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Journal of Neuropsychology (2020)

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Temporal contiguity and ageing: The role of memory organization in cognitive decline

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The temporal contiguity effect is the tendency to form associations between items presented in nearby study positions. In the present study, we explored whether temporal contiguity predicted conversion to cognitively unimpaired-declining (CUD) status from a baseline of unimpaired older adults. Data from 419 participants were drawn from the Wisconsin Registry of Alzheimer's Prevention (WRAP) data set and analysed with binary logistic regressions. Temporal contiguity was calculated using the Rey Auditory Verbal Learning Test. Other predictors included age, years of education, sex, *APOE-ε4* status, and other measures of memory recall. Lower temporal contiguity predicted conversion to CUD after accounting for covariates. These findings support the hypothesis that temporal organization in memory is related to cognitive decline and suggest that temporal contiguity may be used for studies of early detection.

Memories of events typically are recalled following the temporal order in which they have been perceived. This temporal contiguity effect is seen in laboratory settings, when participants recall lists of items in a similar order to how they were presented during the learning phase (Kahana, 1996). Therefore, temporal contiguity reflects the output order of free recall (i.e. the order in which items are retrieved), thus differing from measures of input order of free recall (e.g. serial position) (Bruno *et al.*, 2016). Over the years, several studies have found temporal contiguity to be remarkably consistent across individuals and experimental conditions, including in immediate and delayed memory (for a review see Healey, Long, & Kahana, 2018). Temporal contiguity has been related to general memory performance and intellectual abilities, meaning that greater temporal contiguity tends to be positively related to better total recall in memory tasks and to greater IQ in younger participants (Healey, Crutchley, & Kahana, 2014; Sederberg, Miller, Howard, & Kahana, 2010). However, temporal contiguity decreases in older adulthood (Howard, Kahana, &

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DOI:10.1111/jnp.12219

Wingfield, 2006; Kahana, Howard, Zaromb, & Wingfield, 2002). For instance, Wahlheim and Huff (2015) tested temporal organization in 24 younger and 24 older adults during dual-list free recall tasks. Albeit maintaining a temporal contiguity effect, older adults exhibited lower temporal contiguity compared to younger adults, thus suggesting an age-related deficit in temporal association. Older adults' impairment in temporal contiguity has been proposed previously (Golomb, Peelle, Addis, Kahana, & Wingfield, 2008; Wingfield & Kahana, 2002) and its relation to poorer memory performance has been suggested (Bruno *et al.*, 2016; Sederberg *et al.*, 2010). Failure to cluster items according to their temporal context was reported by Golomb *et al.* (2008), who explored age differences in temporal and semantic associations in free and serial recall. Golomb *et al.* (2008) found that older adults exhibited a deficit in forming temporal associations compared to younger controls, whilst maladaptively compensating with semantic associations. Given Golomb et al.'s findings, it is plausible that temporal contiguity in older adults may predict cognitive decline over time. Implicit evidence of this assumption also comes from one study on temporal order memory (Gillis, Quinn, Phillips, & Hampstead, 2013). Similar to temporal contiguity, which examines the spontaneous order of responses during memory retrieval, temporal order memory explores the ability to remember voluntarily the temporal order of events.

Memory for temporal order is also affected by old age (Naveh-Benjamin, 1990) and appears to be significantly impaired in individuals with Mild Cognitive Impairment (MCI), the clinical precursor of Alzheimer's Disease (AD). Gillis *et al.* (2013) investigated younger and older controls, and patients with MCI on temporal order memory at immediate and delayed recall, by using lists of different span lengths. They found that at delayed recall individuals with MCI performed significantly more poorly than their healthy peers, who in turn performed more poorly compared to younger participants. However, at immediate recall, age differences were detected only in the longest span. Although investigating intentional clustering (i.e. memory for temporal order), Gillis *et al.*'s (2013) findings suggest that analyses of spontaneous recall patterns at delayed rather than immediate memory may be a more sensitive measure of cognitive decline. Consistently, the accuracy of delayed recall in predicting cognitive decline has been reported previously in studies of serial position (Bruno, Reiss, Petkova, Sidtis, & Pomara, 2013; Talamonti, Koscik, Johnson, & Bruno, 2019). However, no research has so far examined the output order of recall, specifically the temporal contiguity effect, as potential marker of longitudinal cognitive decline. In the present study, temporal contiguity at delayed memory was investigated as a predictor of progression to Cognitively Unimpaired-Declining (CUD) status (details on CUD classification in the 'Cognitive status' section) from a healthy baseline of older adults, whilst controlling for established clinical measures. Given previous findings, it was expected that: (a) older adults who progressed to CUD status would exhibit poorer temporal contiguity, compared to those who remained stable across time, and that (b) lower temporal contiguity would be a significant predictor of conversion to CUD status.

