Visual Scanning and Attentional Biases in Alzheimer’s Disease: Assessing Symptoms and Outcomes

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

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ABSTRACT

Current assessments of cognition and behaviour in Alzheimer’s disease (AD) rely on indirect evaluations and are complicated by communication deficits, hampering ability to effectively prescribe and monitor pharmacotherapy. The purpose of this thesis was to determine whether direct measurements of visual scanning behaviour can optimize symptom and outcome assessments in this patient population. In the four studies conducted, a non-verbal eye tracking technique was used to characterize visual scanning behaviour in order to quantify methods of measuring cognition, behaviour and pharmacotherapy-induced changes in AD patients.

To evaluate selective attention towards novel stimuli or novelty preference in AD, mild-to-moderate AD patients (n=41) and elderly controls (n=24) viewed novel and repeated images simultaneously. Compared with controls, AD patients spent less time on novel than repeated images ($F_{1,63}=11.18$, $p=0.001$). Reduced novelty preference was associated with worse cognition (Standardized Mini-Mental State Examination, sMMSE, $r_{63}=0.29$, $p<0.05$) and attention (Digit Span, DS, $r_{63}=0.27$, $p<0.05$). For 32 AD patients, sMMSE was re-assessed
every 6 months for up to 2 years. Linear regressions showed that lower baseline fixation time on novel images (t=2.78, p=0.010) predicted greater cognitive decline ($R^2=0.41$, $F_{3,28}=6.51$, $p=0.002$).

To examine attention towards emotional-themed stimuli, AD patients (apathetic and non-apathetic) were presented slides containing 2 neutral, 1 social and 1 dysphoric image. Seventeen of the 36 AD patients had significant apathy (Neuropsychiatric Inventory, NPI apathy≥4). Repeated-measures analysis of covariance showed that compared to non-apathetic, apathetic patients demonstrated reduced attention towards social but not dysphoric images (fixation time: $F_{1,32}=4.31$, $p=0.046$; frequency: $F_{1,32}=11.34$, $p=0.002$). Eight apathetic patients entered an open-label trial of methylphenidate (MTP, 5-10mg BID) for treatment of apathy for at least 4 weeks. Neuropsychological tests and visual scanning measurements were completed at baseline and follow-up. Spearman correlations showed that improvement on Apathy Evaluation Scale (AES) was associated with increased novelty preference ($\rho_6=0.79$, $p<0.05$). Lower baseline attention towards social images was associated with improvement on AES (fixation time: $\rho_6=0.79$, $p<0.05$; frequency: $\rho_6=0.86$, $p<0.01$)

Eye tracking techniques to measure visual scanning behaviour provide an objective, non-invasive, non-verbal and less cognitively-demanding method, compared to traditional tests, which can improve assessment of symptoms and optimize treatment outcomes in AD patients.
Acknowledgements

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<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>serotonin</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td>Alzheimer's Disease Assessment Scale - Cognitive subscale</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention deficit hyperactive disorder</td>
</tr>
<tr>
<td>ADMET</td>
<td>Apathy in Dementia Methylphenidate Trial</td>
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<tr>
<td>AES</td>
<td>Apathy Evaluation Scale</td>
</tr>
<tr>
<td>AI</td>
<td>Apathy Inventory</td>
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<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>APP</td>
<td>amyloid precursor protein</td>
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<tr>
<td>AS</td>
<td>Apathy Scale</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood-oxygen-level dependent</td>
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<tr>
<td>ChEI</td>
<td>cholinesterase inhibitor</td>
</tr>
<tr>
<td>CPT</td>
<td>Conners’ Continuous Performance Test</td>
</tr>
<tr>
<td>CT</td>
<td>computer-assisted tomography</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>DAT</td>
<td>dopamine transporter</td>
</tr>
<tr>
<td>DSB</td>
<td>Digit Span Backward</td>
</tr>
<tr>
<td>DSF</td>
<td>Digit Span Forward</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th Edition</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>ERP</td>
<td>event-related potential</td>
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<tr>
<td>FDG</td>
<td>fludeoxyglucose</td>
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<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GABA</td>
<td>( \gamma )-aminobutyric acid</td>
</tr>
<tr>
<td>IAPS</td>
<td>International Affective Picture System</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MMS</td>
<td>Modified Mini Screen</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental State Exam</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MTP</td>
<td>methylphenidate</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>Acronym</td>
<td>Term/Description</td>
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<tr>
<td>NET</td>
<td>norepinephrine transporter</td>
</tr>
<tr>
<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association</td>
</tr>
<tr>
<td>NPI</td>
<td>Neuropsychiatric Inventory</td>
</tr>
<tr>
<td>NPS</td>
<td>neuropsychiatric symptoms</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PiB</td>
<td>Pittsburgh compound B</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for Diagnosis</td>
</tr>
<tr>
<td>SHSC</td>
<td>Sunnybrook Health Sciences Centre</td>
</tr>
<tr>
<td>SRI</td>
<td>Sunnybrook Research Institute</td>
</tr>
<tr>
<td>sMMSE</td>
<td>Standardized Mini-mental State Exam</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>VAST</td>
<td>visual attention scanning technology</td>
</tr>
<tr>
<td>VPC</td>
<td>visual paired comparison task</td>
</tr>
<tr>
<td>WAIS-DS</td>
<td>Wechsler Adult Intelligence Scale - Digit Span</td>
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Chapter 1

Introduction

1.1 Statement of Problem

Alzheimer's disease (AD) is associated with several serious adverse health and economic outcomes. Few medications are currently approved for the treatment of AD. One issue that has hampered development of medications in this patient population is the lack of reliable tools to assess symptoms. Cognitive evaluations become increasingly difficult due to progressive communication and language deficits, particularly in the later stages of the disease. Additionally, the complexity of experimental tasks and high reliance on verbal communication represent obstacles in the assessment of cognitively impaired people. Even with relatively intact communication capacity, standard cognitive tests, including the Mini-mental State Exam (MMSE) [1] and the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) [2] are inherently confounded by education. This represents a huge limitation given that AD is prevalent across a broad range of socioeconomic backgrounds and low socioeconomic status may in fact be associated with greater risk of developing AD [3]. Most assessments of behaviour and function depend heavily on input from caregivers (often a family member), who have high rates of emotional distress, depression and poorer physical health [4]. The burden of care placed on caregivers may constrain their ability to accurately judge neuropsychiatric symptoms (NPS) and functional impairments. In the clinical setting, these challenges limit the ability to monitor disease progression and treatment response. In particular, apathy, the most frequently occurring NPS in dementia [5], is difficult to assess and treat due to its overlap in symptoms with depression [6-8]. However, these two NPS have divergent neurobiology [9-12]
and may require different classes of drugs for treatment. Thus, more direct, non-verbal, less cognitively-demanding assessment tools would be of value in exploring the brain functions and effects of pharmacotherapy in dementia patients.

1.2 Purpose and Objectives

1.2.1 Overall Purpose

Eye tracking procedures can be used to measure attentional biases towards visual stimuli in a passive, non-verbal manner. The overall purpose of this work was to apply visual attention scanning technology (VAST) to optimize methods of assessment and treatment monitoring in AD patients by quantifying visual scanning behaviour. This thesis contains four studies where this paradigm was applied to investigate visual scanning behaviour in the context of novel stimuli to measure memory and attention and emotionally-charged stimuli to measure apathy in AD patients. The first two studies focused on the cognitive aspect of AD. In the next two studies, the theme shifted to the behavioural component of AD. First, Study 1 was designed to establish the nature of deficits in visual scanning behaviour in an AD sample and its associations with memory and attention tests. Next, Study 2 examined whether this parameter could predict longitudinal outcomes in cognition. Study 3 was developed to characterize the unique visual attention patterns associated with apathy in an AD sample. Finally, Study 4 examined pharmacotherapy-induced shifts in these visual parameters. Visual attention paradigms may be of value in measuring symptoms, predicting longitudinal changes and monitoring treatment outcomes. Visual attention may be a non-invasive, non-verbal and less cognitively-demanding measurement that can improve assessment of symptoms and thereby optimize treatment outcomes.
1.2.2 Study Objectives

**Study 1: Selective Attention towards Novel Stimuli in AD**

The objective of this study was to observe the spontaneous visual scanning patterns of AD patients in the presence of novel and repeated visual stimuli in order to characterize selective attention towards novelty in a naturalistic setting. By comparing visual scanning patterns of AD patients and cognitively intact elderly controls, novelty processing deficits associated with the disease state can be identified.

**Study 2: Selective Attention towards Novel Stimuli as a Predictor of Cognitive Decline**

The objective of this study was to explore whether attentional bias towards novel stimuli or novelty preference can predict the degree of cognitive decline in patients with cognitive impairments. Measuring early dysfunction in novelty preference can help identify patients who are at greater risk of rapid decline. Determining factors associated with aggressive deterioration would have relevant implications for treatment decisions at earlier stages of the disease, where neurodegeneration is less global and AD-related pathological events may be more modifiable.

**Study 3: Apathy and Selective Attention towards Positive Stimuli**

The objective of this study was to quantify attentional biases towards stimuli with positive and negative emotional themes in apathetic AD patients. While mood-congruent biases (away from positive and towards negative stimuli) have been found in depression, little is known about the
attentional bias patterns associated with apathy. By comparing apathetic and non-apathetic AD patients, this study will determine the specific biases associated with the apathy phenotype.

**Study 4: Effect of Methylphenidate for Apathy on Visual Scanning Behaviour**

The objective of this study was to determine changes in attentional bias parameters associated with methylphenidate treatment for apathetic symptoms. The pattern of visual scanning behaviour associated with AD, established in the previous studies, may be sensitive to pharmacological manipulations and be used to monitor and predict treatment response.

1.3 Review of the Literature

1.3.1 Alzheimer’s Disease

Alzheimer’s disease is characterized by severe deficits in cognition (most prominently memory and attention) and function, as well as disturbances in behaviour or NPS [13]. AD is the most common form of dementia, accounting for approximately 50-75% of cases [14]. Alzheimer’s Disease International estimated that 46.8 million people worldwide were living with dementia in 2015. The prevalence is expected to reach 74.7 million by 2030 [15]. Furthermore, the total economic burden in 2015 was estimated at $818 billion USD and is projected to be $2 trillion USD by 2030. In Canada, there are an estimated 564,000 people currently living with dementia, with 25,000 new cases diagnosed every year [16]. This number was projected to increase by 66% by 2031. With regard to economic burden, the annual estimated direct costs of dementia in 2016 was $10.4 billion CAD and was projected to reach $16.6 billion CAD by 2031 [17]. The risk of mortality in people with dementia is more than doubled compared with
age-matched elderly without dementia [15], further underscoring the global impact of this
disease.

AD may be the consequence of many different aberrant changes in the brain. A large
proportion of research has focused on the amyloid hypothesis. Several disease-modifying drug
candidates currently under clinical development target this pathway. In the non-disease
condition, the transmembrane amyloid precursor protein (APP) is cleaved by the enzyme α-
secreterase to produce a non-toxic soluble protein (sAPPα) [18]. Under the disease state,
cleavage of APP by β-secretase and γ-secretase generates two major species of hydrophobic
Aβ fragments [19, 20], with the species containing 42 amino acids (Aβ42) having greater
propensity for harm than the fragments containing 40 amino acids (Aβ40). Aβ42 monomers
have been found to be more susceptible to further aggregation and formation of toxic
extracellular amyloid plaques [21-23]. Evidence also suggests that increases in Aβ42/Aβ40
ratio and elevation of soluble Aβ oligomers, rather than the polymeric plaques, may be key to
the disease pathology [24-27]. Another prominent pathway linked with AD pathogenesis
involves intra-neuronal changes, particularly axonal microtubule instability.

Hyperphosphorylation of tau, which function to stabilize microtubules during polymerization,
can lead to protein aggregation, causing the proliferation of cytotoxic neurofibrilllary tangles
and loss of cytoskeletal structural integrity [28-31]. Both amyloid and tau pathology have been
observed in the up-regulation of inflammatory cytokines, cyclo-oxygenase and activated
microglia, providing evidence for the neuro-inflammation theory of AD [32-34]. Moreover,
toxic amyloid species may also interfere with regular mitochondrial activity by propagating the
synthesis of reactive oxygen species, leading to further neuronal damage [35, 36]. Overall,
these aberrant changes to neuronal synaptic functioning, alone or combined, can result in the
marked global neurodegeneration observed in AD.
1.3.2 Attention and Working Memory in AD

The pattern of structural and functional changes in the brain, precipitated by upstream pathophysiological events, may account for deficits in memory and attention typical in AD. Computer-assisted tomography (CT) and magnetic resonance imaging (MRI) results indicate atrophy of the temporal and parietal lobes early on in AD and progress to the frontal lobes in the later stages [37]. Greater rates of atrophy have also been strongly correlated with neuron loss [38] and progression of cognitive impairment [39, 40]. Consistent with these results, hypometabolism or hypoperfusion in the temporoparietal cortex have been observed in fludeoxyglucose positron emission tomography (FDG-PET) and single-photon emission computed tomography (SPECT) [41, 42]. Visualization of amyloid plaque burden using PET and the tracer Pittsburgh compound B (PiB) has demonstrated high retention in cortical regions, including the prefrontal, cingulate, parietal and temporal cortex [43-45].

The role of both the temporoparietal and frontoparietal networks in visuospatial attention have been well-established [46-49]. The subsystems of attention can be anatomically and functionally studied in isolation and may have unique susceptibilities to the effects of AD pathology [50]. In order to study these processes in AD, Perry and Hodges [50] classified attention into 3 categories: selective, sustained and divided. Selective attention, or focus and concentration, is defined as the process by which salient stimuli are encoded while irrelevant distractors are filtered out. Sustained attention refers to the ability to maintain concentration on a stimulus over extended periods of time. Finally, Perry and Hodges defined divided attention as the capacity to allocate cognitive resources towards several stimuli simultaneously.

Evidence indicates that deficits in selective and divided attention are associated with the early stages of AD while sustained attention remains relatively intact until the later stages [50-58].
The Stroop task is the most widely used test and current gold standard for evaluating selective attention [59]. In this paradigm, participants are instructed to focus on one aspect of a stimulus while ignoring other features. Interference occurs when non-relevant task components conflict and impede processing of target components, causing increased reaction time, the primary outcome of this task. Large interference effects have been found in early AD compared with healthy elderly controls [60]. However, in a meta-analysis of Stroop studies in dementia patients, Ben-David et al [61] contended that this effect could be partially explained by disease and age-related decreases in processing speed and sensory degradation, specifically in colour perception, and may not accurately reflect selective attention deficits [61].

Another construct of cognition that is important to consider in the context of AD is working memory, defined as the temporary maintenance of information for quick access to facilitate efficient updating in pursuit of goal-directed behaviours [62]. This is considered separate, though related, to short-term memory, which is simply the limited capacity system for temporary storage of information [63]. Working memory includes the coordination of different faculties to utilize for temporarily maintenance and manipulation of information. There is evidence to suggest that compared with controls, patients with mild cognitive impairment (MCI) and AD perform worse on digit, word and spatial span tests [64-66]. MCI is defined by decline in cognitive functioning beyond the normal changes associated with healthy aging and has been linked with increased risk of conversion to AD [67, 68]. The prevailing model of working memory, proposed by Baddeley and colleagues [62], posits that working memory is composed of two subordinate systems responsible for temporary storage of verbal and visuospatial information, the phonological loop and visuospatial sketchpad, respectively. A high order central executive, an attentional component, exerts control over and coordination of the two lower systems. A fourth component, the episodic buffer, was included in later revisions...
to clarify the process by which information is integrated from different sources chronologically [69].

