during correct feeling of knowing trials. Furthermore, a model was constructed based on a unidirectional flow of information from the hippocampus, left inferior prefrontal cortex (LIPC), left temporal cortex, and finally, the ventromedial prefrontal (VMPC) cortex. It was reasoned that the VMPC would be involved in monitoring the contents that were retrieved by the temporal and left inferior frontal cortices. Results showed that this model best accounted for the data, in contrast to monitoring occurring either in the hippocampus or LIPC. This study provides intriguing evidence consistent with the medial prefrontal cortex’s involvement in monitoring and verification.

Finally, in a study by Pannu, Kaszniak, Rapcsak, and Ryan (2004), young participants viewed pictures of famous and novel faces in the scanner and were instructed to recall the name of the person. They made either “know,” “feeling-of-knowing,” or “don’t know” responses. Direct contrasts between the three different responses indicated that the medial prefrontal cortex and anterior cingulate were activated during FOK states. This study provided additional evidence for these regions’ involvement in monitoring of information, using the visual modality of face stimuli. In the present study described here, the Pannu et al. paradigm is extended for healthy older adults in order to investigate whether they share a similar pattern as young adults.
As noted earlier, monitoring and verification processes appear to be important aspects of frontal lobe function. Studies have shown that older adults perform more poorly than younger adults on tasks involving purported frontal functions including measures of cognitive flexibility, generative naming, and abstract reasoning (for a review, see Kaszniak & Newman, 2000). However, Glisky, Polster, and Routhieaux (1995) have shown that there is tremendous variability within normal aging adults with respect to performance on cognitive tasks. They note that despite documented evidence of increasing variability in cognitive function with age, most studies do not take this into account and treat age (old vs. young) as an independent variable. In a landmark study, Glisky et al. (1995) conducted a factor analysis to identify neuropsychological tasks that loaded on a frontal lobe factor and a medial temporal lobe factor to study the relationship between the factors and performance on a source memory task (thought to rely heavily on frontal function) and an item memory task (thought to rely on medial temporal lobe structures). Healthy older adults were classified as 'high-frontal lobe', 'low frontal lobe', 'high medial temporal lobe', or 'low medial temporal lobe' based on their performance on tasks that loaded on each factor. Glisky et al. subsequently demonstrated a double dissociation, such that low frontal subjects performed more poorly on a source memory task, with no difference on an item memory task, and low medial temporal subjects performed more poorly on the item memory task than the high medial temporal subjects, with no differences in source memory.

It is conceivable, therefore, that not all older adults perform equally well on judgments of memory. For instance, older adults classified as “high frontal” might have
more accurate judgments of memory than older adults identified to be “low frontal,” analogous to the results found in metamemory studies of frontal damaged patients. To address this hypothesis, the study described in Chapter 2 employed a verbal FOK metamemory task to examine the relationship between factor score status and judgments of memory. A second goal of study described in Chapter 2 was to examine the relationship between factor score status and self-report of memory problems in everyday life.

The third, and most important goal of the present study, described in Chapter 3, was to investigate the neural correlates of TOT experiences in older adults as a whole, as well as by factor score status. An event-related functional magnetic resonance imaging (fMRI) design was utilized to examine the neural correlates of successful retrieval of face names versus TOT experiences in older adults. Additionally, a goal of the fMRI study was to investigate whether subjects classified as having high frontal or high medial temporal functioning would have more successful retrievals and fewer TOT experiences than low frontal and low medial subjects.
CHAPTER 2
THE RELATIONSHIP BETWEEN METAMEMORY MEASURES AND FACTOR SCORES IN HEALTHY OLDER ADULTS

Frontal damaged patients make less accurate metamemory judgments than healthy control subjects (Pannu et al., 2005; Schnyer et al., 2004). For instance, in a study by Schnyer et al., (2004), frontal damaged subjects and healthy control participants engaged in an episodic verbal feeling-of-knowing (FOK) task. At study, subjects were presented with a list of 18 sentences. After a delay, the subjects were re-presented with the sentences, with the last word from each sentence missing. Subjects were prompted to recall the last word of the sentence, and make FOK judgments (ratings of the probability of successful recognition in the future) if they could not. Results showed that patients with frontal lobe damage were less accurate in their FOK ratings (in relation to the criterion of later recognition memory performance) than control subjects.

As already noted, there is great variability among older adults in their performance on tasks purported to measure frontal function and medial temporal lobe function, allowing for the separation of groups into high or low performers in these two cognitive domains (Glisky et al., 1995). Few studies have examined the relationship between performance on executive function tasks and accuracy in judgments of memory in older adults. One exception is a study by Souchay, Isingrini, & Clarys (2004), who demonstrated that older adults’ performance on the Wisconsin Card Sort and verbal fluency tasks was correlated with performance on a FOK task. However, to the author’s knowledge, there are no studies that examine the relationship between
neuropsychological measures of frontal and medial temporal function in older adults, and metamemory performance. In the present study, a double dissociation was predicted such that “high frontal” older adults would have higher FOK accuracy than low frontal older adults, and that high medial temporal older adults would have greater recall for the last word of the sentences than low medial temporal older adults. This prediction was based on the FOK accuracy differences observed between frontal damaged patients and control subjects (Schnyer et al., 2004), and the vast literature showing that medial temporal lobe function is related to performance on recall tasks.

A second goal of this study was to examine the relationship between factor score status and responses on a self-report measure of memory problems in everyday life (the Memory Functioning Questionnaire). As Gilewski, Zelinski, and Schaie (1990) note, self-report measures of memory function and performance on memory tasks are only modestly correlated. There are several explanations that have been proposed to account for this discrepancy, including that self-efficacy of memory, negative affect, and idiosyncratic individual differences influence self report differently from neuropsychological task performance (Gilewski et al., 1990; Hertzog, Park, & Morrell, 2000). In the present study, it was examined whether frontal and medial temporal factor score status would be related to performance on the MFQ, and specifically, whether high and low frontal and medial temporal groups would respond differently on the subscales of the MFQ task. The metamemory literature has shown that patients with frontal lobe damage often have little insight into their impairments. It was therefore hypothesized that
low frontal factor subjects would report fewer problems with their memories than high frontal subjects.

Additionally, it was investigated whether responses on the MFQ correlated with performance on the FOK task. There have been very few studies that have examined the relationship between performance on self-report measures and performance on experimental metamemory tasks. One exception is a dissertation study conducted by Duke (2000), in which a principal components analysis showed that self-report data was independent of FOK ratings. The present study examined whether self-report data from the MFQ is associated with either FOK or retrospective confidence judgments, or whether they are not related, consistent with prior research.

Method

Participants

34 healthy older adults (16 male, 18 female) between the ages of 60 and 85 participated in this experiment. Demographic data for the participants included in the study are displayed in Table 2.1. Participants were recruited through newspaper ads and flyers distributed to independent living communities in the greater Tucson area. Participants were screened with a comprehensive health and demographic questionnaire. Because the primary motivation for recruiting subjects was for the fMRI study, subjects were excluded if they were left-handed, had ferrous metal in their bodies, a history of substance abuse, neurological illness, or cardiovascular disease. As a result, 38 participants were excluded from participating in this study. Experiment procedures were
approved by the Human Subjects Committee of the University of Arizona prior to recruitment of subjects. Informed consent was obtained from each participant. Each participant was characterized as high or low frontal and medial temporal functioning, based on their performance on neuropsychological testing (described below).

