Published in final edited form as:

Brain Cogn. 2016 August ; 107: 30–36. doi:10.1016/j.bandc.2016.05.008.

The Effect of Interference on Temporal Order Memory in Individuals with Parkinson's Disease

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Abstract

Memory for the temporal order of items or events in a sequence has been shown to be impaired in older adults and individuals with Parkinson's disease (PD). The present study examined the effects of high and low interference on temporal order memory in individuals diagnosed with PD ($n = 20$) and demographically similar healthy older adults ($n = 20$) utilizing a computerized task used in previously published studies. During the sample phase of each trial, a series of eight circles were randomly presented one at a time in eight different spatial locations. Participants were instructed to remember the sequence in which the circles appeared in the locations. During the choice phase, participants were presented with two circles in two different locations and were asked to indicate which circle appeared earliest in the sample phase sequence. The two circles were separated by one of four possible temporal separation lags (0, 2, 4, and 6), defined as the number of circles occurring in the sample phase sequence between the two choice phase circles. Shorter temporal lags (e.g., 0 and 2 lags) were hypothesized to result in higher interference compared to longer temporal lags (e.g., 4 and 6 lags). The results demonstrated that on trials involving high interference, no differences were found between the two groups. However, healthy older adults significantly outperformed individuals with PD ($p < .05$) on trials involving low interference. Although differences were found between the PD and healthy older adult groups, both groups significantly improved on low interference trials compared to high interference trials ($p < .001$). The findings indicate that temporal order memory improves in healthy older adults and individuals with PD when interference is reduced. However, individuals with PD demonstrated poorer temporal order memory even with less interference. Therefore, temporal order memory is differentially affected by interference in healthy older adults and individuals with PD. Given that both groups did improve with lessened interference, behavioral interventions that minimize

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temporal interference potentially could improve memory function in older adults and to a lesser extent in individuals with PD.

Keywords

sequence; interference; visuospatial; frontal lobes; basal ganglia; memory

1. Introduction

Memory for the sequence of occurrence of items or events in time, known as temporal order memory, may be an important aspect of episodic memory (Fouquet et al., 2010) and related to various activities of daily living such as meal preparation and medication management (Schmitter-Edgecombe et al., 2009). The organization and integration of temporal information for the attainment of prospective behavioral goals may be a primary function of the prefrontal cortex (PFC; Fuster, 2001). Evidence from studies involving patients with frontal lobe lesions (Daum & Mayes, 2000; Fuster, 2001; Milner & Petrides, 1984; Shimamura et al., 1990) or neuroimaging of healthy adult subjects (Cabeza et al., 2000; Hayes et al., 2004; Knutson et al., 2004) indicates that the frontal lobes may be particularly important for processing temporal information. Therefore, deficits in temporal order memory are likely to occur in individuals with neurodegenerative diseases that involve disruption of frontal systems, such as in Parkinson's disease (PD).

PD is an incurable, progressive, and debilitating neurodegenerative disorder that is characterized predominantly by significant motor impairment (Samii et al., 2004; Tröster & Woods, 2005). The primary neuropathology in PD is the degeneration of dopamine (DA) producing cells in the substantia nigra pars compacta (SNc). This results in dysfunction of the dopaminergic projection from the SNc to the striatum of the basal ganglia, a brain area important for initiating, executing, and sustaining motor movements (Samii et al., 2004; Tröster & Woods, 2005). The clinical features of PD include motor, affective, sensory, autonomic system, and cognitive impairments. Cognitive impairments associated with PD are variable but most often include deficits in attention, executive function, memory, and visuospatial function (Barone et al., 2011; Pirogovsky et al., 2012; Taylor et al., 1986; Williams-Gray et al., 2006).

Evidence from previous studies indicates that temporal order memory is impaired in individuals with PD (Dubois & Pillon, 1997; Sagar et al., 1988; Taylor et al., 1986; Zakharov et al., 2001). Zakharov and colleagues (2001) found that individuals with PD were impaired on the sequential ordering portion of a memory test. A study by Taylor and colleagues (1986) showed that PD participants experienced difficulty with the order-dependent portion of a memory task, yet preformed normally on the item-dependent portions. In a study by Sagar et al. (1988), PD patients exhibited deficits in recency discrimination on the Verbal Temporal Ordering (VTO) Test despite intact content recognition. Together, the results from these studies provide evidence that temporal order memory is adversely affected by PD related pathology (frontostriatal systems), but this

pathology has less impact on other systems more involved with item memory (e.g., medial temporal lobe memory system).

