Alterations in working memory networks in amnestic Mild Cognitive Impairment

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Introduction

Patients with amnestic Mild Cognitive Impairment (aMCI) have clear deficits in episodic memory and it is considered to be a prodromal phase of Alzheimer's Disease[1]

In contrast, their working memory remains relatively preserved[2]

Some previous fMRI work has looked at working memory in aMCI but results are mixed[3,4,5,6]

Aims

Investigation of fMRI BOLD activity in aMCI patients during a working memory task, compared to healthy controls.

Are there behavioural and/or fMRI BOLD differences between the groups?

Methods

Participants

10 aMCI patients, 11 healthy matched controls

aMCI Diagnosis based on Petersen Criteria[7]:

- Memory complaints
- Objective memory impairment
- Other cognitive function normal
- CDR score of 0.5
- Intact activities in everyday life

Procedure

Neuropsychological assessment carried out to include tests of memory, executive function and intelligence.

fMRI Task - Standard N-Back procedure with three levels; 0-Back, 1-Back, 2-Back.
Presented in separate blocks in a fixed random order.
Each block repeated 3 times.

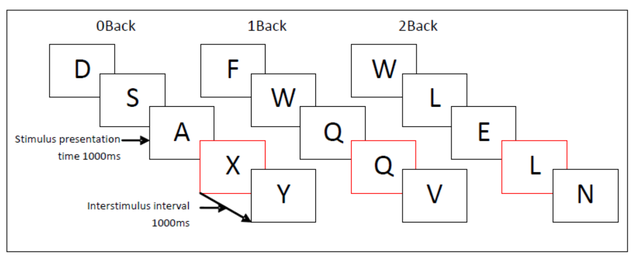


Image Acquisition and Analysis

Scanning was performed on a 3T GE scanner (38 slices, TR 2000ms, TE 30ms). High resolution T1-SPGR structural scan also collected

Pre-processing and analysis used SPM8. Normalisation carried out with DARTEL. Smoothed with an 8mm FWHM Gaussian kernel. Movement included as covariate in 1st level models. Age and IQ included as covariates in 2nd level models

Control group activity looked at first and then compared to aMCI patients

Cluster level statistics reported throughout

Results

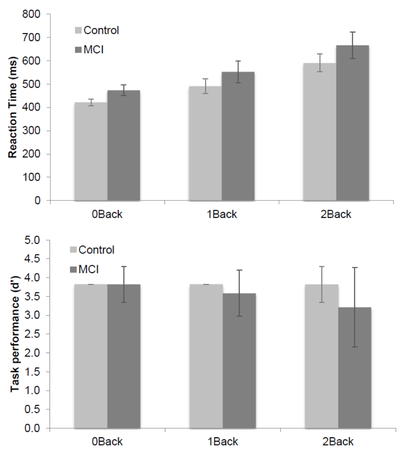
Behaviour: Neuropsychology

aMCI patients only impaired on memory tasks

	Control	aMCI	p(difference)
N	11	12	-
Age	70.27 (6.20)	71.40 (6.35)	.685
No. Male	7	5	-
Intelligence (mean, SD)			
Yrs in education	15.64 (4.13)	16.00 (4.30)	.845
NART IQ	121.55 (6.04)	120.10 (8.24)	.650
WASI IQ	123.73 (15.74)	117.90 (16.20)	.414
CVLT (mean, SD)			
T Score	56.55 (11.34)	38.80 (15.11)	.006
Short Delay	.227 (.848)	-1.350 (1.334)	.004
Long Delay	.409 (.769)	-1.250 (1.670)	.014
WMS-III (mean, SD)			
LM Immediate	11.82 (2.86)	7.80 (3.71)	.011
LM Delay	13.00 (2.00)	9.20 (3.33)	.005
VR Immediate	13.09 (3.08)	8.90 (4.25)	.017
VR Delay	14.82 (2.60)	9.10 (4.18)	.002
Executive Function (mdn, IQR)			
Hayling	6.00 (1.00)	6.00 (3.00)	.214
Brixton	6.00 (5.00)	2.00 (4.00)	.368
TMT (mdn, IQR)			
A Time	34.00 (20.00)	40.00 (19.00)	.136
B Time	61.00 (48.00)	92.00 (49.00)	.119

