Visual Scanning Behaviour in Patients with Alzheimer’s Disease

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Applied Science
Department of Electrical and Computer Engineering
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Abstract

Alzheimer’s disease (AD) is characterised by memory loss and is often accompanied by psychiatric disorders. Since there are difficulties administering standard cognitive and psychiatric tests to patients with AD, it is desirable to develop objective tests of such functions.

Novel tests to assess memory loss and apathy in AD were developed. The tests are based on the analysis of visual scanning behaviour (VSB) when participants look at visual stimuli. Differences between the VSBs of patients and controls are used for the assessments.

When compared to controls, patients with AD had significantly reduced differences between their VSBs on novel and previously shown images. This was used to assess memory loss and to accurately classify patients with AD from elderly controls. Also, apathetic patients with AD showed more uniform VSBs on images with different arousal. The results suggest that analysis of VSB can help to assess memory and psychiatric functions in AD.
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Chapter 1. Introduction

Alzheimer’s disease (AD) is a degenerative disorder that is characterised by memory loss and cognitive impairments [1]. Specifically, the diagnostic and statistical manual of mental disorders fourth edition (DSM-IV-TR) states that the subject must have memory impairments and one of aphasia, apraxia, agnosia or disturbance in executive functioning to be diagnosed with AD [2].

The symptoms of AD were classified by the Alzheimer’s association into stages of severity [3]. During early stages, patients generally do not experience cognitive or memory deficits and interviews with clinicians do not provide evidence of any symptoms [4]. As the disease progresses, the symptoms worsen and ultimately patients are unable to take care of themselves [3]. A quantitative, objective and sensitive measure for the degradation of memory and cognitive functions provides methods to evaluate the severity and the potential for developing the disease.

In addition, AD is often accompanied by psychiatric and mood disorders [5]. Apathy is the most common psychiatric disorder [6] and is associated with emotional indifference, diminished motivation and disinterest [7]. Three longitudinal studies of AD reported that the prevalence of apathy in patients with AD is 50%, 53% and 70% [8][9][10]. The differences between the percentages of apathetic patients in the above studies may be the result of different diagnostic criteria as the diagnosis relies on clinical interviews with the patients’ caregivers [11][12][13].

To improve diagnosis and treatment of patients with AD, it is desirable to develop markers that will help to quantify cognitive and psychiatric functions in these patients. Using modalities such as structural Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single Photon Emission Computed Topography (SPECT) several studies proposed markers for AD [14][15] and apathy in AD [16]. In this thesis, we studied visual scanning behaviour (VSB) as a possible modality for the assessment of cognitive and psychiatric functions in AD. More specifically we developed paradigms for objective assessments of memory loss and apathy in AD. Sensitive assessments of memory loss and apathy during early stages of AD may aid in the planning of optimal pharmaceutical treatment [17]. For example, the detection of apathy in patients with AD is important since the pharmaceutical treatment for apathetic patients is different from the treatment of patients with AD who are not apathetic [6].
1.1 Visual Scanning Behaviour

Visual Scanning Behaviour (VSB) is controlled by both low-level processes (e.g., luminosity and saliency of the image) and high level behavioural processes governed by the subject’s memories, expectations and goals [18]. Using the dot-probe task, past studies have indirectly measured VSB to obtain insight into high-level behavioural processes. For example, MacLoed et al. [19] studied the effects of presenting emotionally threatening stimuli in subjects with high anxiety. Other studies used the dot-probe task to explore emotional processes while presenting: dysphoric images to subjects with depression [20], threatening images to subjects with anxiety [21] and images of angry faces to social phobic subjects [22].

In recent years, direct measures of VSB have been obtained through the use of eye-tracking systems. Biases in VSB were found in patients with autism compared to controls when they were presented with images of faces [23]. Previous studies conducted in Prof. Eizenman’s laboratory showed that patients with depression have biases in their VSB when they look at dysphoric images [24] and patients with anorexia nervosa were shown to exhibit biases in their VSB when they look at body shapes [25]. In this thesis, VSB parameters were studied to objectively assess memory loss and apathy.

