

Longitudinal MEG biomarkers of Alzheimer's disease: sensitivity to disease, severity and progression

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Introduction

Alzheimer's Disease (AD) impairs cognition due to synaptic and neural loss related to amyloid and tau pathology.

Drug development requires sensitive and reliable biomarkers for early phase clinical trials.

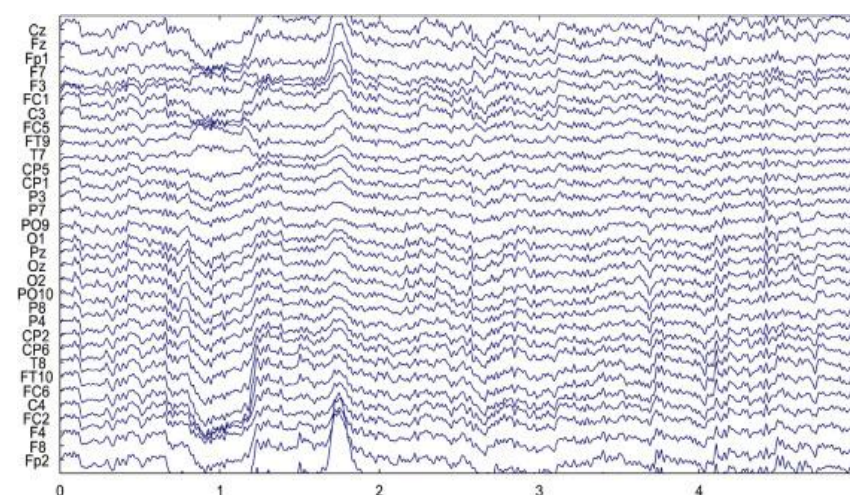
Effects of AD on brain function can be measured by magneto-/encephalography (M/EEG).

An academic-industry collaboration with multi-center longitudinal studies with harmonized MEG protocols to test the sensitivity and reliability of M/EEG biomarkers of AD:

- **NTAD**: New Therapeutics in Alzheimer's Disease study¹
- **SHINE**: Synaptic Health in Neurodegeneration
- **DFP**: Deep and Frequent Phenotyping²

Magnetoencephalography (MEG)

- Measures brain function non-invasively with millisecond precision.
- Well tolerated, patient-friendly, sensitive to neurodegenerative disease.
- Sensitive to changes in synaptic function.



Ageing population

Prodromal AD

Early diagnosis of AD/MCI

Progression

Cam-CAN

DFP

NTAD baseline + 2-week re-test
SHINE baseline

NTAD follow-up
SHINE follow-up (ongoing)

Criteria for M/EEG biomarkers to be suitable to support clinical trials:

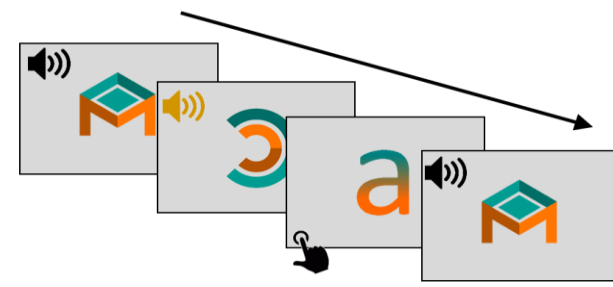
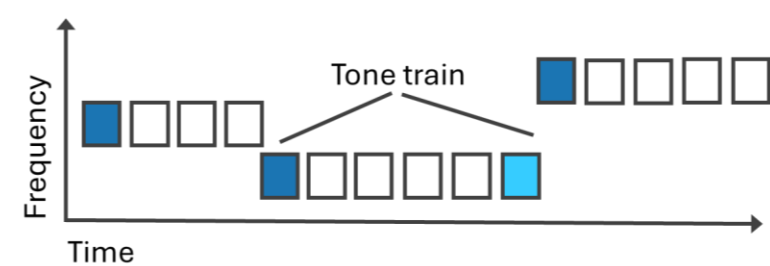
1. Sensitive to the presence of AD