Factor Scores

In order to examine the relationship between frontal and medial temporal factor scores and performance on experimental memory and monitoring tasks, participants first underwent a set of neuropsychological tests similar to Glisky et al.’s (1995) procedure. The tests representing the frontal factor included: number of categories achieved on the Wisconsin Card Sorting Test, the total number of words generated on the Controlled Oral Word Association Test (Benton & Hamsher, 1976), (c) Mental Arithmetic from the Wechsler Adult Intelligence Scale (Wechsler Adult Intelligence Scale-R), Mental Control (Wechsler Memory Scale-III), Backward Digit Span (WMS-III). The tests representing the medial temporal factor included: Logical Memory I and Verbal Paired Associates I from the WMS-III, Visual Paired Associates II from the WMS-R, and the Long-Delay Cued Recall measure from the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). Factor scores were derived based on the formula computed by Glisky et al. (1995). Subjects below the respective formula means were characterized as low frontal or low medial temporal, and subjects above the formula mean were characterized as high frontal or high medial temporal. After applying Glisky’s formula, a median split was performed in order to have two equal group sizes of high and low
frontal functioning. For the frontal factor, four low frontal subjects were reassigned to the high frontal classification after applying the median split. For the medial temporal factor, there were exactly 17 subjects who scored above the median split and 17 who scored below the median split, and no subjects had to be reassigned. Demographic information for the factor groups are shown in Table 2.1. There were no significant group differences for participants characterized as high and low medial temporal functioning for education \[F(1,33) = 2.33, p > .1\], scores on the MMSE \[F(1,33) = 1.24, p > .2\], or sex \(\chi^2 = 0.59, p = 0.44\). There was a small, although statistically significant, difference observed between high and low medial temporal groups with respect to age, such that the high medial temporal group was older than the low medial temporal group \[F(1,33) = 4.51, p = 0.04\]. There were no group differences for participants characterized as high and low frontal for education \[F(1,33) = 1.27, p > .2\], scores on the MMSE \[F(1,33) = .02, p > .8\], age \[F(1,33) = 0, p = 1\], or sex \(\chi^2 = 0.12, p = 0.73\).
Table 2.1.
Demographic data of groups selected according to frontal lobe or medial temporal lobe function.

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Low Function</th>
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<tr>
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<td>Age (years)</td>
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<tr>
<td>Education (years)</td>
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<tr>
<td>MMSE</td>
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<tr>
<td>Female</td>
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</table>

Note. MTL = Medial temporal lobe, FL = Frontal lobe,
MMSE = Mini Mental Status Exam
Materials & Procedure

FOK Task

An episodic sentence FOK memory task was administered to subjects, identical to the task described in Schnyer et al., 2005. The task involved 24 sentences that were drawn from a larger set of 329 sentences. The last word of each sentence was normed on a group of college students (Bloom & Fischler, 1980). The last word was chosen to be the third most prevalent word produced (average completion = 11%) and the six other most prevalent completions were used as possible foils in the recognition task. Before the study portion of the task, the experimenter removed six sentences out of the set of 24 to serve as foils for the test. During study, participants learned the remaining 18 sentences during a single learning trial. After a 20 minute delay, participants were shown 24 sentences (the 18 studied sentences plus the six foils), with the last word missing of the sentence. Subjects were instructed to recall the last word of each sentence. If they could not recall an answer, they were instructed to guess. Immediately after recall, subjects made a retrospective judgment regarding their confidence that they recalled the correct word (1, extremely uncertain/pure guess; 2, very uncertain; 3, somewhat uncertain; 4, somewhat certain; 5, very certain; 6, extremely certain). Subsequent to their confidence judgment, subjects were informed if their answer was incorrect, and, for incorrectly recalled words, were instructed to make a FOK judgment using a four-point scale (1, pure guess; 2, low; 3, medium; 4, high), based on their prediction of future word recognition. Subjects were given a recognition test for the items that they recalled incorrectly. 
immediately after test. They were instructed to choose the correct last word of the sentence out of six choices.

Memory Functioning Questionnaire (MFQ)

The MFQ (Gilewski, Zelinski, & Schaie, 1990) is a 64-item self-report measure of difficulties with memory in everyday life. Subscales in this measure include a general rating of memory, frequency of forgetting (e.g., names, faces, and appointments), frequency of forgetting during reading, remembering past events, seriousness of forgetting, retrospective functioning, and use of mnemonics. Participants are instructed to rate their memories in terms of the problems they have using a Likert scale from 1 (indicating major problems) to 7 (indicating no problems). On this measure, higher scores reflect fewer memory problems as noted by the participant. This measure was administered to participants following the FOK task and before neuropsychological testing.

Results (FOK Task)

Recall & Recognition

The proportion of correctly recalled and recognized sentence word endings is shown in Figure 2.1. Recall performance was based on the number of correct sentence word endings that were recalled out of the 18 studied sentences. A 2 (MTL group) X 2 (frontal group) ANOVA for recall performance indicated that there was a main effect for the medial temporal grouping, such that high MTL subjects had significantly greater
recall than the low medial temporal group [F(1, 33) = 9.9, p = .004]. There was no main effect of the frontal grouping factor with respect to recall [F(1, 33) = 2, p = 0.17]. There was also no significant interaction effect, although there was a trend such that the low frontal/high MTL subjects had the nominally highest recall scores [F(1, 33) = 3.23, p = 0.083].

Recognition performance was based on the number of correct sentence word endings that were recognized out of a multiple choice of six, excluding any words that were previously correctly recalled. A 2 (MTL group) X 2 (frontal group) ANOVA for recognition performance revealed that while there were no significant main effects, low frontal subjects were marginally less accurate in their recognition performance than high frontal subjects [F(1, 33) = 3.48, p = .073]. There was no interaction effect [F(1, 33) = 0.62, p = 0.44].
Fig. 2.1. Proportion of word endings correctly recalled and recognized by factor group. Error bars represent the standard error of the mean.
Confidence and feeling-of-knowing judgments

Three types of statistics were computed to measure monitoring accuracy:
Goodman-Kruskal gamma correlations (Nelson, 1984), Somer’s d correlations (Somers, 1962), and the Hamann index (see Schraw, 1995). Although the two former measures are used in the metamemory literature, one shortcoming of these correlations is that they cannot be computed if subjects use a restricted range of the judgment scale (see Schraw, 1995). The problem of restricted range in metamemory tasks has been previously noted in other studies, necessitating the need for the Hamann index over other measures (see Schnyer et al, 2004). In the study reported here, the gamma and Somer’s d correlations could not be computed for one subject because of the subject’s use of only one FOK judgment for every item. Therefore, only the Hamann index results will be reported. For the Hamann statistic to be applied, rating judgments were converted to binary data such that confidence ratings of 1-3 were grouped as low confidence responses (0) and ratings 4-6 were grouped as high confidence responses (1). Similarly, FOK responses of 1 or 2 were considered low feelings-of-knowing, and responses of 3 and 4 were considered high feelings of knowing. The Hamann correlations were then transformed into Fisher Z scores to make the sampling distribution more normal for hypothesis testing.

