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# Multidomain Event Related Potentials as Functional Biomarkers of Early-Stage Alzheimer's Disease

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## Background

Biomarkers of Alzheimer's Disease (AD) can significantly improve diagnostic accuracy and play an increasingly important role as disease modifying therapies become available. Imaging, CSF, and blood biomarkers are accurate in detecting structural and pathological changes associated with AD but provide no information about brain function and may not be directly associated with cognitive decline. This highlights the need for functional and dynamic markers that may improve early detection, help monitor disease progression, and objectively assess new treatment interventions.

Neurophysiologic tests such as event-related potentials (ERPs) directly assess cortical function and are good candidates as functional biomarkers. Our previous work using ERPs evoked by the radial patterns of visual motion of optic flow (OF-ERPs) has demonstrated that early-stage AD is associated with selective and significant decreases in OF-ERP amplitudes and that these differences are associates with navigational impairments.

We now extend our work by testing three ERP paradigms that assess cortical function related to cognitive domains commonly affected in AD, including visuospatial perception, working memory, language, and attention.

## Hypothesis

We hypothesized that waveform amplitudes would be significantly decreased in AD, and that waveform latencies would not significantly differ between AD and healthy older controls (OCs). We also predicted that AD subjects would have significantly lower task performance for each paradigm, and that ERP amplitudes would help discriminate between groups.

## Methods

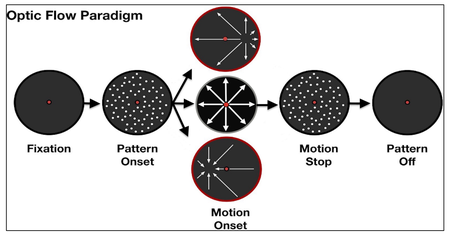
We recruited 16 OCs without cognitive impairment and 16 AD subjects from a memory disorders clinic. Subjects completed a neuropsychological test battery and ERP procedures.

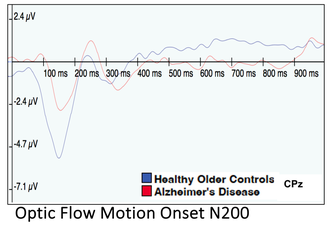
Three ERP paradigms were tested: Optic Flow (OF) with direction of motion-onset discrimination (OF-DMD) to assess dorsal-stream visual processing related to self-motion and navigation. Delayed Match-to-Sample (DMS) with word recognition and Change Detection (CD) with color changing shape arrays. DMS and CD are intended to assess different aspects of frontal and temporal processing (word recognition and color detection)

Participants wear a 128-channel EEG net (EGI) while observing visual stimuli displayed on a rear projection screen (120° x 80° of the visual field).

| Subject Profiles | Group | Mean | Standard Deviation | T-test p-value |
|---|---|---|---|---|
| Age | OC | 68.30 | 5.69 | .065 |
| | AD | 72.37 | 7.51 | |
| Education | OC | 15.27 | 1.71 | .721 |
| | AD | 14.88 | 2.85 | |
| Geriatric Anxiety Index | OC | 1.80 | 3.51 | .646 |
| | AD | 1.56 | 3.74 | |
| Geriatric Depression Scale | OC | 1.60 | 2.97 | .333 |
| | AD | 2.63 | 1.96 | |
| Neuropsychiatric Inventory Questionnaire | OC | 0.46 | 0.78 | .188 |
| | AD | 1.71 | 3.04 | |
| Functional Assessment Scale | OC | 0.00 | 0.00 | <.001 |
| | AD | 8.93 | 0.08 | |
| Activities of Daily Living Questionnaire | OC | 2.67 | 3.50 | <.001 |
| | AD | 25.86 | 17.20 | |
| Clinical Dementia Rating (sum) | OC | 0.08 | 0.19 | <.001 |
| | AD | 3.79 | 2.47 | |
| Clinical Dementia Rating (global score) | OC | 0.00 | 0.00 | <.001 |
| | AD | 0.64 | 0.31 | |
| MoCA | OC | 27.26 | 2.46 | <.001 |
| | AD | 17.56 | 5.86 | |
| Cognivue Computerized Assessment | OC | 79.69 | 8.06 | <.001 |
| | AD | 45.25 | 12.10 | |