Methods

Participants

Data from 419 individuals, who volunteer in the Wisconsin Registry for Alzheimer's Prevention (WRAP; Johnson *et al.*, 2018; Sager, Hermann, & La Rue, 2005), were extracted from a pool of over 1,500 participants. WRAP is an ongoing longitudinal study of

middle-aged individuals, who complete visits, typically every 2 years. Participants were selected after completing at least four visits, were cognitively unimpaired at baseline (CUS status), and were either classified as still cognitively normal or with CUD status at visit 4 (Jack *et al.*, 2018) (details on diagnoses in the Procedure section). Other inclusion criteria included participants to be free of neurological diseases and psychiatric disorders, to be English native speakers, and to be 50 or older (age range: 50–68), at baseline. The follow-up times ranged from 7 to 13 years, with a mean of 9 years (*SD*: 1.76). The study was approved by the ethics committees of the authors' universities and completed in accordance with the Helsinki Declaration.

Procedure

Each WRAP visit includes administration of a neuropsychological battery of tests, clinical measures and laboratory tests (for a detailed description of the WRAP procedure see: Johnson *et al.*, 2018; Sager *et al.*, 2005). Tests used for the current study comprised: Trail Making Test A and B (Reitan, 1958) and Stroop Color-Word Test (Stroop, 1935) for working memory and executive abilities; Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Similarities subtests (Wechsler, 1999), Boston Naming Test (BNT; Goodglass, Kaplan, & Barresi, 2000) and Wide Range Achievement Test (WRAT) Reading Test (Wilkinson & Robertson, 2006) for language and verbal skills; WASI Block Design subtest, WASI Matrix Reasoning and Judgment of Line Orientation (JLO; Benton, Varney, & Hamsher, 1978) for visuospatial abilities; working memory subtests of the Wechsler Adult Intelligence Scale-III (WAIS; Wechsler, 1999) for working memory; and Rey Auditory Verbal Learning Test, (AVLT; Schmidt, 1996) for episodic memory. In the AVLT, participants are read a list of 15 semantically unrelated words and are asked to freely recall words immediately after presentation. This procedure is repeated for five more trials, the sum of which constitutes the AVLT total recall. After the fifth recall, participants are presented with an interference list and asked to recall it. Finally, after 20 min' delay, they are required to recall the original list (AVLT delayed recall).

To calculate temporal contiguity at baseline, the method adopted by Polyn, Norman and Kahana (2009) was utilized. Specifically, the absolute value of the lag of each recall transition was ranked with the absolute values of the lags of all possible transitions during the AVLT delayed recall. This provided a percentile score for each transition, which was then averaged with the other percentile scores of a subject's transitions, therefore providing a temporal factor score.

General cognitive functioning was estimated through calculation of a composite score. This score included the average of four baseline cognitive factor *z*-scores: (1) Speed and Flexibility, obtained using the TMT-A and B and the Stroop Color-Word test; (2) Verbal Abilities, obtained with the WASI vocabulary, WASI similarities, BNT and WRAT; (3) Visuospatial Abilities, using the WASI block design, matrix reasoning and the JLO; and (4) Working Memory, obtained using the digit span back and forward and the letter–number sequencing (details on the factor analyses: Dowling, Hermann, La Rue, & Sager, 2010; Koscik *et al.*, 2014). Finally, APOE-ε4 genotyping information was obtained via blood analysis (Engelman *et al.*, 2013).

