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BRAIN
ORIGINAL ARTICLE

A passive and objective measure of recognition memory in Alzheimer's disease using Fastball memory assessment

George Stothart,[1] Laura J. Smith,[2] Alexander Milton[3] and Elizabeth Coulthard[4]

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

Younger adults, older adults and Alzheimer's disease patients ($n = 20$ per group) completed the Fastball task, lasting just under 3 min. Participants passively viewed rapidly presented images and EEG assessed their automatic ability to differentiate between images based on 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, participants completed a two-alternative forced choice (2AFC) task to measure their explicit behavioural recognition of previously seen stimuli. Fastball EEG detected significantly impaired recognition memory in Alzheimer's disease compared to healthy older adults ($P < 0.001$, Cohen's $d = 1.52$), whereas behavioural recognition was not significantly different between Alzheimer's disease and healthy older adults. Alzheimer's disease 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 2AFC 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 2AFC task.

Early diagnosis of Alzheimer's disease offers potential for early treatment when quality of life and independence can be retained through disease modification and cognitive enhancement. Fastball provides an alternative way of testing recognition responses that holds promise as a functional marker of disease pathology in stages where behavioural performance deficits are not yet evident. 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.

1 Department of Psychology, University of Bath, Bath, UK
2 School of Psychology, University of Kent, Canterbury, UK
3 School of Psychological Science, University of Bristol, Bristol, UK
4 Bristol Medical School, University of Bristol, Bristol, UK

Correspondence to: George Stothart
Department of Psychology, University of Bath
Claverton Down, Bath BA2 7AY, UK
E-mail: G.Stothart@bath.ac.uk

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Keywords: recognition memory; EEG; objective; fastball; fast periodic visual stimulation

Abbreviations: 2AFC = two-alternative forced choice task; FPVS = fast periodic visual stimulation; SNR = signal-to-noise ratio

Introduction

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 is the underlying cause of ~60% of dementia, with an estimated prevalence in Europe and North America of 5–7%.[1,2] 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 Alzheimer's disease patients in clinical trials.[3] It could also increase the efficacy of multimodal lifestyle interventions, demonstrated to reduce the incidence and rate of cognitive decline in at-risk populations,[4] with subsequent healthcare savings modelled at ~£3 billion per year in the UK.[5] 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 Alzheimer's disease before symptoms develop.[6]

Current diagnosis tools

Alzheimer's disease is currently diagnosed using a combination of subjective and objective reports of cognitive decline and standardized neuropsychological assessment, e.g. Mini-Mental State Examination,[7] Addenbrookes Cognitive Exam (ACE)[8] and Montreal Cognitive Assessment.[9] 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.[10] 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.[11] Additionally, their relationship with cognition is unclear. For example, amyloid pathology can present without clinically significant cognitive decline,[12–14] and cognitive decline can present without clinically significant amyloid pathology.[15] To improve diagnostic sensitivity, and improve understanding of disease pathogenesis, structural biomarkers need to be combined with early functional measures that specifically probe Alzheimer's disease-related changes.

Existing neuropsychological measures of functional ability are prone to educational and cultural biases,[16,17] assessment anxiety,[18,19] 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[20] and populations with language impairments, e.g. Down's syndrome.[21] 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 care provision. Objective measures of cognitive function, that do not require active responses, would address these problems.

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 Alzheimer's disease and age-matched control subjects,[22] with a reduction and slowing of the P300 response being the most consistently reported finding.[23] However, the translation through to viable clinical diagnostic tools has never been realized, despite many decades of positive experimental findings. Barriers include the long recording times required to reliably measure ERPs and the high interindividual 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 interexperimental variability in how ERP responses are quantified.[24]

Fast periodic visual stimulation

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.*[25] and developed extensively by Rossion *et al.*,[26–28] FPVS involves frequency tagging standard and oddball stimuli in a classic oddball paradigm. Standard stimuli are presented at a fast rate, typically ~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 ~1 Hz (Fig. 1).

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.[29] Practically, this gain in SNR equates to very short recording times (as little as 1 min) and reliable measures at the level of the individual subject. The approach has been used to measure low-level visual processing,[25] face detection and discrimination,[26,28,30–32] and language processing.[33] We recently adapted the approach to measure two cognitive processes known to deteriorate in dementia: abstract semantic categorization[34,35] and recognition memory.[36]

Fastball memory assessment

We recently demonstrated the successful adaptation of FPVS for the passive, objective measurement of a recognition memory response in younger adults.[36] We present the application of this new tool, which for simplicity we refer to as 'Fastball', in the measurement of recognition memory in Alzheimer's disease.

Recognition memory comprises two processes: (i) familiarity, defined as a sense of previous exposure in the absence of or prior to; (ii) recollection, defined as a conscious retrieval of associated information about the previously experienced event or stimulus. Distinguishing between which process is elicited typically requires self-report. However, experiences of remembering (recollection) and knowing (familiarity) are subjective and are therefore

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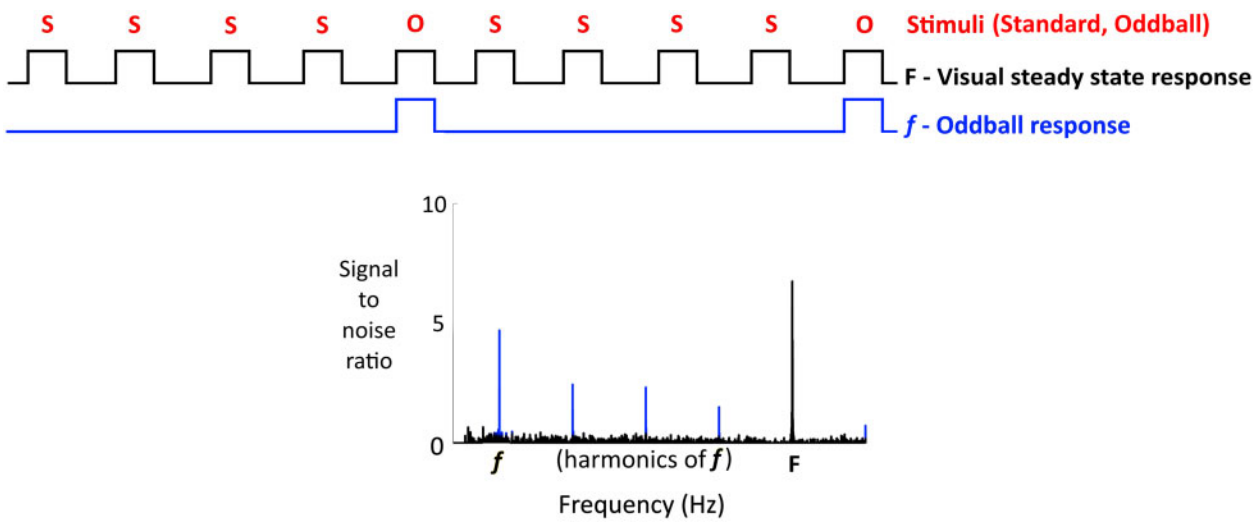

