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Memory monitoring performance and PFC activity are associated with 5-HTTLPR genotype in older adults

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Abstract

Older adults show extensive variability in cognitive performance, including episodic memory. A portion of this variability could potentially be explained by genetic factors. Recent literature shows that the neurotransmitter serotonin plays an important role in memory processes, as enhancements of brain serotonin have led to memory improvement. Here, we have begun to explore genetic contributions to the performance and underlying brain activity associated with source memory monitoring. Using a source recognition memory task during fMRI scanning, this study offers evidence that older adults who carry a short allele (S-car) of the serotonin transporter linked polymorphic region (5-HTTLPR) in the *SLC6A4* gene show specific deficits in source memory monitoring relative to older adults who are homozygous for the long allele (LL). These deficits are accompanied by less neural activity in regions of prefrontal cortex that have been shown to support accurate memory monitoring. Moreover, while the older adult LL group's behavioral performance does not differ from younger adults, their brain activation reveals evidence of compensatory activation that likely supports their higher performance level. These results provide preliminary evidence that the long-allele homozygous profile is cognitively beneficial to older adults, particularly for memory functioning.

Keywords

5-HTTLPR; aging; fMRI; memory monitoring; metamemory; prefrontal cortex; serotonin

1. Introduction

Older adults have consistently shown performance declines in specific aspects of memory compared to younger adults. For instance, older adults are less effective in learning new episodic information, and new associations (Naveh-Benjamin, Guez, Kilb, & Reedy, 2004), and in identifying the source of newly learned episodic information (Glisky, Polster, &

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Routhieaux, 1995). Not all aspects of memory decline in performance with age, for instance, short term memory for newly learned items remains relatively intact (for a review, Balota, Dolan, & Duchek, 2000). However, source memory, or the memory for contextual information associated with an episode, is one domain that has consistently been shown to be impaired in older adults (K. J. Mitchell & Johnson, 2009).

Another domain of memory that has shown changes associated with age is the monitoring of memory performance (Isingrini, Perrotin, & Souchay, 2008). Memory monitoring assesses the potential accuracy of memory retrieval and is important for guiding and directing the retrieval process. The accuracy of memory monitoring can be examined from many angles, and the results often show differing age-related effects, as outlined by Halamish *et al.* (2011). For example, methods using judgments of learning at encoding have sometimes shown that older adults are overconfident when compared to younger adults (Bunnell, Baken, & Richards-Ward, 1999; Connor, Dunlosky, & Hertzog, 1997), but in other studies older adults show no age-related differences (Hertzog, Kidder, Powell-Moman, & Dunlosky, 2002; Rast & Zimprich, 2009). Additionally, one form of predictive retrieval judgments, the feeling-of-knowing tests, have generally shown no age-related differences (Allen-Burge & Storandt, 2000; Bunnell et al., 1999; Hertzog, Sinclair, & Dunlosky, 2010; Marquié & Huet, 2000). However, studies using output monitoring or confidence judgments at the time of retrieval have both uncovered age-related differences in memory monitoring (Dodson, Bawa, & Krueger, 2007a; Kelley & Sahakyan, 2003; Marsh, Hicks, Cook, & Mayhorn, 2007; Pansky, Goldsmith, Koriat, & Pearlman-Avnion, 2009). Our current study focuses on age-related changes in both source memory and source memory monitoring at retrieval, which can be impaired in older adults (Hashtroudi, Johnson, & Chrosniak, 1989; Kelley & Sahakyan, 2003; McIntyre & Craik, 1987; Norman & Schacter, 1997; Schacter, Koutstaal, Johnson, Gross, & Angell, 1997; Simons, Dodson, Bell, & Schacter, 2004).

1.1 Source Memory, Monitoring and Aging

In a study of source memory in aging, Dodson and colleagues (2007a) directly demonstrated a dissociation between simple recognition memory for newly learned information and recognition memory for the source associated with that information. In this task, participants were given sentences associated with a particular speaker (either a male or female voice) and were asked in a subsequent recognition phase to identify first, whether the sentence was previously heard, and second, who the reader of the sentence had been. For both queries, participants were asked to monitor their performance by providing a confidence rating with their response. Elderly participants were equivalent to young participants on the first old/new memory judgment, but were less accurate in indicating the source of the sentence. In addition to this dissociation in recognition memory performance, there was a parallel dissociation in older adults' ability to monitor their performance. While their confidence rating accuracy for recognition memory was equivalent to that of younger participants, their confidence rating accuracy for the source memory component was impaired.

The parallel declines in both memory and confidence rating performance might suggest that they represent the same underlying changes in the aging process, but a second experiment using a group of younger adults whose source memory was tested after a 24-hour delay offers evidence that they are two separate processes. The delay equated the younger and older groups' source memory performance, however the 'impaired' young adults continued to show higher confidence rating accuracy for their source memory decisions and this accuracy was equivalent to the shorter delay ('unimpaired') young group (Dodson, Bawa, & Krueger, 2007a). This study suggests that source memory monitoring performance can be dissociated from actual memory performance and that the declines associated with aging could reflect additional aspects of the cognitive aging process, not solely a decline of source memory ability.

One possible explanation offered for these findings is the “misrecollection account”, whereby elderly individuals incorrectly combine features from separate events that occurred in close proximity resulting in high confidence source memory errors (Kroll, Knight, Metcalfe, Wolf, & Tulving, 1996). Older adults may not simply be remembering less, but might be misremembering more (Dodson & Krueger, 2006; Dodson, Bawa, & Slotnick, 2007b). This view is supported by the performance of young participants whose memory was impaired by the 24-hour delay. Even though they are remembering less, the young adults are nevertheless aware of the lack of source information and are not confused by irrelevant information that comes to mind. Therefore, successful source memory monitoring relies heavily on the ability to focus attention away from information that might be irrelevant to the current test probe, a function that has been shown to be impaired in older adults (Badre & Wagner, 2004; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Park et al., 2002).

1.2 Neural mechanisms of source monitoring

A number of studies have examined the neural architecture involved in episodic memory monitoring and have consistently demonstrated that regions in the prefrontal cortex (PFC) play several strategic roles in mediating and monitoring the memory retrieval process (Chua, Schacter, & Sperling, 2009; Chua, Schacter, Rand-Giovannetti, & Sperling, 2006; Kikyo, Ohki, & Miyashita, 2002; Maril, Simons, Mitchell, Schwartz, & Schacter, 2003; Schnyer, Nicholls, & Verfaellie, 2005; Schnyer et al., 2004; Wagner, Maril, Bjork, & Schacter, 2001a). For instance, the ventral lateral PFC, including portions of the inferior frontal gyrus (IFG), supports the identification, selection and inhibition of contextual details of episodic memory, which are all critical elements for accurate source memory monitoring (Buckner, 2003; Dobbins, Foley, Schacter, & Wagner, 2002; Moscovitch et al., 2005; Schnyer et al., 2005; Wagner, Maril, Bjork, & Schacter, 2001b). Not surprisingly, these same regions of the PFC have also been found to be subject to age-related functional changes. Age-related under-recruitment of these lateral prefrontal regions has been linked to declines in post-retrieval monitoring abilities (Dulas & Duarte, 2011). These results support the frontal aging hypothesis, which suggests that the PFC is disproportionally affected by aging (Raz, 2000; West, 1996) and that alterations in its functioning likely underlie the changes in memory monitoring that have been observed.

Regions of the PFC showing functional variations associated with aging have sometimes revealed evidence of compensatory activity that may work to counteract performance declines. For example, a general pattern of increased bilateral activation for a variety of functional tasks has been observed for older adults in prefrontal and parietal regions. This is thought to help counteract age-related neurocognitive deficits through the engagement of additional neural resources to maintain task performance (Cabeza, 2002; 2004; Cabeza et al., 1997). Little is understood about individual differences in the ability to engage more bilateral regions of the PFC to support task performance, but one potential source of these differences is genetics.

1.3 Genetic contributions to source memory performance

Studies have linked genetic variation within the serotonin system (i.e., the serotonin receptor 2A gene, HTR2A) to memory performance, showing that subjects with genetically blunted receptor responses demonstrate poorer performance on long delay (30 min or more) memory recall tasks (de Quervain et al., 2003; Koppel & Goldberg, 2009). Additionally, positron emission tomography indicates that older adults have a reduced number of 5-HT2A serotonin receptors in the prefrontal cortex (Sheline, Mintun, Moerlein, & Snyder, 2002). Serotonergic systems have also been a recent target for treatment of memory disorders, including both amnesia and Alzheimer’s disease (Perez-Garcia & Meneses, 2008), offering

additional evidence for a potential mediating relationship between serotonin levels and memory functioning. These studies highlight the possible relationship between serotonin function and memory performance and reveal important implications for cognitive functioning in older adults.

