Characterization of cognitive function with the CANTAB in individuals with amnestic MCI in relation to hippocampal volume, amyloid and tau status: Preliminary baseline results from the PharmaCog/European-ADNI Study

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Introduction

- Mild Cognitive Impairment (MCI) is a heterogeneous condition with differential underlying pathophysiologies.
- Accumulation of beta amyloid (Abeta) and/or Tau in the brain is associated with greater neurodegeneration and cognitive decline and a prelude to Alzheimer's disease (AD).
- Understanding MCI populations for hippocampal and fronto-striatal dependent memory deficits and biomarker abnormalities will help identify a more homogeneous population with a greater risk of developing AD.
- The objective of this study was to examine the relationship between performance on the CANTAB tasks probing hippocampal and fronto-striatal function, hippocampal volume and CSF biomarkers.

Methods

- Participants (aged 50-84) were recruited from the PharmaCog (E-ADNI; work package 5), European multicentre study (Table 1).
- Inclusion criteria: 1) subjective memory complaint, 2) 1SD deficit in memory (Logical memory II subscale – delayed paragraph recall), 3) MMSE between 24 and 30; 4) CDI=0.5 (Memory box at least 0.5); 5) diagnosis of amnestic MCI.
- 145 individuals underwent clinical and cognitive evaluation using the CANTAB tests, high resolution 3T MRI with MPRAGE and lumbar punctures for the assessment of cerebrospinal fluid (CSF) levels of Ab42, tau and p-tau. Individuals were divided into Amyloid+ (CSF-POS) and Amyloid- (CSF-NEG) based on CSF Ab42 levels (CSF-POS: >550 pg/ml); CSF-NEG: <550 pg/ml).
- The relationships between biomarkers and cognitive task performance were assessed through a series of linear regression models using LM in R software. All models were adjusted for age and years of education. Differences between CSF-POS and CSF-NEG group were assessed using t-tests or Chi squared tests.

Baseline Characteristics by CSF Amyloid Status								
	CSF Abeta (+ve) N=55		CSF Abeta (-ve) N=90		Overall N=145		Range	Significance
	Mean	SD	Mean	SD	Mean	SD		
Age (years)	69.8	6.7	68.8	7.7	68.2	7.3	50-84	T=-0.8 p=0.40
MMSE	26.0	1.8	27.0	1.8	26.6	1.9	23-30	T=3.1 p>=0.01
	Percent (%)		Percent (%)					
Gender (% male)	43.6	-	42.2	-	42.8	-		0.3 (df=1) p= .87
Education (% <=10y)	45.5	-	56.8	-	53.1	-		2.1 (df=1) p=.15

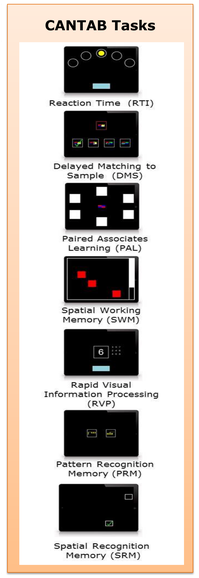
Table 1. Baseline characteristics by CSF Amyloid Status

Results

- At baseline, CSF-POS individuals showed worse performance relative to CSF-NEG individuals on fronto-striatal dependent recognition and working memory tasks (i.e. SRM, DMS and SWM) (Table 2), with effect sizes ranging from -0.12 to -0.66.
- Worse performance on the paired associate learning (PAL) task of episodic memory was associated with reduced hippocampal volume, higher CSF levels of tau and p-tau and increased Tau/Abeta42 ratio (Table 3). Worse performance on the pattern recognition memory (PRM) task (immediate and delayed) was also associated with reduced hippocampal volume. Both PAL and PRM were also associated with a functional outcome measure (i.e. FAQ)(Table 3). Worse performance on the spatial recognition memory (SRM) task was associated with low CSF levels of Abeta42, higher CSF levels of tau and p-tau and increased Tau/Abeta42 ratio (Table 3).
- Significant associations were also found between hippocampal volume, CSF biomarkers and spatial working memory (SWM), delayed matching to sample (DMS) and sustained attention (RVP) (Table 3).

	Overall		CSF Amyloid (+ve)		CSF Amyloid (-ve)	
	Mean	SD	Mean	SD	Mean	SD
RTI Five choice reaction time (median)	417.9	96.4	414.5	97.7	420.5	96.0
DMS % correct all delays	67.9	16.3	62.5***	16.6	72.0	14.9
PAL Total errors adjusted	70.5	40.1	73.3	38.3	68.5	41.6
SWM Between errors	42.4	21.3	47.4**	21.3	38.7	20.6
SWM Strategy	27.2	9.2	28.0	8.9	26.6	9.4
RVP A Prime	0.8	0.1	0.8	0.1	0.8	0.1
PRM Immediate % correct	77.6	15.2	75.5	14.5	79.2	15.6
PRM delayed % correct	65.3	17.9	63.5	17.4	66.6	18.3
SRM % correct	63.7	13.5	58.7***	13.6	67.3	12.3
Neuropsychiatric Inventory	8.8	10.3	9.6	11.1	8.3	9.7
Functional Assessment Questionnaire (FAQ)	2.5	2.3	2.6	2.5	2.5	2.3
Geriatric Depression Scale	2.6	1.9	2.7	1.9	2.6	1.9
Abeta42 (pg/mL)	693.0	293.5	419.1***	86.9	860.4	245.1
p-tau (pg/mL)	67.6	34.8	79.1***	37.6	60.6	31.1
Tau (pg/mL)	475.5	346.4	556.4**	334.5	426.1	346.0
Left-Hippocampal Volume (mm^3)	3176.6	688.9	3131.8	682.2	3207.6	696.9
Right-Hippocampal Volume (mm^3)	3310.6	662.7	3176.1*	606.7	3403.6	687.8
IntraCranialVol (mm^3)	1338396.2	177864.9	1323908.3	186939.6	1348409.9	172006.4
Abeta (Positive) <550mL	37.9					
APOE e4 (%)						
APOE e4 allele (1 copy)	37.3		52.7***		27.8	
APOE e4 allele (2 copies)	8.3		20.0***		1.1	

