

Original Research Article

# Exploring Visual Selective Attention towards Novel Stimuli in Alzheimer's Disease Patients

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## Key Words

Alzheimer's disease · Attention dysfunction/cognition · Visual attention · Selective attention · Novelty preference · Visual scanning

## Abstract

**Background:** Alzheimer's disease (AD) is associated with selective attention impairments, which could contribute to cognitive and functional deficits. Selective attention can be explored through examination of novelty preference. **Aims:** In this study, we quantified novelty preference in AD patients by measuring visual scanning behaviour using an eye tracking paradigm. **Methods:** Mild-to-moderate AD patients and elderly controls viewed slides containing novel and repeated images simultaneously. The outcome measure was time spent on specific images, with novelty preference defined by greater relative fixation time (RFT) on novel versus repeated images. Cognitive status (Standardized Mini-Mental State Examination, SMMSE) and attention (Digit Span, DS) were also measured. **Results:** AD patients (age 79.2 ± 6.7 years, SMMSE 22.2 ± 4.0, n = 41) and controls (age 76.2 ± 6.4 years, SMMSE 28.1 ± 2.0, n = 24) were similar in age, education and sex. Compared with controls, AD patients had lower RFT on novel than on repeated images ( $F_{1,63} = 11.18$ ,  $p = 0.001$ ). Further, reduced RFT was associated with lower scores on SMMSE ( $r_{63} = 0.288$ ,  $p = 0.020$ ) and DS ( $r_{63} = 0.269$ ,  $p = 0.030$ ). Within individuals, novelty preference was detected in 92.3% of patients and in 100% of controls. **Conclusion:** These findings suggest that novelty preference, measured by visual scanning behaviour, can differentiate cognitively healthy and impaired people and may offer a nonverbal, less cognitively demanding method of assessing selective attention.

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## Introduction

Alzheimer's disease (AD) is often accompanied by progressive memory loss as well as impairments in attention, which may contribute to the diminishing cognition and function characteristic of the disease. Evidence has pointed to impairments in selective attention, the ability to focus on a target stimulus while filtering out distractions, in the early stages of AD, which worsen linearly with disease severity [1–5]. Specific impairments in visual attention have been observed in patients with mild AD [6–8] as well as those in the pre-dementia stages [9, 10]. Finke et al. [11] proposed a brain mechanism-based account of visual selective attention deficits, where damage within parietal regions and intrinsic frontoparietal networks in early and prodromal AD may reduce the ability to prioritize relevant over irrelevant visual inputs.

Selective attention towards novel stimuli, referred to as novelty preference or novelty seeking, has been associated with memory and cognitive function. Implicit tasks of novelty preference using eye tracking technology have been investigated in nonhuman primates and human infants. The visual paired comparison (VPC) task, which involves monitoring spontaneous eye movements while subjects are simultaneously presented with both novel and previously displayed images following a delay, showed that cognitively intact monkeys and healthy infants spent more time viewing novel images [12, 13]. In contrast, patients with mild cognitive impairment have demonstrated diminished novelty preference [14–16]. Furthermore, novelty preference has been shown to predict cognitive decline in patients with mild cognitive impairment [15].

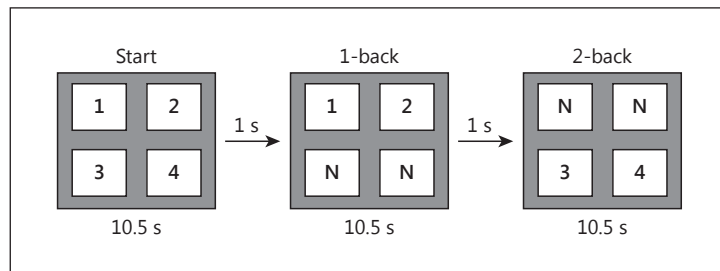
Thus far, the degree of deficits in novelty preference specific to AD has yet to be quantified. In an earlier study, Daffner et al. [17] found that a subset of AD patients spent less time viewing irregular (novel) line drawings compared with age-matched controls [17, 18]. Additionally, the novelty P3 event-related potential, described as the brain response associated with allocation of attention to novel events [19], is significantly reduced in AD patients [20]. Eye tracking procedures can also be used to measure novelty preference in cognitively impaired populations as this method quantifies selective attention and visual scanning patterns without requiring explicit instructions or verbal input from subjects. In the present study, we measured the visual scanning behaviour of AD patients and elderly controls using a modified VPC paradigm to explore selective attention patterns.

