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Alzheimer Disease and Parkinson Dementia distinguished by Cognitive Marker

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Abstract

Background: Temporary Memory Binding (TMB) has been shown to be specifically affected by Alzheimer's Disease (AD) when it is assessed via free recall and titrating the task demands to equate baseline performance across patients. **Methods**: Patients with PD were subdivided into patients with and without cognitive impairment and compared with AD and amnestic MCI (aMCI) patients on their performance on the TMB. **Results**: The results show that only patients with AD dementia present with impaired TMB performance. ROC analyses showed that TMB holds high sensitivity and specificity for aMCI and AD relative to PD groups and healthy controls. **Conclusion**: TMB is sensitive to the neurodegenerative mechanisms leading to AD dementia but not to those underpinning PD dementia. As such, TMB task can aid the differential diagnosis of these common forms of dementia.

Keywords: Alzheimer's Disease, Parkinson's Disease, Temporary Memory Binding, early detection

Introduction

Temporary Memory Binding (TMB) refers to the function that allows different features of objects, such as colours and shapes, to be integrated within unified representations (i.e., a coloured shape) and retained as such on a temporary basis (Allen et al., 2006; Luck & Vogel, 1997, Treisman 2006; Zimmer et al., 2006). The specific form of memory integration that involves objects' surface features is known as conjunctive binding, and a growing number of studies have confirmed that is not affected by age (Rhodes et al., 2015; Rhodes et al., 2017; Parra et al., 2009; Brockmole et al., 2008; Isella et al., 2015), repeated testing (Logie et al., 2009; Colzato et al., 2006), level of education (Parra et al., 2011), or different socio-cultural backgrounds (Della Sala et al., 2016). The function however, has been shown to be sensitive to Alzheimer's Disease (AD) (Parra et al., 2009) but not impaired by chronic depression (Parra et al., 2010a). It reliably detects otherwise asymptomatic carriers of the Presenil-1 gene mutation E280A that leads to familial AD (Parra et al., 2010b) and Mild Cognitive Impairment (MCI) patients who are at a high risk of conversion to AD dementia (i.e., amnestic type; Koppara et al., 2015). Due to these properties, the TMB test has been proposed as a cognitive marker for AD (Logie et al., 2015; Dubois et al., 2016; Costa et al., 2017). TMB has been shown to be independent from the hippocampus functioning and volume (Jonin et al., 2019; Parra, Della Sala, Logie, & Morcom, 2014; Parra et al., 2015).

Della Sala et al. (2012) compared performance of AD patients with that of patients suffering from other types of dementia, such as frontotemporal dementia (FTD), vascular dementia, Lewy body dementia and dementia in Parkinson's disease (PD). Only AD patients showed significant deficits in recalling object-colours bindings. This specificity of the memory binding impairment to AD has been recently replicated in a study comparing the performance of a new sample of patients with AD with that of patients with behavioural variant of FTD (Cecchini et

al., 2017). In these earlier studies, TMB was assessed using a free recall paradigm, and participants performed tasks with different set sizes allowing the titration of the cognitive demand of the task to keep performance level at baseline conditions similar across groups. That is, healthy older adults were presented with a larger number of items and this increase in memory load equated their performance to that achieved by patients. Thus, existing evidence cannot be used to ascertain that TMB is uniquely affected by AD dementia. To uphold such a claim, we need to demonstrate that TMB assessed by other means (e.g., via recognition tests such as the change detection task (Parra, Abrahams, Logie, & Della Sala, 2010), retains the same specificity thus confirming that is the function and not the testing procedure that is sensitive to AD. Some studies have reported preserved (Flowers, Pearce, & Pearce, 1984) while others have reported impaired recognition in PD (Higginson, Wheelock, Carroll, & Sigvardt, 2005). Hence such evidence warrants investigation of TMB using a recognition paradigm. Moreover, titration is a procedure difficult to undertake in clinical settings (Della Sala et al., 2016). The present study addresses the issue of whether TMB is preserved in PD with and without dementia, when the assessment procedure involves recognition and all the participants are tested with the same memory load (i.e., set size). We were interested in investigating if under such experimental conditions the reported specificity of TMB for AD would be upheld.

Information on TMB abilities may increase specificity and sensitivity of the assessment of AD. The TMB task presented here is a brief and easy to use tool which can be administered in community settings with little training (i.e., flash-card version) to screen for age-independent cognitive decline (Della Sala, Kozlova, Stamate, & Parra, 2016). These features together with its strong psychometric properties previously published, grant this test properties of a cognitive marker for dementia based on (Logie, Parra, & Della Sala, 2015) suggestions.

