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A passive, objective and implicit measure of recognition memory in Alzheimer's Disease using Fastball
memory assessment.

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Abstract

Earlier diagnosis of Alzheimer's disease (AD) requires biomarkers sensitive to the structural and functional changes associated with the disease. While considerable progress has been made in the development of structural biomarkers, functional biomarkers of early cognitive change are still needed. We present Fastball, a new EEG method for the passive, objective and implicit measurement of recognition memory, that requires no behavioural response or comprehension of the task.

Younger adults (aged $M=24$ $SD=6$), older adults (aged $M=74$ $SD=4$) and AD patients aged $M=79$ $SD=10$), ($n=20$ per group) completed the Fastball task, lasting just under three minutes. The task required the passive viewing of rapidly presented images and assessed their spontaneous ability to differentiate between images on the basis of previous exposure, i.e. old/new. Participants were not instructed to attend to previously seen images and provided no behavioural response. Following the Fastball task, they completed a cued recall task to measure their explicit recognition of previously seen stimuli.

AD patients showed significantly impaired recognition memory compared to healthy older adult controls in the Fastball task ($p<0.001$, Cohen's $D = 1.52$). AD patients' behavioural recognition memory performance, however, was not significantly different from healthy older adult controls. AD patients could be discriminated with high accuracy from healthy older adult controls using the Fastball measure of recognition memory ($AUC=0.86$, $p<0.001$), whereas discrimination performance was poor using behavioural cued-recall accuracy, ($AUC=0.63$, $p=0.148$). There were no significant effects of healthy ageing, with older and younger adult controls performing equivalently in both the Fastball task and behavioural cued-recall task.

Fastball is sensitive to changes in recognition memory processes in AD that would be missed by behavioural testing alone. It is passive, non-invasive, quick to administer and uses cheap, scalable EEG technology. Fastball provides a new powerful method for the assessment of cognition in dementia and opens a new door in the development of early diagnosis tools.

Keywords: Recognition memory; Oddball; Steady-state; EEG; Implicit; Fastball; Fast Periodic Visual Stimulation.

1 Introduction

1.1 The need for early diagnosis

Early diagnosis tools are greatly needed in dementia research, with diagnosis typically occurring relatively late in the disease process. Alzheimer's disease (AD) is the underlying cause of approximately 60% of dementia, with an estimated prevalence in Europe and North America of 5-7% (Barker *et al.*, 2002; Niu *et al.*, 2017). There are currently no disease modifying treatments and existing pharmacological therapies are only able to transiently reduce symptom severity for a proportion of patients. Early diagnosis could aid drug development, through earlier and more accurate identification and stratification of AD patients in clinical trials (Cummings, 2019). It could also increase the efficacy of multimodal lifestyle interventions, which have been demonstrated to reduce the incidence and rate of cognitive decline in at-risk populations (Ngandu *et al.*, 2015). There is increasing public desire for early diagnosis, with a recent survey conducted by Alzheimer's Research UK showing 74% of people would want to know if they, or a family member, had AD before symptoms develop (Alzheimer's Research UK, 2019).

1.2 Current diagnosis tools

Alzheimer's disease is currently diagnosed using a combination of subjective and objective reports of cognitive decline and standardised neuropsychological assessment, e.g. Mini Mental State Exam (Folstein *et al.*, 1975), Addenbrookes Cognitive Exam (Mathuranath *et al.*, 2000) and Montreal Cognitive Assessment (Nasreddine *et al.*, 2005). Unlike the cognitive functional impairment which emerges relatively late in the disease, neural pathology is estimated to be present for up to 20 years prior to diagnosis (Frisoni *et al.*, 2010). Structural biomarkers, such as CSF and PET measures of amyloid and tau aggregation, are increasingly used in clinical trials and research, but their clinical diagnostic use remains inconsistent due to their invasive nature, high costs and limited availability (Frisoni *et al.*, 2017). Additionally, their relationship with cognition is unclear. For example, amyloid pathology can be present without clinically significant cognitive decline (Giannakopoulos *et al.*, 2003; Bennett *et al.*, 2012; Koychev *et al.*, 2020), and cognitive decline can be present without clinically significant amyloid pathology (Landau *et al.*, 2018). To improve

diagnostic sensitivity, and improve understanding of disease pathogenesis, structural biomarkers need to be combined with early functional measures that specifically probe AD-related changes.

Existing neuropsychological measures of functional ability are prone to educational and cultural biases (Prince *et al.*, 2003; Ng *et al.*, 2018), assessment anxiety (Harris, 2002; Dorenkamp and Vik, 2018), and are clearly insensitive to the earliest stages of the disease process. They require verbal and written communication abilities, rendering them ineffective in illiterate populations (Carnero-Pardo, 2014) and populations with language impairments, e.g. Down's syndrome (O'Caoimh *et al.*, 2013). As dementia progresses, task comprehension during assessment becomes more impaired, rendering neuropsychological assessment progressively less effective. While this is not a consideration for early diagnosis, it is an issue for the measurement of the efficacy of interventions, and our general understanding of cognitive functioning in the severe stages of dementia, with implications for the provision of care. Objective measures of cognitive function, that do not require active responses, would solve these problems.

1.3 Objective measures of cognitive function

EEG can provide an objective and direct measure of neural activity during cognitive functioning. Group level differences in event related potential (ERP) measures have been identified between AD and age-matched controls (e.g. Stothart *et al.*, 2015), with a reduction and slowing of the P300 response being the most consistently reported finding (Hedges *et al.*, 2014). However, the translation through to viable clinical diagnostic tools has never been realised. Barriers include the long recording times required to reliably measure ERPs and the high inter-individual variability, with even the largest components (e.g. P300) difficult to measure reliably at the single subject level. The reliability and reproducibility of ERP research findings are further hindered by inter-experimental variability in how ERP responses are quantified (Kappenman and Keil, 2017).