## Methods

### *Participants*

Participants with AD were recruited from outpatient clinics at Sunnybrook Health Sciences Centre. Elderly controls were either caregivers accompanying patients (frequently a spouse) or recruited from the community. The eligibility criteria for AD patients included diagnosis of possible or probable AD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) [21] and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [22], minimum age of 65 years, no change in anti-dementia medications <1 month prior to the study day and mild-to-moderate cognitive impairment based on a Standardized Mini-Mental State Examination (SMMSE) [23] score of 10–25. The inclusion criteria for elderly controls consisted of a minimum age of 65 years, no current diagnosis of dementia, SMMSE  $\geq 26$  and no evidence of a psychiatric disorder according to the Modified Mini Screen (MMS <6) [24]. All participants were required to be free of any significant eye pathology and communicative impairments. Before the start of the study procedures,

**Fig. 1.** Sample slide structure and sequence. The first slide of each set (Start) contained four novel images (N). The slide following (1-back) contained two novel and two repeated images. The final slide of the set (2-back) contained two images repeated from the first slide and two novel images.



informed consent was provided by all participants or, in the case of dementia patients, a legally authorized representative. The study was approved by the institution's research ethics board.

### Procedures

This was a cross-sectional study. All participants were administered the Wechsler Adult Intelligence Scale-Digit Span (WAIS-DS) [25] and the SMMSE [23], and the controls were administered the MMS [24]. The WAIS-DS [25] was used to assess working memory and auditory attention. Sequences of digits were read and patients were required to repeat them in the same (Digit Span Forward, DSF) or reverse order (Digit Span Backward, DSB). DSF is thought to be a measure of selective attention, while it has been suggested that DSB may reflect executive functioning [26]. Forward and backward scores were combined to establish a total score, which was converted to a scaled score based on standardized age norms. The SMMSE [23], a more systematic and reliable version of the original MMSE [27], was used to describe the severity of cognitive impairment. The MMS [24] is 22-item scale used to identify individuals whom may exhibit symptoms of mood, anxiety and psychotic disorders. MMS questions were based on assessment tools such as the Structured Clinical Interview for DSM Disorders (SCID) and the Mini International Neuropsychiatric Interview (MINI). Following neuropsychological testing, both controls and dementia patients underwent the Visual Attention Scanning Technology (VAST) procedures.

### Recording and Estimating Visual Scanning Parameters

The VAST developed by EL-MAR Inc. (Toronto, Ont., Canada) was used to record and estimate visual scanning parameters. The technology incorporates a binocular eye tracking system [28] that records eye gaze positions and pupil sizes, a display to present visual stimuli, real-time processing algorithms to estimate visual scanning parameters [29, 30] and a monitoring station to control and supervise the progress of the test [31]. The eye tracking system, mounted on the display (a 23" computer monitor with a resolution of 1,920 × 1,080 pixels), consists of infrared light sources, infrared video cameras and a processing unit that estimates binocular gaze position 30 times/s with an accuracy of ±0.5° [28]. The gaze data were processed by algorithms that segment the data into saccades and fixations on images in each slide and estimate visual scanning parameters [31, 32]. During the test, subjects were allowed to move their heads freely within a relatively large volume (25 × 25 × 25 cm<sup>3</sup>), which supported natural viewing of the visual stimuli.

The VAST procedures started with a 9-point eye tracking calibration procedure in which participants followed a moving target on the computer screen. Following the short calibration routine (<30 s) participants looked at a series of slides that were presented on the VAST display and their visual scanning patterns and pupil sizes were recorded (for slide structure see fig. 1). Each slide contained four images that were similar in complexity and neutral in