1.2 Memory and Visual Scanning Behaviour

The visual paired comparison task is a test in which two images, one that is novel and one that was previously seen, are presented simultaneously and the length of time that subjects look at each stimulus is measured. Infants and adults typically perform fewer fixations on images that were previously seen (repeated images) compared to novel images [26][27]. This phenomenon, novelty preference, was reviewed by Hannula et al. [28]. Novelty preference is a robust phenomenon that can be observed under a variety of test conditions [29][30] and can be used as an objective indicator of memory capabilities [31]. Previous studies of novelty preference in patients with cognitive impairments showed that the visual paired comparison task was successful in objectively identifying memory loss in these patients [32].
1.2.1 What form of memory is measured in the visual paired comparison task?

It is not clear whether novelty preference is a reflection of explicit or implicit memory. Explicit (conscious) memory is measured by recognition memory tests (recall tests) and implicit (subconscious) memory is measured by priming tests. Mann et al. [33] tested conscious memory with the VPC task and asked the subjects to recall images that were previously seen. The subjects’ implicit memory capabilities were tested with the VPC task and subjects were required to name the object presented. Mann et al. found that novelty preference was more correlated with the results of the explicit memory test than with the results of the implicit memory test. Snyder et al. [34] tested the subjects’ explicit memory capabilities using the same methods as Mann et al. However, the results of the visual paired comparison task were not correlated with the results of the explicit memory test.

Snyder et al. [35] argued that the visual paired comparison task is logically an implicit memory task as the subjects are not instructed to refer back to prior memory. In addition, Hannula et al. [28] suggested that eye movement based memory effects are due to relational memory (item-context relationship) which is distinct from conscious awareness (i.e., subjects do not explicitly remember the images). Although there is no general consensus on the form of memory that is assessed in the VPC task, the recent literature advocates that novelty preference reflect on implicit memory to a greater degree than explicit memory.

1.2.2 Novelty preference in patients with AD

Numerous studies reported comparisons between the results of implicit memory tasks (e.g., word stem completion) in patients with AD and elderly controls. Fleischman et al. [36] conducted a review and the authors concluded that patients with AD do retain implicit memory capacities. However, this conclusion is controversial as many studies showed significant differences between patients with AD and elderly controls (e.g., [37], [38]) and suggested that patient with AD have impaired implicit memory. Since novelty preference is affected by implicit memory it can provide more insights into this controversy.
1.3 Apathy and Visual Scanning Behaviour

The current diagnostic criteria of apathy in AD requires interviews with caregivers and clinicians’ appraisal of the patient’s condition [12][39]. The limited communication capabilities of patients with AD reduce the accuracy of such appraisals. Instruments (questionnaires) that measure apathy evaluate a wide range of symptoms including emotional indifference, diminished motivation and disinterest [7].

1.3.1 Emotional indifference and visual scanning behaviour

Non apathetic subjects show biases towards emotional (pleasant or unpleasant) images when presented alongside emotionally neutral images [40]. In addition, optimistic students were found to exhibit longer fixations on pleasant images compared to unpleasant images [41] and patients with depression have longer fixations on dysphoric images compared to controls [24].

1.3.2 Diminished motivation, indifference and visual scanning behaviour

Diminished motivation and reduced interest have been investigated extensively in assessing advertisement effectiveness [42]. Pieters and Warlop [43] showed that subjects with lower motivation exhibits a significantly higher number of inter-image saccades compared to subjects with higher motivation. Different viewing states may explain this phenomenon. In the early stages of image viewing (orientation state), subjects view the visual stimuli on a global scale that is characterised by short fixation durations and long saccades (inter-image saccades). In the later stages of image viewing (recognition and identification states), the visual scanning patterns are characterised by long fixation durations and lower amplitude saccades (intra-image saccades) [44]. This may suggest that subjects with diminished motivation spend relatively more time in the orientation state than in the recognition and identification state.