Age-related deficits in memory for the temporal order of occurrence of items or events have been well documented in healthy older adults (Blachstein et al., 2012; Kessels et al., 2007; Newman et al., 2001; Old & Naveh-Benjamin, 2008; Roberts et al., 2014; Tolentino et al., 2012; Ulbrich et al., 2009). Recent studies have demonstrated that temporal interference may play a key role in the ability of older adults to remember sequences of stimuli (Roberts et al., 2014; Rotblatt et al., 2015; Tolentino et al., 2012). Various human and animal studies reviewed by Kesner and Hopkins (2006) have shown that items occurring further apart in a temporal sequence are easier to remember than items that are temporally adjacent. This phenomenon is hypothesized to occur because there is more interference between temporally proximal stimuli in a sequence than temporally distant stimuli (Gilbert et al., 2001; Kesner & Hopkins, 2006; Roberts et al., 2014; Rotblatt et al., 2015; Tolentino et al., 2012).

Although temporal order memory has been shown to be impaired in individuals with PD, little is known about how this deficit might be related to temporal interference. It is important to understand this relationship because an impaired ability to remember sequences of stimuli and/or events when temporal interference is increased could have a significant impact on a variety of daily tasks. Schmitter-Edgecombe and colleagues (2009), for example, found that in older adults with mild cognitive impairment temporal order memory was a unique predictor of everyday activities such as food preparation, medication use, and household activities. These activities all require the ability to complete tasks at a specified time and in a specific sequence (Schmitter-Edgecombe et al., 2009). These results suggest that characterizing the nature of temporal order memory deficits in PD may have important implications for the development of behavioral interventions designed to structure daily living tasks to reduce temporal interference and improve memory function. Therefore, the current study aimed to examine the effects of interference on temporal order memory performance of individuals with PD using a temporal order task utilized in previously published studies (Nicoll et al., 2013; Pirogovsky et al., 2009; Rotblatt et al., 2015; Tolentino et al., 2012; Woods et al., 2013).

2. Methods

2.1. Participants

Study participants included patients diagnosed with PD ($n = 20$) and demographically similar healthy older adults ($n = 20$). Demographic and disease characteristics are summarized in Table 1. PD participants were recruited from a pool of research subjects followed by the UCSD Shiley-Marcos Alzheimer's Disease Research Center, the UCSD Parkinson's Disease Research Consortium, and the laboratory of J. Vincent Filoteo, PhD. PD participants had a diagnosis of idiopathic Parkinson's disease, as determined by a board certified neurologist based on the presence of 2 or more cardinal features of PD and positive response to treatment with L-Dopa or equivalent medication. All PD patients were administered the Unified Parkinson's Disease Rating Scale by a neurologist (see Table 1 for mean scores). Exclusion criteria for the PD group included dementia diagnosis based on formal criteria (Emre et al., 2007), past treatment with deep brain stimulation, use of

anticholinergic or neuroleptic medications, presence of other neurological conditions, significant medical illness, debilitating psychiatric illness (e.g., substance dependence or schizophrenia), or other diseases with features of parkinsonism. Additionally, those with uncorrected vision loss or color blindness were excluded. For this study, PD participants were tested while on their normal medication regimen. All participants were taking one or more dopaminergic medication. The mean levodopa equivalent dose (LED) was 764.68 (SD = 351.76). Data for the healthy older adult group was collected by the Center for Healthy Aging and Neurodegenerative Disease Research. Exclusion criteria for the older adults included a score below 130 on the Dementia Rating Scale (DRS, Mattis, 1976) or a diagnosis of a neurological condition, significant medical illness, severe mental illness (e.g., schizophrenia), or substance dependence.

All procedures were approved by the Institutional Review Boards at San Diego State University and the University of California San Diego and all participants provided informed consent prior to participation in this study.

2.2. Neuropsychological and self-report measures

All participants were administered the DRS (Mattis, 1976) to assess global cognitive functioning. Additionally, participants with PD were administered the Benton Judgment of Line Orientation Test (JoLO; Benton et al., 1994) to assess visuospatial perception. A subset of the PD participants ($n = 16$) were additionally administered the California Verbal Learning Test (CVLT-II, Delis et al., 2000) to assess verbal memory and the Adaptive Digit Ordering Test (DOTA, Werheid et al., 2002) to assess attention. For participants who identified an informant ($n = 12$), the Lawton and Brody Instrumental Activities of Daily Living (iADL) questionnaire was administered. The iADL questionnaire is a widely used measure of complex activities of daily living (e.g., medication management, financial management), which is completed by the patient's informant (Lawton & Brody, 1969).

2.3. Temporal order memory task

Temporal order memory was assessed using a computer-based task utilized in previous studies (Nicoll et al., 2013; Pirogovsky et al., 2009; Rotblatt et al., 2015; Tolentino et al., 2012; Woods et al., 2013). Participants were seated approximately 60 cm from a computer monitor where the temporal order task was displayed. Participants viewed a radial eight-arm maze consisting of eight arms extending from a center similar to spokes on a wheel. The maze appeared on the screen with a diameter of approximately 30 cm. Participants were told that a grey circle would appear at the end of each of the eight arms, one at a time, in a random sequence. Participants were instructed to remember the sequence in which the circles would appear on the arms. Each trial consisted of a sample phase followed by a choice phase. In the sample phase, a gray circle appeared at the end of one of the arms on the maze for 2 s, after which the maze was masked in gray for 2 s to eliminate after image effects. Then another circle appeared at the end of another randomly selected arm on the maze for 2 s, again followed by a gray mask for 2 s. This continued until a circle had appeared at the end of each of the eight arms on the maze. Each trial consisted of a different random sequence.

