

# Utility of the International Shopping List Test for detection of memory impairment associated with prodromal and early Alzheimer's disease in clinical trials



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## Introduction

- Memory impairment is one of the most obvious and consistent manifestations of early Alzheimer's Disease (AD)
- Screening for memory impairment is therefore important for identifying individuals appropriate for inclusion in clinical trials of drugs designed to ameliorate the biological or clinical sequelae of AD
- The International Shopping List Test (ISLT) is a 12-word, 3-trial word learning test with established construct and criterion validity, and high reliability for the detection of memory impairment in AD
- The design of the ISLT allows it to be used for the assessment of memory in individuals from different languages, cultures or geographic regions without the necessity of the complex translations or cultural adaptations that must be applied to other verbal memory tests, such as the Free and Cued Selective Reminding Test (FCSRT) or Wechsler Memory Scale Logical Memory Test (LM), which were developed and validated in well-educated and middle-class settings
- The ISLT has been used extensively to measure the magnitude and nature of memory impairment in experimental and clinical studies; however, there is less information about the utility of the ISLT to screen individuals' memory for entry into clinical trials in prodromal AD

## Objectives

- Study 1: To determine the validity of the ISLT for classification of memory impairment associated with prodromal AD in an experimental sample, and to compare the magnitude of memory impairment associated with prodromal AD between the ISLT and the FCSRT and LM tests
- Study 2: To determine the reliability of the ISLT for classification of memory impairment in a clinical trial setting (the Eisai elenbecestat\* [E2609] Phase 2 study)

## Study 1: Validation study of ISLT in a prodromal AD population

### Methods

#### Sample

- The validation sample in this study is described in Table 1. All individuals were assessed twice, 6 months apart

**Table 1.** Demographic and clinical characteristics of the validation sample

	Cognitively normal (Aβ <sup>-</sup> )	Mild cognitive impairment (Aβ <sup>+</sup> )
N	100	82
Age	74.4 (11.2)	75.7 (10.2)
N Females	62	49
SUVr (range)	1.16 (0.87–1.35)	2.21 (1.5–2.6)
N ApoE4	35 (35%)	61 (74%)
MMSE (SD)	28.8 (1.24)	26.9 (2.9)
Premorbid IQ (SD)	108.7 (7.8)	107.9 (10.1)
Anxiety (SD)	2.8 (2.2)	2.9 (3.4)
Depression (SD)	4.1 (3.2)	4.3 (2.9)
CDR 0/0.5/1	100/0/0	0/82/0
Retest interval	183 days (23)	176 days (35)

### Memory measures

#### International Shopping List Test

- 12-item verbal list-learning task consisting of 3 learning trials and a delayed recall trial
- Words used as stimuli are drawn from items easily obtained in the region
- For each subject, items are presented in a computer-generated randomized order, with the order of the items remaining constant across the 3 learning trials
- Words are presented to the examiner on the screen one at a time at a rate of 1 word per 2 seconds, who reads them to the participant
- The participant cannot see the screen
- The participant is instructed to "try and remember as many items on the shopping list as possible"
- Once all 12 words have been read, subjects are instructed to recall as many items from the list as possible with the statement, "tell me as many items on the shopping list as you can remember"
- As the subject recalls each item, the examiner marks a checkbox by the item on the screen
- If words are repeated, the checkbox is clicked again
- Another checkbox is clicked if the participant says a word that is not on the original list (i.e., an intrusion)
- When the subject indicates that no more items can be recalled, the trial is stopped
- This same process is repeated 2 more times
- For the delayed recall trial, subjects are asked to recall as many items as possible from the initial list after a delay of 15 minutes filled with other cognitive tests

\*proposed International Nonproprietary Name (INN)

#### Free and Cued Selective Reminding Test

- 16 common items (e.g. apple) are presented to each subject on 4 cards
- Test phase consists of 3 recall trials in which the subject has 2 minutes to recall as many items as possible
- Category cues (e.g. fruit) are provided for items not recalled
- The sum of free and cued recall is the total recall
- A delayed recall trial is given where subjects recall as many words from the initial list as possible after a 30-minute delay filled with other neuropsychological tests

#### Logical Memory I and II (LM-I/II)

- In this paragraph story recall task, participants are read a short story, then are required to repeat as much information as they can remember, both immediately after being read the story (LM-I) and after a 30-minute delay (LM-II)

### Study design

- All individuals were assessed on the 3 memory tests as part of a larger neuropsychological battery conducted in individuals being screened for enrollment into the Australian Imaging Biomarkers and Lifestyle (AIBL) Study
- The method of recruitment and assessment for this study have been described in detail elsewhere
- For this study, data from the first assessment with each of the 3 memory tests was used