In Pieters and Warlops study [43], subjects were extrinsically driven as they were promised a gift that was associated with the stimuli being viewed. However, diminished motivation in AD can be associated with impaired intrinsic motivation [45][46]. It is not clear if the effects of extrinsic and intrinsic motivations on VSB are similar.
1.3.3 Apathy and visual scanning behaviour in patients with Alzheimer's disease

Previous studies showed that VSB is affected by the emotional content of the images being viewed. Since one of the symptoms of apathy is emotional indifferences [47], it is expected that the VSB of apathetic patients with AD will show less variability when presented with emotional and non-emotional images. In addition, the reduced interest of apathetic AD patients is expected to reflect in the amplitude and frequency of saccades.

1.4 Goals and Framework of This Thesis

The main goal of the thesis is to study VSB as an objective measure of memory loss and apathy in patients with AD.

Chapter 2 describes the general methodology and framework for studying VSB in patients with AD. This is followed by technical details of software that was developed to automate the data analysis. Finally classification methods and evaluation criteria are discussed.

Chapter 3 describes a new paradigm to assess memory impairment through the study of novelty preference. The study was first conducted with young controls and the insights obtained were applied to the study of novelty preference in patients with AD and elderly controls. Parameters that indicate memory loss were tested with classification techniques and the performance of the classifier was evaluated.

Chapter 4 presents techniques that use VSB parameters to assess apathy in patients with AD. VSB parameters that are most likely to be associated with apathy are identified and discussed.

Chapter 5 presents a summary of the major contributions of the thesis and describes future directions for further exploration.
Chapter 2. Framework for Studying Visual Scanning Behaviors Parameters in Alzheimer’s Disease

The framework used to study VSB parameters in Alzheimer’s disease builds upon the framework developed by Eizenman et al. [24] to study depression. In this framework, multiple sets of slides each containing four images are presented while the subjects’ eye gaze positions are tracked. The presentation of more images (four images compared to two images in other studies) provides subjects with more options in the manner that they can shift attention between images and increase the interaction between peripheral and central vision. The analysis of the data provide a clear distinction between parameters that are associated with early and late processing of images (i.e., the first time an image was viewed compared to the subsequent visits). The current framework is described in the following subsections: experimental procedures, analysis software and classification.

2.1 Experimental Procedures

Visual Attention Scanning Technology (VAST) [48] was used to obtain subjects’ eye gaze positions. VAST incorporates a binocular gaze estimation system [49] to estimate and record gaze position, a display to present visual stimuli and a monitoring station to control and supervise the test. During the tests subjects sat approximately 65 cm away from the monitor. Following a short calibration routine (9-points calibration procedure where subjects were asked to view a moving target), subjects were presented with sets of slides.

2.1.1 Presentation of visual stimuli

Slides were presented on a 23-inch computer monitor and the four images on each slide were arranged in a $2 \times 2$ configuration. The images were either 590 by 460 pixels (15.5 by 12.2 cm) or 320 by 460 pixels (8.5 by 12.2 cm). Each slide was presented for 10.5 seconds and a 1 second blank screen was presented between slides. The images of each slide were chosen to explore specific functions and are described in Section 3.1.1 and Section 4.1.1.

2.2 Analysis Software

During the study, after each set of slides is presented, VAST generates a single output file (each set of slides can be used to test a different cognitive or neuropsychiatric function). The following
The figure depicts the data flow from VAST to data that are selected by the researcher for further analysis (sets of selected VSB parameters).

**Figure 2.1 Data flow of VAST.**

VAST generates a flat file database (called the “Eye tracking data”) consisting of the gaze positions estimates, subject information and visual stimuli properties. For each subject, the “Eye tracking data” is converted into VSB parameters by the Analyzer (see Section 2.2.1) and the “Assembler” generates a “Study data file” (see Section 2.2.2) that combines the data from all the subjects in the study. The “Selector” is used to extract specific information from the “Study data file” (see Section 2.2.2).