Cognitive status

WRAP utilizes a two-tiered consensus conference method to identify participants' cognitive status. If cognitive abnormalities are detected by algorithm on

neuropsychological tests, in depth review of data from participants' visits is undertaken by a consensus review committee consisting of dementia specialists. Detailed criteria for the CUD classification, previously named early-MCI, can be found in Talamonti *et al.* (2019). In summary, this diagnosis is assigned if there is lower-than-expected objective performance on commonly used clinical tests (typically >1.5 SD below internal robust norms), but few or no subjective cognitive complaints or clinically significant deficit, which distinguish this diagnosis from that of MCI. The CUD classification represents consensus conference confirmed pre-MCI cognitive decline analogous to transitional cognitive decline in the 2018 diagnostic framework (Jack *et al.*, 2018; Johnson *et al.*, 2018). Generally, the consensus diagnosis for CUD includes evaluation of AVLT immediate and delayed recall (excluding temporal contiguity data), as part of 15–20 of the cognitive measures considered (e.g. executive function impairments or language impairments were also evaluated). Therefore, although predictor and outcome cannot be thought of as being 100% 'conceptually' independent, the level of circularity is relatively low. For the purpose of the current study, only individuals categorized as either CUS or with CUD at visit 4 were included in the analysis. Participants with more severe classifications (e.g. clinical MCI, dementia) were excluded in this study, in order to specifically investigate the sensitiveness of temporal contiguity to subclinical cognitive decline.

Statistical analysis

First, temporal contiguity was correlated to general cognitive ability and AVLT measures in the CUS and CUD groups combined to assess its sensitivity to global cognition and memory performance. Second, *t* test comparisons were run to determine whether there were differences in demographics, memory measures, and temporal contiguity between those who progressed to CUD status and those who did not. Group differences for general cognitive abilities were explored through the Mann–Whitney test, given that data were not normally distributed. Cohen's *d* was included as measure of effect size. Finally, to test the hypothesis that temporal contiguity predicted conversion to CUD from a healthy baseline, a binary logistic regression was performed with temporal contiguity as the predictor and progression to CUD status as the binary outcome. Since time between first and last visit was not the same for each participant, time was included as a covariate, together with age, gender, *APOE-ε4* status, and years of education. Finally, we also co-varied First Item recalled (FIR) at delayed recall, which may affect contiguity effects, and AVLT immediate and delayed total recall. To avoid issues of multicollinearity between temporal factor, FIR and the AVLT scores (see Bruno, Koscik, Woodard, Pomara, & Johnson, 2018; Talamonti *et al.*, 2019), FIR, AVLT total and delayed recall were regressed out of temporal contiguity and their respective standardized residuals were used for the analysis. We then reversed this analysis by using the temporal factor's standardized residuals (out of FIR and total and delayed AVLT scores) as a sensitivity analysis.

A Pearson's correlation confirmed the independence of these measures, in each analysis. A further sensitivity analysis was performed by using temporal contiguity as the only predictor, in order to explore the independent impact of this variable on the model's outcome.

Finally, to test whether immediate temporal contiguity may be a predictor of conversion to CUD, the binary logistic regression was re-run with temporal contiguity averaged across the five learning trials, as the main predictor. The standardized residuals from the first analysis were replaced by standardized residuals of AVLT total regressed out

of immediate temporal contiguity. Standardized residuals of delayed temporal contiguity were calculated from immediate temporal contiguity and the regressed AVLT total and delayed recall.

Results

Data on demographic variables and comparisons for cognitive and memory scores are reported in Table 1. Data are mean ± standard deviation, unless otherwise stated. Of the 419 cognitively intact participants at baseline, 61 (14.6%) met CUD criteria at the visit 4, whereas 358 (85.4%) remained cognitively intact. 69.2% of the total sample was female, mean age at baseline was 56.65 (±4.38), with 16.70 (±2.93) total years of education. Correlation analyses between general cognitive abilities, memory performance, and temporal contiguity are shown in Table 2. As cognitive ability was not normally distributed, Spearman correlation was run for this variable, whereas Pearson correlation was performed for FIR, AVLT total, and delayed recall. Temporal contiguity was positively related to general cognitive abilities, $r_s(418) = .139$, $p = .004$, FIR, $r(418) = -.215$, $p < .001$, AVLT Total Recall, $r(418) = .155$, $p = .001$, and AVLT Delayed Recall, $r(418) = .385$, $p < .001$.