The Fisher Z transformed Hamann FOK and retrospective confidence judgment accuracy are displayed in Figure 2.2. It was hypothesized that performance on the frontal factor would be associated with greater monitoring accuracy on the FOK task. However, A 2 (MTL group) X 2 (frontal group) ANOVA revealed that there was no significant main effect for the frontal factor grouping [F(1, 33) = 0.28, p = 0.6], the MTL grouping
[F(1, 33) = 0.13, p = 0.72] or interaction [F(1, 33) = 0.58, p = 0.45]. Additionally, a 2 (medial temporal lobe group) X 2 (frontal group) ANOVA revealed that there were no differences between groups on the retrospective confidence judgment task for the frontal factor grouping [F(1, 33) = .97, p = .33] or for the temporal factor grouping [F(1, 33) = 1.56, p = .22],

The Fisher Z transformed FOK and retrospective confidence judgment scores were entered into a correlation analysis to examine whether these two measures of memory monitoring are associated. A Pearson bivariate correlation, utilizing the entire group of subjects, revealed that performance on the FOK task was not significantly correlated with performance on the retrospective confidence task (r = .19, p > .29), suggesting that these two ratings measure different aspects of metamemory functioning.

1. Note: Although the Hamann index is the most appropriate statistic for this analysis, examination of the gamma and Somer’s d correlations did not reveal differences between groups on the FOK task.
Fig. 2.2. Fisher Z transformed Hamann correlations for FOK and confidence judgments by factor group. Error bars represent the standard error of the mean.
Discussion (FOK Task)

Overall, these results provide some support for the utility of the factor scores in predicting performance on experimental memory and monitoring tasks in groups of healthy older adults. Specifically, this study demonstrated that high medial temporal subjects had greater recall on the FOK task than low medial temporal subjects, consistent with expectation, given that the medial temporal factor score is based upon recall measures from standardized neuropsychological tests. Additionally, it was found that low frontal subjects had a nonsignificant trend (p=.073) toward poorer recognition performance than high frontal subjects, with no differences in recognition performance between low and high medial temporal subjects. Cabeza, Locantore, and Anderson (2003) argue that recognition performance is more dependent upon frontal function than recall because of the need to reject distracter items and involve monitoring and verification processes. The partial dissociation between recall and recognition was thus supported in this study through the classification of older adults based on neuropsychological factor scores.

Although differences were expected between high and low frontal subjects in FOK accuracy (hypothesized on prior evidence consistent with the frontal lobes being involved in episodic metamemory judgments) no significant differences were observed between groups. The groups also did not differ in performance on the retrospective confidence judgment task. Although other studies have shown that patients with frontal lobe damage have lower FOK and retrospective confidence scores than healthy older controls (i.e., Schnyer et al., 2004; Pannu, et al., 2005t), high frontal older adults in the
present study did not perform significantly better on the tasks than low frontal older adults. In considering this result, it is important to note that the older adults in the present study, although performing differentially on neuropsychological tasks, are healthy and do not actually have structural frontal lobe damage. Therefore, it is possible that gross frontal damage is required to observe significantly poorer judgments of memory.

However, as figure 2.2 shows, there is a nonsignificant patterning of the data, such that the high frontal and high medial temporal subjects perform nominally better on the metamemory tasks than low frontal and low medial temporal subjects. It is possible that the low factor groups represent an intermediate stage, in which accurate memory of judgments declines, but not to the extent as individuals with frontal lobe damage.

It was also noted in the present study that a Pearson’s correlation between FOK scores and retrospective confidence scores found the two judgment types to be unrelated. This result has also been reported previously by Pannu et al. (2005). In their study, frontal damaged subjects performed poorly on retrospective confidence judgments but not FOK judgments on a face-name retrieval task, providing evidence for the dissociation of these two tasks. The finding that the two metamemory measures (i.e., FOK and retrospective confidence judgments) are not correlated in the present study is consistent with the literature suggesting that metamemory cannot be considered a unitary construct (Leonesio & Nelson, 1990; Pannu et al., 2005). It is clear that the FOK and retrospective confidence tasks require different types of predictions, as the FOK requires predictions about future retrieval, while retrospective confidence judgments require judgments
regarding information that has already been retrieved. However, it is unclear how the processes that underlie each of these judgments differ.

Schnyer et al. (2004) have proposed that in addition to differential processes that are engaged in these two types of judgments, there may also be a difference in the neuroanatomical region associated with each type of judgment. They suggested that while the ventromedial prefrontal cortex is critically involved in FOK judgments, retrospective confidence judgments may be dependent more on lateral frontal regions. This hypothesis was based on their observations of lesion overlap in the ventromedial prefrontal cortex within a group of frontal lobe damaged patients who performed the most poorly on a FOK task. Schnyer et al. also pointed to neuroimaging evidence showing that the right prefrontal cortex was differentially engaged during a post-retrieval monitoring task (Henson and colleagues, 2000). In the Henson et al. (2000) study, participants studied words and were subsequently re-presented with the words along with distracter words. Subjects made old/new judgments, as well as confidence judgments on the words. Results showed that the right prefrontal cortex was activated during when the subjects deemed the word to be old, but were not very confident in their judgment. Therefore, the authors suggest that this area is involved when monitoring demands are the greatest.

Results (MFQ Task)

The second goal of the present study was to examine the relationship between performance on neuropsychological measures and self-report of everyday memory problems. An overall MFQ score, consisting of the sum of all responses, was first
calculated for each participant. Subscores from each of the seven scales were also calculated and compared using multiple analyses of variance.

Overall MFQ scores were not significantly different between the high and low frontal groups [F(1, 33) = .02, p > .9] or between high and low medial temporal groups [F(1, 33) = .17, p = .69]. MFQ ratings by factor score are displayed in Figure 2.3. Two nonsignificant trends emerged from the subscale analyses of the MFQ. The first involved a trend toward a difference between high and low medial temporal subjects such that low medial temporal subjects reported using mnemonics less than high medial temporal subjects [F(1, 33) = 3.28, p = .08]. The second trend emerged for the frontal factor grouping. Low frontal subjects showed a trend toward being more likely to report that their memories are the same now in comparison to the past than was true for high frontal subjects [F(1, 33) = 3.65, p = .066].

Performance on FOK & MFQ Tasks

In this analysis, the correlation between FOK and retrospective confidence accuracy on the metamemory task, and responses on the MFQ subscales was examined. Bivariate Pearson correlations were computed to examine this relationship. Across all 34 subjects, results showed that the retrospective confidence Hamann score was negatively correlated with the retrospective functioning subscale, such that those who had higher retrospective confidence Hamann scores reported that their memories were worse now than in the past (r = .343, p = .047). There were no significant correlations between the FOK Hamann scores and any of the other subscales of the MFQ.
Fig. 2.3. MFQ subscale ratings by factor group. Higher proportions indicate less problems reported. Differences between factor groups were noted on the retrofunc and mnemonics subtests. Error bars represent the standard error of the mean.
Discussion (MFQ Task)

In the analyses of the MFQ and factor score grouping, it was found that low frontal subjects showed a nonsignificant trend toward reporting fewer changes in their memory (in comparison to their perceived memory functioning in the past) than did those in the high frontal functioning group. One explanation that could account for this trend is that low frontal subjects’ memory ability indeed might have remained more stable than that of high frontal subjects’. However, this is not likely, taking into consideration that many of these low frontal factor subjects also had lower medial temporal factor memory scores. A second possibility is that high frontal subjects are somewhat more worried about their memories than low frontal subjects due to an affective disturbance. Some studies have suggested that depression may mediate the association between self-report of memory problems and performance on neuropsychological tests, such that depressed people are more likely to report more memory problems than non-depressed people (Moore, van Gorp, & Hinkin, 1997; van Gorp, Satz, & Hinkin, 1991). However, this possibility is also unlikely because there were no differences reported in current depressive symptoms between the two groups on the health screening questionnaire. Specifically, all older adults included in the study denied current symptoms of depression. Further inspection of the health screening questionnaire revealed that six participants reported having depressive symptoms in the past (3 low frontal/low medial temporal, 2 high frontal/low medial temporal, 1 high frontal/high medial temporal). All of these subjects reported that their symptoms have since remitted, and one subject (low
frontal/low medial temporal) reported their depressive symptoms to be well controlled with the use of the medication Prozac.