### 2.2.1 Estimation of VSB parameters

The “Eye tracking data” file includes the eye gaze positions (x, y positions for the left and right eye), subject information and visual stimuli information. The Analyzer converts the “Eye tracking data” into VSB parameters with the following steps: merging data from the right and left eyes, estimating the fixation sequence and calculating the VSB parameters.

**Merging data from the left and right eye**

The eye gaze positions generated by VAST includes independent estimates of the x, y gaze-positions of each eye (gaze positions are provided in the screen coordinate system). As the gaze-positions of the two eyes are similar, this information is somewhat redundant and the data from the two eyes can be merged. Three methods were developed to merge data from the left and right eyes:

- For each slide, select data from the eye with the most valid eye-position estimates (samples).
- For each image, select data from the eye with the most valid eye-position estimate for this image.
- Select data from a specific eye based on the location of the image on the screen.

Figure 2.2 shows the data prior to merging and Figure 2.3, 2.4 and 2.5 shows the results of each method.

Figure 2.2 Data prior to merging left and right eye (pink: left eye, yellow: right eye).

Figure 2.3 Combined data calculated by selecting the eye with most valid samples.

Figure 2.4 Combined data calculated by the selecting the eye with most valid samples per image.

Figure 2.5 Combined data calculated by the selecting the eye dependent on the location of the image.
For the majority of the subjects, more than 85% of the estimated eye positions are valid (the remaining 15% are not valid due to blinks or estimates that are outside of the boundaries of the screen). Occasionally, external interferences (e.g., reflections from eye glasses) can cause the number of eye positions estimates from one eye to decrease and different algorithms can be used to combine data from the left and right eyes. The following table shows the average number of gaze positions that were retained per slide (perfect tracking will result in 310 estimates per slide) after merging data from the left and right eyes for 57 subjects (each subject looked at 106 slides). The third method provided the largest number of estimated samples.

<table>
<thead>
<tr>
<th>Method to select eye</th>
<th>Average # of samples per slide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most valid samples</td>
<td>266.19</td>
</tr>
<tr>
<td>Most valid samples per image</td>
<td>273.56</td>
</tr>
<tr>
<td>Dependent on the location</td>
<td>274.65</td>
</tr>
</tbody>
</table>

Table 2.1 Average number of gaze position estimates after merging the left and right eyes per slide

Estimation of fixations and saccades

Gaze positions were classified into fixations and saccades by algorithm developed by Cassel and Eizenman [50]. Fixations were detected if gaze estimates were within a specific radius (1 degree) for a minimum duration (165 msec). For more detail please refer to Cassel and Eizenman [51]. The amplitudes of saccades are calculated by the differences between the positions of consecutive fixations.

Parameters of visual scanning behaviour

This section describes VSB parameters that were calculated from the estimated sequences of fixations and saccades.
Basic parameters of VSB

The basic set of VSB parameters characterise properties of fixation and saccadic eye movements when subjects view an image. The basic set of VSB parameters were calculated over the full viewing duration of the visual stimuli.

1) Number of fixations within an image
2) Average fixation duration: The average fixation duration is the mean of the duration of all discrete fixations within an image.
3) Average saccadic amplitude: The average saccadic amplitude is calculated by taking the mean of the position differences between consecutive fixations.
4) Number of transitions to an image: The number of transitions to an image is defined as the number of times that the subject shifts his gaze from a fixation outside the boundaries of an image to a fixation point inside the boundaries of an image.
5) Transitional probability: The transitional probability is defined by the transitions between images types within the same slide. The transitional probability was used to provide more insights into the probability of transitions from one type of images to another type of images.

Sequential parameters of VSB

Sequential parameters of VSB are dependent on the order in which images are looked at. For sequential analysis, the fixation data were integrated to larger units: visits (See Figure 2.6 for an illustration of the definition of visits). The sequential parameters were separated into early processing that is when the subject first visited the image or the late processing is the parameter averaged over the subsequent visits (the average was calculated so that parameters of early and late processing could be compared). The first visit occurs during the orientation phase of the visual scanning process and is usually characterised by short fixation durations and long saccadic amplitudes. The subsequent visits occur during the recognition and identification phases of the visual scanning process which are characterised by longer fixations durations and shorter saccades [44]. The number of fixations, fixation duration and saccadic amplitude during early and late processing were calculated.
Figure 2.6 Illustration depicting the fixations associated with each visit. The dots represent a fixation and the numbers represent the visits.