The neural basis of working memory has been studied using the n-back continuous performance task, a test that requires responding to a particular letter when the letter appeared on the screen n letters previous [70, 71]. Memory loads tested were typically 1 to 3 spans back. A meta-analysis of pooled neuroimaging results concluded that there were largely consistent data showing frontal and parietal activation associated with performance on different variations of the n-back test [71]. AD patients show lower accuracy on this task and had decreased frontal activation during performance compared with controls [72]. However, studies evaluating the psychometric properties of the n-back suggested that it is not a measure of working memory as a single construct but may involve other processes [73-75].

1.3.3 Interactions between Attention and Working Memory

Interactions between working memory and attention, particularly visual selective attention, is crucial during the many steps of information processing [76-78]. As suggested in the previous section, many neuroscientists now view selective attention and working memory as overlapping constructs with common neural substrates [78-82]. Indeed, evidence supports the notion that working memory deficits in AD patients may reflect damage to the frontal cortex [83, 84]. Furthermore, the posterior parietal lobe may also play a role in working memory [80, 85]. Acting as the central executive, selective attention can modulate or bias encoding of relevant sensory information for working memory during the initial phases of visual stimulus processing [78, 86]. Attention continues to exert top-down modulatory influence throughout
the encoding, maintenance and retrieval stages of working memory as a means to optimize performance [76].

The relationship between working memory and selective attention also flows in the direction of working memory representations guiding visual selective attention. Visual search tasks, where subjects are required to hold information in working memory while performing a goal-directed search task, are typically employed to study this relationship. Items congruent with representations in working memory have been shown to capture attention [87, 88]. Increasing memory load resulted in decreasing the attentional guidance effect, measured by response time and accuracy during a discrimination task [89-92]. Furthermore, individuals with greater working memory capacity were better at selectively attending to relevant information and were less influenced by distracters [92]. However, studies have also demonstrated that attention can also be directed away from memory-congruent contents in the visual field [93, 94]. These authors suggest that many factors are involved in orienting attention towards or away from memory-matching inputs, including the goals of the task. Thus, working memory can be utilized in a flexible top-down, goal-dependent manner to guide attention.

1.3.4 Processing of Novel and Repeat Stimuli

Another interpretation of why attention can be biased away from working memory-congruent items in the visual environment may lay in the natural salience of novel stimuli. Evolutionarily speaking, identifying and ascribing attentional resources to processing novel inputs allow for the exploration of new opportunities and aids in adaptation to changing environments. Novel stimuli can facilitate enhanced sensory perception [95], strengthen reward processing [96, 97] and visual working memory encoding [98]. The stages of novelty processing include: 1)
detection of novel stimuli guided by top-down memory inputs, 2) allocation of attentional resources and finally, 3) sustained processing of the stimuli. Studies using electroencephalography (EEG) to measure brain electrical activity suggest that the N2, an early event-related potential (ERP) localized in the frontal cortex, may be associated with automatic detection of novelty and may not require great demands on attention [99, 100]. Many researchers believe the later P3 ERP component, measured over the parietal lobes, indexes the orientation of attention towards novel stimuli [100, 101]. The oddball paradigm has been used widely in these EEG studies [102]. Brain ERPs were measured while subjects are presented with both repeated and infrequent novel stimuli. Results consistently suggest reduced amplitude and prolonged peak latency of the P3 wave in AD patients compared with controls in response to novel stimuli [103, 104].

Selective attention to novel stimuli or novelty preference has been studied as a means to assess declarative memory or explicit memory [105-107]. The models of working memory and selective attention described above presupposes that these constructs operate within the framework of conscious awareness [108]. Snyder et al [107] have suggested that preference for novelty is strongly linked with attention and implicit memory processes. Traditionally, explicit and implicit memory retrieval (recognition and familiarity, respectively) have been deemed to operate under distinct neural mechanisms [109, 110]. However, an emerging alternative view contends that recognition and familiarity are not so easily separable, may share neural mechanisms and function in an integrated manner [111, 112]. Recent research using priming paradigms suggests that non-conscious inputs can be encoded and maintained in working memory and utilized for task-relevant responses [113, 114]. Additionally, functional neuroimaging results suggest that the prefrontal cortex may be involved in mediating working memory operations beyond the confines of conscious awareness [115].
Bias towards novelty might reflect more efficient processing of contents that have already been viewed and encoded into working memory. Some researchers [107, 116, 117] have attributed the underlying mechanism of enhanced novelty signalling to repetition suppression or priming, defined as reduced neural activation within visual processing pathways following repeated exposure. Three models have been proposed to account for this phenomenon [118]. The fatigue model posits that the amplitude of all stimulus-responsive neurons decrease during repeated exposure as a result of synaptic depression. In the sharpening model, neurons coding irrelevant features will demonstrate decreased firing, resulting in sparse representation of the stimuli. The facilitation model predicts that while firing amplitude remains unchanged, duration of neural firing is shortened in order to support quick processing. Functional MRI (fMRI) results have demonstrated repetition effects, called fMRI adaptation, in both the temporal [119] and frontal cortices [120], areas associated with attention and working memory. It is important to note that effects of repetition on blood-oxygen-level dependent (BOLD) signals varied depending on the experimental paradigm. Findings from an fMRI study suggested reduced repetition suppression activity in the medial temporal lobe of AD patients compared with controls [121]. The researchers also found that decreasing fMRI adaptation was correlated with poorer performance on tests of recognition and episodic memory. Given that processing of novel and repeat stimuli operate within the domains of attention and memory, further examination of novelty preference may provide interesting insights into the specific cognitive consequences of dementia.
1.3.5 Visual Scanning and Novelty Preference in AD

Selective attention towards novel stimuli can be quantified using visual attention scanning methods that work by tracking eye movements during stimulus viewing. The direction of eye movement is considered to be a good indicator of attention allocation [122-124]. Furthermore, eye movement research has advanced understanding of the visual as well as cognitive deficits expressed in AD. With respect to changes in basic ocular function, AD patients appear to have disordered prosaccades (eye movement directed towards a target) and antisaccades (eye movements directed away from a target). Patients demonstrate slower saccade velocity and increased latency to initiate movement [125, 126]. With regard to more complex viewing behaviours, which involve top-down goal-driven processes, AD patients demonstrated longer fixation durations during visual search tasks and difficulties disengaging attention from targets [127-129]. In scene exploration tasks, AD patients showed eye movement patterns which were distinct from controls [130, 131]. Specifically, patients viewed fewer regions in the scene and spent less time fixating on novel regions [131]. The researchers hypothesized that declines in motivation and curiosity or apathy, a prevalent syndrome in AD, may account for these observations. Apathy will be discussed further below.

The visual paired comparison (VPC) task, which involves monitoring spontaneous eye movements while subjects are simultaneously presented with both novel and repeated images following a delay, showed that cognitively intact monkeys and healthy infants had longer viewing durations on novel images [132, 133]. Greater time spent on images have been associated with larger P3 amplitudes, indicating increased attentional orientation towards novelty [100]. Patients with MCI have demonstrated diminished attentional bias towards novel stimuli compared with controls [105, 106, 134]. Interestingly, significant difference between
MCI and controls occurred when the delay between stimuli was 2 minutes and not 2 seconds. Novelty preference was similar when the delay between first and second stimuli presentation was almost immediate. This raises some question about the memory duration limits of cognitively impaired people and the types of memory accessed with different delay times.

Atkinson and Shiffrin's model posits that information held in short-term memory decays within 15-30 seconds [63]. Diminished attentional bias towards novel stimuli has also been associated with increased risk of converting to dementia in MCI patients and to MCI in cognitively intact elderly [106]. These findings suggest that novelty preference may represent a less cognitively and physically demanding tool to assess memory and selective attention capacity in non-verbal populations.

Novelty signals in the brain have been associated with activity in neurotransmitter systems, in particular, acetylcholine (ACh) and dopamine (DA) [135]. Further discussion of these two systems, specifically in the context of apathy and attention, is provided below. 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 [136, 137]. However, to date, no studies have examined the effect of ChEIs on novelty preference behaviour in the dementia population. Additionally, the DAergic system is most prominently implicated in processing novelty [138, 139]. Pharmacological manipulations of this system have resulted in changes in fMRI adaptation [136] and EEG novelty signals [140]. Given that the global neurodegeneration characteristic of AD is accompanied by altered neurotransmitter function [141-143], the study of novelty preference can also advance understanding of attention and memory in dementia.
1.3.6 Apathy in AD

Given the pathophysiological, structural and functional changes in the brain, the cognitive deficits characteristic of AD commonly occur in conjunction with behavioural disruptions. One NPS that has been linked with attention deficits is apathy. Apathy has been described as a syndrome characterized by lack of motivation that is not due to diminished levels of consciousness, cognitive impairments or emotional distress [144]. A validated diagnostic criteria [145, 146] for apathy specific to AD has been proposed [147] (Table 1). According to the criteria, diagnosis requires the presence of reduced motivation, initiation and environmental responsiveness - all of which are rooted in behaviour, cognition and emotion. Importantly, these symptoms must considerably affect daily functioning and not be explained by physical/mental disabilities or the effect of a substance.

Apathy is the most frequently reported symptom, occurring throughout the spectrum of dementia severity as well as in the MCI population. Several studies indicate a point prevalence in the range of 32% and 93% in outpatients using the Neuropsychiatric Inventory (NPI) [12, 148-154]. Studies using more specific tests of apathy, such as the Apathy Evaluation Scale (AES), Apathy Scale (AS) and Apathy Inventory (AI) report rates of 24% to 86% in AD patients within the community [149, 150, 155-158]. Prevalence rates of apathy in residents of nursing homes and long-term care facilities with dementia were similar [159-161]. Concerning MCI, studies have reported a prevalence of over 35% in this population [162-164]. The wide range of rates of apathy reported across studies may be accounted for by variations in the clinical evaluative tools and cut-off values used.
Table 1. Clinical diagnostic criteria for apathy [147].

<table>
<thead>
<tr>
<th>Domain A</th>
<th>Loss of or diminished motivation in comparison to previous level of functioning and not consistent with age or culture. These changes may be reported by the patient or by the observations of others.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain B</td>
<td>Presence of at least 1 symptom in at least 2 of the following domains for a period of at least 4 weeks and present most of the time.</td>
</tr>
</tbody>
</table>
| Goal-directed Behaviour: | **Initiation**: loss of self-initiated behaviour (eg: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)  
**Responsiveness**: loss of environment-stimulated behaviour (eg: responding to conversation, participating in social activities) |
| Goal-directed Cognition: | **Initiation**: loss of spontaneous ideas and curiosity for routine and new events (ie, challenging tasks, recent news, social opportunities, personal/family and social affairs).  
**Responsiveness**: loss of environment-stimulated ideas and curiosity for routine and new events (ie, in the person’s residence, neighbourhood or community). |
| Goal-directed Emotion: | **Initiation**: loss of spontaneous emotion, observed or self-reported (eg: subjective feeling of weak or absent emotions, or observation by others of a blunted affect).  
**Responsiveness**: loss of emotional responsiveness to positive or negative stimuli or events (eg: observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news). |
| Domain C | Symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning. |
| Domain D | Symptoms (A - B) not exclusively explained or due to physical disabilities (eg: blindness and loss of hearing), motor disabilities, diminished level of consciousness or physiological effects of a substance. |
Though there have been some debate about the relationship between apathy and depression, apathy is now regarded as a distinct syndrome or set of frequently co-occurring symptoms [6, 7, 144, 165]. However, apathy is still often misdiagnosed as depression due to the overlap in some symptoms such as decreased energy, social withdrawal and emotional blunting [6-8]. Depression in AD consists of an additional emotional component and has a distinct prevalence of 30-50% [166-168]. While there are now separate diagnostic criteria proposed for apathy [147] and depression [169] in those with cognitive impairment, decreasing communication skills may make diagnosis more difficult as the disease progresses.

Evidence suggests that apathy, independent of depression, is associated with deficits in global functioning, cognition, executive functioning, as well as instrumental and basic activities of daily living [170-174]. High burden and distress levels have been reported in caregivers of patients with apathy [174-176]. Apathy was also correlated with poorer insight into personal problems [177-179] and higher mortality rate in a cohort of nursing home patients [180]. According to longitudinal analyses, apathetic symptoms can contribute to more rapid progression of cognitive and functional decline in AD [155, 170, 181]. Furthermore, MCI patients diagnosed with apathy had a higher risk of developing AD [182-184]. Given these factors, apathy in AD can lead to higher rates of institutionalization [185] and consequently, greater economic burden [186].

### 1.3.7 Pathological Correlates of Apathy and Treatment

Factors considered key to AD pathogenesis, including amyloid plaque formation [23, 187-189] and hyperphosphorylated tau aggregation [28, 190-192], might contribute to neuronal damage, giving rise to both cognitive deterioration and apathy. Post-mortem AD brain analyses showed
that greater apathy was associated with increased presence of neurofibrillary tangles in the frontal, parietal and anterior cingulate cortex [193-195]. Further, studies using PET amyloid imaging with PiB found that greater Aβ plaque deposition in the prefrontal cortex of AD [196] and cortical regions of MCI patients [197] were associated with more severe apathy. However, one study [198] conducting cerebral spinal fluid evaluations found greater apathy associated with total and phosphorylated tau but not Aβ42 concentrations.

Aberrant neurotransmission systems such as DA [199], NE [200], serotonin (5-HT) [200], γ-aminobutyric acid (GABA) [201] and ACh [202] have all been implicated in the manifestation of NPS. With respect to apathy, evidence suggests dysfunction in ACh and DA activity. Using a nicotinic cholinergic receptor ligand with PET imaging, Sultzer et al [203] found an association between more severe apathy and reduced binding in the anterior cingulate, orbitofrontal cortex and hippocampus. A SPECT study using a dopamine transporter (DAT) radioligand to measure DA reuptake provides clearer evidence for the role of DA in apathy [204]. Decreased DAT availability in the striatum, particularly the putamen and caudate of the basal ganglia, was associated with lack of initiative and interest on a measure of apathy, suggesting loss of DAergic neurons and involvement of subcortical systems in the expression of apathy.
**Figure I.** Cholinesterase inhibitors mechanism of action. ChEIs block AChE from breaking down ACh, prolonging its activity in the synapse. AChE=acetylcholinesterase, A=acetate, C=choline, ACh=acetylcholine, ChEI=cholinesterase inhibitor

Pharmacotherapies targeting the DA and ACh systems have demonstrated positive effects in ameliorating apathy symptoms. Cholinesterase inhibitors (ChEIs), including donepezil, rivastigmine, galatamine, approved for the symptomatic treatment of the cognitive symptoms in AD have demonstrated some benefit for apathy, as a secondary outcome [205-207]. ChEIs increase central ACh neurotransmission by blocking the hydrolyzing activity of the enzyme acetylcholinesterase [208-210] (Figure I). Methylphenidate (MTP) has thus far been the most studied psychostimulant in apathy treatment (See Table 2 for a summary of the trials). Its mode
of action includes inhibition of DA and norepinephrine (NE) reuptake in the synapse through the DAT and norepinephrine transporter (NET) on the presynaptic membrane [211-213] (Figure II). The use of MTP to manage symptoms of apathy in dementia has shown promise in case reports [214, 215], open label trials [216, 217] and randomized placebo-controlled trials [218, 219]. The first randomized placebo-controlled crossover trial of MTP in 13 apathetic AD patients found modest but significant improvements in the active treatment group following 5 weeks (2 weeks in each treatment arm with a 1-week wash-out period) [218]. Further evidence for the use of psychostimulants in the AD population was established in the Apathy in Dementia Methylphenidate Trial (ADMET). In this phase 2 parallel-group, double-blind, randomized controlled trial (RCT) to evaluate the efficacy and safety of MTP for the treatment of apathy in 60 AD patients, significant improvements were observed in the active drug group compared with placebo following 6 weeks [219]. A larger 6-month trial of MTP (ADMET2), aiming to randomize 200 patients is currently underway. Evidence of the benefit of other psychostimulants, including dextroamphetamine and modafinil, is less consistent and have not been studied extensively in RCTs [220]. DA agonists, such as amantadine [221-225] and bromocriptine [226-229], have not been studied specifically in AD patients but demonstrated promise in other clinical populations.
Figure II. Methylphenidate mechanism of action. MTP binds DAT and NET to block reuptake of DA and NE into the presynaptic terminal, resulting in increased concentrations of these neurotransmitters in the synapse.