After a sequence had been presented, participants were presented with the choice phase in which two circles appeared on two different arms of the maze for 5 s. The participant was asked to indicate which circle appeared earlier in the sequence. The participant was presented with three choice phases after each sample phase. Temporal separation lags involving high (0 lag and 2 lag) and low (4 lag and 6 lag) levels of interference were randomly selected for each choice phase. The temporal lag represented the number of circles that appeared during the sample phase sequence between the two circles presented in the choice phase (see figure 1). For example, a choice phase with a 2 lag temporal separation meant that the participant was presented with two circles that had 2 circles presented between them on the previous sample phase (e.g., 3rd circle presented and 6th circle presented). There were a total of 16 trials, each with 3 choice phases, with a 15 s inter-trial interval. To minimize fatigue, the trials were split into two sets of 8 trials each. The two sets were identical in design. Participants were either administered the JoLO or given a 5–10 min break between sets.

As reviewed above, 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. In order to compare the performance of the two groups on high interference and low interference trials, 0 and 2 lag trials were averaged and constituted the high interference condition, while 4 and 6 lag trials were averaged to constitute the low interference condition. This approach was used in a recently published study from our laboratory (Rotblatt et al., 2015) and was based on the findings from a prior study demonstrating that performance on 0 and 2 lag trials did not differ, nor did performance on 4 and 6 lag trials in healthy adults (Tolentino et al., 2012). Therefore, combining the 0 and 2 lag trials and the 4 and 6 lag trials offers a more robust measure of performance on high and low interference conditions by increasing the number of trials used in each condition.

3. Results

The data were analyzed using a 2×2 repeated measures analysis of variance (ANOVA), with group (PD patients, older adults) as the between-group factor and interference condition (high, low) as the within-group factor. As shown in Fig. 1, the analysis revealed a statistically significant main effect of group, $F(1, 38) = 10.07$, $p < .01$, $\eta^2 = .21$, with older adults outperforming individuals with PD. There was a significant main effect of interference condition, $F(1, 38) = 73.01$, $p < .001$, $\eta^2 = .62$, with better performance in the low interference condition compared to the high interference condition. Additionally, there was a significant group $\times$ interference condition interaction, $F(1, 38) = 6.76$, $p < .05$, $\eta^2 = .06$.

A Newman-Keuls post-hoc comparison test of the group $\times$ interference condition interaction revealed that older adults significantly outperformed ($p < .05$) the PD group on trials involving low levels of interference and this was associated with a large effect size ($d = 1.25$). However, when interference was high, there were no group differences in performance ($p > .05$). Both groups performed significantly better on trials involving low interference compared to trials involving high interference ($p < .05$), which was associated with a large effect size (older adults: $d = 1.93$, PD: $d = .90$).

Temporal order memory is known to decline with age. Therefore, Pearson r correlations were conducted to assess the relationship between age and performance on the temporal order memory task in each group. Age was not significantly correlated with performance on either interference condition of the temporal order memory task for either group (all $ps > .49$). In addition, the PD and older adult groups did not differ significantly in age (see Table 1). Since general cognitive deficits could contribute to impairment on the temporal order task, group differences on the DRS were analyzed. A one-way ANOVA with group (PD, older adults) as the independent variable revealed no significant differences between the PD group and older adults on the DRS, $F(1, 38) = .31$, $p = .58$, $\eta^2 = .01$. As shown in Table 2, DRS scores were found to correlate significantly with performance on low interference trials ($r = .53$, $p < .05$) but not high interference trials ($p > .20$) in healthy adults. No significant correlations were found between DRS scores and performance on either interference condition of the temporal order task in the PD group ($ps > .70$).

Performance on the temporal order memory task may be related to performance on other standardized measures of episodic memory. As shown in Table 2, in the PD patients, scores on the CVLT-II total immediate free recall index were found to correlate significantly with performance on high interference trials ($r = .664$, $p < .001$) and at a trend level with low interference trials ($r = .468$, $p = .056$). Scores on the CVLT-II delayed free recall index were found to correlate significantly with performance on high interference ($r = .561$, $p < .05$) and low interference ($r = .562$, $p < .05$) trials.

Attentional deficits are common in PD and also could contribute to deficits on the temporal order memory task. Therefore, Pearson r tests were conducted to assess the relationship between performance on the temporal order task and scores on the DRS attention subscale and the DOTA in the PD group. As shown in Table 2, neither DRS attention subscale scores nor DOTA scores were significantly correlated with performance on either interference condition of the temporal order memory task (all $ps > .20$). In addition, given that deficits in visuospatial judgment could contribute to deficits on the temporal order task, Pearson r correlations were conducted to assess the relationship between performance on the temporal order memory task and the JoLO in the PD group. Scores on the JoLO were not significantly correlated with scores on the temporal order memory task at any of the temporal separations (all $ps > .08$). Furthermore, scores on the JoLO for the PD participants were compared to age-corrected norms from the Mayo's Older Normative Studies (Ivnik et al., 1996). None of the PD participants scored lower than one standard deviation below the mean relative to age-corrected scaled scores.