Figure 1 Schematic illustration of the FPVS frequency tagging design. Letters in red indicate a stream of visual presented standard and oddball stimuli. Black and blue lines represent the hypothesized neural response to the stimuli. The frequency plot illustrates the narrowband responses to stimulation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

notoriously difficult to measure accurately.[37] These judgements require the participant to retrospectively state, following a discrimination response between two stimuli, whether they explicitly recognized the stimulus (remember) or just felt the stimulus was familiar (know). This can be a difficult concept to consistently convey to participants, requiring the subjective interpretation of the experiences of remembering and knowing and can introduce high intersubject variability.[37,38]

Fastball, however, is designed to provide an alternative measure of recognition based on the neural response to previously encountered images. Fastball comprises three conditions, designed to quantify the role of pre-task stimulus encoding and repetition. In the recognition condition, oddball stimuli are viewed and encoded prior to the Fastball task, then repeatedly presented during the task. In the repetition condition oddball stimuli are not viewed prior to the task, but are repeatedly presented, and in the control condition all stimuli are novel.

The task neither asks nor tests for a subjective experience, meaning that the response could involve both familiarity and recollection. This is especially likely where stimuli are encoded prior to the Fastball trial. The task also likely involves the activation of a memory representation that is common to both perceptual priming and familiarity.[39,40] We do not attempt to tease apart the respective presence of these processes here but propose that Fastball at a minimum captures the initial and automatic activation of a memory representation for previous stimulus exposure. The current study's primary focus is to explore the clinical utility of Fastball as a passive measure of recognition, however, as disease-evoked change can shed light on underlying cognitive mechanisms, we do explore the theoretical implications of our work as a secondary outcome.

Fastball and Alzheimer's disease

Neuropsychological and neuroimaging evidence suggests familiarity and conscious recollection are dependent on brain areas known to be affected in early Alzheimer's disease; the perirhinal cortex and hippocampus, respectively.[41–48] Earlier accounts of memory proposed a consciousness-based distinction wherein implicit memory was considered as a separate system to explicit memory such as familiarity and recollection.[49] More recent evidence suggests that the implicit and explicit tasks may share common memory representations,[39,40] and that medial temporal lobe areas typically thought to be involved only in explicit memory are also associated with implicit memory tasks.[50–53] The examination of unconscious recognition in Alzheimer's disease has demonstrated a dissociation between impaired conceptual priming and preserved perceptual priming.[54–57] This dissociation has been proposed to reflect the progression of Alzheimer's disease pathology, with impairments in conceptual priming attributed to anterior cortical damage and maintenance of perceptual priming supported by posterior cortical preservation.[58]

In terms of conscious recognition processes healthy older adults typically show impaired recollection and maintained familiarity performance, with deficits in familiarity only observable when using Remember/Know judgements. Alzheimer's disease patients also show consistent deficits in recollection, with more variable findings in familiarity performance.[59] Significant difficulties arise with the behavioural testing of familiarity in cognitive impaired populations, due to the subjective interpretation of familiarity requiring a high level of linguistic/semantic function, and biases created by the delivery, complexity and comprehension of task instructions.[47] 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 Alzheimer's disease patients in the current study.

Aims and hypotheses

The current study aims to passively and objectively measure recognition memory in Alzheimer's disease patients using Fastball. We predicted patients with Alzheimer's disease would show reduced recognition memory performance, as a consequence of medial temporal lobe pathology, indexed by a decrease in the Fastball response compared to healthy older adults. With familiarity responses typically maintained in healthy ageing we also predicted no difference in recognition memory performance between younger and healthy older adult control subjects.

Materials and methods

Subjects

Participant demographics are presented in Table 1. Twenty patients with Alzheimer's disease were recruited from memory

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clinics in the Southwest of England. The diagnosis of Alzheimer's disease 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[60] and NINCDS-ADRDA guidelines.[61] Patients were in the mild-to-moderate stage of the disease according to ACE-III scores[62] (Table 1). Seventeen patients were taking cholinergic medication commonly prescribed in the early stages of Alzheimer's disease, 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 control subjects 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 (logMar $\leqslant$ 0.1), except for four older adults and eight Alzheimer's disease patients. No relationship between visual acuity, contrast sensitivity and the dependent variables in the current study was found. 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.

Stimuli

Images were selected from the Bank of Standardised Stimuli v2.0,[63] a previously validated set of 1468 high quality colour images. All images were 512 × 512 pixels, 96 dpi, subtending 10° visual angle when viewed from a distance of 70 cm. Importantly each image was only used once, i.e. as a standard, oddball or foil. Example images are provided in Fig. 2.

Standards

Standard stimuli [mean image intensity of 0.82 (standard deviation, 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.

Oddballs

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

Foils

For the pre-Fastball encoding two alternative forced choice (2AFC) task, eight images [mean image intensity = 0.77 (SD 0.29)] were preselected as foils, i.e. distracting previously unseen images, and were consistent across subjects. For the 2AFC 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.