1.3.8 Attention and Apathy

The link between apathy and attention is apparent considering that the pharmacotherapies for apathy described above also modulate attention. Restoring cholinergic activity via ChEIs has produced modest improvements in memory and overall function in AD patients [230-232]. Interestingly, galantamine, a ChEI that additionally stimulates the nicotinic receptors, showed positive effects on attention in RCTs of AD patients [233-235]. As nicotinic ACh receptor activity has been shown to regulate DA release [236-238], it was then proposed that
galantamine’s additional association with the DA system may contribute to its benefit for behaviour symptoms such as apathy [239-241].

Psychostimulants are the preferred pharmacotherapy for the treatment of attention deficit hyperactive disorder (ADHD) and has been shown to improve attention in younger populations [242-244]. The DA and NE systems have connections throughout the prefrontal and limbic areas and are important in modulating attention, arousal and emotion [245-247], components which may be disordered and subsequently lead to apathy. In particular, DAergic neurons make projections to attention networks in the brain, including apathy associated regions in the frontal lobe [248-250]. Thus, increasing neurotransmission of DA and NE in these brain regions through MTP may mitigate apathy in AD patients by modulating their attention. Specifically, the interaction between midbrain DAergic limbic pathways and the motor striatum, occurring indirectly through several circuits, work to link motivation with motor outcomes [251].

The regulation of both motivation and attention through the actions of DA [252, 253] may signify that attention and apathy are operating under similar mechanisms. In a RCT of AD patients, MTP improved both apathy and selective attention [219]. Lanctôt et al [254] used a dextroamphetamine drug challenge to probe the function of the DA system in apathetic AD patients. Compared with non-apathetic patients, patients with apathy had reduced feelings of positive effects after a single dose of drug, suggesting response to DAergic agents was blunted by apathy. Interestingly, the patients who demonstrated inattention in response to dextroamphetamine showed improvements in apathy in a trial of MTP to treat their apathy symptoms [218]. This suggests that attention may be a predictor of apathy treatment response. In other words, attention, as an indicator of intrinsic DA functioning, might be telling of a patient’s ability to respond to treatment outcomes.
Table 2. Clinical trials assessing methylphenidate for the treatment of apathy in patients with dementia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind randomized controlled trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Rosenberg &amp; Lanctôt et al [219]</td>
<td>n=60 mild to moderate AD</td>
<td>Methylphenidate (20 mg/day) or placebo</td>
<td>6 weeks</td>
<td>NPI apathy ↓ (in MTP compared with placebo)</td>
</tr>
<tr>
<td>*Herrmann et al [218]</td>
<td>n=13 AD</td>
<td>Methylphenidate (20 mg/day) or placebo</td>
<td>2 weeks</td>
<td>AES ↓ (in MTP compared with placebo)</td>
</tr>
<tr>
<td>Open label studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Padala et al [216]</td>
<td>n=23 AD</td>
<td>Methylphenidate (20 mg/day)</td>
<td>12 weeks</td>
<td>AES ↓</td>
</tr>
<tr>
<td>Galynker et al [217]</td>
<td>n=27 AD &amp; VaD</td>
<td>Methylphenidate (10-20 mg/day)</td>
<td>3-14 days</td>
<td>SANS ↓</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease, VaD=vascular dementia, NPI=neuropsychiatric inventory, AES=apathy evaluation scale, SANS=scale for the assessment of negative symptoms
↓ indicates decrease in apathy scores, * indicates studies using apathy as the primary outcome

Apathy may reflect deficits in attention networks that interact closely with frontal cortex functioning. For example, studies have reported links between executive dysfunction and apathy in AD patients [173, 255, 256]. Thus, apathy and attention may have similar neural substrates and mechanisms. Evidence for this premise can be linked with the findings of increased amyloid and tau burden in key frontal areas discussed above [193-198]. Similarly, structural and functional imaging provide data to support this relationship. Results from SPECT studies consistently show hypoactivity in the anterior cingulate gyrus and orbitofrontal cortex of apathetic AD patients [157, 257-262]. Moreover, many studies have controlled for the effects of depression and found distinct anatomical and functional patterns in depressed
compared with apathetic subjects [9-12]. A PET study found similar results using a negative symptoms scale [263]. Additionally, structural MRI studies showed that reduced gray matter volume and white matter (axonal) integrity were correlated with greater apathy severity in the anterior cingulate and frontal regions [264-267]. Neuroimaging data in AD patients also suggests that the different components of apathy are each associated with unique patterns of brain activation and structural changes [11, 268]. Using SPECT, Benoit et al. [11] found that lack of initiative (behavioural 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 [269]. Despite these underlying links, little is known of the connection between apathy and attention in AD. Thus, a closer examination of the processes associated with apathy in AD and the involvement of attention will lead to better understanding of this syndrome and its treatment.

1.3.9 Visual Scanning in Apathy

As with selective attention, mood symptoms can be studied using eye tracking techniques. Specifically, research in psychiatry have investigated mood congruent attentional biases for emotional images in affective disorders. Eizenman et al [270-273] developed an eye tracking system that monitors real-time point-of-gaze while allowing for free head movements. The paradigm involves presentation of multiple visual stimuli that compete for the viewer’s attention while monitoring the viewer’s point-of-gaze. Analysis of visual scanning patterns provide a set of measurements that can be used to characterize attentional biases. They applied this paradigm to study the visual scanning behaviour of depressed patients in the presence of
dysphoric (negatively valenced) and social (positively valenced) images [270]. The results showed that depressed patients fixated more on dysphoric images compared with their non-depressed counterparts, indicating a clear attentional bias associated with the disorder. Additionally, the data suggested that healthy controls spent more time on social images compared with patients. More recent studies employing the same methodology observed similar results [274-276]. A meta-analysis [276] found that compared with non-depressed controls, depressed patients maintained longer total fixations on dysphoric and shorter durations on positive images, with medium to large effect sizes reported. The pooled analyses also found greater bias for threatening stimuli in patients with anxiety. Interestingly, a study that additionally examined treatment outcomes found that remitted depressed people had gaze durations for positive stimuli which were comparable to non-depressed healthy controls [275]. Alternatively, attentional biases towards dysphoric images were higher in both currently and remitted depressed subjects compared with controls.

The effect of apathy was not considered in those studies. Symptoms of social disinterest and emotional blunting, the defining components of apathy, suggest that apathy may be a factor in influencing the visual response to social or positive-themed stimuli. With regard to AD, where apathy is particularly prevalent, few studies have sought to characterize visual scanning behaviours associated with these symptoms. While viewing emotional faces, AD patients spent less time fixating on regions of interest, particularly the face and eyes, and were more focused on irrelevant aspects of the images compared with elderly controls [277]. In another eye tracking study, Daffner et al [278] found that apathetic AD patients demonstrated less interest in novel (incongruous) visual stimuli and distributed their overall viewing time evenly among all types of stimuli compared with non-apathetic patients. Furthermore, greater apathy was correlated with reduced novelty P3 amplitude [279]. These findings suggest that visual
scanning methods can be applied not only to measure cognitive domains, such as selective attention and working memory, but also neuropsychiatric symptoms in dementia. A key advantage of employing passive viewing tasks is the ability to overcome stress related to cognitively-demanding tests, [280, 281] as well as physical limitations typical in elderly populations. This technology represents a tool not only for direct measurements of visual scanning behaviour, but also allows the study of attentional bias in a more naturalistic manner.

1.4 Research Hypotheses and Rationale

1.4.1 Study 1

**Hypothesis 1:** Alzheimer's disease patients will demonstrate reduced attentional bias towards novel stimuli compared with cognitively healthy elderly controls.

**Hypothesis 2:** Increased attentional bias towards novel stimuli will be associated with higher scores on standard tests of attention.

**Rationale:** 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 continue to worsen linearly with disease severity [52, 53, 55-57]. Specific impairments in visual attention have been observed in mild AD [50, 282, 283] as well as those in the pre-dementia stages [284, 285]. Finke et al [81] proposed a brain mechanism-based account of visual selective attention deficits, where damage within parietal regions and intrinsic fronto-parietal 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, has been associated with memory and attention [105-107]. Implicit tasks of novelty preference using eye tracking
technology have been investigated in nonhuman primates and human infants. The 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 [132, 133, 286, 287]. In contrast, patients with MCI have demonstrated diminished novelty preference [105, 106, 134]. Thus far, the degree of deficits in novelty preference specific to AD have yet to be quantified. In an earlier study, Daffner et al [278] found that a subset of AD patients spent less time viewing irregular (novel) line drawings compared with age-matched controls [131, 278]. Additionally, the novelty P3 event-related potential, described as the brain response associated with allocation of attention to novel events [288], is significantly reduced in AD patients [279]. Thus, AD patients will likely demonstrate reduced time spent on novel items as a function of their memory and attention deficits.

1.4.2 Study 2

**Hypothesis 3:** Reduced attentional bias for novel stimuli will be associated with greater deterioration in cognition over two years in Alzheimer’s disease patients.

**Rationale:** Evidence suggests that the assessment of attention may be of value in predicting disease progression in the early stages of dementia [289-291]. Using the VPC task, reduced novelty preference was found to be associated with increased risk of converting to dementia in MCI patients, as well as conversion to MCI in cognitively intact elderly [106]. Novelty signals in the brain have been associated with activity in neurotransmitter systems, in particular, ACh and DA [135]. Neurotransmitter dysfunction is also characteristic of the Alzheimer’s disease pathology [141-143]. Early dysfunction in novelty preference may reflect underlying
pathophysiological events, including neurotransmitter dysfunction, which would accelerate the deterioration process. Thus, a novelty preference visual attention paradigm can be applied to predict longitudinal changes in cognition.

1.4.3 Study 3

*Hypothesis 4:* Attentional biases toward social or positively themed stimuli will be reduced in apathetic compared with non-apathetic Alzheimer’s disease patients.

*Rationale:* Apathy, characterized by reduced motivation, social disinterest and emotional blunting in the absence of mood-related changes [145, 146], is the most frequently occurring symptom in AD [150, 154, 292]. 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 [9, 267]. Eizenman et al [270] developed a non-verbal methodology to determine attentional biases in depressed patients through the measurement of visual scanning behaviour. They found that, compared with non-depressed controls, young depressed patients fixated longer on dysphoric or negatively valenced images, but spent less time fixating on social images. Furthermore, non-depressed controls fixated on social images more compared with depressed patients, indicating a clear attentional bias associated with mood disorders. Another research group applied the same methodology and observed that strong biases for dysphoric images were sustained for a 30-second duration [293]. 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 demonstrate the attentional bias for social-themed images seen in non-apathetic people.
1.4.4 Study 4

**Hypothesis 5:** Improvement in apathy symptoms will be associated with increased attentional bias towards novel stimuli.

**Hypothesis 6:** Improvement in apathy symptoms will be associated with increased attentional bias towards social themed stimuli.

**Rationale:** Apathy has been associated with the mesocorticolimbic DAergic pathway [294] and psychostimulants, which work by increasing DA and NE levels, have demonstrated efficacy in improving symptoms [216, 218, 219]. Clinically, methylphenidate, a DAergic agent, improved apathy as well as selective attention in a randomized placebo-controlled trial of dementia patients with apathy [295]. Psychostimulants such as methylphenidate may be modulating both apathy and attention via a common pathway. Thus, improvements in apathy symptoms may accompany improvements in novelty processing. Additionally, increased bias towards social stimuli with methylphenidate, suggesting greater social interest, may be a marker of apathy improvement.
Chapter 2

Selective Attention towards Novel Stimuli in AD

2.1 Materials and Methods

2.1.1 Participants

Participants with AD were recruited from outpatient clinics at Sunnybrook Health Sciences Centre (SHSC). Eligibility 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) [13] and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [296], minimum age of 65, no change in anti-dementia medications for at least 1 month prior to study day and mild to moderate impairment (sMMSE ≥ 10). Elderly controls were either caregivers accompanying patients (frequently a spouse) or recruited from the community. Inclusion criteria for elderly controls consisted of a minimum age of 65, no current diagnosis of dementia, sMMSE ≥ 26 and no evidence of a psychiatric disorder according to the Modified Mini Screen [297] (MMS < 6).
Table 3. Eligibility criteria

<table>
<thead>
<tr>
<th>Control</th>
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<tbody>
<tr>
<td>➢ Minimum 65 years of age</td>
</tr>
<tr>
<td>➢ No indication of psychological disturbances (MMS &lt; 6)</td>
</tr>
<tr>
<td>➢ No diagnosis of AD or other cognitive impairments (sMMSE ≥ 26)</td>
</tr>
<tr>
<td>➢ No presence/history of neurological illnesses or traumatic brain injury</td>
</tr>
<tr>
<td>➢ No significant eye pathology</td>
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<table>
<thead>
<tr>
<th>Alzheimer’s Disease</th>
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<tbody>
<tr>
<td>➢ Minimum 65 years of age</td>
</tr>
<tr>
<td>➢ Diagnosis of possible/probable AD (DSM-IV-TR and NINCDS-ADRDA criteria)</td>
</tr>
<tr>
<td>➢ sMMSE ≥ 10</td>
</tr>
<tr>
<td>➢ No presence/history of other neurological illnesses or traumatic brain injury</td>
</tr>
<tr>
<td>➢ No change in anti-dementia medications less than 1 month prior to study day</td>
</tr>
<tr>
<td>➢ No significant eye pathology</td>
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</table>

2.1.2 Procedures

This was a cross-sectional study. Participants and caregivers provided information regarding age, ethnicity, level of education, current medications, medical and psychiatric history. All participants were administered the Wechsler Adult Intelligence Scale (WAIS) - Digit Span (DS) [298] and sMMSE [299] and the controls were administered the MMS [297]. Following these tests, both controls and dementia patients underwent the VAST procedures. Before initiation of procedures, patients were screened according to the eligibility criteria. The study purpose, procedures, risks and benefits were verbally explained to participants and caregivers. Participants were given time to read the informed consent form and ask questions to the study personnel. Written informed consent was provided by all participants or in the case that patients could not provide consent, a legally authorized representative (caregiver) signed the
forms. This study was approved by the Sunnybrook Research Institute (SRI) research ethics board.

2.1.3 Neuropsychological Assessments

*Standardized Mini-Mental State Examination*

The sMMSE [299], a more systematic and reliable version of the original MMSE [300], was used to describe severity of cognitive impairment. This 10-item scale, administered directly to AD patients, measured domains such as orientation, memory, attention and language abilities. Total scores may range from 0-30, with higher values indicating better cognitive function.

*Wechsler Adult Intelligence Scale - Digit Span*

The WAIS-DS [298] is valid tool for the assessment of working memory and auditory attention. Sequences of digits were read and patients were required to repeat them in the same (forward, DSF) or reverse (backward, DSB) order. DSF is thought to be a measure of selective attention while it has been suggested that DSB may reflect executive functioning [301]. One point was given for each correct sequence and the test was terminated when patients were unsuccessful on two trials of the same sequence length. The forward task consisted of 8 items, 2 trials of the same digit length for each item, with a maximum score of 16. The backward task consisted of 7 items, giving a possible maximum score of 14. Forward and backward scores were combined to establish a total score, which was converted to a scaled score based on standardized age norms.
**Modified Mini Screen**

The MMS [297] is a 22-item scale used to identify individuals whom may exhibit symptoms of mood, anxiety and psychotic disorders. Questions were based on assessment tools such as the Structured Clinical Interview for Diagnosis (SCID) and the Mini International Neuropsychiatric Interview (MINI).

