

Alzheimer's disease



- Alzheimer's disease the most common cause of dementia affects 4 million US citizens
 - As more and more Americans live longer, the number affected by Alzheimer's disease will continue to grow unless a cure or effective prevention is discovered.
- Current therapies (cholinesterase inhibitors) have significant limitations
 - Side-effects including nausea, diarrhoea, vomiting
 - Little or no effect on disease progression
- Need for an well tolerated treatment that slows or halts disease progression
- Registration trials require large numbers of patients
- Potential for Experimental Medicine studies to select best compound(s) for late stage trials

Strategies and Solutions using pFMRI and Spatial Memory

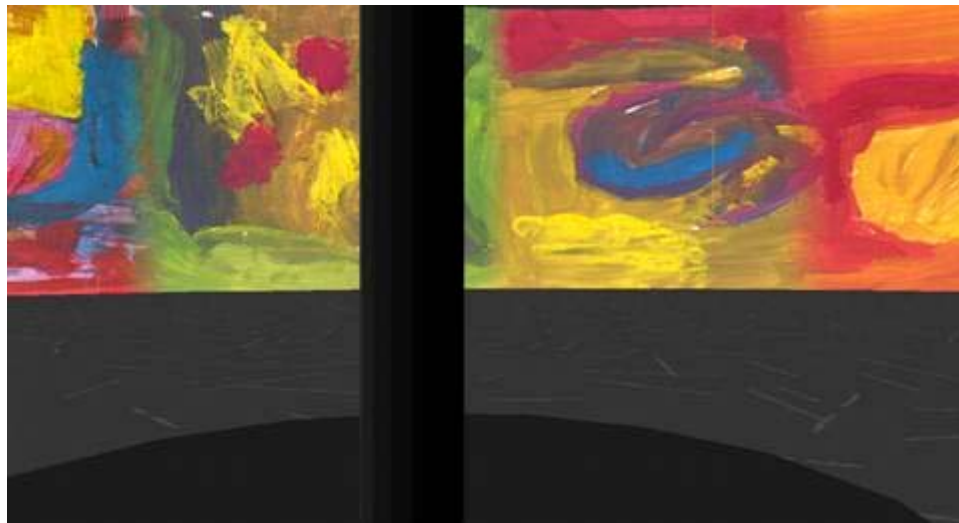
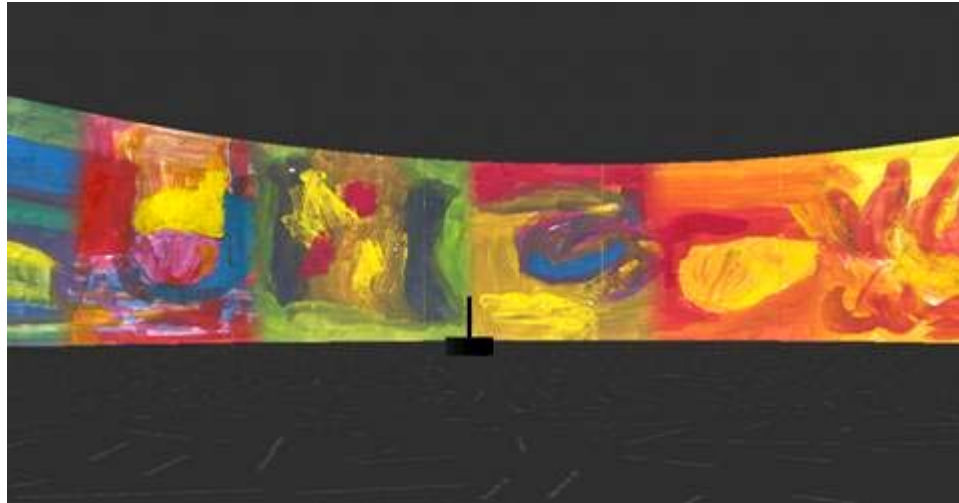
A collaboration with Robin Morris, Mick Brammer and Steve Williams, Institute of Psychiatry

