Journal of Alzheimer's Disease 51 (2016) 837–846
DOI 10.3233/JAD-151026
IOS Press

Apathy and Attentional Biases in Alzheimer's Disease

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Accepted 27 December 2016

Abstract.
Background: Apathy, one of the most prevalent neuropsychiatric symptoms in Alzheimer's disease (AD), can be difficult to assess as cognition deteriorates. There is a need for more objective assessments that do not rely on patient insight, communicative capacities, or caregiver observation.
Objective: We measured visual scanning behavior, using an eye-tracker, to explore attentional bias in the presence of competing stimuli to assess apathy in AD patients.
Methods: Mild-to-moderate AD patients (Standardized Mini-Mental Status Examination, sMMSE >10) were assessed for apathy (Neuropsychiatric Inventory [NPI] apathy, Apathy Evaluation Scale [AES]). Participants were presented with 16 slides, each containing 4 images of different emotional themes (2 neutral, 1 social, 1 dysphoric). The duration of time spent, and fixation frequency on images were measured.
Results: Of the 36 AD patients (14 females, age = 78.2 ± 7.8, sMMSE = 22.4 ± 3.5) included, 17 had significant apathy (based on NPI apathy ≥4) and 19 did not. These groups had comparable age and sMMSE. Repeated-measures analysis of covariance models, controlling for total NPI, showed group (apathetic versus non-apathetic) by image (social versus dysphoric) interactions for duration ($F_{1,32} = 4.31$, $p = 0.046$) and fixation frequency ($F_{1,32} = 11.34$, $p = 0.002$). Apathetic patients demonstrated reduced duration and fixation frequency on social images compared with non-apathetic patients. Additionally, linear regression models suggest that more severe apathy predicted decreasing fixation frequency on social images ($R^2 = 0.26$, Adjusted $R^2 = 0.19$, $F_{3,32} = 3.65$, $p = 0.023$).
Conclusion: These results suggest that diminished attentional bias toward social-themed stimuli is a marker of apathy in AD. Measurements of visual scanning behavior may have the potential to predict and monitor treatment response in apathy.

Keywords: Alzheimer's disease, apathy, attention, cognition, eye movements

INTRODUCTION

Alzheimer's disease (AD), the most common form of dementia, is often accompanied by neuropsychiatric symptoms or behavioral and psychological symptoms. Apathy, characterized by reduced motivation, social disinterest, and emotional blunting in the absence of mood-related changes [1, 2], is the most frequently occurring symptom [3–5]. Epidemiological studies have reported point prevalence ranging from 25% to 93% in community-dwelling outpatients [3–5] and similar rates in nursing home

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ISSN 1387-2877/16/$35.00

patients [6–8]. Furthermore, these prevalence rates increase with more severe cognitive impairment [9, 10]. In addition to being common, apathy has been associated with negative effects such as more rapid cognitive and functional decline [11–14], increased care giver burden [15–17], and higher risk of mortality [18, 19]. The wide range in rates of apathy might be explained by methodological differences between studies, such as the use of different clinical evaluative tools and cut-off values. There is currently no standard approach to assessment though diagnostic criteria for apathy in dementia have been proposed and validated [1].

Efforts have been made to delineate the neurobiologic underpinnings of apathy. Apathy has been associated with themesocorticolimbic dopaminergic (DAergic) pathway [20] and psychostimulants, which work by increasing DA and/or norepinephrine (NE) levels, have demonstrated efficacy in improving symptoms [21–23]. Three domains of apathy are now recognized: Decreased goal-directed overt behavior (including symptoms of decreased effort, initiative, perseverance, and productivity), reduced goal-directed cognition (including reduced interests, lack of planning and concern about one's health and function), and deficits in emotional concomitants of goal-directed behavior (including flat affect and decreased emotional responsivity to positive or negative events) [24]. Neuroimaging data in AD patients have suggested that the different components of apathy are each associated with unique patterns of brain activation and structural changes [25, 26]. Using single photon emission computed tomography, Benoit et al. [26] found that lack of initiative (behavioral apathy), lack of interest (cognitive apathy), and emotional blunting were correlated with hypoperfusion in the anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex, respectively. As such, understanding the apathy domains is a current area of research [27].