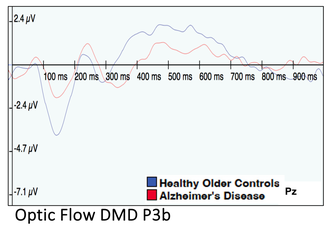
## ERP Paradigms and Group Average Waveforms



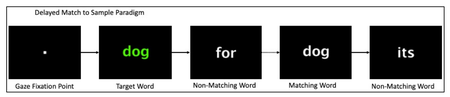




**Optic Flow:** Random dots appear, then move radially toward or away from a focus of motion (optic flow), stop moving, and then disappear. Standard stimuli have a focus of motion (FOM) at mid-screen. Target stimuli have a FOM shifted 30° to the left or right of mid-screen and subjects press a left or right button accordingly. Target stimuli probability is 25%. Motion duty cycle is 20%.

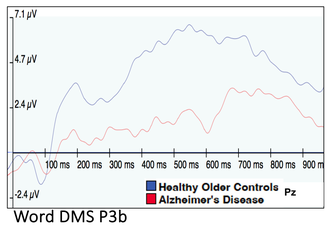
Optic Flow Motion Onset N200
OCs: 201.94ms, 6.31µV
ADs: 217.06ms, 3.86µV



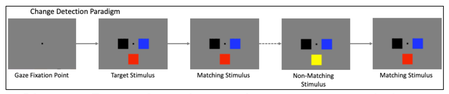

Optic Flow DMD P3b
OCs: 499.25ms, 6.00µV
ADs: 504.75ms, 3.04µV



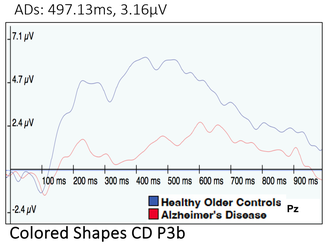

**Delayed Match to Sample:** A word appears in green font. This is followed by five test words in white font, one of which (the target) matches the sample. Participants press a button when the target word appears. Target stimuli probability is 20%.




Word DMS P3b
OCs: 484.38ms, 7.00µV
ADs: 497.13ms, 3.16µV




**Change Detection:** A sample appears consisting of three different colored squares. This is followed by five test images, one of which is different from the sample in having a single different colored square. Participants press a button when the non-matching target appears. Target stimuli probability is 20%.




Colored Shapes CD P3b
OCs: 490.00ms, 6.29µV
ADs: 524.88ms, 2.94µV

**Neurophysiologic Testing Results**

| | | Mean | Standard Deviation | T-test p-value |
|---|---|---|---|---|
| **N200 Motion Onset Latency** | OC | 201.60ms | 11.71ms | .004 |
| | AD | 217.06ms | 15.27ms | |
| **N200 Motion Onset Amplitude** | OC | 5.96µV | 1.30µV | <.001 |
| | AD | 3.85µV | 2.84µV | |
| **P3b Latency: Optic Flow Direction Discrimination** | OC | 513.13ms | 66.33ms | .405 |
| | AD | 504.75ms | 53.11ms | |
| **P3b Amplitude: Optic Flow Direction Discrimination** | OC | 5.90µV | 2.19µV | .003 |
| | AD | 3.61µV | 1.70µV | |
| **P3b Latency: Word Match-to-Sample** | OC | 488.53ms | 68.73ms | .263 |
| | AD | 474.18ms | 80.48ms | |
| **P3b Amplitude: Word Match-to-Sample** | OC | 6.88µV | 2.49µV | <.001 |
| | AD | 3.29µV | 1.04µV | |
| **P3b Latency: Colored Shape Change Detection** | OC | 516.33ms | 61.42ms | .209 |
| | AD | 490.64ms | 90.20ms | |
| **P3b Amplitude: Colored Shape Change Detection** | OC | 5.71µV | 1.50µV | <.001 |
| | AD | 3.29µV | 1.66µV | |

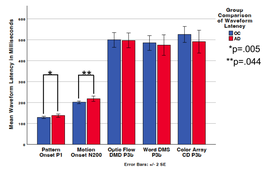
## Neurophysiologic Results

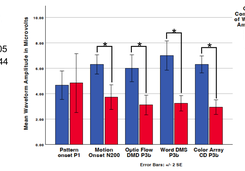
**Group Results by AD Status:** (Using independent-samples t-test.)