Spatial Memory Flat Mapping & fMRI

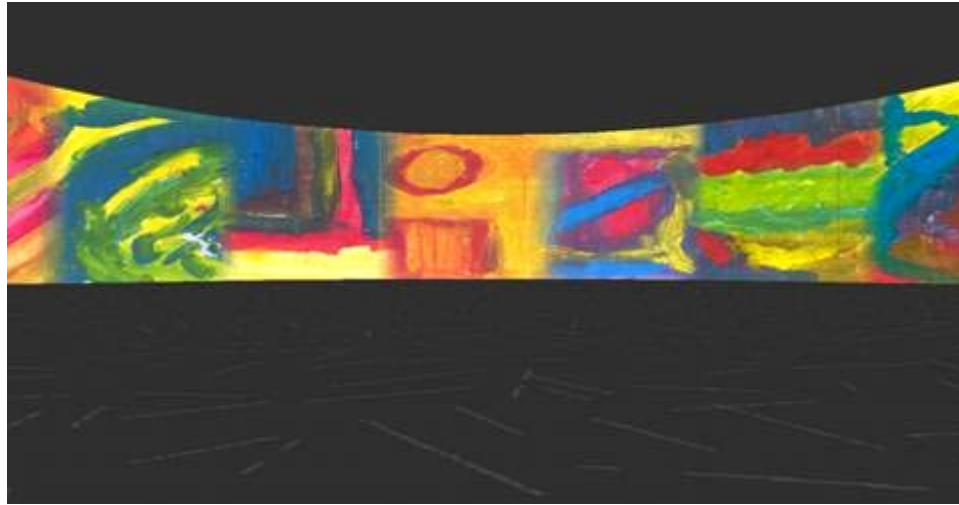


- Develop spatial learning/memory paradigms that engage hippocampal processing
- Image subjects to ensure hippocampal activation during task
- Test subjects during encoding and recall to determine differential activation
- Determine effects of age on performance
- Determine effects of drugs on performance
- Optimise fMRI methods for clinical trials

Arena Pole Paradigm: Encoding



Arena Pole Paradigm: Retrieval



Arena Pole Paradigm: Visual Control Task



Experimental Setup



[Play Movie](#)