One potential target of study is the serotonin transporter gene (*SLC6A4*), which is responsible for determining the duration and intensity of serotonin communication with postsynaptic receptors and targets by controlling the reuptake of serotonin. Importantly, the efficiency with which the serotonin (5-HTT) system returns serotonin to the presynaptic neuron appears to be influenced by a polymorphism in the promoter region of the serotonin transporter linked region (5-HTTLPR) of the *SLC6A4* gene. This common insertion/deletion polymorphism results in 2 variants: a short (S) allele and a long (L) allele. The presence of one or two S alleles, rather than two copies of the L allele, is associated with reduced transcriptional efficiency of the target gene that results in a significant decreas (approximately 50%) in serotonin reuptake (Caspi et al., 2003; Hu et al., 2005).

While the 5-HTTLPR genotype has typically been studied in relation to mood disorders in humans, previous work has demonstrated interesting associations between 5-HTTLPR and differences in brain structure in regions that have been shown to be critical for memory and memory monitoring. For instance, the white matter microarchitecture along a tract connecting important memory related regions of the medial temporal lobe (MTL) to regions of ventral medial and ventral lateral PFC has been shown to be significantly affected by the 5-HTTLPR serotonin transporter genotype. Genetic analysis combined with diffusion tensor MRI revealed an inverse association between fractional anisotropy values (a measure of white matter microarchitecture) and the number of short alleles (Pacheco et al., 2009). Further, the 5-HTTLPR genotype has been shown to modulate the association of lateral PFC volume with biased attention to emotional cues (Beevers, Pacheco, Clasen, McGeary, & Schnyer, 2010). In short allele carriers, there is an inverse correlation between lateral PFC volume and the ability to effectively shift attention away from emotionally salient, but irrelevant stimuli. As mentioned previously, the process of focusing attention away from irrelevant stimuli has been shown to be crucial for successful source memory retrieval and source memory retrieval monitoring. Given that the regions revealed here are associated with memory performance changes in aging, one hypothesis that emerges from this is that 5-HTTLPR status may be associated with individual differences in memory and memory monitoring performance in elderly individuals.

1.4 Present Study

In the current study, we examine the influence of the 5-HTTLPR genotype on source memory and source memory monitoring in older adults by taking advantage of a well established paradigm that demonstrates dissociations between memory types (item and source recognition) as well as between source memory accuracy and source memory monitoring (Dodson, Bawa, & Krueger, 2007a). It is expected that older adults will show decreased performance for source memory and source memory monitoring, when compared with younger adults. Most importantly, we expect that individual differences in performance will be moderated by 5-HTTLPR allele status, with the lowest performance expected from short 5-HTTLPR allele carriers.

While this paradigm has not yet been examined using functional neuroimaging, it is expected that source memory and source memory monitoring will rely heavily on prefrontal regions that aid in the inhibition and selection of information. There are two potential patterns of brain activation that we might expect to see as a result of 5-HTTLPR allele status. Older adult short allele carriers (S-car) may show decreased activation in key PFC regions compared to their long allele homozygote (LL) counterparts and young adults.

Alternatively, it is possible that the LL group may engage compensatory mechanisms that bring online greater PFC activation (either unilaterally, bilaterally or both) when compared to short allele carriers and younger adults. Most importantly, this greater engagement of critical PFC regions will be accompanied by enhanced source memory and source memory monitoring performance.

2. Methods

2.1 Participants

Seventeen younger adults from the University of Texas at Austin community (YA; 5 male, mean age = 23.3 ± 3.4 years, age range = 19–30 years) and twenty-three older adults (OA; 12 male, mean age = 66.8 ± 6.3 years, age range = 60–81 years) were included in the final analyses. Participants were recruited from the greater Austin community, were all right-handed, healthy individuals and were paid $25 per hour for participating in the imaging session. All participants were free from psychological and neurological illness, none were taking medications with known central nervous system effects, and all were screened for contraindications to MRI. Each subject provided written informed consent approved by the Institutional Review Board at the University of Texas at Austin. Individuals enrolled in the older group underwent a comprehensive neuropsychological battery during an initial visit, separate from the imaging session. All older adults included in the study were consistently within 1 SD of normal performance across each neuropsychological domain. In each group, three subjects were excluded from the final analysis: one subject in each group for extreme head motion during scanning, and two others for failure to respond during a significant portion of the source memory task.

While DNA samples from the younger adults were unavailable, the older participants were characterized by the number of short 5-HTTLPR alleles present: 0, 1, or 2. Of the 22 older adults successfully genotyped, 6 were long allele homozygotes (L/L), 15 were heterozygotes (L/S) and 1 was a short allele homozygote (S/S). These groups were further collapsed into two based on whether they were short-allele carriers (S-car; n = 16, 9 male, mean age = 67.1 ± 6.5 years, age range = 60–79 years) or long-allele homozygotes (LL; n=6, 3 male, mean age = 66.5 ± 6.7 years, age range = 61–81 years). There were no significant group differences between the S-car and LL groups on age, education, verbal IQ or gender (all $p > 0.50$).

2.2 Genotyping

Saliva samples were collected from all of the older adults, however one sample did not produce reliable information. DNA collection was initiated after the YA group was run through the task, and thus genetic information was not available for this group. Genomic DNA was isolated from buccal cells using a modification of published methods (Freeman et al., 1997; Lench, Stanier, & Williamson, 1988; Meulenbelt, Droog, Trommelen, Boomsma, & Slagboom, 1995; Spitz et al., 1996). The cheeks and gums were rubbed for 20 seconds with three sterile, cotton-tipped wooden swabs. The swabs were placed in a 50-ml capped polypropylene tube containing lysis buffer (500 μl of 1 M Tris-HCl; 200 mM disodium ethylene diaminetetracetic acid (EDTA), pH 8.0; 500 μl of 10% sodium docecyl sulfate; and 100 μl of 5 M sodium chloride). The subjects then rinsed out the mouth vigorously with 10 ml of bottled water for 20 seconds, and added this to the 50-ml tube. The tubes were stored at 4°C or less until the DNA was extracted. Polymerase chain reaction (PCR) was used for DNA amplification using established primers (Pacheco et al., 2009) and the resulting fragments were used to identify the presence of a long or short allele of the 5-HTTLPR gene.

2.3 Image acquisition

All scanning was performed at The University of Texas at Austin Imaging Research Center using a whole body 3T GE MRI scanner with an 8-channel phase array head coil. Head motion was minimized with foam inserts and a forehead strap. Stimuli were viewed utilizing a back projection screen and a mirror mounted on the top of the head coil. MRI compatible audio headphones were used for presentation of auditory stimuli, and prior to the scan all subjects confirmed adequate hearing to a test recording. Additionally, MR safe glasses were provided as needed to correct vision to normal levels. Responses were collected with a single 4-button MR compatible optical transmission device, held in the participants' right hand.

2.2.1 Functional image acquisition—Functional EPI images using a parallel imaging approach with GRAPPA reconstruction were collected utilizing whole head coverage with slice orientation to reduce artifact (approx. 20 degrees off the AC-PC plane, TR = 2 sec., TE = 30 msec., 31 axial slices oriented for best whole head coverage, acquisition voxel size = 3.125 × 3.125 × 3 mm with a 0.3 mm inter-slice gap). The first four EPI volumes were discarded to allow scans to reach equilibrium.

2.2.2 Structural image acquisition—At least one high-resolution T1-weighted SPGR structural image data set (TR = 9.7, TE = 4, flip angle = 10 degrees, slice thickness = 1.4 mm, 134 slices, FOV = 25cm and matrix size = 256×256 mm) was collected on each participant for the anatomical coregistration with functional imaging datasets. The SPGR scans have been empirically optimized for high contrast between gray matter (GM) and white matter (WM), and GM and cerebrospinal fluid (CSF). For some subjects two SPGR scans were collected, and in these cases the two T1 scans were motion corrected and averaged to create a single high signal, high contrast volume.

2.4 Source Memory task

A two-part memory task was used to assess memory monitoring for both item and source recognition (see Figure 1 for a schematic, based on a task by Dodson, Bawa, & Krueger, 2007a). Part one was a study phase that was performed while the subject was in the scanner. Images were not collected during study in order to minimize the interference of scanner noise with the auditory presentation of task stimuli. Each individual study phase consisted of a series of 24 sentences displayed visually in the center of the screen, progressing in a self-paced manner. Simultaneously, the sentence was presented aurally through headphones, read aloud by either a male (Dan) or female (Kim) speaker, with a photograph of the speaker and their name presented above each sentence. The two speakers, Dan and Kim, alternated randomly and were presented an equal number of times. Subjects were asked to provide a plausibility judgment during this phase, as proof that the sentences were being read and encoded. The sentences, which were all true, were selected from the trivia book *Salted Peanuts* (McKenzie, 1976). They were chosen pseudorandomly to be topically unique and are similar to the following example:

> Eighty four percent of a raw apple is water.