Methods

Participants

Five groups of patients and a group of healthy volunteers acting as a control group were recruited for the study. PD was diagnosed by a neurologist (N.T.) with expertise in movement disorders and familiar with the widely used Queen Square Brain Bank criteria for PD (Hughes et al, 2002; Beradelli et al., 2013). The diagnosis was based on the presence of at least two of the following symptoms: a) resting tremor; b) bradykinesia; 3) rigidity, the absence of atypical symptoms and positive response to dopaminergic medication. The duration of illness prior to participation was on average 5.97 years (SD=3.53). Two patients were classified as tremor-dominant, 6 were akinetic-rigid, and 25 were mixed (tremor and akinetic-rigid) (Kang et al., 2005). Twenty-eight patients were treated with their normal regiment of dopaminergic medication and 5 were without any medication at the time of testing. None of the patients were taking antipsychotic or antidepressant medications.

PD patients were subdivided into those with no cognitive impairment (N= 20) and those with mild cognitive impairments (PD-MCI, N=20; Winblad et al., 2009) or dementia (PD-D; N=18; Jessen et al., 2014). PD-MCI and PD-D were diagnosed based on the clinical interview of the patients and their examination, and in accordance to the MDS (Movement Disorder Society, See Table 1 for criteria) Task Force recommendations (Litvan et al., 2012; Berg et al., 2015). In addition, as cognitive screening for PD-MCI we used a MMSE score ≥ 24 (M = 24.75; SD = 1.74) and minimal or no impairment in IADL. For PD-D the criteria were Mini Mental State Examination (MMSE; Nasreddine et al., 2005) score ≤ 24 (M = 23.00; SD = 2.33) and presence of IADL impairments that would interfere with everyday functional activities. The 1-year rule was applied, i.e., PD-D was diagnosed only if the dementia process started at least one year after the onset of PD (Aarsland et al., 2017). Mean MMSE score for PD patients without cognitive impairment was 27.90 (SD =1.33).

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

Patients with amnestic MCI (aMCI, N = 15; MMSE score = 24.93; SD = 1.28) and patients with mild AD dementia (mild-AD, N= 24; MMSE score = 20.50; SD = 3.76) were diagnosed by an old age psychiatrist (M.G.) according to the *National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association* (NINCDS-ADRDA) (Albert et al., 2011) and was based on evidence gathered via clinical interviews held with informants, neuropsychological evaluation, and standardized clinical mental status examination.

Exclusion criterion for all participants was the presence of any concomitant brain disorder (head injury, tumour or any other neurological or psychiatric disorders either than depression). In addition, participants were excluded from the study if they had a problem with colour vision or failed a perceptual binding test used as a screening tool (Parra et l., 2010a).

Control participants were screened for history of significant neurological disease, serious psychiatric disorder, and substance abuse. They were selected so they would not differ from the patients groups in terms of average age and education. They were not recruited into the study if they scored 25 or less on the MMSE; their average MMSE was 27.77 (SD = 1.36).

Informed consent was obtained from all control participants and PD patients with no cognitive impairment; PD-MCI, PD-D, aMCI and mild-AD patients gave their informed consent together with their caregivers. The study was approved by the National Health Services (NHS-MREC) and Lothian REC (MREC Ref. 06/MRE07/40; Lothian R&D Ref. 2006/P/PSY/22).

Procedures

Background Neuropsychological tests

All participants underwent a neuropsychological screening evaluation. Cognitive measure included MoCA (Folstein, Folstein & McHugh, 1975) and functional abilities were assessed with the Lawton Instrumental Activities of Daily Living (IADL, Lawton and Brody, 1969) that is the self-report scale developed to assess self-maintenance and lifestyle across 8 activities: the ability to use the telephone, to shop, prepare food, handle finances, do housework, managing medications, do laundry and to travel.

Flash-Card Version of the Temporary Memory Binding

The TMB task assesses short-term memory for arrays of stimuli such as shapes (random polygons) 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 brief unfilled retention interval (about 1 sec) the test display is shown. Participants are instructed to respond as accurately and as fast as possible by saying out loud "same" or "different" depending on whether or not they detected a change. Although this procedure does not allow recording individual's trial's response times, the examiner, who was the same throughout the study, did record the time it took for every participant to complete each task condition. The Flash-card version of the TMB task (Della Sala et al., 2016) includes 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 combinations below and above the line are the same or different, independently of their location. In keeping with previous literature (Parra et al, 2009,

2010a), participants enter the next stage of the experimental protocol (i.e., memory binding) if they score 8 or above on the Perceptual Condition. 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"). One conditions assesses single features (Shape Only) and one assesses feature binding (Shape-colour Binding). Before the test proper, 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 task which takes 15 minutes to administer is illustrated in Figure 1.

