A transcultural cognitive marker of Alzheimer's Disease

Temporary Binding:
A transcultural cognitive marker of Alzheimer's Disease.

Sergio Della Sala[(1,2)]✉, Irina Kozlova[(1)], Andreea Stamate[(1)], and Mario A. Parra[(2-7)]

(1) Human Cognitive Neuroscience, Psychology Department, University of Edinburgh, UK

(2) Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, UK

(3) School of Life Sciences, Psychology, University Heriot-Watt, UK

(4) Scottish Dementia Clinical Research Network, NHS Scotland, UK

(5) Alzheimer's Scotland Dementia Research Centre

(6) UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego Portales University, Psychology, Chile

(7) Universidad Autónoma del Caribe, Barranquilla, Colombia

✉Sergio Della Sala**,** *Human Cognitive Neuroscience, Psychology, University of Edinburgh, UK. 7 George Square, Edinburgh, EH8 9JZ. +44 (0)131 651 324, sergio@ed.ac.uk*

Key words: Alzheimer's Disease; temporary binding; flash-cards; cognitive marker; selective reminding.

Key points:

- Temporary Binding proves to be sensitive and specific to AD
- Specificity of temporary binding is higher than that of Selective Reminding
- Temporary binding is a good transcultural assessment tool
- Flash cards version of Temporary Binding allows for clinical testing

Abstract

Objective. Temporary Binding (TB) is sensitive and specific to Alzheimer's Disease (AD), is not affected by age, repeated testing or level of education. Hence, TB is useful to assess patients with very different socio-cultural backgrounds. However, the current computerized version of the test is not suitable for use in clinical settings. The aim of this study was to investigate whether a clinically friendly version of the TB task results in overlapping outcomes compared to the computerised version.

Methods. A newly devised Flash-card version of the TB assesses temporary visual binding for arrays of stimuli such as shapes (polygons), colours, or combinations of shapes and colours. In Experiment 1 this version was compared with the laboratory computerised version. In Experiment 2, 33 AD patients and 33 matched controls, recruited from various geriatric centres in Romania, were assessed with the new TB test and with Free and Cued Selective Reminding test.

Results. The results with the Flash-card version of the TB test were comparable to those obtained with the computerised version. TB was not affected by age but it was impaired by AD. The sensitivity and specificity of the new TB test were found to be greater than those achieved by a Selective Reminding test.

Conclusions. TB deficits may be conceived as a fundamental marker of AD. The Flash-card version is suitable for clinical use also in primary care facilities and in intervention trials, requires minimal training for administration and scoring, is quick to administer, non-invasive, inexpensive and facilitates cross-cultural studies.

Introduction

The most widely used tests for the identification of the cognitive deficits associated with Alzheimer's Disease (AD) are based on associative memory, list learning or delayed recall (e.g., Fowler et al. 2002; Lowndes and Savage, 2007; Swainson et al., 2001). These tests are failed also by people affected by several other disorders, including chronic depression and are impaired even in healthy ageing, making the diagnosis of early AD difficult (Pfennig, Littmann and Bauer, 2007; Wright and Persaud, 2007). Moreover, performance on classic memory tests reaches floor very early in AD making them a poor marker of disease severity and progression (e.g., Frisoni et al., 2010). On the other hand, in less severe patients and in healthy volunteers, memory tests show practice effects (e.g., Rabbitt et al., 2004; Foley et al., 2015). Therefore, although memory deficits characterise AD, deficits on classic memory tests are not specific to AD and these tests are not ideal in the follow-up.

An alternative approach has come from evidence showing that patients with AD have problems dealing with multiple sources of information (e.g., Della Sala et al., 2010; Logie et al., 2004; MacPherson et al., 2012). A specific form of this on-line cognitive processing is known as temporary binding (TB), which defines the processes whereby different features are bound together on a temporary basis as an integrated object. In daily living, TB is essential to keep track of, for example, whether the white round pill or the yellow oval pill has just been taken. In laboratory tasks, individual features like colours and shapes are bound to form a coloured shape (Allen, Baddeley and Hitch, 2006; Logie, Brockmole and Vandenbroucke, 2009; Luck and Vogel, 1997; Treisman, 2006).