Recent evidence supports a link between attention and apathy symptoms [21, 28]. Several imaging studies showed that brain regions associated with attention, particularly the anterior cingulate and frontal cortices, have reduced activity and increased atrophy in apathetic compared with non-apathetic AD patients [29, 30]. Clinically, a DAergic agent that improved apathy also improved selective attention in a randomized placebo-controlled trial of dementia patients with apathy [28]. One component of attention that is highly mood and reward dependent is attentional bias or heightened sensitivity to a particular stimulus resulting in enhanced attention toward that stimulus [31, 32]. Eizenman et al. [33] developed a nonverbal methodology to determine attentional biases through the measurement of visual scanning behavior. They found that, compared with their non depressed counterparts,young depressed patients fixated longer on dysphoric or negatively valenced images, but spent less time fixated on social images. Another research group applied the same methodology and observed that strong biases for dysphoric images were sustained for a 30-s duration [34]. However, the effect of apathy was not considered in those studies. Symptoms of social disinterest and emotional blunting, the defining components of apathy, suggest that apathetic patients may not have the attentional bias for social-themed images seen in non-apathetic patients.

In the present study, we compared the visual scanning behavior of apathetic and non-apathetic AD patients in order to characterize the effect of apathy on attentional bias in the presence of emotional stimuli. We hypothesized that attentional biases toward social or positively themed stimuli will be reduced in apathetic compared with non-apathetic AD patients. We also explored the effects of the different apathy subdomains, in addition to overall cognitive and attention abilities, on visual scanning behavior.

MATERIALS AND METHODS

Subjects

Participants were recruited from outpatient clinics at Sunnybrook Health Sciences Centre. Eligibility criteria included: Diagnosis of possible or probable AD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) [35] and NINCDS-ADRDA criteria [36], mild to moderate disease severity (Standardized Mini-Mental State Exam [37], sMMSE $\geq$10) and no change in anti-dementia medications less than 1 month prior to study day. Apathetic AD patients were additionally required to have significant apathy (Neuropsychiatric Inventory [38], NPI apathy subscore $\geq$4 for at least 4 weeks) and no significant depression (NPI depression subscore $<$4). Patients were excluded if they had significant eye pathology, communicative impairments, or other neurological illnesses. All participants and/or their legally authorized representative provided informed consent before the start of study procedures. This study was approved by the research ethics board at the Sunnybrook Research Institute.

Procedures

This was a cross-sectional study. The sMMSE [37] and the Conners' Continuous Performance Test (CPT) [39] were administered to each participant. The sMMSE [37], a systematic and reliable version of the original MMSE [40], was used to describe severity of cognitive impairment. Greater scores indicated better cognitive abilities. The CPT [39] is a computerized test of attention, used widely in attention deficit hyperactivity disorder research.We previously found a significant association between higherCPT inattention and greater improvements in apathy in a clinical trial of methylphenidate in apathetic AD patients [21]. This supports the usefulness of this test in probing attention abilities in the present study population. 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 indicating greater deficits. Behavior disturbances, including apathy were assessed through interviews with caregivers using the NPI and Apathy Evaluation Scale (AES) [41]. The NPI [38] is a widely used assessment of the frequency and severity of behavior disturbances in dementia, including: Apathy, agitation, delusions, hallucinations, depression, euphoria, aberrant motor behavior, irritability, disinhibition, anxiety, sleeping, and eating. Total scores range from 1 to 144 and domain scores range from 1 to 12 with higher scores indicating greater behavioral disturbance. The NPI apathy cut-off score of $\geq$4 (described above) has consistently been used to define clinically significant apathy [22, 42–44] and represents "often", "frequent" or "very frequent" apathy of "moderate" or "marked" severity. The AES [41] informant version is a reliable and valid measure of apathy widely used in clinical research [45]. Total scores range from 18–72, with higher scores representing more severe apathy. As an additional advantage, this scale also provided subscores for each of the domains of apathy, including behavior, cognition, and emotion [41].