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

Analyses

The data were analysed using R-Studio (version 3.2.2) package "psych" (Revelle, 2017) by means of mixed ANOVAs (6 Groups x 2 Conditions) to determine whether performance on the TMB task revealed a group by condition interaction informing on specific TMB impairments in a given group. As a between subject factor we entered 6 groups (Healthy controls, PD with unimpaired cognition, PD-MCI, PD-D, aMCI, and mild-AD); the within subject factor were the two experimental conditions (Shapes Only and Shape-Colour Binding) with interaction terms between these variables. For multiple testing adjustments we used False Discovery Rate (FDR) q-corrected values ($q_{FDR)}$ which is more stringent threshold to account for multiple testing compare to Bonferroni correction (Pike, 2011; Reiss et al., 2012). The effect size was calculated using eta-squared (η^2).

A Receiver-operating curve (ROC) analysis was performed to establish the cut-off scores of the Shape-colour Binding Condition and its sensitivity and specificity to correctly differentiate AD patients from PD patients with and without cognitive impairment, as well as from controls.

The Area Under a Curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and per cent correctly diagnosed were calculated for the Shape-colour Binding Condition. The optimal screening cut-off point was defined as the lowest value that achieved >80% sensitivity and NPV; the optimal diagnostic cut-off point was defined as the highest value that achieved >80% specificity and PPV. The analysis was carried using the "pROC" package for R (Robin et al., 2011).

Results

The demographic, global cognitive, and functional measures of the six groups of participants are summarized in Table 2**.** One-way ANOVA did not reveal significant difference in age or years of formal education across the groups.

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

Post-hoc contrasts revealed that patients with AD performed significantly worse than healthy controls and other patient groups across all tests, however, compared to PD-D, patients with AD did not differ on the performance on MoCA and Lawton. Patients with PD-D performed worse than healthy controls, PD with normal cognition, PD-MCI and aMCI on MoCA and Lawton tests. The PD-D patients scored higher than controls, aMCI and mild-AD on the Geriatric Depression Scale (GDS 15; Sheikh & Yesavage, 1986).

The mean performance on the Shape Only and Shape-colour Binding Conditions of the TMB task for the 6 groups is shown in Table 3. There was a significant main effect of Group [$F(1, 248) = 15.66$ $p < 0.001$, $\eta^2 = 0.47$], Condition, [$F(1, 248) = 24.17$, $p < 0.001$, $\eta^2 = 0.20$], and a significant interaction between Group and Condition, [$F(1, 248) = 5.62$, $p = 0.01$, $\eta^2 = 0.05$]. Only mild-AD patients performed worse than controls ($q_{FDR,} < 0.001$), aMCI ($q_{FDR,} < 0.001$), and all PD patient groups ($q_{FDR,} < 0.001$), on both conditions of the TMB task (Shapes Only and

Shape-colour Binding). aMCI performed worse on the Shape-colour Binding condition compared to healthy controls, PD with normal cognition ($q_{FDR,}$<0.001) and PD-MCI ($q_{FDR,}$=0.002). There was no significant difference between all PD patient groups and controls on their performance on both conditions of the TMB task.

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

Table 4 shows the outcome from the ROC analyses for six groups on the Shape-colour Binding Condition. AUCs for mild-AD and aMCI are >90% (with the cut-off point at 0.75 and 0.82 respectively), suggesting that the Shape-colour Binding Condition discriminates well these two patient groups from controls. The Shape-colour Binding Condition discriminates moderately well between mild-AD and PD-D (AUC is 71.2% when the cut-off point is 0.85) and aMCI and PD-MCI patients (AUC is 84.3% when the cut-off point is 0.82). Low discrimination accuracy was found between PD-D and PD-MCI patients and the control group.