Table 2. Cognition and Biomarker data; ***p<0.01 , **p<0.05 and *p<0.1 compared to CSF Amyloid (-ve)



	Memory Tasks						Executive Function	Sustained Attention	Processing Speed
	Episodic Memory	Working Memory	Recognition /Working Memory	Recognition Memory	Recognition Memory	Recognition Memory			
	PAL Errors	SWM Errors	DMS	SRM	PRM Immediate	PRM Delayed	SWM Strategy	RVP	RTI
Tau	***		**	*				***	
Ptau	**	*	*	**				***	
Abeta		***	***	**			**	*	
LHPV	***			*		**		**	
RHPV	***		*		**	*		***	
IC Vol							***		
CSF Abeta (+ve)		**	***	***					
Tau/Abeta	***	***	***	***				***	
GDS									
FAQ	***					***	**		
NPI		**					***		

Table 3. Relationship between cognitive function and biomarkers. *p <= 0.10, ** p<=0.05, *** p<0.01.
Paired Associates Learning (PAL) Total Errors Adjusted, Spatial Working Memory (SWM) Between Errors, Strategy Score, Delayed Matching to Sample (DMS), Spatial Recognition Memory (SRM), Pattern Recognition Memory (PRM), Immediate and Delayed (% correct), Rapid Visual Processing (RVP) A Prime, Reaction Time (RTI), Median 5 Choice Reaction Time, Functional Assessment Questionnaire (FAQ)Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI). Left Hippocampal Volume (LPHV), Right Hippocampal Volume (RPHV), Intra-Cranial Volume (IC Vol).

Discussion

- CSF Amyloid+ individuals showed greater deficits in CANTAB tasks measuring fronto-striatal function compared to CSF Amyloid- individuals. These findings suggest that despite both groups having amnestic MCI with subjective and objective memory deficits at screening, Amyloid+ amnestic MCI individuals also show additional fronto-striatal deficits.
- CANTAB tasks measuring recognition and working memory and sustained attention were significantly associated with, 1) CSF Abeta42, tau, p-tau, Tau/Abeta42 and 2) hippocampal volume, with worse performance on these tasks associated with higher CSF tau, p-tau and tau/Abeta42 and lower Abeta42 and hippocampal volume (Figure 1).
- Hippocampal dependent tasks including PAL and PRM were associated with hippocampal volume. Performance on the PAL task of episodic memory was highly correlated with hippocampal volume (accounting for 26% of the variance) suggesting that it may be a useful diagnostic marker for use alone or in combination with other biomarkers (i.e. hippocampal volume or CSF biomarkers) in identifying patients at risk of MCI.
- Hippocampal dependent memory (i.e. PAL and PRM) and fronto-striatal executive function (i.e. SWM strategy) were also associated with functional outcome.
- The findings have implications for identifying MCI patients at risk of developing AD and enriching a more homogenous population for clinical trials with fronto-striatal and hippocampal dependent attention and memory deficits, neurodegeneration and CSF biomarker abnormalities consistent with prodromal AD populations.

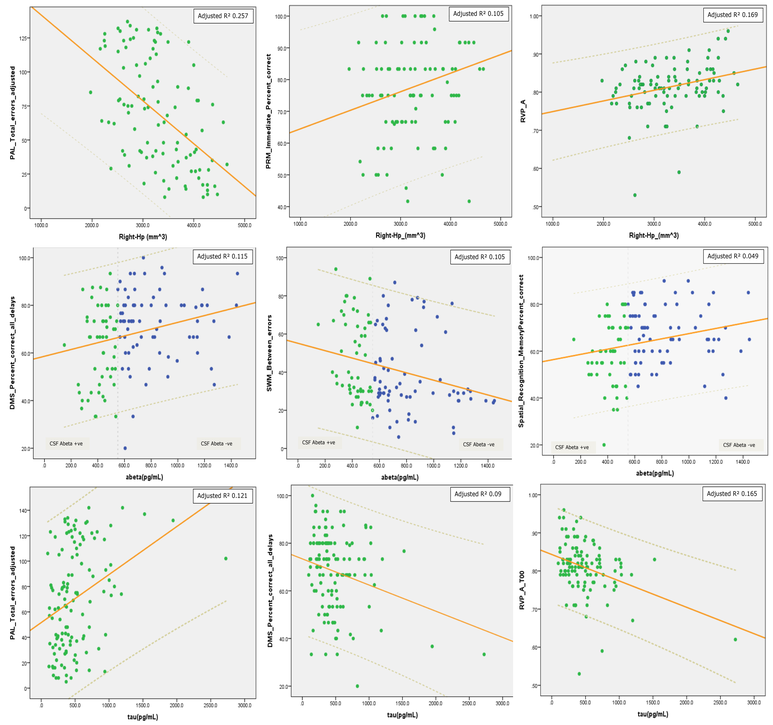


Figure 1. Relationship between cognitive function, CSF biomarkers and hippocampal volume.

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