Procedure

Subjects completed three conditions: recognition, repetition and control. To ensure that cognitively impaired populations were able to complete the encoding phase of the recognition condition, the number of test items to be initially encoded was kept low, at only eight items. Consequently, test items had to be repeatedly presented during the Fastball stimulation phase and this introduced a repetition priming confound. To control for this, the repetition condition was included. 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.

Pre-Fastball encoding

Subjects viewed the eight preselected oddball images centrally for 3 s and were asked to name the image 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-randomized to ensure equal presentations to the left and right of the screen. In the case of an incorrect response, subjects were informed that the response was incorrect via onscreen feedback and asked to try again. The subject could not move on to the

Table 1 Participant demographics, neuropsychological and visual performance

	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
ACE-III				
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)[a]	–0.19 (0.06)	0.03 (0.15)	0.17 (0.24)	Young < Old = AD
Contrast sensitivity (LogCS)[b]	2.27 (0.26)	1.80 (0.51)	1.50 (0.39)	Young > Old = AD

Values other than counts indicate means (SD). Groups were compared using one-way ANOVA with Bonferroni corrected post hoc comparisons, sex was compared using a Mann-Whitney U-test. ACE-III = Addenbrooke's Cognitive Examination-III; AD = Alzheimer's disease. The less than and greater than symbols (> and <) indicate significant statistical differences $P < 0.05$. The equal symbol (=) indicates no significant statistical difference $P > 0.05$.

[a]Higher score = worse acuity.

[b]Higher score = better sensitivity.

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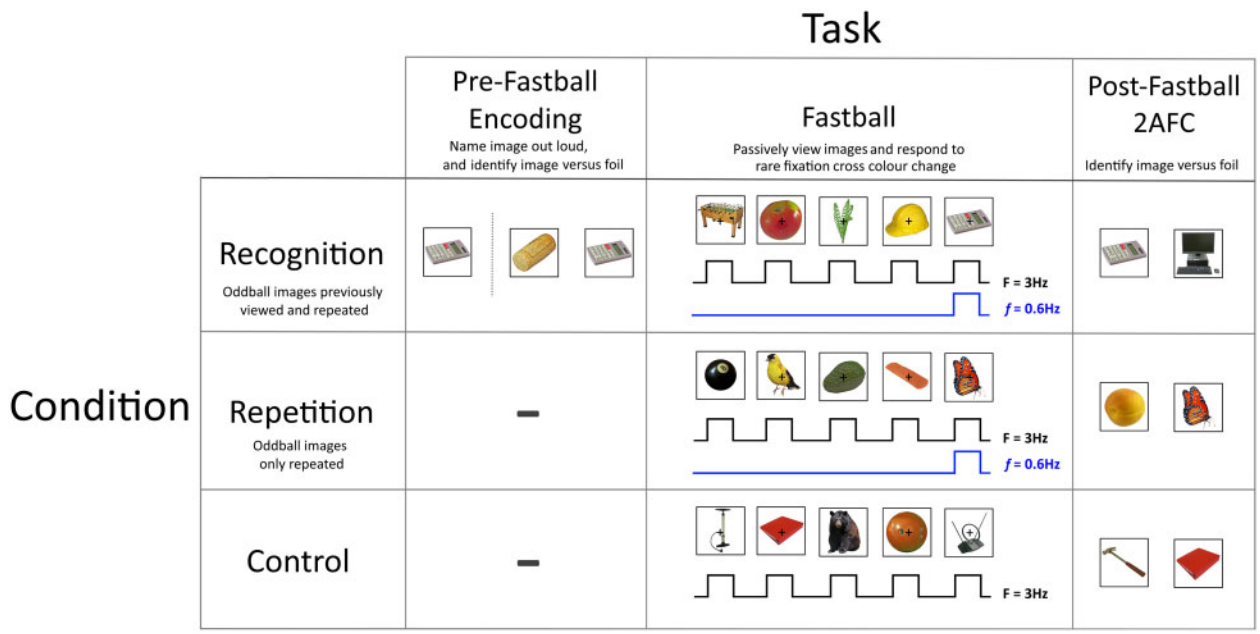

Figure 2 Task designs across the recognition, repetition and control conditions. Pre-Fastball Encoding: In the recognition condition only subjects named the image out loud, then identified the image in a 2AFC discrimination task paired with previously unseen image (foil). Fastball: For all three conditions a base frequency *F* is elicited in response to the presentation of every image at 3 Hz. Black and blue lines indicate the hypothesized neural response to standard and oddball images. 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. Post-Fastball 2AFC: Subjects identified previously seen oddballs and a randomly selected subset of standard images in a 2AFC task. Previously seen images were presented alongside novel, previously unseen images (foils).

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.[64] All Alzheimer's disease 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.

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 on-screen for 166 ms with an interstimulus interval of 166 ms. An example of this sequence is presented in Fig. 2. This design elicits two distinct steady state responses. The standard presentation frequency of 3 Hz, and the oddball presentation frequency of 0.6 Hz. 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 173 s. In the control condition, 520 previously unseen novel stimuli were presented in a random order. The order of the conditions was counterbalanced across subjects.

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 (1.66 s). The number of correctly identified targets was recorded for each participant. Some Alzheimer's disease 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 Alzheimer's disease patients responded to targets verbally, for the experimenter to record manually, reaction time data were not analysed.

Post-Fastball 2AFC task

Immediately following each of the three Fastball tasks subjects completed a 2AFC task. 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 on-screen 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.