### Data analyses

#### Comparison of groups

- Group mean performance on the ISLT, FCSRT and LM tests was compared between the cognitively normal (CN) Aβ<sup>-</sup> and mild cognitive impairment (MCI) Aβ<sup>+</sup> groups using independent groups' t-tests
- The magnitude of differences between the groups was expressed using Hedge's g
- The construct validity of the ISLT was also determined by computing the magnitude of association between performance on each ISLT measure and performance on the immediate and delayed measures from the FCSRT and LM tests

#### Sensitivity to memory impairment in individuals

- Performance on the total recall and delayed recall trials of each memory test were compared to the normative data for those tests
- Poor performance was classified if an individual returned a score  $\leq -1$  standard deviation from the age- and gender- appropriate normative data for that same measure
- Proportions of individuals classified with having poor performance on the total and delayed recall trials of the ISLT was compared to the same measures from the FCSRT and LM tests using chi square tests

### Results

#### Comparison of groups

- Performance on the immediate and delayed recall performance indices on the 3 memory tests was significantly worse in the MCI Aβ<sup>+</sup> than in the CN Aβ<sup>-</sup> group (Table 2), with the magnitude of impairment greater in the ISLT and FCSRT tests than for the LM test (Figure 1)
- Performance on the total recall and delayed recall measures from the ISLT was strongly associated with similar measures from the FCSRT and LM tests (Table 3). The 6-month test-retest reliability of the ISLT total recall was 0.95 and for delayed recall was 0.69 in the MCI group

**Table 2.** Group mean performance on the immediate and delayed recall trials of the ISLT, FCSRT and LM tests in the CN Aβ<sup>-</sup> and the MCI Aβ<sup>+</sup> groups. For the MCI Aβ<sup>+</sup> group the percentage of scores classified as abnormal for each memory measure is also shown

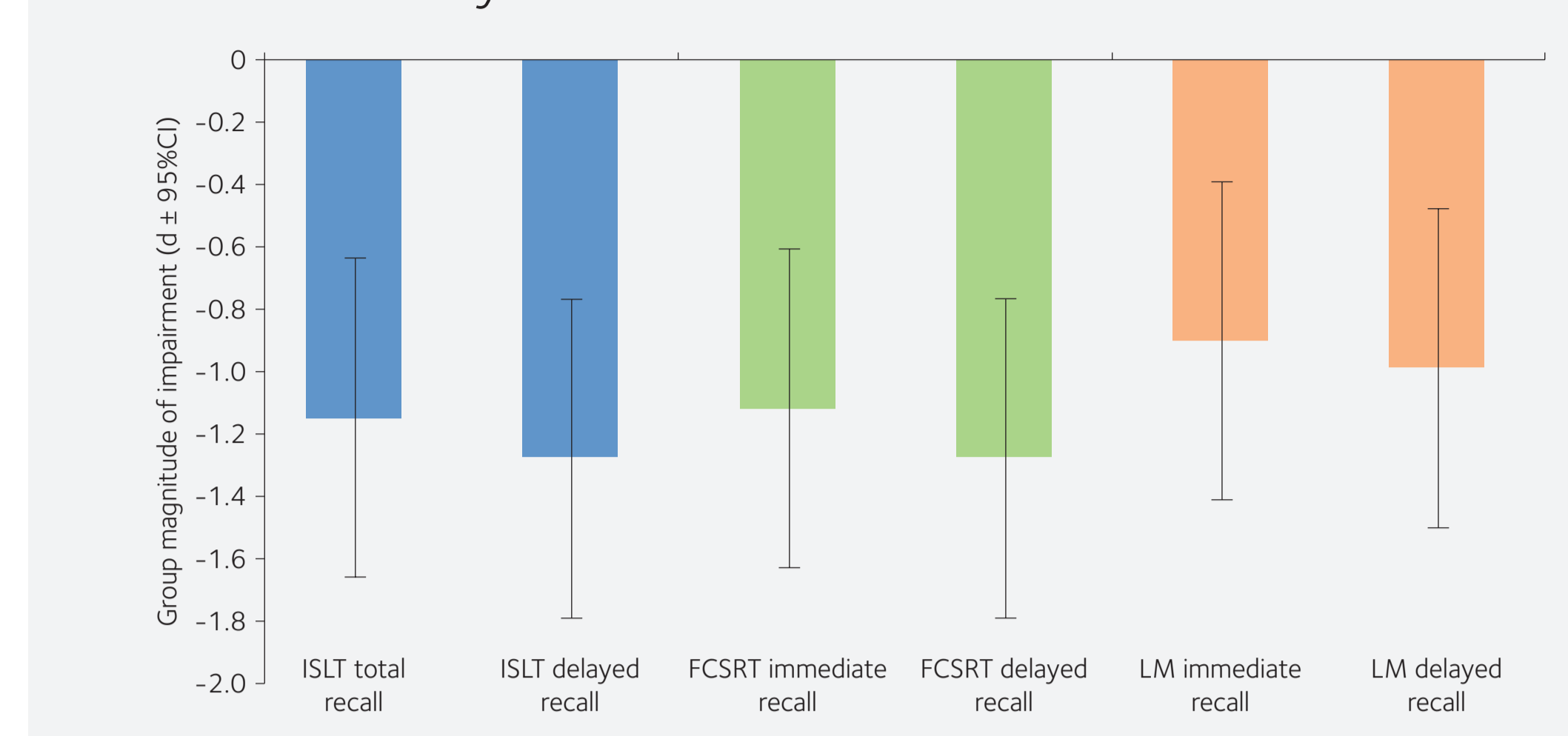
Memory test and measure	CN Aβ <sup>-</sup>		MCI Aβ <sup>+</sup>		N abnormal scores
	Mean	SD	Mean	SD	
ISLT total recall	25.96	5.7	19.23	5.9	72%
ISLT delayed recall	8.92	4.03	4.19	3.3	82%
FCSRT immediate recall	41.9	8.4	32.1	9.1	69%
FCSRT delayed recall	15.2	4.2	9.3	5.1	71%
LM immediate recall	13.64	5.78	8	6.7	54%
LM delayed recall	12.3	6.2	6.45	5.6	58%