### 2.1.4 Recording and estimating visual scanning parameters

The VAST developed by EL-MAR Inc. (Toronto, Ontario, Canada) was used to record and estimate visual scanning parameters. The technology incorporated a binocular eye tracking system [273] that recorded eye gaze positions and pupil sizes, a display to present visual stimuli, real-time processing algorithms to estimate visual scanning parameters [270, 302] and a monitoring station to control and supervise the progress of the test [272]. The eye tracking system, mounted on the display (a 23” computer monitor with a resolution of 1920 *1080 pixels), consisted of infrared (IR) light sources, IR video cameras and a processing unit that estimated binocular gaze position 30 times/sec with an accuracy of ± 0.5º [273]. The gaze data was processed by algorithms that segmented the data into saccades and fixations on images in each slide and estimated visual scanning parameters [271, 272]. During the test, subjects were allowed to move their heads freely within a relatively large volume (25x25x25 cm³) 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 (less than 30 seconds) participants looked at a series of slides that were presented on the VAST display and their visual scanning patterns and pupil-sizes were recorded. Refer to
Figure III for slide structure. Each slide contained four images that were similar in complexity. Participants sat at a distance of approximately 65 centimetres from the monitor so that the visual angle subtended by each of the four images on each slide was approximately 15.5° x 12.2°. The horizontal and vertical separation between any two images was greater than 2.5°.

**Figure III.** Sample slide structure and sequence of the novelty preference paradigm. The first slide of each set (start) contained 4 novel images. The slide following (1-back) contained 2 novel and 2 repeated images. The final slide of the set (2-back) contained the other 2 images repeated from the start slide and 2 novel images.

### 2.1.5 Visual Stimuli

In this paradigm, each slide contained 4 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 (mismatched items), 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 4 novel images and the 2 subsequent slides contained 2 novel images and 2 images that were repeats of images on the start slide (See Figure III). Repeated images were presented in the same positions on the start slide and on subsequent slides. Each slide was displayed for 10.5 seconds and was followed by 1 second of a uniform grey screen. Thus, the delay between presentations of repeated images was 1 second when the repeated images were presented immediately following the start slide (1-back condition) and 12.5 seconds when they were presented on the second slide that followed the start slide (2-back condition). The 1-second 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 the 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.

2.1.6 Visual Scanning Parameters

Relative fixation time was the primary outcome measure. This parameter has been used previously to characterize visual scanning behaviour of patients with eating disorders [272] and
depression [270] and was 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 relative fixation times on novel and repeated images on a slide. Greater biases (larger differences in relative fixation time) indicate stronger novelty preferences. Additionally, to obtain further insight into differences between the visual scanning behaviour of AD patients and controls in this modified VPC task, the two basic components of relative fixation time: the number of discrete fixations (fixation frequency within images) and the average duration of discrete fixations (average fixation duration in milliseconds) on novel/repeated images for each slide were analyzed. For each participant, relative fixation time (novel – repeat), average fixation duration and fixation frequency within images (for the 1- and 2-back conditions, separately) were determined by calculating the means of these parameters on the corresponding 16 test slides.

2.1.7 Statistical Analyses

Demographic, neuropsychological and visual scanning data were summarized using proportions or mean ± standard deviation (SD). Analyses were conducted using IBM SPSS Statistics 20.0 for Windows (IBM Corp., Armonk, NY). Sample size calculations for all hypotheses were conducted using G*Power 3.1 [303, 304].

Relative fixation time (novel – repeat) was summarized using mean ± standard error of the mean (SEM). Clinical and demographic characteristics were compared between AD and controls using analysis of variance (ANOVA) for continuous variables and $\chi^2$ for categorical variables. To compare the basic component parameters of the relative fixation time of AD and
controls at baseline (i.e., slides with only novel images), one-factorial ANOVAs were performed on average fixation duration and fixation frequency within images per image for start slides. Two-factorial repeated-measures ANOVA models were performed 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 frequency within images per image in both the 1- 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 within-subject conditions (1-back, 2-back), as well as interaction between factors for relative fixation time difference (Hypothesis 1). This model, with up to 2 covariates included, required 38 participants (2 groups of 19) in order to achieve a power of 0.8 and detect medium to large effect size at an α of 0.05. The proportion of participants in each group who displayed any novelty preference behaviour in the paradigm was also calculated. Novelty preference in individual participants was defined as relative fixation time (novel - repeat) greater than 0 in either the 1- 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 (Hypothesis 2). This analysis required a sample size of 44 participants to detect medium to large effect sizes (power = 0.80, α = 0.05). All analyses were considered significant at an α of 0.05 with no corrections made for multiple comparisons.
2.2 Results

The results of this study were published in Dementia and Geriatric Cognitive Disorders Extra (Chau SA, Herrmann N, Eizenman M, Chung J, Lanctôt KL. Exploring visual selective attention towards novel stimuli in Alzheimer’s disease patients. Dement Geriatr Cogn Disord Extra 2015; 5(3):492-502) [305].

Table 4. Participant Characteristics. Values are mean ± SD or n (%). One-factorial analysis of variance tests were completed for age, sMMSE, DS Total, DSF and DSB scores. χ² tests were performed for sex and education. Digit span total were age-corrected scaled scores.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>AD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>76.2 (6.4)</td>
<td>79.2 (6.7)</td>
<td>0.090</td>
</tr>
<tr>
<td>Sex, female</td>
<td>50.0%</td>
<td>46.3%</td>
<td>0.776</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade school</td>
<td>12.5%</td>
<td>24.4%</td>
<td>0.138</td>
</tr>
<tr>
<td>High school</td>
<td>41.7%</td>
<td>31.7%</td>
<td></td>
</tr>
<tr>
<td>Post-secondary</td>
<td>45.8%</td>
<td>43.9%</td>
<td></td>
</tr>
<tr>
<td>Standardized Mini-Mental State</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination</td>
<td>28.1 (2.0)</td>
<td>22.2 (4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digit Span Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>12.1 (4.1)</td>
<td>9.9 (2.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Backward</td>
<td>9.9 (3.2)</td>
<td>9.2 (1.9)</td>
<td>0.279</td>
</tr>
<tr>
<td></td>
<td>7.3 (2.4)</td>
<td>5.2 (2.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease

Forty-one AD patients and twenty-four elderly controls participated. See Appendix A for patient recruitment flow chart. Fifty-two AD patients consented and 11 were excluded (2 cataracts, 5 calibration issues, 4 refused to continue). Twenty-nine healthy elderly provided
consent and 5 were excluded in the final analyses (1 cataracts, 2 psychiatric disorder, 1 calibration issues, 1 refused to continue). Groups were comparable in age, education and sex. Controls performed better on tests of attention and cognition (sMMSE, DS Total, See Table 4).

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 frequency within images ($F_{1,63} = 0.23$, $p = 0.6$) per image (See Table 5). However, in the presence of repeated stimuli, there were significant differences between the visual scanning behaviour of control and AD participants (See Table 5). 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 frequency within images in the 1-back condition. Post-hoc analysis revealed greater fixation frequency 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 were no significant main effect of group for fixation frequency within images. The total number of discrete fixations on all the images on 1-back and 2-back slides are 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. Results for average fixation duration in the 2-back condition were similar.
Table 5. Visual scanning behaviour for controls and AD. Values are mean ± SD. Two-factorial analysis of variance tests were conducted using between-group (control, AD) and within-subject (novel, repeat) factors.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 24)</th>
<th>AD (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start Slide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixation Frequency Within Images</td>
<td>5.4 (0.6)</td>
<td>5.3 (0.7)</td>
<td>0.632</td>
</tr>
<tr>
<td>Average Fixation Duration (msec)</td>
<td>431.8 (66.8)</td>
<td>454.6 (79.8)</td>
<td>0.242</td>
</tr>
<tr>
<td><strong>1-back Slide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixation Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within Images novel</td>
<td>6.3 (0.9)</td>
<td>5.4 (0.8)</td>
<td>0.342 (group)</td>
</tr>
<tr>
<td></td>
<td>4.4 (0.9)</td>
<td>4.9 (0.9)</td>
<td>&lt;0.001 (image type) &lt;0.001 (group X image)</td>
</tr>
<tr>
<td>Average Fixation Duration (msec)</td>
<td>443.5 (51.6)</td>
<td>498.7 (120.3)</td>
<td>0.018 (group)</td>
</tr>
<tr>
<td>Within Images repeat</td>
<td>401.2 (56.4)</td>
<td>442.4 (85.2)</td>
<td>&lt;0.001 (image type) 0.544 (group X image)</td>
</tr>
<tr>
<td><strong>2-back Slide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixation Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within Images novel</td>
<td>5.9 (1.1)</td>
<td>5.3 (1.0)</td>
<td>0.921 (group)</td>
</tr>
<tr>
<td></td>
<td>4.6 (0.8)</td>
<td>5.2 (1.0)</td>
<td>&lt;0.001 (image type) &lt;0.001 (group X image)</td>
</tr>
<tr>
<td>Average Fixation Duration (msec)</td>
<td>442.3 (72.1)</td>
<td>484.1 (130.6)</td>
<td>0.088 (group)</td>
</tr>
<tr>
<td>Within Images repeat</td>
<td>403.2 (63.0)</td>
<td>444.9 (101.4)</td>
<td>&lt;0.001 (image type) 0.999 (group X image)</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease

Analyses of difference in relative fixation time 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 ± 2.4 % more time fixating on novel compared with 1-back repeat images and 9.7 ± 2.2 % more time fixating on novel
compared with 2-back repeat images (Figure IV). AD patients spent 5.3 ± 1.6 % more time on novel compared with 1-back and 3.7 ± 1.5 % more time on novel compared with 2-back images. The ANOVA model revealed 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 ($F_{1,63} = 0.037, p = 0.848$). The relative fixation time difference between 1- and 2-back was comparable for all participants. Overall, within individuals, 100% of controls and 92.3% of patients displayed novelty preference behaviour (relative fixation time mean difference for either 1- or 2-back greater than 0).

**Figure IV.** Relative fixation time difference (%) per slide for 1- and 2-back conditions (mean difference between novel and repeat ± standard error of the mean). Higher values represent preference for novel over repeated images.
Pearson correlations for differences in relative fixation times on novel and repeated images and other neuropsychological measures were performed for all 65 participants (Table 6). Overall, sMMSE and DS total scaled scores were significantly correlated with relative fixation time difference for both 1- 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 relative fixation time difference. In the 2-back condition, sMMSE accounted for 8.3% ($r_{63} = 0.288$, $p = 0.020$) and DS Total accounted for 7.2% ($r_{63} = 0.269$, $p = 0.030$) of the variance in relative fixation time mean difference. When considering the DSF and DSB subscores separately, DSF scores were correlated with relative fixation time 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 relative fixation time 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 ($r_{63} = 0.123$, $p = 0.330$).

**Table 6.** Pearson correlation coefficients between parameters (n = 65).

<table>
<thead>
<tr>
<th>Measure</th>
<th>sMMSE</th>
<th>DS Total</th>
<th>DSF</th>
<th>DSB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Fixation Time Difference (1-back)</td>
<td>0.281*</td>
<td>0.258*</td>
<td>0.271*</td>
<td>0.123</td>
</tr>
<tr>
<td>Relative Fixation Time Difference (2-back)</td>
<td>0.288*</td>
<td>0.269*</td>
<td>0.092</td>
<td>0.383**</td>
</tr>
</tbody>
</table>

Significant correlations: *$p < 0.05$; **$p < 0.01$

sMMSE = Standardized Mini-Mental State Examination; DS Total = Digit Span Total (age-corrected scaled score); DSF = Digit Span Forward; DSB = Digit Span Backward
Chapter 3

Selective Attention towards Novel Stimuli as a Predictor of Cognitive Decline

3.1 Materials and Methods

3.1.1 Participants

AD participants were recruited from an outpatient memory clinic at SHSC. This study included patients diagnosed with possible or probable AD based on the DSM-IV-TR [13] and NINCDS-ADRDA criteria [296]. Eligibility criteria included: no change in anti-dementia medications for at least 1 month prior to study day and mild to moderate cognitive impairment (sMMSE ≥ 10). Furthermore, all eligible patients had no significant eye pathology, severe impairments in communication or diagnosis of other neurological illnesses. Specifically, patients were excluded if they developed any concurrent neurological illnesses, such as stroke, which would result in cognitive decline not related to AD

3.1.2 Procedures

This was a longitudinal study. At the baseline study visit, all participants were administered the sMMSE [299] and the Conners’ Continuous Performance Test (CPT) [306]. 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. As in Study 1, patients were screened according to the eligibility criteria before initiation of VAST procedures. Detailed descriptions of the VAST
procedures and novelty preference visual stimuli paradigm were provided in the previous sections (2.1.4 and 2.1.5). The study purpose, procedures, risks and benefits were verbally explained to participants and caregivers. Participants were given time to read the informed consent form and ask questions to the study personnel. Written informed consent was provided by all participants or in the case that patients could not provide consent, a legally authorized representative (caregiver) signed the forms. This study was approved by the institution’s research ethics board.

3.1.3 Neuropsychological Tests

*Standardized Mini-Mental State Examination*

The sMMSE [299], a more systematic and reliable version of the original MMSE [300], was used to describe severity of cognitive impairment. Total scores may range from 0-30, with higher values indicating better cognitive function. This 10-item scale, administered directly to AD patients, measured domains such as orientation, memory, attention and language abilities.

*Conners’ Continuous Performance Test*

The CPT [306] is a 15-minute computerized test of attention, used widely in attention deficit hyperactivity disorder research. A significant association between higher CPT inattention and greater improvements in apathy in a clinical trial of methylphenidate in apathetic AD patients was previously reported [218]. 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.

### 3.1.4 Visual Scanning 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 two basic visual parameters: average fixation duration and the fixation frequency (described in detail above in section 2.1.6). 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 time to represent novelty preference for each subject. Higher values indicated stronger preferences for the novel images.

### 3.1.5 Statistical Analyses

Baseline demographic, neuropsychological and visual scanning data were summarized using proportions or mean ± standard deviation (SD). Analyses were conducted using IBM SPSS Statistics 20.0 for Windows (IBM Corp., Armonk, NY). Sample size calculations for all hypotheses were conducted using G*Power 3.1 [303, 304].

A multivariate linear regression model with backward elimination was 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). For
this model, 43 subjects were needed to achieve a power of 0.80, \( \alpha \) of 0.05 and \( R^2 = 0.25 \) (Hypothesis 3). Covariates were chosen based on findings suggesting interactions 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 [1, 307].

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 [308]) 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. Patients on different classes of anti-dementia medications (ChEIs versus memantine) were compared in ANOVA models to explore potential associations with novelty preference at baseline.

### 3.2 Results

Thirty-two patients with mild to moderate AD were included in this analysis (See Table 7 for baseline data). Appendix A provides the patient recruitment flow chart. Follow-up sMMSE scores for 34 AD patients were available - 2 were excluded in the final analyses due to occurrence of stroke during the follow-up period. The primary analysis included the most recent score available within the 2-year period for each participant. The mean length of follow-

Table 7. Patient baseline characteristics (n = 32). Values are mean ± standard deviation or proportions.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>77.9 (7.8)</td>
</tr>
<tr>
<td>Standardized Mini-mental State Examination</td>
<td>22.2 (4.4)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56.3%</td>
</tr>
<tr>
<td>Female</td>
<td>43.8%</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
</tr>
<tr>
<td>Grade school</td>
<td>18.8%</td>
</tr>
<tr>
<td>High school</td>
<td>34.4%</td>
</tr>
<tr>
<td>Post-secondary</td>
<td>21.9%</td>
</tr>
<tr>
<td>Graduate</td>
<td>25.0%</td>
</tr>
<tr>
<td>Cognitive Enhancers (%)</td>
<td></td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>75.0%</td>
</tr>
<tr>
<td>Memantine</td>
<td>25.0%</td>
</tr>
<tr>
<td>Conners’ Continuous Performance Test Inattention</td>
<td>534.2 (175.3)</td>
</tr>
<tr>
<td>Difference between Frequency of Fixations on novel and repeat images</td>
<td>0.61 (1.39)</td>
</tr>
<tr>
<td>Difference between Average Fixation Duration on novel and repeated images (msec)</td>
<td>79.8 (108.5)</td>
</tr>
<tr>
<td>Difference between Relative Fixation Times on novel and repeated images (%)</td>
<td>7.0 (8.7)</td>
</tr>
</tbody>
</table>
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).