Alternatively, the trend observed in the study could suggest that low frontal subjects are somewhat less aware of the decline of their memories. If this is the case, then the data can be seen as consistent with the previous finding of impaired retrospective confidence judgments on experimental metamemory tasks in frontal damaged patients (Pannu et al., 2005), and consistent with the low frontal factor group trend of less accurate judgments reported in this study. On the retrospective subscale, subjects must reflect upon the past to decide whether their memories have declined. Similarly, on the retrospective confidence task, subjects reflect on the past to decide whether they recalled the correct answer. A significant Pearson correlation between responses on the retrospective functioning subscale of the MFQ and retrospective confidence accuracy was also demonstrated, supporting the notion that these two measures are related.

A second nonsignificant trend that emerged from the results is that low medial temporal subjects tended to report using mnemonics marginally less than high medial temporal subjects. A potential implication of this trend is that low medial temporal subjects might perform as well as high medial temporal subjects if they indeed utilized better strategies and mnemonics. It is also possible that low medial temporal subjects tend to not remember to use mnemonics, as a result of poorer memory. Future research could investigate whether low medial temporal subjects could be instructed to utilize mnemonics in everyday life, and given strategies to organize material that would help on
neuropsychological tests of memory, and whether these strategies would help to increase future performance.
NEURAL CORRELATES OF TOT & SUCCESSFUL RETRIEVAL IN HEALTHY OLDER ADULTS

Retrieval attempts from memory can result in successful retrieval of an item, unsuccessful retrieval due to absence of knowledge, or unsuccessful retrieval accompanied by a tip-of-the-tongue (TOT) or a feeling-of-knowing experience. Most memory studies in the literature address only successful or unsuccessful retrieval, ignoring the processes that occur during partial retrieval. Additionally, the few studies that have investigated judgments of memory that reflect partial retrieval have only been conducted in young adults. The study reported here addressed this gap in the literature by examining the neural correlates of successful and unsuccessful retrieval, and TOT responses, in older adults.

The neural correlates of successful retrieval from memory have been studied extensively. According to the hemispheric encoding and retrieval model (HERA; Nyberg, Cabeza, & Tulving, 1996), left prefrontal cortex activity is associated with encoding of episodic memory, as well as retrieval from semantic memory, while right prefrontal cortex activity is associated with retrieval from episodic memory. Additionally, the left anterior inferior frontal gyrus (aLIFG) has been shown to be implicated in semantic retrieval and semantic processing (Daselaar et al., 2005; Poldrack, 1999). For instance, Daselaar et al. (2005) demonstrated that LIFG activity reductions were noted in both young and older adults on a repetition priming word stem completion task, indicating that this area was involved in processing the semantic information. In their brief review,
Noppeney, Phillips, and Price (2004) note that the LIFG has been implicated for different types of processing, including retrieval demands, selection of items from among competing alternatives, and depth of semantic analysis. Although various studies favor one interpretation over another, it is generally agreed that the LIFG’s role in semantic retrieval reflects executive processes, rather than storage of semantic information.

While the LIFG has been shown to be important for executive retrieval processes, the left anterior temporal lobe has been shown to be important for storage of proper names. For instance, Tsukiura et al. (2002) found that left anterior temporal cortex was activated when young subjects retrieved the names of famous persons. Given reports available in the neuroimaging literature, it is likely that the left inferior frontal gyrus and left anterior temporal lobe work in concert to produce successful retrieval of names from memory.

As already noted, the neural correlates of successful retrieval have been well studied. The few studies examining the neural correlates of partial retrieval have shown that the medial prefrontal cortex and anterior cingulate are activated during TOT or FOK states (Maril et al., 2001; Maril et al., 2003; Pannu et al., 2004; Schnyer et al., 2005). For instance, Maril et al. (2001) demonstrated that the anterior cingulate was activated in young adults during a TOT state on a general knowledge task (see Chapter 1). Pannu et al. (2004) demonstrated that anterior cingulate activity during FOK states in young adults is not limited to verbal materials, but that this region was also activated during a face-name retrieval task, in which subjects were shown a famous face and were instructed to recall the correct name. Furthermore, Schnyer et al. (2005) showed that a structural
equations model defining the ventromedial prefrontal cortex as a memory monitor best fit their feeling-of-knowing fMRI data. This study thus provided intriguing evidence consistent with the medial prefrontal cortex’s involvement in monitoring and verification.

While there are a growing number of studies investigating metamemory judgments utilizing fMRI in younger adults (e.g., Maril et al., 2001, Pannu et al., 2004, Schnyer et al., 2005), there have not been any previous studies investigating TOTs in older adults. The present study was conducted in an effort to address the questions surrounding the neural changes that underlie retrieval and TOT experiences in healthy aging.

It was predicted that, similar to the evidence obtained from studies of younger adults, greater activation in the medial prefrontal cortex and the anterior cingulate would be associated with the TOT states in the older adult group, presumed to be reflecting monitoring processes. This hypothesis is based on the behavioral experimental literature suggesting that older adults are usually as accurate as young adults in their metamemory judgments, supporting the notion that older adults engage in monitoring processes to the same degree as young adults. Additionally, it was hypothesized that left anterior temporal areas and left inferior frontal cortex would be associated with successful retrieval from memory.

A final question that the current study addressed is whether there are differences in neural activation in relation to neuropsychological factor score status. Neuroimaging research has shown that, as a group, older adults are more likely to engage the prefrontal cortex (PFC) bilaterally in comparison to young adults during performance of various
cognitive tasks (see Cabeza, 2002 for a review). In one study, young subjects significantly activated left PFC during a semantic task, while older adults activated both the left and right PFC (Logan & Buckner, 2001). This pattern of bilateral activity is observed across different tasks and materials and has been conceptualized as hemispheric asymmetry reduction in older adults (HAROLD) and may reflect functional compensation (Cabeza, 2002; Cabeza et al., 1997). However, these studies have characterized all older adults as one group, not acknowledging the possibility that subsets of older adults may have differential neural activations that reflect differences in behavioral performance (i.e., on neuropsychological tasks). In the present study, the question of whether older adults differ in laterality of activation based on their neuropsychological profile was examined. It was hypothesized that high frontal and high medial temporal functioning older adults would show bilateral prefrontal cortex activation during the task relative to low frontal and low medial temporal functioning older adults.

