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Visual Selective Attention Toward Novel Stimuli Predicts Cognitive Decline in Alzheimer's Disease Patients

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Abstract.
Background: Alzheimer's disease (AD) is associated with selective attention impairments, which could contribute to cognitive and functional deficits. Using visual scanning parameters, selective attention toward novel stimuli, or novelty preference, can be measured by a non-verbal, non-invasive method that may be of value in predicting disease progression.
Objective: In this longitudinal study, we explored whether novelty preference can predict cognitive decline in AD patients.
Methods: Mild to moderate AD patients viewed slides containing both novel and repeat images. The number of fixations, the average fixation time, and the relative fixation time on the two types of images were measured by an eye-tracking system. Novelty preference was estimated by the differences between the visual scanning parameters on novel and repeat images. Cognition and attention were assessed using the Standardized Mini-Mental Status Examination (sMMSE) and the Conners' Continuous Performance Test (CPT), respectively. Cognition was re-assessed every 6 months for up to 2 years.
Results: Multivariate linear regressions of 32 AD patients (14 females, age = 77.9 ± 7.8, baseline sMMSE = 22.2 ± 4.4) indicated that reduced time spent on novel images ($t = 2.78$, $p = 0.010$) was also associated with greater decline in sMMSE scores ($R^2 = 0.41$, Adjusted $R^2 = 0.35$, $F_{3,28} = 6.51$, $p = 0.002$), adjusting for attention and baseline sMMSE.
Conclusion: These results suggest that novelty preference, measured by visual attention scanning technology, may reflect pathophysiological processes that could predict disease progression in the cognitively-impaired.

Keyword: Alzheimer's disease, novelty processing, selective attention, visual scanning

INTRODUCTION

Alzheimer's disease (AD) is typically characterized by progressive deterioration in cognition, function, and behavior. Deficits in attention, a domain of cognition, occur in the early stages of the disease and may share a common mechanism of dysfunction with memory impairments [1]. Specifically, impairments in selective attention or the ability to focus on a relevant stimulus while filtering out distractions are observed in patients with mild cognitive impairment (MCI) and mild AD [2, 3]. Currently, the complexity of experimental tasks and high reliance on verbal

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communication capabilities represent obstacles in the assessment of cognitively impaired people. Thus, less cognitively demanding assessment tools would be of value in exploring the brain functions of dementia patients.

The innate ability of humans, primates, and rodents to identify, process, and ascribe greater attentional resources to novel stimuli is essential for exploring new opportunities and consequently, adapt to changing environments. Selective attention to novel stimuli or novelty preference has been studied as a means to assess declarative memory [4–6]. Novelty can serve to enhance perception [7], improve encoding of visual working memory [8], and reinforce reward processing [9, 10]. Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies have investigated the different stages of novelty processing, including detection of novelty, allocation of attentional resources, and, subsequently, sustained processing of these items. The N2, an early event-related potential (ERP) found in frontal brain regions, is believed to be associated with automatic detection of novel stimuli and may not require great demands on attention [11, 12]. However, the later P3, specifically P3a, ERP component is thought to index the orientation of attention toward novelty [12, 13]. Some researchers [6, 14, 15] have described one of the underlying mechanism as repetition suppression or the bias for reduced neural activation within visual processing pathways following repeated exposure. This may, thereby, increase the salient qualities of novel events within the environment and play a role in implicit memory [16, 17].

Novelty signals in the brain have been associated with activity in neurotransmitter systems, in particular, acetylcholine (ACh) and dopamine (DA) [18]. Cholinesterase inhibitors (ChEIs), including donepezil, galantamine, and rivastigmine, work to enhance ACh tone in the central nervous system and are currently prescribed for the treatment of AD. Pharmacologic studies in cognitively intact young participants have shown that ChEIs can modulate response to novel stimuli [19, 20]. However, to date, no studies have examined the effect of ChEIs on novelty preference behavior in the dementia population. Given that the global neurodegeneration characteristic of AD is accompanied by altered neurotransmitter function [21–23], the study of novelty preference can advance understanding of attention and memory in dementia.