To examine whether performance on the temporal order memory task is associated with day-to-day functioning, Pearson r correlations were conducted to assess the relationship between performance on the temporal order memory task and the iADL questionnaire in PD participants. As shown in Table 2, scores from the high temporal order interference condition significantly correlated with the iADL score ($r = .72$, $p < .01$), while scores from the low temporal order interference condition did not ($p > .20$).

Greater disease severity can be associated with lower performance on cognitive measures and poorer everyday functioning. Thus, relationships between years of disease duration and

behavioral measures were examined in the PD group. Disease duration was not significantly correlated with performance on either interference condition of the temporal order memory task, JoLO, CVLT (total recall and long-delay free-recall), or DOTA (all p s > .09). However, disease duration was significantly correlated with iADL scores ($r = -.62$, $p < .05$).

Dopaminergic medication dosage can be associated with cognitive function and day-to-day function in PD. Thus, correlations between levodopa equivalent dosage (LED) and the cognitive measures were assessed. LED did not significantly correlate with performance on either interference condition of the temporal order memory task, JoLO, CVLT indices, DOTA, or iADL scores (all p s > .14).

4. Discussion

Healthy older adults outperformed the PD group on the temporal order memory task on trials with low levels of interference (i.e., when temporal separation lags were large) and this difference was associated with a large effect size. In contrast, no group differences were detected on trials with high levels of interference (i.e., when temporal separation lags were short). The lack of a group difference on high interference trials is not due solely to floor effects. Even on 0 lag trials, both groups performed well above chance, which is 50% [PD $M = 70\%$ ($SD = 3.05$), Older Adults $M = 67.5\%$ ($SD = 3.31$)]. This finding is consistent with recent research showing that even healthy older adults experience difficulty on this task (Rotblatt et al., 2015; Tolentino et al., 2012) and other similar tasks (e.g. Roberts et al., 2014) when interference is high. Deficits in healthy older adults on temporal order memory tasks involving high levels of interference are hypothesized to stem from age-related changes in the frontal lobes (Rotblatt et al., 2015; Tolentino et al., 2012). The present results suggest that when temporal interference is high, the task is difficult for both the PD and healthy older adult groups. Despite differences between the PD and control groups on low interference trials, both groups performed significantly better on low interference trials than on high interference trials, and this difference was associated with a large effect size. When interference is reduced, performance improves in both groups, presumably due to lessened interference, but this improvement is smaller in those with PD. Thus, PD associated pathology leads to a disproportionate impairment in temporal order memory, even when interference is lessened. Given that both groups improved with a reduction in interference, behavioral interventions that minimize temporal interference could potentially improve memory function in older adults and to a lesser extent in individuals with PD. For example, to improve medication management, we would suggest that one place medications taken in the morning in a different location in the home than medications taken in the evening to minimize the potential for confusion and error.

Although the PD group was found to be impaired in low interference conditions relative to older adults, it is important to reiterate that temporal order memory did improve in PD patients on trials involving low interference compared to trials involving high interference. While cognitive impairment in various domains is common in individuals with PD, this finding suggests that the present deficits are not likely due to a general cognitive deficit since the attentional, visuospatial, and working memory demands of the task are equal across trials and interference conditions. During the encoding of each sample phase sequence, the

cognitive demands are identical. The participant is required to remember the sequence without being given any indication as to which particular circles will be presented in the choice phase. For each choice phase trial, the participant is asked to recall which of two circles appeared earliest in the sample phase sequence. The spatial distance between choice phase circles and the spatial locations used were balanced across trials and lags. The only aspect of the task that differs between choice phase trials is how many circles occurred in the sample phase sequence between the two circles presented (i.e., the temporal separation). This manipulation was specifically designed to assess memory for temporal order, while keeping all other cognitive aspects of the task identical. In addition, the performance of the PD group on the temporal order task did not correlate with performance on the JoLO and all PD participants scored in the normal range on the test, indicating that deficits on the temporal order task were not likely due to a visuospatial deficit. Similarly, performance on the temporal order task in the PD group was not found to correlate with measures of attention. Furthermore, the PD and older adult groups did not differ significantly on the DRS. Although global cognitive impairment and deficits in specific cognitive domains (e.g. attention, visuospatial perception) cannot be completely ruled out as a contributing factor to the present results, the data suggest the current findings represent a deficit in temporal order memory when interference is decreased in the PD group. As would be expected, performance on the temporal order task was found to correlate significantly with two indices from the CVLT-II, a standardized measure of memory. In summary, the present findings indicate that performance on the temporal order test correlates with a standardized measure of memory but not with measures of attention, visuospatial perception, and global cognition. The data provide evidence that temporal order memory deficits associated with PD may be most strongly related to memory abilities, but less related to other cognitive abilities such as attention, which are important for temporal order memory and adversely affected by PD.

