The effect of interference on temporal order memory for random and fixed sequences in nondemented older adults

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Two experiments tested the effect of temporal interference on order memory for fixed and random sequences in young adults and nondemented older adults. The results demonstrate that temporal order memory for fixed and random sequences is impaired in nondemented older adults, particularly when temporal interference is high. However, temporal order memory for fixed sequences is comparable between older adults and young adults when temporal interference is minimized. The results suggest that temporal order memory is less efficient and more susceptible to interference in older adults, possibly due to impaired temporal pattern separation.

Impaired memory for the temporal order of events or items in sequence may have adverse consequences on daily living skills and may affect a variety of cognitive functions (Pirogovsky et al. 2009). A primary function of the prefrontal cortex may be to integrate temporal information for the attainment of prospective behavioral goals (Fuster 2001). The prefrontal cortex is suggested to temporally organize fragments of information that are distributed spatially across cortical networks (Fuster 2001) and may support memory for the temporal order of items in a sequence (Shimamura 1995). Evidence from studies involving humans with frontal lobe damage (Milner et al. 1985; Daum and Mayes 2000) and studies using functional neuroimaging (Cabeza et al. 2000; Hayes et al. 2004; Knutson et al. 2004) have demonstrated that the frontal lobes play a critical role in memory for temporal sequences. In addition, several animal studies have reported that the frontal lobes are important for temporal order memory in nonhuman primates (Inoue and Mikami 2006) and rats (Hannesson et al. 2004). Studies involving humans with damage to the temporal lobes (Hopkins et al. 1995; Mayes et al. 2001), functional neuroimaging studies in humans (Ekstrom and Bookheimer 2007; Lehn et al. 2009), and studies in rats (Gilbert et al. 2001; Fortin et al. 2002; Manns et al. 2007; Howland et al. 2008) suggest that the temporal lobes also play a role in memory for the temporal order of items in a sequence. Therefore, as demonstrated recently by Devito and Eichenbaum (2011) and Ekstrom et al. (2011), there is evidence that both the frontal and temporal lobes are essential for temporal order memory.

Age-related changes in gray matter and white matter have been documented in many regions of the brain (Peters and Rosene 2003; Allen et al. 2005; Ziegler et al. 2010; Driscoll et al. 2009; Kennedy and Raz 2009), including those critical for temporal order memory such as medial temporal and frontal lobes. Specifically, volumetric reductions have been reported in the medial temporal and prefrontal regions of the human brain (Kramer et al. 2007; Fjell and Walhovd 2010; Raz et al. 2010; Cardenas et al. 2011). Age-related white matter changes also have been reported

in frontal and temporal regions of the human brain (Davis et al. 2009; Salat et al. 2009; Murray et al. 2010; Ziegler et al. 2010). These structural changes in gray and white matter have been associated with age-related cognitive decline (Kramer et al. 2007; Fjell and Walhovd 2010; Murray et al. 2010; Ziegler et al. 2010; Cardenas et al. 2011).

Given the structural changes in the frontal and temporal regions of the brain, it is not surprising that studies have reported significant age-related impairments in the ability to encode, organize, and accurately retrieve the sequential order of stimuli and events (Parkin et al. 1995; Fabiani and Friedman 1997; Trott et al. 1999; Newman et al. 2001; Kessels et al. 2007; Old and Naveh-Benjamin 2008; Ulbrich et al. 2009). However, normal temporal order memory also has been reported in older adults (Sekuler et al. 2006). It is possible that the level of temporal interference generated in these various tasks may influence the performance of older adults. For example, studies have shown that items occurring further apart in a temporal sequence are easier to remember than items that are temporally adjacent in both humans and animals (for review, see Kesner and Hopkins 2006). This phenomenon is assumed to occur because there is more interference and a greater need to separate temporally proximal stimuli than temporally distant stimuli in a sequence (Gilbert et al. 2001). Although studies have examined temporal order memory in healthy older adults, few if any studies to date have conducted systematic manipulations of temporal interference.

