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Age related-changes in the neural basis of self-generation in verbal paired associate learning

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ABSTRACT

Verbal information is better retained when it is self-generated rather than when it is received passively. The application of self-generation procedures has been found to improve memory in healthy elderly and in individuals with impaired cognition. Overall, the available studies support the notion that active participation in verbal encoding engages memory mechanisms that supplement those used during passive observation. Thus, the objective of this study was to investigate the age-related changes in the neural mechanisms involved in the encoding of paired-associates using a self-generation method that has been shown to improve memory performance across the lifespan. Subjects were 113 healthy right-handed adults (Edinburgh Handedness Inventory >50; 67 females) ages 18–76, native speakers of English with no history of neurological or psychiatric disorders. Subjects underwent fMRI at 3 T while performing didactic learning ("read") or self-generation learning ("generate") of 30 word pairs per condition. After fMRI, recognition memory for the second word in each pair was evaluated outside of the scanner. On the post-fMRI testing more "generate" words were correctly recognized than "read" words ($p < 0.001$) with older adults recognizing the "generated" words less accurately ($p < 0.05$). Independent component analysis of fMRI data identified task-related brain networks. Several components were positively correlated with the task reflecting multiple cognitive processes involved in self-generated encoding; other components correlated negatively with the task, including components of the default-mode network. Overall, memory performance on generated words decreased with age, but the benefit from self-generation remained consistently significant across ages. Independent component analysis of the neuroimaging data revealed an extensive set of components engaged in self-generation learning compared with didactic learning, and identified areas that were associated with age-related changes independent of performance.

1. Introduction

Verbal information is better retained when it is self-generated rather than received passively (Backman and Mantyla, 1988; Basso et al., 1994; Craik, 2002; Kanfer and Schefft, 1988; McDaniel et al., 1988; Olofsson and Nilsson, 1992; Schefft and Biederman, 1990; Slamecka and Graf, 1978). Specifically, self-generation involves an individual's production of verbal information based on a cue or set of cues (semantic, phonological, or visual), as opposed to hearing or reading the full phonological or orthographic form. In the clinical setting, the application of self-generation procedures has been found to improve memory in both nondemented elderly individuals and patients with Alzheimer's disease (Barrett et al., 2000; Lipinska et al., 1994; Multhaup and Balota, 1997; Souliez et al., 1996), frontal lobe dementia (Souliez et al., 1996), and in a number of other conditions (Barrett et al., 2000; Chiaravalloti and Deluca, 2002; Marshall et al., 1992; Schefft et al., 2008a; Schefft et al., 2008b; Smith, 1996; Vinogradov et al., 1997). Overall, these clinical studies support the notion that active participation during verbal encoding engages memory mechanisms that supplement those used during passive observation, leading to improvements in memory performance (Barrett et al., 2000; Lipinska et al., 1994; Multhaup and Balota, 1997; Schefft et al., 2008a; Schefft et al., 2008b; Souliez et al., 1996).

The efficacy of self-generation encoding procedures likely lies in the fact that the individual takes an active role in producing material to be remembered rather than passively responding to stimuli provided. Memories are enhanced as a result of self-generation of information because there is an increase in distinctiveness in the to-be-remembered

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items (Mantyla and Nilsson, 1988; McDaniel et al., 1988), and also, the strategy enforces processing information at a deeper semantic level, which causes verbal information to be better remembered (Backman and Mantyla, 1988; Craik, 2002; Lespinet-Najib et al., 2004).

For older adults, the memory benefit associated with self-generation of words compared to simply reading is as large as it is for younger adults, but overall memory performance decreases with age (Rabinowitz, 1989). Some differences in the generation effect for older and younger adults have been observed; for example, older adults do not receive as much memory benefit as younger adults from simply reading words aloud compared to silent reading (Lin and MacLeod, 2012), suggesting that the memory benefit for generating words may derive from the deep semantic processing associated with the generation process. In addition, while older adults see a memory benefit for self-generated items, they may not remember features of these items (Rabinowitz, 1989) to the extent that younger adults do.

The changes that take place in the neural mechanism underlying self-generation with age are not well defined. In young adults, neuroimaging studies of verbal encoding, which have made use of a variety of tasks and materials, have revealed a general pattern suggesting involvement of a multi-lobar network of brain regions. In general, "deeper" semantic processing at encoding, may be associated with additional participation of the frontal and medial temporal regions when contrasted with shallower encoding (Nyberg, 2002; Otten et al., 2001). Frontal mechanisms for "deeper" encoding have also been suggested to be left-lateralized (HERA model; Tulving et al., 1994). The self-generation task also depends on encoding and retrieval of paired verbal associates, which has been found to involve parahippocampal regions, visual integration areas, bilateral prefrontal cortex and cingulate gyrus, in both encoding and retrieval (Krause et al., 1999; Mottaghy et al., 1999). Studies of "subsequent memory effects", which examine patterns of activation during encoding of information that is later successfully remembered are also relevant, since the generation effect promotes more successful encoding. A recent meta-analysis showed that left inferior frontal cortex/insula, bilateral fusiform cortex, and left mesial temporal regions were most often engaged during successful encoding of verbal associates (H. Kim, 2011). Using the self-generation encoding task also used in the present study, we previously found increased activation for self-generation encoding of words compared to reading in inferior/middle frontal gyri, anterior cingulate, caudate nucleus, and the temporo-parietal–occipital junction bilaterally (Vannest et al., 2012). A largely overlapping pattern of results was recently observed by Rosner et al. in another similar self-generation task (Rosner et al., 2013). On the whole, these studies support a frontal–temporal–occipital network that is necessary for successful verbal encoding. However, none of these studies have focused on the change in the verbal encoding network that occurs with aging.