Visual stimuli

The visual stimuli consisted of a series of slides, each displayed for 10.5 s, followed by 1 s of a uniform grey screen. Each slide contained four images of different emotional themes: 1 dysphoric, 1 social, and 2 neutral images. Dysphoric and social images were similar in complexity. Images were selected from the International Affective Picture System (IAPS), a standardized database of images used to study emotion and attention. Images were chosen based on IAPS ratings for valence (feelings of pleasure versus displeasure): Neutral images had an approximate valence of 5, social images ranged from 6 to 8 while dysphoric images had valence ratings of 2 to 4. Additionally, the dysphoric and social images on each slide had IAPS ratings of arousal (feelings of excitement versus calm) between 4 and 6, with a maximum rating difference of 2, while the neutral images had arousal ratings between 2 and 4. The four images on each slide were arranged in a 2 by 2 configuration, with the positions (top-left, top-right, bottom left, and bottom right) of the different emotional themes uniformly distributed between the 16 test slides. Ten filler slides were used at the beginning of the presentation to familiarize subjects with the presentation format and filler slides were inserted randomly between test slides. The sets of images used in the present study are similar to those used by Eizenman et al. [33] to differentiate depressed and non-depressed younger adults in a previous study. However, they have yet to be validated in the apathetic AD patient population. The apathy test was one component of a battery of tests that included measurements for "novelty preference" and depression. The slides for the different tests were intermixed and a total of 106 slides were presented. To analyze apathy, only data from the 16 test slides with one dysphoric image, one social image, and two neutral images were used. The testing procedure was divided into two sessions of approximately 10 min each. In between the two sessions the subjects were given a 5-min break.

Point-of-gaze estimation methodology

The visual attention scanning technology, developed by EL-MAR Inc. (Toronto, Ontario, Canada), incorporated a binocular eye tracking system [46] that records eye-gaze positions and pupil-sizes, a display to present visual stimuli, real time processing algorithms to estimate visual scanning parameters [33, 47], and a station to control and monitor the progress of the test [48]. The eye tracking system, mounted on a display monitor (a 23" screen with a resolution of 1920 * 1080 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 $\pm 0.5^{\circ}$ [46]. During the test, subjects were allowed to move their heads freely within a relatively large volume ($25\times25\times25$ cm^3) which supported natural viewing of the visual stimuli. Participants sat at a distance of approximately 65 centimeters 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 greater than 2.5°. A calibration procedure, in which participants were required to follow a moving target on the computer screen, was completed before testing. Following the short calibration routine (less than 30 s), visual scanning patterns and pupil-sizes were recordedas participants viewed the visual stimuli presentation.

Relative fixation time and fixation frequency within images, parameters used previously to characterize visual scanning behavior in young patients with eating disorders [48] and depression [33], were our outcome measures. Relative fixation time is the ratio of time spent on a particular image over the total time spent on all four images of a slide, expressed as a percent. This measure is an indicator of the relative interestin an image, taking into account all other images on the slide that are competing for the viewer's attention. Thus, it was used rather than real time because it allows for better comparison of preference for specific images within a slide. Fixation frequency describes the total count or number of discrete fixations within an image. Biases were summarized by subtracting mean relative fixation time and fixation frequency on neutral from social and dysphoric images (bias toward social = social – neutral; bias toward dysphoric = dysphoric – neutral). For each participant, biases for social and dysphoric images were determined by calculating the means of these parameters on the 16 relevant test slides.

Statistical analysis

Demographic, neuropsychological, and visual scanning data were summarized using counts or mean ± standard deviation (SD). Clinical and demographic characteristics were compared between apathetic and non-apathetic groups using analysis of variance (ANOVA) for continuous variables and χ^2 for categorical variables. We used two-factorial repeated-measures analysis of covariance (ANCOVA) models, with up to two covariates, to explore within-subject effects of image type (social bias, dysphoric bias), between group effects (apathetic, non-apathetic), and interaction between factors for relative fixation time and fixation frequency. Covariates were chosen based on the group comparison analyses in order to control for significant differences in clinical and neuropsychological parameters between apathetic and non-apathetic groups. Hierarchical multiple regression analyses were used to test the contribution of overall apathy (AES Total), controlling for cognition (sMMSE) and attention (CPT Inattention), in predicting social biases (both relative fixation time and fixation frequency). sMMSE and CPT Inattention were entered in Step 1 and AES Total was entered in Step 2 of the model. To further explore the contributions made by specific AES subdomains, the regression models were repeated with sMMSE and CPT Inattention entered in Step 1 and the AES subscores entered at Step 2 in a stepwise procedure. 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-six (19 non-apathetic and 17 apathetic) AD patients with a mean (±SD) age of 78.2 ± 7.8 and a mean sMMSE score of 22.4 ± 3.5 were included (Table 1). Groups were comparable in age, gender, education, concomitant medications use, cognition (sMMSE), and attention (Conners' CPT). Apathetic patients had higher scores on the NPI Total, NPI apathy, AES Total, and all AES domain scores (behavior, cognition, and emotion). All participants, including those with significant apathy, had low scores on the NPI depression.