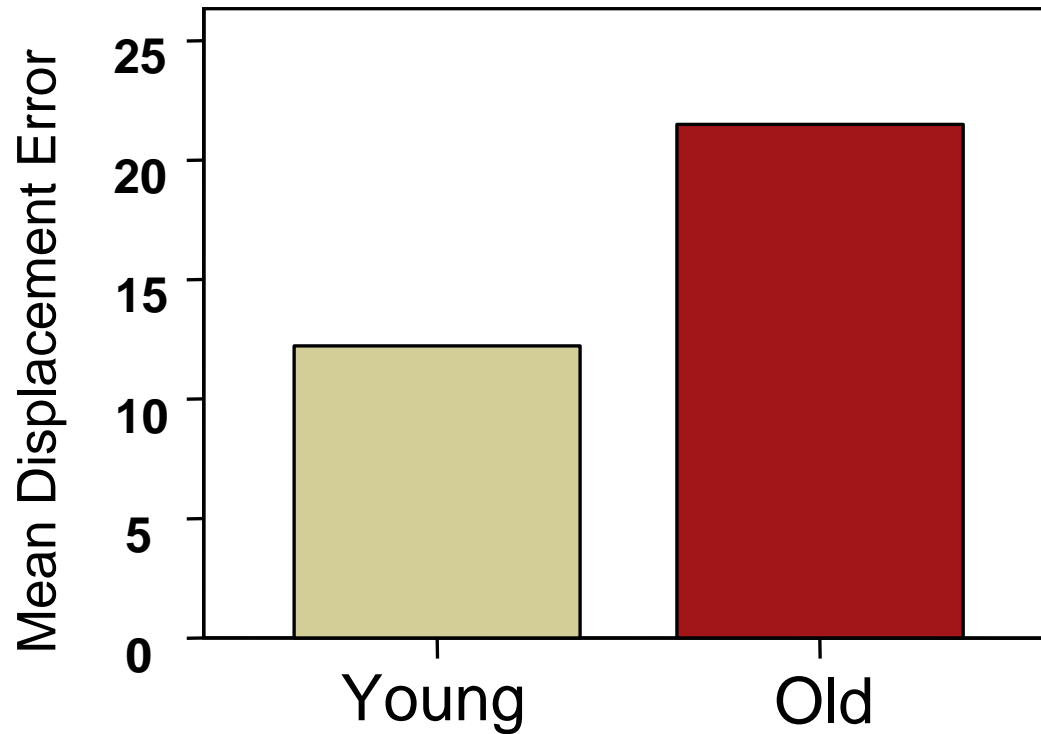
Study 2: Aging effects



Procedures

- Groups
 - Young healthy adults (Mean age = 24 years
age range = 20-26, n=11)
 - Elderly healthy adults (Mean age = 72 years
age range = 64-79, n =9)
- Young participants trained on 18 trials to criterion
- Older participants trained on 36 trials to criterion

Behavioural Results: Young vs Old



Older participants performed significantly worse across three experimental blocks of trials (each block = 6 trials, $t_{17} = -3.542$, $p = .003$)

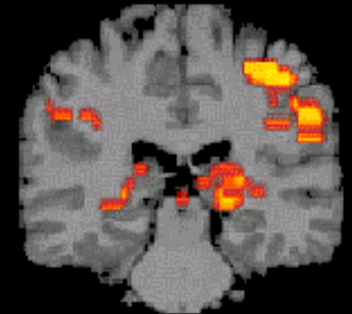
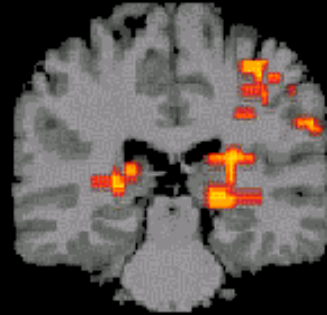
Reduced Hippocampal Activation in Elderly Subjects



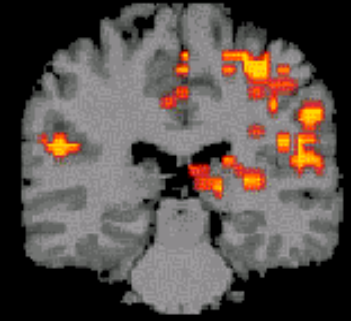
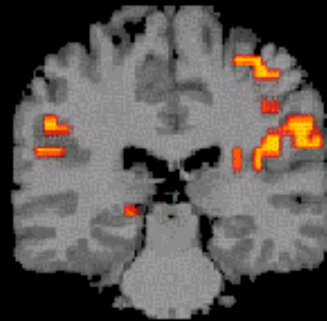
Encoding

Retrieval

Study 2 Young Male
(20-26 years old)



Study 2 Elderly Male
(65-79 years old)



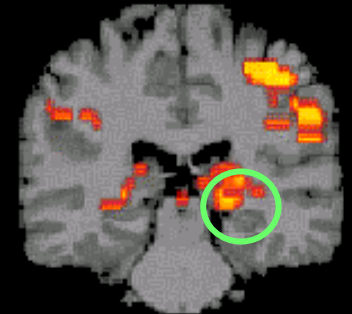
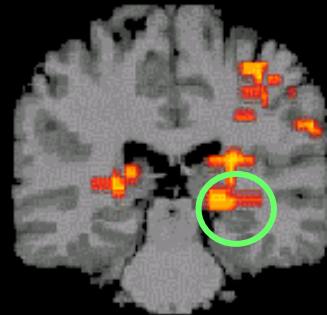
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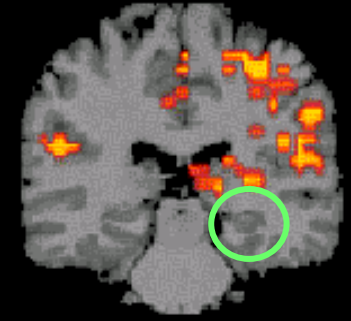
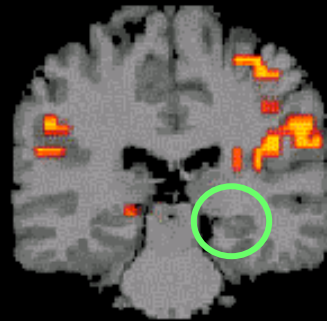
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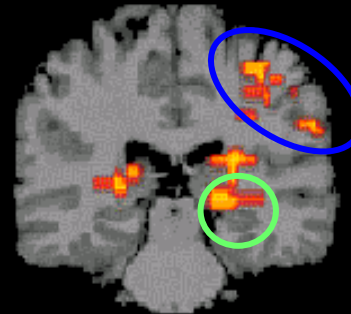
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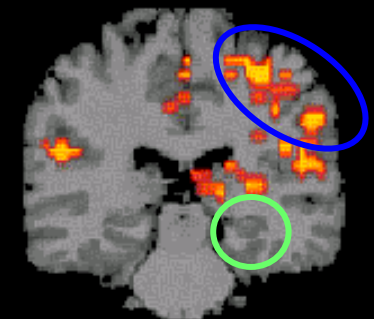
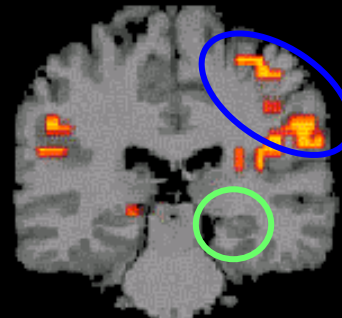
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Retrieval