A test phase immediately followed the study phase and incorporated twenty of the original sentences seen at study, excluding the first and last two sentences to account for primacy and recency effects. Additionally, 10 sentences that were not seen previously were intermixed as recognition foils. The test phase was also self-paced, with a time limit of 10 seconds. During this phase, participants read a sentence on the screen and were asked whether this sentence was presented during the study phase ("old") or if it was a new sentence ("new"). Participants responded with one of four choices in order to indicate their old/new decision and an associated confidence level: *Certainly Old, Probably Old, Probably*

New, and *Certainly New*. Subjects were trained prior to the task to use *Certainly* only when the answer came to mind easily, and *Probably* on items of which they were less confident. Once the item recognition question was answered, the same sentence appeared again with prompts asking which speaker had delivered the sentence. Again, there were four answer choices that reflected the participant's response and associated confidence level: *Certainly Dan, Probably Dan, Probably Kim,* and *Certainly Kim*. A black visual fixation cross was presented between every trial (item and source recognition of one sentence, as well as source recognition and item recognition of the next sentence), jittered randomly for 3, 5, or 7 seconds. Also intermixed randomly throughout the entire run were 10 control conditions that consisted of a string of x's where one x appeared in red and the participants were instructed to indicate if the red x was on the *left* or *right* of the screen. This control involves a visual search through a string of text and a response, but lacks any verbal, memory or memory monitoring component.

A total of four study/test runs were administered per subject, however some runs were excluded for reasons of excessive head motion or less than acceptable response levels during the run. In the younger group, there were 10 subjects with a complete set of four runs, 5 subjects with three useable runs, and 2 subjects with only two usable runs. For the older group, there were 16 subjects with a complete set of four runs, 6 subjects with three useable runs, and 1 subject with two useable runs.

2.5 Behavioral analysis

Responses from the source memory task were used to calculate a score of recognition success (correct new/old distinction, correct source identification) as well as monitoring accuracy (correct determination of retrieval success). For each subject, all runs of the task were combined for analysis of behavioral responses. Each item recognition response was classified as either a true hit, true miss, false alarm or correct rejection, and a corrected memory accuracy score was calculated as: (True Hit – False Alarm) / Total Items. Each source recognition response was classified as either correct or incorrect, and source memory accuracy was calculated for each subject as the proportion of items correctly recognized as old and attributed to the correct source.

To characterize memory monitoring accuracy, we used the percentage correct for all responses given a *Certainly* distinction. This reflects items where subjects had both good memory performance and good monitoring performance. Because subjects were not allowed to skip a response, the lower-confidence answers likely contain a fair amount of guessing. In contrast, the higher-confidence responses should reflect only those responses that participants were fully confident in. For any individual subject, if they are accurately monitoring their memory performance, the percentage correct for the higher-confidence responses should be elevated. Finally, previous studies have shown that a higher proportion of monitoring errors in aging are high confidence errors (Dodson, Bawa, & Krueger, 2007a) and therefore this rating is likely to best reflect differences in monitoring abilities.

2.6 fMRI data analysis

Functional data analysis was accomplished using tools available through the software package FSL v 4.1 (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl/). Images were first motion corrected and then a high pass filter of 60 seconds was used to remove low frequency drift components. Data were resampled and spatially smoothed with a 5mm full width half maximum Gaussian kernel and rescaled to a mean signal value of 100. Finally, mean functional images for each subject were spatially normalized to fit the MNI (Montreal Neurological Institute) standard brain template in order to obtain conversion matrices to apply for higher-level statistical analysis. Responses were collapsed across confidence level

and categorized based on their monitoring accuracy. For example, the "Accurate Source" condition contains responses to the source memory question that were rated as high confidence and answered correctly, as well as responses that were rated with low-confidence and answered incorrectly. Also modeled were the fixation periods (FIX), the visual-motor control (CONT) task conditions and finally, the remaining confidence responses and the motion parameters as nuisance variables.

Individual events were modeled as a canonical hemodynamic response and its first-order temporal derivative. The resulting least squares parameter estimates, reflecting mainly the height of the modeled hemodynamic response for each condition, were then contrasted for each subject. Contrasts from individual subject runs were then combined into a second level analysis for each subject using a fixed effects model. Finally, spatially normalized contrast maps were combined and tested at the third level to examine group effects. All higher-level analysis utilized the FLAME (FMRIB's Local Analysis of Mixed Effects) approach in FSL with cluster corrections for multiple comparisons. The more general omnibus contrasts (e.g., Source Memory versus CONT) were corrected for multiple comparisons using a clustering approach where clusters were determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$ (Worsley, 2001). A small volume correction was used for specific contrasts examining the effects of genotype, where the data were masked with the clustered map from the omnibus contrast before thresholding to $p < 0.05$. To avoid circularity, the cluster-corrected map of the younger adults (shown in Figure 3, summarized in Table 2) was used in subsequent analyses as a small-volume correction mask to correct for multiple comparisons in contrasts using only the older adults. Similarly the cluster-corrected map of the older adults was used as a small volume correction for contrasts involving only the younger adults (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009).

2.7 Functional region of interest analysis

Five functional regions of interest (ROIs) were generated from the activation map of accurate monitoring (Figure 5, peak voxels described in Table 3) by masking this activation with binarized anatomical ROIs, using the Harvard-Oxford cortical atlas found in FSL. Percent signal change values were extracted from each ROI for the contrast of accurate monitoring compared to the visual search control task using a baseline-to-max scale factor (as described in http://mumford.fmripower.org/perchange_guide.pdf). Using the percent signal change values from the ROIs, the signals for each of the three groups (YA, LL, and S-car) were compared directly using one-way ANOVA models. The functional activation map primarily reflected activation in the left hemisphere, however, in order to examine the response in homologous region, the ROIs showing a significant group difference were reversed to the right hemisphere.

3. Results

3.1 Behavioral results

3.1.1 Younger adults versus older adults—The behavioral results for all runs were combined into a mean value for each subject, and analyses were done to examine memory performance for item memory and source memory. Across the entire group, previous patterns of behavioral results were replicated for memory performance (Chua et al., 2009; Dodson & Krueger, 2006; Dodson, Bawa, & Krueger, 2007a; Dodson, Bawa, & Slotnick, 2007b; Kelley & Sahakyan, 2003; Norman & Schacter, 1997), and are summarized in Figure 2. A repeated measures ANOVA (see Table 1 for ANOVA results) was used to explore performance for memory type (item or source) between the two groups (YA and OA). This revealed a significant main effect of memory type ($F(1,37)=247.54$, $p<0.001$) as well as a significant interaction between memory type and group ($F(2,37)=13.01$, $p<0.001$). There

were no deficits for OA during sentence recognition, but they performed significantly worse on the source memory question; two-tailed, two-sample t-tests showed significant overall reduction in source memory performance for OA as compared to their younger counterparts (OA=64.9%, YA=75.5%, p=0.004, Figure 2a). A similar analysis was done for memory monitoring accuracy, which revealed a significant main effect of monitoring type ($F(1,37)=63.70$, $p<0.001$) as well as a significant interaction between monitoring type and group ($F(2,37)=7.76$, $p<0.01$). Confirmed by subsequent t-tests, OA showed a significant decline in source memory monitoring when compared to the YA (OA=73.7% YA=84.7% p=0.017, Figure 2b, Table 1). In summary, while OA showed equivalent recognition memory and recognition memory monitoring performance as YA, they were significantly impaired in their source recognition and source monitoring abilities

3.1.2 Older adult 5-HTTLPR short-allele carriers versus long-allele homozygotes—Age-effects were explored within the OA group alone. Age was not found to correlate significantly with older adult performance on this task (all $r(23)$ between −0.13 and 0). In order to assess the effect of having one or more copies of the short 5-HTTLPR allele on memory performance, the older adult group was divided into those who carried the 5-HTTLPR short allele (S-car) and those who did not (LL). A repeated measures ANOVA with memory type as a within subjects factor and genotype as a between subjects factor (summarized in Table 1) was used to explore performance for memory type (item or source) between the two groups (LL and S-car). This revealed a significant main effect of memory type ($F(1,22)=202.7$, $p<0.001$), however there was no significant interaction between memory type and genotype group (shown in barplots in Figure 2a).

The same analysis was done for memory monitoring accuracy using accuracy on high confidence judgments, which revealed a significant interaction between genotype group (LL and S-car) and monitoring type (item, source) ($F(2,20)=12.38$, $p=0.002$, Figure 2b). Subsequent t-tests indicated that having a short allele resulted in greater impairment for source monitoring (LL: 89.1%; S-car: 66.2%, $p < 0.001$) with no differences in recognition monitoring. Given the higher level of performance in the older adult LL group, they were compared directly to the YA, revealing no significant differences in source memory performance (YA: 74.7% LL: 72.9%, $p = 0.38$) or source monitoring (YA: 84.7% LL: 87.3%, $p = 0.44$) of these two groups; older adult LL homozygotes have behavior rates equivalent to the YA. In contrast, there were significant differences between the YA and S-car group for both source memory (YA: 74.7% S-car: 60.3%, $p < 0.001$) and source monitoring (YA: 84.7% S-car: 66.2%, $p < 0.001$; shown in, Figure 2b).

To ensure specificity of these genetic effects, confirmatory post-hoc analyses were done using two other commonly assessed genotypes, COMT and BDNF. Subjects were split into two groups, for each gene, based on their genetic status; Val-carriers (n = 16) were compared to Met homozygotes (n = 6) for COMT, and Met-carriers (n = 9) were compared to Val homozygotes (n = 13) for BDNF. Using the same repeated measures ANOVA models for memory and monitoring, we found the same main effect of memory or monitoring type, as reported above, and no further interaction with either COMT or BDNF (Memory × Gene: $F(2,20) = 1.24$, $p = 0.28$; $F(2,20) = 0.011$, $p = 0.75$ Monitoring × Gene: $F(2,20) = 1.52$, $p = 0.23$; $F(2,20) = 0.45$, $p = 0.51$ for COMT and BDNF respectively). These results indicated that neither memory nor monitoring performance within the OA were accounted for by either COMT or BDNF genetic status.