This particular TB task, known as *conjunctive* binding, does not involve the hippocampus (Parra et al., 2014; 2015) and is not affected by healthy ageing (Brockmole et al., 2008; Isella et al., 2015; Parra et al., 2009b; Read, Rogers, and Wilson, 2016; Rhodes, Parra and Logie, 2015). Conjunctive TB seems to engage regions of the ventral visual stream (Parra et al., 2014; Staresina and Davachi, 2010) known to remain preserved in healthy ageing (Insausti et al., 1998) but affected by AD even earlier than the hippocampus damage becomes overt (Didic et al., 2011; Juottonen et al., 1998).

Due to its reliance on simple non-verbal shapes and colours, the TB test can be used with people with limited language skills. Moreover, it is not affected by repeated testing (Logie et

al., 2009), or by the level of education (Parra et al., 2011), so it can be used to test people with low levels of literacy as well as people who are highly educated and in assessing patients with very different socio-cultural backgrounds (Parra et al., 2011).

TB shows a clear and specific effect in AD (Parra et al., 2009a), and is not impaired in chronic depression (Parra et al., 2010a). It detects otherwise asymptomatic carriers of the Presenil-1 gene that leads to familial AD (Parra et al., 2010b) as well as other forms of familial AD (Liang et al., 2016). Converter Mild Cognitive Impairment patients show TB deficits similar to those observed in mutation carriers (Koppara et al., 2015). Additionally, TB is specifically impaired in AD compared with other forms of dementia (Della Sala et al., 2012). These main results have been replicated in several contexts and countries including Columbia, Brazil, Argentina, Chile, USA, Italy, Spain, and Russia.

As population profiles in most countries become increasingly distinct (Manly, 2005; Grober et al., 2010), neuropsychological tests will have to meet certain requirements in order to be applicable in clinical practice. These include: insensitivity to linguistic, ethnic and cultural influences and ease to use for screening in primary care facilities (Grober et al., 2008; Logie, Parra, and Della Sala, 2015). Although computerized cognitive assessment has some advantages (Rentz, 2016), when conducting fieldwork in geographically challenging areas or when assessing frail older people, friendly, affordable versions of the tests are welcome (Parra, 2014). We have therefore developed a Flash-cards version of the test.

The aims of this study were to investigate whether the Flash-card version of the TB task results in overlapping outcomes compared to the computerised version (Experiment 1), to assess how the Flash-card version fares as cognitive marker of AD versus normal ageing (Experiment 2) and (also Experiment 2) to check how TB compares against the most sensitive and specific memory test currently available to assess AD, i.e. the Free and Cued Selective Reminding Test (FCSRT) (Auriacombe et al., 2010; Dubois et al., 2007, 2010; Grober et al., 1988; Lemos et al., 2014).

Experiment 1: Flash-card vs Computer version of the TB task

The task assesses visual TB for arrays of stimuli such as shapes (random polygons), colours, or combinations of shapes and colours. Shapes and colours were selected so that it is easy to discriminate them visually, but difficult to name them (Parra et al., 2010a). The task is based on a change detection paradigm. The initial fixation cross is followed by the study display presented for 2 sec. After a very brief unfilled retention interval (about 1 sec) the test display is shown. The participant has to recognise if the items presented in the test display are the same or different from those presented at study, independently of their location. In 50% of the trials the items were the same in both displays (i.e., "same trials"). In the other 50%, two items in the test display were different (i.e., "different trials"). Two conditions assess TB for single features (Shape only and Colour only) and one assesses the binding of these features (Shape-colour binding). A typical TB task is illustrated in Figure 1.