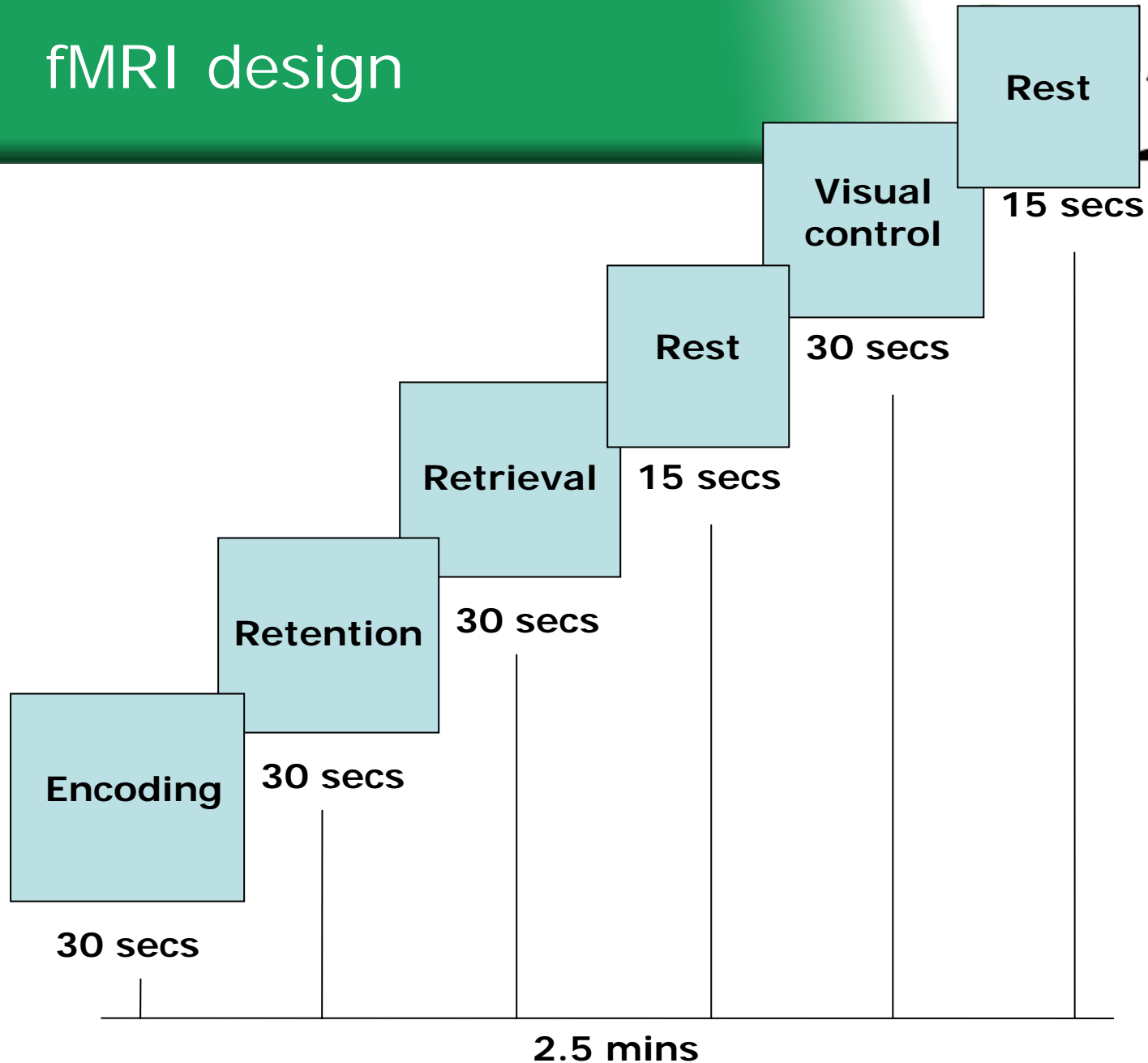
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(20-26 years old)