3.2 Imaging results

3.2.1 Source memory network—Whole brain fMRI were collected during the test phase of the memory task in order to explore the regions that are involved in memory monitoring.

Initially, a test of source memory versus the visual search control task was performed to reveal the functional neural network involved in source memory. These maps were generated both for all subjects combined (YA and OA) and separately for each younger and older adult group. This initial contrast revealed a network of regions previously shown to be involved in source memory processes - areas of the lateral and medial PFC (Shimamura, 1994; Stuss, 1984), MTL (Cohen & Eichenbaum, 1993; Squire, 1992), and parietal cortex (Buckner & Wheeler, 2001; Rugg, Otten, & Henson, 2002; Wagner, Shannon, Kahn, & Buckner, 2005).

3.2.2 Accurate memory monitoring—In order to examine the regions involved in memory monitoring and their differences between groups, an analysis contrasting accurate memory monitoring responses to the control task was performed. Initial comparisons between the YA and OA groups revealed no regions of significant difference. When each group was analyzed separately, significant activation was observed in regions of the left lateral IFG (BA 44 and 45), the left dorsolateral PFC (BA 9), and the paracingulate gyrus. Additionally, examining these maps indicated a great degree of overlap between the YA and OA groups (shown in Figure 4).

Since behavioral analyses revealed important differences associated with genotype, namely the older adult S-car performed worse than the LL group, an analysis was conducted within the older group, contrasting LL and S-car for accurate memory monitoring responses relative to the control condition. The resulting network included regions of the left inferior frontal gyrus, middle frontal gyrus and anterior paracingulate cortex (shown in Figure 5, summarized in Table 3). This network appeared similar to regions revealed in the YA group (Figure 6), suggesting that both YA and LL groups were recruiting the lateral PFC and paracingulate more than the S-car older adults are when making accurate monitoring judgments. This observation was tested statistically using functionally defined regions of interest.

For the reverse contrast, we found no significant regions where S-car showed greater activation than the LL group. Further comparisons were made between the YA group and the S-car group, and showed greater activation for the YA in smaller regions of the lateral IFG (MNI coordinates: 69 71 37).

3.2.3 ROI analysis—Five ROIs were constructed from the map of accurate memory monitoring (shown in Figure 5) and the percent signal change was extracted from the contrast of accurate monitoring compared to the control task for each group (YA, LL and S-car). One-way ANOVAs were used, comparing the signal change for each group within each ROI, and indicated that there were significant differences in the operculum (BA 44) and the pars triangularis (BA 45). The ROIs for these two regions were then reversed to the right hemisphere, and percent signal change was extracted in the same manner. Subsequent independent t-tests (Figure 7) comparing the two older adult genotype groups revealed a greater percent signal change in both the left and right operculum for LL as compared to the S-car (left: $t(21)=2.195, p=0.040$; right: $t(21)=2.076, p=0.050$) and YA (left: $t(21)=2.335, p=0.030$; right: $t(21)=2.097, p=0.048$).

Examining the differences between the older adult groups and the younger group directly, the LL group showed significantly greater percent signal change when compared to the YA group in the left pars triangularis ($t(21)=2.487, p=0.021$), but there were no significant differences seen in the right triangularis, or with the S-car group. No other regions showed significant older and younger group differences. Bar graphs showing the pattern of these effects (Figure 7) show a consistently greater signal change in the older adult LL group when looking within these bilateral regions of the IFG during accurate memory monitoring.

While the older adult LL group did not differ in their behavioral performance from the YA, they appear to have activated a critical region of the PFC to a greater extent than either the young or older S-car groups.

One critical question is whether activation in these ROIs is associated directly with source monitoring. To explore this hypothesis, activity was correlated with task performance, using the measure of source memory accuracy. For the entire older adult group (both LL and S-car combined), significant correlations were seen in the right operculum ($r(19)=0.438, p=0.047$) and bilaterally in the triangularis (left: $r(19)=0.572, p=0.007$; right: $r(19)=0.483, p=0.027$). Within the YA, no significant correlations were seen between PFC activation and source memory monitoring accuracy. These findings suggest that there is a relationship between amount of prefrontal activity and source monitoring accuracy for older adults.

In summary, older adults were, as a whole, impaired in source memory and source monitoring performance. However, there was a significant divide within the older adults, and when separated by 5-HTTLPR status, the LL group resembled the YA in performance. The LL group displayed differential neural function, compared to both the younger and S-car groups, showing greater PFC activation associated with accurate source memory monitoring.

4. Discussion

This study had two main goals. First, we wanted to investigate whether the genotype of the 5-HTTLPR polymorphism could account for individual differences in older adults' source memory and source memory monitoring performance. Second, we wished to examine whether individual differences in performance were associated with corresponding differences in brain activation. Using a task previously employed in behavioral examinations of memory monitoring in aging (Dodson, Bawa, & Krueger, 2007a), we replicated the overall expected behavioral results with older adults performing worse relative to YA at source memory and source monitoring, but with no deficit for item memory or monitoring. However, by splitting the older subjects into groups based on their genotype for the serotonin transporter polymorphism (5HTTLPR), we uncovered important differences in performance that correspond to specific genotypes. Older adults who carry at least one copy of the short 5-HTTLPR allele performed worse than older adults who are homozygous for the long allele. Perhaps more interestingly, the older adult LL homozygotes perform at behavioral levels no different from that of younger adults.

Given the level of behavioral performance, we examined the functional neural network associated with this task in order to determine if there were corresponding changes in this network associated with age or genotype status. Results of the fMRI analysis revealed portions of the PFC, including the lateral and inferior regions, which play an important role during accurate source memory monitoring on this task. Further, subdividing the older adults into the two genotype groups revealed that these regions of the PFC were activated to a greater extent by LL older adult than for either older adult S-car or young adults. Taken together, the behavioral and functional results point to an interesting relationship between the 5-HTTLPR genotype and age-related deficits in source memory monitoring. Older adults homozygous for the long 5-HTTLPR allele performed behaviorally like younger adults and showed higher levels of activation in PFC regions associated with accurate monitoring.

4.1 5-HTTLPR effects on source memory monitoring performance

These results suggest an important association between the 5-HTTLPR gene and memory performance in elderly adults. Prior work has uncovered associations between 5-HTT genetics and cognitive processing, though many reports have failed to find any significant

relationships between 5-HTTLPR genotype and performance on tests of attention or working memory (Canli et al., 2005; Hariri, 2002). More recently, a few studies have uncovered associations between the 5-HTTLPR genotype and long delayed memory recall (O'Hara et al., 2007), as well as complex memory recall (Marini et al., 2011). Marini *et al.*, (2011) compared performance of older adult (mean age = 64.5 ± 8.2 years) S-carriers and LL homozygotes on a variety of neuropsychological and personality tests. The S-carriers showed significantly lower performance on the Rey-Osterrieth complex figure, a test of visuo-spatial long-term memory. A similar study by O'Hara *et al.*, (2007) demonstrated that S-carriers showed decreased performance on the delayed recall portion of the Rey Auditory Verbal Learning Task in a sample of older adults (mean age = 71.1 ± 8.8 years). Taken together, these two studies implicate the S allele in poorer performance for complex aspects of memory, both visual and verbal.

Both of these studies, however, used samples consisting of only older adults and did not compare the performance of either genotype group to younger individuals. In the current work, we compared both groups of older adults (short-allele carriers and long-allele homozygotes) to a group of younger adults. These comparisons revealed important additional information, namely, no significant differences between younger adults and the older adult long-allele homozygotes. Given that there were no differences between the LL group and the S-car group in age, gender, IQ or education, and that all of our subjects were cognitively normal, this result has some striking implications for older adults. Instead of the short-allele carriers being more susceptible to cognitive decline, the homozygous long-allele genetic profile may help older adults delay the normally observed age-related decline. A larger, longitudinal study of aging would be needed to resolve this hypothesis.

4.2 Neuroanatomical underpinnings of accurate source memory monitoring in older adults

Results from our functional task have highlighted regions of the prefrontal cortex, particularly the inferior frontal gyrus, as important for maintaining high behavioral performance. These regions were known to play critical roles in inhibitory control including inhibition of irrelevant details (Aron, Robbins, & Poldrack, 2004; Nee, Wager, & Jonides, 2007), cue specification (Buckner, 2003; Dobbins & Han, 2006; Kirchhoff & Buckner, 2006) and making choices between competing options (Eakin & Hertzog, 2006; Hirshorn & Thompson-Schill, 2006). During memory retrieval, two distinct roles of the ventral lateral prefrontal cortex have been identified (Badre & Wagner, 2007); the anterior regions (pars orbitalis, BA47) subserve a more controlled retrieval of semantic information (Badre & Wagner, 2005; Poldrack et al., 1999; Wagner, Maril, Bjork, & Schacter, 2001b), whereas the posterior regions (pars triangularis, BA45) are responsible for selection of task relevant information (Buckner, 2003; Thompson-Schill, Bedny, & Goldberg, 2005). In the latter, participants rely on post-retrieval monitoring to resolve conflicts that arise from multiple retrieval products. For our task, engagement of this selection process is beneficial to older adults when excessive irrelevant information is retrieved in error (Braver, Gray, & Burgess, 2007; Velanova, Lustig, Jacoby, & Buckner, 2006). The inhibitory and selection functions associated with these regions would be critical to overcome misremembering during source memory monitoring, and those older adults who are able to more accurately assess their retrieval products are likely able to make accurate judgments about their memory responses.