1.4 Fast Periodic Visual Stimulation (FPVS)

Fast Periodic Visual Stimulation (FPVS) is a new EEG technique that solves many of the aforementioned problems. It provides an objective measure of a range of cognitive functions, with high signal to noise ratio (SNR) and short recording times. Crucially, it requires no task comprehension or behavioural response,

making it an ideal tool for the assessment of cognitive function in patient populations. First demonstrated by Heinrich *et al.* (2009) and developed extensively by Rossion *et al.* (Rossion *et al.*, 2015; e.g. Alp *et al.*, 2016; Liu-Shuang *et al.*, 2016), FPVS involves frequency tagging standard and oddball stimuli in a classic oddball paradigm. Standard stimuli are presented at a fast rate, typically around 6 Hz, with oddball stimuli embedded in the train of standard stimuli at fixed intervals, resulting in a slower equivalent presentation rate for oddball stimuli, typically around 1Hz, see Figure 1 for an example illustration.

Figure 1: Schematic illustration of the FPVS frequency tagging design. Letters in red indicate a stream of visually presented standard and oddball stimuli. Black and blue lines represent the hypothesised neural response to the stimuli. Frequency plot illustrates the narrowband responses to stimulation frequencies.

The advantage of this approach in signal processing terms is that the analysis can focus on particular frequencies in the EEG, defined *a priori* which include only a small proportion of the broadband ‘noise’ associated with ongoing activity, providing very high SNR (see Norcia *et al.*, 2015b for a review). Practically, this gain in SNR equates to very short recording times (as little as 1 minute) and reliable measures at the level of the individual subject. The approach has been used to measure low-level visual processing (Heinrich *et al.*, 2009), face detection and discrimination (Dzhelyova and Rossion, 2014; Liu-Shuang *et al.*, 2014, 2016; Rossion, 2014; Rossion *et al.*, 2015; Dzhelyova *et al.*, 2017; Xu *et al.*, 2017), and language processing (Lochy *et al.*, 2015). Recently we have adapted the approach to measure two cognitive processes known to deteriorate in dementia: abstract semantic categorisation (Stothart *et al.*, 2017) and recognition memory (Stothart *et al.*, 2020).

1.5 Fastball and AD

Measuring recognition memory precisely is notoriously difficult. We present an adaptation of FPVS for the passive, objective and implicit measurement of recognition memory, which for simplicity we refer to as **Fastball**. Recognition memory is comprised of two processes: 1) Familiarity, defined as a sense of previous exposure in the absence of or prior to, 2) Recollection, defined as a conscious recollection of details about a previously experienced event. Neuropsychological and neuroimaging evidence suggests familiarity and conscious recollection are dependent on brain areas known to be affected in early AD; the perirhinal cortex and hippocampus respectively (Aggleton and Brown, 1999; Brown and Aggleton, 2001; Yonelinas *et al.*, 2005; Bowles *et al.*, 2007, 2009, 2010; Koen and Yonelinas, 2016; Allen *et al.*, 2019).

Healthy older adults typically show impaired conscious recollection and variable, task-dependent familiarity performance, with deficits only observable when using Remember/Know judgements (Koen and Yonelinas, 2014). AD patients also show consistent deficits in recollection, with more variable findings in familiarity performance (Schoemaker *et al.*, 2014). Significant difficulties arise with the behavioural testing of familiarity in cognitive impaired populations, stemming from the subjective interpretation of familiarity, and biases created by the delivery, complexity and comprehension of task instructions (Koen and Yonelinas, 2016). Fastball provides a new method for the assessment of recognition memory that avoids many of these pitfalls and is used for the first time with AD patients in the current study.

1.6 Aims and hypotheses

The current study aims to objectively measure implicit recognition memory in AD patients using Fastball. We predicted AD patients would show reduced recognition memory performance indexed by a decrease in the Fastball response compared to healthy older adults. We also predicted no difference in recognition memory performance between younger and healthy older adult controls.

2 Materials and Methods

2.1 Subjects

Participant demographics are presented in Table 1. Twenty AD patients were recruited from memory clinics in the South West of England. The diagnosis of AD was determined by clinical staff using neurological, neuroimaging, physical and biochemical examination together with the results of family interview, neuropsychological and daily living skills assessment according to DSM-V (*Diagnostic and Statistical Manual of Mental Disorders*, 2013) and NINCDS-ADRDA guidelines (Dubois *et al.*, 2007). Patients were in the mild to moderate stage of the disease according to ACE-III scores (Giebel and Challis, 2017), see Table 1. Seventeen patients were taking cholinergic medication commonly prescribed in the early stages of AD, i.e. donepezil, rivastigmine, galantamine or the NMDA antagonist memantine.

Healthy older adult controls were recruited from memory clinics' research volunteer panels and were in normal general health and had no evidence of a dementing or other neuropsychological disorder. Younger adult controls were recruited from the University of Bath student population and declared themselves to be in normal health.

Exclusion criteria for all groups included poor general health or a history of transient ischaemic attack or stroke, significant head injury or any other significant psychiatric disorder or neurological disease. All participants had normal or corrected to normal vision ($\log\text{Mar} \leq 0.1$), except for four older adults and eight AD patients. No relationship between visual acuity, contrast sensitivity and the dependent variables in the current study was found, see section 2.6.1. Appropriate approvals for our procedures were obtained from the National Research Ethics Committee South West – Bristol, Ref. 18/SW/0111. All participants had capacity to consent, provided written informed consent in accordance with the Declaration of Helsinki, and were free to withdraw at any time.