Method

Participants

24 of the original 34 participants from the study discussed in chapter 2 agreed to participate in the fMRI study. Potential subjects were excluded from participating if they were left-handed, had a history of substance abuse, neurological illness, cardiovascular disease, or had ferrous metal in their bodies. Of the 24 participants, five participants were excluded from fMRI data analysis (3 due to response bias of ‘don’t know’ and too few “TOTs,” or “know” responses, and two were excluded due to technical problems with the
scanner). 19 participants (10 female) were included in the final analysis. Demographic
information for the participants included in the imaging study is shown in Table 3.1. A
one-way ANOVA did not indicate significant group differences for participants
characterized as high versus low medial temporal functioning for age \[ F(1, 18) = 2.2, p >
.1 \], education \[ F(1, 18) = 2.4, p > .1 \] or sex \( \chi^2 = 1, p = 0.45 \). Similarly, there were no
group differences for participants characterized as high and low frontal for age \[ F(1, 18)
= .59, p > .45 \], education \[ F(1, 18) = .35, p > .5 \] or sex \( \chi^2 = 0.58, p = 0.32 \).
Table 3.1.
Demographic data of groups selected according to frontal lobe or medial temporal lobe function for fMRI study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High Function</th>
<th>Low Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontal Lobe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.6</td>
<td>69.8</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.2</td>
<td>15.4</td>
</tr>
<tr>
<td>MMSE</td>
<td>29</td>
<td>29.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Medial Temporal Lobe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.2</td>
<td>68.8</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.6</td>
<td>14.8</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Note. MTL = Medial temporal lobe, FL = Frontal lobe,
MMSE = Mini Mental Status Exam
Statistical Analyses

Image pre-processing and statistical analyses were performed with Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk) executed in MATLAB (Version 6.0, Mathworks, Inc., Sherborn, MA). All individual functional images were corrected for motion artifacts by realignment to the first volume of the session. A sinc interpolation was used to reslice the realigned volumes. All images were spatially normalized to a standard template of 2 mm × 2 mm × 2 mm voxels (MNI-space). Finally, images were spatially smoothed with an 7 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

Contrasts of interest were created based on a general linear model employed by SPM2. Contrasts of interest were defined for each subject, followed by a random effects group analysis.

fMRI Experimental Paradigm

During the fMRI portion of the study, participants were presented with famous and novel faces and were instructed to try to name the face. When subjects viewed a face, they were instructed to recall the person's name and then make one of the following mouse button-press responses: 'know,' indicating successful retrieval, 'TOT,' indicating
the name was on the tip-of-their-tongue, or 'don't know,' indicating that the face was unknown. The task was self-paced. However, subjects had up to five seconds to make their response. If they did not make a response after five seconds, the program moved on to the next face. The control condition was a fixation cross. During control trials, subjects were instructed to press any mouse button within five seconds. There was a 2 second inter-stimulus interval. Participants viewed a total of 220 faces within two counterbalanced scripts, of which 180 were famous faces of varying familiarity, and 40 were novel faces.

After the imaging procedure, participants engaged in a post scanner retrieval task, in which the participant viewed previously seen faces that were categorized as know or TOT. Subjects were asked to name the faces they had indicated they knew in the scanner and were asked to choose the correct name out of an 8 name multiple choice for the faces for which they had indicated they had a TOT for in the scanner. Only correct responses were included in the final analysis. All other responses were modeled out of the analysis.

Results

Behavioral Performance

Overall accuracy rate for know responses was 87%. Overall accuracy rate for TOT responses was 95%. Accuracy for TOT responses were significantly greater than for know responses (t(19) = .03). This is likely due to the more stringent criteria for a know response to be included; any know response that was made in the scanner and could not be verified by recall outside of the scanner was discarded. However, subjects could
choose their response from an 8-multiple choice set of alternatives for TOT responses, making the task easier if subjects truly did know the name. Repeated-measures ANOVAs indicated that there were no group differences between high and low frontal subjects or high and low medial temporal subjects on number of successfully recalled names, number of TOT responses, or don’t know responses (p > .5). The mean proportion of all responses that were characterized as know, TOT, and don’t know responses for groups is shown in table 3.2.

Examination of reaction times for know, TOT, and don’t know responses revealed that subjects were significantly slower in their TOT responses than know responses (t(18) = 11.7, p < .001), and in turn, know responses were slower than don’t know responses (t(18) = 3.4, p = .003).
Table 3.2

Proportion of correct know, TOT, & dk trials for high and low MTL and Frontal factor groups.

<table>
<thead>
<tr>
<th></th>
<th>KNOW</th>
<th>TOT</th>
<th>DK</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>22%</td>
<td>27%</td>
<td>93%</td>
</tr>
<tr>
<td>Low</td>
<td>28%</td>
<td>26%</td>
<td>98%</td>
</tr>
<tr>
<td>FRONTAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>22%</td>
<td>30%</td>
<td>93%</td>
</tr>
<tr>
<td>Low</td>
<td>28%</td>
<td>24%</td>
<td>98%</td>
</tr>
<tr>
<td>ALL</td>
<td>25%</td>
<td>27%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Note. TOT = Tip-of-the-tongue, DK = don’t know, MTL = Medial temporal lobe. Know & TOT responses are out of 180 famous faces. DK responses are out of 40 novel faces.
Imaging Data

Overall Group Results

To examine the pattern of activation associated with tip-of-the-tongue states in the 19 older adults as a group, direct comparisons between TOT, know, and don’t know responses were performed. A p value of .005 was selected as the threshold for significant activation. However, if activation was not observed at this p value, the threshold was lowered to either .01 or .05. The p value of each contrast is noted in each section below.

TOT – Know

When a tip-of-the-tongue state is compared with successful retrieval, it was expected that activation in neuroanatomical regions thought to be important for monitoring and verifying the contents of memory would be observed. As noted earlier, previous research has implicated the ventromedial prefrontal cortex and anterior cingulate as being critical areas (Maril et al., 2001; Pannu et al., 2004; Schnyer et al., 2005). In the present study, activation in both of these areas was observed, along with multiple activations in other frontal, temporal, and parietal cortices. Figure 3.1(a & b) shows activation in ventromedial prefrontal cortex (BA 25) and anterior cingulate cortex (BA 32) in this contrast, with uncorrected $p = .005$.

TOT – DK
As in the previous TOT – Know contrast, activation in the medial prefrontal cortex and anterior cingulate was expected in the TOT – DK condition. As figure 3.1 (c) shows, medial prefrontal cortex activity was observed in the TOT – DK contrast. Importantly, anterior cingulate activity was also observed in this contrast (fig. 3.1(d)), similar to the activation in the TOT – Know contrast with uncorrected $p = .005$.

**Know – TOT**

In the Know – TOT contrast, activity in the left anterior temporal cortex and the inferior frontal gyrus was expected. As predicted, left inferior prefrontal cortex activation was observed, along with bilateral activation in the lingual gyrus, some activation in the right fusiform gyrus, and right temporal cortex (uncorrected $p = .05$). No activation was observed in the left anterior temporal cortex. Figure 3.2a shows activation in this contrast.