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fMRI design



Scopolamine and Morris Maze Analogue



- Scopolamine study
- 0.4 mg sc
- 20 young participants
- Scopolamine versus placebo
- Cross-over study
- fMRI measurement
- 3-Tesla

Scopolamine and Morris Maze Analogue



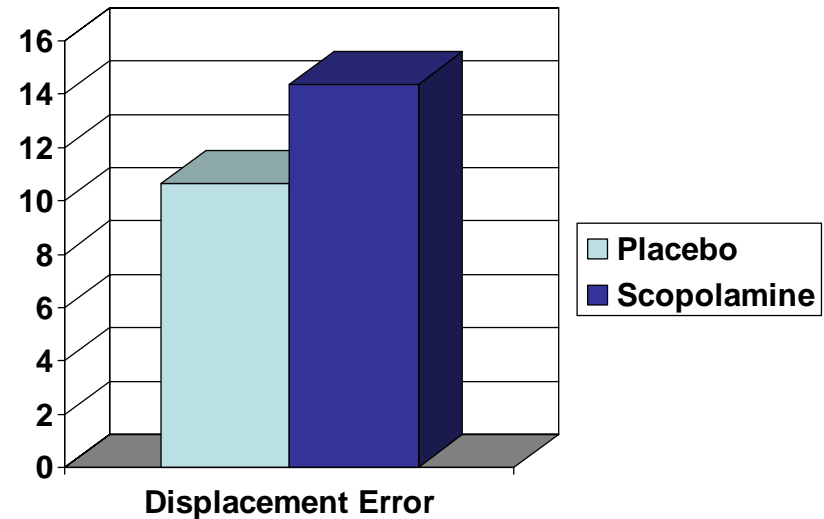
Scopolamine condition showed significantly worse performance

Placebo group:

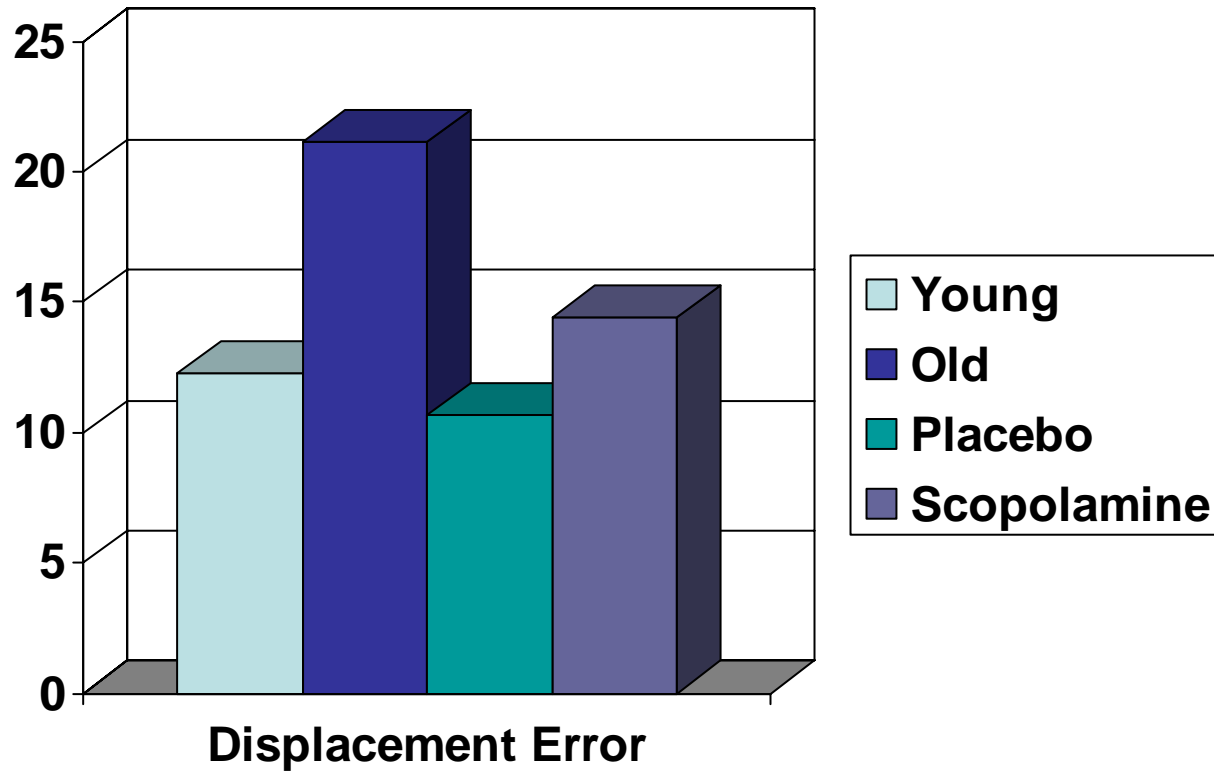
Mean displacement error = 10.67, SD = 4.22