	Younger adult controls	Healthy older adult controls	Alzheimer's disease patients	Group differences
n	20	20	20	-
age	24 (6)	74 (4)	79 (10)	Young<Old=AD
Number of males	8	11	11	Young=Old=AD
Total (/100)	92 (7)	94 (5)	62 (15)	Young=Old>AD
Attention (/18)	18 (1)	17 (1)	11 (4)	Young=Old>AD
Memory (/26)	23 (3)	24 (3)	11 (4)	Young=Old>AD
Verbal fluency (/14)	13 (1)	12 (1)	6 (3)	Young=Old>AD
Language (/26)	23 (3)	25 (1)	22 (3)	Young=Old>AD
Visuospatial (/16)	16 (1)	15 (1)	11 (4)	Young=Old>AD
Visual acuity (LogMAR) (higher score = worse acuity)	- 0.19 (0.06)	0.03 (0.15)	0.17 (0.24)	Young<Old=AD
Contrast Sensitivity (LogCS) (higher score = better sensitivity)	2.27 (0.26)	1.80 (0.51)	1.50 (0.39)	Young>Old=AD

Table 1: Participant demographics, neuropsychological and visual performance. Values other than counts indicate means (SD).

Groups were compared using 1-way ANOVA with Bonferroni corrected post-hoc comparisons, sex was compared using a Mann-Whitney U test.

> or < indicate significant statistical differences $p<0.05$ = indicates no significant statistical difference $p>0.05$

2.2 Stimuli

Images were selected from the Bank of Standardised Stimuli v2.0 (Brodeur *et al.*, 2014) a previously validated set of 1,468 high quality colour images. All images were 512x512 pixels, 96dpi, subtending 10° visual angle when viewed from a distance of 70cm. Importantly each image was only used once, i.e. as a standard, oddball or foil. Example images are provided in Figure 2.

2.2.1 Standards

Standard stimuli (mean image intensity of 0.82 (SD 0.28)), were randomly selected and varied across subjects. Each image was only presented once, with 416 unique images used in the recognition and repetition conditions, and 520 in the control condition.

2.2.2 Oddballs

Eight oddball stimuli (mean image intensity of 0.82 (SD 0.25)), were pre-selected for the recognition and repetition conditions and were consistent across subjects. Equal numbers of natural and non-natural objects were pre-selected in order to ensure no systematic semantic categorical difference between standards and oddballs.

2.2.3 Foils

For the pre-Fastball encoding two alternative forced choice (2AFC) task, eight images (mean image intensity = 0.77 (SD 0.29)) were pre-selected as foils, i.e. distracting previously unseen images, and were consistent across subjects. For the cued-recall tasks 16 images (mean image intensity of 0.80 (SD 0.29)) were randomly selected as foils for the recognition, repetition and control conditions and varied across subjects.

2.3 Procedure

Subjects completed three conditions; recognition, repetition and control. In the recognition condition oddball stimuli were viewed prior to, and repeated 13 times pseudo-randomly during, the Fastball task. In the repetition condition oddball stimuli were not viewed prior to, but were repeated 13 times pseudo-randomly during, the Fastball task. In the control condition subjects viewed a stream of novel stimuli with no oddballs or repetition.

Figure 2: Task designs across the recognition, repetition and control conditions.

Pre-Fastball Encoding – In the recognition condition only subjects named out loud the image, then identified the image in a 2AFC discrimination task paired with previously unseen image (foil).

Fastball – For all three conditions a base frequency **F** is elicited in response to the presentation of every image at 3Hz.

For the recognition condition an oddball response **f** is elicited due to the previous viewing of the images during the encoding task **and** the repeated presentation (13 times each, pseudo-random order) of the oddball images during the Fastball task.

For the repetition condition an oddball response **f** is elicited **only** due to the repeated presentation (13 times each, pseudo-random order) of the oddball images during the Fastball task.

Subjects attended to the fixation cross and pressed a key when the cross turned red in 10% of randomly selected standard images. Black and blue lines indicate the hypothesised neural response to standard and oddball images.

Cued Recall - Subjects identified previously seen oddballs and a randomly selected subset of standard images in a 2AFC cued recall task. Previously seen images were presented alongside novel, previously unseen images (foils).

2.3.1 Pre-Fastball encoding

Subjects viewed the 8 pre-selected oddball images centrally for 3s and were asked to name the object out loud. The image was then presented alongside a foil, and the subject was asked to indicate using the left and right arrow keys which image they had just seen. The location of the previously seen oddball images was pseudo-randomised to ensure equal presentations to the left and right of the screen. The subject could not move on to the next image until they had provided the correct response. The purpose of naming the object out loud, and then making a discriminatory choice about the object, was to strengthen the encoding of the object as the depth of processing has been repeatedly demonstrated to be critical to successful encoding (see Brown and Craik, 2000 for a review). All AD patients were able to follow instructions and complete the encoding task, with some patients requiring help providing keyboard responses. In these cases, the experimenter asked them to provide their response verbally, e.g. “left”, and pressed the arrow key for them. Subjects then immediately completed the Fastball task.

2.3.2 Fastball

Images were presented in sequences of five images, with the first four images being selected from the standard category and every fifth image from the oddball category. Images were presented onscreen for 166ms with an inter-stimulus interval of 166ms. An example of this sequence is presented in Figure 2. This design elicits two distinct steady state responses. The standard presentation frequency of 3Hz, and the oddball presentation frequency of 0.6Hz. Each standard stimulus was randomly sampled from the standard image pool and presented only once. Oddball stimuli in the recognition and repetition conditions were presented 13 times each in a pseudo-random order that ensured no consecutive presentations. In total 520 stimuli were presented in one trial lasting 173s. In the control condition 520 previously unseen novel stimuli were presented in a random order. The order of the conditions was counterbalanced across subjects.

