Oculomotor responses linked to cognitive markers for Alzheimer's disease can enhance risk profiling in patients with Mild Cognitive Impairment

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Background

Combining eye-tracking methodologies with a cognitive marker for Alzheimer's disease (AD), namely the Short-Term Memory Binding Test (STMBT), has enhanced the effectiveness of the assessment increasing its sensitivity and specificity to 100% (1). Whether such a classification accuracy would help identify patients with Mild Cognitive Impairment (MCI) who present with a short-term memory binding (STMB) phenotype compatible with that seen in AD remains unexplored.

Methods

Pupil behaviours were recorded from 61 patients with MCI and 11 age and education matched healthy controls while they performed the STMBT.

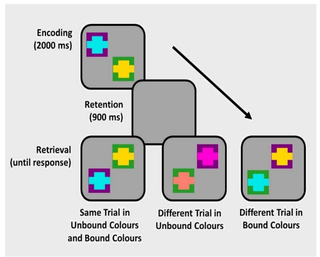


Fig 1. The STMBT assesses the ability to temporarily hold colours presented in bicoloured objects either as individual features (Unbound Colours - **UC**) or integrated within object representations (Bound Colours - **BC**).

Patients were also assessed with standard cognitive screening tests (MMSE, ACE-R, IFS).

We applied ROC-derived cut-off scores recently obtained by Fernández et al. (1,2) from a sample of patients with AD dementia. We used the memory score and pupil size which achieved >80% and 100% classification accuracy, respectively.

We aimed to investigate the usefulness of this new assessment method to identify oculomotor-behavioural profiles in MCI patients using markers for AD.

Results

Table 1. Descriptive statistics and group comparisons using the neuropsychological and STMBT scores.

	Healthy Controls (n=11)			MCI AD Profile (n=28)			MCI non-AD Profile (n=33)			Stat
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
MMSE	29.8	0.4	29 - 30	26.7	2.1	21 - 30	26.9	2.8	20 - 30	*
INECO	29.5	0.5	29 - 30	19	5.9	8 - 29	18.5	5.8	3 - 28	*
ACER	98.2	1.7	94 - 100	78.1	9.3	61 - 91	78.5	13	47 - 98	*
Bound Colours (%)	82.4	10.9	56.3 - 96.9	63.7	12.1	37.5 - 84.38	62	16.3	15.6 - 90.6	*
Unbound Colours (%)	88.6	6.9	75 - 96.9	70	14.7	25 - 93.8	72.5	17.9	28.1 - 96.9	*

** = significant differences between the three groups; MCI AD profile = patients below cut-off ; MCI non-AD profile = patients above cut-off .*

Traditional screening tests and both conditions of the STMBT (UC and BC) discriminated between MCI patients and controls.

Table 2. Correlations between neuropsychological, STMBT scores, and pupil size.

		MMSE	INECO	ACER	Pupil Size BC	Pupil Size UC
MMSE	r		.679**	.860**	.317**	.317**
	p-value		0.000	0.000	0.007	0.007
INECO	r	.679**		.807**	.267*	.319**
	p-value	0.000		0.000	0.023	0.006
ACER	r	.860**	.807**		.273*	.295*
	p-value	0.000	0.000		0.020	0.012
Mem Score BC	r	.465**	.508**	.558**	0.172	0.142
	p-value	0.000	0.000	0.000	0.150	0.233
Mem Score UC	r	.502**	.568**	.549**	0.128	0.123
	p-value	0.000	0.000	0.000	0.286	0.305

Performance on the STMBT and Pupil Size correlated with traditional neuropsychological test scores but not with each other.

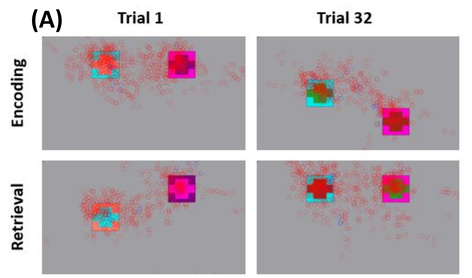
Table 3. Oculomotor-behavioural profiles of MCI patients based on AD-related cut-off scores.

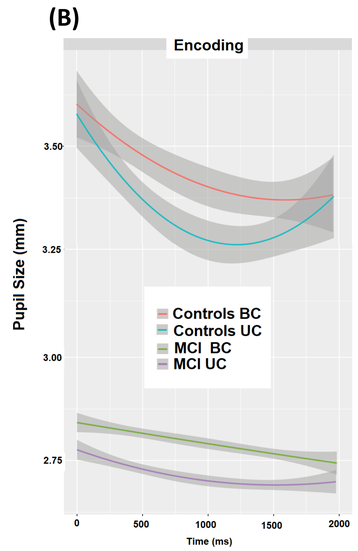
			n	Group Differences				
				Behaviour		Pupil		Neuropsychology
		Behaviour		BC	UC	BC	UC	
Pupil	Above Cut-Off	(A)bove Cut-Off	6	(B)<(A)	(B)~(A)	n.s.	n.s.	(B)<(A)
		(B)elow Cut-Off	27					
	Below Cut-Off	(A)bove Cut-Off	5	(B)<<(A)	n.s.	n.s.	n.s.	n.s.
		(B)elow Cut-Off	23					
Behaviour		Pupil						
	Above Cut-Off	(A)bove Cut-Off	6	(B)<<(A)	(B)~(A)	n.s.	n.s.	n.s.
		(B)elow Cut-Off	5					
	Below Cut-Off	(A)bove Cut-Off	27	n.s.	n.s.	n.s.	n.s.	n.s.
		(B)elow Cut-Off	23					

All significantly different from controls (p<0.05); ~ marginal differences

When abnormal pupil responses were accompanied by impaired STMB performance, the typical AD pattern was found (BC<<UC), and when above cut-off STMB performance was accompanied by below cut-off pupil responses, such a pattern also emerged.

Fig 2. (A) Average fixations across participants during the encoding and retrieval stages of the STMBT. The two items were visually scanned throughout the task, thus ruling out strategies such as gazing at one item. **(B)** Relative to controls, patients' pupil response was significantly reduced during both the UC and BC condition throughout encoding.





Conclusions

1. **Pupil behaviours during the STMBT identify MCI patients who show a profile compatible to that found in AD dementia.**
2. **Such a profile was found even when none of the neuropsychological tests could distinguish between MCI patients.**
3. **The relationship between the cognitive marker (STMB) and derived biomarker (pupillometry) seems complex as although independent, they appear to be complementary.**
4. **The extent to which such relationships are reflecting the presence of AD pathology in those positive to this combined cognitive biomarker and a higher risk of progressing to dementia need confirmation in future validation studies.**

(1) Fernández et al. (2018). Alzheimer's & Dementia;14(7):P399-P400. (2) Fernandez et al. (2018). J Alzheimer's Dis.; 63(1):185-94.