Composite parameters of VSB

The composite parameters of VSB are calculated from multiple basic parameters. This includes:

1) Fixation time: The fixation time is the total time of all fixations on an image. The fixation time is equal to the number of fixation on an image multiplied by the average fixation duration.

2) Relative fixation time: The relative fixation time is the proportion of fixations time on each image on a slide. The relative fixation time is more robust than fixation time to large variations in tracking performance between slides.
2.2.2 Assembling and selecting

For each subject, the VSB parameters that were generated by the Analyzer were assembled into a “Study file” (the study file includes data from all the subjects in a specific study). Before the data were assembled the program verified that:

1. All the data in an assembled “Study data” file were generated with the same fixation segmentation parameters (See Section 2.2.1).
2. The same visual stimuli were used for all the data in a “Study data” file.
3. Similar data are not already stored in the “Study data” file (comparing the checksum of the data).

The assembler creates a flat file database consisting of subject information, analysis parameters, stimuli information and VSB parameters and an example is shown in Table 2.2.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Gender</th>
<th>imgType</th>
<th>slideType</th>
<th>Fixation time</th>
<th>Average saccadic amplitude</th>
<th>Average fixation duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA001</td>
<td>M</td>
<td>1-back</td>
<td>start</td>
<td>129</td>
<td>2.468</td>
<td>396.768</td>
</tr>
<tr>
<td>VA001</td>
<td>M</td>
<td>1-back</td>
<td>1-back</td>
<td>75</td>
<td>1.122</td>
<td>642.826</td>
</tr>
<tr>
<td>VA001</td>
<td>M</td>
<td>Social</td>
<td>Valence arousal</td>
<td>65</td>
<td>2.171</td>
<td>328.179</td>
</tr>
<tr>
<td>VA002</td>
<td>F</td>
<td>1-back</td>
<td>start</td>
<td>5</td>
<td>1.107</td>
<td>439.828</td>
</tr>
<tr>
<td>VA002</td>
<td>F</td>
<td>1-back</td>
<td>1-back</td>
<td>130</td>
<td>0.857</td>
<td>490.577</td>
</tr>
<tr>
<td>VA002</td>
<td>F</td>
<td>Social</td>
<td>Valence arousal</td>
<td>50</td>
<td>1.446</td>
<td>964.238</td>
</tr>
</tbody>
</table>
Specific information can be selected from the “Study data” file using a prototype that is similar to the SQL select-where\(^1\) however this was implemented on a flat file rather than on a relational database. For example, if we want to select the fixation time on “Social” images and group the data according to the subject category and subject ID (shown below).

\[
\text{SELECT subject category, subject ID, image type, VSB parameter FROM Alzheimer_data WHERE image type = “Social”, VSB parameter = “Fixation time”}
\]

Obtaining this information naively will require iterating through every row and every column of the “Study Data” searching for specific values (e.g., “Social” images). This method has a time complexity of \(O(m \times v \times n)\) where \(m\) is the number of columns to be selected, \(v\) is the maximum number of unique values per column and \(n\) is the number of entries. A b-tree was implemented to speed up this process. This requires an initialisation step to create a tree where the nodes are the unique values of the selected columns. Using this method, the algorithm will not be required to search through the unique values every iteration, reducing the time complexity to \(O(m \times n)\). The time complexity of the initialisation step can be ignored since \(n\) is much larger than \(v\). An example of selection is shown below:

![Figure 2.7 b-tree consisting of subject category, subject ID, image type and VSB parameter.](image)

The output of the selector creates a binary data file of the same format as the b-tree and data exploration is done by an in-order traversal of the b-tree.