Selective attention toward novel stimuli can be quantified using a visual attention scanning technology that works by tracking eye movements during stimulus viewing. There is compelling evidence to support the premise that cognitively intact monkeys and healthy infants spend more time viewing novel images when presented with both novel and repeated images [24, 25]. In contrast, patients with MCI have demonstrated diminished novelty preference compared with controls [4, 5, 26]. Consistent with those observations, our previous findings [27] demonstrated that novelty preference differentiated cognitively healthy and impaired people. In our paradigm [27], participants passively viewed novel and repeated images simultaneously while an eye tracker measured the number and duration of fixations on the two types of images. The results indicated that AD patients had significantly reduced attention toward novel stimuli compared with healthy age-matched elderly. Additionally, greater novelty preference was correlated with better scores on tests of attention. Consistent with this observation, larger novelty P3 amplitudes, suggested to be a marker for the allocation of attentional resources in EEG studies, have been associated with longer viewing durations [12]. Thus, novelty preference may represent a non-verbal, less cognitively and physically demanding tool to assess memory and selective attention capacity. Evidence also suggests that the assessment of attention may be of value in predicting disease progression in the early stages of dementia [28–30] and reduced novelty preference has been associated with increased risk of converting to dementia in MCI patients [5]. We propose that a novelty preference visual attention paradigm can be applied to predict longitudinal changes in cognition. Early dysfunction in novelty preference may reflect underlying pathophysiological events, including neurotransmitter dysfunction, which would accelerate the deterioration process.

In the present study, we assessed whether novelty preference can predict the degree of cognitive decline in patients with cognitive impairments. We hypothesized that greater deficits in selective attentional bias for novel stimuli would be associated with greater deterioration in cognition over two years. Additionally, we explored the relationship between ChEIs and novelty preference behavior in these AD patients.

METHODS

Subjects

Cognitively impaired participants were recruited from an outpatient memory clinic at Sunnybrook

Health Sciences Centre. This study included patients diagnosed with possible or probable AD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) [31] and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [32]. Eligibility criteria included mild to moderate disease severity (Standardized Mini-Mental State Examination [33], sMMSE $\geq$10) and no change in anti-dementia medications less than 1 month prior to study visit. Furthermore, all eligible patients had no significant eye pathology, severe impairments in communication, or diagnosis of other neurological illnesses, including stroke during the two-year study period. Prior to the start of study procedures, all patients or their legal substitute decision-maker provided written informed consent. This study was approved by the research ethics board at the Sunnybrook Research Institute.

Procedures

Neuropsychological testing

This was a longitudinal study. At the baseline study visit, all participants were administered the sMMSE [33] and the Conners' Continuous Performance Test (CPT) [34]. The sMMSE [33], a systematic and reliable version of the original MMSE [35], was used to assess severity of cognitive impairment. Scores range from 0 to 30 with greater values indicating better cognitive abilities. The CPT [34] is a computerized test of attention, used widely in attention deficit hyperactivity disorder research. This test has been used in other studies to probe attention abilities in the AD population [36, 37]. Test-takers were instructed to press a space bar whenever letters other than X appeared on the screen. Scores summarizing inattention, vigilance, and disinhibition were calculated, with higher scores reflecting greater deficits. Follow-up scores on the sMMSE, administered by the study psychiatrist, were then collected from patient charts every 6 months for up to 2 years.

Point-of-gaze estimation methodology

The visual attention scanning technology (VAST) (EL-MAR Inc., Toronto, Ontario, Canada) was used to record and estimate visual scanning parameters. This technology included a binocular eye tracking system [38] that recorded eye gaze positions and pupil sizes, a monitor to display visual stimuli (23" computer monitor : 1920 * 1080 pixel resolution), algorithms to process and estimate visual scanning parameters in real time [39, 40], and a monitoring station to control and supervise the progress of the study [41]. The eye tracking system included infrared (IR) light sources, IR video cameras, and a processing unit that estimated binocular gaze position 30 times/s with an accuracy of $\pm 0.5^{\circ}$ [38]. Processing of eye-gaze data includes the segmentation of gaze-position data to saccades and fixations, the association of fixations and saccades with specific regions on the visual stimuli and the calculations of visual scanning parameters [41, 42].

