

**Title:** Connected Speech and Proper Name Recall Are Associated with Gray and White Matter Microstructure in Adults at risk for Alzheimer’s Disease



PRESENTER:  
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**BACKGROUND:** Connected speech and language (CSL) changes in preclinical and early Alzheimer’s disease (AD) are ecologically valid and clinically meaningful measures that are closely associated with core AD biomarkers (e.g., PET amyloid, CSF, plasma p-tau217).<sup>1-5</sup> However, their neural correlates, particularly the underlying patterns of brain degeneration, remain poorly understood. Multi-shell diffusion weighted-imaging (DWI)–derived microstructural markers in white and gray matter are associated with AD biomarkers and cognition,<sup>6-8</sup> making DWI models well suited to test potential associations between sensitive CSL markers and early neurodegenerative patterns in AD.

**OBJECTIVE:** To investigate associations between CSL, including metrics derived from picture description tasks and proper names from delayed story recall, and DWI measures of white matter microstructure from a priori white matter and cortical gray matter regions of interest.

**METHODS**

Sample  
N=327

NODDI

CSL Data

Analyses

- Participants from WRAP and ADRC cohorts with a processed DWI scan and CSL recordings from neuropsychological testing.
- The neurite orientation dispersion and density imaging (NODDI) model was applied to DWI scans to obtain two measures used in analyses: neurite density index (NDI) and orientation dispersion index (ODI)
- Cookie Theft picture description samples were transcribed and automated feature extraction applied to derive 4 metrics of interest.
- Proper names score from delayed story recall was obtained using item-level analysis from test administration forms.
- Linear regressions with NODDI as outcome & CSL as predictor
- Benjamini-Hochberg correction for multiple corrections
- Partial R<sup>2</sup> quantified effect sizes
- Repeated analyses in cognitively unimpaired (CU) participants only

**RESULTS**

- Significant CSL-DWI associations were found between white matter and gray matter regions (Table 2).
- Two survived correction: (1) in the mixed cognitive status sample, greater parahippocampal gyrus NDI was associated with more PNs recalled; (2) in the CU only sample, lower anterior inferior temporal gyrus ODI was associated with higher use of content words (Figure 1).

**CONCLUSIONS**

- We demonstrated differences in CSL and proper name recall were associated with gray matter microstructural metrics in regions vulnerable to early AD.
- Our results support that CSL metrics are associated with early AD-related neurodegeneration, warranting further evaluation of CSL as an outcome measure for use in AD clinical trials.

**Limitations:** homogeneity of sample

**Future directions:** evaluate additional DWI metrics, associations with AD biomarkers & hemispheric effects

Measures from everyday speech are associated with gray matter microstructure in a largely cognitively healthy sample.