Pattern separation is a mechanism for separating partially overlapping patterns of activation so that one pattern may be retrieved as separate from other patterns. A pattern separation mechanism may reduce interference among similar memory representations and increase the likelihood of accurate encoding and retrieval (Gilbert and Brushfield 2009). The hippocampus, and specifically the dentate gyrus (DG) and CA3 subregions, have been reported to support pattern separation (for review, see Kesner 2007; Gilbert and Brushfield 2009; Rolls 2010; Yassa and Stark 2011; Schmidt et al. 2012). Age-related changes in the DG and CA3 hippocampal subregions have been hypothesized to result in less-efficient pattern separation due to strengthened processing of stored information at the expense of processing new information (Wilson et al. 2006; Yassa et al. 2011). In support of

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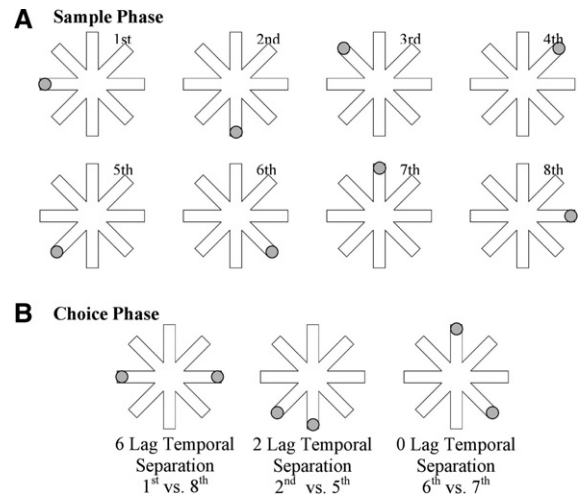
this hypothesis, studies have reported impaired pattern separation for visual and spatial information in older adults (Toner et al. 2009; Stark et al. 2010; Yassa et al. 2010; Holden et al. 2012). However, no studies have examined age-related changes in pattern separation for temporal sequences of stimuli in humans. The present study investigated the effects of varying levels of interference on temporal order memory for random and fixed sequences of visuospatial stimuli in young and older adults. As described below, interference was manipulated by systematically varying the temporal separation between items in a sequence.

The sample consisted of 40 nondemented older adults over the age of 65 and 40 young adults between the ages of 18 and 25. Demographic data are provided in Table 1. Older adults were community-dwelling individuals who were screened for dementia using the Dementia Rating Scale (DRS) (Mattis 1976). The average DRS score for the older adults was 135.66 ($SE = 0.81$). A task published by Pirogovsky et al. (2009) was used to assess the effects of interference on temporal order memory for random sequences of visuospatial stimuli. The participant was seated ~60 cm from a computer monitor. At the beginning of each trial, the participant was prompted to focus on the monitor where a computerized version of a radial 8-arm maze was presented. The participant was told that a circle would appear at the end of each arm one at a time and he/she should remember the sequence in which the circles were presented.

Each trial consisted of a sample phase followed by a choice phase. On the sample phase, a gray circle (3-cm diameter) appeared at the end of a randomly selected arm for 2 sec, and then the display was masked for 2 sec by a gray mask to eliminate afterimage effects. Then, another circle appeared at the end of a different randomly selected arm for 2 sec, followed by a 2-sec mask. This continued until a circle had been presented once at the end of each of the eight arms in a random sequence that varied on each trial (Fig. 1A). On the choice phase, the participant was presented simultaneously with two circles for 5 sec, one at the end of one study phase arm and the other at the end of another study phase arm. The participant was asked to indicate which circle appeared earlier in the sequence.

Temporal separations of 0, 2, 4, and 6 lags were randomly selected for each choice phase and represented the number of circles that occurred during the sample-phase sequence between the two circles presented simultaneously during the choice phase (Fig. 1B). For example, a 6-lag separation trial would consist of two choice-phase circles that occurred with six circles between them during the sample-phase sequence (e.g., first circle vs. eighth circle presented). As reviewed above, evidence suggests that items occurring further apart in a temporal sequence are easier to remember than items that are temporally adjacent. Therefore, it was hypothesized that there was more interference and a greater need to separate temporally proximal circles on 0 and 2 lag trials than temporally distant circles on 4 and 6 lag trials. Following each sample-phase sequence, three choice phases were conducted involving three of the four temporal separations that were counterbalanced across sequences. Sixteen different sample-phase sequences were presented with three choice phases for each sequence. There were a total of 12 choice phase trials for each of the four temporal separations. A 15-sec intertrial interval was implemented between each trial.

An identical procedure was used to assess the effects of interference on temporal order memory for fixed sequences of visuospatial stimuli. However, on the fixed-sequence version of the task, the same sequence of eight gray circles paired with the same eight arms on the maze was presented on each trial.

