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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.

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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, & 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 (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, McGillivray, and Castel. (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,

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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 Colleageues (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-h 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 et al., 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-h 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 post-synaptic 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