2.3.2.1 Fixation cross colour change detection

To avoid lapses of attention that might otherwise exist in a purely passive task, subjects were instructed to maintain their gaze on a central fixation cross and to press a key in response to the fixation cross turning red. This occurred randomly on 10% of sequences and lasted the duration of the sequence (1.66s), the number of

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correctly identified targets was recorded for each participant. Some AD patients found it challenging to respond using the keyboard whilst maintaining their gaze on the computer screen, as they felt the need to avert their gaze to the keyboard when responding. Consequently, as most AD patients responded to targets verbally, for the experimenter to record manually, reaction time data was not analysed.

2.3.3 Cued-Recall task

Immediately following each of the three Fastball tasks subjects completed a cued-recall task in which they were presented with a 2AFC discrimination. Sixteen images previously seen during the Fastball task were paired with 16 foils (novel, previously unseen images), and the subject was asked to indicate which image they had seen during the experiment. Images remained onscreen until participants provided a response, and subsequent image pairs appeared immediately following the response. In the recognition and repetition conditions the previously seen images were the eight oddball stimuli and a random selection of eight standard stimuli, and in the control condition they were a random selection of 16 standard stimuli.

Responses to previously seen oddball and standard stimuli were analysed separately.

2.3.4 General cognition and vision assessment

After completing the Fastball tasks and taking a short break, participants completed the ACE-III (Mathuranath *et al.*, 2000) and the Freiburg Visual Acuity Test (Bach, 1996).

2.4 EEG recording

EEG signals were sampled at 1000Hz from 65 channel HydroCel Geodesic Sensor Net electrodes using a GES 400 system (Electrical Geodesics Inc; EGI, Eugene, OR, USA), with a common Cz reference and online low-pass filtered at 250Hz. Impedances were below 50k Ω . Recordings were analysed offline using Brain Electrical Source Analysis software v5.3 (BESA GmbH), Matlab (Mathworks Inc.) and the Fieldtrip toolbox (Oostenveld *et al.*, 2011). Blinks and eye movement artifacts were corrected using BESA automatic artifact correction (Berg and Scherg, 1994).

2.5 EEG analysis and steady state response

Data were re-referenced offline to a common average reference, downsampled to 256Hz, and two electrooculogram electrodes were excluded from further analysis. To avoid aliasing artifacts an 85Hz 24db zerophase lowpass filter was applied. The steady-state response was calculated according to the procedures described in Stothart et al.(2020). Epochs from 0 to 173s around trial onset were defined for each condition. This epoch length represents an integer number of cycles (104) of the oddball stimulus (0.6Hz) ensuring that a frequency bin corresponding to the exact oddball frequency and its harmonics, including the standard frequency (3Hz), were created. The frequency resolution was .0057Hz. Epochs were polynomially detrended to remove DC and slow wave artifacts.

As we used single epochs of a long duration, visual inspection revealed occasional instances of gross artifacts, e.g. large physical movement artifacts. Any artifact $\pm 250\mu\text{V}$ was removed from the data and replaced with zeros. To avoid discontinuities in the remaining data, data on either side of any removed section was tapered to zero using half a Hanning window over 670 points of data. Across subjects, the mean percentage of data removed by this procedure was 1.8% ($SD=4.2\%$) in the recognition condition, 0.9% ($SD=1.3\%$) in the repetition condition and 1.5% ($SD=3.7\%$) in the control condition.

For each subject and each electrode, amplitude was computed on these windows using the Fourier transform. SNR was then calculated by dividing the amplitude in each frequency bin by the mean amplitude of surrounding bins within a $\pm 0.10\text{Hz}$ range (17 frequency bins) (Srinivasan *et al.*, 1999; e.g. Alp *et al.*, 2016; Stothart *et al.*, 2017) excluding the immediately adjacent bins (first neighbouring bin on each side). Excluding the immediately adjacent bins from this correction meant that the amplitude correction was less likely to include any spread of the signal to proximal frequency bins (e.g. for 0.6Hz adjacent bins were 0.5941 & 0.6059Hz).

Previous research has shown a robust SSVEP response to the oddball frequency and many of its harmonics (Norcia *et al.*, 2015a; Rossion *et al.*, 2015) with oddball detection more reliably and accurately measured when including the harmonics of the oddball response (e.g. Stothart *et al.*, 2017). Consequently the SNR was calculated for 2 values: the standard frequency F (3Hz) and the mean of the oddball frequency and

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significant harmonics f^+ . To identify which harmonics to include in the calculation of f^+ , group Z scores were calculated for each harmonic (based on the global average of all electrodes averaged across the three conditions) relative to the neighbouring frequency bins within a $\pm 0.10\text{Hz}$ range. This identified the highest significant harmonic ($Z > 1.96$) at 7.2Hz for both younger and older adults, therefore for further analyses f^+ for all three groups was calculated as the mean SNR of 0.6, 1.2, 1.8, 2.4, 3.6, 4.2, 4.8, 5.4, 6.6 and 7.2Hz. These three values were calculated for each subject and electrode for all three conditions.

2.6 Statistical analyses

2.6.1 Sample size and power calculations

Younger adult control data, collected before the healthy older adult and AD patient data, showed large effect sizes (Cohen's $D = 1.52$) in the recognition vs control comparison (Stothart *et al.*, 2020). To replicate this effect at α of 0.01 and a β of 0.95 required a sample size of $n=10$. However, the effects of healthy ageing and AD on Fastball recognition oddball responses were unknown and there were no previous studies on which to base between group effect size estimates, consequently sample sizes were doubled to $n=20$.

