ORIGINAL RESEARCH

Effect of Methylphenidate for Apathy on Visual Attention Scanning Behavior: a Pilot Study

Sarah A. Chau, PhD[1,2], Nathan Herrmann, MD, FRCP(C)[1,3], Jonathan Chung, MSc[4,5], Moshe Eizenman, PhD[4,5,6], Krista L. Lanctôt, PhD[1,2,3]

[1]Neuropsychopharmacology Research Group, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON; [2]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON; [3]Department of Psychiatry, University of Toronto, Toronto, ON; [4]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON; [5]Department of Electrical and Computer Engineering, University of Toronto, Toronto, ON; [6]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada

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ABSTRACT

Background

The purpose of this pilot study was to explore the potential of eye-tracking technology in monitoring symptoms and predicting outcomes in apathetic Alzheimer's disease (AD) patients treated with methylphenidate (MTP).

Methods

Neuropsychological tests and eye-tracking measurements were completed at baseline and following at least four weeks of treatment with MTP (5–10 mg BID). Eye-movements were measured while patients viewed novel and social stimuli. Cognition, behavior, and apathy were assessed using the Standardized Mini-Mental State Exam (sMMSE), Neuropsychiatric Inventory, and Apathy Evaluation Scale (AES), respectively.

Results

Nine patients were included in the analysis (age: median=75, interquartile range=8; sMMSE: median=22, interquartile range=14). Spearman correlations showed that improvement on the AES was associated with increased visual attention towards novel stimuli (ρ_7=-0.809, p=.008). Additionally, lower baseline attention towards social images was associated with improvement on the AES (ρ_7=0.905, p=.001).

Conclusions

Eye-tracking techniques can be developed as an objective and nonverbal method of monitoring symptoms and treatment outcomes in AD patients.

Key words: Alzheimer's disease, apathy, methylphenidate, eye-tracking

INTRODUCTION

Apathy, characterized by reduced motivation, social disinterest, and emotional blunting,[1] is the most frequently occurring neuropsychiatric symptom in Alzheimer's disease (AD).[2] Apathy has been associated with the mesocorticolimbic dopaminergic (DAergic) pathway involved in reward and motivation.[3] Psychostimulants such as methylphenidate (MTP), which work by increasing DA and norepinephrine, have been shown to improve symptoms of apathy as well as attention.[4,5]

Current assessments of apathy depend heavily on subjective input from caregivers. However, a high burden of care may constrain the capacity of caregivers to accurately evaluate patients, limiting the clinician's ability to monitor symptoms and treatment responses.[6] Apathy is particularly difficult to assess and treat due to its overlap with depression.[7] Furthermore, these two syndromes have divergent neurobiology[8] and require different drugs for treatment. More direct and nonverbal assessment tools would be of value in exploring the effects of pharmacotherapy in these patients.

Currently, no direct measure that can accurately distinguish apathy from depression has been validated. However, using eye-tracking techniques, we previously demonstrated that in nondepressed AD patients, those with significant apathy had reduced selective attention towards social or positive stimuli compared to those without apathy.[9] Furthermore, AD patients displayed less attention towards novel stimuli (novelty preference) compared with elderly controls.[10] This parameter also predicted longitudinal decline.[11] MTP may modulate apathy and selective attention via common pathways. As such, visual scanning behavior associated with

apathy and selective attention, established in previous studies,[9,10] may be sensitive to pharmacological manipulations. The objective of this study was to determine changes in attentional bias parameters associated with MTP treatment.

METHODS

Participants

Patients with mild-to-moderate AD and clinically significant apathy were recruited from outpatient clinics at Sunnybrook Health Sciences Centre. For those included, an independent clinical decision to treat apathy with methylphenidate had been made. Additionally, eligibility for the eye-tracking study included: significant apathy (NPI apathy subscore ≥4, as used previously[4]), no change in antidementia medications for at least one month, and no significant eye pathology. Written informed consent was provided by all participants or a legally authorized representative. This study was approved by the Sunnybrook Research Institute Research Ethics Board.

Procedures

Eye-tracking measurements and neuropsychological assessments were completed immediately before beginning MTP treatment (5–10 mg BID), and at the first follow-up visit (approximately four weeks later). At each study visit, the Standardized Mini-mental State Exam (sMMSE),[12] Neuropsychiatric Inventory (NPI),[13] and Apathy Evaluation Scale (AES)-Informant[14] were administered to assess cognition, behavior, and apathy, respectively.

Eye-Tracker and Visual Stimuli

The visual attention scanning technology (VAST, EL-MAR Inc., Toronto, Canada) used has been described previously.[9,10,15] Participants viewed images on a computer screen while the eye-tracking system estimated visual scanning parameters. The visual stimuli consisted of slides displayed for 10.5 s each, followed by a 1-s grey screen. Slides consisted of four simultaneously presented images (arranged 2 by 2) selected from the International Affective Picture System (IAPS). For the novelty paradigm,[10,11] all four images had similar complexity and IAPS ratings for valence (neutral) and arousal (low). Two images on each slide were novel and two were shown previously (1-back and 2-back repeats were tested). The position of the novel and repeated stimuli were randomly intermixed. There were 16 of these slide series (total of 48) presented in this portion of the test. The stimuli for the social paradigm[9] comprised of a series of 16 slides each containing 1 social, 1 dysphoric, and 2 neutral images. The position of each theme was randomly intermixed. Social images had high valence and arousal, while dysphoric images had low valence and high arousal. The total testing procedure was 20 minutes.