----- Insert Figure 1 about here -----

In this experiment the Flash-card version of the TB was compared with the laboratory-computerized version. Previous versions of the TB test included two conditions to assess memory for single features (i.e., Shape only and Colour only) and a condition to assess memory for combined features (i.e., Shape-colour Binding) (Allen et al., 2006; Parra et al., 2014; Wheeler and Treisman, 2002). To be clinically practical (i.e., shorter) this paradigm has been recently modified to include solely the condition Shape only as baseline; this version retains the same psychometric properties of the longer version (Koppara et al., 2015). However, the current study was aimed for the first time at introducing the Flash-cards version of the TB. We therefore opted to relying on Shape-only and Shape-colour Binding for the initial comparison of the two versions of the task but to use all the three conditions for validation purposes in the clinical study.

Material and procedures

In our previous studies (Parra et al., 2009a; 2010a) we have titrated the number of items presented to the individual ability of each participant to minimise unwanted effects simply due to differential response to cognitive demands rather to a fundamental deficits on TB. In clinical setting this would be challenging. The Flash-card version therefore presents trials of

two items each, which proved to elicit a near ceiling effect in healthy volunteers, yet showing the typical drop in AD patients (Parra et al., 2010a; 2010b).

The Flash-card version of the TB task consists of 32 trials per condition. Each trial consists of two stimuli to be recognized as either same of different. A Perceptual Condition is used to exclude participants who cannot form bindings in perception. This Perceptual Condition consists of 10 trials in each one of which two arrays of two coloured shapes are presented simultaneously separated by a horizontal line. Participants are asked to detect whether the colour-shape combination below and above the line are the same or different, independently of their location. In keeping with previous literature (Parra et al., 2009a; 2010a), participants enter the next stage of the experimental protocol if they score 8 or above. Previous studies have shown that scores below 8 are indicative of colour vison problem as assessed by the Ishihara Colour Vision Test or of perceptual binding deficits (Parra et al., 2009a; Parra et al., 2010a & 2010b).

Participants are presented with a series of run-in trials until the examiner is satisfied that they fully understood the instructions of the task. The whole test takes about 15 minute to administer.

Participants

A total of 32 healthy volunteers entered the experiment. Sixteen were postgraduate psychology students (11 males, mean age 27, SD = 2.8), 16 participants (8 males, mean age 70, SD = 7.7) were older adults recruited from the University of Edinburgh volunteer panel.

Analyses

The data was analysed using R-Studio (version 3.2.2) package "lme4" (Bates, Maechler and Bolker, 2012) to perform linear mixed effect analyses of the impact of different mode of presentation (Flash-card and Computer) on the performance of the TB test by young and older adults. As fixed effects, we entered groups (Young vs. Old), conditions (Shapes vs. Binding), and tasks (Flash-card vs. Computer) with interaction terms between these variables.

Results

The mean performances (correct responses) on the tasks are summarized in Table 1. The average mean difference between two modes of the test representation was 0.03 of the scale

range. In other words, on a 0 to 1 scale, the mean of the scores from the Flash-card measure was 0.03 points higher than the mean of the scores from the Computer version.

----- Insert Table 1 about here -----

Estimates of the fixed effects revealed that mean performance on the Flash-card and on the Computer did not differ (β = 0.018, P = 0.19); the Bayes factor (BF) (for a sample difference between computer and the flash cards of .93, SE = .02) was 0.77 (1/ 3 > BF < 3), which is strong evidence supporting the null versus alternative hypotheses This indicates that the mode of the presentation of the test did not impact on the performance on TB task. Mean performance on Shapes only was not significantly different from the mean performance on the Binding condition (β = -0.007, P = 0.59), BF = 1.91 (M = .96, SE = 0.6). The older adults' mean performance did not differ from the younger adults' performance on the TB task (β = -0.003, P = 0.79), BF = 1.49 (M = .95, SE = 0.65), confirming the lack of age-related effect on the test, independently of the mode of the presentation. All the interactions were far from significance.