Figure 2 (top) shows the mean ($\pm$SE) percent correct performance of young and older adults on the random sequence temporal order memory task as a function of 0, 2, 4, and 6 temporal separation lag trials. A 2 × 4 analysis of variance (ANOVA) with group (young, old) as the between-group factor and temporal separation lag (0, 2, 4, 6) as the within-group factor revealed significant main effects of group $F_{(1,38)} = 27.57$; $P < 0.001$ and temporal separation lag $F_{(3,114)} = 19.42$; $P < 0.001$. However, the group × temporal separation lag interaction was not significant $F_{(3,114)} = 0.37$; $P = 0.77$. The main effect of the group revealed that young adults significantly outperformed older adults ($P < 0.001$). A Newman-Keuls post hoc comparison test of the temporal separation lag main effect revealed that 0 and 2 lag trials differed significantly ($P < 0.05$) from 4 and 6 lag trials.

Figure 2 (bottom) shows the mean ($\pm$SE) percent correct performance of young and older adults on the fixed sequence temporal order task as a function of temporal separation lag. A 2 × 4 ANOVA revealed a significant main effects of group $F_{(1,38)} = 4.49$, $P < 0.05$ and temporal separation lag $F_{(3,114)} = 13.60$, $P < 0.001$. In addition, the analysis revealed a significant group × temporal separation lag interaction $F_{(3,114)} = 2.80$, $P < 0.05$. A Newman-Keuls post hoc comparison test of the interaction demonstrated that young adults significantly outperformed older

Figure 1. A schematic of a sample-phase temporal sequence showing locations of the first through the eighth arms presented in a sequence (A) and a choice phase (B) consisting of a 6-temporal separation lag trial, a 2-temporal separation lag trial, and a 0-temporal separation lag trial.

Table 1. Demographic data for the young adults and older adults tested on the random and fixed sequence temporal order memory tasks
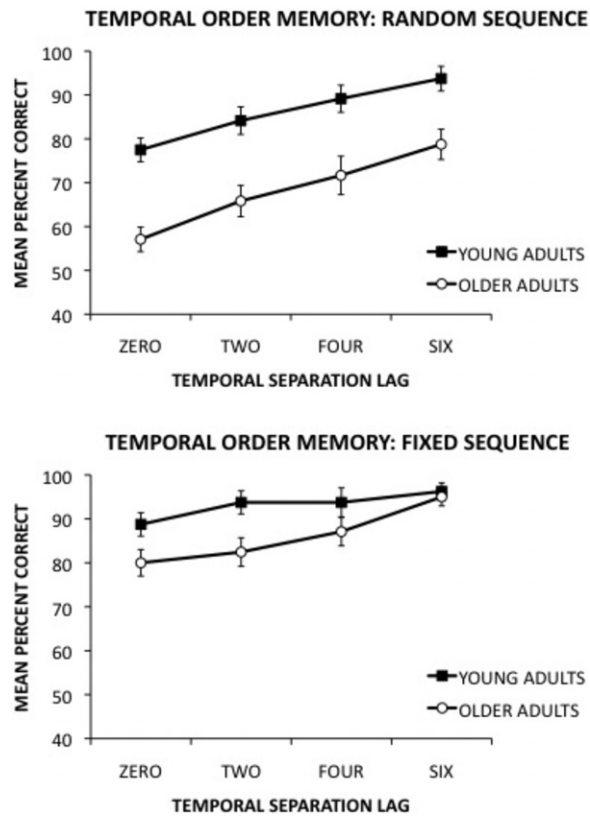
	Random sequence task		Fixed sequence task	
	Young adults	Older adults	Young adults	Older adults
Age (years)	18.55 (0.21)	75.65 (1.62)	19.40 (0.36)	74.15 (1.67)
Gender (M/F)	6/14[a]	10/10[a]	11/9[b]	8/12[b]
Education (years)	13.40 (0.17)[c]	15.8 (0.68)[c]	14.35 (0.35)[d]	16.55 (0.59)[d]

[a]A χ^2 analysis did not reveal a significant gender difference between groups, χ^2 (1, $N = 40$) = 1.67, $P = 0.20$.
[b]A χ^2 analysis did not reveal a significant gender difference between groups, χ^2 (1, $N = 40$) = 0.90, $P = 0.34$.
[c]A one-way analysis of variance revealed that the older adults achieved more years of education than the young adults, $F_{(1,38)} = 11.64$, $P < 0.01$.
[d]A one-way analysis of variance revealed that the older adults achieved more years of education than the young adults, $F_{(1,38)} = 6.93$, $P < 0.05$.