Participants sat at a distance of approximately 65 cm from the monitor. In order to enable natural viewing of stimuli, the system allowed for free movement of the head within a relatively large volume ($25 \times 25 \times 25$ cm^3). The procedures started with a 9-point eye-tracking calibration step in which participants followed a moving target on the display screen. Following calibration (approximately 30 s), participants viewed a series of slides presented on the monitor and their eye movements were recorded. The non-contact, point of gaze estimation method used has been shown to effectively tolerate head movement and calculate accurate gaze-positions [38].

Visual stimuli

The visual stimuli have been described in detail in our previous study [27]. Each slide contained four images, arranged in a 2 by 2 configuration, that were similar in complexity and neutral in content. All images generally contained one or two simple items with a similar theme for each slide in order to maintain task simplicity and minimize attentional bias based on deviance, respectively. For example, one slide series contained images of different varieties of fruit and another included images of different furniture. Neutral images were similar to those found in the International Affective Picture System (IAPS) database with medium ratings for valence (feelings of pleasure versus displeasure) and low ratings for arousal (feelings of excitement versus calm). The series of slides included 16 sets of test slides and 58 filler slides. Each set of test slides were 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 on the start slide (See Fig. 1). 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.

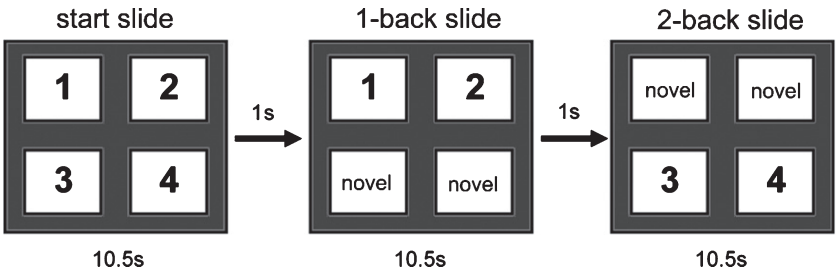

Fig. 1. Sample structure and sequence of a slide set. The first slide of each set (start) contained four novel images. The slide following (1-back) contained two novel and two repeated images. The final slide of the set (2-back) contained two images repeated from the first slide and two novel images. There was a blank grey screen that appeared for one second in between each slide. The position of repeat images was randomized between slide sets.

Thus, 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 1-s blank screen acted to mask repeated images, which occurred in the same position within each slide set. This presentation structure maintained both spatial and stimulus familiarity for the repeated images, in order to simplify the task for our study participants. 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 set-up 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 48 test-slides were analyzed. The testing was divided into 2 sessions of approximately 10 min each. In between the two sessions, the subjects were given a 5-min break.

Visual scanning parameters

Visual scanning behavior was summarized using the average duration of discrete fixations on each image in milliseconds (average fixation duration) and the number of discrete fixations on each image (fixation frequency within images). Another parameter, relative fixation time, defined as the ratio of total duration of discrete fixations on novel images relative to total duration of fixations on all images of a slide, was calculated from the average fixation duration and the fixation frequency. All these parameters have been described previously [27]. Novelty preference was estimated by subtracting the values of relative fixation time for repeat images from novel images on each 1-back and 2-back slide (novel - repeat). The average of all 16 test slides were calculated for each patient. The mean values for the 1-back and 2-back conditions were then added in order to obtain a single value for relative fixation duration to represent novelty preference for each subject. Higher values indicated stronger preferences for the novel images.

Statistical analysis

Baseline demographic, neuropsychological, and visual scanning data were summarized using counts or mean ± standard deviation (SD). Multivariate linear regressions with backward elimination were used to test the novelty preference parameter, relative fixation time, as a predictor of sMMSE change (follow-up - baseline), controlling for baseline sMMSE, age, education, and attention (CPT Inattention). Covariates were chosen based on findings suggesting interaction with cognitive abilities or sMMSE scores. Age and education are known to have an effect on sMMSE scores, with older age and lower education associated with lower sMMSE [43, 44]. Overall attention, a domain of cognition, may have an effect on changes in sMMSE scores and could interact with visual scanning parameters associated with attentional bias. For exploratory analyses, all patients were divided into those who declined significantly or reliably on the sMMSE (defined as a decrease of 3 or more points [45]) within the 2-year period. Receiver operating characteristic (ROC) analyses were used to test whether relative fixation time could correctly classify or predict significant decline versus no decline. We also compared patients on different classes of anti-dementia medications (ChEIs versus

memantine) in analysis of variance (ANOVA) models to explore potential associations with novelty preference at baseline.