Wais *et al.*, (Wais, Kim, & Gazzaley, 2011) explored the role of the ventrolateral prefrontal cortex, specifically the pars triangularis, during distracted episodic retrieval using repetitive transcranial magnetic stimulation. During episodic retrieval of complex visual stimuli participants were shown to be susceptible to external visual distraction as evidenced by performance decreases in the presence of irrelevant visual distractors. Subsequent to perturbation of the left ventrolateral prefrontal cortex, susceptibility to distraction by external cues increased. In the absence of external distractors, under an eyes closed

condition, perturbation by rTMS resulted in no change in episodic retrieval. Similar fMRI studies have shown a positive correlation between the activation of this region and proactive interference during short-term memory retrieval (Nee & Jonides, 2008). Taken together, these studies are consistent with a crucial role for the posterior ventrolateral PFC in monitoring and inhibition of competing retrieval cues required for successful memory monitoring.

In our study, a subset of older adults demonstrated equivalent task performance when compared to younger adults, along with increased functional activation of regions that are important for task performance. This suggests that these older adults are utilizing compensatory mechanisms. The scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009) suggests that as older adults face more challenges, primarily due to degradation of cortical regions and connections, they rely on secondary scaffolding structures. These “scaffolds” involve strengthened existing connections, newly generated connections, and retirement of faulty connections (Goh & Park, 2009; Park & Reuter-Lorenz, 2009). STAC implicates the PFC as a flexible structure in which scaffolding can occur, as opposed to more dedicated cortical structures. Physical evidence of scaffolding is seen in older adults as bilateral activation, increases in prefrontal activation, distributed processing, and neurogenesis (Park & Reuter-Lorenz, 2009). Numerous studies, using both PET and fMRI data, have suggested that older adults typically show more bilateral activation for tasks that are primarily unilateral in younger adults (Cabeza, 2002; Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz & Cappell, 2008). This over-activation and recruitment of homologous regions is often viewed as neural compensation, particularly when it is associated with preserved task performance, as it was with our sample of LL older adults.

Our work is also consistent with this view. Elderly adults who were LL-homozygous for the 5HTTLPR gene showed greater activity in these regions bilaterally, and this increased activation was directly associated with better performance on the task. So, while behavioral performance was equivalent to young adults, it is clear that this level of performance is achieved through the ability to engage regions of PFC to a greater extent than either the YA or the S-car. Finally, their ability to do this may be directly tied to genetic differences in the serotonin system.

4.3 Effects of 5-HTTLPR genotype on memory monitoring

While some research has begun to reveal important relationships between cognition, aging and the 5-HTTLPR gene using behavioral methods (O’Hara, 2007; Marini, 2011), none have used neuroimaging to better understand the neural basis of any demonstrated differences. One of the main goals of this study was to examine 5-HTTLPR effects on the functional regions critical for accurate memory monitoring. Our results indicated that those older adults who have an LL profile for the 5-HTTLPR genotype perform at levels equivalent to younger adults on source memory and source monitoring tasks, which are typically declined for older adults. These older adults recruited more prefrontal structures to facilitate their performance on the task.

The effects of serotonin levels on inhibitory control have been explored using acute tryptophan depletion (ATD), a noninvasive technique resulting in global depletion of brain serotonin (Young, Ervin, Pihl, & Finn, 1989). Behavioral studies have shown that ATD impairs inhibition and cognitive control across a variety of tasks in younger adults (Murphy, Smith, Cowen, Robbins, & Sahakian, 2002; Walderhaug et al., 2002) and older adults (Porter, Lunn, & O'Brien, 2003). More recently, the effects of ATD on brain function in older adults has been explored using fMRI and an inhibitory control task (Lamar et al., 2009). Compared to sham ATD, older adults show decreased activation in the ventrolateral

prefrontal regions associated with inhibitory control when their global serotonin levels are depleted. Conversely, fMRI studies using serotonin agonists report enhancing effects on prefrontal regions during inhibition (Evers et al., 2006; Rubia et al., 2005). These results suggest a strong influence on the amount of serotonin available throughout the brain and the degree of activation within the prefrontal cortex during tasks that require inhibitory control. These studies provide a direct linkage between the brain regions revealed in the current study, serotonin, and inhibitory control of cognitive processes. In light of our findings, we propose that the LL-homozygotes are more readily engaging inhibitory control over the memory retrieval products, as evidenced by better performance on a source memory task. In addition, greater activation in prefrontal regions previously associated with inhibitory control, and more recently shown to be influenced by serotonin level, is correlated with task performance.

4.4 Limitations

There are a number of important limitations to our current study, including the low number of LL homozygotes within our older adults group. Although we see some robust behavioral differences, there is room for more exploration with a larger sample. However, even with the small sample size in this study, we believe this result is novel and exciting, and introduces a role for the 5-HTTLPR genotype in mediating neural functioning on complex memory processes. Secondarily, the presented work is purely cross-sectional and, as such, it is hard to resolve whether the sample of LL older adults began with high cognitive performance or if, as proposed, they are not declining in a similar fashion as their S-car counterparts.

Genetic information was unavailable for the younger adult sample in the current study. A future study that includes genotypes from the younger group, as well as following the older group in a longitudinal fashion, would be beneficial in tracking the putative cognitive decline associated with 5-HTTLPR status. We would expect to see similar involvement of the 5-HTTLPR genotype in younger adults as our previous work has shown an association between 5-HTTLPR and changes in PFC/MTL pathways (Pacheco et al., 2009), as well as left inferior PFC differences related to cognitive control in younger adults (Beevers et al., 2010).

Lastly, there is the possibility of a third variable driving the genetic association, such as other genetic variants in linkage disequilibrium, population stratification, epigenetics, or unmeasured variables. However, if the association is driven by a third variable that covaries with 5-HTTLPR status, we would not expect that findings from the ATD studies (Lamar et al., 2009) to be complementary to ours. Additionally, there is at least one report (Langenecker et al., 2007) showing that activation during an inhibitory control task predicts success of Major Depressive Disorder treatment with a selective serotonin reuptake inhibitor. Our results, along with these two studies, converge on a relationship between cognition, functional activation and serotonergic modification.

4.5 Summary

In summary, this study provides preliminary evidence that the 5-HTTLPR genotype is associated with cognition in older adults. Specifically, the lack of a short allele may alter the trajectory of age-related decline for memory monitoring processes in older adults. Prior work has implicated a crucial role for the PFC in memory monitoring, and our current work agrees. Regions of the left IFG and lateral PFC were shown to be involved in accurate memory monitoring for the entire group of older adults in this study. These regions are crucial for resolving competition of memory representations post-retrieval, which is a necessary strategy for success on our task. Better engagement of these regions for the long-allele homozygous adults allows for more accurate assessment of their memory retrieval.

While the benefit of the long-allele homozygous genotype may not be limited to this process, this study indicates that there is a benefit for older adults who lack a short allele of the serotonin transporter gene during complex memory tasks.

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Highlights

- 5-HTTLPR genotype potentially beneficial to source memory monitoring in older adults.
- Older adults with L/L profile perform similarly to younger adults on task.
- Activation of key PFC regions is also related with increased task performance.
- The short allele is associated with lower performance and less PFC recruitment.