On average, apathetic patients spent 10.5 ± 10.7% more time on social images than on neutral images while non-apathetic patients spent 20.0 ± 17.0% more time on social images than on neutral images. Mean relative fixation times on dysphoric images were 13.3 ± 10.5% higher than that on neutral images for apathetic and 14.3 ± 8.5% higher for non-apathetic patients. Controlling for differences in overall neuropsychiatric symptoms (NPI), we foundan image (dysphoric versus social) by apathy (non-apathetic versus apathetic) interaction ($F_{1,32} = 4.31$, $p = 0.046$, $\eta_p{}^2 = 0.12$, power = 0.52) for relative fixation time (Fig. 1). No significant group ($F_{1,32} = 0.93, p = 0.341$) or image ($F_{1,32} = 0.28$, $p = 0.598$) main effects emerged. *Post-hoc* analyses showed no differences between apathetic and non-apathetic patients in relative fixation time on social images ($F_{1,32} = 3.06, p = 0.090$) or dysphoric images ($F_{1,32} = 0.62, p = 0.437$). Mean fixation frequency on

Table 1
Clinical and demographic characteristics. Values are mean ± standard deviation or counts

	Non-apathetic $n = 19$	Apathetic $n = 17$	p-value
Age, years	77.6 (8.6)	78.8 (6.9)	0.639
Gender, % female	52.6%	29.4%	0.335
Education, %			
Grade school	11.1%	29.4%	
High school	27.8%	35.3%	0.113
Post-secondary	38.9%	5.9%	
Graduate	22.2%	29.4%	
Concomitant medications, %			
Cholinesterase Inhibitors	84.2%	88.2%	0.727
Memantine	21.1%	5.9%	0.189
Anti-depressants	47.4%	47.1%	0.985
Methylphenidate	10.5%	23.5%	0.296
Standardized Mini-Mental State Exam	22.8 (2.9)	22.0 (4.2)	0.507
Neuropsychiatric Inventory	5.7 (6.6)	22.2 (10.1)	<0.001*
Apathy subscore	0.6 (1.0)	6.8 (2.2)	<0.001*
Depression subscore	0.7 (1.2)	0.4 (0.8)	0.422
Apathy Evaluation Scale	34.1 (6.6)	55.5 (8.0)	<0.001*
Behavior	8.4 (2.0)	14.2 (3.3)	<0.001*
Cognition	15.3 (3.8)	25.0 (3.3)	<0.001*
Emotion	3.8 (1.2)	6.2 (1.6)	<0.001*
Conners' Continuous Performance Test			
Inattention	544.0 (194.5)	567.5 (248.8)	0.763
Vigilance	102.0 (17.4)	108.7 (43.0)	0.770
Impulsivity	201.6 (84.7)	189.0 (56.3)	0.203

*Indicates statistical significance ($p < 0.05$).

social images was higher than that on neutral images by 2.0 ± 1.9 fixations for apathetic patients and by 3.4 ± 1.7 fixations for non-apathetic patients. On average, fixation frequency on dysphoric images was higher than that on neutral images by 2.4 ± 1.6 fixations for apathetic patients and 2.7 ± 1.6 fixations for non-apathetic patients. There was a significant image by apathy interaction ($F_{1,32} = 11.34$, $p = 0.002$, $\eta_p{}^2 = 0.26$, power = 0.91, See Fig. 2) but no group (non-apathetic versus apathetic, $F_{1,32} = 0.97$, $p = 0.333$) or image (dysphoric versus social, $F_{1,32} = 0.05$, $p = 0.831$) main effects, controlling for group differences in overall neuropsychiatric symptoms (NPI). Compared with non-apathetic patients, those with apathy had reduced fixation frequency on social images ($F_{1,32} = 5.83$, $p = 0.021$) but no difference on dysphoric images ($F_{1,32} = 0.81$, $p = 0.374$). To explore the effect of gender imbalances between the non-apathetic and apathetic groups, ANCOVA models were repeated with gender as an additional covariate. Results indicated that gender did not significantly affect the outcome of models for relative fixation or fixation frequency.