All analyses were considered significant at an α of 0.05 with no corrections made for multiple comparisons. Analyses were conducted using IBM SPSS Statistics 20.0 for Windows (IBM Corp., Armonk, NY).

RESULTS

Thirty-two patients with mild to moderate AD were included in this analysis (See Table 1 for baseline data). The primary analysis included the most recent score available within the 2-year period for each participant. The mean length of follow-up was 1.7 ± 0.4 years. Mean sMMSE score significantly decreased from 22.3 ± 4.5 at baseline to 19.6 ± 5.4 at follow-up ($t_{31} = 4.86$, $p < 0.001$). In the linear regression model, relative fixation time ($t = 2.78$, $p = 0.010$, tolerance = 0.95, variance inflation factor = 1.05), CPT Inattention ($t = -2.88$, $p = 0.008$, tolerance = 0.61, variance inflation factor = 1.63), and baseline sMMSE ($t = -2.20$, $p = 0.036$, tolerance = 0.63, variance inflation factor = 1.58) were significant predictors of sMMSE change scores. Age and education were not significant predictors and therefore removed from the final model in the backward elimination method. Reduced time spent on novel compared with repeat images, controlling for overall attention and cognition at baseline, predicted greater decline in cognition (See Fig. 2). This model accounted for 41% of the variance in sMMSE change scores ($R^2 = 0.41$, Adjusted $R^2 = 0.35$, $F_{3,28} = 6.51$, $p = 0.002$, Table 2). A model that included only baseline sMMSE and CPT Inattention as predictors of sMMSE change accounted for 25% of the variance ($R^2 = 0.25$, Adjusted $R^2 = 0.20$, $F_{2,29} = 4.80$, $p = 0.016$). Thus, relative fixation time accounted for an additional 16% of the variance in sMMSE change scores.

Of the 32 AD patients included in the study, 14 had a significant decline in sMMSE scores ($\geq$3 points decrease) while 18 did not. ROC analyses performed on all 32 patients indicated that relative fixation time had an area under the curve of 0.72 (95% confidence

Table 1
Patient baseline characteristics ($n = 32$). Values are mean $\pm$ standard deviation or counts

Measure	Value
Age	77.9 ± 7.8
Standardized Mini-Mental State Examination	22.2 ± 4.4
Gender (%)	
Male	56.3%
Female	43.8%
Education (%)	
Grade school	18.8%
High school	34.4%
Post-secondary	21.9%
Graduate	25.0%
Cognitive Enhancers (%)	
Cholinesterase inhibitors	75.0%
Memantine	25.0%
Conners' Continuous Performance Test Inattention	534.2 ± 175.3
Difference between Frequency of Fixations on novel and repeat images	0.61 ± 1.39
Difference between Average Fixation Duration on novel and repeated images (ms)	79.8 ± 108.5
Difference between Relative Fixation Times on novel and repeated images (%)	$7.0 \pm 8.7\%$

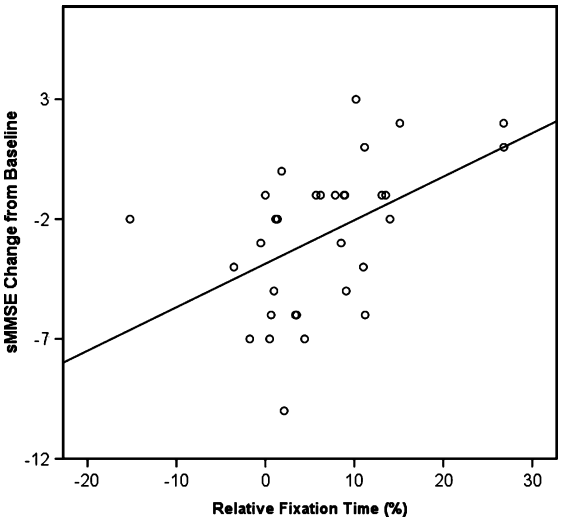

Fig. 2. sMMSE change from baseline versus relative fixation time (novel - repeat). Reduced baseline novel relative fixation time predicted greater decline in sMMSE scores.