2. Sensitive to the severity of AD

3. Sensitive to the progression of AD

4. Reliable (test-retest)

MEG tasks



Roving mismatch negativity

- MEG responses to unexpected sounds

Audio-visual oddball task

- Associative-mismatch paradigm
- MEG responses to unexpected sounds based on associative learning

Audio-visual motor-task

- Tests early sensory MEG responses
- Control task

Scene repetition task

- Passive memory test
- MEG responses to repeated items

Resting state:

- Eyes open
- Eyes closed
- Spontaneous brain activity

MEG analysis

Preprocessing: standard OSL (Oxford Centre for Human Brain Activity Software Library in Python) pipeline

Epoching & Evoked responses

Sensor level analysis:
Gradiometer Root Mean Square (RMS) responses
Mean RMS amplitude per time-window

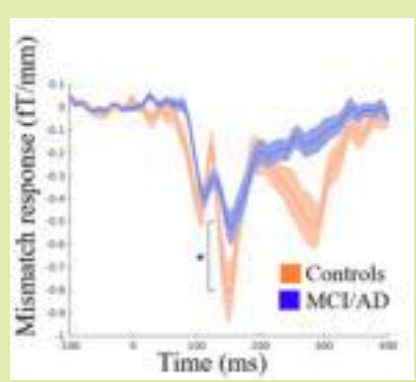
Source space analysis:
Co-register with MRI
Compute source estimates
Mean amplitude per time-window ROI analysis

Statistical analysis (non-parametric)

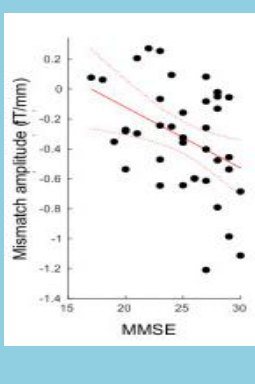
Results

NTAD results from auditory mismatch negativity tasks looking at evoked activity of deviants versus standards