**Table 8.** 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).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Fixation Time</td>
<td>0.41</td>
<td>2.78</td>
<td>0.010</td>
</tr>
<tr>
<td>Conners’ CPT Inattention</td>
<td>-0.53</td>
<td>-2.88</td>
<td>0.008</td>
</tr>
<tr>
<td>sMMSE Baseline</td>
<td>-0.40</td>
<td>-2.20</td>
<td>0.036</td>
</tr>
</tbody>
</table>

CPT = Continuous Performance Test, sMMSE = Standardized Mini-mental State Examination

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 Figure V). 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 8). 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.
**Figure V.** sMMSE change from baseline versus relative fixation time (novel - repeat). Lower baseline novel relative fixation time predicted greater decline in sMMSE scores (unadjusted values).

Of the 32 AD patients included in the study, 14 had a significant decline in sMMSE scores (≥ 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 interval = 0.55 to 0.90, p = 0.033, Figure VI), indicating moderate ability of this single visual scanning parameter to classify patients into those who did and did not decline. The sensitivity and specificity of various cut-off values for relative fixation time are given in Table 9.
Figure VI. Receiver operating characteristic (ROC) curve for relative fixation time (Area under the curve = 0.72, 95% confidence interval = 0.55 to 0.90, p = 0.033, n = 32).

Table 9. Cut-off values of relative fixation time with sensitivity and specificity.

<table>
<thead>
<tr>
<th>Cut-off Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.26</td>
<td>0.214</td>
<td>0.944</td>
</tr>
<tr>
<td>1.05</td>
<td>0.429</td>
<td>0.889</td>
</tr>
<tr>
<td>5.05</td>
<td>0.714</td>
<td>0.722</td>
</tr>
<tr>
<td>8.67</td>
<td>0.786</td>
<td>0.556</td>
</tr>
<tr>
<td>9.63</td>
<td>0.857</td>
<td>0.444</td>
</tr>
<tr>
<td>11.08</td>
<td>0.929</td>
<td>0.339</td>
</tr>
</tbody>
</table>
There were 24 patients on ChEIs, 4 on memantine monotherapy and 4 not taking any anti-dementia 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 $2.3 \pm 9.0\%$, respectively). 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 ($F_{1,22} = 4.34, p = 0.049$).
Chapter 4

Apathy and Selective Attention towards Positive Stimuli

4.1 Materials and Methods

4.1.1 Participants

Participants were recruited from outpatient clinics at SHSC. Eligibility for AD patients included: diagnosis of possible or probable AD based on the DSM-IV-TR [13] and NINCDS-ADRDA criteria [296], minimum age of 65, no change in anti-dementia medications for at least 1 month prior to study day and mild to moderate cognitive impairment (sMMSE ≥ 10). Apathetic AD patients were additionally required to have significant apathy (NPI apathy subscore ≥ 4 for at least 4 weeks) and no significant depression (NPI depression subscore < 4). The NPI apathy cut-off score of ≥ 4 has consistently been used to define clinically significant apathy [219, 310-312] and represents “often”, “frequent” or “very frequent” apathy of “moderate” or “marked” severity. See Table 10 for full criteria. Patients were excluded if they had significant eye pathology, communicative impairments or other neurological illnesses.

4.1.2 Procedures

This was a cross-sectional study. Participants and caregivers provided information regarding age, ethnicity, level of education, current medications, medical and psychiatric history. The sMMSE [299] was administered to assess cognitive status and the Conners’ CPT [306] was used to evaluate attention. Behaviour disturbances, including apathy were assessed through
interviews with caregivers using the NPI and Apathy Evaluation Scale (AES) [313]. Following these tests, patients underwent the VAST procedures with the social/dysphoric stimuli paradigm. Section 2.1.4 provided a detailed description of the VAST recording procedures. Before initiation of procedures, patients were screened according to the eligibility criteria. The study purpose, procedures, risks and benefits were verbally explained to participants and caregivers. Participants were given time to read the informed consent form and ask questions to the study personnel. Written informed consent was provided by all participants or in the case that patients could not provide consent, a legally authorized representative (caregiver) signed the forms. This study was approved by the SRI research ethics board.

Table 10. Eligibility criteria

<table>
<thead>
<tr>
<th>Alzheimer’s Disease – No Apathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Diagnosis of possible/probable AD (DSM-IV-TR and NINCDS-ADRDA criteria)</td>
</tr>
<tr>
<td>➢ sMMSE ≥ 10</td>
</tr>
<tr>
<td>➢ No significant apathy or depression (NPI subscore &lt; 4)</td>
</tr>
<tr>
<td>➢ No presence/history of other neurological illnesses or traumatic brain injury</td>
</tr>
<tr>
<td>➢ No change in anti-dementia medications less than 1 month prior to study day</td>
</tr>
<tr>
<td>➢ No significant eye pathology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alzheimer’s Disease - Apathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Diagnosis of possible/probable AD (DSM-IV-TR and NINCDS-ADRDA criteria)</td>
</tr>
<tr>
<td>➢ sMMSE ≥ 10</td>
</tr>
<tr>
<td>➢ Significant apathy (NPI apathy ≥ 4)</td>
</tr>
<tr>
<td>➢ No significant depression (NPI depression &lt; 4)</td>
</tr>
<tr>
<td>➢ No presence/history of other neurological illnesses or traumatic brain injury</td>
</tr>
<tr>
<td>➢ No change in anti-dementia medications less than 1 month prior to study day</td>
</tr>
<tr>
<td>➢ No significant eye pathology</td>
</tr>
</tbody>
</table>
4.1.3 Neuropsychological Assessments

See Section 3.1.3 for full description of the sMMSE [299] and Conners’ CPT [306].

*Neuropsychiatric Inventory*

The NPI [314] is a widely used assessment of behaviour disturbances in dementia, including: apathy, agitation, delusions, hallucinations, depression, euphoria, aberrant motor behaviour, irritability, disinhibition, anxiety, sleeping, and eating. Caregivers were asked to judge the frequency and severity of all existing symptoms in the past 4 weeks and in relation to the patient’s behaviour before development of dementia. The frequency score was judged on a 4-point scale from “Occasionally” (1) to “Often” (2) to “Frequently” (3) to “Very Frequently” (4). The severity score was judged on a 3-point scale from “Mild” (1) to “Moderate” (2) to “Marked” (3). The frequency and severity scores were multiplied to generate a composite score, ranging from 0 to 12, for each domain. Total scores range from 1 to 144 with higher scores indicating greater behavioural disturbances.

*Apathy Evaluation Scale*

The AES [315] informant version is a reliable and valid measure of apathy widely used in clinical research. Severity on each of the 18 items was characterized with a 4-point Likert scale using the following descriptions: “Not at All”, “Slightly”, “Somewhat” and “Very Much”. Scores ranged from 18 to 72. Higher values were allocated for stronger presence of specific symptoms and thus, a higher total score indicated greater apathy. As an additional advantage,
this scale also provided subscores for each of the domains of apathy, including behaviour, cognition and emotion [313].

4.1.4 Visual Stimuli

The visual stimuli for this paradigm consisted of a series of slides, each displayed for 10.5 seconds, followed by 1 second of a uniform grey screen. Each slide contained four images of different emotional themes: 1 dysphoric, 1 social and 2 neutral images (Figure VII). 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 vs. 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 vs. calm) between 4 and 6, with a maximum rating difference of 2 to maintain consistency within slides. Neutral images had low 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. The sets of images used in the present study are similar to those used by Eizenman et al [270] 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. These slides were a component of a battery of tests that included measurements for novelty preference (described above) 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 1 dysphoric, 1 social and 2
neutral images were used. The total testing procedure, including novelty preference slides, was divided into 2 sessions of approximately 10 minutes each. In between the 2 sessions the subjects were given a 5-minute break.

Figure VII. Sample format of social/dysphoric paradigm slide. Each slide contained 1 social (bottom left), 1 dysphoric (bottom right) and 2 neutral (top left and right) images. The position of image types were randomly intermixed between slides.

4.1.5 Visual Scanning Parameters

Relative fixation time and fixation frequency within images, parameters used previously to characterize visual scanning behaviour in young patients with eating disorders [272] and depression [270], were the chosen 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 interest in 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 allowed for better comparisons of preferences between specific images within a slide. Fixation frequency described the total count or number of discrete fixations within an image. This was a basic eye movement parameter used in combination with average fixation duration to calculate relative fixation time. Biases were summarized by subtracting mean relative fixation time and fixation frequency on neutral from social and dysphoric images (bias towards social = social – neutral; bias towards 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.

4.1.6 Statistical Analyses

Baseline demographic, neuropsychological and visual scanning data were summarized using counts or mean ± standard deviation (SD). Analyses were conducted using IBM SPSS Statistics 20.0 for Windows (IBM Corp., Armonk, NY). Sample size calculations for all hypotheses were conducted using G*Power 3.1 [303, 304].

Clinical and demographic characteristics were compared between apathetic and non-apathetic groups using ANOVA for continuous variables and $\chi^2$ for categorical variables. Two-factorial repeated-measures analysis of covariance (ANCOVA) models, with up to 2 covariates, were conducted 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 (Hypothesis 4). A sample size of 38 (2 groups of 19) was required to detect medium to large effect sizes (power = 0.80, $\alpha = 0.05$). 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 in Step 2 using a stepwise procedure. All analyses were considered significant at an $\alpha$ of 0.05 with no corrections made for multiple comparisons.

4.2 Results

This work was published in the Journal of Alzheimer’s Disease (Chau SA, Chung J, Herrmann N, Eizenman M, Lanctôt KL. Apathy and attentional biases in Alzheimer’s disease. J Alzheimers Dis 2016; 51: 837-46.) [316].

Thirty-six (19 non-apathetic and 17 apathetic) AD patients with a mean (±SD) age of 78.2 ± 7.8 and a mean MMSE score of 22.4 ± 3.5 were included (Table 11). Appendix A provides the patient recruitment flow chart. 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 (behaviour, cognition and emotion). All participants, including those with significant apathy, had low scores on the NPI depression.
Table 11. Clinical and demographic characteristics. Values are mean ± standard deviation or proportions.

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

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-apatheic patients.

Controlling for differences in overall neuropsychiatric symptoms (NPI), an image (dysphoric vs. social) by apathy (non-apatheic vs. apathetic) interaction (F_{1,32} = 4.31, p = 0.046, \eta^2 = 0.12, power = 0.52) for relative fixation time was found (Figure VIII). 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-apatheic 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 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-apatheic 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-apatheic patients. There was a significant image by apathy interaction (F_{1,32} = 11.34, p = 0.002, \eta^2 = 0.26, power = 0.91, See Figure IX) but no group (non-apatheic vs. apathetic, F_{1,32} = 0.97, p = 0.333) or image (dysphoric vs. social, F_{1,32} = 0.05, p = 0.831) main effects, controlling for group differences in overall neuropsychiatric symptoms (NPI). Compared with non-apatheic 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-apatheic 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 time or frequency.
Figure VIII. 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.

Figure IX. 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 12). The total model accounted for 26% of the variance ($R^2 = 0.26$, Adjusted $R^2 = 0.19$, $F_{3,32} = 3.65$, $p = 0.023$). There were no significant predictors of relative fixation time on social images or fixation frequency and relative fixation time on dysphoric images.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>$\beta$</th>
<th>$t$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sMMSE</td>
<td>-0.62</td>
<td>-3.09</td>
<td>0.004*</td>
</tr>
<tr>
<td>Conners’ CPT Inattention</td>
<td>-0.36</td>
<td>-1.93</td>
<td>0.063</td>
</tr>
<tr>
<td>AES Total</td>
<td>-0.35</td>
<td>-2.09</td>
<td>0.044*</td>
</tr>
</tbody>
</table>

*sMMSE = Standardized Mini-mental State Exam; CPT = Continuous Performance Test; AES = Apathy Evaluation Scale*
Hierarchical regression models with AES behaviour, cognition and emotion entered at Step 2 in the 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 13). 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 $R^2 = 0.24$, $F_{3,32} = 4.62$, $p = 0.009$, $n = 36$). Models for relative fixation time on social images and fixation frequency and relative fixation time on dysphoric images as dependent variables were not significant.

Table 13. 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.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>$\beta$</th>
<th>$t$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sMMSE</td>
<td>-0.56</td>
<td>-3.02</td>
<td>0.005*</td>
</tr>
<tr>
<td>Conners’ CPT Inattention</td>
<td>-0.28</td>
<td>-1.51</td>
<td>0.140</td>
</tr>
<tr>
<td>AES Emotion</td>
<td>-0.41</td>
<td>-2.61</td>
<td>0.014*</td>
</tr>
<tr>
<td>AES Cognition</td>
<td>-0.16</td>
<td>-0.62</td>
<td>0.537</td>
</tr>
<tr>
<td>AES Behaviour</td>
<td>-0.06</td>
<td>-0.30</td>
<td>0.763</td>
</tr>
</tbody>
</table>

sMMSE = Standardized Mini-mental State Exam; CPT = Continuous Performance Test; AES = Apathy Evaluation Scale
Chapter 5

Effect of Methylphenidate for Apathy on Visual Scanning Behaviour

5.1 Materials and Methods

5.1.1 Participants

Participants were recruited from outpatient clinics at SHSC. Patients with clinically significant apathy in which a medication was deemed beneficial by the study physician were recruited for this open label trial of MTP. Eligibility included: diagnosis of possible or probable AD based on the DSM-IV-TR [13] and NINCDS-ADRDA criteria [296] in the mild to moderate stage (sMMSE ≥ 10), no change in anti-dementia medications for at least 1 month prior to study day and significant apathy (NPI apathy subscore ≥ 4 for at least 4 weeks). The NPI apathy cut-off score of ≥ 4 has consistently been used to define clinically significant apathy [219, 310-312] and represents “often”, “frequent” or “very frequent” apathy of “moderate” or “marked” severity. Exclusion for the trial included: current use of antipsychotics, failure of treatment with MTP for apathy in the past, treatment with a medication that would prohibit the safe concurrent use of MTP such as monoamine oxidase inhibitors and tricyclic antidepressants. Patients were also excluded if they had significant eye pathology, communicative impairments or other neurological illnesses.
5.1.2 Procedures

This was an open label trial. Participants and caregivers provided information regarding age, level of education, current medications, medical and psychiatric history. Eligible apathetic patients were prescribed MTP (immediate release formulation, 5-10 mg BID) following their baseline visit. MTP is known to reach peak plasma concentrations after 2 hours and has a pharmacokinetic half-life of 2-3 hours [317]. VAST and neuropsychological assessments were repeated following approximately 4 weeks of treatment. A double-blinded placebo controlled cross-over trial of MTP found benefit for apathy after 2 weeks [218]. In a randomized double-blind placebo controlled trial [219] of MTP in AD patients, improvements in apathy were observed after 6 weeks of treatment. Additionally, increases in selective attention (measured by the WAIS-DS) emerged following 4 weeks and improved further at week 6 in the active treatment group compared with placebo [295]. Thus, 4 weeks of treatment was deemed a suitable duration to observe changes on both apathy and attention measures.