**Table 3.** Strength of associations (Pearson's r) between the ISLT, FCSRT and LM performance measures

	FCSRT immediate	FCSRT delay	LM immediate	LM delay
ISLT total recall	0.93**	0.87**	0.85**	0.82*
ISLT delayed recall	0.75**	0.79**	0.69*	0.75*

\*p<0.01, \*\*p<0.001

**Figure 1.** Magnitude of impairment (g ± 95%CI) in MCI Aβ<sup>+</sup> group compared to CN Aβ<sup>-</sup> group for the immediate and delayed recall trials on the 3 verbal memory tests



#### Sensitivity to memory impairment in individuals

- Performance measures from the ISLT and FCSRT classified abnormal memory in a greater proportion of the MCI Aβ<sup>+</sup> group than the LM test (Table 2)

## Conclusion

- Compared to the CN Aβ<sup>-</sup> group, the MCI Aβ<sup>+</sup> group showed impairment on each of the memory tests
- The magnitude of impairment observed for the ISLT was equivalent to the FCSRT with memory impairment greater in both than that observed with the LM test
- The sensitivity to memory impairment in individuals with MCI Aβ<sup>+</sup> was greatest and equivalent for the ISLT and FCSRT and again both tests showed greater sensitivity than the LM test
- These data suggest the ISLT has utility as an instrument to classify abnormal memory in screening studies

## Study 2: Reliability of ISLT for classification of memory impairment in a clinical trial setting

- The ability of the ISLT to identify memory impairment in individuals at risk of AD was determined in subjects undergoing screening for the Eisai elenbecestat (E2609) Phase 2 study
- Reliability of memory impairment classification was determined by the consistency of abnormality classification between the screening visit and the baseline assessment for each ISLT measure

### Study design

- The ISLT was administered to individuals being evaluated for entry into the Eisai elenbecestat (E2609) Phase 2 study and then again at the baseline assessment of this study

### Data analyses

- Measures of agreement were computed for classification of impaired performance between the screening and baseline assessment on the ISLT total and ISLT delayed recall measures

### Results

- There was high consistency in classification of impaired performance between the screening and baseline assessments for both ISLT measures (Table 4)

**Table 4.** Agreement between classification of memory impairment between the screening and baseline assessment on the ISLT total recall and delayed recall scores for individuals entering the Eisai elenbecestat (E2609) Phase 2 study

Classification at screening	ISLT - total recall		ISLT - delayed	
	Classification at baseline		Classification at baseline	
	Not impaired	Impaired	Not impaired	Impaired
Not impaired	11 (84.6%)	2 (15.4%)	1 (33.3%)	2 (66.7%)
Impaired	2 (4.0%)	48 (96.0%)	1 (1.7%)	58 (98.3%)

The percentages are the proportion of subjects in each classification at screening

## Conclusions

- The ISLT is a valid and reliable measure of verbal episodic memory that has high sensitivity to the memory impairment associated with MCI
- The ISLT can be used as a screening tool for identification of individuals with early AD
- Studies to date using the ISLT in this way indicate that both performance measures provide reliable classification of memory impairment



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