Dynamic causal modelling of the neurophysiology of Alzheimer's disease

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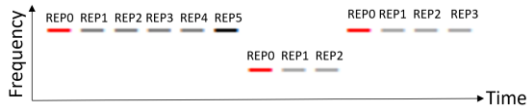
Introduction: Alzheimer's disease is associated with neuronal and synaptic loss, and reduced neurotransmitters such as acetylcholine.[1] Together, these changes affect the physiology underlying cognitive function. Models of cognitive physiology may facilitate clinical trials, and bridge clinical and preclinical models of disease. Here we use Dynamic Causal Modelling (DCM) of MEG to examine the impact of disease on cortical neurons, including superficial pyramidal cells. A disease effect is set in the context of cholinesterase inhibition's effect on the generators of negativity responses, particularly the gain of superficial pyramidal cells.[2]

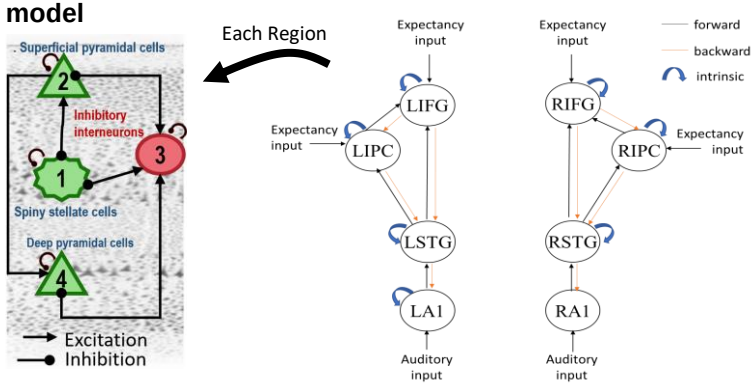
Hypotheses: Alzheimer's disease (1) changes neural responses in a roving mismatch task, (2) reduces the auto-regulation of superficial pyramidal cell gain.

Methods: MEG data was collected from 48 people with Alzheimer's disease or Mild Cognitive Impairment (AD/MCI, amyloid positive) and 14 healthy controls (HC, amyloid negative). Scalp MEG data confirmed group differences. Dynamic causal modelling and parametric empirical Bayes examined the causes of these differences, in terms of intrinsic and extrinsic connectivity in a network of canonical microcircuits.

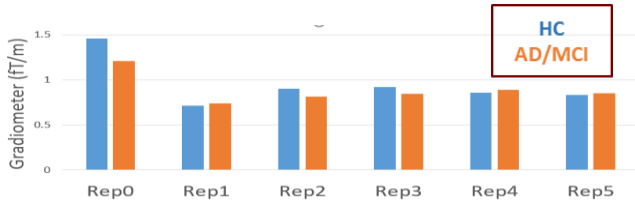
Roving MMN Task



DCM model



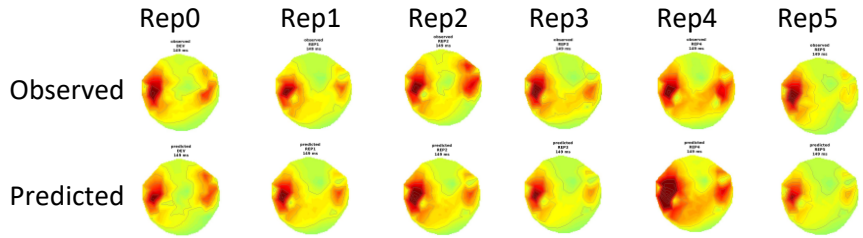
Sensor space results: Mixed ANOVA of scalp ERF responses between 140ms and 160ms:



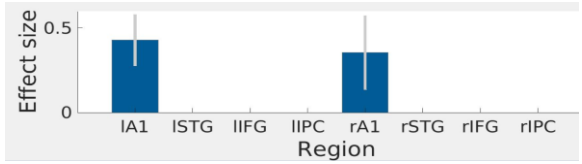
Repeated ANOVA	d.f.	F	p
repetition	5,280	37.8	**>.001**
group	1,56	0.21	.650
repetition x group	5,280	2.26	**.049**

Repetition = repetitions 0-5, group = controls vs patients

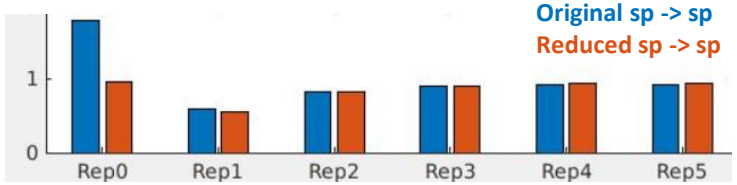
DCM accurately generates the MMN responses over repetitions:



Group differences in auto-regulation of superficial pyramidal cell gain (Bayesian confidence > 95%)



Reduced superficial pyramidal cell gain in auditory cortex in patients contributes to ERF reduction (140-160ms)



Sp->Sp = auto-regulation of superficial pyramidal cell gain.

Conclusion

Alzheimer's disease pathology (AD/MCI) reduces neural responses to deviant tones in a mismatch negativity paradigm.

Parametric Empirical Bayes for group-wise analysis of the parameters of the dynamic causal model confirmed that the physiological difference can be explained by changed gain of superficial pyramidal cells, consistent with prior work with galantamine modulation of acetylcholine.

Future drug studies can test the hypothesis in people with AD/MCI as a prelude to clinical trials of novel therapies.

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