At each study visit, the sMMSE [299] was administered to assess cognitive status. The WAIS-DS was used to assess working memory and auditory attention [298]. Sequences of digits were read and patients were required to repeat them in the same (forward, DSF) or reverse (backward, DSB) order. Behaviour disturbances, including apathy were assessed through interviews with caregivers using the NPI and AES [313]. Details of these tests are available in Section 2.1.3 (sMMSE, WAIS-DS) and 4.1.3 (NPI, AES). Following this battery of tests, both controls and dementia patients underwent the VAST procedures with both the novelty preference and social/dysphoric stimuli paradigm. Section 2.1.4 provides a detailed description of the VAST recording procedures.
Before initiation of procedures, patients were screened according to the eligibility criteria. The study purpose, procedures, risks and benefits were verbally explained to participants and caregivers. Participants were given time to read the informed consent form and ask questions. Written informed consent was provided by all participants or in the case that patients could not provide consent, a legally authorized representative (caregiver) signed the forms. This study was approved by the SRI research ethics board.

5.1.3 Visual Stimuli

Specific details of the novelty preference and social/dysphoric stimuli were provided in section 2.1.5 and 4.1.4, respectively. The visual stimuli consisted of slides displayed for 10.5 seconds each, followed by 1 second of a uniform grey screen. Ten filler slides were used at the beginning of the presentation to familiarize subjects with the presentation set-up. The novelty preference stimuli comprised of a series of slides each containing four images simultaneously presented. All four images had similar complexity and IAPS rating for valence and arousal. Two images on each slide were novel and two were repeats of images that were shown previously - 1-back and 2-back repeats were tested. The four images on each slide were arranged 2 by 2, with the position of the novel stimuli and previously shown stimuli randomly intermixed. There were 16 of these slide series for a total of 48 slides presented in this portion of the test. The visual stimuli for the social/dysphoric paradigm comprised of a series of slides each containing four images (1 dysphoric, 1 social and 2 neutral images), selected from the IAPS collection. A total of 16 slides were presented. In this slide series, images were chosen from the IAPS ratings for valence (feelings of pleasure vs. displeasure): neutral images had medium valence, social images had high valence and dysphoric images had low valence.
ratings. Additionally, the social and dysphoric images on each slide had similar IAPS ratings of arousal (feelings of excitement vs. calm). The four images on each slide were arranged 2 by 2, with the specific spatial position of each theme randomly inter-mixed. There were 16 test slides presented in this portion of the test. The total testing procedure, including both novelty preference and social/dysphoric slides (106 total slides), was divided into 2 sessions of approximately 10 minutes each. In between the two sessions the subjects were given a 5-minute break.

5.1.4 Visual Scanning Parameters

The visual scanning parameters used in this study were the number of discrete fixations on each image (fixation frequency within images) and the ratio of total duration of discrete fixations on novel images relative to total duration of fixations on all images of a slide (relative fixation time). These parameters were investigated in previous sections of this thesis. Novelty preference was estimated by subtracting the values of relative fixation time and frequency 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 (both duration and frequency parameters) for the 1-back and 2-back conditions were then added in order to obtain a single value to represent novelty preference for each subject. Higher values indicated stronger preferences for the novel images. Social biases were summarized by subtracting mean relative fixation time and fixation frequency on neutral from social images (bias towards social = social – neutral). For each participant, biases for social images were determined by calculating the means of these parameters on the 16 relevant test slides.
5.1.5 Statistical Analyses

Baseline and treatment scores on neuropsychological and psychiatric tests were compared using two-tailed paired Student’s t-tests. Spearman correlations were conducted to explore associations between change in visual scanning behaviour (treatment - baseline) and AES scores (treatment - baseline). Relative fixation time and frequency on novel images were used to examine the effect of MTP on novelty preference (Hypothesis 5). To explore the relationship between change in apathy and novelty preference with standard tests of attention/working memory, further correlations were conducted for AES, fixation parameters and DS scores (Total, Forward and Backward). Relative fixation time and frequency on social images were used to analyze treatment effects on processing of positive stimuli (Hypothesis 6). As in Study 3, exploratory analyses were performed to examine the distinct relationship between each AES subdomain and attentional bias for positive stimuli. A sample size of 20 would be required to detect large effect sizes (power = 0.80, $\alpha = 0.05$). Spearman correlations were also conducted to explore baseline predictors of change in apathy (AES). To examine whether apathy remission was associated with different attentional bias patterns, patients were categorized into groups based on change in NPI apathy scores. Remitters or treatment responders were defined as patients who had an NPI apathy score decrease below 4 following treatment and non-remitters were those who maintained scores above or at 4. Two-factorial repeated-measures ANOVA models were employed to explore within-subject effects of MTP (baseline, follow-up), between group effects (remitter, non-remitter) and interaction between factors for attentional bias parameters. All analyses were considered significant at an $\alpha$ of 0.05 with no corrections made for multiple comparisons.
5.2 Results

Table 14. Clinical and demographic characteristics (n=8). Values are mean ± standard deviation or proportions.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>76.0 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardized Mini-mental State Exam</td>
<td>21.8 (6.3)</td>
<td>21.0 (7.5)</td>
<td>0.378</td>
</tr>
<tr>
<td>Gender</td>
<td>2 Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, n</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade school</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-secondary</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications, n</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholinesterase Inhibitors</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>22.9 (6.5)</td>
<td>19.9 (13.1)</td>
<td>0.524</td>
</tr>
<tr>
<td>Apathy subscore</td>
<td>7.1 (2.0)</td>
<td>4.8 (3.9)</td>
<td>0.137</td>
</tr>
<tr>
<td>Depression subscore</td>
<td>3.8 (4.1)</td>
<td>2.0 (3.7)</td>
<td>0.247</td>
</tr>
<tr>
<td>Apathy Evaluation Scale</td>
<td>55.8 (8.3)</td>
<td>46.6 (18.1)</td>
<td>0.265</td>
</tr>
<tr>
<td>Behaviour</td>
<td>14.6 (2.0)</td>
<td>13.8 (2.2)</td>
<td>0.195</td>
</tr>
<tr>
<td>Cognition</td>
<td>25.3 (4.1)</td>
<td>24.3 (2.9)</td>
<td>0.465</td>
</tr>
<tr>
<td>Emotion</td>
<td>6.1 (1.0)</td>
<td>6.3 (1.6)</td>
<td>0.732</td>
</tr>
<tr>
<td>Digit Span Total Scaled</td>
<td>9.8 (2.9)</td>
<td>10.1 (4.2)</td>
<td>0.612</td>
</tr>
<tr>
<td>Forward</td>
<td>9.3 (2.2)</td>
<td>9.1 (2.4)</td>
<td>0.879</td>
</tr>
<tr>
<td>Backward</td>
<td>5.0 (2.1)</td>
<td>5.6 (2.9)</td>
<td>0.217</td>
</tr>
</tbody>
</table>

Eight AD patients with clinically significant apathy, as determined by the study psychiatrist, were treated with methylphenidate (5-10 mg BID). Appendix A provides the patient recruitment flowchart. In this study, all eligible candidates screened for the open label trial participated and were included in the analyses. The mean follow-up length was 6.1 ± 4.6 weeks.
and the average dose of the 8 patients was 15 mg per day. No patients experienced adverse events during treatment. On average, patients had numerical decreases in apathy test scores (AES and NPI apathy), though these changes were not statistically significant. Four patients remitted based on NPI apathy scores (baseline NPI apathy at least 4 and follow-up scores decreased to below 4) and 4 patients did not respond to treatment (no change in scores). There were also small decreases in overall behaviour and depressive symptoms (Table 14).

**Table 15.** Spearman correlation coefficients between changes in novelty preference parameters and apathy (n = 8). Attentional bias values were novel minus repeat for both 1- and 2-back images.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Change in Relative Fixation Time on Novel Images</th>
<th>Change in Fixation Frequency Within Novel Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in AES</td>
<td>-0.583</td>
<td>-0.786*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant correlations: *p < 0.05
AES = Apathy Evaluation Scale

Spearman correlations showed that baseline to follow-up improvements in apathy on the AES was significantly associated with increase in fixation frequency on novel images ($\rho_6 = -0.786$, $p = 0.021$, Table 15). Additional correlations were conducted to examine the relationship between changes in selective attention/working memory, novelty preference and apathy. Changes in DSB scores trended towards significant correlations with change in relative fixation time ($r_6 = 0.660$, $p = 0.075$), fixation frequency ($\rho_6 = 0.672$, $p = 0.068$) and apathy ($\rho_6 = -0.669$, $p = 0.070$, Table 16). Specifically, increase in fixations (both duration and frequency) on novel images was associated with improved DSB scores. Improvements in apathy on the
AES were also associated with improvements in DSB. There were no significant or trending relationships with DSF scores.

Exploratory analysis showed that remitters had a numerically larger, though statistically non-significant, increase in time spent on novel images compared with the non-remitted group (group main effect: $F_{1,6} = 1.70, p = 0.240$, treatment main effect: $F_{1,6} = 1.77, p = 0.231$, group x treatment interaction: $F_{1,6} = 3.42, p = 0.114$, Figure X). Remitters had a relative fixation time on novel images of $10.5 \pm 11.6\%$ at baseline and $12.0 \pm 16.6\%$ following treatment. Non-remitters had a relative fixation time on novel images of $6.3 \pm 7.6\%$ at baseline, which decreased to $-3.1 \pm 6.3\%$ following treatment. Thus, patients who did not respond to apathy treatment switched their attention towards repeated images post treatment.

### Table 16. Spearman correlation coefficients between changes in novelty preference parameters, apathy and attention (n = 8). Attentional bias values were novel minus repeat for both 1- and 2-back images.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Change in Relative Fixation Time on Novel Images</th>
<th>Change in Fixation Frequency Within Novel Images</th>
<th>Change in AES Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in DS Total</td>
<td>0.417</td>
<td>0.135</td>
<td>-0.340</td>
</tr>
<tr>
<td>Change in DSF</td>
<td>0.099</td>
<td>-0.284</td>
<td>0.079</td>
</tr>
<tr>
<td>Change in DSB</td>
<td>0.660†</td>
<td>0.672†</td>
<td>-0.669†</td>
</tr>
</tbody>
</table>

Trending correlations: †$p < 0.1$

AES = Apathy Evaluation Scale; DS Total = Digit Span Total (age-corrected scaled score); DSF = Digit Span Forward; DSB = Digit Span Backward
Figure X. Mean relative fixation time on novel images with standard deviation bars for apathy remitters (n=4) and non-remitters (n=4) following methylphenidate treatment.

Spearman correlation analyses were also used to determine associations between changes in apathy scores and attentional bias towards positive or social themed images. There were no significant correlations between changes in relative fixation time or fixation frequency on social images (social – neutral) and improvements in apathy scores (Table 17). However, exploratory analyses suggested that improvement in apathy symptoms on the AES was associated with lower baseline attentional bias for social images, measured by both relative fixation time ($\rho_6 = 0.786, p = 0.021$) and frequency ($\rho_6 = 0.872, p = 0.006$, Table 18). Further, there was a trending correlation between lower baseline attentional bias for social images, both relative fixation time ($\rho_6 = 0.665, p = 0.072$) and frequency ($\rho_6 = 0.665, p = 0.072$), and
improvements in AES emotion domain scores. There were no other baseline predictors of improvement in apathy or attention.

Table 17. Spearman correlation coefficients between changes in attentional bias towards social stimuli and changes in apathy (n = 8). Attentional bias values were social minus neutral images.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Change in Relative Fixation Time for Social Images</th>
<th>Change in Fixation Frequency Within Social Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in AES Total</td>
<td>-0.571</td>
<td>-0.167</td>
</tr>
<tr>
<td>Change in AES Behaviour</td>
<td>-0.073</td>
<td>0.146</td>
</tr>
<tr>
<td>Change in AES Cognition</td>
<td>-0.279</td>
<td>-0.012</td>
</tr>
<tr>
<td>Change in AES Emotion</td>
<td>-0.548</td>
<td>-0.456</td>
</tr>
</tbody>
</table>

Significant correlations: *p < 0.05 †p < 0.1
AES = Apathy Evaluation Scale; DS Total = Digit Span Total (age-corrected scaled score)

Table 18. Spearman correlation coefficients between baseline attentional bias towards social stimuli and changes in apathy (n = 8).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline Relative Fixation Time for Social Images</th>
<th>Baseline Fixation Frequency Within Social Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in AES Total</td>
<td>0.786*</td>
<td>0.862**</td>
</tr>
<tr>
<td>Change in AES Behaviour</td>
<td>0.244</td>
<td>0.146</td>
</tr>
<tr>
<td>Change in AES Cognition</td>
<td>0.424</td>
<td>0.582</td>
</tr>
<tr>
<td>Change in AES Emotion</td>
<td>0.665†</td>
<td>0.665†</td>
</tr>
</tbody>
</table>

Significant correlations: *p < 0.05 **p < 0.01 †p < 0.1
AES = Apathy Evaluation Scale; DS Total = Digit Span Total (age-corrected scaled score)
Chapter 6

Discussion

6.1 Selective Attention towards Novel Stimuli in AD

6.1.1 Discussion of Findings

The goal of this study was to determine whether AD patients demonstrate reduced attention bias towards novel stimuli compared with healthy elderly controls. The associations between attentional bias towards novel stimuli and scores on standard tests of attention were also tested. The 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 [131], which found that AD patients exhibited reduced exploration of novel stimuli. Disrupted neural processing of novelty has been reported in other neurological and psychiatric disease populations. Parkinson's patients have shown increased frontal P3 latency and diminished amplitude in response to novel stimuli [318, 319]. In schizophrenic patients presenting with symptoms of delusions, alterations in frontolimbic functional connectivity were observed during processing of novel stimuli in a visual target detection task [320]. Patients with frontal lobe damage, due to both cortical and subcortical strokes, also show reduced P3 [321, 322] and N2 [323] response to novel stimuli.
The findings in this study were similar to results reported by Crutcher et al [105] using the VPC task. However, there were some key discrepancies that are important to highlight. In that study, the authors found significantly lower fixation times on novel images in MCI compared with controls when the delays between the familiarization and test slides were long (2 minutes) [105]. MCI patients performed similar to controls when the delay was shorter (2 seconds). In the present study, short delays of 1 second and 12.5 seconds invoked differences in novelty preference behaviour between mild to moderate AD patients and healthy elderly controls. This inconsistency might be explained by differences between the patient populations of the two studies and by differences between the testing paradigms. Patients in the present study were more cognitively impaired (MMSE for MCI patients in that study was 27.5 ± 2.8 compared with 22.2 ± 4.0 for AD patients in the present study) and thus, working memory capacity may decay within a shorter period of time. A 2-second delay may not be sufficient to detect limitations in the working memory capacity of MCI patients, who would have more preserved cognitive functions than AD patients. With regard to the methodology, the paradigm used in this study allotted longer viewing times (10.5 seconds) in contrast to the 5 seconds allowed in Crutcher et al [105]. This was done in order to integrate differences in visual scanning behaviour over longer time periods and improve the signal to noise ratio of the estimated visual scanning behaviour parameters. This, thereby, enhanced ability to detect differences between groups. Visual scanning patterns of MCI patients may begin to differentiate between healthy controls with extended observation durations. As it has been suggested that short-term and working memory are limited to 12-30 second durations [63], the 2-minute delay period used by Crutcher et al may in fact be accessing more long-term based memory capacities.

Interestingly, the data 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- and 2-back repeat images, respectively. Even though novelty preference behaviour was reduced when compared with age-matched controls, the paradigm described in this paper was sensitive enough to detect selective attention towards novel stimuli in 92% of the AD patients. Furthermore, as the 1-back repeats immediately preceded the 2-back repeats, 1-back stimuli functioned as a distractor for the 2-back stimuli. As there was no significant condition main effects, relative fixation times on novel images were comparable for both 1-back and 2-back. Thus, novelty preference was largely preserved in controls even in the presence of distracters within the 12.5-second time-frame (2-back condition). While AD patients had lower novelty preference compared with controls, presence of distracters did not significantly reduce their performance further. While the VPC paradigm typically contained slides with only 2 images simultaneously presented, VAST displayed 4 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 [50], displaying more images on a slide will increase the differences between the visual scanning behaviour of cognitively impaired patients and cognitively healthy controls. The more complex stimulus structure in this paradigm may be more reflective of real-world conditions where the brain must continually process and filter several competing visual inputs in the visual environment.