\(^1\) [http://www.w3schools.com/sql/sql_where.asp](http://www.w3schools.com/sql/sql_where.asp)
2.3 Classification

The multi-parameter analysis of VSB in patients with AD can be interpreted as an exploration of an n-dimensional feature space. Decision boundaries for the feature space can be learnt to maximise the differences between the groups (e.g., patients with AD, elderly controls). The following section describes the classification algorithms and the cross validation method that were used in the thesis.

2.3.1 Cross validation

The models for classification were tested with a leave-one-out cross validation scheme which was selected due to the limited number of independent samples [52]. The leave-one-out cross validation scheme uses one sample as the test set and n – 1 samples as the training set. The test set is iterated across all samples and the test accuracy refers to the number of correct classifications.

2.3.2 Classification algorithms

Maximum a posteriori (MAP):

MAP is a simple method to classify subjects into two classes based on the posterior distribution \( P(X = x_{ni} | Y = k) \) where \( x_{ni} \) is the data per feature (i) and k is the class label. This MAP implementation assumes that the features for the two classes have Gaussian distributions. The subject is classified into the group with larger posterior probabilities. Algorithm 2.2 describes the major steps in our implementation of MAP.

---

Algorithm 2.2: Maximum A posteriori algorithm.

Training:
1. For each class label k
   - Calculate the parameters to estimate \( \mu_k, \sigma_k \) where \( P(Y = k) = N(\mu_k, \sigma_k) \)
2. For data sample \( x_{ni} \)
   - For each class label k
     - Calculate posterior distribution \( P(Y = k | X = x_{ni}) \propto P(X = x_{ni} | Y = k) \cdot P(Y = k) \)
     - \( P(X = x_{ni} | Y = k) = N(X = x_{ni} | \mu_k, \sigma_k) \)
     - Classification result is \( c \) where \( \text{argmax}_c P(Y = c | X = x_{ni}) \)

Testing \( x_{ni} \):
1. For each class label k
   - Calculate posterior distribution \( P(Y = k | X = x_{ni}) \)
   - Classification result is \( c \) where \( \text{argmax}_c P(Y = c | X = x_{ni}) \)
The current MAP implementation only supports classification using one parameter, we explored averaging and voting as possible simple methods to combine multiple parameters.

Averaging:

The simplest method to combine features for MAP is to calculate the average of the features. The averaging classifier does not assume independence in the features however, the features must be standardised. In this thesis, the averaging classifier was used as the baseline classifier.

Voting:

Another method to combine features for MAP is to use a voting classifier. The voting classifier is a basic ensemble learning method that uses the mode of multiple MAP classifiers learners as classification results. This algorithm does not assume independence and does not assume that the features are standardised. However, the algorithm will not consider the results of all the parameters. In this thesis, many VSB parameters are correlated and the estimated parameters suffer from relatively large variances. The voting classifier may be suitable for classification because the majority of the correlated features will vote for the same class and noisy VSB parameters will be ignored.

Logistic regression:

Logistic regression is a basic discriminative classifier that predicts the class labels based on an n-dimensional feature space. The feature space is mapped with a set of weights (w) to a logistic function and the weights are learnt to maximise the class differences. The algorithm is shown below.

Algorithm 2.3: Logistic regression.

Training:
1. Initialise \( w \in \{0, 1\} \)
2. For data sample \( x_n \)
   - Calculate weighted feature space \( z = w^T \cdot x_n + b \)
   - Calculate log-likelihood function
     \[
     L(z) = y \cdot \log(P(z)) + (1 - y) \cdot \log(1 - P(z)) + 
     \]
   - Where \( P(z) = P(Y | X = x_n) = \frac{1}{1 + e^{-z}} \)
   - Calculate the derivative of the log-likelihood function
     \[
     \frac{dL}{dw} = (y - P(z)) \cdot x_n
     \]
   - Update weights
     \[
     w = w + \mu \cdot \frac{dL}{dw}
     \]

Testing \( x_n \):
1. Apply weights to calculate \( z = w^T \cdot x_n + b \)
2. Classification results \( c \) where \( \arg \max_c P(Y = c | X = x_n) \)
As many of the VSB parameters are correlated, logistic regression may be suitable, as it does not assume feature independence. However, logistic regression assumes that the data are linearly separable.