A few recent studies examining age-related changes in the verbal encoding network have shown effects of age on the involvement of temporal/parietal versus frontal regions in older adults. Older adults, compared to younger adults, show increased engagement of prefrontal cortex, and decreased engagement of medial temporal regions during encoding tasks, though they exhibit the same level of performance (Dennis et al., 2007; Sambataro et al., 2012). Age-related shifts in activation from temporal or parietal to frontal regions are suggested to indicate increased reliance on attentional and/or executive processes in older adults as a "compensatory" strategy (Rajah and D'Esposito, 2005; Sambataro et al., 2012). This compensation may also go hand-in-hand with *dedifferentiation* — the theory that in aging, brain networks become less dedicated to specialized functions. For example, frontal regions dedicated to executive function or attention earlier in life support other functions such as memory encoding later (Geerligs et al., 2014; Rajah and D'Esposito, 2005; Sambataro et al., 2012; St-Laurent et al., 2011).

Functional connectivity analyses of fMRI have further contributed to our understanding of age-related changes in task-specific brain networks supporting cognitive function, including verbal encoding. Studies of verbal encoding have found that in older adults medial temporal regions become more connected with dorsolateral frontal regions (Daselaar et al, 2006; Grady et al, 2003) and that there is age-related decrease in connectivity between hippocampal and temporo-parietal regions (Daselaar et al., 2006). These results are consistent with the age-related shift toward increased prefrontal engagement found in other fMRI studies. However, findings of age-related decreases in connectivity in parietal regions are not universal. For example, Matthaus et al. found that, networks engaged during memory tasks showed increased parietal connectivity in older adults (Matthaus et al., 2012).

Default-mode network connectivity has also been shown to decrease with age (Grady et al., 2010). This has been observed in default-mode suppression during a task. For example, Geerligs et al. (2014) found decreased default-mode connectivity in older adults compared to younger adults during a sustained attention task. They also found decreased connectivity in older adults compared to younger adults in dorsal attention/somato-motor networks that were active during the task. Age-related decreases in default-mode connectivity have also been observed in a number of resting-state studies (Mevel et al., 2013; Mowinckel et al., 2012; see Ferreira and Busatto, 2013; Goh, 2011 for reviews). These decreases have been described as a biomarker of cognitive decline in aging (Ferreira and Busatto, 2013; Grady et al., 2010; Mevel et al., 2013; Worsley and Friston, 1995) and are perhaps related to the increased distractibility in older adults (Grady et al., 2010); they are suggested to reflect dedifferentiation as networks are decreasing in specificity with age (Geerligs et al., 2014; Goh, 2011; Sambataro et al., 2012).

In the present study we aimed to investigate age-related changes in the neural mechanisms involved in the encoding of paired-associates using a self-generation method that has been shown to improve memory performance across the lifespan (Barrett et al., 2000; Lipinska et al., 1994; Multhaup and Balota, 1997; Schefft et al., 2008a; Schefft et al., 2008b; Souliez et al., 1996). Our hypothesis was that with increasing age there would be a decrease in memory performance, but no change in the degree of performance improvement associated with self-generation. We also expected age-related changes in the network supporting self-generation encoding (Rosner et al., 2013; Vannest et al., 2012), as examined with fMRI and independent component analysis (Ferreira and Busatto, 2013; Goh, 2011). Finally, we also expected decreased connectivity with age in both task-related networks, particularly those that involve temporal and parietal regions, as well as decreased connectivity in task-negative "default mode" networks.

2. Methods

2.1. Subjects

Subjects were 113 healthy right-handed adults (67 females) ages 18–76, native speakers of English with no history of neurological or psychiatric disorders. Some of these subjects were included in our previous publications (Siegel et al., 2012; Vannest et al., 2012). Age and gender distribution of the examined cohort are included in Fig. 1. Subjects were recruited from a local Cincinnati community via print and word-of-mouth advertising as part of a larger study (Allendorfer et al., 2012; Siegel et al., 2012; Szaflarski et al., 2013; Vannest et al., 2012). The project was reviewed and approved by the Institutional Review Boards at the University of Cincinnati, the Cincinnati Children's Hospital Medical Center and the University of Alabama at Birmingham, and all subjects were provided written informed consent.

2.2. Materials

Materials were 60 pairs of related familiar words consisting of 3–6 letters as in previous studies (Basso et al., 1994; Schefft et al., 2008a;