**Know+TOT – DK**

In the conjunction of “know” and “TOT” responses in comparison to “don’t know” responses, activation in regions associated with retrieval attempts, such as medial temporal lobe regions, was expected. Activation was observed in the anterior cingulate, left inferior and superior frontal gyrus, and posterior cingulate (uncorrected $p = .005$), as shown in Figure 3.2b & c.
a. TOT – KNOW (Anterior cingulate activation)

b. TOT – KNOW (Ventromedial prefrontal cortex activation)

c. TOT – DK (Inferior medial prefrontal cortex activation)

d. TOT – DK (Anterior cingulate activation)

Fig. 3.1. Neural correlates of TOT states. a and b show activation in TOT states in comparison to successful retrieval. c and d show activation in TOT in comparison to don’t know states.
Fig. 3.2. Neural correlates of KNOW and TOT states. a shows activation during successful retrieval in comparison to a TOT state. b and c show activation during retrieval attempt.

a. KNOW – TOT (Left inferior frontal gyrus)

b. KNOW + TOT – DK (Anterior cingulate activation)

c. KNOW + TOT – DK (left inferior frontal gyrus activation)
Factor Score Analyses

Subjects’ imaging data were pooled into a group analysis based on their high and low frontal or medial temporal factor status. A p value of .005 was selected as the threshold for significant activation. However, if activation was not observed at this p value, the threshold was lowered to either .01 or .05. The p value of each contrast is noted in each section below.

Frontal Factor

It was examined whether there were frontal factor group differences in activation during the task. The TOT+KNOW – DK contrast was selected to determine differences between groups, because it was expected that this contrast would show activation associated with retrieval attempts from semantic memory. An analysis for the high frontal group for this contrast shows multiple activations in frontal, temporal, and parietal regions, shown in figure 3.3a (p = .005). The analysis for the low frontal group revealed circumscribed activation in few areas, including left inferior frontal gyrus, shown in figure 3.3.b (p = .005). Overlap between the two groups was observed in left inferior frontal gyrus shown in figure 3.3c (p = .05). A two-sample t test revealed additional right and left hemisphere activation in the high frontal group in comparison to the low frontal group (BAs 9 & 10), and are shown in figure 3.3d (p = .005).

Medial Temporal Factor
Inspection of the group analyses for high and low medial temporal subjects in the TOT+KNOW > DK condition revealed that high medial temporal subjects showed greater activity in multiple areas, including prefrontal, temporal, and parietal cortices (figure 3.4a, p = .005), while low the low medial temporal group showed activity in the left parahippocampal/hippocampal gyrus (figure 3.4b, p = .005). A two-sample t-test comparing the two groups revealed that high medial temporal subjects had greater frontal activity, including bilateral activity in the area of BA 6 during this contrast, while the low medial temporal subjects had greater medial temporal activity, specifically in the left hippocampus. Figure 3.4c (p = .005) shows greater activity in the left parahippocampal gyrus for the low medial temporal group, in comparison to the high medial temporal group.
a. Know + TOT – DK  (High Frontal Group Analysis)

![Image of brain scan](image1.png)

b. Know + TOT – DK  (Low Frontal Group Analysis)

![Image of brain scan](image2.png)

c. Know + TOT – DK  (Common regions between high and low frontal factor)

![Image of brain scan](image3.png)

d. Know + TOT – DK  (High frontal group – low frontal group)

![Image of brain scan](image4.png)

Fig. 3.3. Neural correlates of frontal factor group for the condition of Know + TOT – DK. a and b show one-sample group analyses for high and low frontal factor groups. c shows overlap of common regions between groups. d shows activation in a two-sample t-test.
a. Know + TOT – DK  (High medial temporal group)

b. Know + TOT – DK  (Low medial temporal group)

c. Know + TOT – DK  (Low medial temporal group – High medial temporal group)

Fig. 3.4. Neural correlates of medial temporal factor group for the condition of Know + TOT – DK. a and b show one-sample group analyses for high and low medial temporal factor groups. c shows activation in a two-sample t-test.
Four-Factor Group Analyses

The activation associated across the four factor groups (i.e., high frontal/high MTL, high frontal/low MTL, low frontal/high MTL, high frontal/high MTL) was examined using one sample t tests (p = .005). There were not enough subjects in the high frontal/low MTL and low frontal/high MTL factor groups to produce reliable results (two subjects and three subjects, respectively). However, examination of the high frontal/high MTL and low frontal/low MTL groups indicates that a similar pattern is observed to the activation associated when the frontal and MTL groups are collapsed. Specifically, bilateral prefrontal cortex activity was observed in the high frontal/high MTL group (see Figure 3.5a), and parahippocampal activity was observed in the low frontal/low MTL group (see Figure 3.5b).
Fig. 3.5. Neural correlates for the condition of Know + TOT – DK. a shows one sample group analysis for the high frontal/high MTL group. b shows one sample group analysis for the low frontal/low MTL group.
Discussion

The present study is the first to observe medial prefrontal cortex and anterior cingulate activity during TOT states in healthy older adults. In support of the stated hypothesis, older adults showed differential activation when they were in a TOT state, versus when they were able to successfully retrieve a name or did not know the target name. Specifically, robust activation in BA 32 and 25 was observed, similar to what has been reported from neuroimaging studies conducted in younger adults (i.e., Schnyer et al., 2005). These results provide further support for the medial prefrontal cortex and anterior cingulate cortex as critical regions during a TOT state, and likely reflect monitoring and verification processes during retrieval from memory. The present results add to the literature by replicating previous results (based on studies of young adults) in a group of healthy older adults, and utilizing a face-name retrieval task (rather than an entirely verbal task).

Conversely, left inferior prefrontal cortex activity was observed during successful retrieval. The left inferior prefrontal cortex, particularly the anterior portion, has been associated with semantic processing. In a study by Wagner et al. (1997), there was evidence for repetition priming in this area when subjects made semantically based judgments, such as a living/nonliving judgment for words and pictures. Importantly, Wagner et al. suggest that this area may not be specific only for the retrieval of words, but also for processing of the semantic features of non-verbal materials, such as pictures. In support of this hypothesis, the present study found left inferior frontal activity when subjects viewed pictures of famous faces and attempted name retrieval. The activation
was observed particularly in the successful “know” condition, and is consistent with the proposal that this area is important for semantic processing of pictures.

In contrast to expectation, activation in the left anterior temporal cortex was not observed in the successful retrieval condition. One possible explanation for this lack in activation is the susceptibility of this area to signal-dropoff. While the spiral in-and out imaging sequence used in the present study is an improved method for scanning brain regions that are susceptible to signal-dropoff, the possibility that this occurred in the present study cannot be ruled out.

The behavioral results in this task indicated that older adults who were neuropsychologically classified as having high frontal or high medial temporal functioning did not have more successful retrievals than older adults classified as having low frontal or low medial temporal functioning. Although results from the present health older adult groups cannot generalize to patient populations, the results suggest that at least within the normal variation of aging, older adults who perform more poorly on particular neuropsychological tasks do not necessarily have more difficulty in face-name retrieval. In fact, some of the participants who performed well above their peers on neuropsychological tasks showed the greatest number of TOTs. In order to explain these results, it may be helpful to consult the research that has been published on phonological processing in the language retrieval literature. Phonological deficits have been well-studied in the TOT literature. One particularly well-supported hypothesis, the transmission-deficit hypothesis, states that TOTs occur when the activated semantic representation of a word does not sufficiently prime the phonological representation of
that word, producing a deficit in “transmission” between semantic characteristics and phonological characteristics (Burke et al., 1991). For example, if given the definition, “an object used for the protection from the rain or sun,” a semantic and visual representation may be retrieved, but the definition does not activate the phonological representation (i.e., the word "umbrella"). This hypothesis has gained support from behavioral studies that show phonological priming to increase the number of correct responses, and decrease the number of TOTs (Rastle & Burke, 1996). In the present study, the neuropsychological measures that composed the frontal and medial temporal factors did not directly measure phonological processing ability. However, it was possible to examine whether the transmission deficit hypothesis was supported in the present study by examining neural activation. The Overall group analyses in the conditions of know > TOT and TOT > know were examined to determine whether areas of brain that are implicated in phonological processing (i.e., the left posterior inferior frontal gyrus, pLIFG; see Bookheimer, 2002) would be activated in the know > TOT condition. It was hypothesized that older adults would show greater pLIFG activation, reflecting phonological processing, when they have a successful retrieval of a word, in comparison to when they have a TOT experience. This would support the hypothesis that TOTs result from the deterioration of the link between semantic and phonological processes. However, the present results show that the activation observed in the successful retrieval condition was more anterior, rather than posterior, possibly reflecting semantic processing instead of phonological processing. Although evidence for phonological processing during successful retrieval was thus not found in this study, further
examination of the link between semantic and phonological retrieval in older adults is warranted given the behavioral literature regarding the hypothesized basis of TOT experiences.