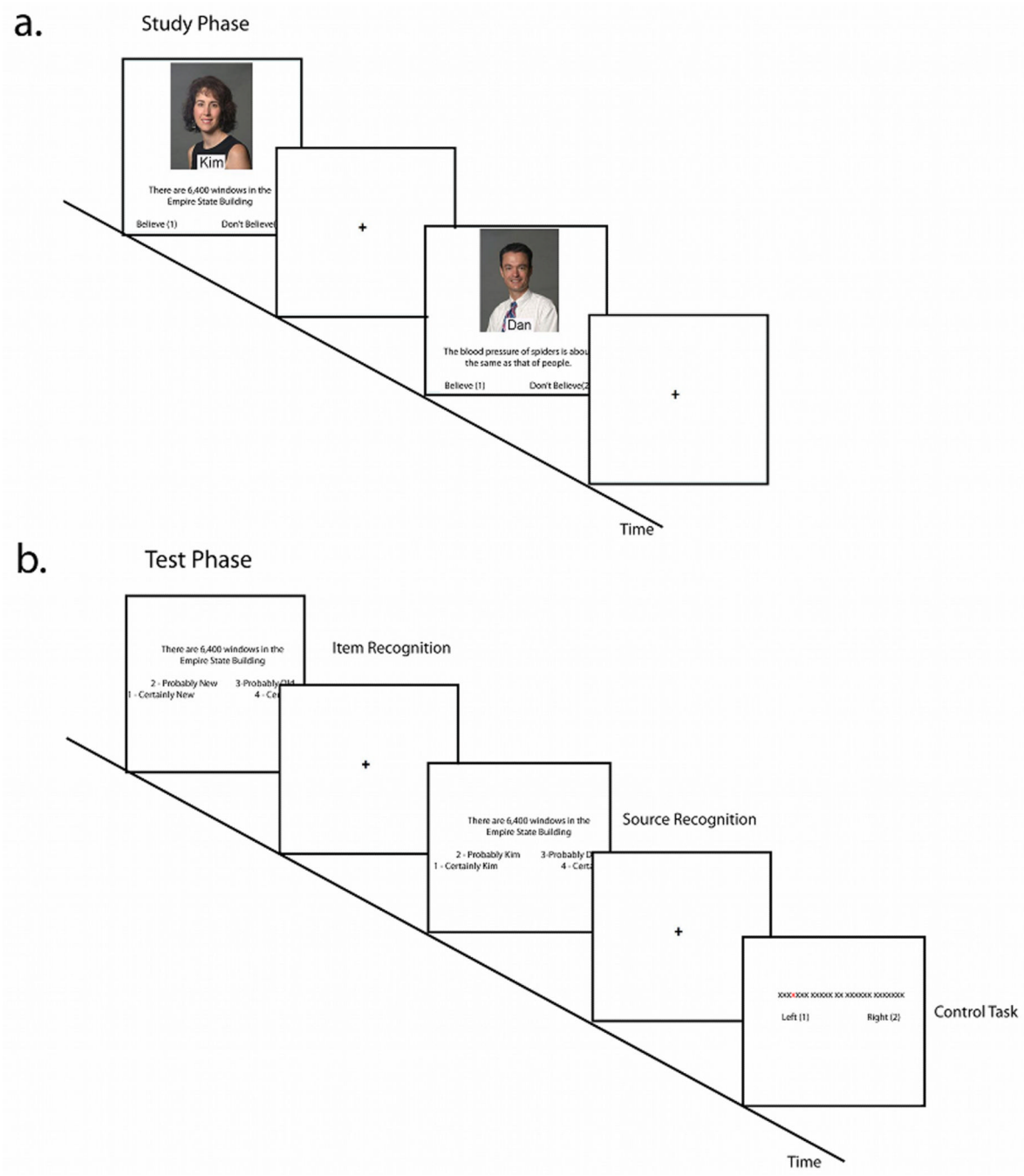

Figure 1. Schematic of the source memory task

Panel **a.** depicts the study phase, during which the scanner was not running. Subjects saw a total of 24 unique sentences per study run, each separated by a variable fixation cross (3, 5, or 7 seconds). Responses to this phase were only used to ensure encoding of the sentences. Panel **b**. depicts the test phase, when fMRI scans were collected. Subjects saw 20 of the previous sentences and 10 new sentences, presented in random order. Included in this phase were 10 control trials, distributed randomly, where the subjects were asked to indicate on which side (right or left) a red x appears.

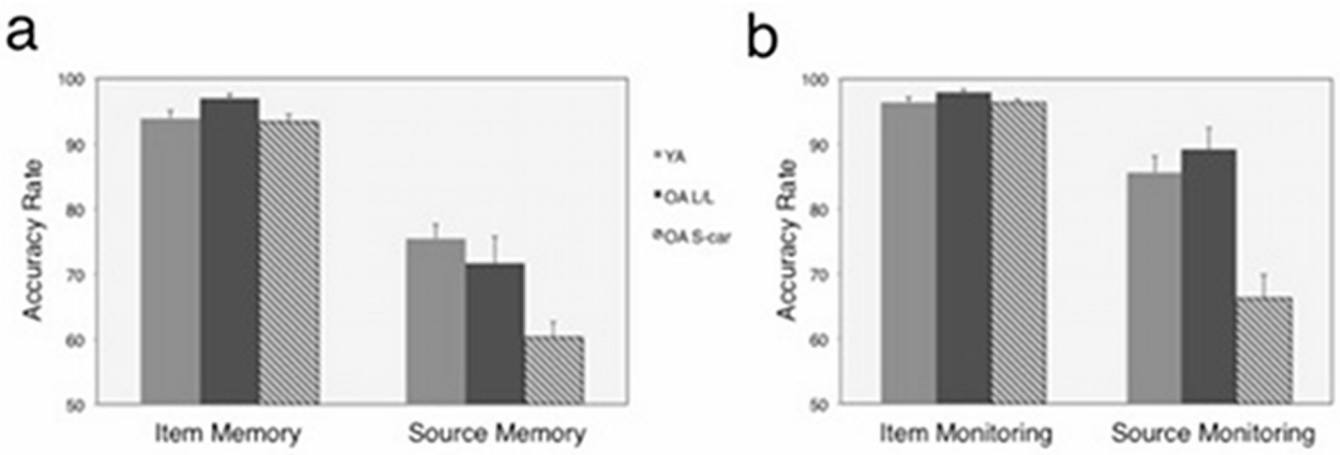

Figure 2. Accuracy rates for item and source memory and memory monitoring

Panel **a** shows accuracy rates for item and source memory – younger adults (YA; shown in light gray), older adult (OA) long allele homozygotes (LL; shown in dark gray), and older adult s-allele carriers (S-car; shown in stripes). Between the two OA groups, a significant interaction exists between memory and group, showing the OA S-car are significantly worse at source memory. Similarly, panel **b** shows the accuracy rates for item and source memory monitoring. Again, a significant interaction exists between memory and group. It should be noted that in panels **a** and **b** there is no significant differences between YA and OA L/L groups. Error bars represent the standard error.

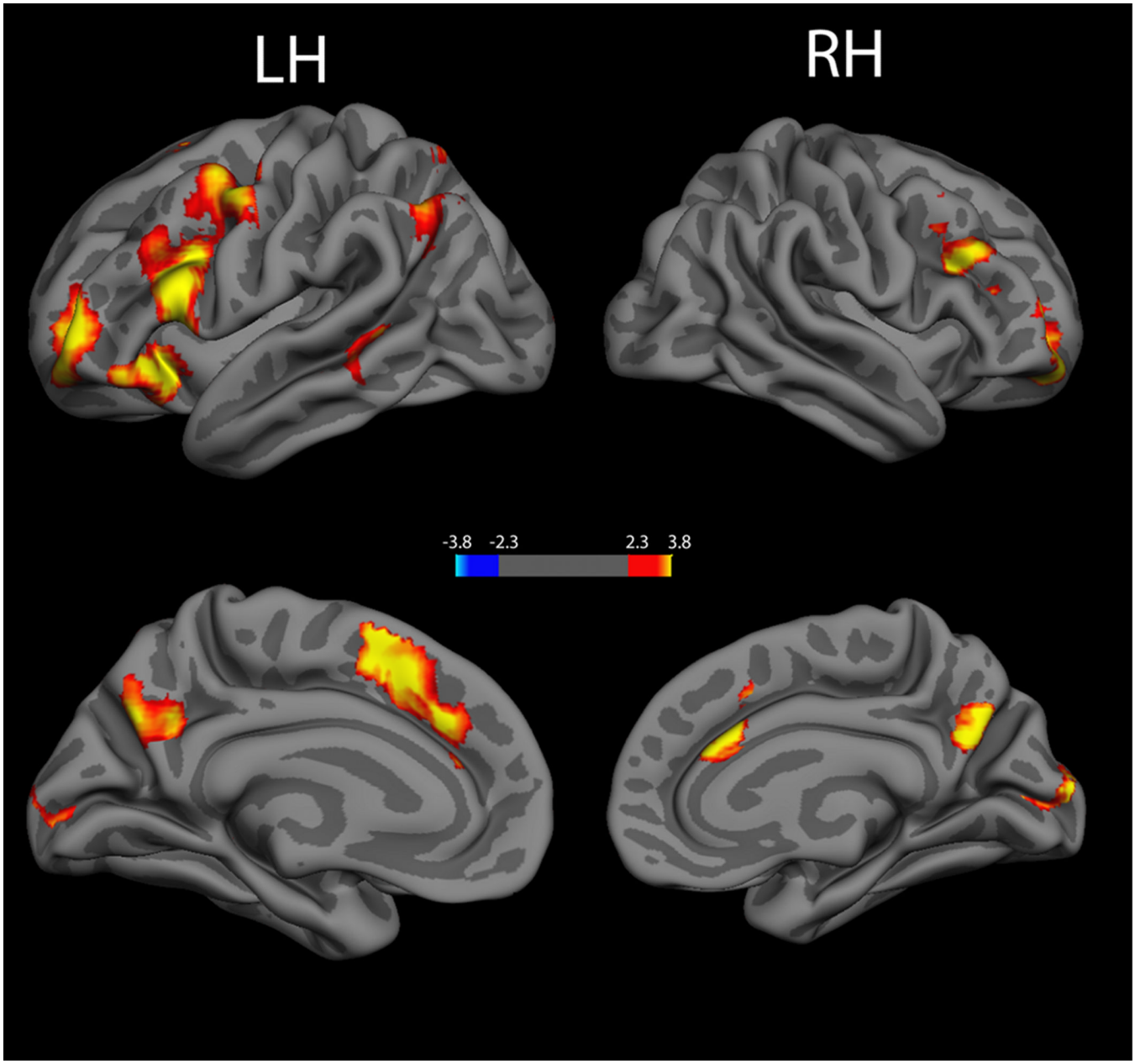

Figure 3. Source memory neural network for younger adults

Using an omnibus contrast to look at all the source memory questions (regardless of whether they were answered accurately or not) compared to the control task reveals a network of regions known to be involved in source memory. Regions include: medial and lateral portions of the PFC, and parietal lobe. Images are corrected for multiple comparison using a clustering approach where clusters were determined by $z > 2.3$ with a corrected cluster significance threshold of $p < 0.05$. This map of source memory was used in subsequent analyses, to constrain the statistical search.