content. Participants sat at a distance of approximately 65 cm from the monitor so that the visual angle subtended by each of the four images on each slide was approximately  $15.5^\circ \times 12.2^\circ$ . The horizontal and vertical separation between any two images was  $>2.5^\circ$ . The series of slides included 16 sets of test slides and 58 filler slides. Each set of test slides was comprised of three slides that were presented consecutively. The start slide of each set contained four novel images and the two subsequent slides contained two novel images and two images that were repeats of images that had been shown previously in the start slide. Repeated images were presented in the same positions on the start slide and on subsequent slides. Each slide was displayed for 10.5 s and was followed by 1 s of a uniform grey screen. The delay between presentations of repeated images was 1 s when the repeated images were presented on the first slide that followed the start slide (1-back condition) and 12.5 s when they were presented on the second slide that followed the start slide (2-back condition). The four images on each slide were arranged in a 2 by 2 configuration. The positions of repeated images on the slides (top left, top right, bottom left and bottom right) were uniformly distributed between the 16 test sets. A total of 48 test slides were presented (16 start, 16 1-back and 16 2-back slides). Ten filler slides were used at the beginning of the presentation to familiarize subjects with the presentation format and 48 filler slides were inserted randomly between test sets (1–4 filler slides between two consecutive test sets) to mask the structure of the sets. A total of 106 slides were presented but only the test slides (48) were analysed. The testing procedure was divided into two sessions of approximately 10 min each. Between the two sessions the subjects were given a 5-min break.

Relative fixation time (RFT) was chosen as our primary outcome measure. This parameter has been used previously to characterize the visual scanning behaviour of patients with eating disorders [31] and depression [29] and is calculated by dividing the fixation time on novel/repeated images on a slide by the total fixation time for all four images on a slide. The bias towards novel images (novelty preference) was characterized by the difference between the RFTs on novel and repeated images on a slide (RFT difference). Higher biases (larger differences in RFT) indicate stronger novelty preferences. Additionally, to obtain more insights into differences between the visual scanning behaviour of AD patients and controls in our modified VPC task, the two components of RFT – the average duration of each discrete fixation (average fixation duration) and the number of discrete fixations (fixation within images) – on novel/repeated images for each slide were calculated. For each participant, RFT, average fixation duration, fixation time within images and biases towards novel images (RFT difference), for the 1-back and 2-back conditions, were determined by calculating the means of these parameters on the corresponding 16 test slides.

### *Statistical Analysis*

Demographic, neuropsychological and visual scanning data were summarized using means  $\pm$  standard deviation. RFT difference was summarized using mean  $\pm$  standard error of the mean. Clinical and demographic characteristics were compared between AD patients and controls using analysis of variance (ANOVA) for continuous variables and  $\chi^2$  test for categorical variables. To compare the components of the RFT of AD patients and controls at baseline (i.e. slides with only novel images), one-factorial ANOVA was performed on average fixation duration and fixation time within images per image for start slides. We used two-factorial repeated measures ANOVA models to explore within-subject effects of image type (novel, repeat), between group effects (control, AD) and interaction between factors for average fixation duration and fixation time within images per image in both the 1-back and 2-back conditions. Paired Student's t tests were performed to determine specific differences between novel and repeated images within each study group. A two-factorial repeated measures ANOVA was performed to determine the effect between groups (AD, control) and

**Table 1.** Participant characteristics

Measure	Control	AD	p value
Age, years	76.2±6.4	79.2±6.7	0.090
Female sex	50.0%	46.3%	0.776
Education			0.138
Grade school	12.5%	24.4%	
High school	41.7%	31.7%	
Post-secondary	45.8%	43.9%	
SMMSE	28.1±2.0	22.2±4.0	<0.001
DS Total <sup>1</sup>	12.1±4.1	9.9±2.5	0.009
DSF	9.9±3.2	9.2±1.9	0.279
DSB	7.3±2.4	5.2±2.1	<0.001

Values are mean ± standard deviation or percentage. One-factorial ANOVA tests were completed for age, SMMSE, DS Total, DSF and DSB scores.  $\chi^2$  tests were performed for sex and education.

<sup>1</sup> Age-corrected scaled score.

within-subject conditions (1-back, 2-back), as well as interaction between factors for RFT difference. We also examined the proportions of participants in each group who displayed any novelty seeking behaviour in our paradigm. Novelty preference in individual participants was defined as RFT difference >0 in either the 1-back and 2-back conditions, representing longer fixation times on novel compared with repeated images. Pearson correlations were conducted to explore associations between visual scanning behaviour outcomes and neuropsychological test scores, including the SMMSE, DS Total, DSF and DSB. All analyses were considered significant at an  $\alpha$  of 0.05 and conducted using the SPSS software.

## Results

Forty-one AD patients and twenty-four elderly controls participated in this study. The groups were comparable in age, education and sex. Controls performed better on tests of attention and cognition (SMMSE, DS Total) (table 1).