General cognition and vision assessment

After completing the Fastball tasks and taking a short break, participants completed the ACE-III and the Freiburg Visual Acuity Test.[65]

EEG recording

EEG signals were sampled at 1000 Hz from 65 channel HydroCel Geodesic Sensor Net electrodes using a GES 400 system (Electrical

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Geodesics Inc; EGI), with a common Cz reference and online low-pass filtered at 250 Hz. Impedances were <50 kΩ. Recordings were analysed offline using Brain Electrical Source Analysis software v5.3 (BESA GmbH), MATLAB (Mathworks Inc.) and the Fieldtrip toolbox.[66] Blinks and eye movement artefacts were corrected using BESA automatic artefact correction.[67]

EEG analysis and steady state response

Data were re-referenced offline to a common average reference, downsampled to 256 Hz, and two electrooculogram electrodes were excluded from further analysis. To avoid aliasing artefacts, an 85 Hz 24 db zero phase lowpass filter was applied. The steady state response was calculated according to the procedures described in Stothart *et al.*[36] Epochs from 0 to 173 s around trial onset were defined for each condition. This epoch length represents an integer number of cycles (104) of the oddball stimulus (0.6 Hz) ensuring that a frequency bin corresponding to the exact oddball frequency and its harmonics, including the standard frequency (3 Hz), were created. The frequency resolution was 0.0057 Hz. Epochs were polynomially detrended to remove DC and slow wave artefacts.

As we used single epochs of a long duration, visual inspection revealed occasional instances of gross artefacts, e.g. large physical movement artefacts. Any artefact ±250 μV 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 ±0.10 Hz range (17 frequency bins)[27,34,68] 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 0.6 Hz adjacent bins were 0.5941 and 0.6059 Hz).

Previous research has shown a robust steady state visual evoked potential response to the oddball frequency and many of its harmonics[29] with oddball detection more reliably and accurately measured when including the harmonics of the oddball response.[34] Consequently, the SNR was calculated for two values: the standard frequency *F* (3 Hz) and the mean of the oddball frequency and 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 ±0.10 Hz range. This identified the highest significant harmonic ($Z > 1.96$) at 7.2 Hz 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 7.2 Hz. These three values were calculated for each subject and electrode for all three conditions.

Statistical analyses

Sample size and power calculations

Younger adult control data, collected before the healthy older adult and Alzheimer's disease patient data, showed large effect sizes (Cohen's $d = 1.52$) in the recognition versus control comparison.[36] To replicate this effect at an α of 0.01 and a β of 0.95 required a sample size of $n = 10$. However, the effects of healthy ageing and Alzheimer's disease 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 $n = 20$.

Covariates

There was a non-significant trend for some older adults to show increased basic visual steady state responses, F. 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.

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) × 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) × 3 (group: young, old, Alzheimer's disease) ANOVA was conducted. To explore topographic differences in the difference in $f+$ between group pairs (young versus old, old versus Alzheimer's disease) across all electrodes for each condition (recognition, repetition, control) cluster-based permutation analysis with 10 000 permutations and an initial cluster formation alpha ⩽0.05 were performed.[69]

Behavioural responses to the 2AFC 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 versus Alzheimer's disease) based on Fastball responses, a receiver operator characteristic curve was calculated.

Data availability

The study was preregistered 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://gsto thart.github.io/Fastball/ and complete anonymized data are available on the on the Open Science Framework (https://osf.io/dpmec/?view_only=8035aa10b781425390b02d5db11c7aa9).

Results

Neural recognition performance

Alzheimer's disease patients showed impaired recognition memory responses compared to healthy older adult control subjects (Fig. 3A).

Main effects of group and condition

A 3 (group) × 3 (condition) ANCOVA was conducted to determine the effect of group on oddball responses ($f+$) across the three

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conditions (recognition, repetition, control), controlling for basic steady state magnitude (*F*) (Table 2). 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.

Post hoc analyses of group effects

The effects of healthy ageing (young versus old) and Alzheimer's disease (old versus Alzheimer's disease) 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. Alzheimer's disease patients, however, had significantly reduced responses in the recognition condition compared to the healthy older adult controls after correction for multiple comparisons (Table 2).

Post hoc analyses of group × condition interaction

The differences in condition effects across groups was further explored using *post hoc* pairwise comparisons (Table 2). 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.

Visuo-attentional performance

There were no differences between groups in visuo-attentional engagement with the task as indexed by the magnitude of the mean basic 3 Hz steady state response to image presentation (Fig. 3). Data were not normally distributed and Levene's test showed significantly unequal variances [$F(2,57) = 3.28$, $P = 0.045$]. A non-parametric Kruskal-Wallis test showed no effect of group on the median SNR of *F* across the three conditions $\chi^2(2) = 3.97$, $P = 0.137$.

Relationship with neuropsychological performance

Patients with Alzheimer's disease showed no statistically significant ($P < 0.05$) correlations between ACE-III total score, or subscale scores, with $f+$ in any condition.

Region of interest analysis

Having established clear differences between Alzheimer's disease 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 versus old, old versus Alzheimer's disease) was statistically assessed across all electrodes for each condition (recognition, repetition, control) using cluster-based permutation analysis[69] with 10 000 permutations, initial cluster formation alpha $\leqslant 0.05$.

Young versus old

Permutation analyses confirmed the scalp average *post hoc* analyses, with no significant electrode clusters identified in younger versus healthy older adult control subjects in any of the three conditions.

Old versus Alzheimer's disease

Older adults had significantly larger $f+$ responses in the recognition condition compared to Alzheimer's disease patients across a 28-electrode cluster with differences in the SNR of $f+$ strongest at lateral occipital and left frontal areas, cluster $P = 0.0009$ (Fig. 3C). Older adults also showed significantly larger $f+$ responses in the repetition condition compared to Alzheimer's disease patients, across a seven electrode cluster with differences in the SNR of $f+$ strongest at the central occipital electrodes and the vertex areas, cluster $P = 0.011$ (Fig. 3C). There were no significant clusters identified in the control condition.

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) × 3 (group: young, old, Alzheimer's disease) ANOVA. Ten Alzheimer's disease patients failed to respond to any fixation cross colour changes in one or more conditions (Supplementary material).

There was no main effect of condition [$F(2,114) = 1.05$, $P = 0.335$, partial $\eta^2 = 0.018$] on fixation cross colour change detection. There was a significant effect of group [$F(2,57) = 28.72$, $P < 0.001$, partial $\eta^2 = 0.502$]. *Post hoc* tests using the Bonferroni correction revealed that patients with Alzheimer's disease 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 [$F(4,114) = 0.40$, $P = 0.808$, partial $\eta^2 = 0.014$].