Roving mismatch negativity^{3,4}

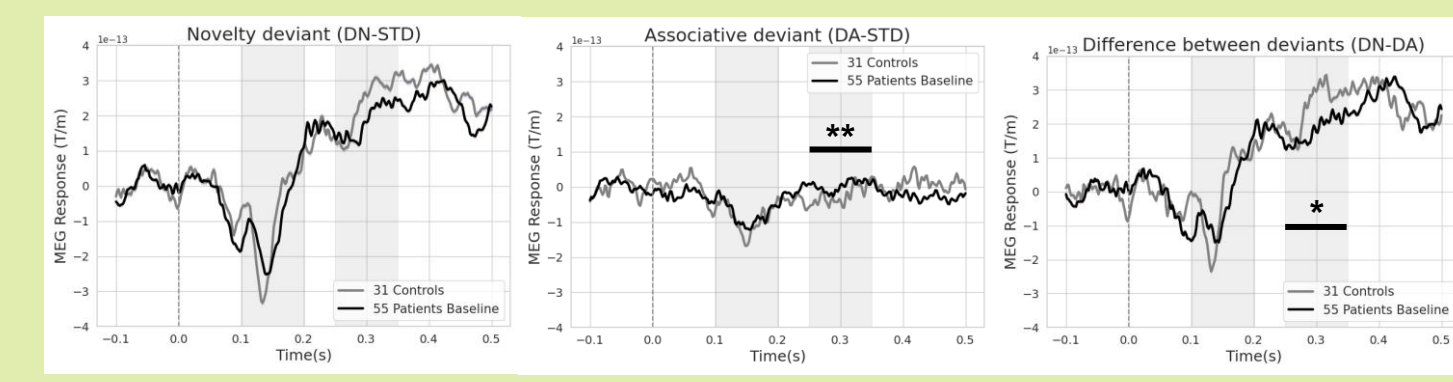


→ AD/MCI reduces mismatch negativity response

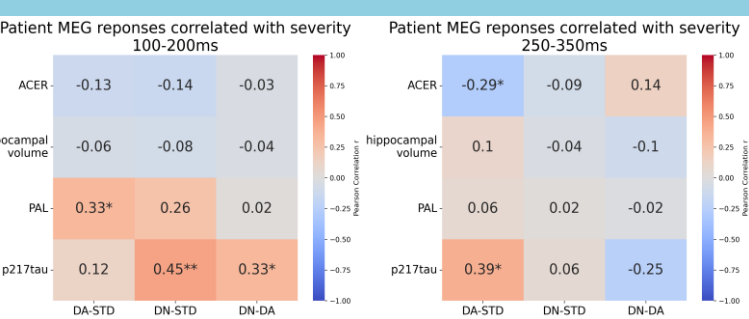


→ Smaller mismatch negativity is associated with poorer cognitive performance

Audio-visual oddball task⁵



→ AD/MCI reduces response to mismatching image-sound pairings



→ Smaller associate deviant responses associated with:

- Poorer cognitive performance
- Impaired associative learning
- Higher levels of p-tau 217

Test criteria

Sensitive to the presence of AD?



Sensitive to the severity of AD?



Sensitive to progression of AD?



Reliable?



Acknowledgements

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References

1. Lanskey JH, Kocagoncu E, Quinn AJ, Cheng YJ, Karadag M, Pitt J, Lowe S, Perkinton M, Raymont V, Singh KD, Woolrich M, Nobre AC, Henson RN, Rowe JB: NTAD study group. New Therapeutics in Alzheimer's Disease Longitudinal Cohort study (NTAD): study protocol. *BMJ Open*. 2022 Dec 15;12(12):e055135.
2. Koychev I, Lawson J, Chessell T, Mackay C, Gunn R, Sahakian B, Rowe JB, Thomas AJ, Rochester L, Chan D, Tom B, Malhotra P, Ballard C, Chessell I, Ritchie CW, Raymont V, Leroi I, Lengyel I, Murray M, Thomas DL, Gallacher J, Lovestone S. Deep and Frequent Phenotyping study protocol: an observational study in prodromal Alzheimer's disease. *BMJ Open*. 2019 Mar 23;9(3):e024498.

Publications

Roving mismatch negativity:

3. Lanskey JH, Jafarian A, Hughes LE, Karadag M, Kocagoncu E, Rouse MA, Adams NE, Naessens M, Raymont V, Woolrich M, Singh KD, Henson RN, Rowe JB. Alzheimer's disease and memantine effects on NMDA-receptor blockade: non-invasive in vivo insights from magnetoencephalography. *Mol Psychiatry*. 2026 Mar;31(3):1587-1596. doi: 10.1038/s41380-025-03288-3.
4. Lanskey JH, Jafarian A, Karadag M, Kocagoncu E, Williams RS, Yadav P, Quinn AJ, Pitt J, Thayanandan T, Lowe S, Perkinton M, Timmers M, Raymont V, Singh KD, Woolrich M, Nobre AC, Henson RN, Rowe JB. Alzheimer's disease and its progression reduce pyramidal cell gain and connectivity. *Alzheimers Dement*. 2025 Oct;21(10):e70805. doi: 10.1002/alz.70805.

Reliability of MEG:

- Jafarian A, Assem MK, Kocagoncu E, Lanskey JH, Williams R, Cheng YJ, Quinn AJ, Pitt J, Raymont V, Lowe S, Singh KD, Woolrich M, Nobre AC, Henson RN, Friston KJ, Rowe JB. Reliability of dynamic causal modelling of resting-state magnetoencephalography. *Hum Brain Mapp*. 2024 Jul 15;45(10):e26782. doi: 10.1002/hbm.26782.

Coming soon:

- NTAD data release and data paper: van Es, Perquin, et al. (in preparation).
- Resting state: van Es et al. (in preparation).
- 5. Audio-visual oddball task and audio-visual motor-task: Krugliak et al. (in preparation).

Conclusion

MEG based biomarkers to AD are sensitive and reliable to detect the presence, severity, and progression of AD.

With this level of reliability we propose that MEG is suitable to support experimental medicine studies of AD/MCI.

The data will be made available via the DPUK Data Portal

<https://portal.dementiasplatform.uk/>