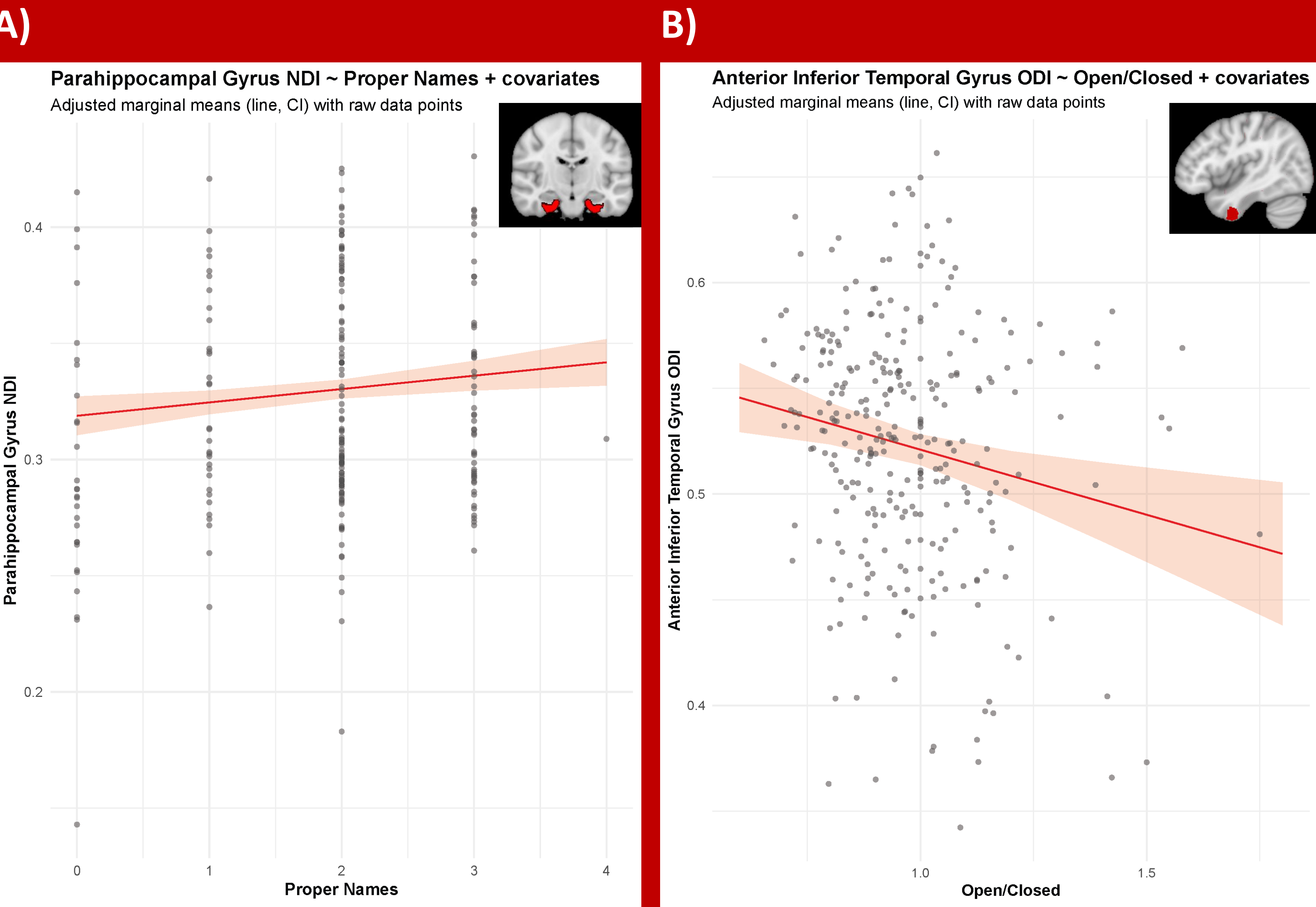
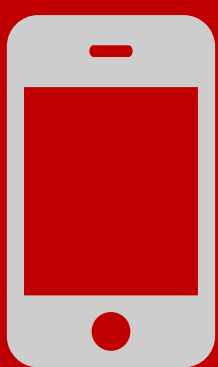


**Figure 1. Plots of the marginal means with 95% confidence interval and raw data points for DWI and CSL associations that survive false discovery rate correction. (A)** depicts the positive association between neurite density index in the anterior parahippocampal gyrus and the number of proper names recalled during delayed Logical Memory or Craft Story recall in the mixed cognitive status sample. **(B)** depicts the negative association between orientation dispersion index in the anterior inferior temporal gyrus and open/closed ratio in the cognitively unimpaired only sample. Covariates included were age at imaging, sex, time between speech sample and imaging, and binary variable for 3-shell versus 5-shell DWI protocol. Significant results that survived correction remained after 1 influential observation was removed for proper names and 1 influential observation was removed for open/closed. Significant results remained after removing n=4 participants with a first language other than English. CSL measures of interest: # of filled pauses, ratio of content words to function words [open/closed ratio], # of content information units [CIUs], and # of CIUs per minute, # of PNs from delayed story recall  
\*Mixed cognitive status sample=91.4% cognitively unimpaired



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|                                                 | Dementia<br>N = 6 | MCI<br>N = 22 | CU<br>N = 299 | Overall<br>N = 327 | p      |
|-------------------------------------------------|-------------------|---------------|---------------|--------------------|--------|
| Age at DWI, mean (sd)                           | 71.61 (8.97)      | 75.88 (7.92)  | 67.02 (7.37)  | 67.70 (7.75)       | <0.001 |
| Age at Speech Sample, mean (sd)                 | 74.12 (10.63)     | 76.89 (8.17)  | 67.84 (7.27)  | 68.56 (7.75)       | <0.001 |
| Age Difference (Speech – DWI, years), mean (sd) | 2.51 (2.17)       | 1.01 (2.24)   | 0.82 (2.84)   | 0.87 (2.80)        | 0.3    |
| Education (years), mean (sd)                    | 15.83 (2.64)      | 15.86 (2.53)  | 16.55 (2.15)  | 16.49 (2.19)       | 0.2    |
| MMSE, mean (sd)                                 | 23.83 (4.17)      | 27.57 (1.89)  | 29.51 (0.79)  | 29.28 (1.36)       | <0.001 |
| R-AVLT, mean (sd)                               | 28.80 (6.83)      | 30.53 (8.13)  | 52.49 (9.48)  | 50.82 (11.04)      | <0.001 |
| Sex (Female), n (%)                             | 2 (33%)           | 9 (41%)       | 195 (65%)     | 206 (63%)          | 0.02   |
| APOE ε4 Carrier (Positive), n (%)               | 4 (67%)           | 9 (41%)       | 108 (36%)     | 121 (37%)          | 0.3    |
| Race, n (%)                                     |                   |               |               |                    | 0.11   |
| American Indian or Alaska Native                | 0 (0%)            | 1 (4.5%)      | 5 (1.7%)      | 6 (1.8%)           |        |
| Black or African American                       | 2 (33%)           | 2 (9.1%)      | 17 (5.7%)     | 21 (6.4%)          |        |
| Unknown                                         | 0 (0%)            | 0 (0%)        | 2 (0.7%)      | 2 (0.6%)           |        |
| White                                           | 4 (67%)           | 19 (86%)      | 275 (92%)     | 298 (91%)          |        |
| Family History of Dementia (Positive), n (%)    | 4 (67%)           | 16 (73%)      | 205 (69%)     | 225 (69%)          | >0.9   |
| Plasma p-tau217 Group, n (%)                    |                   |               |               |                    | 0.001  |
| Negative                                        | 2 (33%)           | 6 (27%)       | 192 (64%)     | 200 (61%)          |        |
| Intermediate                                    | 2 (33%)           | 6 (27%)       | 56 (19%)      | 64 (20%)           |        |
| Positive                                        | 2 (33%)           | 10 (45%)      | 50 (17%)      | 62 (19%)           |        |
| Handedness (Right)                              | 6 (100%)          | 20 (91%)      | 268 (90%)     | 294 (90%)          | 0.4    |