This finding raises the possibility that other experimental effects in the Alzheimer's disease group may reflect lower attentional engagement with the task. However, as demonstrated, basic visual steady state responses (*F*) did not differ between the groups. Overt attention to visual stimuli has repeatedly been shown to increase the amplitude of visual steady state responses,[29,70] therefore if Alzheimer's disease patients' attentional engagement with the stimuli was lower, their basic visual steady state responses (*F*) would also have been lower than that of controls, which was not the case.

Post-Fastball 2AFC performance

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 (Table 3).

Recognition of oddball stimuli

Oddball recognition performance was high, but significantly different across the three groups in the recognition condition (Fig. 4). *Post hoc* analyses revealed this group effect was driven by the difference between young adult controls and Alzheimer's disease patients. Neither the young versus old, nor old versus Alzheimer's disease comparisons showed 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 patients with Alzheimer's disease compared to healthy older adults; however, the trend did not survive correction for multiple comparisons.

Recognition of standard stimuli

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

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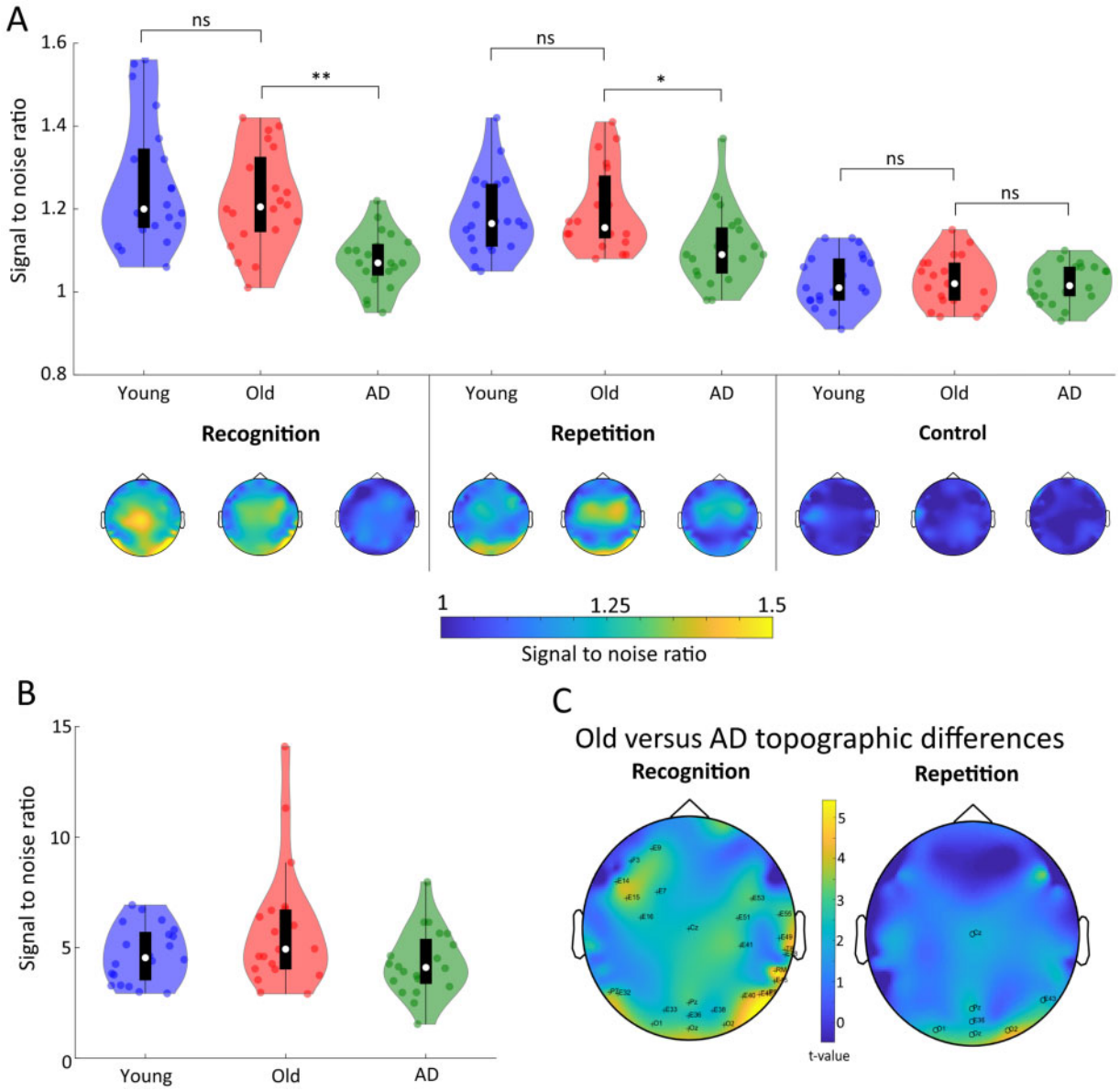

Figure 3 Neural recognition performance. (**A**) Violin plots showing oddball recognition responses (quantified as the signal to noise ratio of $f+$) for the three conditions and three groups, averaged across all electrodes (n = 63). Tukey box plots reflect the median and interquartile ranges, width of the violin plots reflects kernel density estimated using MATLAB's ksdensity function. Brackets indicate statistical significance of *post hoc* comparisons of young versus old and old versus Alzheimer's disease (AD). $^{**}P < 0.01$, $^{*}P < 0.05$, ns = $P > 0.05$. Topographic plots illustrate the SNR of $f+$ in the three conditions, for the three groups. Topographic plots illustrating the baseline corrected amplitude of $f+$ are provided in the Supplementary material. Key results are summarized below and in full in the text. Recognition: Alzheimer's disease 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: Alzheimer's disease 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. (**B**) Violin plots illustrating SNR of F, the 3 Hz steady state response to image presentation for the three groups, averaged across all electrodes (n = 63). Tukey box plots reflect the median and interquartile ranges, width of the violin plots reflects kernel density estimated using MATLAB's ksdensity function. (**C**) Topographic plots illustrate the electrodes identified by cluster permutation analysis as showing significant differences between older adults and Alzheimer's disease patients in the SNR of $f+$ in the recognition and repetition conditions.