Comment

Mean differences between the Flash-card and Computer version were small, suggesting equivalence.

As predicted from previous data (Brockmole et al., 2008; Isella et al., 2015; Parra et al., 2009b; Read et al., 2016; Rhodes et al., 2015), no effect of age emerged and with two items per trial performance was near ceiling in both groups which, should there be a fundamental impairment of TB in AD, will maximise sensitivity.

During the debriefing session younger volunteers stated that they felt more comfortable with the Computer-based task whereas older participants found the Flash-card version friendlier. Some older participants on the Computer version of the tasks noticed their limited computer literacy and questioned their performance. This should be taken into consideration in order to improve compliance in older people.

In sum, the Flash-card, which is portable, inexpensive, and accommodates clinical needs proved to be a sound alternative to the Computer version of the TB task.

Experiment 2: Temporary Binding as a cognitive marker for AD

This study is aimed at assessing whether the TB test presented via Flash-cards shows the same capacity for detecting AD as laboratory based versions.

Material and procedures

The same Flash-card version of the TB presented in Experiment 1 was used here. All the participants who performed the TB test were also given the FCSRT.

The visual version of the 12-item FCSR (Frasson et al., 2011) was used. The administration of the test followed the standardised instructions and scoring. The test material for this test includes three cards, each depicting 4 high quality pictures belonging to different semantic categories. Participants have first to identify the pictures. Then, prompted by a semantic cue (name of a category) they are asked to retrieve all the 4 items. The items not named correctly in response to the cue are presented again. This process is repeated for all three cards. Next the memory phase follows. This is composed of three trials. At the start of each trial, participants are instructed to count backwards in 3s from a number for 20 seconds. Participants were then given up to two minutes to recall as many of the words as they could in any order (free recall). After free recall is completed, participants are presented with the categories of items that they did not remember (cued recall). The sum of a participant's free and cued recall represents their total recall. Participants complete two more trials of the test phase. The same procedure is repeated (once) after 30 minutes (delayed recall).

The sensitivity and specificity for each variable was determined by means of Receiver operating characteristic (ROC) curve analyses. To assess and compare the diagnostic accuracy of each measurement we calculated the area under the curve (AUC) (with a 95% CI) using DeLong et al.'s method (DeLong, DeLong, and Clarke-Pearson, 1988). Of all the FCSRT measures, immediate free recall (IFR) and delayed free recall (DFR) proved to be the most promising. This is in line with previous studies reporting on FCSR tests in the assessment of people at risk of dementia which have indicated that measures of free recall are the most sensitive variables of these tests (Auriacombe et al., 2010; Grober et al., 2010, 2000; Lemos et al., 2015). We also calculated the cost of binding, which reflects any cognitive

resource needed to hold features together over and above those needed to represent the features individually (Parra et al., 2014). For the current analysis we calculated this cost of binding for each individual by subtracting the mean performance on Shape-only (i.e., baseline condition) from the mean performance on Shape-colour Binding. Greater values of this variable indicate that binding is more cognitively costly that holding features separately. We then entered these scores in the ROC analyses (see Figure 2).

Participants

A total of 66 participants entered the study: 33 mild AD patients and 33 cognitively healthy individuals acted as controls (HC). Their demographic and clinical features are reported in Table 2. The clinical sample was recruited from various geriatric centres in Romania. The diagnosis of mild AD was based on international criteria (DSM-IV-TR; American Psychiatric Association, 2000; NINCDS-ADRDA; McKhann et al., 1984) and confirmed after six months follow-up as well as with routine CT scans[1]. The control sample was recruited from GP surgeries and from local communities. Additional inclusion criteria for all participants included the lack of colour vision or perception deficits, psychiatric conditions, history of neurological conditions, including alcohol or drugs abuse or head trauma. These criteria were documented by self-reports and by GP's records.