During presentation of the start slides, when all four images were novel, control and AD participants had similar average fixation duration ( $F_{1,63} = 1.39$ ,  $p = 0.2$ ) and fixation time within images ( $F_{1,63} = 0.23$ ,  $p = 0.6$ ) per image (table 2). However, in the presence of repeated stimuli, there were significant differences between the visual scanning behaviour of control and AD participants (table 2). There was a significant effect of image type ( $F_{1,63} = 78.10$ ,  $p < 0.001$ ) and group by image type interaction ( $F_{1,63} = 27.03$ ,  $p < 0.001$ ) but no between-group effects ( $F_{1,63} = 0.92$ ,  $p = 0.3$ ) for fixation time within images in the 1-back condition. Post hoc analysis revealed greater fixation time within images on novel compared with repeated images in both the control and AD groups. Similar results were observed in the 2-back condition. Note that for both the 1-back and 2-back conditions there was no significant main effect of group for fixation time within images (i.e. the total number of discrete fixations on all the images on 1-back and 2-back slides was similar for the two groups). For average fixation duration in the 1-back condition, there was a significant main effect of image type ( $F_{1,63} = 18.30$ ,  $p < 0.001$ ) and group ( $F_{1,63} = 5.92$ ,  $p = 0.018$ ) but no interaction between factors ( $F_{1,63} = 0.37$ ,  $p = 0.5$ ). Higher average fixation duration occurred on novel compared with repeated images in both groups. The results for average fixation duration in the 2-back condition were similar.



**Table 2.** Visual scanning behaviour for controls and AD patients

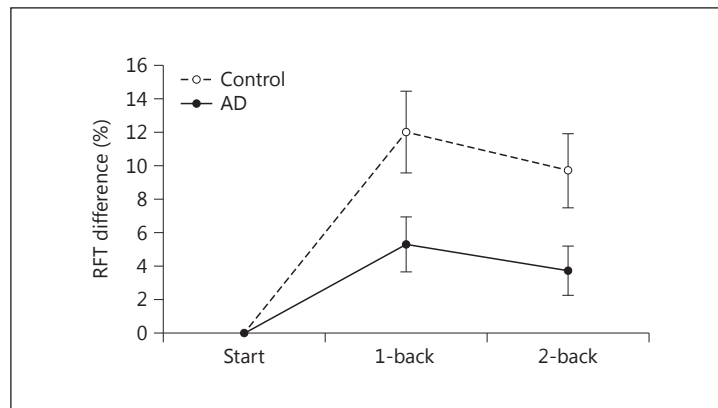
Parameter	Controls (n = 24)	AD patients (n = 41)	p value
<i>Start slide</i>			
Fixation time within images	5.4±0.6	5.3±0.7	0.632
Average fixation duration	431.8±66.8	454.6±79.8	0.242
<i>1-back slide</i>			
Fixation time within images			0.342 (group)
Novel	6.3±0.9	5.4±0.8	<0.001 (image type)
Repeat	4.4±0.9	4.9±0.9	<0.001 (group × image)
Average fixation duration			0.018 (group)
Novel	443.5±51.6	498.7±120.3	<0.001 (image type)
Repeat	401.2±56.4	442.4±85.2	0.544 (group × image)
<i>2-back slide</i>			
Fixation time within images			0.921 (group)
Novel	5.9±1.1	5.3±1.0	<0.001 (image type)
Repeat	4.6±0.8	5.2±1.0	<0.001 (group × image)
Average fixation duration			0.088 (group)
Novel	442.3±72.1	484.1±130.6	<0.001 (image type)
Repeat	403.2±63.0	444.9±101.4	0.999 (group × image)

Values are mean ± standard deviation. Two-factorial ANOVA tests were completed using between-group (control, AD) and within-subject (novel, repeat) factors.

Analyses of difference in RFT between novel and repeated images (a composite of average fixation duration and fixation time within images) also suggested significant differences between groups. Elderly controls spent  $12.0 \pm 2.4\%$  more time fixating on novel compared with 1-back repeat images and  $9.7 \pm 2.2\%$  more time fixating on novel compared with 2-back repeat images (fig. 2). AD patients spent  $5.3 \pm 1.6\%$  more time on novel compared with 1-back images and  $3.7 \pm 1.5\%$  more time on novel compared with 2-back images. The ANOVA model revealed a significant group main effect ( $F_{1,63} = 11.18$ ,  $p = 0.001$ ) but no condition main effect ( $F_{1,63} = 1.03$ ,  $p = 0.315$ ) or interaction between factors ( $F_{1,63} = 0.037$ ,  $p = 0.848$ ). However, the RFT difference between 1-back and 2-back was comparable for all participants. Overall, within individuals, 100% of controls and 92.3% of patients displayed novelty preference behaviour (RFT mean difference for either 1-back or 2-back >0).