2.6.2 Covariates

There was a non-significant trend for some older adults to show increased basic visual steady state responses (F), see Supplementary Information A. Therefore, to control for individual differences in the magnitude of F , the mean SNR value of F across the three conditions was included as a covariate in all subsequent statistical analyses of f^+ . Age, visual acuity and contrast sensitivity did not significantly correlate with any EEG or behavioural measure either when calculated collapsed across the groups, or within the groups, and were therefore not included as covariates in any subsequent statistical analyses.

2.6.3 Main effects and post-hoc tests

To determine the effect of group on oddball responses (f^+) across the three conditions (Recognition, Repetition, Control), controlling for basic steady state magnitude (F), a 3 (group) x 3 (condition) ANCOVA was conducted with Bonferroni corrected post-hoc pairwise comparisons. To measure fixation cross colour change detection a 3 (condition: recognition, repetition, control) x 3 (group: young, old, AD) ANOVA was conducted.

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Behavioural responses to the cued recall tasks were not suitable for parametric statistics therefore Kruskal Wallis tests were conducted for each condition to examine the effect of group on performance. Post hoc analyses of significant group effects were conducted using Bonferroni corrected Mann Whitney U tests.

To examine the relationship between Fastball and behavioural measures Spearman's Rho correlations were conducted. Finally, to establish the diagnostic ability of a binary classifier system (Healthy old vs AD) based on Fastball responses a receiver operator characteristic curve was calculated.

2.7 Pre-registration, data and code sharing

The study was pre-registered on the Open Science Framework (<https://osf.io/bgv74>). We have made all the analysis code freely available and modifiable through the Fastball toolbox, <https://gstothart.github.io/Fastball/> and complete anonymised data is available on the on the Open Science Framework (https://osf.io/dpmec/?view_only=8035aa10b781425390b02d5db11c7aa9).

3 Results

3.1 Neural recognition performance

AD patients showed impaired recognition memory performance compared to healthy older adult controls, see Figure 3.

Figure 3: Violinplots showing oddball recognition responses (quantified as the signal to noise ratio of f^+) for the three conditions and three groups, averaged across all electrodes ($n=63$). Tukey boxplots reflect the median and inter-quartile ranges, width of the violinplots reflects kernel density estimated using Matlab's `ksdensity` function. Brackets indicate statistical significance of post-hoc comparisons of young vs old and old vs AD. ** $p < 0.01$, * $p < 0.05$, ns $p > 0.05$. Topographic plots illustrate the signal to noise ratio of f^+ in the three conditions, for the three groups. Key results are summarised below and in full in text.

Recognition – AD patients showed significantly impaired recognition memory compared to older adults, indexed by the reduced oddball response to previously seen images. There was no significant difference between younger and older adult controls.

Repetition – AD patients showed reduced repetition detection compared to older adults, indexed by the reduced oddball response to repeated images. There was no significant difference between younger and older adult controls.

Control – There were no significant differences between the groups in the control condition.

3.1.1 Main effects of group and condition

A 3 (group) x 3 (condition) ANCOVA was conducted to determine the effect of group on oddball responses (f^+) across the three conditions (Recognition, Repetition, Control), controlling for basic steady state magnitude (F), see Table 2a. Levene's test and normality checks were carried out and the assumptions met. There was a significant difference in f^+ across the three participant groups, no significant difference across the three conditions, and a significant interaction between group and condition.

3.1.2 Post-hoc analyses of group effects

The effects of healthy ageing (young vs old) and AD (old vs AD) on oddball responses for each of the conditions were further explored with post-hoc pairwise comparisons. The younger and older adult control groups showed no significant differences in any condition. AD patients however had significantly reduced responses in the recognition condition compared to the healthy older adult controls after correction for multiple comparisons, see Table 2b.

3.1.3 Post-hoc analyses of group x condition interaction

The differences in condition effects across groups was further explored using post-hoc pairwise comparisons, see Table 2c. Both younger and older adult healthy controls showed large significant oddball responses in the recognition compared to the control condition. Only younger adults showed a significantly increased oddball response in the recognition condition compared to the repetition condition. All three groups showed significant oddball responses in the repetition condition compared to the control condition.

Topographic analyses of f^+ using cluster permutation analysis replicated the scalp averaged effects, and are presented in Supplementary Information B.

a) Main effects

	df	<i>F</i>	<i>p</i>	Partial eta ²
Group (Young, Old, AD)	2,112	10.9	<0.001	0.28
Condition (Recognition, Repetition, Control)	2,56	2.3	0.104	0.04
Group x Condition	4,112	5.8	<0.001	0.17

b) Post-hoc analyses of group effects

	Young vs Old				Old vs AD			
	Mean difference <i>f</i> ⁺	95% CI	<i>p</i>	Cohen's D	Mean difference <i>f</i> ⁺	95% CI	<i>p</i>	Cohen's D
Recognition	0.06	-0.10, 0.14	0.089	0.28	0.11	0.04, 0.19	0.003	1.52
Repetition	0.01	-0.46, 0.07	0.708	0.15	0.06	0.00, 0.12	0.048	0.94
Control	0.01	-0.03, 0.05	0.626	0.03	-0.00	-0.04, 0.04	0.876	0.13

c) Post-hoc analyses of group x condition interaction

	Recognition vs Control				Recognition vs Repetition				Repetition vs Control			
	Mean difference in <i>f</i> ⁺	95% CI	<i>p</i>	Cohen's D	Mean difference in <i>f</i> ⁺	95% CI	<i>p</i>	Cohen's D	Mean difference in <i>f</i> ⁺	95% CI	<i>P</i>	Cohen's D
Young	0.24	0.18,0.30	<0.001	1.35	0.08	0.02,0.13	0.006	0.58	0.16	0.12,0.20	<0.001	1.53
Old	0.18	0.12,0.24	<0.001	1.65	0.03	0.03,0.08	0.367	0.23	0.16	0.11,0.20	<0.001	1.80
AD	0.07	0.00,0.12	0.029	0.63	-0.03	0.08,0.02	0.269	0.27	0.10	0.05,0.14	<0.001	0.88