A Mann–Whitney test was performed to compare baseline cognitive functioning of the two groups and results showed a statistically significant difference between CUD (median = −0.21, range = −1.34 to 0.90, mean rank = 147.95) and CUS (median = 0.24, range = −1.76 to 1.73, mean rank = 220.57), $U = 7{,}134$, $z = -4.329$, $p < .001$, $r = .21$. As data were normally distributed, independent samples t tests were run to determine whether there were differences between the two groups in memory measures, including immediate and delayed total recall and temporal contiguity. Statistically significant differences on memory measures were found for immediate total recall ($t(417) = 7.169$, $p < .001$, $d = .35$) between CUD and CUS participants. Significant differences were also found for delayed total recall ($t(417) = 5.908$, $p < .001$, $d = .29$) between the two groups. Lastly, temporal contiguity was statistically lower in the CUD compared to the CUS group ($t(417) = 4.718$, $p < .001$, $d = .23$).

Table 1. Demographics, cognitive level, and temporal contiguity between CUD and CUS participants

	CUD ($n = 61$)	CUS ($n = 358$)	p value
Gender (females)	37 (60.7%)	253 (70.7%)	.118
APOE-ε4 presence	21 (34.4%)	128 (35.8%)	.842
Age at baseline	57.08 ± 4.33	56.57 ± 4.38	.401
Years of education	16.70 ± 3.21	16.70 ± 2.88	.982
Ethnicity (White/Caucasian)	60 (98.4%)	351 (98%)	.868
General cognitive abilities	−0.16 ± 0.57	0.22 ± 0.63	<.001
Time between visits	9.16 ± 1.00	9.04 ± 0.97	.364
First item recalled (delayed)	3.31 ± 3.90	3.04 ± 3.661	.599
AVLT total recall	46.72 ± 6.25	53.41 ± 6.81	<.001
AVLT delayed recall	9.15 ± 2.31	11.06 ± 2.49	<.001
Delayed temporal contiguity	0.60 ± 0.16	0.69 ± 0.13	<.001

Note. AVLT = Auditory Verbal Learning Test; CUD = Cognitively Unimpaired-Declining; CUS = Cognitively Unimpaired Stable; Time = time between visit 1 and 4.

Table 2. Pearson's and Spearman's correlations between cognitive, memory performance, and temporal contiguity

	1	2	3	4	5	6
1. Immediate temporal contiguity	–					
2. Delayed temporal contiguity	.450*	–				
3. General cognitive functioning	.194*	.211*	–			
4. First item recalled (delayed)	−.136*	−.215*	.002	–		
5. AVLT total recall	.327*	.155*	.340*	−.175*	–	
6. AVLT delayed recall	.318*	.385*	.275*	.735*	−.218*	–

*Correlation significant at $p < .01$.

Pearson's correlation was performed in order to guarantee that there was no correlation between temporal contiguity and regressed AVLT Total Recall ($r(418) = -.008$, $p = .866$) and regressed AVLT Delayed Recall ($r(418) = .021$, $p = .664$). The first logistic regression model was statistically significant, $\chi^2(7) = 41.560$, $p < .001$. The model overall explained 17% (Nagelkerke R2) of the variance in conversion to CUD and correctly classified 85.4% of cases. The analysis yielded two significant predictors: regressed AVLT total recall and delayed temporal contiguity. Other not significant variables are shown in Table 3. To note, the regression model remained statistically significant when the regressed AVLT measures were excluded from the analysis, $\chi^2(6) = 13.246$, $p = .039$.