The underlying mechanisms of novelty preference may involve both selective attention and working memory. EEG studies have found ERP signals in the frontal and parietal lobes during the stages of novelty processing [99-101]. fMRI studies have found reduced neural activation in frontal and temporal regions following repeated exposure to a particular stimuli, now referred to as repetition suppression [46-49, 107, 116, 117]. Both temporoparietal and frontoparietal networks have been linked with visuospatial attention [46-49] and working memory functions [80, 83-85]. Furthermore, these brain regions have been found to have
greater atrophy [37, 39, 40] and reduced activity [41-45] in AD patients. The results from the correlation analyses provide further support for the links between novelty preference and selective attention and working memory. Specifically, significant associations were found between greater relative fixation time on novel images and higher cognitive status, as well as selective attention and working memory. Furthermore, the 1- and 2-back conditions were correlated with different subtests. The results showed 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 and working memory [301, 324], 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.

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 DA and NE systems [295, 325], disrupted this behaviour [326, 327]. 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 DAergic tone [328]. 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 DA and NE activity, via
methylphenidate, improved selective attention and symptoms of apathy in AD patients [295]. Furthermore, ChEIs, the first-line pharmacotherapy for treatment of cognitive symptoms in AD, have been shown to modulate visual selective attention [329, 330].

6.1.2 Limitations

There are some limitations to consider when interpreting the results of this study. Although the novelty preference 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 preference behaviour, which may have genetic underpinnings [331, 332], might also be a factor in the expression of bias towards novel images. These characteristics could have confounded results and likely accounted for the relatively large standard deviations in the mean visual scanning parameters. Although the healthy elderly controls recruited in this 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 [333]. Thus, the potential effects prodromal dementia may have on visual scanning behaviour in the control sample could not be accounted for in this case.

Some considerations should also be given to the strengths and weaknesses of the standard tests of attention and cognition used in this study. Given that the WAIS-DS and sMMSE independently accounted for up to only a small amount of the variance in the Pearson correlation analyses, other domains of attention and cognition 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. The
sMMSE and WAIS-DS were administered by several research staff, which may introduce confounding factors due to inter-rater variability. The DS required administrators to read aloud a series of digits, adhering to a rhythm of 1 digit per second. Tempo may differ between raters and may even differ within each rater at different time points in the study. This may influence patient performance. For example, random short and long delays between clusters of digits might facilitate better attention and memory for a select cluster. However, it should be noted that in this study, all research staff received training and practice on administering this test in a standardized manner. Additionally, within an elderly population, auditory perception may not be optimal, resulting in difficulty hearing and concentration on the task. Thus, poor performance might be due to physical disability and would not truly reflect attention deficits.

6.1.3 Significance

In summary, reductions in biases towards novel images differentiated cognitively intact from mild to moderate AD patients, and was associated with standard measures of attention and cognitive status. This study established that measurements of visual scanning behaviour can be used to differentiate cognitively impaired patients and cognitively intact elderly. As communication becomes increasingly difficult as the disease progresses, non-verbal methods will provide an alternative means of evaluating symptoms. Other measures of visual selective attention and working memory, such as the Stroop [59] and n-back [71] respectively, require specific instructions and button presses as a measure of performance. In addition to deficits in cognition, reduced motor function typical in the elderly [334] may further amplify the difficulty of these tasks. The methodology in this study may offer a less cognitively-
demanding, non-verbal and more naturalistic method of assessing visual selective attention in the dementia population.

6.2 Selective Attention towards Novel Stimuli as a Predictor of Cognitive Decline

6.2.1 Discussion of Findings

In this study, selective attention towards novel stimuli as a predictor of longitudinal changes in cognition was investigated. The results suggest that novelty preference, measured by visual scanning behaviour, 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 findings were not unexpected as deficits in attention and executive function have been associated with greater cognitive deterioration [50, 289]. Furthermore, studies have found higher rates of disease progression in patients with greater initial cognitive impairment, indicated by the lower MMSE scores [335-337]. Results of the present study 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. Using the VPC, Zola et al [106] showed that reduced novelty preference was associated with greater risk of conversion to MCI in healthy elderly or to AD in MCI patients. The analyses combined both groups and the authors did not report subgroup analyses for conversion to MCI and AD separately. Significant effects were found for percent fixation time on novel images.
using a 2-minute delay interval between familiarization and test phases. As discussed above, the 2-minute delay may be accessing more long-term memory processes compared with the short delay paradigm used in this study. However, those results largely agree with findings from the present on relative fixation time. Visual scanning can provide important information with regard to disease progression.

Altered activity of neurotransmitter systems, elements of the AD pathogenesis, may generate early deficits in selective attention towards 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 [338]. 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 [339]. 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 [340]. Pharmacological manipulation of the cholinergic system, including the use of ChEIs, has been shown to modulate novelty processing. For example, rivastigmine was found to enhance the novelty P3 ERP in response to novel sounds [137], while the anticholinergic agent scopolamine reduced frontal P3 response to both infrequently occurring visual [341] and auditory stimuli [342]. Furthermore, scopolamine attenuated repetition suppression effects, reducing differences between the fMRI hemodynamic responses towards novel and repeated stimuli in frontal and extrastriate brain regions [343]. 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, in this study, 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 [233, 235]. Consistent with these results, other groups have found that galantamine blunted repetition suppression in mesolimbic areas of healthy adults in a fMRI study [136] and shifted novelty signals from the medial temporal lobe to the prefrontal cortex in a magnetoencephalography study [140]. 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 [138, 139]. 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 [138, 139]. There is also evidence that DA can modulate ACh neurotransmission in AD patients, establishing a functional relationship between two systems associated with dementia [344]. Furthermore, psychostimulants, drugs which amplify DA and NE, have been shown to improve cognitive functions, including attention in patients with AD [295], Parkinson’s disease [345] and ADHD [242]. 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 behaviour [346]. fMRI studies in humans [97, 347, 348] have linked novelty processing with mesolimbic structures, integral components of DA-associated pathways. Bunzeck et al [136] 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.
Levodopa also increased the onset of ERPs in the medial temporal lobe in response to novel scenery [140]. 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 [135]. In contrast, inconsistent results have been found regarding the connection between DA and the later processing of novel stimuli. Pharmacological manipulation of DA activity does not appear to affect the P3 ERP, a later component of the novelty signal [349, 350]. In an EEG experiment, Mikell et al [351] observed increases in N2 amplitude but no change in P3 in Parkinson’s patients ON versus OFF medication. Thus, Rangel-Gomez and Meeter [135] suggested 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 [352, 353]. However, facilitation of GABAergic activity via the GABA-A agonist thiopental also led to attenuation of these event-related potentials in healthy adults [352]. The role of 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 [354]. However, decreased 5-HT 2a receptor function was associated with a weaker response to novel stimuli in the hippocampus [355]. Given that NE is a direct analog of DA as well as its strong reciprocal interaction with ACh [356], NE may also be an important
factor in novelty preference behaviour [357]. Additionally, NE is known to mediate selective attention [358, 359] and may be an important factor of the neural basis of the P3 component [360]. Overall, deficits in the processing of novel stimuli may signify neurochemical changes related to underlying pathophysiological events typical of AD.

### 6.2.2 Limitations

Several limiting factors should be taken into consideration when interpreting the findings of this study. The analyses were limited by sample size. *A priori* power calculations for a linear regression with up to 5 covariates indicated that 43 subjects were required to detect large effect sizes (power = 0.80, $\alpha = 0.05$). However, in the backward regression models, no more than 3 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 $\alpha$ 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.

While the sMMSE, the dependent variable in this study, is a widely used screen for cognitive impairments [361, 362], it is not a comprehensive test of cognition [363, 364]. Typically, floor effects are associated with lower education [307] and gender [365] while ceiling effects are observed in MCI [363, 364] and highly educated individuals [366]. Furthermore, variability in scores within individuals represents another confounder [367]. Adding more extensive cognitive batteries would be an interesting next step in this line of research. The ADAS-Cog [368], the standard outcome measure in clinical trials of AD treatment, should be considered. However, because of recent failures of drugs to improve ADAS-cog scores in RCTs,
researchers have questioned whether this scale is sensitive to subtle changes in the mild range of disease severity. Indeed, studies have demonstrated ceiling effects in MCI and mild AD patients [369, 370]. This is relevant as the population under study is AD patients with mild to moderate disease severity. Thus, more difficult tests such as the CANTAB can also be included when assessing patients at the mild and prodromal stages. The CANTAB is a computerized visual cognitive battery which assesses domains such as reaction time, spatial working memory and rapid visual information processing. There are batteries assessing core cognition, in addition to ones specific for AD, MCI and ADHD. The overall battery and its subtests are sensitive to age-related decline [371] and has been shown to differentiate MCI and mild AD [372, 373]. This can provide useful information with regard to the relationship between novelty preference and specific domains of cognition.

6.2.3 Significance

Early deficits in selective attention and ability to process or explore salient novel stimuli may be a valuable marker of risk of rapid disease progression. In summary, reduced visual attention towards novel stimuli was associated with greater decline in cognition in AD 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 be a less cognitively-demanding tool to help clinicians identify those most at risk of decline in order to adapt treatment and management plans. Furthermore, these findings may have relevant implications with regard to clinical trial designs. Heterogeneity in disease progression, suggesting different underlying disease mechanisms, can produce variable and unreliable changes on the chosen cognitive outcomes. This may have contributed to the largely
unsuccessful development of disease-modifying treatments for AD. Drug candidates might be exerting distinct effects on the different progression subtypes. Future clinical trials of AD can use various tools, including visual attention, to account for these patient subtypes in order to more accurately evaluate drug efficacy.

6.3 Apathy and Selective Attention towards Positive Stimuli

6.3.1 Discussion of Findings

In this study, visual attentional biases associated with apathy in dementia patients were examined. The results suggest that apathetic patients had decreased attentional bias for social stimuli compared with non-apathetic patients. This behaviour is consistent with the symptoms of social disinterest and emotional blunting characteristic of apathy [145, 146]. Findings from previous eye tracking studies have also shown reduced bias towards social images in young adults with clinical depression compared with age-matched controls [270, 293]. 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 depressed patients. It has been proposed that the mesocorticolimbic DAergic system, thought to mediate incentive salience [374, 375] and reward-motivated behaviours [245, 252, 253], is involved in the expression of apathetic symptoms in patients with AD [294]. A SPECT study found that reduced striatal DA transporter uptake was correlated with greater apathy in dementia patients [204]. 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 towards dysphoric images.
The patient sample used here had low levels of depression based on the NPI depression subscore, which would account for this lack of bias towards dysphoric images.

The linear regression analysis suggested that more severe apathy (measured by AES total) predicted reduced attentional bias towards 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 multicollinearity. The linear regression analyses also indicated that cognition and attention influenced visual scanning behaviour. Given that greater deficits in cognition and attention have been associated with apathy in AD [155, 170, 181, 282], the interplay between apathy, cognition and attention may function to direct visual scanning behaviour 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.

Exploratory analyses of the subtypes of apathy suggested that, in particular, emotional blunting is more relevant with regard to attentional bias towards social images. 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. In a previous study with similar visual stimuli [270], fixation frequency was higher on images with higher valence and arousal. For social stimuli, the increase in fixation frequency due to higher arousal was amplified by the increase in fixation frequency due to higher valence. The combined effect for non-apathetic AD patients was an increased bias towards social images; the mean fixation frequency on social images was 3.4
fixations/image higher on social images than on neutral images. As emotional blunting decreases the effects of valence and arousal on visual scanning parameters, the bias towards social images in patients with apathy was decreased to 2.0 fixations/image. Further, there were no significant predictors of attentional bias towards dysphoric images. The dysphoric stimuli in this study had higher arousal and lower valence compared with neutral images. For dysphoric stimuli, the increase in fixation frequency due to higher arousal are reduced by the decrease in fixation frequency due to lower valence. The combined effect for non-apathetic AD patients was a lower attention bias towards dysphoric stimuli (compared with the bias towards social stimuli). The mean fixation frequency on dysphoric images was 2.7 fixations/image higher than on neutral images. For dysphoric images, emotional blunting attenuated the effects of both higher arousal (i.e. the increase in fixation frequency due to higher arousal was reduced) and lower valence on fixation frequency (i.e. the reduction in fixation frequency due to lower valence was reduced). Thus, the net effect of emotional blunting for dysphoric images was rather small and the bias towards dysphoric images of apathetic AD patients was similar to that of non-apathetic AD patients. For apathetic AD patients the average fixation frequency on dysphoric images was 2.4 fixations/image higher than on neutral images. Thus, diminished response to high valence (positive) stimuli may be an important manifestation of the emotional blunting feature of apathy.

This provides further insight into the reduced bias towards social stimuli previously observed in clinically depressed patients [270, 274-276]. Strong biases for dysphoric stimuli were observed and can be explained by mood-specific symptoms such as sadness, hopelessness and worthlessness. However, apathy was not considered in those studies. By investigating a population with prevalent apathy and reducing the effect of depression in the patient sample, the distinct effect of apathy could be studied. 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 (i.e. social images). These results are consistent with previous imaging findings of different neural activation patterns and structural changes associated with each apathy domain [11, 268]. The domains of apathy may have different pathological mechanisms and influence both cognitive and attentional abilities.

6.3.2 Limitations

Several factors should be considered when interpreting the results of this study. Although this paradigm used many test slides with different items, personal attraction towards particular images within each individual may compete for attentional resources. For example, strong personal interest or preference for particular neutral images may act as distractors and interfere with biases towards images with emotional content. Additionally, patients with cognitive deficits may not have the capacity to interpret the complex emotional themes depicted in the images. Several studies [376-378] have reported impairments in processing and decoding of information with emotional content, including facial expression and scenes, in AD patients. Again, apathy and other non-cognitive features of AD were not considered in those studies. This represents a possible alternative interpretation of the underlying basis of reduced attentional biases for social images found in apathetic compared with non-apathetic patients. Inability to effectively process positive and negative stimuli as well as overall disinterest, may be a component of apathy.

The data might also be limited by sample size. A priori power calculations for the repeated-measures ANCOVA with up to 2 covariates (primary analysis) indicated that 38 patients (19 in each group) were required to detect medium to large effect sizes (power = 0.80, α = 0.05).
However, the repeated-measures ANCOVA model with the current sample size of 36 yielded large effect sizes and power of 0.91 for the fixation frequency parameter. 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, results for two outcome variables (relative fixation time and fixation frequency), which have been used successfully in past studies, were presented [270, 272, 293]. 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 behaviour.

The NPI cut-off scores used to define patients have yet to be psychometrically validated in clinical and research settings. Although NPI depression subscores were low and comparable between the study groups, the cut-off score of 4 has not been validated and may not be clinically relevant. However, this value has previously been used to screen out significant psychosis, delusions and agitation/aggression [219, 295]. Additionally, the NPI apathy subscore ≥ 4 was used to define patients with significant apathy in clinical trials investigating treatments for apathy [219, 295, 310, 312]. A study [145] aimed at estimating the concurrent validity of the proposed diagnostic criteria for apathy used the NPI apathy as a comparator. It was reported that those defined as apathetic under the criteria had a mean NPI apathy of 6.9 ± 3.3, indicating that a cut-off of 4 would fall within this standard deviation range. Overall, these factors could have confounded observations and may have contributed to the relatively large standard deviations in the mean visual scanning parameters.

It should be noted that although apathetic and non-apathetic patients were not matched 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 these findings, others [9, 258, 267, 379, 380] 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 [263] 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 [155, 170, 181, 381]. Thus, future studies with larger target sample sizes should further explore visual scanning behaviour and apathy in more severely impaired patient populations.

6.3.2 Significance

Currently, there are several barriers to the assessment of apathy in the dementia population. In addition to associations with more rapid decline [155, 170, 181, 381], apathy is also linked with higher risk of conversion to AD from MCI [182, 184]. Experts in the field have emphasized the need to identify biomarkers and risk factors of AD in the early and pre-symptomatic stage [382]. 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 [145, 383], which may nevertheless be ambiguous and time-consuming. Furthermore, apathy can often be misdiagnosed as depression due to the overlap in symptoms.