Pearson correlations for differences in RFTs on novel and repeated images and other neuropsychological measures were performed for all 65 participants (table 3). Overall, SMMSE and DS Total scaled scores were significantly correlated with RFT difference for both 1-back and 2-back conditions. In the 1-back condition, SMMSE accounted for 7.9% ( $r_{63} = 0.281$ ,  $p = 0.023$ ) and DS Total accounted for 6.7% ( $r_{63} = 0.258$ ,  $p = 0.038$ ) of the variance in RFT difference. In the 2-back condition, SMMSE accounted for 8.3% ( $r_{63} = 0.288$ ,  $p = 0.020$ ) and DS Total for 7.2% ( $r_{63} = 0.269$ ,  $p = 0.030$ ) of the variance in RFT mean difference. When considering the DSF and DSB subscores separately, we found that DSF scores were correlated with RFT differences (i.e. larger biases towards novel images) in the 1-back condition, accounting for 7.3% of the variance ( $r_{63} = 0.272$ ,  $p = 0.029$ ), but not in the 2-back condition ( $r_{63} = 0.092$ ,  $p = 0.5$ ). Interestingly, DSB scores were correlated with RFT differences in the 2-back condition, accounting for 14.7% of the variance ( $r_{63} = 0.383$ ,  $p = 0.002$ ), but not in the 1-back condition ( $r_{63} = 0.123$ ,  $p = 0.330$ ).

**Fig. 2.** RFT difference (%) per slide for the 1-back and 2-back conditions (mean difference between novel and repeat  $\pm$  standard error of the mean). Higher values represent preference for novel over repeated images.



**Table 3.** Pearson correlation coefficients between parameters (n = 65)

Measure	SMMSE	DS Total <sup>1</sup>	DSF	DSB
RFT difference (1-back)	0.281*	0.258*	0.271*	0.123
RFT difference (2-back)	0.288*	0.269*	0.092	0.383**

Significant correlations: \* p < 0.05; \*\* p < 0.01.

<sup>1</sup> Age-corrected scaled score.

## Discussion

The goal of the current study was to explore novelty preference behaviour in AD using a visual attention bias paradigm. Our data showed that cognitively impaired participants had decreased bias towards novel images compared with elderly controls. Specifically, in the presence of novel images and images repeated from 1 and 2 slides previous, patients with mild-to-moderate AD spent less time fixating on novel images compared with elderly volunteers. This is in line with an earlier eye tracking study of novelty preference in patients with cognitive deficits [18], which found that AD patients exhibited reduced exploration of novel stimuli. However, our data also suggest that AD patients do retain some capacity for novelty preference and selective attention. Specifically, patients spent 5.3 and 3.7% more time fixating on novel compared with 1-back and 2-back repeat images, respectively. Even though novelty seeking behaviour was reduced when compared with age-matched controls, the paradigm described in this paper was sensitive enough to detect novelty seeking behaviour in 92% of the AD patients.

The decreased fixation time on novel images in mild-to-moderate AD patients compared to healthy elderly controls, for repeated images with short delays between familiarization (start slide) and test (1 and 12.5 s), is inconsistent with the results of Crutcher et al. [14]. In that study there were no differences between the fixation times of mild cognitive impairment subjects and controls on novel images when the delays between the familiarization and test slides of the VPC task were short (2 s). This inconsistency might be explained by differences between the patient populations of the two studies (our patients were more cognitively impaired) and by differences between the testing paradigms. Our paradigm allotted longer viewing times (10.5 s) in contrast to the 5 s allowed in Crutcher et al. [14] in order to integrate differences in visual scanning behaviour over a longer time period and to improve the signal to noise ratio of the estimated visual scanning behaviour parameters. This, thereby, enhances our ability to detect differences between groups. Additionally, while the VPC paradigm used

by Crutcher et al. [14] presented slides with only two images simultaneously, VAST displayed four different images simultaneously, heightening the competition for the participant's attention. As AD patients tend to have deficits in disengaging and shifting attention between images [6], displaying more images on a slide will increase the differences between the visual scanning behaviour of cognitively impaired patients and cognitively healthy controls. Furthermore, as the 1-back repeats immediately preceded the 2-back repeats, 1-back stimuli functioned as a distractor for the 2-back stimuli. Significant differences between groups in the 2-back condition suggest that novelty preference was preserved even in the presence of distractors within a 12.5-s time frame. The more complex stimulus structure in our paradigm may be more reflective of real-world conditions where the brain must continually process and filter several competing visual inputs in the outside environment.