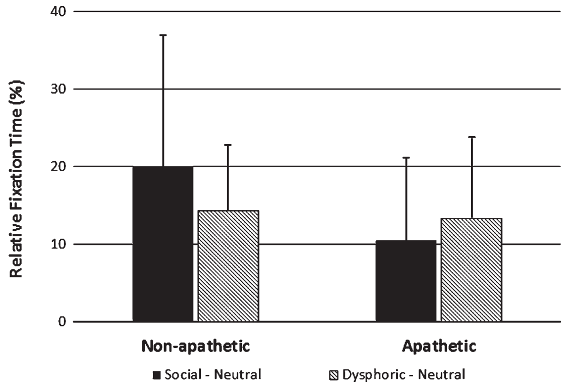

Fig. 1. Mean relative fixation time with standard deviation error bars for social and dysphoric (minus neutral) themed images for non-apathetic ($n = 19$) and apathetic ($n = 17$) AD patients.

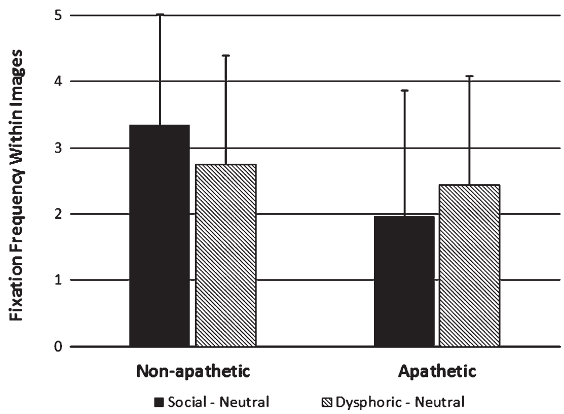

Fig. 2. Mean fixation frequency within images with standard deviation error bars for social and dysphoric (minus neutral) themed images for non-apathetic ($n = 19$) and apathetic ($n = 17$) AD patients.

Linear regressions with AES Total, CPT Inattention, and sMMSE as predictors were performed separately for fixation frequency and relative fixation time on social images. For fixation frequency within social images, AES Total ($t = -2.09$, $p = 0.044$, tolerance = 0.85, variance inflation factor = 1.18) and sMMSE ($t = -3.09$, $p = 0.004$, tolerance = 0.58, variance inflation factor = 1.73) were significant predictors of fixation frequency on social images (Table 2). The total model accounted for 26% of the variance ($R^2 = 0.26$, Adjusted $R^2 = 0.19$, $F_{3,32} = 3.65$, $p = 0.023$). We did not find significant predictors for relative fixation time on social images or fixation frequency and relative fixation time on dysphoric images.

Table 2
Linear regression model for predictors of fixation frequency within social images ($R^2 = 0.26$, Adjusted $R^2 = 0.19$, $F_{3,32} = 3.65$, $p = 0.023$, $n = 36$). AES Total and sMMSE were significant predictors

Predictors	β	*t*	*p*-value
Standardized Mini-Mental State Exam	–0.62	–3.09	0.004*
Conners' Continuous Performance Test Inattention	–0.36	–1.93	0.063
Apathy Evaluation Scale Total	–0.35	–2.09	0.044*

*Indicates statistical significance ($p < 0.05$).

Table 3
Linear regression model of predictors of fixation frequency within social images ($R^2 = 0.30$, Adjusted $R^2 = 0.24$, $F_{3,32} = 4.62$, $p = 0.009$, $n = 36$). AES Emotion and sMMSE were significant predictors

Predictors	β	*t*	*p*-value
Standardized Mini-Mental State Exam	–0.56	–3.02	0.005*
Conners' Continuous Performance Test Inattention	–0.28	–1.51	0.140
Apathy Evaluation Scale Emotion	–0.41	–2.61	0.014*
Apathy Evaluation Scale Cognition	–0.16	–0.62	0.537
Apathy Evaluation Scale Behavior	–0.06	–0.30	0.763

*Indicates statistical significance ($p < 0.05$).