Scopolamine group:

Mean displacement error = 14.39, SD = 7.37



Morris Maze Analogue



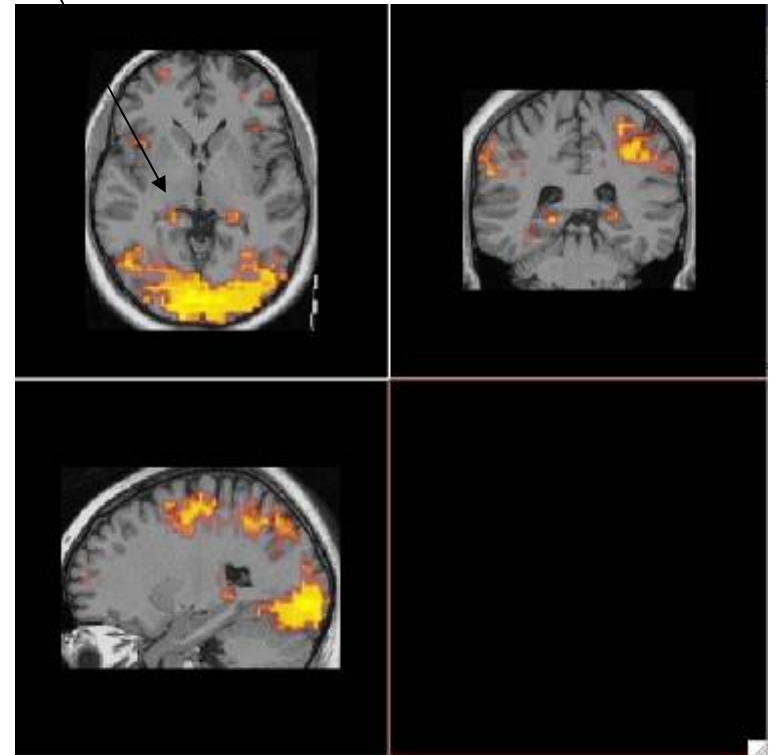
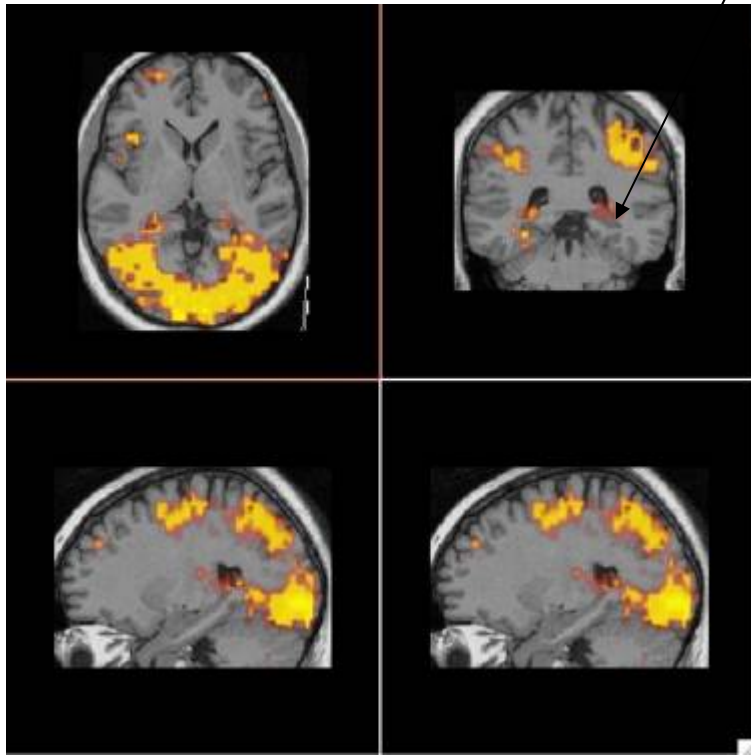
Scopolamine and Morris Maze Analogue