Relationship with neural measures and neuropsychological performance

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.

Patients with Alzheimer's disease showed a positive correlation between behavioural oddball recognition and ACE-III total score [$r(19) = 0.51$, $P = 0.027$] in the recognition condition. Examination of ACE-III subscales revealed that this effect was driven by performance on the memory [$r(19) = 0.60$, $P = 0.006$] and language [$r(19) = 0.59$, $P = 0.007$] subscales. There were no significant correlations with the attention [$r(19) = 0.44$, $P = 0.057$] fluency [$r(19) = 0.38$, $P = 0.104$], or visuospatial [$r(19) = 0.08$, $P = 0.744$] subscales.

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Table 2 Neural recognition performance

Main effects	df	F	P	Partial η^2
Group (Young, Old, Alzheimer's disease)	2112	10.9	<0.001	0.28
Condition (Recognition, Repetition, Control)	256	2.3	0.104	0.04
Group × Condition	4112	5.8	<0.001	0.17

Post hoc analyses of group effects

	Young versus Old				Old versus Alzheimer's disease			
	Mean diff. *f*+	95% CI	P	Cohen's *d*	Mean diff. *f*+	95% CI	P	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

Post hoc analyses of group × condition interaction

	Recognition versus Control				Recognition versus Repetition				Repetition versus Control			
	Mean diff. *f*+	95% CI	P	Cohen's *d*	Mean diff. *f*+	95% CI	P	Cohen's *d*	Mean diff. *f*+	95% CI	P	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**
Alzheimer's disease	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**

The 'Main effects' section shows 3 (group) × 3 (condition) ANCOVA to determine the effect of group on oddball responses (*f*+) across the three conditions, controlling for basic steady state magnitude (F). *Post hoc* pairwise comparisons of group. Values in bold indicate significant differences after applying a Bonferroni correction of 0.05/6, $P = 0.008$. Values in bold indicate significant differences after applying a Bonferroni correction of 0.05/9, $P = 0.006$.

There was no significant correlation between neuropsychological performance and behavioural recognition of oddball stimuli in the repetition condition [$r(19) = –0.04$, $P = 0.858$], or standard stimuli in any condition ($P < 0.05$).

Classifying Alzheimer's disease using neural and behavioural recognition memory performance

Patients with Alzheimer's disease 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 (CI): 0.73–0.98, $P < 0.001$] (Fig. 5). Discrimination performance was poor using behavioural 2AFC accuracy (AUC = 0.63, 95% CI: 0.46–0.80, $P = 0.148$). Cut-off scores are provided in the Supplementary material.

Cluster permutation analysis of old versus Alzheimer's disease *f*+ in the recognition condition identified a cluster of 28 electrodes. By taking an average of the SNR of *f*+ across these electrodes, opposed to a scalp average of all 63 electrodes, discrimination could be improved further (AUC = 0.92, 95% CI: 0.82–1.0, $P < 0.001$). It should be noted that this is statistical 'double dipping' and should serve only to guide future *a priori* defined region of interest analyses.

The scalp average SNR of *f*+ in the repetition condition gave more moderate classification accuracy (AUC = 0.78, 95% CI: 0.63–0.92, $P = 0.003$). Discrimination performance was also moderate using behavioural 2AFC accuracy (AUC = 0.72, 95% CI: 0.55–0.88, $P = 0.020$). Discrimination was not improved in the repetition condition by using an average across the seven electrodes defined in the region of interest analysis (AUC = 0.77, 95% CI: 0.62–0.92, $P = 0.003$).

Discussion

We demonstrate a passive and objective measure of recognition memory that is sensitive to Alzheimer's disease and unaffected by healthy ageing. Fastball memory responses in Alzheimer's disease showed the greatest reduction when they were dependent on a brief pre-Fastball encoding task, while behavioural measures of explicit recognition memory were less sensitive to Alzheimer's disease. Fastball provides a new tool for clinicians and researchers in the assessment of memory in Alzheimer's disease with many practical benefits. The task requires a short encoding session with minimal requirements and demands and, critically, the memory response is recorded quickly with subjects not asked to reflect on, respond or remember the items. We note that it is compatible with cheap, readily available, portable technology.

Recognition memory in Alzheimer's disease

Fastball is sensitive to changes in recognition memory in Alzheimer's disease that do not manifest behaviourally. However, the passive 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 recognition that is sensitive to changes in Alzheimer's disease and avoids the confounds that muddy the water of behavioural familiarity measurement. With no requirement for task comprehension or response during the Fastball trial itself, there is reduced scope for the confounding influences of language, executive function, introspection, strategy or guessing.

At a minimum, we propose that Fastball reflects the initial automatic stages of familiarity processing. It is likely to comprise a combination of previously documented event-related neural responses to familiarity, perceptual priming and non-target oddball detection, e.g. the N250r, FN400 and vMMN.[72–76] Given the previously documented maintenance of perceptual priming[56] and non-target oddball detection[22] in Alzheimer's disease, we propose that the reductions in Alzheimer's disease patients' Fastball responses observed in the current study may specifically reflect impairments in familiarity processing. This is particularly the case for the recognition condition where the pre-trial encoding task

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Table 3 Behavioural recognition performance

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

Post hoc analyses of the effects of group on recognition accuracy								
	Young versus Old			Cohen's *d*	Old versus Alzheimer's disease			Cohen's *d*
	U	*Z*	*P*		*U*	*Z*	*P*	
Oddball								
Recognition	160	–2.08	0.038	0.35	147	–1.75	0.080	0.47
Repetition	136	–2.05	0.040	0.56	114	–2.42	0.016	0.79