Table 2
Linear regression model of relative fixation time as a predictor of sMMSE change ($R^2 = 0.41$, Adjusted $R^2 = 0.35$, $F_{3,28} = 6.51$, $p = 0.002$, $n = 32$)

Predictors	β	t	p-value
Relative Fixation Time	0.41	2.78	0.010
Conners' CPT Inattention	–0.53	–2.88	0.008
sMMSE Baseline	–0.40	–2.20	0.036

CPT, Continuous Performance Test; sMMSE, Standardized Mini-Mental State Examination.

interval = 0.55 to 0.90, $p = 0.033$, Fig. 3), indicating moderate ability of this single visual scanning parameter to classify those patients who did and did not decline. The sensitivity and specificity of various cut-off values for relative fixation time are given in Table 3.

There were 24 patients on ChEIs, 4 on memantine monotherapy and 4 not taking any antidementia medications. Overall, AD patients on ChEIs had higher, though non-significant ($F_{1,30} = 2.93$, $p = 0.097$), relative fixation time on novel images compared to those not on any ChEIs ($7.9 \pm 7.7\%$ versus $2.3 \pm 9.0\%$). Within the ChEI group, the three patients taking galantamine had a mean relative fixation time of $15.9 \pm 6.7\%$ compared with $7.9 \pm 8.7\%$ in patients on donepezil and rivastigmine ($F_{1,22} = 4.34$, $p = 0.049$).

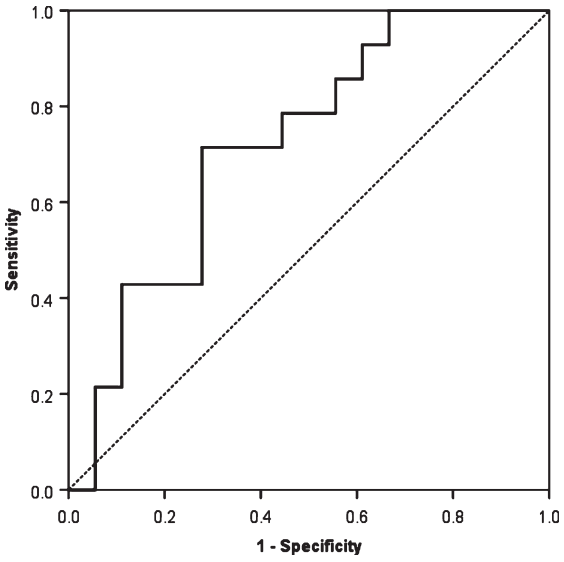

Fig. 3. Receiver operating characteristic (ROC) curve for relative fixation time for the 32 patients (Area under the curve = 0.72, 95% confidence interval = 0.55 to 0.90, $p = 0.033$).

Table 3
Cut-off values of relative fixation time with sensitivity and specificity

Cut-off Value	Sensitivity	Specificity
–0.26	0.214	0.944
1.05	0.429	0.889
5.05	0.714	0.722
8.67	0.786	0.556
9.63	0.857	0.444
11.08	0.929	0.339

DISCUSSION

In the present study, we investigated selective attention toward novel stimuli as a predictor of longitudinal changes in cognition. The results suggest that novelty preference, measured by visual scanning behavior, can predict significant decline in cognitively impaired elderly people. Specifically, less time spent on novel compared with repeat images predicted decrease in sMMSE scores within 6 to 24 months. Attention, measured by the CPT, and baseline sMMSE contributed significantly to the regression models. These finding were not unexpected as deficits in attention and executive function have been associated with greater cognitive deterioration [28, 46]. Furthermore, studies have found larger rates of disease progression in patients with greater initial cognitive impairment, indicated by the lower MMSE scores [47–49]. Our results suggest that overall attention capabilities may be modulating the relationship between novelty preference and cognitive changes.

