

Background

Event-related potentials (ERPs) provide dynamic, temporally precise measures of cortical responsiveness to external stimuli. As molecular and imaging biomarkers increasingly define Alzheimer's disease (AD), ERPs may offer complementary, objective indicators of functional impairment linked to AD neuropathology. This study examined whether working-memory-related ERPs can detect cortical dysfunction in early-stage AD.

Methods

Twenty-nine biomarker-confirmed AD participants and thirty biomarker-negative, cognitively normal age-matched controls completed a comprehensive neuropsychological battery and EEG recording. ERPs were collected during a delayed match-to-sample (DMS) task and a change-detection (CD) task.

During the ERP assessments, participants wore a 128-channel EEG net (EGI) while observing visual stimuli displayed on a rear projection screen (120° x 80° of the visual field). The averaged waveform of the electrodes around POz was used to generate the waveforms for both DMS and CD match and deviant paradigms.

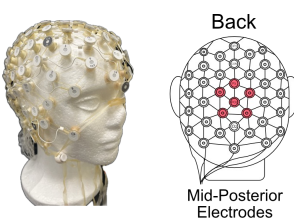


Figure 1: EGI 128-channel electrode cap (Left) Electrodes averaged for generating waveforms (Right)

In the DMS paradigm, participants viewed a three-letter sample word followed by sequential probe words and responded when a match occurred.

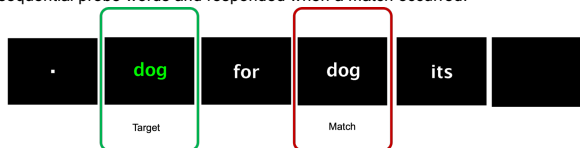


Figure 2. Delayed Match to Sample (DMS) Paradigm: Target word is followed by a series of 3-letter words, one of which will be a match. Subjects press the button when they recognize the matching word.

In the CD task, participants viewed repeated arrays of colored squares and responded when a single-square color change appeared. Target-related ERP components were extracted, and peak amplitudes and latencies were quantified.

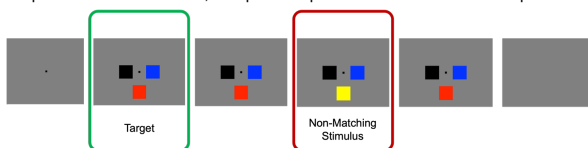


Figure 3. Change detection (CD) paradigm: Target pattern is followed by copies of the same pattern until a change in color occurs in one of the presented shapes. Subjects press the button when they detect the change.

Clinical-burden subgroups were identified within AD using K-means clustering across five cognitive-domain composites: Memory, Executive, Visuospatial/Navigation, Language, and Working Memory. The clusters were clinically validated using MoCA, CDR, ADLQ, and FAS.

Demographics and Cognitive Testing

Table 1: Demographic and Cognitive testing data comparing AD and OC groups.

Subject Profiles	AD	OC	t-Test p-value	Significance
Age (Years)	72.61 (7.35)	71.83 (6.68)	0.6721	ns
Education (Years)	14.62 (2.40)	15.60 (2.43)	0.1247	ns
Clinical Dementia Rating (Sum)	2.67 (2.38)	0.02 (0.09)	<0.0001	****
Clinical Dementia Rating (Global Score)	0.58 (0.27)	0.02 (0.09)	<0.0001	****
MoCA	29.90 (4.70)	27.17 (2.41)	<0.0001	****
Cognivue Computerized Assessment	51.81 (17.17)	74.79 (17.41)	<0.0001	****
Verbal Fluency: F+L Words	24.03 (7.17)	28.73 (8.19)	0.0224	*
Digit Span Backward Total	5.45 (1.80)	7.33 (1.58)	<0.0001	****

Results Overview

Both tasks elicited the expected ERP components (N100, P300, N2b, P3b). Relative to controls, AD participants showed reduced P3b amplitudes across paradigms, indicating altered working-memory-related cortical processing. Within AD, cognitive-domain clustering identified lower- and higher-clinical-burden subgroups, and several DMS/CD ERP markers further differentiated these groups, supporting ERPs as markers of both disease-related dysfunction and clinical heterogeneity.