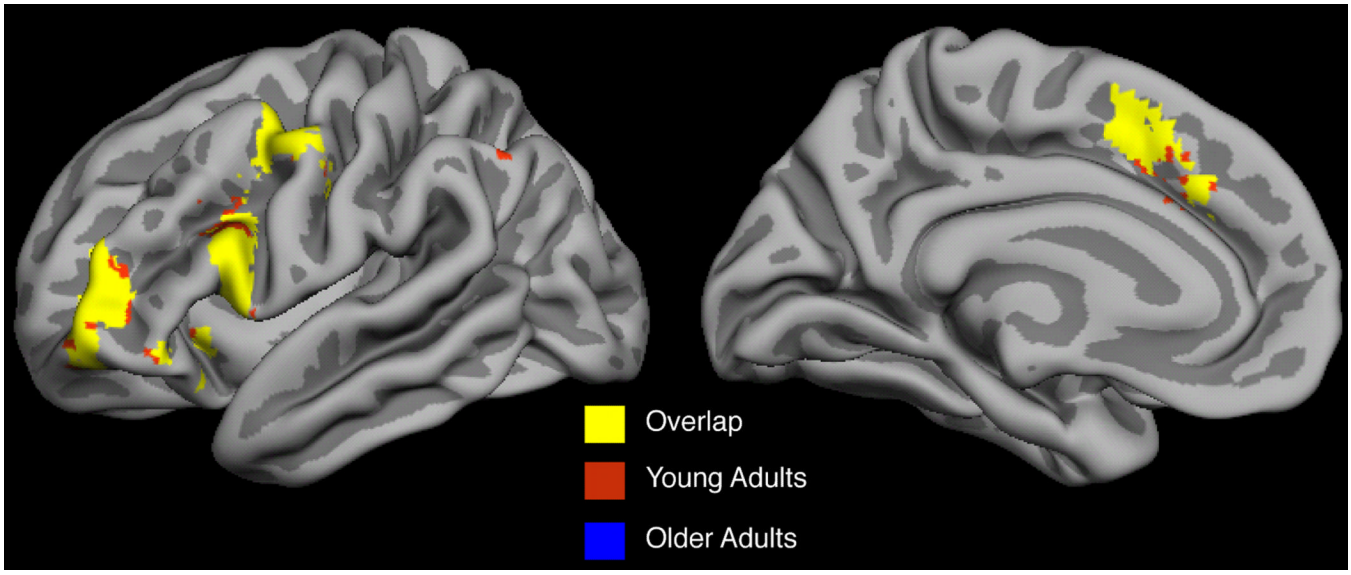

Figure 4. Overlap of accurate memory monitoring neural network in younger and older adults

A contrast of accurate memory monitoring responses verses the control task was run separately for younger and older adults; both revealed regions of significant activation in the inferior frontal gyrus, middle frontal gyrus, and anterior paracingulate cortex. There is a great deal of overlap, shown in yellow, between the younger and older adults and the map shows that the older adult (OA) activation is completely within the boundaries of the younger adult (YA) activation.

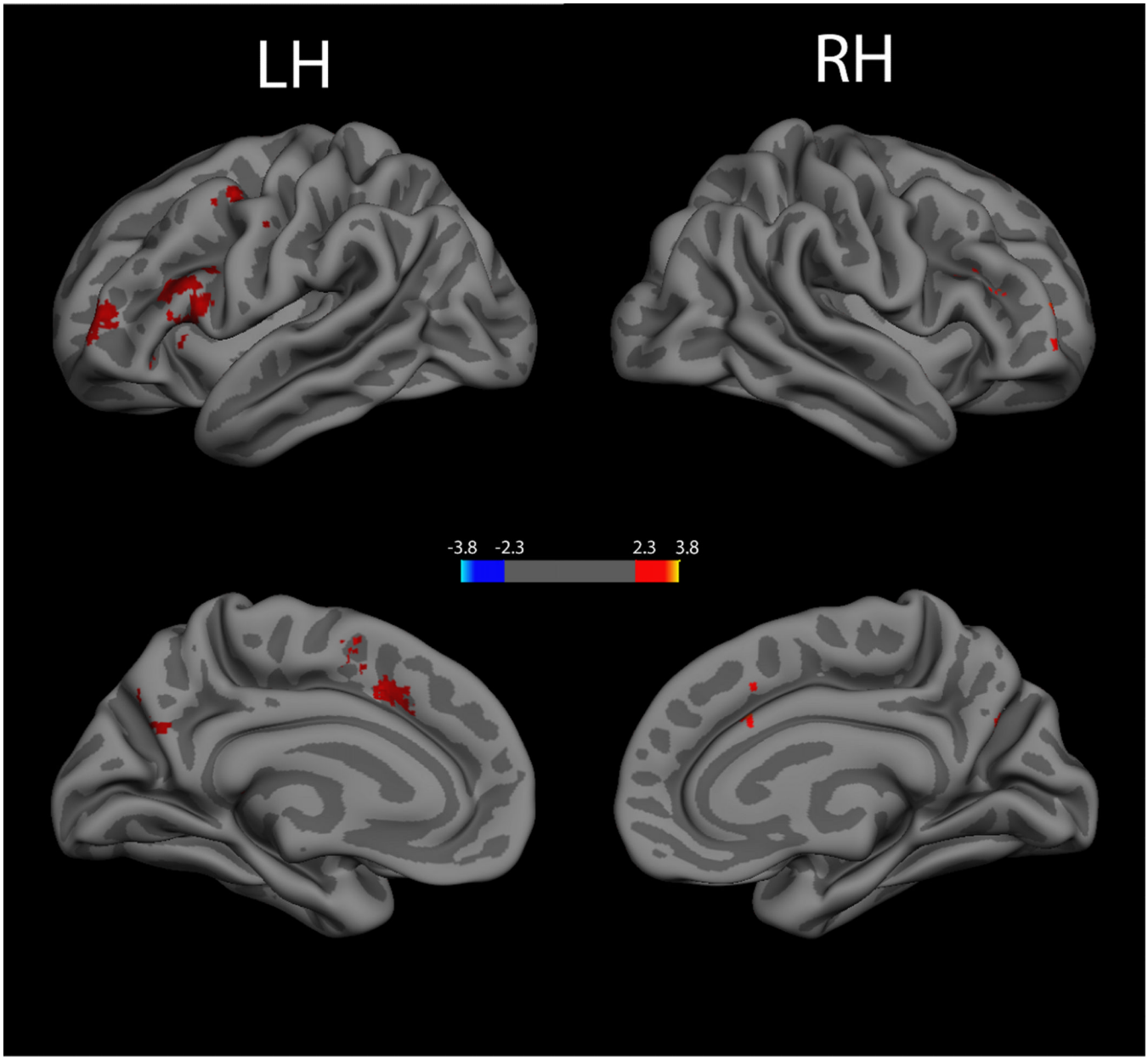

Figure 5. Cortical regions of significantly greater activation for LL compared to S-car during accurate memory monitoring

Allele differences in activation in the older group were analyzed within the source memory network (analysis was constrained with the source memory mask). The resulting contrast revealed regions of the left lateral IFG (BA 44 and 45), the left dorsolateral PFC (BA 9), and the paracingulate gyrus that show significantly more activation for the LL group during accurate monitoring responses than for the S-car group. It should be noted that accurate monitoring is irrespective of memory success; accurate monitoring includes both times when the subject felt highly confident and got the source correct as well as times when the subject felt less confident and got the source incorrect.