Together, these findings suggest that deficits in processing novelty (reduced time allocated to novel compared with repeat stimuli) were associated with greater decline in cognitive ability. Consistent with these results, our previous findings [27] indicated that dementia patients were impaired in the visual scanning parameters that we investigated in the present study. Specifically, relative fixation time on novel images were reduced in patients compared with control elderly participants. Using a visual paired comparison task, Zola et al. [5] showed that reduced novelty preference was associated with greater risk of conversion to MCI in healthy elderly or to AD in MCI patients. The researchers found significant effects using percent fixation time on novel images. Those results correspond with our findings on relative fixation time. Thus, visual scanning can provide important information with regards to cognition and attention.

Altered activity of neurotransmitter systems, elements of the AD pathogenesis, may generate early deficits in selective attention toward novel stimuli which in turn, could signal advancing cognitive deterioration. Detection of novelty could be disrupted by altered ACh neurotransmission, the pathway most associated with the cognitive symptoms of AD.

Cholinergic neurons in the basal forebrain project to areas associated with memory and cognition, including the hippocampus and orbitofrontal cortex [50]. Recordings from a group of cells in the basal

forebrain of primates have shown increased neural response to novel visual stimuli, which decreased with repetition [51]. Impairments in spatial and object recognition were induced by targeted ablation of different groups of neurons in the basal forebrain of mice and rescued with ChEI administration [52]. Pharmacological manipulation of the cholinergic system, including the use of ChEIs, the current treatment for AD, have been shown to modulate novelty processing. For example, rivastigmine was found to enhance the novelty P3 event-related potential in response to novel sounds [20], while the anticholinergic agent scopolamine reduced frontal P3 response to both infrequently occurring visual [53] and auditory stimuli [54]. Furthermore, scopolamine attenuated repetition suppression effects, reducing differences between the fMRI hemodynamic responses toward novel and repeated stimuli in frontal and extrastriate brain regions [55]. Deficits in attention and memory through cholinergic dysfunction may reduce capacity to recognize old information and result in attenuated repetition suppression and novelty signals. As such, we found that patients on ChEIs had numerically greater novelty preference compared with those on memantine monotherapy or no anti-dementia medications. Furthermore, the three patients on galantamine demonstrated greater novelty preference compared to those on rivastigmine or donepezil. Galantamine has been shown to improve different domains of attention in AD patients, possibly through its specific interaction with nicotinic cholinergic receptors [56, 57]. Consistent with our results, other groups have found that galantamine blunted repetition suppression in mesolimbic areas of healthy adults in an fMRI study [19] and shifted novelty signals from the medial temporal lobe to the prefrontal cortex in a magnetoencephalography study [58]. These findings suggest that the effect of ACh on novelty processing may vary across different attention-related regions in the brain.

The DAergic system is most prominently implicated in encoding novelty. [59, 60]. With regard to dementia, reduced expression of DA receptors in the cortex and hippocampus have been observed in AD patients compared with age-matched controls [59, 60]. There is also evidence that DA can modulate ACh neurotransmission in AD patients, establishing a functional relationship between two systems associated with dementia [61]. Furthermore, psychostimulants, drugs which amplify DA and norepinephrine (NE), have been shown to improve cognitive functions, including attention in patients with AD [62], Parkinson's disease [63], and attention deficit/hyperactive disorder [64]. It has been proposed that novel inputs elicit phasic firing of DA neurons in the ventral tegmental area, projecting to the hippocampus, in order to motivate exploratory behavior [65]. fMRI studies in humans [10, 66, 67] have linked novelty processing with mesolimbic structures, integral components of DA-associated pathways. Bunzeck et al. [19] combined a pharmacologic challenge with fMRI to explore the effect of DA on blood oxygen level-dependent signals related to viewing of novel and familiar/repeated images. The administration of the DA precursor levodopa to healthy adults attenuated repetition suppression effects in the hippocampus, parahippocampal cortex, and the substantia nigra/ventral tegmental area. Similarly, levodopa increased the onset of event-related potentials in the medial temporal lobe in response to novel scenery [58]. An event-related potential associated with early response to novelty, the N2b component, was also observed to increase following administration of apomorphine, a D1/D2 receptor agonist [18]. Contrastingly, inconsistent results have been found regarding the connection between DA and later processing of novel stimuli. Pharmacological manipulation of DA activity does not appear to affect the P3 event-related potential, a later component of the novelty signal [68, 69]. In an EEG experiment, Mikell et al. [70] observed increases in N2 amplitude but no change in P3 in Parkinson's patients ON versus OFF medication. Thus, Rangel-Gomez and Meeter [18] suggest that dopamine may exert stronger influences over early response and detection of novelty. Furthermore, the effect of DA on different cognitive domains may adhere to an inverted U-shaped response curve. Overall, this suggests that less active scanning on novel images may be a consequence of aberrant DA functioning and could signify increase risk of further cognitive deterioration.