Behaviour: N-Back

No differences between groups for reaction time (RT), some differences on easier levels for performance

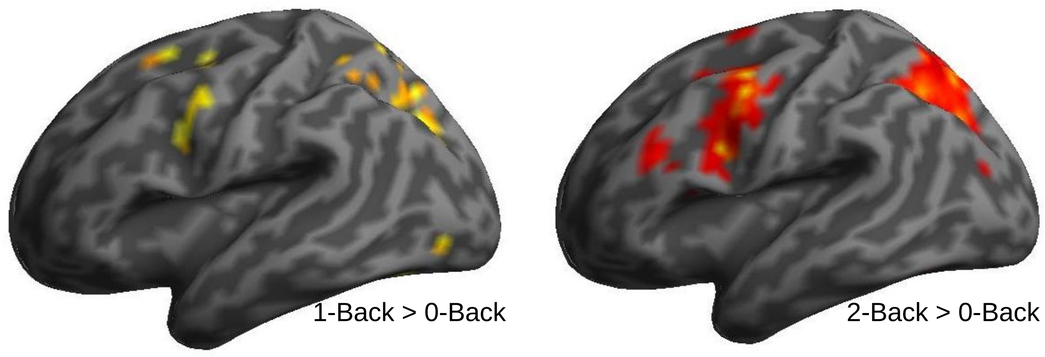


(A) Behavioural performance as indicated by reaction time (Mean, SEM). (B) Behavioural performance as indicated by d' (Mdn, IQR)

RT repeated measures ANOVA (group by difficulty). Main effect of difficulty ($F(2,38)=24.91$, $p<.001$) significant. Main effect of group and interaction non-significant ($F=2.17$ and $F=.1$ Accuracy data required non-parametric analysis. Slight group differences at 0Back ($Z=-2.261$, $p=.035$) and 1Back ($Z=-2.165$, $p=.029$), but not 2Back ($Z=-1.525$, $p=.132$)