-----Insert Table 4 about here ----

Discussion

The present study was set out to investigate whether TMB is affected by PD when the assessment procedure involves recognition and no titration procedures. Moreover, we investigated if TMB differentiates between AD and PD-D using a clinically suitable version of the task based on Flash-cards. The results show that only patients with AD present with impaired performance on the TMB task. Compared to either cognitively healthy elderly individuals or PD patients with normal cognition, patients with PD-D did not show a significantly impaired TMB. This finding supports a number of previous studies showing a specific TMB deficit in AD compared to healthy elderly individuals and other types of dementias (Della Sala et al., 2012; (Cecchini et al., 2017) and also patients with depression

(Parra, Abrahams, Logie, & Della Sala, 2010). ROC analyses confirmed that the Shape-colour Binding Condition yielded the best discrimination between AD patients, controls and patients with PD.

Earlier studies demonstrating the specificity of binding deficits in AD compared to other dementia (Della Sala et al., 2012; Cecchini et al., 2017) used a free recall paradigm and did not consider the cognitive continuum of PD from normal to dementia. Therefore, the current study provides novel evidence on (1) preserved TMB functions along the continuum of PD, (2) that a clinically friendly version of the TMB task can aid the differential diagnosis between AD and PD-D, and (3) that such preserved function is task-independent.

It is worth noting that the PD-D sample also had mild clinical depression. This co-morbidity did make this group of patients more prone to TMB deficits. Indeed, contrary to other memory task, chronic depression does not interfere with TMB performance (Parra, Abrahams, Logie and Della Sala, 2010).

Preserved TMB function in PD is task-independent

This is an important finding, especially if we consider that earlier studies have shown discrepant findings in PD samples during assessments of similar cognitive constructs using different tasks (e.g., (Flowers et al., 1984) (Higginson et al., 2005). In the context of TMB, we have shown that in cases of AD the specific binding impairments are found regardless of the task used (i.e., verbal free recall (Cecchini et al., 2017; Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Parra et al., 2009) or visual recognition (Della Sala et al., 2016; Parra, Abrahams, Logie, & Della Sala, 2010; Parra, Abrahams, Logie, Mendez, et al., 2010). The outcomes of the present study demonstrate that the lack of such impairments in PD is also task-independent (i.e., verbal recall, or visual recognition as shown here). Such evidence confirms that TMB is affected by AD and not by other neurodegenerative diseases. In addition, in our

study the TMB task was presented on the clinically and user-friendly Flash-cards. There is evidence that populations with low literacy or poor cultural backgrounds find verbal recall tasks more challenging than visual recognition tasks (Boivin, Bangirana, & Smith, 2010). For instance, the Free and Cued Selective Reminding Test has been produced in "Word" and "Picture" versions and while both versions have been shown to be sensitive to AD the visual version yields higher scores than the verbal version (Delgado et al., 2016). That is not an issue with the TMB task even when retrieval is achieved via free recall of non-typical bindings between common objects and primary colours (Yassuda et al., 2019).

It should be noted that only patients with PD and AD forms of dementia were included in this study. Some evidence exists that short-term binding tasks could differentiate between AD and other forms of dementia; however, this evidence comes from experimental paradigms using free recall (Cecchini et al., 2017; Della Sala et al., 2012). It remains to be seen how well the change detection version of the TMB task, used in this study, differentiates AD form other types dementias.

A clinically friendly version of the TMB to aid the early diagnosis of AD

One major challenge recently recognised by a recent EU consensus group is the lack of brief, reliable, simple to apply methods to assess AD (Costa et al., 2017). Evidence has accrued indicating that the TMB holds potential to meet these needs (Logie et al., 2015).

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Conflict of interest: None declared.

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Figure caption

Figure 1.

TMB task procedure presented on the Flash-cards.