Visual Scanning Parameter

The visual scanning parameter was the number of discrete fixations on each image (fixation frequency within images). Novelty preference was estimated by subtracting parameter values for repeat from novel images on each 1-back and 2-back slide. The 1-back and 2-back values were added in order to obtain a single value to represent novelty preference for each patient. Social biases were summarized by subtracting mean fixation frequency on neutral from social images. For each participant, biases for social images were determined by calculating the mean fixation frequency on the 16 relevant test slides. Higher values indicated stronger preferences for novel or social images.

Statistical Analyses

Baseline and follow-up scores on neuropsychological and psychiatric tests were compared using Wilcoxon signed-rank tests. Spearman correlations were conducted to explore associations between changes in visual scanning (treatment-baseline) and AES scores (treatment-baseline). Spearman correlations were conducted to explore baseline predictors of change in AES. To examine whether apathy remission was associated with differential bias patterns, patients were categorized as remitters based on an NPI apathy score below 4 following treatment, and nonremitters were those who maintained scores above or at 4. Repeated-measures ANOVA models explored within-subject effects of MTP (baseline, follow-up) and between group effects (remitter, nonremitter) for attentional bias parameters. All analyses were considered significant at an α of 0.05, consistent with the exploratory nature of the trial. No corrections were made for multiple comparisons.

RESULTS

Nine AD patients being treated with MTP for apathy agreed to participate. The median length of treatment exposure at time of follow-up was 4.0 weeks (range: 3–17 weeks) and the average dose was approximately 15 mg/day. No patients experienced adverse events. Overall, there were trending decreases in apathy test scores (AES and NPI apathy) following treatment (Table 1). Five of nine patients remitted based on NPI apathy scores.

Improvement on the AES was significantly associated with increased fixation frequency on novel (minus repeat) images (ρ_7=-0.809, p=.008). There was no significant correlation between change in fixation frequency on social (minus neutral) images and improvement in AES score (ρ_7=-0.200, p=.606). However, lower baseline fixation frequency for social images predicted improvement in apathy symptoms on the AES (ρ_7=0.905, p=.001).

Overall, compared with patients who remitted, those who did not remit had a greater decrease in mean fixation frequency within novel (minus repeat) images following

TABLE 1.
Clinical and demographic characteristics (n=8), with values expressed as median (interquartile range) or proportions; statistical comparisons were conducted using Wilcoxon signed-rank tests

	Baseline	*Treatment*	*p-value*
Age, years	75 (8)		
Standardized Mini-mental State Exam	22 (14)	22 (14)	.552
Gender	3 Females 6 Males		
Education, n			
High school or below	14		
Post-secondary	5		
Concomitant medications, n			
Cholinesterase Inhibitors	6		
Antidepressants	2		
Neuropsychiatric Inventory	22 (14)	22 (26)	.594
Apathy subscore	8 (3)	3 (7)	.058
Depression subscore	6 (8)	0 (8)	.461
Apathy Evaluation Scale	58 (15)	54 (11)	.151

treatment (remitters: 1.81±1.55 to 1.38±1.76; nonremitters: 0.97±1.11 to -0.71±0.92). There was a significant treatment main effect ($F_{1,7}$=6.59, p=.037) but no group main effect ($F_{1,7}$=2.81, p=.137). Remitters also showed a slight increase in mean fixation frequency for social (minus neutral) images following treatment (2.35±0.95 to 2.39±1.36), while nonremitters had a decrease (3.65±2.04 to 1.86±1.21). There was no significant main effect of treatment ($F_{1,7}$=3.30, p=.112) or group ($F_{1,7}$=0.21, p=.664).

DISCUSSION

This pilot study explored the effect of MTP treatment for apathy on the processing of novel and positive themed stimuli in AD patients. We found that improvements in apathy were significantly associated with an increased number of fixations on novel images. Consistent with our results, Daffner et al.[16] found that apathetic AD patients demonstrated decreased exploration of novel visual stimuli. Additionally, more severe apathy was associated with reduced P3 event-related potentials (ERPs), an electroencephalogram (EEG) index of the orientation of attention towards novel stimuli.[17] Reduced novelty P3 amplitude has been associated with apathy in patients with Parkinson's, a disease characterized by depletion of DAergic neurons in the nigrostriatal pathway.[18] The DAergic system is most prominently implicated in encoding novelty. One study reported increases in the N2 ERP amplitude, an EEG signal associated with novelty detection, in Parkinson's patients on the DA precursor levodopa versus off medication.[19] A study of healthy adults showed increases in the N2b response to novelty following administration of apomorphine, a DA D1/D2 receptor agonist.[20] However, no pharmacological studies of novelty preference have given special consideration to the effect of apathy.