The frontal lobes are adversely affected by both normal aging and PD (Cabeza et al., 2000; Raz et al., 1997; Taylor et al., 1986). Processes that temporally organize stimuli or events are believed to be supported by the prefrontal cortex and the disruption of these processes may lead to impairments in executive functioning (Fuster, 2001). The temporal order memory deficits observed in the healthy older adult group at high levels of interference likely stem from age-related frontal lobe dysfunction. Although the performance of the PD group improved with lessened interference, frontostriatal dysfunction associated with the disease may lead to impairments in temporal order memory even when interference is minimized. While temporal order memory seems to decline with normal aging, the results of the current study provide some evidence that frontostriatal pathologies may lead to greater impairment in temporal order memory among those with PD compared to healthy older adults. Executive function impairment is a common cognitive feature of PD that begins to decline in the early stages of the disease and is believed to be a result of disruptions in frontostriatal circuitry (Cameron et al., 2010; Cools et al., 2001; Owen et al., 1997; Williams-Gray et al., 2006).

Previous studies have examined performance on the present task in individuals in the premanifest and manifest stages of Huntington's disease (HD) (Nicoll et al., 2013; Pirogovsky et al., 2009), a neurodegenerative disorder that causes deterioration of the basal ganglia and subsequent frontostriatal dysfunction. Those with premanifest and manifest HD

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were found to be impaired on the temporal order memory test. Individuals with manifest HD were found to be impaired when interference was high or low. Those in the premanifest stage of HD showed impairments when interference was high but improved to the level of healthy adults when interference was minimized. Coupled with the present findings, the studies show that performance on the present temporal order memory test is impaired in individuals with frontostriatal dysfunction. However, the pattern of deficits differs between individuals with HD and PD, suggesting that the mechanisms underlying the deficits may differ between the two groups. These differential patterns of impairment may stem from differences in neuropathology of the two diseases. While HD involves direct degeneration of cells in the striatum, PD involves cell loss in the substantia nigra. Future studies will need to directly compare these clinical populations in order to better characterize the differences in temporal order memory ability.

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Although previous research has shown temporal order memory to be impaired in PD (Dubois & Pillon, 1997; Sagar et al., 1988; Taylor et al., 1986; Zakharov et al., 2001), this is the first study, to the authors' knowledge, to examine the effect of interference on temporal order memory in PD. The findings provide novel insight into a processing deficit that may have an impact on multiple cognitive functions and the execution of various daily living skills in individuals with PD. Indeed, we found that worse performance on the high interference condition of the temporal order memory task was associated with poorer day-to-day functioning (iADL questionnaire), and this relationship was associated with a large effect size. In addition, temporal order memory tests may be useful in other age-related neurodegenerative diseases. For example, recent studies have found that temporal order memory is impaired in older adults with mild cognitive impairment (Gillis et al., 2013) and these impairments might be a selective behavioral marker of Alzheimer's disease (AD; Bellassen et al., 2012). Although future studies are needed to examine the incremental and ecological validity of temporal order memory tasks relative to standard neuropsychological tests, the findings of the current and recent studies suggest that cognitive evaluations in older adults with PD and suspected AD may be improved by the addition of temporal order memory measures, particularly tasks that manipulate the level of temporal interference. In addition, the identification of temporal order memory deficits in an individual may lead to the implementation of behavioral interventions that structure daily living tasks to reduce temporal interference and improve memory function (e.g., place medications taken at different times of the day in different locations in the home or park the car in the same general region of a parking lot each week at the grocery store to reduce confusion across visits).

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Although the current findings provide important insight, the present study is not without limitations. The current study involved a relatively small sample of PD participants. However, the present findings were associated with large effect sizes, suggesting that group differences on the task were robust even in the context of a relatively small sample size. While the effect of interference on temporal order memory in healthy older adults has been previously well established (Roberts et al., 2014; Rotblatt et al., 2015; Tolentino et al., 2012), future studies using larger samples of PD patients are needed in order to better characterize the effect of varying levels of interference on temporal order memory functioning in this population. In addition, future studies with larger sample sizes should

examine the incremental validity of temporal order memory tests relative to other standardized cognitive measures in predicting real-world functioning in older adults and individuals with PD. Given that temporal order memory has been shown to be related to various activities of daily living such as meal preparation and medication management (Schmitter-Edgecombe et al., 2009), future studies should examine the ecological validity of the present task for predicting declines in everyday functioning skills. In addition, studies are needed to compare how performance on temporal order memory tests relates to performance on standardized cognitive tests in healthy adults and PD patients, which is a limitation in the current study as we only examined these relationships in individuals with PD. While these future studies are needed, the present findings provide novel insight into the effect of interference on temporal order memory in individuals living with PD.