fMRI: Control Group Task Activations

1-Back and 2-Back versus 0-Back
Significant activations in expected areas



1-Back > 0-Back

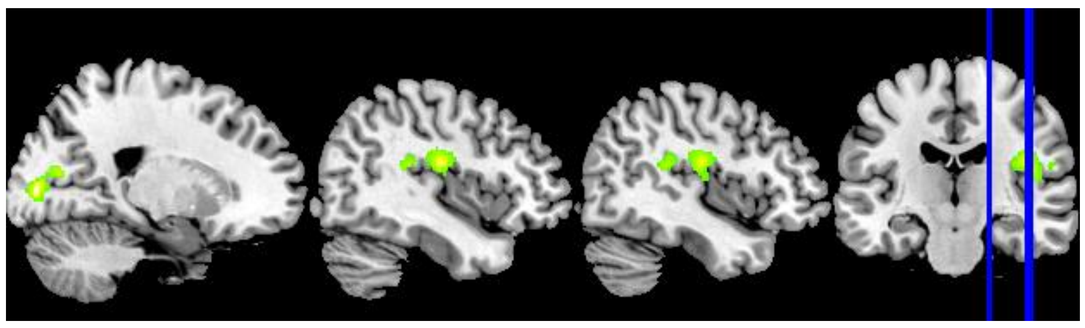
2-Back > 0-Back

fMRI: aMCI versus Control Activations

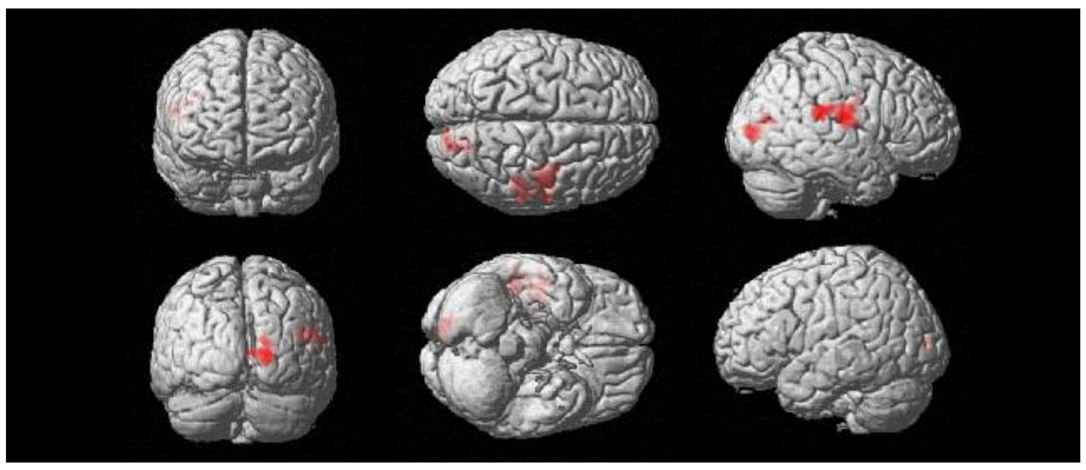
Greater activations in aMCI patients in lingual gyrus and insula
No areas of greater activations in controls than patients

Region	BA Area	Peak MNI Co-ordinates	Cluster Size	$p_{(FWE-corr)}$
R Lingual Gryus	17	20 -85 4	565	.017
R Insula	13	42 -15 19	965	.001
R Insula	13	44 -36 18	477	.033

Slices through the peak voxels from table above:



Rendering of significant clusters:



Discussion

Patients recruited additional brain regions compared to controls, in particular, the right insula:

- Known to be recruited in working memory tasks[9]
- Grey matter loss is a common feature of MCI[10,11]
- Associated with increased rCBF in MCI[12]
- Shows increased activation in MCI patients on a variety of tasks including associative memory[13] and the Stroop Task[14]
- Activity also increased in older adults at genetic risk of Alzheimer's Disease[15]

Could this be a mechanism to compensate for mild neuronal loss?

These network differences were present despite only mild impairment in behaviour

Expanding beyond spatial and episodic memory tasks in MCI may help understand neural changes more fully

1.Gauthier et al (2006) *The Lancet 367(9518),1262-70* 2.Bennett et al. (2002) *Neurology 59(2),198-205* 3.Döhnel et al (2008) *Neuropsychologia 46*(1),37-48 4.Rombouts et al (2005) *Hum Brain Mapp 26*(4),231-9 5.Saykin et al (2004) *Brain 127*(7),*1574-83* 6.Bokde et al (2010) *J Alzheimers Dis 21*(1),103-18 7.Petersen et al (2001) *Arch Neurol 58*(12),*1985-92* 8.Owen et al (2005) *Hum Brain Mapp 25(1),6-59* 9.Kurth et al (2010) *Brain Struct Funct 214(5-6),519-34* 10.Karas et al (2004) *Neuroimage 23,708-16* 11.Pennanen et al (2005) *J Neurol Neurosurg Psychiatry 76,11–14* 12.Scarmeas et al (2004) *Neuroimage 23(1),35-45* 13.Hämäläinen et al (2007) *Neurobiol Aging 28(12),1889-1903* 14.Kaufmann et al (2006) *Cortex 44,1248-55* 15.Yassa et al, (2008) *Neurology 70(20),1898-1904.*

This study was supported by the P1vital CNS Experimental Medicine Consortium (members AstraZeneca, GlaxoSmithKline, Lundbeck, Organon (a subsidiary of Merck) and Pfizer). GKW was partly supported by the NIHR Comprehensive Biomedical Research Centre Programme, Oxford. AS and SCRW were partly supported by the NIHR Biomedical Research Centre for Mental Health.