In summary, apathetic AD patients demonstrated reduced attentional bias towards social images compared with non-apathetic patients and more severe apathy was associated with
decreased preference for social images. This study provides insight into the visual scanning
behaviour of apathetic AD patients in the presence of emotional-themed 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.

6.4 Effect of Methylphenidate Treatment for Apathy on Visual Scanning Behaviour

6.4.1 Discussion of Findings

This pilot study explored the effect of MTP treatment for apathy on processing of novel and
positive-themed stimuli in AD patients. For novelty preference, it was found that
improvements in apathy were significantly associated with increased number of fixations on
novel images compared with repeat images. Furthermore, patients who achieved remission,
had increases in time spent on novel images following treatment compared with the decrease in
novelty preference observed in those whom did not remit. However, this model did not reach
statistical significance. These findings are in line with findings of associations between novelty
processing and apathy. Daffner et al [278] found that apathetic AD patients demonstrated
decreased exploration of novel visual stimuli and distributed their overall viewing time evenly
among all types of stimuli. Additionally, more severe apathy was associated with reduced P3
ERP amplitudes [279]. Daffner et al [322] also reported similar results in cortical stroke
patients with frontal lobe lesions. Prolonged latency and reduced amplitude of the novelty P3
ERP over the frontal lobes were observed in subcortical stroke patients with apathy compared
to those without apathy [321]. More severe apathy was also correlated with both longer latency
and decreased amplitude. 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 [318, 384].

As discussed in Study 2, the DAergic system is most prominently implicated in encoding novelty [138, 139]. Pharmacological manipulations of DA activity can affect early N2 ERP amplitudes in EEG studies [135, 351] as well as repetition suppression in fMRI investigations [136] in response to novel stimuli. In healthy adults, the administration of the DA precursor levodopa to healthy adults attenuated fMRI repetition suppression effects in the hippocampus, parahippocampal cortex and the substantia nigra/ventral tegmental area [136]. One study reported increases in the early N2 ERP amplitude but no change in P3 in Parkinson's patients ON versus OFF medication [351]. Another EEG study showed increases in the N2b response to novelty following administration of apomorphine, a D1/D2 receptor agonist [135]. However, pharmacological manipulations of DA activity do not appear to affect the P3 ERP, the later component of novelty signals [349, 350]. Given these findings, it was suggested that DA may play a key role in mediating early but not later EEG responses to novel stimuli [135]. No pharmacological studies of novelty preference have given special consideration to the effect of apathy.

In a randomized placebo-controlled clinical trial of MTP for the treatment of apathy in AD, patients on the active treatment for 6 weeks improved on tests of both apathy [219] and attention [295]. However changes in apathy, measured by the NPI apathy and AES, and attention, measured by the DS Total, were not significantly correlated [295]. In the present study, no significant correlations between change in DS Total scores and change in AES or visual scanning parameters were found. Interestingly, when DS Total scores were parsed into its subscores, associations between change in DSB scores and novelty preference as well as
apathy trended towards significance. Improvements in DSB were associated with increased novelty preference and improvements in apathy. This was not observed with DSF scores. As discussed briefly in Study 1, DSF is purported to be reliant on the subordinate phonological loop and visuospatial sketchpad described in Baddeley’s model of working memory [324]. The DSB is thought to encompass additional executive and working memory functions [301]. Thus, the DSB and not DSF, may be accessing frontoparietal attention and working memory networks that are common with apathy. MTP may be mitigating the effects of apathy through these circuits. This analysis provides additional evidence to support the involvement of higher-order attention and working memory processes in novelty preference.

While results from Study 3 suggested lower attentional bias towards social images in apathetic compared with non-apathetic AD patients, no significant correlations were found between change in apathy and visual scanning on social stimuli following MTP treatment in this study. A sample size of 8 was likely not sufficiently powered to detect a relationship between these two variables with large effect sizes. However, baseline attentional bias towards social images (both relative fixation time and frequency) was significantly correlated with change in apathy on the AES. Lower baseline bias towards positive images predicted greater improvements in apathy after MTP treatment. Thus, patients with greater dysfunction in the processing of social or positive themed stimuli may benefit more from apathy treatment. Post hoc analyses further suggested that improvements in the emotional domain of apathy may be the key contributor in this relationship. In Study 3, greater AES emotion subscore emerged as the main predictor of reduced attentional bias toward social images. Visual scanning behaviour in the presence of social stimuli may be sensitive to MTP-induced changes in the emotional blunting aspect of apathy.
Overall, scores on tests of apathy (AES and NPI) decreased from baseline to follow-up, though this did not reach statistical significance. Interestingly, depressive symptoms, measured by NPI subscore, also decreased. Psychostimulants are not recommended for the treatment for depression. However, MTP has shown to ameliorate depressive symptoms in treatment resistant depression [385], post-stroke [386], palliative care and terminal cancer patients [387, 388]. In an open label study of MTP for treatment of apathy in 23 patients, significant improvements in both apathetic and depressive symptoms were observed after 12 weeks [216]. In that study, 78% of patients were reported to have comorbid depression at the start of the trial. The mean baseline NPI depression score in this study was 3.8 ± 4.1, signifying presence of depressive symptoms in these patients. These findings collectively highlight the difficulties with separating these two syndromes. Interestingly, clinicians have noted the development of apathy associated with the use of a selective-serotonin reuptake inhibitor (SSRI) in cases of non-AD psychiatric patients [389-392] and geriatric patients [393]. It was also noted that symptoms were improved or resolved upon discontinuation or reduction of SSRI medication [389-393]. Though the mechanism of action is unclear, it has been suggested that SSRIs indirectly modulate DA neurotransmission via its effect on the frontal cortex [390]. Evidence indicates that serotonergic neurotransmission can inhibit [394] and excite [395] endogenous DA release in both the forebrain and midbrain. Alternatively, the underlying presence of apathy may be unmasked following successful treatment of the depressed symptoms. Thus, methods to separate depression from apathy and predictors of response to different treatments will be essential to improving patient outcomes.
6.4.2 Limitations

The results of this study should be very carefully interpreted in light of the small sample size. A priori power calculations suggest that a sample size of 20 would be needed to achieve a power of 0.80 to detect a large effect size ($\rho = 0.5$) in the correlation analyses. However, significant correlations with very large effect sizes ($\rho = 0.8$) were detected. A robust relationship may exist between changes in visual scanning parameters and apathy, suggesting that a lower sample size may be sufficient in this case. This was a pilot study conducted in order to inform a larger and more comprehensive investigation. With larger sample sizes, covariates can be included in a multivariate linear regression to control for several clinical covariates, such as cognition, age and gender.

In the present study, the AES informant version was used as the apathy outcome variable for the correlation analyses. Variability leading to confounders might exist due to differences in each informant’s interpretation of questions on the AES, which may be ambiguous. The higher recommended cut-off score for the caregiver version (41.5) suggests that compared to self (36.5) and clinician (40.5) reports, informants might be overestimating apathy symptoms in patients [315]. In order to standardize this method of assessment, the AES clinician version can be used. This version of the AES is administered as a semi-structured interview in which a trained rater utilizes both verbal and non-verbal data to determine the patient’s apathy level on each item of the test. The AES-Clinician, though a reliable and valid scale for apathy [313, 396], is psychometrically less robust with regard to diagnostic performance than the AES-Informant, according to Clarke et al [396]. The researchers proposed that the AES-Informant was a better quick screen of apathy symptoms and training level of raters may have lowered performance ability of the clinician version. The 4-6 hours experience with the scale suggested
by the test developers [313] might not be sufficient for reliability. Thus, a caveat to using the AES-Clinician in future studies is that it should be administered by a trained clinician who knows the patients well, such as the primary physician, and who has had opportunities to observe their behaviours.

All patients tolerated MTP well with no serious adverse events reported. Medication compliance was determined through interviews with caregivers. Based on these evaluations compliance was not reported to be an issue. However, patients with memory impairments may neglect to follow the dose schedule, particularly if not aided by the caregivers. Patients may fail to properly store drugs in dry and room temperature conditions, degrading the drugs and rendering them less effective. These events would confound results as the true effect of MTP would not be measured in each case.

Remission status in the comparison of responders analysis was defined as those patients who dropped below a 4 on their NPI apathy subscore at the follow-up visit. As described above, this cut-off score has been used in previous trials of methylphenidate to defined clinically significant apathy [219, 295, 310, 312]. However, the clinical relevance of this score has yet to be determined.

6.4.3 Significance

In summary, improvement in apathy symptoms was associated with increase in attentional bias towards novel stimuli in AD patients treated with MTP for apathy. Additionally, lower baseline attentional bias for social stimuli predicted better response to apathy treatment. This study provided preliminary data to suggest that visual scanning behaviour and attentional biases may be sensitive to pharmacological manipulation. Treatments for apathy and depression differ.
Clinicians have observed the development of apathy following SSRI treatment for depression in psychiatric and geriatric patients [389-393]. 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 biases may represent a reliable marker of pharmacotherapy-induced behavioural changes.

6.5 Recommendations for Future Studies and Clinical Implications

Study 1 and 2 demonstrated the utility of novelty preference in differentiating dementia and cognitively intact elderly as well as temporally predicting cognitive decline. Eye tracking measures have been used to study novelty processing in infants [286, 287, 397]. The novelty preference paradigm explored in these studies may be of value in probing selective attention and working memory across all ages and cognitive capacities, in order to advance understanding of information processing throughout the human developmental stages. In future studies, the novelty preference of MCI, prodromal AD patients and individuals with high dementia risk factors can be monitored longitudinally to better understand the trajectory of cognitive decline and identify potential predictors of conversion. Individuals can be tracked throughout development, from infancy and beyond, to explore the effects of age and cognitive impairments on the different cognitive domains. The impact of AD may appear earlier on tests of visual scanning behaviour than on the traditional neuropsychological assessments. These patients can then be enrolled in clinical trials of disease-modifying treatments. Early interference of underlying pathological events, including amyloid, hyperphosphorylated tau and neuroinflammation, may better preserve cognition and function in these patients.
Several modifications to the current paradigm can also be implemented to explore factors that might influence novelty preference. One modification would be to increase the number of repetitions. In 3- and 6-month old infants, preference shifted from familiar to novel images with increasing exposure [397]. This might also be the case for cognitively impaired patients. The limits of novelty preference can be studied further by increasing the duration between first and second exposure to an image. At different ages and cognitive capacities, memory for items will decay at different rates. This would also allow for the study of implicit long-term memory.

To further investigate the neurobiology of attentional biases associated with apathy, in addition to monitoring the effects of MTP, a drug challenge can be used to investigate whether response immediately following a single dose of psychostimulant can predict apathy outcome in the open label trial. Herrmann et al [218] used a drug challenge to probe the function of the DA system in apathetic AD patients. Greater inattention scores on the Conners’ CPT induced by another psychostimulant, dextroamphetamine, was predictive of better response to subsequent MTP treatment for apathy. The observed inattention or increase in susceptibility to distracters may signify activation of the DA system in response to dextroamphetamine, suggesting that these patients had a more intact neurotransmitter system. This may be a better approach to speculating status of neurotransmitter systems and underlying neurobiological mechanisms than assessments of baseline visual scanning patterns to predict response to pharmacotherapy.

In Study 4, a total of 4 out of 8 patients experienced remission (decreases in NPI apathy score below 4), indicating that response to MTP was variable. If shifts in visual attention patterns can be detected following a single dose of MTP, responders can be identified before starting a course of treatment for apathy. Given that psychostimulants have been associated with cardiovascular events [398] in addition to behaviourally activating effects such irritability, agitation and psychosis [216-218], information on a patient’s response likelihood will help
physicians make better risk-benefit evaluations of treatment options. In frail populations where concurrent medical conditions and polypharmacy are common, identifying reliable predictors is of value toward guiding treatment decisions.

Steps should also be taken to develop drug challenge studies that specifically target depression in AD. The studies described in this thesis did not focus explicitly on depression. However, overlaps between depression and apathy do occur. For instance, the apathetic patients recruited had low levels of depression, according to their NPI depression subscores. The distinction between apathy and depression is important as there is evidence that antidepressants are not effective for treating apathy and may indeed worsen this condition [389-393]. Neuronal damage and consequent dysfunction of the amygdala and frontoparietal pathways, thought to regulate the attentional bias towards emotionally salient information within the environment [399], may propel some AD patients towards depression. Antidepressants, specifically those that alter the 5-HT system, have been shown to normalize fMRI signals in the amygdala and frontoparietal circuitry during exposure to negatively valenced stimuli [400]. This was observed together with improvements in mood. 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 [401, 402]. Eizenman et al [403] found that fixation shifts away from dysphoric images within 1 week of duloxetine treatment for major depression predicted better response to treatment following 6 weeks. Thus, an antidepressant challenge can also be applied to determine those most likely to benefit from the drug and more importantly, identify patients who might develop apathy. Furthermore, as there are several different antidepressants with distinct mechanisms currently indicated for depression, visual scanning can be used to pinpoint the most effective drug. The best course of treatment may necessitate targeting one syndrome independently or both apathy and depression in conjunction.
The large standard deviation for visual scanning parameters indicate that patients had unique responses to the many stimuli presented. Additionally, as discussed in Study 3, AD patients may have difficulty interpreting the emotional content in complex scenes. The results might be improved if images that elicited strong responses from patients with dementia were included in the stimulus paradigm. Thus, the image presentation should be optimized according to the intention of its application. For example, images that robustly discriminate apathetic and depressed patients should be selected for development of a diagnostic tool to differentiate these two syndromes. Some images may be more sensitive to drug manipulations and should be included in pharmacotherapy paradigms.

Relative fixation time and fixation frequency within images were used in these studies to summarize attentional biases toward novel and emotional stimuli. These parameters were also presented in previous eye tracking studies [107, 270, 274-276, 286, 287, 397]. Relative fixation time provided a description of how much time was spent on specific images. Fixation frequency within images, a basic component used to calculate relative fixation time, described how much subjects are moving their eyes within the confines of an image. These parameters have provided valuable information on the visual attention patterns of AD patients. Examination of other parameters, as well as different methods of analyzing the visual scanning data would be the next steps to progress understanding of attentional biases. Visual scanning data can be segmented to explore whether response to images change during the entire 10.5 seconds allotted per slide. Reduced cognitive capacity or behaviour symptoms such as apathy may be associated with different patterns during early and late processing. The visual attention scanning technology generates a wealth of information about different parameters of eye movements, allowing for enormous opportunity to further explore visual information processing.
6.6 Conclusions

Overall, in these studies, the visual scanning patterns associated with attention, memory and behaviour deficits in AD patients were investigated. Dementia patients and cognitively intact elderly controls demonstrated divergent eye movement patterns in the presence of novel and repeated visual stimuli. This reduced ability to process novel stimuli in AD patients predicted temporal declines in cognition. Within the AD group, apathetic patients demonstrated a different pattern of visual scanning in the presence of emotionally-charged stimuli compared with non-apathetic patients. Shifts in attentional biases within apathetic patients were induced through modulating DA and NE activity. Thus, attentional bias paradigms may be an effective and more naturalistic method of tracking cognitive deficits and neuropsychiatric symptoms in dementia patients, as well as detecting pharmacotherapy-induced changes. This is of particular significance in disease populations where currently available assessments of symptoms are complicated by progressive communication and language deficits, as well as barriers due to varying education levels. Attention bias paradigms such as these can circumvent the need to rely on subjective information provided by caregivers for evaluation. The measure of visual scanning behaviour using eye tracking techniques provide an objective, non-invasive, non-verbal and less cognitively-demanding method that can improve assessment of symptoms and optimize treatment outcomes.
Chapter 7

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Appendix A: Study Flowchart

Patient recruitment flowchart for Study 1-4