TEMPORAL ORDER MEMORY: RANDOM SEQUENCE

TEMPORAL ORDER MEMORY: FIXED SEQUENCE

Figure 2. Mean (± SE) percent correct performance of young and older adults on the random (*top*) and fixed (*bottom*) sequence temporal order memory task as a function of temporal separation lag (0, 2, 4, 6).

adults on temporal separation 0, 2, and 4 lag trials ($P < 0.05$). However, there were no significant differences between young and older adults on 6 lag temporal separation trials. A follow-up analysis examined task performance as a function of temporal separation lag across trials. The 48 trials were separated into two blocks of 24 trials. A $2 \times 2 \times 4$ ANOVA with group as a between group factor and block and lag as within group factors revealed significant main effects of group $F_{(3,38)} = 4.18$, $P < 0.05$, block $F_{(1,38)} = 25.49$, $P < 0.001$, and lag $F_{(3,114)} = 12.76$, $P < 0.001$, along with a group × lag interaction $F_{(3,114)} = 3.35$, $P < 0.05$. However, no significant interactions were found between block and group ($P = 0.51$) or lag ($P = 0.36$). These finding suggest that group differences across lags did not change significantly across trials. In addition, the performance of young adults on 6-lag trials was 96% (shown in Fig. 2); therefore, it is possible that their performance had reached ceiling. However, this follow-up analysis revealed that age-related performance across lags on the first block of 24 trials (data not shown) was remarkably similar to the data shown in Figure 2. Importantly, the young group averaged only 92.5% on 6-lag trials on the first block of trials (well below ceiling), providing evidence that the similar performance level of young and older adults on 6-lag trials (Fig. 2) was unlikely due solely to ceiling effects.

For the present tasks, it is hypothesized that as temporal separation lag decreased (i.e., choice phase circles were closer together in time during the sample-phase sequence), interference was likely to increase, resulting in poorer temporal order memory. The results from the random sequence task demonstrate that the performance of young and older adults improved as a function of increased temporal separation lag and decreased temporal in-

terference. However, young adults outperformed older adults across temporal separations with high, moderate, and low temporal interference. These findings suggest that temporal order memory for random sequences is less efficient in older adults compared with young adults.

The results from the fixed sequence task demonstrate that the performance of young and older adults also improved as a function of decreased temporal separation, presumably due to lessened temporal interference. Young adults outperformed older adults on trials involving high (e.g., 0 and 2 lags) and moderate temporal interference (e.g., 4 lag). However, there were no significant age-related differences on trials with low interference (e.g., 6 lag). The data suggest that temporal order memory for fixed sequences is less efficient in older adults when temporal interference is high or moderate. However, their performance was comparable to young adults when interference was minimized. Given that participants viewed the fixed sequence 16 times, whereas each of the 16 random sequences was viewed once, the amount of training per sequence varied between the two tasks. Although future studies are needed to better examine the relationship between temporal interference and the amount of training on a sequence, an analysis of the present data (data not shown due to space limitations) did not reveal a significant temporal lag × task interaction, offering some preliminary indication that temporal interference did not interact with training on the sequences.

Disruption in sequence memory may affect various cognitive domains critical to the execution of daily living skills. Given that memory for temporally sequenced events, stimuli, or actions may be important for aspects of executive function (e.g., strategic planning, problem solving), temporal order memory impairment may contribute to executive dysfunction in older adults. In addition, temporal order memory for sequences also may be critical for episodic memory. One key feature of episodic memory is that elements must be associated into a context to demarcate the episode in space and time. The hippocampus may support mnemonic processes, such as temporal pattern separation, to enhance episodic memory accuracy. However, age-related changes in this region may have adverse effects on pattern separation.

Therefore, one possible interpretation of the present findings may suggest that pattern separation for temporal sequences is less efficient in older adults. Trials involving shorter temporal separation lags and greater temporal interference may have required the operation of a pattern separation mechanism to separate memory representations for the items in the sequence. This hypothesis is supported by the present data showing that performance on both tasks improved as a function of increased temporal separation lag. Since older adults were impaired across all temporal separation lags on both the tasks, with the exception of the 6 lag on the fixed task, it is possible that temporal pattern separation may be less efficient in older adults. However, when temporal interference was reduced on the 6-lag separation trials on the fixed sequence task, the need for pattern separation may have been minimized, resulting in optimized performance in older adults. Therefore, less-efficient pattern separation, potentially resulting from age-related changes in the hippocampus, may adversely affect temporal order memory for sequences of stimuli. Although studies reviewed above have provided evidence that pattern separation for visual object and spatial stimuli may be impaired in older humans, this may be the first study to demonstrate age-related changes in pattern separation for temporal sequences of stimuli. Behavioral interventions that minimize temporal interference and structure daily living tasks into repetitive, fixed sequences may improve memory and perhaps could increase functional independence in older adults. In addition, a recent study reports that impaired temporal order memory may be a selective behavioral marker of Alzheimer's disease (Bellassen et al. 2012). Therefore,

the present findings potentially may have both basic science and clinical implications.

Acknowledgments

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