Acknowledgments

This research was supported by National Institutes of Health Grant R01AG034202 awarded to Paul E. Gilbert, Department of Veterans Affairs Merit Award CX12004 awarded to J. Vincent Filoteo, National Institutes of Health Grant AG05131 to the University of California San Diego, and the Shiley-Marcos Alzheimer's Disease Research Center. Emily J. Van Etten was supported by National Institutes of Health Grant R25AG043364. Kelly M. Landy was supported by National Institutes of Health Grant F31 AG039247. The authors thank all of the participants for their contributions to this study.

References

- Barone P, Aarsland D, Burn D, Emre M, Kulisevsky J, Weintraub D. Cognitive impairment in nondemented parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2011; 26(14):2483–2495. DOI: 10.1002/mds.23919 [PubMed: 22170275]
- Bellassen V, Igloi K, de Souza LC, Dubois B, Rondi-Reig L. Temporal order memory assessed during spatiotemporal navigation as a behavioral cognitive marker for differential Alzheimer's disease diagnosis. *Neurobiology of Disease*. 2012; 32(6):1942–1952. DOI: 10.1523/JNEUROSCI.4556-11.2012
- Benton, A., Sivan, A., Hamsher, K., Varney, N., Spreen, O. Contributions to neuropsychological assessment: A clinical manual. 2. New York, NY: Oxford University Press; 1994.
- Blachstein H, Greenstein Y, Vakil E. Aging and temporal order memory: A comparison of direct and indirect measures. *Journal of Clinical and Experimental Neuropsychology*. 2012; 34(1):107–112. DOI: 10.1080/13803395.2011.625352 [PubMed: 22098473]
- Cabeza R, Anderson ND, Houle S, Mangels JA, Nyberg L. Age-related differences in neural activity during item and temporal-order memory retrieval: A positron emission tomography study. *Journal of Cognitive Neuroscience*. 2000; 12(1):197–206. DOI: 10.1162/089892900561832 [PubMed: 10769316]
- Cameron I, Watanabe M, Pari G, Munoz D. Executive impairment in Parkinson's disease: Response automaticity and task switching. *Neuropsychologia*. 2010; 48(7):1948–1957. DOI: 10.1016/j.neuropsychologia.2010.03.015 [PubMed: 20303998]
- Cools R, Barker R, Sahakian B, Robbins T. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain: A Journal of Neurology*. 2001; 124(Pt 12):2503–2512. DOI: 10.1093/brain/124.12.2503 [PubMed: 11701603]
- Delis, DC., Kramer, JH., Kaplan, E., Ober, BA. California Verbal Learning Test. 2. San Antonio, TX: The Psychological Corporation; 2000.
- Daum I, Mayes A. Memory and executive function impairments after frontal or posterior cortex lesions. *Behavioural Neurology*. 2000; 12(4):161–173. DOI: 10.1155/2000/327304 [PubMed: 11568428]
- Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. *Journal of Neurology*. 1997; 244(1):2–8. DOI: 10.1007/PL00007725 [PubMed: 9007738]

- Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, ... Dubois B. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders*. 2007; 22:1689–1707. DOI: 10.1002/mds.21507 [PubMed: 17542011]
- Fouquet C, Tobin C, Rondi-Reig L. A new approach for modeling episodic memory from rodents to humans: The temporal order memory. *Behavioral Brain Research*. 2010; 215(2):172–179. DOI: 10.1016/j.bbr.2010.05.054
- Fuster J. The prefrontal cortex-an update: Time is of the essence. *Neuron*. 2001; 30(2):319–333. DOI: 10.1016/S0896-6273(01)00285-9 [PubMed: 11394996]
- Gilbert PE, Kesner RP, Lee I. Dissociating hippocampal subregions: A double dissociation between dentate gyrus and CA1. *Hippocampus*. 2001; 11:626–636. DOI: 10.1002/hipo.1077 [PubMed: 11811656]
- Gillis MM, Quinn KM, Phillips PAT, Hampstead BM. Impaired retention is responsible for temporal order memory deficits in mild cognitive impairment. *Acta Psychologica*. 2013; 143(1):88–95. DOI: 10.1016/j.actpsy.2013.03.001 [PubMed: 23542809]
- Hayes S, Ryan L, Schnyer D, Nadel L. An fMRI study of episodic memory: Retrieval of object, spatial, and temporal information. *Behavioral Neuroscience*. 2004; 118(5):885–896. DOI: 10.1037/0735-7044.118.5.885 [PubMed: 15506871]
- Ivnik R, Malec J, Smith G, Tangalos E, Petersen R. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. *Clinical Neuropsychologist*. 1996; 10(3):262–278. DOI: 10.1080/13854049608406689
- Kesner RP, Hopkins RO. Mnemonic functions of the hippocampus: A comparison between animals and humans. *Biological Psychology*. 2006; 73(1):3–18. DOI: 10.1016/j.biopsycho.2006.01.004 [PubMed: 16473455]
- Kessels RPC, Hobbel D, Postma A. Aging, context memory and binding: A comparison of “what, where and when” in young and older adults. *International Journal of Neuroscience*. 2007; 117(6):795–810. DOI: 10.1080/00207450600910218 [PubMed: 17454244]
- Knutson K, Wood J, Grafman J. Brain activation in processing temporal sequence: An fMRI study. *NeuroImage*. 2004; 23(4):1299–1307. DOI: 10.1016/j.neuroimage.2004.08.012 [PubMed: 15589094]
- Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*. 1969; 9(3):179–186. DOI: 10.1093/geront/9.3_Part_1.179 [PubMed: 5349366]
- Mattis, S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellack, L., Katsau, TB., editors. *Geriatric psychiatry: A handbook for psychiatrists and primary care physicians*. New York, NY: Grune & Stratton; 1976. p. 77-121.
- Milner B, Petrides M. Behavioural effects of frontal-lobe lesions in man. *Trends in Neurosciences*. 1984; 7(11):403–407. DOI: 10.1016/S0166-2236(84)80143-5
- Newman MC, Allen JJB, Kazniak AW. Tasks for assessing memory for temporal order versus memory for items in aging. *Aging, Neuropsychology, and Cognition: A Journal on Normal and Dysfunctional Development*. 2001; 8(1):72–78. DOI: 10.1076/anec.8.1.72.849
- Nicoll D, Pirogovsky E, Collazo A, Tierney S, Corey-Bloom J, Gilbert P. The effect of interference on temporal order memory in premanifest and manifest Huntington's disease. *Journal of Huntington's Disease*. 2013; 2(3):297–304. DOI: 10.3233/JHD-130064
- Old SR, Naveh-Benjamin M. Differential effects of age on item and associative measures of memory: A meta-analysis. *Psychology and Aging*. 2008; 23(1):104–118. DOI: 10.1037/0882-7974.23.1.104 [PubMed: 18361660]
- Owen A, Iddon J, Hodges J, Summers B, Robbins T. Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia*. 1997; 35(4):519–532. DOI: 10.1016/S0028-3932(96)00101-7 [PubMed: 9106280]
- Pirogovsky E, Goldstein J, Peavy G, Jacobson M, Corey-Bloom J, Gilbert P. Temporal order memory deficits prior to clinical diagnosis in Huntington's disease. *Journal of the International Neuropsychological Society*. 2009; 15(5):662–670. DOI: 10.1017/S1355617709990427 [PubMed: 19635179]

- Pirogovsky E, Woods S, Vincent Filoteo J, Gilbert P. Prospective memory deficits are associated with poorer everyday functioning in Parkinson's disease. *Journal of the International Neuropsychological Society*. 2012; 18(6):986–995. DOI: 10.1017/S1355617712000781 [PubMed: 22846463]
- Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, ... Acker JD. Selective aging of the human cerebral cortex observed in vivo: Differential vulnerability of the prefrontal gray matter. *Cerebral Cortex*. 1997; 7(3):268–282. DOI: 10.1093/cercor/7.3.268 [PubMed: 9143446]
- Roberts JM, Ly M, Murray E, Yassa MA. Temporal discrimination deficits as a function of lag interference in older adults. *Hippocampus*. 2014; 24:1189–1196. DOI: 10.1002/hipo.22303 [PubMed: 24811482]
- Rotblatt LJ, Sumida CA, Van Etten EJ, Turk EP, Tolentino JC, Gilbert PE. Differences in temporal order memory among young, middle-aged, and older adults may depend on the level of interference. *Frontiers in Aging Neuroscience*. 2015; 7(28)doi: 10.3389/fnagi.2015.00028
- Sagar H, Sullivan E, Gabrieli J, Corkin S, Growdon J. Temporal ordering and short-term-memory deficits in Parkinson's disease. *BRAIN*. 1988; 111:525–539. DOI: 10.1093/brain/111.3.525 [PubMed: 3382911]
- Samii A, Nutt JG, Ransom BR. Parkinson's disease. *The Lancet*. 2004; 363(9423):1783–93. DOI: 10.1016/S0140-6736(04)16305-8
- Shimamura AP, Janowski JS, Squire LR. Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia*. 1990; 28(8):803–813. DOI: 10.1016/0028-3932(90)90004-8 [PubMed: 2247207]
- Schmitter-Edgecombe M, Woo E, Greeley DR. Characterizing multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment. *Neuropsychology*. 2009; 23:168–77. DOI: 10.1037/a0014186 [PubMed: 19254090]
- Taylor A, Saint-Cyr J, Lang A. Frontal lobe dysfunction in Parkinson's disease: The cortical focus of neostriatal outflow. *Brain: A Journal of Neurology*. 1986; 109(Pt 5):845–883. DOI: 10.1093/brain/109.5.845 [PubMed: 3779372]
- Tolentino J, Pirogovsky E, Luu T, Toner C, Gilbert PE. The effect of interference on temporal order memory for random and fixed sequences in nondemented older adults. *Learning & Memory*. 2012; 19(6):251–255. DOI: 10.1101/lm.026062.112 [PubMed: 22615480]
- Tröster, AI., Woods, S. Neuropsychology of Parkinson's disease and its dementias. In: Bush, SS., Martin, TA., editors. *Geriatric neuropsychology: Practice essentials*. Philadelphia, PA: Taylor & Francis; 2005. p. 243-300.
- Ulbrich P, Churan J, Fink M, Wittmann M. Perception of temporal order: The effects of age, sex, and cognitive factors. *Aging, Neuropsychology, and Cognition: A Journal on Normal and Dysfunctional Development*. 2009; 16(2):183–202. DOI: 10.1080/13825580802411758
- Werheid K, Hoppe C, Thone A, Muller U, Mungersdorf M, von Cramon DY. The Adaptive Digit Ordering test: Clinical application, reliability, and validity of a verbal working memory test. *Archives of Clinical Neuropsychology*. 2002; 17:547–565. DOI: 10.1093/arclin/17.6.547 [PubMed: 14591855]
- Williams-Gray C, Foltynie T, Lewis S, Barker R. Cognitive deficits and psychosis in Parkinson's disease: A review of pathophysiology and therapeutic options. *CNS Drugs*. 2006; 20(6):477–505. [PubMed: 16734499]
- Woods S, Hoebel C, Pirogovsky E, Rooney A, Cameron M, Grant I, Gilbert PE. Visuospatial temporal order memory deficits in older adults with HIV infection. *Cognitive and Behavioral Neurology*. 2013; 26(4):171–180. DOI: 10.1097/WNN.000000000000013 [PubMed: 24378603]
- Zakharov V, Akhutina T, Yakhno N. Memory impairment in Parkinson's disease. *Neuroscience and Behavioral Physiology*. 2001; 31(2):157–163. DOI: 10.1023/A:1005256122649 [PubMed: 11388367]