Hierarchical regression models with AES behavior, cognition, and emotion entered at Step 2 in stepwise method, following CPT Inattention and sMMSE entered at Step 1 (described above), showed the distinct contribution of each domain score on fixation frequency within social images (Table 3). AES emotion ($t = –2.61$, $p = 0.014$, tolerance = 0.89, variance inflation factor = 1.12) and sMMSE ($t = –3.02$, $p = 0.005$, tolerance = 0.64, variance inflation factor = 1.57) were significant predictors of fixation frequency on social images. Higher AES emotion subscores (more severe symptoms) were associated with a decreased number of fixations on social images. The overall model accounted for 30% of the variance ($R^2 = 0.30$, Adjusted $R^2 = 0.24$, $F_{3,32} = 4.62$, $p = 0.009$). Models for relative fixation time on social images and fixation frequency and relative fixation time on dysphoric images as dependent variables were not significant.

DISCUSSION

In the current study, we examined the visual attentional biases associated with apathy in dementia patients. The results suggest that apathetic patients had decreased attentional bias for social stimuli compared with non-apathetic patients. This behavior is consistent with the symptoms of social disinterest and emotional blunting characteristic of apathy [1, 2]. Findings from previous eye-tracking studies [33, 34] have also shown reduced bias toward social images in young adults with clinical depression compared with age-matched controls. While apathy was not investigated in those studies, the principle features of apathy that overlap with depression may be a factor in driving attentional biases away from social stimuli in the depressed patients. It has been proposed that the mesocorticolimbic DAergic system, thought to mediate incentive salience [49, 50] and reward-motivated behaviors [51–53], is involved in the expression of apathetic symptoms in patients with AD [20]. A single-photon emission computed tomography study found that reduced striatal DA transporter uptake was correlated with greater apathy in dementia patients [54]. Thus, disruptions in this pathway may dampen the salient and rewarding qualities of positive stimuli, prompting patients to orient away from social images. The results of the present study also showed no differences between groups on biases toward dysphoric images.Our patient sample had low levels of depression based on the NPI depression subscore, which would account for this lack of bias toward dysphoric images.

The linear regression analysis suggested that more severe apathy (measured by the AES) predicted reduced attentional bias toward social images, based on the fixation frequency parameter. Additionally, better cognition (measured by the sMMSE) and reduced attention (measured by the CPT Inattention) were also significant predictors in the model. As the variance inflation factors for each covariate were relatively low, there was little concern for multi collinearity. Exploratory analyses of the subtypes of apathy suggested that, in particular, emotional blunting is more relevant with regards to attentional bias toward social images. We observed that reduced emotional responsivity (higher AES emotion subscores) was associated with lower fixation frequencies on social images. The social stimuli used in this study had both higher valence and arousal compared with neutral images. Further, there were no significant predictors of attentional bias toward dysphoric images. Given that the dysphoric stimuli in the present study paradigm had higher arousal but lower valence than neutral images, diminished response to high valence is an important manifestation of the emotional blunting feature of apathy. This provides further insight into the reduced bias toward social stimuli previously observed in depressed patients [33]. Flat affect, a component of both depression and apathy, may be the key factor in driving attention away from positive stimuli with both high arousal and valence (e.g., social images). These results are consistent with previous imaging findings of different neural activation patterns and structural changes associated with each apathy domain [25, 26]. The domains of apathy may have different pathological mechanisms and impact on both cognitive and attentional abilities.

The linear regression analyses also indicated that cognition and attention influenced visual scanning behavior. Given that greater deficits in cognition and attention have been associated with apathy in AD [11–13, 55], the interplay between apathy, cognition, and attention may function to direct visual scanning behavior in the presence of social or positive stimuli. Interestingly, there were no significant predictors for relative fixation time on social images. Attentional biases based on discrete number of fixations or exploratory eye movements within social images may be more sensitive to differences in levels of apathy than total time allocated to social images.