Table 2 a) 3 (group) x 3 (condition) ANCOVA to determine the effect of group on oddball responses (*f*⁺) across the three conditions, controlling for basic steady state magnitude (*F*).

b) Post-hoc pairwise comparisons of group. Values in bold indicate significant differences after applying a Bonferroni correction of 0.05/6, *p*=0.008.

c) Post-hoc pairwise comparisons of the group x condition interaction. Values in bold indicate significant differences after applying a Bonferroni correction of 0.05/9, *p*=0.006.

3.2 Fixation cross colour change detection

The accuracy of detection of fixation cross colour changes were compared across conditions and groups using a 3 (condition: recognition, repetition, control) x 3 (group: young, old, AD) ANOVA. 10 AD patients failed to respond to any fixation cross colour changes in one or more condition, see Supplementary Information C.

There was no main effect of condition ($F(2,114) = 1.05, p = 0.335, \eta^2 = .018$) on fixation cross colour change detection. There was a significant effect of group ($F(2,57) = 28.72, p < 0.001, \eta^2 = .502$). Post hoc tests using the Bonferroni correction revealed that AD patients were significantly less accurate (mean difference = -48.33% , $p < 0.001$) than older adults. There were no significant differences between healthy younger and older adults (mean difference = 2.50% , $p = 0.999$). There was no significant interaction between condition and group ($F(4,114) = 0.40, p = 0.808, \eta^2 = 0.014$).

3.3 Behavioural cued-recall performance

Figure 4: Violinplots illustrating % accuracy for the cued-recall tasks. Scores reflect the correct recognition of either an oddball or standard stimulus compared to a foil in a 2AFC. Tukey boxplots reflect the median and inter-quartile ranges, width of the violinplots reflects kernel density estimated using Matlab's ksdensity function.

Oddball stimuli recall – Performance was significantly different between groups, driven by the difference between younger adults and AD patients. Post hoc comparisons of young vs old and old vs AD comparisons showed no significant differences.

Standard stimuli recall – There were no significant differences between the groups in the recognition of standard stimuli, with performance around chance level (50%).

Data were not normally distributed and Levene's test indicated homogeneity of variance assumptions were also violated, therefore Kruskal Wallis tests were conducted for each condition to examine the effect of group on performance. Post hoc analyses of significant group effects were conducted using Bonferroni corrected Mann Whitney U tests, see Table 3.

a) Main effect of group on recognition accuracy

		Kruskal-Wallis H	p
Oddball	Recognition	11.96	0.003
	Repetition	16.58	<0.001
Standard	Recognition	2.45	0.294
	Repetition	1.71	0.426
	Control	4.23	0.120

b) Post-hoc analyses of the effects of group on recognition accuracy

		Young vs Old			Cohen's D	Old vs AD			Cohen's D
		U	Z	p		U	Z	p	
Oddball	Recognition	160	-2.08	.038	0.35	147	-1.75	0.080	0.47
	Repetition	136	-2.05	.040	0.56	114	-2.42	0.016	0.79

Table 3:

a) Kruskal Wallis H tests to examine the main effect of group on recognition accuracy. Figures in bold indicate significant differences, $p < 0.05$.
b) Post-hoc Mann Whitney U tests to examine the effect of age and AD on oddball recognition accuracy. Bonferroni corrected alpha = $0.05/4$, $p = 0.0125$.
Effect sizes were calculated using an online effect size conversion calculator (Lenhard and Lenhard, 2016).

3.3.1 Recognition of oddball stimuli

Oddball recognition performance was high, but significantly different across the three groups in the recognition condition, see Figure 4. Post-hoc analyses revealed this group effect was driven by the difference between young adult controls and AD patients. Neither the young vs old, nor old vs AD, comparisons showing significant differences after controlling for multiple comparisons. A larger group difference was observed in the repetition condition and post-hoc analyses revealed a trend for reduced oddball recognition accuracy in AD patients compared to healthy older adults, however the trend did not survive correction for multiple comparisons.

3.3.2 Recognition of standard stimuli

There were no significant differences between the groups in the recognition of standard stimuli, with performance around chance level (50%).

3.3.3 Relationship with neural measures

There were no significant correlations of oddball recognition accuracy with f^+ in either the recognition or repetition condition for any group. Correlations could not be calculated for younger adults in the recognition condition given the ceiling effect in the behavioural data.

3.4 Classifying AD using neural and behavioural recognition memory performance

Figure 5: Receiver Operator Characteristics plots indicating the classification accuracies of AD versus Healthy Older Adult controls using neural (f^+) and behavioural measures (% accuracy) of recognition memory.

AD patients could be discriminated with high accuracy from healthy older adult controls using the scalp average SNR of f^+ in the recognition condition (AUC=0.86, 95% confidence interval: 0.73-0.98, $p<0.001$), see Figure 5. Discrimination performance was poor using behavioural cued-recall accuracy, (AUC=0.63, 95% confidence interval: 0.46-0.80, $p=0.148$).

The scalp average SNR of f^+ in the repetition condition gave more moderate classification accuracy, (AUC=0.78, 95% confidence interval: 0.63-0.92, $p=0.003$). Discrimination performance was also moderate using behavioural cued-recall accuracy, (AUC=0.72, 95% confidence interval: 0.55-0.88, $p=0.020$).