For the second binary logistic regression model, Pearson's correlation confirmed the independence between immediate temporal contiguity and the regressed AVLT total recall ($r(418) = .014$, $p = .784$), AVLT delayed recall ($r(418) = .011$, $p = .820$), and delayed temporal contiguity ($r(418) = .000$, $p = .996$). The regression model was statistically significant, $\chi^2(8) = 51.116$, $p < .001$. The model explained 20% (Nagelkerke R2) of the variance in conversion to CUD and correctly classified 85.4% of cases. The results are shown in Table 4 and showed that immediate temporal contiguity was also

Table 3. Logistic regression predicting progression to CUD based on delayed temporal contiguity at baseline

Measures	*B*(*SE*)	Wald	*p*	Exp(*B*)	95% CI
Delayed temporal contiguity	−3.586 (1.194)	9.024	.003	0.028	[0.003–0.288]
AVLT total recall (residuals)	−1.035 (0.179)	33.334	<.001	0.355	[0.250–0.505]
AVLT delayed recall (residuals)	−.075 (0.151)	0.248	.618	0.928	[0.691–1.246]
First item recalled (residuals)	−.099 (0.153)	0.416	.519	0.906	[0.617–1.223]
Age	.012 (0.035)	0.115	.735	1.012	[0.945–1.083]
Years of education	.034 (0.049)	0.480	.488	1.035	[0.939–1.140]
Sex	.419 (0.343)	1.499	.221	1.521	[0.777–2.976]
APOEε4 presence	−.016 (0.320)	0.002	.961	0.985	[0.526–1.843]
TIME	−.009 (0.016)	0.332	.565	0.991	[0.961–1.022]

Note. 95% CI = 95% confidence interval; AVLT delayed recall = standardized residuals regressed out from delayed temporal contiguity; AVLT total recall = standardized residuals regressed out from delayed temporal contiguity and AVLT delayed recall; *B* = unstandardized regression coefficient; CUD = cognitively unimpaired-declining; Exp(*B*) = odds ratio; *SE* = standard error of the coefficient.

predictive of CUD conversion, although delayed temporal contiguity remained a stronger predictor. Specifically, greater use of temporal contiguity at delayed recall was associated with a greater reduction in the likelihood of converting to CUD, compared to both AVLT total recall and temporal contiguity at immediate recall. Moreover, the regression model did not remain statistically significant when the regressed AVLT measures and delayed temporal contiguity were excluded, $\chi^2(6) = 9.564$, $p = .144$.

Finally, the third logistic regression was performed to explore whether temporal contiguity was a better predictor of conversion compared to overall recall. The model was statistically significant, $\chi^2(6) = 51.001$, $p < .001$, explained 20% (Nagelkerke R2) of the variance and correctly classified 85.6% of cases. AVLT total recall was the only significant predictor, as shown in Table 5.

Discussion

The current study was the first, to the best of our knowledge, to investigate temporal contiguity longitudinally in subclinical cognitive decline. The binary regression analysis revealed that temporal organization in memory was associated with cognitive decline. Specifically, differences in temporal contiguity at baseline predicted increased risk of progression to CUD status after approximately 9 years and after adjusting for established diagnostic measures, such as AVLT total and delayed recall and *APOE-ε4* genotype. To note, the CUD status describes cognitive decline that is not sufficiently severe for a diagnosis of MCI, but that increases conversion to a clinical status (Johnson *et al.*, 2018). Therefore, these results suggested the potential applicability of temporal contiguity in clinical settings. The main findings are in line with the Associative Deficit Hypothesis (ADH; Naveh-Benjamin, 2000), wherein age-related decline in episodic memory performance was explained by an inability to form associations. In a series of four experiments, Naveh-Benjamin (2000) compared memory for items and memory for associative relationships between items in younger vs. older participants and found that older adults exhibited, other than lower performance in all tasks, a specific and relevant deficit in memory for associative relationships. In following works, the suggested ADH was tested

Table 4. Logistic regression predicting progression to CUD based on immediate temporal contiguity at baseline