Highlights

With high interference, sequence memory did not differ in older adults and PD group

With low interference, sequence memory was better in older adults than PD group

Both groups improved with low interference compared to high interference

Interventions to lower interference may improve memory in older adults, less so in PD

Figure 1.

A schematic of a sample phase temporal sequence showing locations of the 1st through the 8th arms presented in a sequence (A) and a choice phase (B) consisting a 6 temporal separation lag trial, a 2 temporal separation lag trial, and a 0 temporal separation lag trial.

Figure 2. Mean percent correct responses on a temporal order memory test involving high and low interference conditions for PD patients and healthy older adults. * Indicates significant difference, $p < .05$.

Table 1

Demographic, disease-specific, and cognitive characteristics of study participants

	PD	Healthy Adults	F	(df)	p
Age (years)	68.85 (6.05)	72.00 (6.77)	2.40	(1, 38)	.13
Education (years)	16.70 (2.87)	16.65 (1.95)	.004	(1, 38)	.95
Gender (% female)	20%	20%			
DRS Total	139.30 (3.92)	138.70 (2.87)	0.31	(1, 38)	.58
LED	764.68 (351.76)	----			
PD Disease Duration (years)	8.80 (5.32)	----			
UPDRS (Part 3)	21.35 (16.11)	----			
CVLT-II Total Immediate Free Recall	36.88 (13.88)	----			
CVLT-II Delayed Free Recall	7.75 (4.39)	----			
DOTA	5.69 (2.15)	----			
JoLO	24.35 (4.22)	----			
iADL	12.58 (3.58)	----			

Note. DRS = Mattis Dementia Rating Scale. LED = Levodopa Equivalent Dose. UPDRS = Unified Parkinson's Disease Rating Scale, Part 3. CVLT-II = California Verbal Learning Test, second edition. DOTA = Adaptive Digit Ordering Test. JoLO = Benton Judgment of Line Orientation. iADL = Lawton and Brody Instrumental Activities of Daily Living.

Table 2

Pearson *r* correlations coefficients and *p*-values for relationships between performance on high and low interference conditions of the temporal order memory test and other cognitive measures in individuals with Parkinson's disease

	Low Interference		High Interference	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
CVLT-II Total Immediate Free Recall	.468	.056	.664	< .001 *
CVLT-II Delayed Free Recall	.562	< .05 *	.561	< .05 *
DRS Total	.081	.735	-.002	.993
DRS Attention	.110	.644	-.099	.679
DOTA	.335	.205	.224	.404
JoLO	.391	.089	.161	.499
iADL	.389	.211	.720	< .01 *

Note. DRS = Mattis Dementia Rating Scale. CVLT-II = California Verbal Learning Test, second edition. DOTA = Adaptive Digit Ordering Test. JoLO = Benton Judgment of Line Orientation. iADL = Lawton and Brody Instrumental Activities of Daily Living.

* Indicates statistical significance.