Alternatively, it is possible that group differences in the number of TOT experiences and successful retrievals were not observed due to the small sample size of this study. Although there was no trend toward differences between the groups in the expected direction (i.e., the low frontal and low medial temporal groups had numerically more ‘know’ responses) this possibility cannot be completely ruled out, even if this appears to be an unlikely explanation.

The present results add to a growing literature suggesting that the medial prefrontal cortex (MPFC) and anterior cingulate (ACC) network is important for monitoring and verification. However, an alternative hypothesis for the imaging results must be considered. The differences in reaction times for each response type indicated that participants spent more time in a TOT state than in know or don’t know states. Therefore, the activations that were observed in this condition could also reflect increasing task difficulty. To address this question, the ‘know’ responses were divided by a median split on reaction time, and activations accompanying the “knowslow” (i.e., slow reaction times) and “knowfast” (i.e., fast reaction times) trials were compared with the TOT condition. In the TOT > knowslow contrast, which represents the activation associated with TOT states after taking out activation associated with a delayed but successful retrieval, MPFC activation was still observed, but it was much reduced. This result is not entirely surprising, as it is likely that subjects must monitor the contents of
memory when they are attempting to retrieve items from memory, even though they eventually get the answer after a longer latency. This monitoring that occurs during the “knowslow” condition therefore likely reduced the activation observed when this condition is compared with TOT.

Conversely, in the TOT > knowfast contrast, robust VMPC and ACC activation is observed. In the reverse contrast (knowfast > TOT), activation is restricted to few areas, and in particular, the left inferior prefrontal cortex. Although the possibility cannot completely be ruled out that these areas are involved due to increasing task difficulty, other studies are available that have equated reaction time data and have continued to observed robust activity in these areas during a TOT or FOK state (see Maril et al., 2001; Pannu et al., 2004; Schnyer et al., 2005).

In the present study, contrasts between high frontal and low frontal subjects revealed overlap in the inferior frontal gyrus and right frontal hemisphere. Additional activation was observed in the high frontal group during the TOT+KNOW > DK condition, suggesting that the high frontal group recruited more areas when performing the face-name task. Similarly, differences in frontal activation emerged between the high and low medial temporal groups, such that the high medial temporal group showed greater bilateral prefrontal cortex activity. These results provide evidence for a neural correlate of the factor groups identified by Glisky et al. (1995). Cabeza et al. (1997) have previously shown that older adults who perform as well as young adults on cognitive tasks show activation in additional areas, particularly within the left hemisphere on episodic memory tasks. Similarly, the older adult factor groups in the present study did
not differ in their performance on the task, but did show differences in neural activation. This additional activation may reflect differences in task-related strategies employed by the high frontal group. However, it is difficult to speculate in more depth on what the additional activation is associated with, as there were no differences in performance between high and low frontal subjects on the behavioral task. This question could be further explored in follow-up studies employing an episodic face-name task, in which older adults have to learn new associations of novel faces and names. This type of episodic memory task, which is inherently more challenging, may reveal differences in retrieval performance between groups on the behavioral task that are tied to the differences observed in neural activity.

The results of the present study also reveal that the low medial temporal group had greater medial temporal lobe activation than the high medial temporal group. Although there are a number of potential reasons for the hyperactivation, one possibility is that the increased activation reflects a compensation mechanism, allowing the low medial temporal group to perform as well on the task as the high medial temporal group. There is some evidence in the literature to suggest that the medial temporal lobes are activated to a greater extent in individuals with memory impairment. Dickerson et al. (2005) found increased activation in the hippocampus in mild cognitively impaired patients relative to healthy older adults during a face-name association encoding task. By contrast, Alzheimer’s patients showed hypoactivation in the hippocampus relative to healthy controls during the task. The authors suggest that during the prodromal phase of progressive memory impairment, there is increased activation in comparison to healthy
older adults. Furthermore, the increased activation could represent a number of processes, including increased resource utilization to compensate for neuropathology, use of a different encoding strategy, or the recruitment of regions other than the medial temporal lobes. In the present study, greater activity in the medial temporal lobes was observed during the retrieval of face-name associations. It is possible that the results obtained here parallel the results found in the Dickerson et al. study and also reflect one of the aforementioned posited processes.
CHAPTER 4

GENERAL DISCUSSION

This dissertation study is the first to incorporate findings from experimental metamemory tasks, self-report measures of memory, and neuroimaging during performance of a metamemory task to investigate differences between groups of healthy older adults defined by their neuropsychological test performance. The study yielded three main findings. First, the factor score method developed by Glisky et al. (1995) proved largely useful in partitioning the variability of performance within healthy older adults, and in predicting how older adults would perform on experimental tasks. The second finding is that the factor score grouping showed a nonsignificant trend toward association with a self-report measure of memory difficulties in everyday life. Finally, differential neural activation was observed during successful retrieval and TOT states, providing insight into the neural correlates of TOT experiences in older adults. These three findings are considered in separate sections below.

Factor Scores & Experimental tasks

The present study showed that the medial temporal factor groups differed, as expected, on the recall portion of a FOK task, while there were no differences in recall between high and low frontal groups on the recall measure. Conversely, a nonsignificant trend toward a difference between the high and low frontal factor groups was noted on the recognition portion of the task, consistent with previously published evidence suggesting that the frontal lobes play a role in recognition memory (see Cabeza et al.,
2003). Although differences between the frontal factor groups were predicted on the FOK and retrospective confidence judgment tasks, no differences were found between groups on the memory monitoring measures. However, a nonsignificant pattern in performance was noted, showing that the high frontal and high medial temporal subjects tended to perform somewhat better on the metamemory tasks than the low frontal and low medial temporal subjects. Given this data, it is possible that the low factor groups represent an intermediate stage, in which accuracy of memory of judgments declines, but not to the same extent as individuals with frontal lobe damage.

In the present study, it was observed that performance on the FOK task did not correlate with performance on the retrospective confidence task. This is not entirely surprising, as it has been documented in the literature that the two measures often do not correlate (Pannu et al., 2005; Schnyer et al., 2004). Schnyer et al. proposed that in addition to differential processes that are engaged in these two types of judgments, there may also be a difference in the neuroanatomical region associated with each type of judgment. They suggested that while the ventromedial prefrontal cortex is critically involved in FOK judgments, retrospective confidence judgments may be dependent more on lateral frontal regions. This hypothesis was based on the neuropsychological research conducted using patients with frontal lobe damage, and the neuroimaging work by Henson and colleagues (2000). Furthermore, there may be a dissociation between types of neuropsychological tasks that are related to each type of metamemory judgment. The present study and the Schnyer et al. (2004) study showed that there was no relationship between FOK ratings and performance on certain neuropsychological tasks. Many of the
tasks that define the frontal factor in the present study are purported to measure working memory, which has been hypothesized to be related to dorsolateral prefrontal cortex functioning. An area of potentially productive future research would be to investigate whether working memory is an important variable in retrospective confidence judgments, and whether incorporating neuropsychological tasks that appear to involve monitoring into the frontal factor, such as the Stroop task, would strengthen its relationship with performance on the FOK measure.