Kruskal-Wallis H-tests were used to examine the main effect of group on recognition accuracy. Values in bold indicate significant differences, $P < 0.05$. *Post hoc* Mann-Whitney U-tests were used to examine the effect of age and Alzheimer's disease on oddball recognition accuracy. Bonferroni corrected alpha = 0.05/4, P = 0.0125. Effect sizes were calculated using an online effect size conversion calculator.[71]

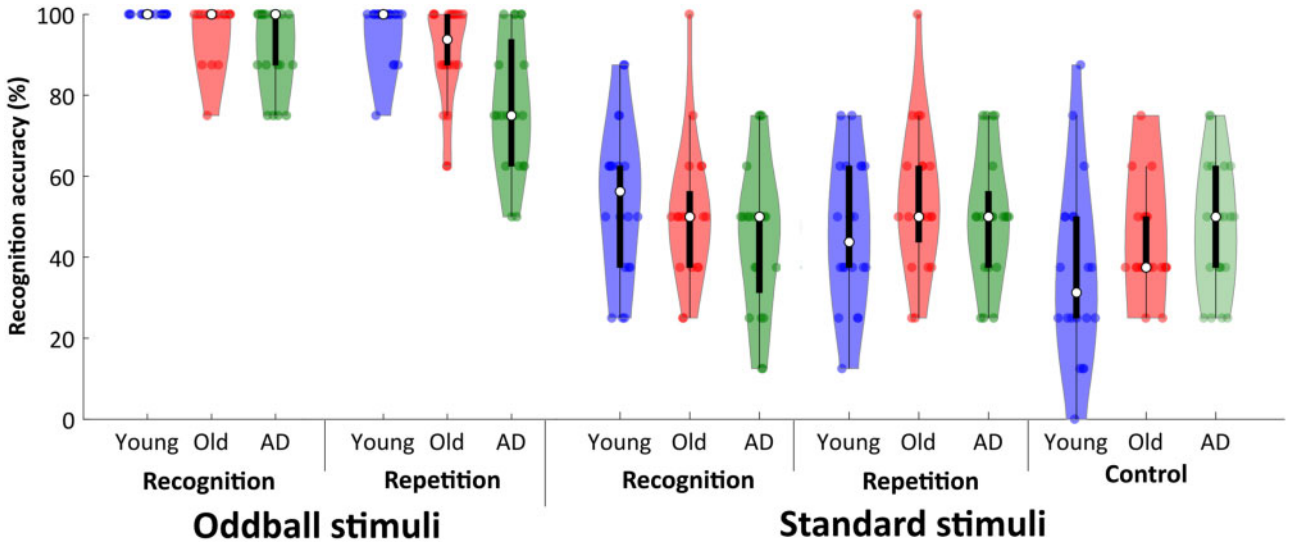

Figure 4 Behavioural recognition performance. Violin plots illustrating % accuracy for the 2AFC tasks. Scores reflect the correct recognition of either an oddball or standard stimulus compared to a foil in a 2AFC. Tukey box plots reflect the median and interquartile ranges, width of the violin plots 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 patients with Alzheimer's disease (AD). *Post hoc* comparisons of young versus old and old versus Alzheimer's disease 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%).

required a depth of processing that would have favoured a familiarity response, even though participants were not instructed to remember the images.

We did not observe a difference in the oddball magnitude between recognition and repetition conditions for older adults or patients with Alzheimer's disease. This could suggest that the observed recognition memory response is similar between the two conditions. As we did not collect data on whether subsequent behavioural recognition in the 2AFC was based on Remember, Know or Guess responses, we cannot determine whether the repetition condition led to explicit awareness of the oddball stimuli. However, we propose that this is likely given that each oddball stimulus was repeated 13 times and shown for 166 ms at full opacity. It is therefore likely that the recognition and repetition conditions involved overlapping or similar recognition processes, and future studies could better examine the underlying responses by collecting indices of subsequent recognition and confidence.

The region of interest analysis showed topographic differences between older adults and patients with Alzheimer's disease in the recognition condition that extended to left hemisphere frontal electrodes. This topographic difference was not observed in the repetition condition in which differences between older adults and patients with Alzheimer's disease were limited to medial occipital electrodes. This suggests that areas beyond sensory cortices were involved in the recognition condition, further supporting the claim that the reduction of these responses in Alzheimer's disease were driven by deficits in familiarity processing and may reflect functional consequences of entorhinal cortex pathology. Such claims

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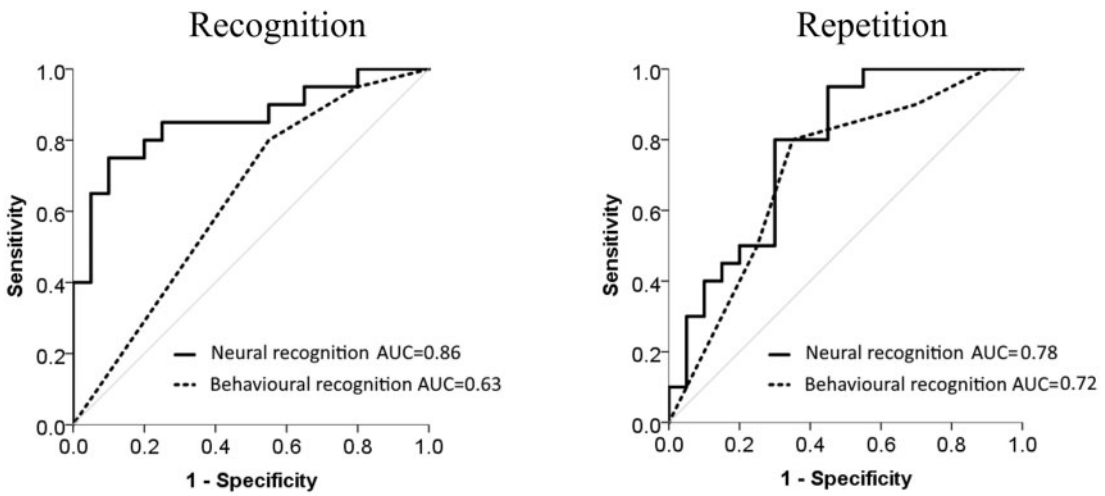