----- Insert Table 2 about here -----

Results

AD patients' performance on the task was significantly worse than that of the HC group in all 3 conditions (see Table 3). A mixed ANOVA revealed a significant effects of group [$F(1,64) = 116.8$, $p < 0.001$], of condition [$F(2,128) = 167.4$, $p < 0.001$] and of the group x condition interaction [$F(2,128) = 100.8$, $p < 0.001$]. This indicated that AD patients performed overwhelmingly poorly on the binding condition. Notably, there was no overlap in performance between the two groups in this condition, none of the AD patients scored above 81 per cent, none of the HC scored below 84 per cent.

[1]A total of 47 AD patients were referred as suitable. One patient had a stroke between AD diagnosis and testing, four patients withdrew from further assessment, six were no further considered as at the time of testing as their MMSE score was either too low (5 cases) or too high with respect to the set inclusion criteria, three patients failed to fully grasp instructions or could not distinguish between colours.

----- Insert Table 3 about here -----

Figure 2 and Table 4 show the outcomes from ROC analyses with the two best measures of the FCSRT and the two TB measures (see Table 2 for raw scores). The Binding condition raw scores showed accuracy of 100% (AUC 1.00), sensitivity 1 and specificity 1 (95% CI: 1-1). At a threshold of 82.81, the Shape-colour Binding task was able to classify correctly all the 66 subjects (classification accuracy: PPV-100% and NPV-100%).

----- Insert Table 4 and Figure 2 about here -----

Comment

The results showed a clear TB impairment in AD. In line with previous studies (Parra et al., 2010a; 2010b), the finding demonstrated that it is the binding aspect of the task rather than memory for individual features that is more severely affected by AD and which can differentiate AD from HC. The performance of the two groups does not overlap indicating a fundamental deficit of TB in AD. This impairment is characterized by the loss of the ability to represent objects integrated as a whole in temporary memory, probably due to disconnection of relevant brain regions (i.e., domain specific and visual association cortex).

The outcome from the study based on the Flash-card version of the task is relevant as it allows us to claim the use of TB in clinical settings as an early indicator of possible AD. The results also show that using two items to remember for all participants avoids the need to titrate the performance according to individuals' scores on single features reducing considerably the testing time, making the Flash-cards version attractive for clinical use.

Cognitive markers of early AD should be both sensitive and specific to impairments that are not associated with healthy cognitive aging. Our results show that both the FCSR and the TB task are sensitive to AD, although the proportion of correct allocation to either group is higher in the TB. Both measures significantly correlate with the MMSE and with one another thus indicating that they do inform about progressing cognitive decline (MMSE and TB: $r=0.847$, $p<0.001$; MMSE and FCSR-IFR: $r=0.831$, $p<0.001$; TB and FCSR-IFR: $r=0.766$, $p<0.001$). Nevertheless, contrary to the FCSRT, TB is not affected by age and shows impairments in stages where these other measures remain within the normal limits. Such properties of the TB test avoid the use of age-adjusted norms to establish the cut-off scores which can lead poor discrimination in very old populations (Bondi et al., 2003). Free recall as

an indicator of AD must be approached with caution (Carlesimo, Perriand and Caltagirone, 2011; Gainotti et al., 2014).

The ROC analyses show that the raw binding scores have the best sensitivity and specificity in disentangling AD patients from healthy controls, better also than the binding cost. This indicates that for a quick assessment, testing participants with the binding condition only is sufficient, with no need to compare binding with the performance on single features (as done in the past with the computerised version of the test); this further reduces the time of testing, making the test even more appealing for clinical use.

General Discussion

A recent report by Alzheimer Disease International - ADI (2013) entitled *Policy Brief for Heads of Government* pointed out that despite the greater impact of dementia in developing countries, fewer people are receiving an early diagnosis. This is largely due to unaffordable or culturally invalid methodologies.