4 Discussion

4.1 Summary of results

We demonstrate a passive, objective and implicit measure of recognition memory that is sensitive to AD and unaffected by healthy ageing. Fastball memory responses in AD showed the greatest reduction when they were dependent on a brief pre-Fastball encoding task, while behavioural measures of explicit recognition memory were insensitive to AD. Fastball provides a new tool for clinicians and researchers in the assessment of memory in AD with many practical benefits. It requires no comprehension of the task, beyond fixating on the screen, or response from the patient, and uses cheap, readily available, portable technology.

4.2 Recognition memory in Alzheimer's disease

Fastball is sensitive to changes in recognition memory in AD that do not manifest behaviourally. However, the implicit nature of Fastball makes it difficult to draw direct parallels with the classic behavioural constructs of familiarity and conscious recollection. We propose that Fastball provides a new, simpler measure of implicit recognition that is sensitive to changes in AD, and that avoids the confounds that muddy the water of behavioural familiarity measurement. With no requirement for task comprehension or response, there is no scope for the confounding influences of language, executive function, introspection, strategy or guessing.

Fastball reflects the initial automatic stages of familiarity processing. It is likely to be comprised of a combination of previously documented event related neural responses to familiarity, repetition and non-target oddball detection, e.g. the N250r, FN400 and vMMN (Rugg *et al.*, 1998; Tales *et al.*, 1999; Curran *et al.*, 2006; Vilberg *et al.*, 2006; Polich, 2007). Changes in familiarity processing in AD may reflect functional consequences of entorhinal cortex pathology, although such claims are beyond the remit of the current study and require further studies complemented with structural biomarkers of cortical pathology. Genetic evidence does however point towards familiarity impairment being a marker of early entorhinal cortex pathology, with a recent study demonstrating that apolipoprotein E (APOE) $\epsilon 4$ carriers show impaired familiarity processing in the absence of other cognitive deficits (Schoemaker *et al.*, 2016).

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Explicit recognition, as measured by the post-Fastball cued-recall task, was high in AD patients and not significantly different from healthy older adult controls. This demonstrates that with unlimited time, and a foil against which to compare the strength of their familiarity response, AD patients can perform equivalently to healthy older adults. Given the similarities in behavioural performance across groups it would not be accurate to refer to the neural differences observed in AD as impairments, instead we propose that they reflect the limitations of the recognition system when placed under the “pressure” of experimental manipulation. This pressure stems from two potential sources, the short duration of stimuli and the masking effect of subsequent stimuli.

Stimuli were presented rapidly in the Fastball task, i.e. 166ms with an equivalent inter-stimulus interval. Previous studies of perceptual speed and visual short-term memory have demonstrated that AD patients’ recognition memory is more sensitive to temporal constraints. Bublak and colleagues demonstrated that a period of ~300ms was required for recognition and retention of stimuli for subsequent recollection. When stimuli were presented for half this time, i.e. ~150ms, recognition performance was significantly impaired (Bublak *et al.*, 2011). Longer inter-stimulus intervals, and therefore greater total processing time per stimulus during the initial encoding of stimuli, have also been shown to result in improved subsequent recognition (Intraub, 1980). These previous examples differ from the current study in that the measure of recognition was explicit, not implicit, but it is clear that shorter presentation durations have an impact on recognition performance.

The rapid, sequential presentation of images also raises the possibility that oddball images were backward masked by the subsequent standard images, with previous research demonstrating that AD patients have a greater temporal window for the effect of backward masking, extending up to 150ms (Schlotterer *et al.*, 1984; Cronin-Golomb *et al.*, 1991; Cronin-Golomb, 1995). However, since the duration of inter-stimulus presentations (333ms, including ISI) in the current study is more than double this duration, we therefore think it unlikely that backward masking contributed to the group differences.

4.3 The role of encoding and repetition

Younger adults were the only group to show a statistically significant increase in oddball responses in the recognition condition compared to the repetition condition. Nevertheless, the greatest differences between older adults and AD patients were clearly observed in the recognition condition, with larger post-hoc group comparison effect sizes (Cohen's d 1.53 vs 0.94) and better classification accuracy (AUC=0.86 vs 0.78) in the recognition compared to repetition condition. Our interpretation of these effects is that while the priming benefit of pre-Fastball encoding appears to weaken with healthy ageing, it still influences the strength of the recognition response and improves the sensitivity of the test to AD, beyond that of repetition alone.

The repetition condition's primary function during the development of this technique was that of an active control condition, allowing for the dissociation of recognition effects from those of online learning (see Stothart *et al.*, 2020). Repetition priming has previously been shown to have a complex pattern of preservations and deficits in AD, with the greatest deficits shown when priming is related to the conceptual, rather than perceptual, properties of stimuli (Fleischman *et al.*, 2005). In the current study oddball stimuli shared no common perceptual properties, with the only common characteristic being that they were repeated during the stimulation epoch. In both the neural (f^+) and behavioural (explicit post-Fastball cued-recall accuracy) data AD patients showed a trend for reduced detection of repetition compared to healthy older adults, however in both cases these trends did not survive correction for multiple comparisons.