Figure 5 Alzheimer's versus healthy older adult classification. Receiver operator characteristics (ROC) plots indicating the classification accuracies of Alzheimer's disease versus healthy older adult controls using neural (*f*+) and behavioural measures (% accuracy) of recognition memory. Control: There were no significant differences between the groups in the control condition.

naturally 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) ε4 carriers show impaired familiarity processing in the absence of other cognitive deficits.[77]

Explicit recognition, as measured by the post-Fastball 2AFC task, was high in the recognition condition and Alzheimer's disease patients and not significantly different from healthy older adult controls. In the repetition condition, patients with Alzheimer's disease showed reduced explicit behavioural recognition compared to healthy older adult control subjects. There was a positive correlation between recognition of oddball stimuli and ACE-III performance in the recognition but not the repetition condition. These data lead to two interpretations. First, when stimuli are learned in an explicit encoding task, subsequent conscious recognition is increasingly impaired as Alzheimer's disease progresses, but is difficult to separate from typical healthy ageing performance in the mild stages, in line with previous research.[59] Second, when stimuli are learned incidentally rather than explicitly (as occurred in the repetition condition) subsequent conscious recognition is reduced, and the relationship with Alzheimer's disease severity weakened. This suggests that although Alzheimer's disease patients showed reductions in both recognition and repetition oddball responses, the two conditions might be tapping into only partially overlapping processes. The association of ACE-III scores to the recognition condition does lend itself to the proposal that this condition is more reliant on medial temporal lobe structures that are affected by Alzheimer's disease pathology. The previous encoding of items may have more strongly engaged familiarity and recollection responses than the incidental learning in the repetition condition.

Given the similarities in behavioural performance across groups it would not be accurate to refer to the neural differences observed in Alzheimer's disease 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. 166 ms with an equivalent inter-stimulus interval. Previous studies of perceptual speed and visual short-term memory have demonstrated that Alzheimer's disease patients' recognition memory is more sensitive to temporal constraints. Bublak and colleagues[78] demonstrated that a period of ∼300 ms was required for recognition and retention of stimuli for subsequent recollection. When stimuli were presented for half this time, i.e. ∼150 ms, recognition performance was significantly impaired.[78] 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.[79] These previous examples differ from the current study in that the measure of recognition was explicit, not passive, 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 patients with Alzheimer's disease have a greater temporal window for the effect of backward masking, extending up to 150 ms.[80–82] However, since the duration of inter-stimulus presentations (333 ms, including inter-stimulus interval) in the current study is more than double this duration, we therefore think it unlikely that backward masking contributed to the group differences.

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 Alzheimer's disease patients were clearly observed in the recognition condition, with larger *post hoc* group comparison effect sizes (Cohen's *d* 1.53 versus 0.94) and better classification accuracy (AUC = 0.86 versus 0.78) in the recognition compared to repetition condition. Our interpretation of these effects is that while the 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 Alzheimer's disease, beyond that of repetition alone.

New diagnosis tools

Fastball can detect changes in recognition memory processing that are not observable behaviourally, giving the technique considerable potential as an early diagnostic tool. The current study shows that classification accuracy of Alzheimer's disease versus old was

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highest when using Fastball over the behavioural measure of recognition (post-Fastball 2AFC task). It should be noted that there was a clear ceiling effect in the 2AFC task, which limited its sensitivity. Future studies should use more sensitive standardized measures of recognition memory, such as the Warrington Recognition Memory Test[83] to enable more equitable comparisons with behavioural testing. Based on the current data, we therefore cannot make any generalized claims that Fastball is more sensitive to Alzheimer's disease than behavioural measures; however, we do propose that Fastball reflects an alternative method for assessing recognition response whose utility should be explored.

Using the technique to detect changes in recognition memory performance in the mild cognitive impairment stage, and even presymptomatic stages of Alzheimer's disease is a logical next step. Fastball/FPVS has been shown to be effective at capturing semantic,[34] visual,[25] language,[33] and memory[36] 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.[24] 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 anxiety-induced performance impairment that can occur during traditional neuropsychological assessment.[18,19] 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 functional MRI and PET for the objective assessment of cognitive function. Its non-invasive nature also avoids the difficulties associated with the extraction of CSF biomarkers.

Limitations

Alzheimer's disease patients showed greater difficulty in the fixation cross colour change task. Half the patients provided no response, and many patients had to response verbally to the experimenter rather than pressing a key. This raised the possibility that other experimental effects observed were simply due to lower attentional engagement with the task; however, we do not believe this to the be the case. An analysis of the magnitude of the steady state response to all visual images revealed equivalent magnitudes across groups, which was not indicative of reduced attention. Attentional engagement in patients with Alzheimer's disease was further demonstrated by their successful recognition of repeatedly presented oddball stimuli in the repetition condition, i.e. their 2AFC performance. We propose that Alzheimer's disease patients' low compliance and accuracy in the fixation cross colour change task reflects difficulty multi-tasking and following task instructions, rather than lower attentional engagement with the Fastball memory assessment, reinforcing the value of passive measures of cognitive function. Future studies should investigate whether a simpler orthogonal task, such as a simple continuous fixation instruction, would be sufficient for participants to adequately engage with the stimuli without introducing potential multi-tasking confounds.

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 to potentially improve the sensitivity of the task to Alzheimer's disease. Deconstructing the different subcomponents of familiarity may also help us further understand the processes that are vulnerable to Alzheimer's disease, 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 Alzheimer's disease group. Future studies should examine performance in unmedicated Alzheimer's disease patients. This may help establish the value of Fastball as a measure of intervention efficiency for future clinical trials.

There was no relationship between Fastball responses and Alzheimer's disease severity, as measured by ACE-III scores. Quantifying disease severity using neuropsychological performance in isolation is an imperfect approach and future studies should use structural biomarkers to quantify cortical atrophy and amyloid load to more accurately estimate disease severity.

Conclusions

In summary, we present a new method for objectively measuring visual recognition memory in Alzheimer's disease, 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 Alzheimer's disease 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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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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