Previous eye-tracking studies found a reduced bias towards social images in depressed young adults compared with age-matched controls.[15,21] While results from our previous study[9] suggested lower attentional bias towards social images in apathetic compared with nonapathetic AD patients, we found no significant correlations between change in apathy and visual scanning on social stimuli following MTP treatment in this study. A sample size of nine was likely not sufficiently powered to detect a relationship. However, lower baseline bias towards social images predicted greater improvements in apathy after MTP treatment. Thus, patients with greater dysfunction in the processing of social or positive stimuli may benefit more from treatment.

The results of this pilot study should be very carefully interpreted in light of the small sample size. These findings can inform a larger and more comprehensive investigation. A sample size of 20 would be needed to achieve a power of 0.80 to detect a large effect size (ρ=.5) in correlation analyses.

CONCLUSION

This study provided preliminary data to suggest that visual scanning behavior and attentional biases may be sensitive to pharmacological manipulations. Apathy is often misdiagnosed as depression, despite differing treatments. Clinicians have observed the development of apathy following treatment for depression using selective serotonin reuptake inhibitors in psychiatric and geriatric patients.[22] 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 detrimental courses of therapy. The measurement of attentional biases may represent a reliable marker of pharmacotherapy-induced behavioral changes.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

REFERENCES

1. Mulin E, Leone E, Dujardin K, *et al*. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry*. 2011;26(2):158–65.

2. Chase TN. Apathy in neuropsychiatric disease: diagnosis, pathophysiology, and treatment. *Neurotox Res*. 2011;19(2):266–78.
3. Mitchell RA, Herrmann N, Lanctôt KL. The role of dopamine in symptoms and treatment of apathy in Alzheimer's disease. *CNS Neurosci Ther*. 2011;17(5):411–27.
4. Rosenberg PB, Lanctot KL, Drye LT, *et al*. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(8):810–16.
5. Lanctôt KL, Chau SA, Herrmann N, *et al*. Effect of methylphenidate on attention in apathetic AD patients in a randomized, placebo-controlled trial. *Int Psychogeriatr*. 2014;26(2):239–46.
6. Kahle-Wrobleski K, Ye W, Henley D, et al. Assessing quality of life in Alzheimer's disease: Implications for clinical trials. Alzheimers Dement. 2017;6:82-90.
7. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry*. 2008;79(10):1088–92.
8. Kang JY, Lee JS, Kang H, *et al*. Regional cerebral blood flow abnormalities associated with apathy and depression in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2012;26(3):217–24.
9. Chau SA, Chung J, Herrmann N, *et al*. Apathy and attentional biases in Alzheimer's disease. *J Alzheimers Dis*. 2016;51(3):837–46.
10. Chau SA, Herrmann N, Eizenman E, *et al*. Exploring visual selective attention towards novel stimuli in Alzheimer's disease patients. *Dement Geriatr Cogn Disord Extra*. 2015;5(3):492–502.
11. Chau SA, Herrmann N, Sherman C, *et al*. Visual selective attention toward novel stimuli predicts cognitive decline in Alzheimer's disease patients. *J Alzheimers Dis*. 2017;55(4):1339–49.
12. Molloy DW, Alemayehu E, Roberts R. Reliability of a Standardized Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. *Am J Psychiatry*. 1991;148(1):102–05.
13. Cummings JL, Mega M, Gray K, *et al*. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308–14.
14. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res*. 1991;38(2):143–62.
15. Eizenman M, Yu LH, Grupp L, *et al*. A naturalistic visual scanning approach to assess selective attention in major depressive disorder. *Psychiatry Res*. 2003;118(2):117–28.
16. Daffner KR, Mesulam MM, Cohen LG, *et al*. Mechanisms underlying diminished novelty-seeking behavior in patients with probable Alzheimer's disease. *Neuropsychiatry Neuropsychol Behav Neurol*. 1999;12(1):58–66.
17. Daffner KR, Rentz DM, Scinto LF, *et al*. Pathophysiology underlying diminished attention to novel events in patients with early AD. *Neurology*. 2001;56(10):1377–83.
18. Kaufman DA, Bowers D, Okun MS, *et al*. Apathy, novelty processing, and the P3 potential in Parkinson's disease. *Front Neurol*. 2016;7:95.
19. Mikell CB, Sheehy JP, Youngerman BE, *et al*. Features and timing of the response of single neurons to novelty in the substantia nigra. *Brain Res*. 2014;1542:79–84.
20. Rangel-Gomez M, Meeter M. Neurotransmitters and novelty: a systematic review. *J Psychopharmacol*. 2016;30(1):3–12.
21. Kellough JL, Beevers CG, Ellis AJ, *et al*. Time course of selective attention in clinically depressed young adults: an eye tracking study. *Behav Res Ther*. 2008;46(11):1238–43.
22. Padala PR, Padala KP, Monga V, *et al*. Reversal of SSRI-associated apathy syndrome by discontinuation of therapy. *Ann Pharmacother*. 2012;46(3):e8.

Correspondence to: Krista Lanctôt, PhD, Neuropsychopharmacology Research Group, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Suite FG08, Toronto, ON, Canada M4N 3M5
E-mail: Krista.Lanctot@sunnybrook.ca