Dementia diagnosis is based on performance on cognitive tests. However, scores in these tests are influenced by factors such as education and culture (Ardila et al., 2010; Brucki and Nitrini, 2009; Yassuda et al., 2010). The challenge faced by health professionals operating in middle and low-income countries, as well as by those dealing with minority groups, is to interpret the outcomes from cognitive tests which were originally developed to assess populations with a different cultural background (Brucki and Nitrini, 2009; Parra, 2014; Rosselli and Ardila, 2003). This generates false positive among the less educated seniors and low sensitivity among the highly educated ones. TB is not affected by demographic factors, and proved to be rather specific to AD.

TB is not biased by cultural factors: younger, little educated patients with Familiar AD from Colombia and older, better educated patients with Sporadic AD from the UK showed similar TB binding (Parra et al., 2011). This finding was recently reinforced by the observation that illiterate participants from rural Brazil show the same cost of binding as more educated participants, up to university level (M. Cecchini and M. Yassuda, personal communication, April 6, 2016). The current study, recruiting AD patients from a number of surgeries in

Romania (County Clinical Hospital Brasov, County Clinical Hospital Timisoara, County Clinical Hospital Targul Mures, Centre for Memory Disorders Bucharest, and Otopeni Geriatrics Institute) tested with a Flash-card version of the task, replicated the outcome of previous studies carried out in the UK and elsewhere using the computerised version of the task. The version presenting only two items to remember and with binding as the only measure, could be administered easily in a few minutes.

Compared to another test, the FCSRT, sensitive to clinical and preclinical AD (Grober and Kawas, 1997; Grober et al., 2008), TB proved to be better in disentangling patients with AD from healthy controls.

In sum, TB is a good transcultural marker of AD and an ideal cognitive test for aiding its diagnosis as: It is not affected by healthy ageing, proved to be sensitive and specific to early stages of AD, it does not show improvement in repeated testing, it avoids very low performance levels when the symptoms become severe, is targeted at cognitive impairments shown in AD but not in other disorders, is insensitive to the cultural background and literacy levels of those assessed. The Flash-card version of the task is suitable for clinical use also in primary care facilities and in intervention trials, requires minimal training for administration and scoring, is quick to administer, is non-invasive and inexpensive and facilitates cross-cultural studies.

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Table 1. Mean proportion of correct recognition on the TB tasks by the two groups with the computerised and the Flask-card versions, standard deviations are given in brackets.

	Computer		**Flash Cards**	
	Shapes	Binding	Shapes	Binding
Older	0.96 (0.03)	0.90 (0.1)	0.98 (0.01)	0.96 (0.06)
Younger	0.96 (0.03)	0.95 (0.03)	0.98 (0.02)	0.98 (0.04)

Table 2. Demographical and clinical features of the participants at the time of the study.

	HC group (n=33)		**AD group (n=33)**	
	Mean (SD)	Range	Mean (SD)	Range
Education	13.30 (3.32)	(7-18)	13.27 (3.17)	(6-18)
Age	73.87 (8.51)	(55-87)	75.24 (7.72)	(57-87)
MMSE	29.33 (0.78) *	(28-30)	24.36 (2.56)	(19-28)
Gender (F:M)	(22:11)		(20:13)	
Reisberg Scale			4.24 (0.66)	(3-6)
ADAS-Cog			20.70 (4.19)	(13-30)
GDS			5.12 (1.58)	(1-8)
Clock Drawing			7.64 (1.45)	(3-10)

*Key: *p < 0.01; AD = Alzheimer's disease; HC = healthy control; MMSE = Mini-Mental State Examination (Folstein et al., 1975), GDS = Geriatric Depression Scale (Yesavage et al., 1982), Reisberg = Global Deterioration Scale (Reisberg et al., 1982), Clock Drawing test (Sunderland et al., 1989).*

Table 3. Group descriptive statistics for the Flash-card version of the TB given in percentage of correct responses and the two most sensitive measures of the FCSRT percentage of correct recall (Immediate Free Recall – IFR - and Delayed Free Recall - DFR).