Placebo -Encoding

Placebo - Retrieval

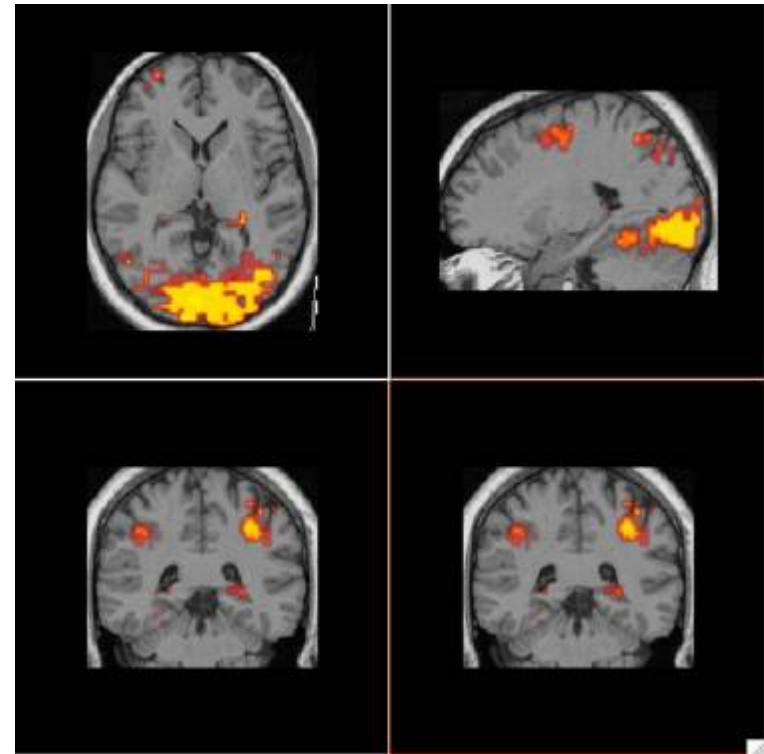
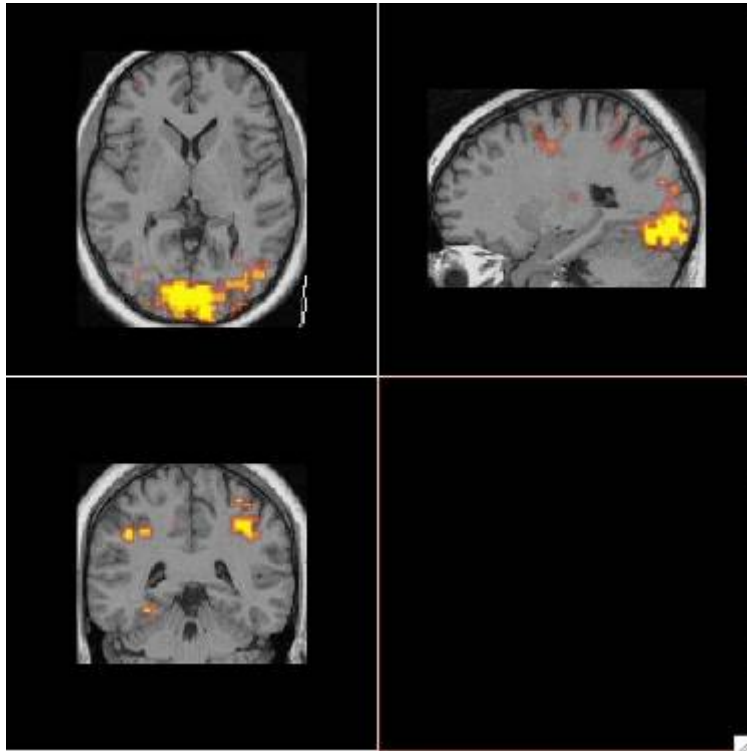
Hippocampus