Measures	*B*(*SE*)	Wald	*p*	Exp(*B*)	95% CI
Immediate temporal contiguity	−5.504 (2.157)	6.510	.011	0.004	[0.000–0.279]
Delayed temporal contiguity (residuals)	−.408 (0.151)	7.279	.007	0.665	[0.494–0.894]
AVLT total recall (residuals)	−1.039 (0.183)	32.276	<.001	0.354	[0.247–0.506]
AVLT delayed recall (residuals)	−.067 (0.148)	0.206	.650	0.935	[0.700–1.250]
Age	.012 (0.035)	0.123	.726	1.012	[0.946–1.084]
Years of education	.036 (0.050)	0.522	.470	1.037	[0.940–1.143]
Sex	.412 (0.343)	1.445	.229	1.510	[0.771–2.957]
APOE-ε4 presence	−.020 (0.321)	0.004	.950	0.980	[0.522–1.839]
TIME	.193 (0.159)	1.470	.225	1.212	[0.888–1.655]

Note. AVLT delayed recall = standardized residuals regressed out from immediate temporal contiguity; AVLT total recall = standardized residuals regressed out from immediate temporal contiguity and AVLT delayed recall; Delayed Temporal contiguity = standardized residuals regressed out from immediate temporal contiguity, and standardized AVLT Total and delayed recall.

Table 5. Logistic regression predicting progression to CUD based on regressed delayed temporal contiguity at baseline

Measures	*B*(*SE*)	Wald	*p*	Exp(*B*)	95% CI
Regressed temporal contiguity	−.093 (0.148)	0.392	.531	0.911	[0.681–1.219]
AVLT total recall	−.162 (0.026)	37.523	<.001	0.850	[0.807–0.896]
Age	.016 (0.035)	0.210	.647	1.016	[0.949–1.088]
Years of education	.033 (0.050)	0.451	.502	1.034	[0.938–1.140]
Sex	.401 (0.343)	1.372	.242	1.494	[0.763–2.923]
APOE-ε4 presence	−.030 (0.319)	0.009	.924	0.970	[0.519–1.814]
TIME	−.009 (0.016)	0.336	.562	0.991	[0.961–1.022]

Note. 95% CI = 95% confidence interval; *B* = unstandardized regression coefficient; CUD = cognitively unimpaired-declining; Exp(*B*) = odds ratio; *SE* = standard error of the coefficient; Regressed temporal contiguity = standardized residuals regressed out from FIR, AVLT total and delayed recall.

on different types of associations and a deficit specifically for temporal order was reported in healthy old age (Old & Naveh-Benjamin, 2008). Alternative models have also been proposed where age differences in temporal contiguity were explained through model simulations as the consequence of a deficit in restoring previous temporal information during memory search, rather than as a mere difficulty in forming new associations (Healey & Kahana, 2016). In the present study, greater difficulty in temporally binding items was found in individuals who received a subsequent CUD diagnosis compared to those who remained cognitively stable across time, thus indicating that the age-related deficit increases relatively to the older person's cognitive status.

Following these findings, in the present study temporal contiguity was analysed at delayed recall, which occurred 20 min after the last immediate free recall trial. Delayed memory performance has been shown to be a sensitive predictor of cognitive decline compared to other serial position measures (Bruno *et al*., 2013; Talamonti *et al*., 2019), and Bruno *et al*. (2016) reported that measures of output order taken at delayed performance, including information on the temporal order of free recall, were linked to general cognitive functioning (as measured by the MMSE), and to hippocampal volume in healthy older adults. The relationship between temporal contiguity at delayed recall and general cognitive functioning was confirmed in the present study through partial correlation analysis. The interlink between temporal contiguity and memory ability at immediate and delayed recall was also reported, thus confirming previous studies showing the contiguity effect to be positively associated with recall accuracy (Healey *et al*., 2014; Healey *et al*., 2018; Sederberg *et al*., 2010).

These results suggest that temporal contiguity at immediate recall may also be a predictor of progression to CUD. To confirm this point, the same binary regression was re-run by adding temporal contiguity, averaged across the five learning trials, as the main predictor. The results showed that immediate temporal contiguity was also predictive of CUD conversion. However, the following sensitivity analysis showed that the regression model was not significant when the controlling variables were excluded, thus confirming delayed temporal contiguity as a better predictor.