DMS and CD Group Averages

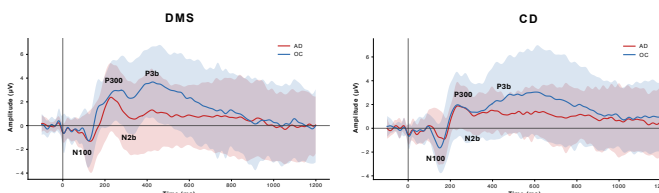


Figure 4. DMS and CD group-average ERP waveforms: Both tasks elicited expected N100, P300, N2b, and P3b responses. Compared with older controls, AD participants showed reduced later positive activity, especially across the P300/P3b time window, suggesting impaired working-memory-related cortical processing.

DMS and CD ERPs Differentiate AD and OC

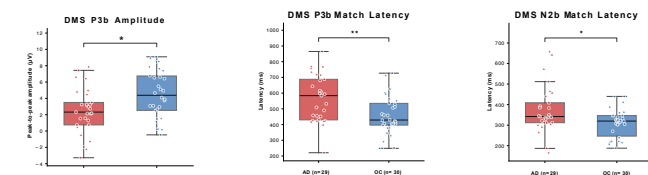


Figure 5. DMS P3b Amplitude: Reduced in AD, suggesting weaker match-related working-memory response.

Figure 6. DMS P3b Match Latency: Delayed in AD, indicating slower late-stage match processing.

Figure 7. DMS N2b Match Latency: Delayed in AD, suggesting slower target discrimination/cognitive control.

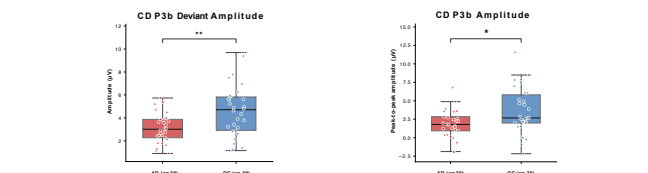


Figure 8. CD P3b Deviant Amplitude: Reduced in AD, indicating weaker response to color-change detection.

Figure 9. CD P3b Amplitude: Reduced in AD, supporting impaired deviant/change-related cortical processing.

DMS and CD ERP Markers Differentiate Lower vs Higher Clinical Burden Within Alzheimer's Disease

Clinical-burden labels were supported by established clinical anchors. Validation measures supported the clinical meaning of the burden groups: MoCA indexed global cognition, CDR indexed dementia severity, and ADLQ/FAS indexed functional impairment. These measures significantly differed between clusters, with the higher-burden group showing worse cognition and greater functional decline.

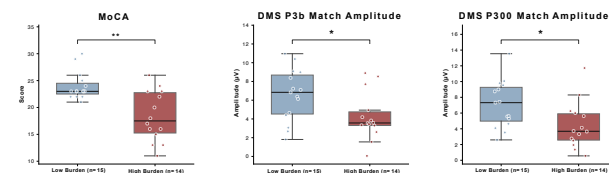


Figure 10. MoCA: Higher clinical burden was associated with lower MoCA scores, indicating worse global cognition.

Figure 11. DMS P3b Match Amplitude: Lower in the higher-burden group, suggesting reduced working-memory-related response.

Figure 12. DMS P300 Match Amplitude: Lower in the higher-burden group, indicating weaker match-related cortical response.

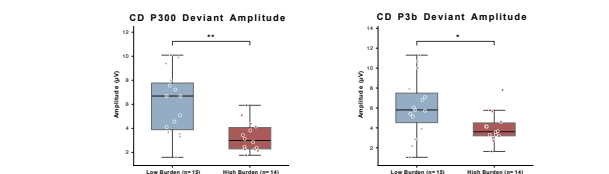


Figure 13. CD P300 Deviant Amplitude: Lower in the higher-clinical-burden group, suggesting reduced cortical response to color-change detection.

Figure 14. CD P3b Deviant Amplitude: Lower in the higher-clinical-burden group, suggesting weaker response to color-change detection.

Conclusion

Working-memory ERPs distinguished biomarker-confirmed AD participants from older controls, with reduced P3b-related responses across DMS and CD tasks. Within AD, cognitive-domain clustering identified lower- and higher-clinical-burden subgroups, and DMS/CD ERP markers further differentiated these groups.

References

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