There has been less focus on the role of other neurotransmitter systems in novelty encoding. Modulation of glutamate and GABA does exert an effect on novelty processing, though results appear to be variable. Inhibition of glutamatergic activity with ketamine led to attenuation of the P3 and N2 amplitude in response to novel auditory and visual stimuli [71, 72]. However, facilitation of GABAergic activity via the GABA-A agonist thiopental also led to attenuation of these event-related potentials in healthy adults [71]. The role of serotonin (5-HT) in novelty processing, which has mainly been addressed in genetic studies, is also ambiguous. Lower 5-HT availability, linked

with expression of the 5-HT transporter, was associated with enhanced P3 component [73]. However, decreased 5-HT 2a receptor function was associated with a weaker response to novel stimuli in the hippocampus [74]. Given that NE is a direct analog of DA as well as its strong reciprocal interaction with ACh [75], NE may also be an important factor in novelty preference behavior [76]. Additionally, NE is known to mediate selective attention [77, 78] and may be an important factor of the neural basis of the P3 component [79]. Overall, deficits in the processing of novel stimuli may signify neurochemical changes related to underlying pathophysiological events typical of AD.

Several limiting factors should be taken into consideration when interpreting the findings of this study. Our analyses were limited by sample size. A priori power calculations for a linear regression with up to five covariates indicated that 43 subjects were required to detect large effect sizes (power = 0.80, $\alpha = 0.05$). However, in our models using the backward regression method, no more than three covariates survived significance. *Post-hoc* sample size calculations in this case indicated that 32 subjects are sufficient to detect large effect sizes with a power of 0.80 and α of 0.05. This study was exploratory and findings should be considered preliminary. Future studies should be conducted with larger patient sample sizes in order to confirm these results as well as allow for more covariates to be considered. Although the images in our paradigm were chosen based on neutral content, personal interest or attraction toward particular images within each individual may interfere with preference for novel stimuli. In the same vein, individual variability in attraction toward novelty, which may have genetic underpinnings [80, 81], might also be a factor in the expression of bias toward novel images. While the sMMSE, our dependent variable in this study, is a widely used screen for cognitive impairments [82, 83], it is not a comprehensive test of cognition due to the presence of ceiling effects in mild and prodromal dementia [84, 85]. Furthermore, variability in scores within individuals represents another confounder [86]. Future studies can incorporate more comprehensive cognitive batteries used in dementia studies such as the Alzheimer's Disease Assessment Scale – Cognition [87], the standard outcome measure in clinical trials of AD treatment. This can provide useful information with regard to the relationship between novelty preference and specific domains of cognition.

Early deficits in selective attention and ability to process or explore salient novel stimuli may be a valuable marker of risk for rapid disease progression. A key advantage of employing a passive viewing task is the capability to overcome language and communication barriers. Furthermore, increased stress related with more active tests of selective attention may actually dampen attention and thus, disrupt novelty processing [88, 89]. In summary, we found that reduced visual attention toward novel stimuli was associated with greater decline in cognition in cognitively impaired patients following 2 years. These findings provide further insight into the attentional deficits associated with AD. Novelty preference measurements using visual attention scanning technology might offer a non-verbal, non-invasive, and less cognitively demanding tool to help clinicians identify those most at risk of decline in order to adapt treatment and management plans.

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