Researchers have described novelty preference as a method of quantifying memory deficits and declarative memory [14, 15, 33]. Additionally, Snyder et al. [33] described the underlying mechanism as repetition suppression or the bias for reduced neuronal activation within visual processing pathways following repeated exposure to specific stimuli. This, thereby, may function to increase the saliency of novel events within the environment and play a role in implicit memory [34, 35]. Given the results of our correlation analyses, novelty preference may also be used to quantify selective attention deficits. We found significant associations between greater RFT on novel images and higher cognitive status, as well as selective attention and working memory. Furthermore, the 1-back and 2-back conditions were correlated with different subtests. We found significant associations between novelty preference and higher DSF scores in the 1-back condition, while in the 2-back condition, novelty preference was associated with better performance on DSB. As the DSF subtest has been characterized as a measure of selective attention while the DSB subtest has been thought to tap into additional executive functions [26], different neurological correlates may be involved in processing the 1-back and 2-back conditions. Response to immediately repeated stimuli in the 1-back condition may require simple selective attention. Longer duration and the presence of distractors in the 2-back condition may involve more executive functioning in order to process visual inputs.

There are some limitations to consider when interpreting the results of this study. Although our paradigm used multiple presentations of novel and repeated stimuli of neutral content, personal interest or attraction towards particular images within each individual may compete with the natural preference for novel stimuli. Similarly, individual variability in novelty seeking behaviour, which may have genetic underpinnings [36, 37], might also be a factor in the expression of bias towards novel images. These characteristics could have confounded our observations and likely accounted for the relatively large standard deviations in the mean visual scanning parameters. Although the healthy elderly controls recruited in our study were not diagnosed with dementia or any cognitive impairment, pathophysiological events involved in the expression of symptomatic AD are thought to begin well before official diagnosis [38]. Thus, we cannot account for the potential effects prodromal dementia may have on scanning behaviour in our control sample. Given that WAIS-DS and SMMSE independently accounted for up to only a small amount of the variance, other domains of attention and cognition as well as the phenomenon of repetition suppression [33] may affect novelty preference. More comprehensive neuropsychological tests might be employed in future studies to explore the neurological processes associated with visual attention bias towards novel stimuli.

Novelty seeking has been studied in rodent models of drug addiction using variations of a free-choice place preference task. Typically, control animals demonstrated a natural preference for novel over familiar environments while exposure to psychostimulants, known to increase attention and reward salience via the dopamine and norepinephrine systems [39,



40], disrupted this behaviour [41, 42]. Similarly, a study of primates in an explicit decision-making task, using an eye tracking system to determine preference, showed bias towards novel images in untreated monkeys and further exacerbation of this bias under conditions of augmented dopaminergic tone [43]. Aberrant neurotransmitter activity associated with AD may mediate reductions in the salient quality of novel visual inputs, thereby impairing the inherent tendencies to explore novel objects in the environment. For example, modulation of dopamine and norepinephrine activity via methylphenidate has been shown to improve selective attention and symptoms of apathy in AD patients [39]. Furthermore, cholinesterase inhibitors, the first-line pharmacotherapy for treatment of cognitive symptoms in AD, have been shown to modulate visual selective attention [44, 45]. Thus, assessment of attention may provide valuable information for monitoring treatment course and evaluating drug response. Future studies should explore the sensitivity of the VAST parameters (number of images on a slide, presentation time, etc.) to pharmacological manipulations.

In summary, we found that a reduction in the bias towards novel images differentiated cognitively intact from mild-to-moderate AD patients and was associated with standard measures of attention and cognitive status. This is of particular significance in AD as communication becomes increasingly difficult as the disease progresses. The methodology described in this paper may offer a less cognitively demanding, nonverbal and more naturalistic method of assessing visual selective attention in the dementia population.

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### Disclosure Statement

Moshe Eizenman is a director in EL-MAR Inc.

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