Several factors should be considered when interpreting the results of this study. Although this paradigm used many test slides with different items, personal attraction toward particular images within each individual may compete for attentional resources. For example, strong personal interest or preference for a particular neutral image may act as a distractor and disrupt biases toward the emotionally valenced images. Our data might also be limited by sample size. *A priori* power calculations for the repeated-measures ANOVA with up to two covariates (primary analysis) indicated that 38 patients (19 in each group) are required to detect medium to large effect sizes (power = 0.80, $\alpha = 0.05$). However, we observed large effect sizes and power of 0.91 in the repeated-measures ANCOVA model for fixation frequency using our current sample size. This study was exploratory and findings should be considered preliminary. Future studies should be conducted in order to determine whether these results hold in larger patient sample sizes. In this study, we presented results for two outcome variables (relative fixation time and fixation frequency), which have been used successfully in past studies [33, 34, 48]. However, these parameters might not fully elucidate the process of visual attention bias associated with apathy. Future studies should focus on developing other parameters, which may provide further insight into visual scanning behavior. Additionally, although NPI depression subscore scores were low and comparable between the study groups, the cut-off score of 4 has yet to be validated and may not be clinically relevant. However, this value has previously been used to screen out significant psychosis, delusions and agitation/aggression [22, 28]. Additionally, the NPI apathy subscore $\geq$4 was used to define patients with significant apathy [22, 28, 42, 44]. Overall, these factors could have confounded our observations and may have contributed to the relatively large standard deviations in the mean visual scanning parameters. It should be noted that although we did not specifically match apathetic and non-apathetic patients based on levels of cognition and attention, only participants in the mild to moderate range were recruited. As a result, groups had comparable scores on the sMMSE and all CPT subscores. Similar to our findings, others [29, 30, 56–58] have also observed non-significant, though numerically lower MMSE scores in apathetic compared with non-apathetic patients in the mild-to-moderate AD stage. One study [59] did find significantly lower MMSE scores in apathetic compared with non-apathetic patients. In general, higher levels of apathy are associated with more severe cognitive and functional deficits [11–14]. Thus, future studies with larger target sample sizes should further explore visual scanning behavior and apathy in more severely impaired patient populations.

Currently, there are several barriers to the assessment of apathy in the dementia population.In addition to associations with more rapid decline [11–14], apathy is also linked with higher risk of conversion to AD from mild cognitive impairment [60, 61]. Experts in the field have emphasized the need to identify biomarkers and risk factors of AD in the early and pre-symptomatic stage [62]. As such, assessments of apathy may provide a potential avenue for prevention and early treatment of dementia. As discussed above, methods of assessment in research and clinical environments rely heavily on informant interview, which may be subjective. Current recommendations advocate the use of a clinician's objective evaluation in corroboration with separate interviews with caregivers and patients [1, 63], which may nevertheless be ambiguous and time-consuming. Furthermore, apathy can often be misdiagnosed as depression due to the overlap in symptoms. Clinicians have observed the development of apathy following SSRI treatment for depression in psychiatric and geriatric patients [64–68]. Those case studies also reported that symptoms were improved or resolved upon discontinuation or reduction of SSRI medications.These points highlight the significance of exploring more precise methods of evaluation in order to better measure symptoms, inform treatment decisions and prevent the prescription of ineffective or even detrimental courses of therapy.

The measurement of attentional bias may provide a nonverbal, direct and objective approach to assessing symptoms and may represent a reliable marker of pharmacotherapy-induced behavioral changes. A single dose of an antidepressant can alter the processing of emotional stimuli in both depressed and healthy individuals only a few hours following drug administration [69, 70]. SSRIs have been shown to normalize functional magnetic resonance signals in the amygdala and frontoparietal circuitry during exposure to negatively valenced stimuli [71]. This was observed together with improvements in mood. In apathetic patients, psychostimulants might promote motivated behaviors by strengthening salient qualities of reward and positively valenced stimuli. In a randomized placebo-controlled clinical trial of methylphenidate, a psycho stimulant, for the treatment of apathy in AD, patients on the active treatment improved on tests of both apathy [22] and attention [28]. Furthermore, inattention induced in a dextro-amphetamine challenge can predict subsequent response to methylphenidate treatment for apathy [21]. As such, attentional bias may predict treatment response.

In summary, we found that apathetic AD patients demonstrated reduced attentional bias toward social images compared with non-apathetic patients and more severe apathy was associated with decreasing preference for social images. This study provides insight on the visual scanning behavior of apathetic AD patients in the presence of emotionally valenced stimuli as well as the distinct effects of the different apathy subtypes. Given the high prevalence of apathy in dementia and assessment problems arising from memory and communicative difficulties, a focus on more studies to develop objective technologies to evaluate apathy in both the clinical and research environment should be considered.

ACKNOWLEDGMENTS

The authors wish to thank Abby Li, MyuriRuthirakuhan, Romeo Penheiro, MarlyIsen, and Julia Hussman for assistance with data collection.

This work was supported by the Consortium of Canadian Centres for Clinical Cognitive Research; the Natural Sciences and Engineering Research Council of Canada (grant number 130149); and by the Vision Science Research Program, Toronto Western Hospital.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-1026r2).

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