	AD (n=33)		**HC (n=33)**	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
Shape only	87.5 (11.29)	(53 - 100)	96.97 (2.64)	(90 -100)
Colour only	92.71 (5.93)	(71 - 100)	97.63 (3.82)	(84 -100)
Shape-colour Binding	64.20 (9.69)	(50 - 81)	94.03 (4.57)	(84 - 100)
IFR	20.61 (7.00)	(10 – 33)	32.37 (2.13)	(27 – 36))
DFR	7.58 (3.66)	(0 – 12)	11.18 (0.64)	(10 – 12)

Table 4. Results from ROC analysis using the most sensitive variables from the FCSRT (Immediate free recall- IFR and Delayed Free Recall – DFR) and the Flash-card version of the TB test.

	AUC	**SE**	**P-Value**	**95% CI**	
				Lower Bound	Upper Bound
Shape-colour Binding	1.00	0.00	<0.001	1.00	1.00
Binding Cost	0.97	0.02	<0.001	0.93	1.00
IFR	0.96	0.02	<0.001	0.91	1.00
DFR	0.84	0.05	<0.001	0.74	0.95

AUC: Area Under the Curve; SE: Standard Error of AUC

Figures Captions

Figure 1. Test for temporary memory of two shapes, of two colours, or of two coloured shapes. Participants are asked to decide if the items presented in the test display match those shown in the study display, independently of location. They are given multiple trials with different shapes, colours, or coloured shapes on each trial. On half of the occasions there is a match, and on the other half of the occasions they do not match, as shown here.

Figure 2. ROCs for the most sensitive variables of the FCSRT and the Flash-card version of the TB test.

Fig. 1 [note to copy editor: this figure could be printed in grey scale]