Performance on self-report measures

Results from the present study show two subscales of the MFQ to have nonsignificant trends toward relationships with both factor score groupings and metamemory task performance. Specifically, it was observed that low frontal subjects tended to deem their memories to be more stable over time than high frontal subjects, suggesting a possible lack of awareness of memory decline. Interestingly, it was also observed that subjects who were less accurate in their retrospective confidence judgments on the experimental metamemory task also tended to report fewer changes of their memory over time. This suggests that the two measures, although one is experimental in nature and the other is self-report, may tend to be measuring the same underlying concept. It was also found in the present study that low medial temporal subjects nonsignificantly trended toward reporting using fewer mnemonics than high medial temporal subjects.

Although these nonsignificant trends emerged from the data, the effects were small and the majority of measures on the MFQ were not related to factor score
performance or metamemory task performance. It has been well-established that responses on self-report measures often do not correlate with performance on memory tasks (see McDonald-Miszczak, Hertzog, & Hultsch, 1995). McDonald et al. (1995) have suggested that, in addition to reflecting monitoring of memory, self-report responses could also reflect implicit beliefs about the nature of memory. For example, results from their longitudinal study showed that responses on self-report memory measures stayed relatively stable across time, even when actual memory performance declined. Similarly, in the present study, a majority of the responses on the MFQ task did not vary as a function of the neuropsychological factor scores. For instance, although low medial temporal subjects performed more poorly on memory tasks than their peers, they did not report having any more memory problems in everyday life than their high medial temporal functioning counterparts. Lane and Zelinski (2003) suggest that personality may also have an impact on self-reports, including the variables of conscientiousness and neuroticism. Additional research is warranted to identify moderating and mediating variables that affect self reports of memory.

Neural & Behavioral correlates of TOT

This is the first study to report medial prefrontal cortex and ACC involvement in TOT states in older adults. In younger adults, activation within these areas during a TOT or FOK state has been demonstrated in several studies (Maril et al., 2000, 2001; Pannu et al., 2004; Schnyer et al., 2005). As noted earlier, FOK and TOT judgments are likely to be based on cue familiarity and retrieval accessibility, and the observed medial prefrontal
and ACC activation may be a reflection of the monitoring processes occurring during partial retrieval. An intriguing similarity appears to exist between the metamemory findings reported here, and the concept of “felt-rightness,” which refers to judgments of memory retrieval that are intuitive and represent a “cognitive check” on the memory’s “plausibility” (Moscovitch & Winocur, 2002, p. 202). Although Moscovitch and Winocur do not directly mention metamemory in their paper, the concept of felt-rightness is similar to the concept of monitoring the contents of memory described here. Furthermore, Moscovitch and Winocur propose that the ventromedial prefrontal cortex is important for judging felt-rightness, and cite studies that have shown patients with damage to this area cannot correctly monitor and verify the appropriateness of their actions toward a desired reward (see Bechara, Tranel, & Damasio, 2000). These studies call for further research examining the interaction between monitoring on laboratory tasks and the monitoring that is important in everyday life, particularly in social situations and in pursuing goals.

The present study also adds to the growing literature showing that the ACC and medial prefrontal cortex are activated in a number of different neuroimaging studies, and across various tasks (Posner & Badgaiyan, 1998; Carter, Botvinik & Cohen, 1999; Chein & Schnieder, 2005). The present study provides evidence for the role of these brain areas in monitoring of information, through the direct contrast of successful retrieval versus unsuccessful retrieval that is accompanied by TOT experiences. ACC and medial prefrontal activity has been observed regardless of the type of materials used (e.g. verbal sentence tasks, face-name associations), and across types of memory systems (e.g. episodic and semantic memory). Anterior cingulate and medial prefrontal cortex activity
may therefore reflect generalized processes that are important for any task that requires checking, verification, and monitoring of responses, and thus are observed across several neuroimaging studies.

An important finding of the present study was that activations in lateral prefrontal cortex and medial temporal areas during the behavioral task varied systematically with frontal and temporal lobe factor scores. First, it was observed that the high frontal group showed bilateral frontal activity in comparison to the low frontal group. Other studies have shown that when older adults perform as well as young adults on a cognitive task, they recruit additional prefrontal cortex brain regions (Cabeza et al., 1997). The results reported here argue against the possibility that the additional activation reflects compensation, as there were no differences on the behavioral task between the high and low frontal groups. Indeed, for the compensation hypothesis to be supported, the low frontal group would have to show greater bilateral activity, rather than the reverse. It is possible that the bilateral activity observed in this study and others reflects a general task strategy employed by older adults who are high functioning in the frontal domain, regardless of the type of task or task difficulty.

There were also differences observed in activation between high and low medial temporal subjects, such that low medial temporal subjects showed greater medial temporal lobe activity during a retrieval attempt. These results are consistent with previous findings showing increased medial temporal lobe activity in a group of patients with mild cognitive impairment (Dickerson et al., 2005). Because the subjects in the present study were still within the normal (although the low end of normal) range of
performance in comparison to their peers, the results suggest that the increased activity in
the medial temporal lobes may occur even before older adults reach the mild cognitively
impaired stage. Follow-up studies are warranted to investigate the relationship between
the low medial temporal factor classification, future mild cognitive impairment status,
and risk for developing Alzheimer’s disease.

Limitations of the Present Study

The present set of studies had several limitations that must be acknowledged in
interpreting these results. In the study reported here, the orthogonal classification of
factor groups reported in Glisky et al. (1995) was not replicated. The frontal factor and
the medial temporal lobe factor were correlated in the present study such that high frontal
subjects also tended to be high medial temporal subjects, and the reverse was also true:
low frontal subjects also tended to be low medial temporal subjects. It is possible that the
group recruited for the present study is not representative of the population of older adults
as a whole, as different inclusion criteria were applied for the present study (i.e., subjects
were excluded from the study if they were unable to undergo MRI, due to metal in the
body, history of cerebrovascular risk factors, or left handedness). This resulted in a large
number of older adults who were excluded because they did not meet inclusion criteria
for the study. Although there is no apparent necessary relationship between factor score
status and the presently employed inclusion/exclusion criteria, it is unknown whether an
inadvertent association reduced the number of cross-factor group subjects (i.e., high
frontal/low medial temporal, and low frontal/high medial temporal) included in the study.
Additionally, it is important to note that the findings that emerged from the factor group imaging data should be considered with caution due to the small sample size for the group analyses. Indeed, there were too few subjects in the cross-factor groups (i.e., high frontal/low MTL and low frontal/High MTL) to extract meaningful imaging results. However, in general, the present findings show that classifying participants based on their neuropsychological factor score status as outlined by Glisky et al. (1995) is fruitful in examining differences in executive and medial temporal lobe function, and that further research is warranted to investigate the neural correlates of cognitive function in these groups.
REFERENCES