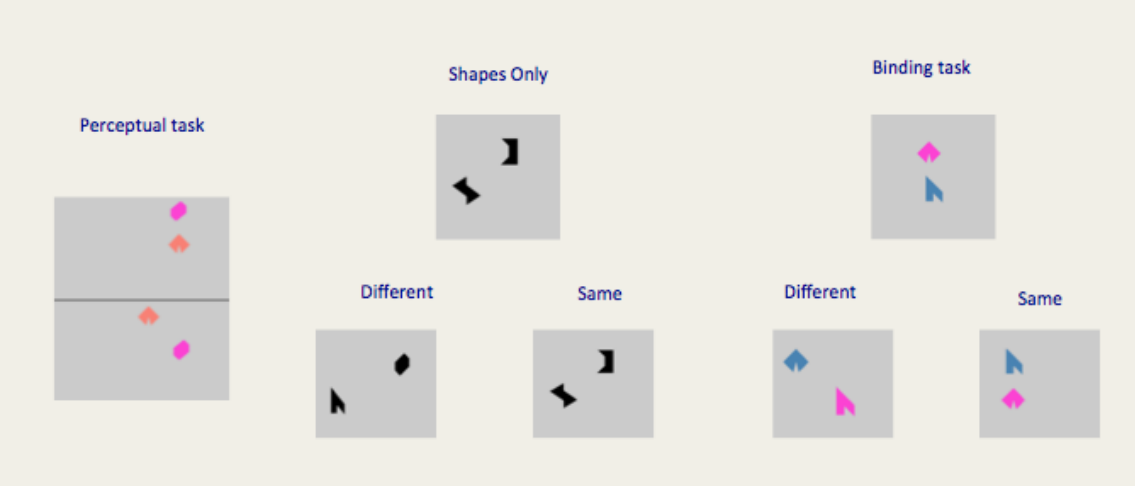

Table 1. Parkinson's Disease Criteria.

PD Without cognitive impairment.

Step 1. Diagnosis of Parkinsonian Syndrome

The presence of two of the cardinal features:

- Muscular rigidity
- Bradykinesia
- Rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communication hydrocephalus on imaging study
- Negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with **step one**

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

PD With Mild Cognitive Impairment:

Step 1 Established diagnosis of Parkinson's disease.

- See the criteria above

Step 2 MCI Diagnosis

- MMSE score ≥ 24
- Absence of everyday functional impairment
- Presence one of the behavioral symptoms:
  - Apathy
  - Depressed mood
  - Anxiety
  - Hallucinations

PD With Dementia:

Step 1 Established diagnosis of Parkinson's disease.

- See the criteria above

Step 2 Dementia Diagnosis:

- Insidious onset
- Slow progression
- MMSE score ≤ 24
- Cognitive dysfunction interferes with daily living functioning.
- Presence one of the behavioral symptoms:
  - Apathy
  - Depressed mood
  - Anxiety
  - Delusions (often with paranoia or phantom boarder themes)
  - Hallucinations
  - Excessive daytime sleepiness (hypersomnolence) and compromised daily life activities.

Table 2. Demographic, global cognitive and functional measures for six groups of participants.

	Controls (n =31)		PD (normal cognition) (n = 20)		PD-MCI (n =20)		PD-D (n =18)		aMCI (n = 15)		mild-AD (n =24)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	69.10 (8.42)	59-91	68.20 (8.16)	58-86	68.75 (7.89)	56-80	69.33 (11.75)	54-85	69.53 (7.94)	55-80	72.58 (8.16)	54-88
% Male	55	-	66	-	50	-	61	-	36	-	41	-
Education	14.42 (2.87)	10-20	16.20 (1.77)	14-19	15.03 (2.47)	10-20	15.78 (2.94)	10-20	15.53 (1.41)	13-18	14.67 (2.87)	8-20
MoCA	26.26 (1.84)	24-30	26.70 (1.53)	24-30	23.90 (1.37)	20-26	18.44 (2.41)	14-22	26.07 (1.75)	21-28	17.50 (2.67)	12-22
IADL	43.81 (1.72)	40-45	43.40 (2.16)	39-45	40.95 (1.23)	40-45	35.56 (3.17)	30-42	43.93 (1.91)	40-45	37.71 (6.17)	28-45
GDS15	3.13 (2.51)	0-10	5.50 (2.98)	0-11	5.70 (3.05)	1-11	7.50 (4.44)	1-15	2.93 (1.94)	1-7	2.92 (1.28)	0-7

Abbreviations: GDS15, Geriatric Depression Scale; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; IADL, Lawton Instrumental Activities of Daily Living.

Table 3. Mean proportion of correct recognition on the TMB Conditions by the six groups.

	Shape Only	**Range**	**Shape-Colour Binding**	**Range**
Controls	0.97 (0.04)	0.84-1.00	0.92 (0.08)	0.75-1.00
PD (normal cognition)	0.97 (0.03)	0.90-1.00	0.91 (0.07)	0.81-1.00
PD-MCI	0.94 (0.04)	0.87-0.97	0.85 (0.10)	0.62-0.97
PD-D	0.91 (0.07)	0.75-0.97	0.81 (0.13)	0.62-1.00
aMCI	0.86 (0.14)	0.62-1.00	0.72 (0.09)	0.59-0.84
mild-AD	0.76 (0.17)	0.53-1.00	0.58 (0.12)	0.37-0.84

Table 4. ROC analyses for the Shape-Colour Binding Condition.