The shape of temporal contiguity can be illustrated using the lag-conditional response probability (lag-CRP), a curve computing the probability of recalls as a function of lag (distance between recalled items) (Kahana, 1996). The lag-CRP is typically asymmetrical, as transitions between recalled items are more likely to be for forward, rather than

backward, positions, and it is larger for items presented at adjacent positions (Kahana, 1996). Given that the lag-CRP decreases in older adulthood (Kahana *et al*., 2002) and is disrupted in individuals with impaired memory (Palombo, Lascio, Howard, Verfaellie, & Sciences, 2019), we used the lag-CRP in order to explore whether the CUD classification may influence the shape of contiguity effect. Figure 1 shows the lag-CRP at immediate and delayed recall in participants with CUD vs. CUS status. The temporal contiguity effect is evident in both groups at both time points, with the lag-CRP being higher for short transitions (|lag| = 1) and lower for longer lags. As expected, the size of contiguity effect was influenced by clinical classification: at both time points, the lag-CRP is smaller in individuals with CUD status, compared to CUS.

To test whether delayed temporal contiguity alone predicts conversion to CUD beyond measures of total recall, a third regression was performed where temporal contiguity was regressed out of FIR, AVLT total, and delayed recall. In this analysis, AVLT

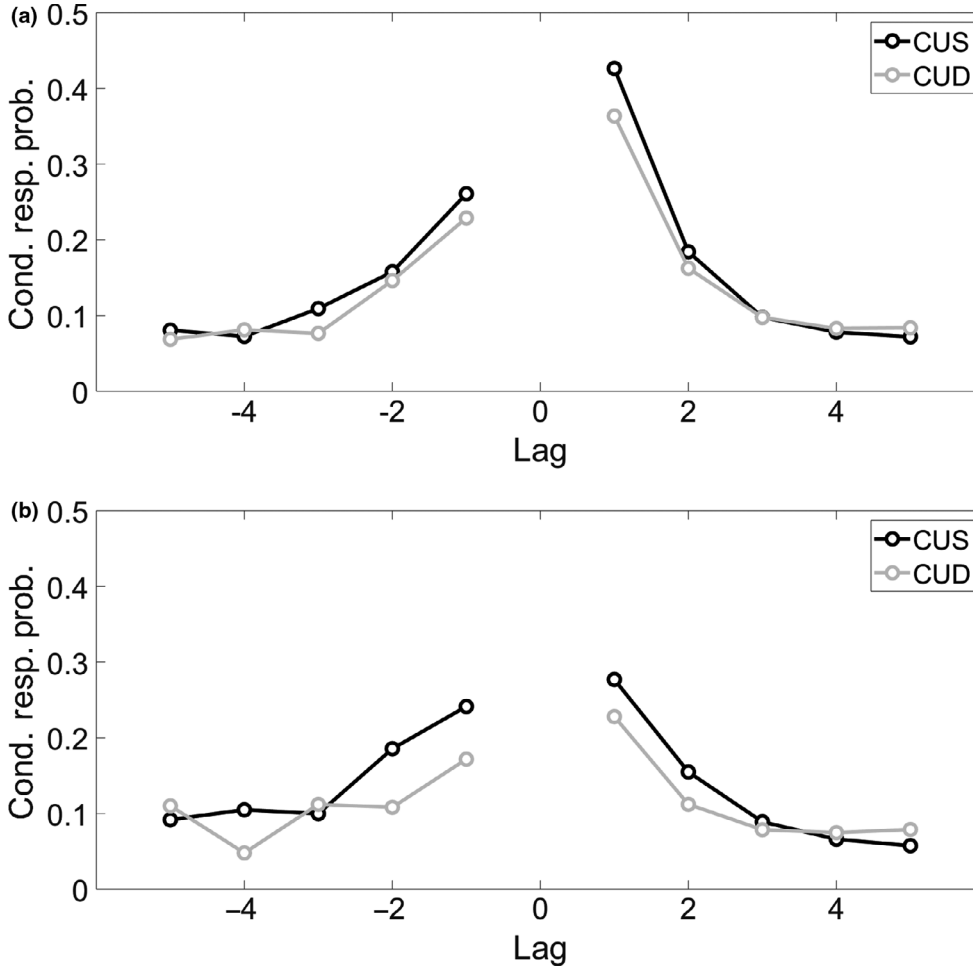

Figure 1. Shape of the temporal contiguity effect. (a) lag-CRP for individuals with Cognitive Unimpaired Status (CUS) vs. Cognitive Unimpaired-Declining (CUD) at immediate recall. (b) lag-CRP for CUS and CUD calculated at delayed recall.

total recall, used as measure of overall recall, was the only significant measure to predict conversion to CUD. These results may suggest that measures of overall recall are a better predictor of conversion than temporal contiguity scores. However, it has to be noted that in this study, AVLT total scores were directly examined to derive the CUD and CUS classifications, thus this interpretation is possibly biased by a circularity issue. Future studies should address this limitation by circumventing circularity by utilizing outcomes that do not directly depend on memory test scores, such as biomarker-based classifications (e.g. Mueller *et al.*, 2019).

In the present study, we provide some preliminary evidence that temporal contiguity may contribute to predicting cognitive decline above and beyond other variables that are thought to impact cognitive functioning, such as genetic risk factors (i.e. *APOE-ε4*). Therefore, temporal contiguity has the potential to be considered as one of the cognitive markers in the search for clues to neurodegeneration. For instance, temporal contiguity may be considered in association with biomarker variables in studies of early detection, in order to ameliorate measures for the early diagnosis of dementia-related pathologies. Our results also demonstrated that temporal contiguity at delayed recall was related to memory performance and cognitive functioning in healthy older adults.