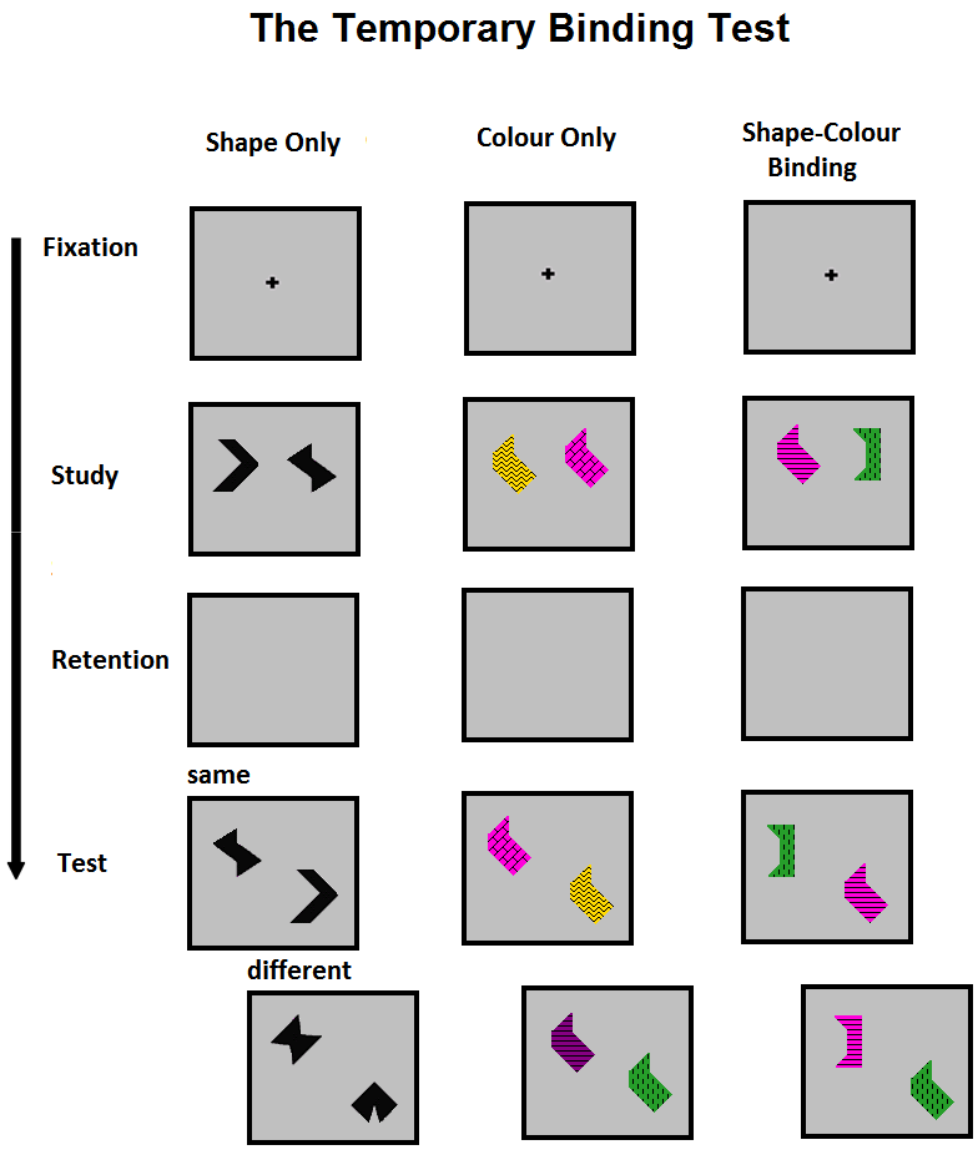
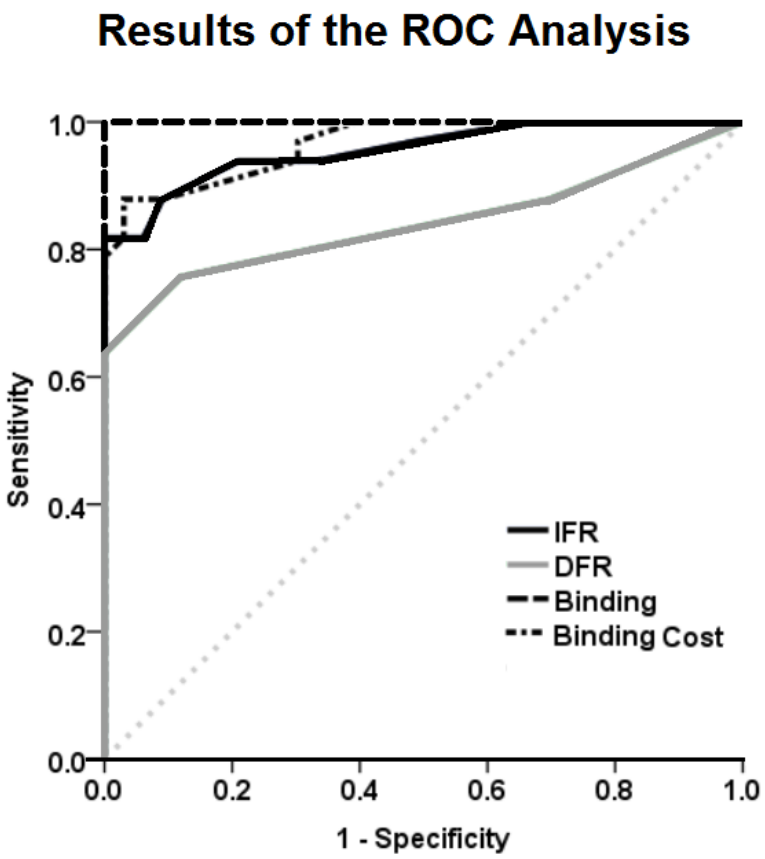


Fig 2.


Results of the ROC Analysis
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
IFR
DFR
Binding
Binding Cost