Shape-Colour Binding	**cut-off**	**AUC**	**sensitivity**	**specificity**	**ppv**	**npv**
Controls vs mild-AD	≤0.75	91.3	0.91	0.96	0.95	0.93
Controls vs aMCI	≤0.82	91.0	0.93	0.87	0.77	0.96
Controls vs PD-D	≤0.89	52.0	0.27	0.93	0.71	0.69
Controls vs PD-MCI	≤0.95	63.5	0.30	0.70	0.40	0.61
mild-AD vs PD-D	≤0.85	71.2	0.62	0.88	0.88	0.64
aMCI vs PD-MCI	≤0.82	84.3	0.93	0.75	0.73	0.93

Abbreviations: AUC - Area under the curve, PPV – positive predictive value, NPV – negative predictive value

SUPPLEMENTARY MATERIAL

We also calculated a binding cost, which is a difference in performance on the Shape-colour Binding and Shape Only Conditions.

1.00 - (Shape-colour Binding/ Shape Only Conditions)

The binding cost represents how much extra cognitive recourses were put in order to perform Shape-colour Binding condition compare to Shape Only Condition (Table 1).

Table 1. Mean proportion of correct recognition on the TMB Conditions and Binding cost by the six groups.

	Shape Only	**Range**	**Shape-Colour Binding**	**Range**	**Cost**	**Range**
Controls	0.97 (0.04)	0.84-1.00	0.92 (0.08)	0.75-1.00	0.05 (0.08)	-0.11 - 0.18
PD (normal cognition)	0.97 (0.03)	0.90-1.00	0.91 (0.07)	0.81-1.00	0.06 (0.07)	-0.03 – 0.19
PD-MCI	0.94 (0.04)	0.87-0.97	0.85 (0.10)	0.62-0.97	0.10 (0.10)	-0.05 – 0.29
PD-D	0.91 (0.07)	0.75-0.97	0.81 (0.13)	0.62-1.00	0.11 (0.12)	-0.10 – 0.29
aMCI	0.86 (0.14)	0.62-1.00	0.72 (0.09)	0.59-0.84	0.15 (0.09)	0.00 – 0.29
mild-AD	0.76 (0.17)	0.53-1.00	0.58 (0.12)	0.37-0.84	0.23 (0.14)	0.00 – 0.49

The mean performance on the Shape Only, Shape-colour Binding Conditions of the TMB task and cost of binding for the 6 groups is shown in Table 2. There was a significant main effect of Group [$F(1, 378) = 70.32$, $p < 0.001$, $\eta^2 = 0.15$], Condition, [$F(1, 378) = 2325.57$, $p < 0.001$, $\eta^2 = 0.92$], and a significant interaction between Group and Condition, [$F(1, 378) = 103.83$, $p = 0.01$, $\eta^2 = 0.35$]. Post-hoc contrasts were carried out to check if the cost of the Binding condition six groups (alpha corrected 0.05/18 = 0.003). Only binding cost for mild-AD patients was different from that of control participants and all other patient groups.

Binding cost discriminate moderately well between healthy controls and mild-AD, healthy controls and aMCI, and between mild-AD and PD-D (AUC is 84.3%, 77.6% and 73.8% respectively). Low discrimination accuracy was found between PD-D and PD-MCI patients and the control group, and between aMCI and PD-MCI.

Table 2. The ROC analysis for the cost

Binding Cost	**cut-off**	**AUC (%)**	**sensitivity**	**specificity**	**ppv**	**npv**
Controls vs mild-AD	0.11	84.3	0.79	0.80	0.76	0.83
Controls vs aMCI	0.10	77.6	0.73	0.77	0.61	0.86
Controls vs PD-D	0.03	63.1	0.77	0.45	0.45	0.77
Controls vs PD-MCI	0.03	60.3	0.75	0.41	0.45	0.72
mild-AD vs PD-D	0.04	73.8	0.95	0.44	0.70	0.89
aMCI vs PD-MCI	0.15	64.5	0.53	0.80	0.66	0.69
Shape-Colour Binding						
Controls vs mild-AD	0.75	91.3	0.91	0.96	0.95	0.93
Controls vs aMCI	0.82	91.0	0.93	0.87	0.77	0.96
Controls vs PD-D	0.89	52.0	0.27	0.93	0.71	0.69
Controls vs PD-MCI	0.95	63.5	0.30	0.70	0.40	0.61
mild-AD vs PD-D	0.85	71.2	0.62	0.88	0.88	0.64
aMCI vs PD-MCI	0.82	84.3	0.93	0.75	0.73	0.93