There are some limitations in the present study that ought to be considered. CUD is a preclinical classification; thus, caution should be used when generalizing our findings to clinical populations, such as MCI or AD. Moreover, although genetic information was considered in the present study, no data were available on fluid or imaging biomarkers, which are currently considered as the premier tools for early diagnosis. Future research may investigate the interaction between early markers of neurodegeneration (e.g. PET tracers) and temporal contiguity in cognitive decline. Finally, as there are no established norms on the calculation of temporal contiguity, the reliability of this measure varies significantly across studies (Sederberg *et al.*, 2010). Delayed temporal factor may not be necessarily a stable predictor of recall performance. Thus, future studies should consider whether our results replicate with memory tests other than the AVLT and should test intra-individual reliability by employing multiple item lists for each participant. In summary, the present study investigated whether temporal contiguity predicted progression to CUD status, a diagnosis linked to increased risk of MCI (Johnson *et al.*, 2018), and demonstrated that temporal contiguity is significantly lower in this group. Moreover, the predictive value of temporal contiguity, taken at delayed recall, was maintained when variables commonly used in research were considered (i.e. *APOE-ε4*). Future research may explore temporal contiguity as a predictor of conversion to clinical diagnoses, such as MCI or AD, in order to investigate its potential for early detection.

Acknowledgements

This work was supported by an Early Career Researcher Studentship Award and by a National Institute on Aging (R01AG27161). This study was also supported by the Clinical and Translational Science Award programme, through the National Institute of Health National Center for Advancing Translational Sciences (UL1TR000427).

Conflicts of interest

All authors declare no conflicts of interest.

Author contributions

Deborah Talamonti (Conceptualization; Formal analysis; Visualization; Writing – original draft; Writing – review & editing). Rebecca Koscik (Data curation; Resources; Validation). Sterling Johnson (Funding acquisition; Project administration). Davide Bruno (Funding acquisition; Methodology; Supervision; Validation).

Data availability statement

The data that support the findings of this study are available from the Wisconsin Alzheimer's Institute (WAI) – Wisconsin Registry of Alzheimer's Prevention (WRAP) project. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the second and third authors with the permission of the WAI and WRAP.

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Received 28 October 2019; revised version received 2 June 2020