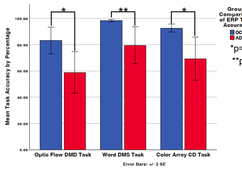
P3b waveform latencies did not differ significantly between the cohorts. Pattern Onset (P1) and Motion Onset (N200) response latencies were significantly greater in the AD group.

P3b and N200 waveform amplitudes were significantly lower in the AD group compared to the OCs, but P1 amplitudes were not significantly different between the cohorts.

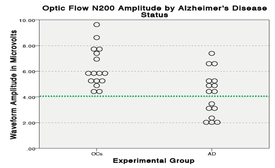
Task accuracy was significantly lower in the AD group in all three ERP paradigms.

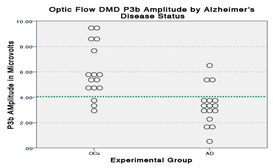


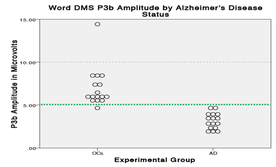



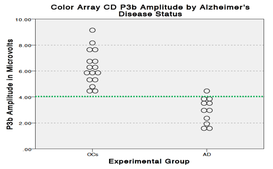




### Visualizing Group Results by Paradigm:



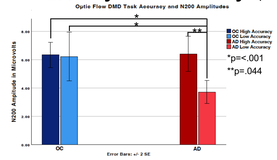



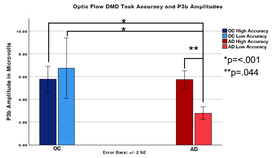



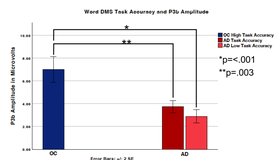

Optic Flow waveform amplitudes exhibit overlap between groups. This paradigm identifies visuospatial impairment and differentiates between AD phenotypes.

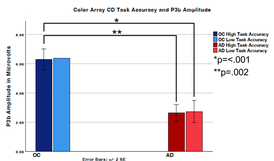
Cutoff values can be established for both the DMS and CD paradigms that discriminate between subjects with and without cognitive impairment at a high degree of accuracy.

**Results by Task Accuracy:** (One-way ANOVA with Tukey post hoc test)




OF paradigm N200 and P3b amplitudes for AD subjects with low task accuracy were significantly reduced. P3b and N200 amplitudes of AD participants with high task accuracy did not differ significantly from OCs.

In the DMS and CD paradigms, P3bs had significantly lower amplitude in AD regardless of task accuracy but did not differ between high and low performers.

## Discussion

Early state AD was associated with significantly decreased P3b amplitudes for all three ERP paradigms.

For the DMS and CD, amplitude differences were independent of task accuracy and clearly discriminate between subjects with and without cognitive impairment.

For the OF paradigm, P3b amplitudes were only reduced among AD subjects with low task accuracy. This was true for N200 amplitudes as well, demonstrating that low-accuracy subjects have impaired cortical function related to the perception of self-motion.

P1 responses did not differ between groups, or according to task accuracy, confirming that amplitude differences are not the result of a global decrease in cortical responsiveness but rather a measure of selective and domain specific dysfunction.

## Conclusion

Our results show that multidomain ERPs can accurately discriminate early-stage AD from normal cognitive aging. Furthermore, our findings suggest that DMS and CD paradigms are more sensitive for identifying those with cognitive dysfunction, but OF-ERPs provide a more specific measure of domain specific cortical disfunction and may discriminate between functional phenotypes of AD.

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