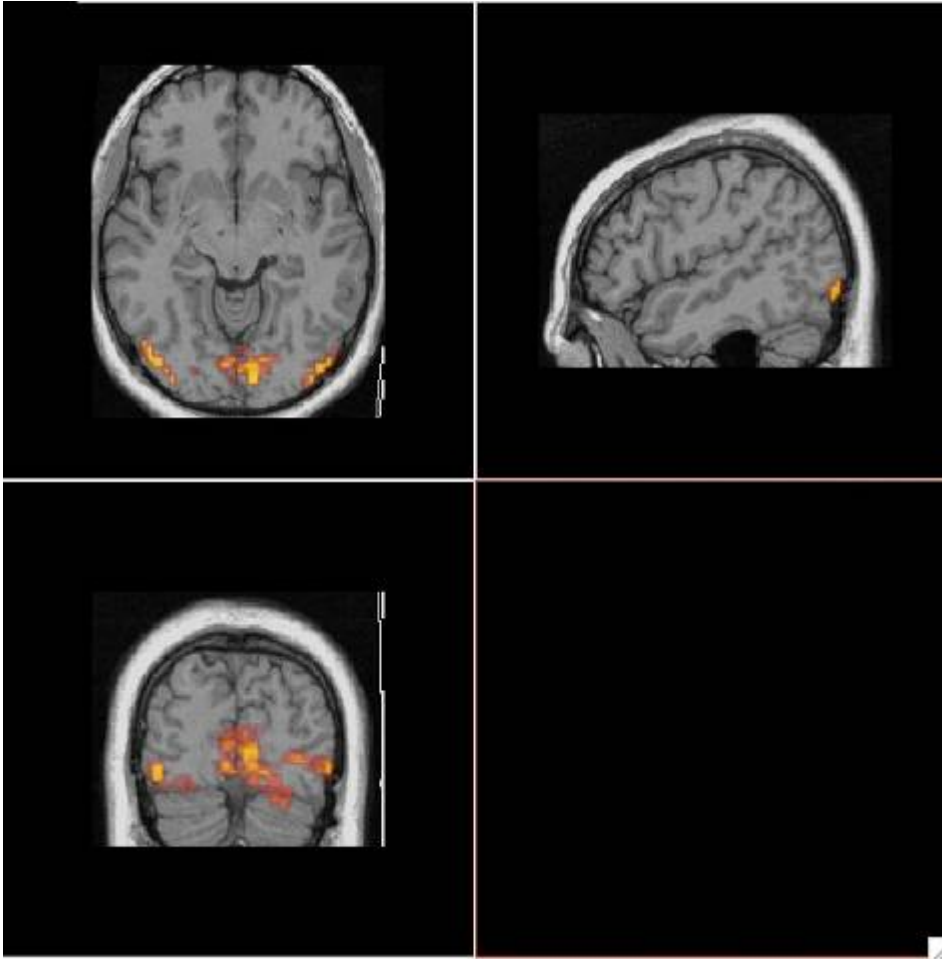
Scopolamine and Morris Maze Analogue



Placebo > Scopolamine
Encoding Retrieval



Scopolamine and Morris Maze Analogue



Placebo
>
Scopolamine

Future Developments



- Software validated with young healthy volunteers given placebo, scopolamine and butylscopolamine
- Flat mapping development parallels testing
- Spatial learning in a natural environment (e.g. shopping trip)