**Table 1. Demographics and clinical characteristics of mixed cognitive status sample.** n=203 were from the WADRC and n=124 were from the WRAP. The NODDI model was applied to most recent DWI data. The speech sample from the neuropsychological visit nearest DWI was used to collect CSL measures. Diagnostic plasma p-tau217 groups (Ashton et al., 2024) are shown here to provide additional clinical information. Sample characteristics between cognitive status groups were compared using Kruskal-Wallis rank sum test or Fisher’s exact test. Abbreviations: APOE- ε4 = apolipoprotein E4 allele; CU = cognitively unimpaired; DWI = diffusion-weighted imaging; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination (Folstein et al., 1983) harmonized between WRAP and ADRC cohorts, previously described (Jonaitis et al., 2024); PACC3 = a harmonized version of WRAP’s Preclinical Cognitive Composite Score-3 (Donohue et al., 2014; Jonaitis et al., 2024) comprised of an average of z-scores of the following three tests: R-AVLT, Wechsler Memory Scale-Revised delayed Logical Memory (Wechsler, 1987), and Trail Making Test Part B (War Department, 1944). R-AVLT = Rey Auditory Verbal Learning Test (Schmidt, 1996); sd = standard deviation.

| Model                         | p       | Adjusted p | Effect Size (R <sup>2</sup> <sub>partial</sub> ) |
|-------------------------------|---------|------------|--------------------------------------------------|
| Mixed Cognitive Status Sample |         |            |                                                  |
| PHG NDI ~ PN_Del              | 0.005** | 0.032*     | 0.036                                            |
| UF_r NDI ~ PN_Del             | 0.043*  | 0.083      | 0.019                                            |
| UF_r NDI ~ open_closed        | 0.023*  | 0.180      | 0.016                                            |
| SLF_r NDI ~ Filled Pauses     | 0.035*  | 0.286      | 0.014                                            |
| SLF_l NDI ~ open_closed       | 0.017*  | 0.18       | 0.018                                            |
| SLF_l ODI ~ open_closed       | 0.016*  | 0.232      | 0.018                                            |
| ITG_a NDI ~ Filled Pauses     | 0.036*  | 0.286      | 0.014                                            |
| STG_a ODI ~ CIUs/Min          | 0.037*  | 0.799      | 0.014                                            |
| CU Only                       |         |            |                                                  |
| STG_a NDI ~ open_closed       | 0.045*  | 0.384      | 0.014                                            |
| MTG_to NDI ~ CIUs/Min         | 0.042*  | 0.451      | 0.014                                            |
| MTG_a ODI ~ open_closed       | 0.010*  | 0.083      | 0.022                                            |
| ITG_a ODI ~ open_closed       | 0.003** | 0.039*     | 0.030                                            |

**Table 2. Significant associations between DWI metrics and CSL measures.** \* indicates significance at p<0.05 and \*\* indicates significance at p<0.01. Delayed PN recall (available for n=219 participants). Abbreviations: CIUs/Min = # of content information units per minute; ITG\_a = anterior inferior temporal gyrus; MTG\_a = anterior middle temporal gyrus; MTG\_to = temporooccipital middle temporal gyrus; NDI = neurite density index; ODI = orientation dispersion index; open\_closed = open/closed ratio; PHG = anterior parahippicampal gyrus; PN\_Del = delayed proper name recall; SLF\_r = right superior longitudinal fasciculus; SLF\_l = left superior longitudinal fasciculus; UF\_r = right uncinate fasciculus.

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