4.4 New diagnosis tools

Fastball can detect changes in recognition memory processing that are not observable behaviourally, giving the technique considerable potential as an early diagnosis tool, and the current study shows that classification accuracy of AD vs Old was highest when using Fastball over behavioural measures. Using the technique to detect changes in recognition memory performance in the MCI stage, and even pre-symptomatic stages of AD is the logical next step. Fastball/FPVS has been shown to be effective at capturing semantic (Stothart *et al.*, 2017), visual (Heinrich *et al.*, 2009), language (Lochy *et al.*, 2015), and memory (Stothart *et al.*, 2020) processing. There is now the possibility of constructing an objective battery of Fastball tasks that reflect the key cognitive domains affected in early dementia. Naturally, there may be

cognitive functions not suited to Fastball measurement, such as working memory, but there is potential to capture a broad range of cognitive functions passively and objectively.

The selection of electrodes and epochs for EEG analysis have previously been shown to be significant sources of user-bias and are barriers to clinical translation (Kappenman and Keil, 2017). The quantification of Fastball responses however avoids these entirely as effects are observable simply by averaging across all electrodes, and the frequency domain analysis removes the need for epoch selection.

There are also considerable practical benefits to the Fastball approach. It avoids confounding genuine cognitive impairment with that of performance anxiety induced impairment that can occur during traditional neuropsychological assessment (Harris, 2002; Dorenkamp and Vik, 2018). It is passive, quick to administer and uses cheap, non-invasive scalable EEG technology that sidesteps many of the practical challenges associated with using neuroimaging tools such as fMRI and PET for the objective assessment of cognitive function. Its non-invasive nature also avoids the difficulties associated with the extraction of cerebrospinal fluid biomarkers.

4.5 Limitations

AD patients showed greater difficulty in the fixation cross colour change task. Half the patients provided no response, and many patients had to respond verbally to the experimenter rather than pressing a key. This raises the possibility that other experimental effects observed were simply due to lower attentional engagement with the task. We do not however believe this to be the case. Overt attention to visual stimuli has repeatedly been shown to increase the amplitude of visual steady state responses (Norcia *et al.*, 2015a). If AD patients' attentional engagement with the stimuli was lower, then their basic visual steady state responses (F) would be lower than that of younger or healthy older adult controls. This was not the case and is illustrated in Supplementary Information A. Attentional engagement in AD patients is further demonstrated by their successful recognition of repeatedly presented oddball stimuli in the repetition condition, i.e. their cued recall performance. We propose that AD patients' low compliance and accuracy in the fixation cross colour change task reflects difficulty multi-tasking and following task instructions, rather

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than lower attentional engagement with the Fastball memory assessment, reinforcing the value of passive measures of cognitive function.

The current study demonstrates the potential of the Fastball approach and is a useful starting point for the development of an early diagnosis tool. However, presentation frequency, number of repetitions of oddball stimuli, ratio of standards:oddballs, total presentation duration and stimulus type are all parameters that can be manipulated in order to potentially improve the sensitivity of the task to AD. Deconstructing the different subcomponents of familiarity may also help us further understand the processes that are vulnerable to AD, with implications for the development of cognitive training strategies aimed at slowing decline. The impact of cholinesterase medication was not controlled for in the current study, however it is unlikely to have made recognition performance worse in the AD group. Future studies should examine performance in unmedicated AD patients, this may help establish the value of Fastball as a measure of intervention efficiency for future clinical trials.

4.6 Conclusions

In summary we present a new method for objectively measuring implicit visual recognition memory in AD, that is fast to implement and requires no comprehension of the task or behavioural response. Importantly, Fastball is sensitive to changes in recognition memory processes in AD that would be missed by behavioural testing alone. Fastball provides a new powerful method for the assessment of cognition in dementia and opens a new door in the development of early diagnosis tools.

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Declaration of Authorship

We certify that we have read and approved the final version of the manuscript. We agree to take public responsibility for its contents. The work reported in the paper has not been and is not intended to be published anywhere except in Brain.

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Competing interests statement

The authors declare no competing interests.

5 Supplementary Information A – Steady State Visual Evoked Potentials

Figure S11: Violinplots illustrating SNR of F, the 3Hz steady state response to image presentation for the three groups, averaged across all electrodes (n=63). Tukey boxplots reflect the median and inter-quartile ranges, width of the violinplots reflects kernel density estimated using Matlab's ksdensity function.

Levene's test showed significantly unequal variances ($F(2,57)=3.28$, $p=.045$). A non-parametric Kruskal-Wallis test showed no effect of group on the mean SNR of F across the three conditions $X^2(2) = 3.97$, $p = 0.137$.

6 Supplementary Information B - Cluster Permutation Testing

Having established clear differences between AD patients and healthy older adult controls in data averaged across the scalp, cluster permutation analyses were subsequently conducted to further examine the topographic differences in the oddball responses. The difference in f^+ between group pairs (young vs old, old vs AD) was statistically assessed across all electrodes for each condition (recognition, repetition, control) using cluster-based permutation analysis (Maris & Oostenveld, 2007) with 10,000 permutations.

Figure SI2 illustrates the topographic distribution of f^+ across the three conditions for the three groups.

Permutation analyses confirmed the scalp average post-hoc analyses, with no significant electrode clusters identified in younger vs healthy older adult controls in any of the three conditions.

Cluster permutation analysis revealed that older adults had significantly larger f^+ responses in the recognition condition compared to AD patients across a 28 electrode cluster with differences in the SNR of f^+ strongest at lateral occipital and left frontal areas, cluster $p = 0.0009$ see Figure SI2. Older adults also showed significantly larger f^+ responses in the repetition condition compared to AD patients, across a 7 electrode cluster with differences in the SNR of f^+ strongest at central occipital electrodes and the vertex areas, cluster $p = 0.011$.

Figure SI2: Topographic difference plots illustrate the electrodes identified by cluster permutation analysis as showing significant differences in the SNR of $f+$ between older adults and AD patients for the recognition and repetition conditions.

7 Supplementary Information C – Fixation Cross Colour Change detection

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