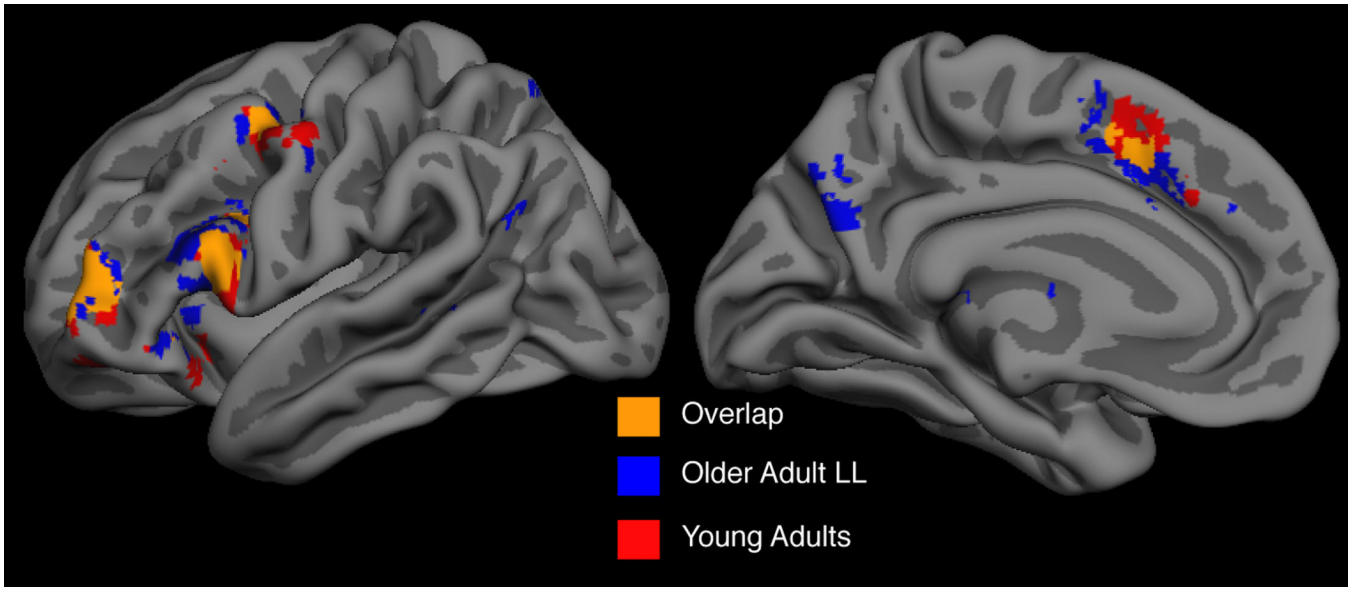

Figure 6. Neural regions of overlap between younger adults and older adult LL homozygotes during accurate memory monitoring

Whole brain analysis within the younger group (shown in red) was done to uncover regions of significant activation for accurate memory monitoring. The regions revealed a great deal of overlap (shown in yellow) with the regions revealed for analyses comparing long-allele homozygotes (LL) to short-allele carriers (S-car) for accurate monitoring responses (shown in blue).

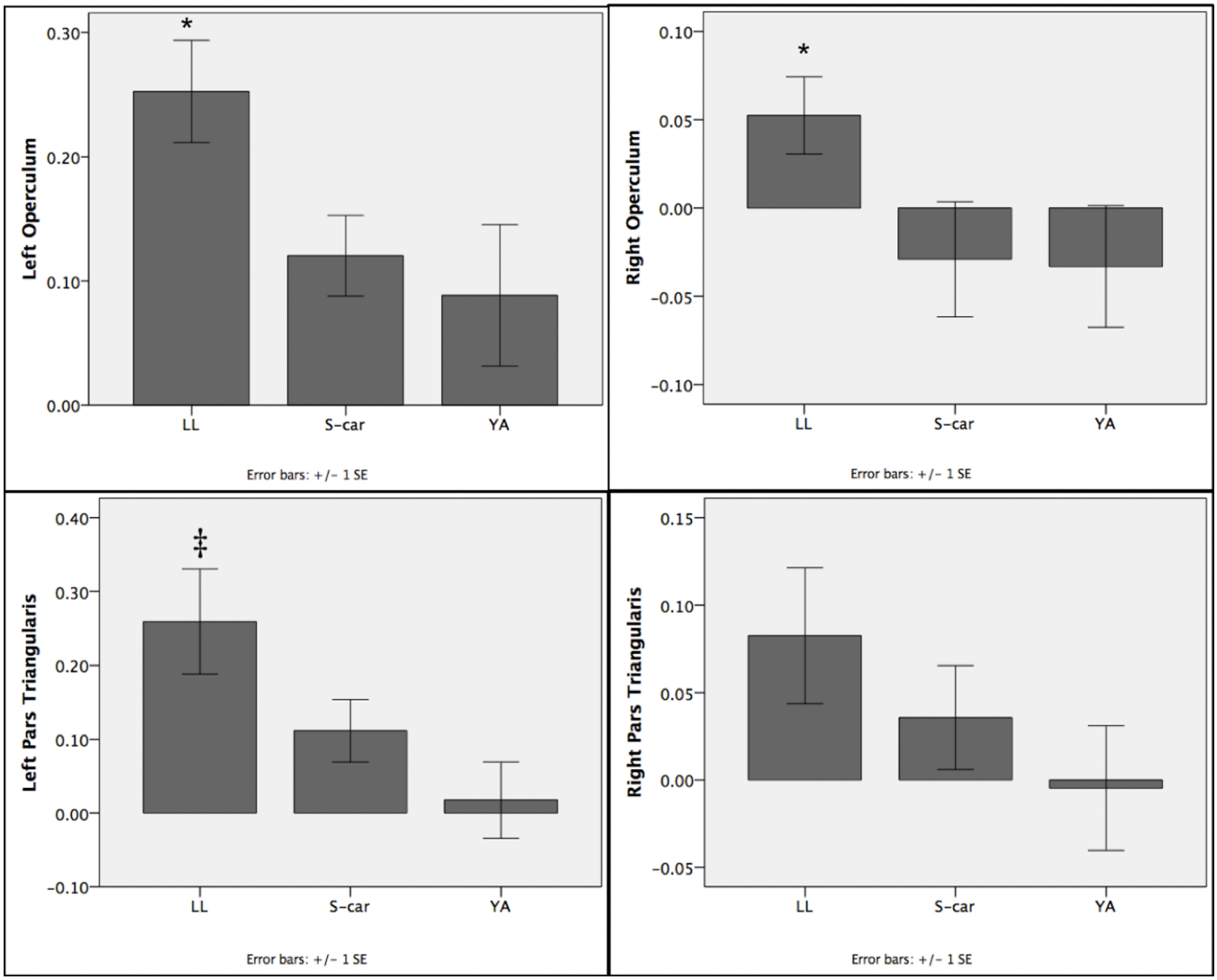

Figure 7. Neural responses in functionally defined PFC ROIs

Out of a total of 5 functionally defined bilateral ROIs that were examined, 2 regions of PFC showed differences in the level of activation during accurate memory monitoring as compared to the control task. Bar graphs show percent signal change for correct high confidence source monitoring judgments in all three groups for regions of the left and right inferior frontal gyrus and pars triangularis. Bilaterally for the inferior frontal gyrus, the LL group shows a significantly greater percent signal increases when compared to the S-car and YA groups ($p < 0.05$). In the left pars triangularis, the LL group has a significantly greater percent signal increase than the YA group ($p < 0.05$). The data are consistent with the view that the LL group may be recruiting homologous right hemisphere regions along with greater recruitment of the left hemisphere to aide in task success.

Table 1

Repeated Measures ANOVA results for OA vs. YA and LL vs. S-car

	OA vs. YA		LL vs. S-car	
	Mean Square	**F(37)**	**Mean Square**	**F(22)**
Memory Performance				
Memory Type	1.094	247.54 ǂ	0.903	202.795 ǂ
Memory Type × Group	0.058	13.01 ǂ	0.016	3.696
Monitoring Performance				
Memory Type	0.537	63.70 ǂ	0.344	50.30 ǂ
Memory Type × Group	0.065	7.76 *	0.085	12.38 **

* $p<0.01$;

** $p<0.005$;

ǂ $p<0.001$

Table 2

Clusters of YA Source Memory Network

Brain Regions	Hemisphere	Voxels	Max Z-stat	x	y	z
Frontal Pole	L	536	5.27	−32	58	12
Paracingulate/Superior Frontal Gyrus	midline	463	4.8	−6	14	50
Inferior Frontal Gyrus - operculum/triangularis	L	162	4.15	−48	18	14
Frontal Orbital Cortex/Insula	L	117	4.07	−36	24	−6
Lateral Occipital Cortex/Angular Gyrus	L	40	4.2	−30	−66	56
Middle Frontal Gyrus/Precentral Gyrus	L	25	3.65	−48	−4	46

Voxels: number of activated voxels per cluster; Max Z-stat: maximum z statistic for each cluster; x, y, z are MNI coordinates for the peak of each cluster

Table 3

Clusters of LL verses S-car for Accurate Memory Monitoring

Brain Regions	Hemisphere	Voxels	Max Z-stat	x	y	z
Paracingulate/Superior Frontal Gyrus	midline	278	3.04	47	75	55
Inferior Frontal Gyrus - triangularis	L	123	2.83	68	76	40
Middle Frontal Gyrus/Precentral Gyrus	L	25	2.55	65	64	61
Inferior Frontal Gyrus - operculum	L	19	2.47	64	71	46
Inferior Frontal Gyrus - triangularis	L	11	2.45	62	90	40

Voxels: number of activated voxels per cluster; Max Z-stat: maximum z statistic for each cluster; x, y, z are MNI coordinates for the peak of each cluster