Naïve Bayes:

The naïve Bayes classifier is a basic generative classifier. It is based on applying Bayes’ theorem to predict class labels and the features are conditionally independent given the class labels. This naïve Bayes classifier implementation assumes that the features are Gaussian distributed.

**Algorithm 2.4: Naïve Bayes.**

**Training:**
1. Calculate $P(Y = k)$ for $k = \text{class labels}$
2. For each class label $k$
   - Calculate $\mu_{x=k}$ and $\sigma_{x=k}$
3. For data sample $x_n$
   - Estimate the likelihood $P(X = x_n|Y = k) = \prod_{i=1}^{n} P(X = x_{ni}|Y = k)$
   - Obtain the posterior distribution $P(Y = k|X = x_n) = P(X = x_n|Y = k) \cdot P(Y = k)$
   - Classification is $c$ for $\arg \max_c P(Y = c|X = x_n)$

**Testing $x_n$:**
1. Estimate the likelihood $P(X = x_n|Y = k) = \prod_{i=1}^{n} P(X = x_{ni}|Y = k)$
2. Obtain the posterior distribution $P(Y = k|X = x_n) = P(X = x_n|Y = k) \cdot P(Y = k)$
3. Classification is $c$ for $\arg \max_c P(Y = c|X = x_n)$

The naïve Bayes classifier is less prone to over fitting. However, because the parameters in our study are high correlated they are not conditionally independent.

Discrete adaptive boosting:

Discrete adaptive boosting (adaboost) is an ensemble method that uses multiple decision stumps as weak learners to weighted samples. The classification results were calculated by taking the sum of the weighted decision stumps.

**Algorithm 2.5: Discrete adaboost.**

**Training:**
1. Set each sample $w_i = 1 / N$
2. Iterate
   - Fit weak classifier $f_m(x_n)$ using weights $w_i$ on training data
   - Compute $e_m = E_w[1(y \neq f_m(x_n))]$, $c_m = \log((1 - e_m)/e_m)$
   - Set $w_i = w_i \cdot e^{c_m \cdot (y \neq f_m(x_n))}$ and renormalize so that $\sum w_i = 1$
3. Classification $c$ where $c = \text{sign} [\sum c_m \cdot f_m(x_n)]$

**Testing $x_n$:**
1. Apply $\text{sign} [\sum c_m \cdot f_m(x_n)]$ to test data
The adaboost algorithm is known to be less susceptible to over fitting which is advantageous for our data set. However adaboost is prone to errors if the data are noisy [53].

Real adaptive boosting:

Real adaboost is a generalised version of discrete adaboost that uses class probabilities estimates instead of the weighted sum of the classification results of weak learners. The algorithm is similar to discrete adaboost and is shown below:

**Algorithm 2.6**: Real adaboost.

**Training**:
1. Weight each sample $w_i = 1 / N$
2. Iterate
   - Fit class prob. estimate $p_m(x_n) = P(Y = 1|X = x_n)$ using weights $w_i$ on the training data
   - Set $f_m(x_n) = \frac{1}{2} \log(\frac{p_m(x_n)}{1-p_m(x_n)})$
   - Set $w_i = w_i \cdot e^{-y_i \cdot f_m(x_i)}$ and renormalize so that $\sum w_i = 1$
3. Output of the classifier $\text{sign}[\sum f_m(x_n)]$

**Testing $x_n$**:
1. apply $\text{sign}[\sum f_m(x_n)]$ to test data

Real adaboost has similar advantages to adaboost but using the class probabilities instead of the weighted sum makes the algorithm less prone to noisy data.

2.3.3 Classification evaluation

The evaluation of the binary classification algorithms used the following metrics:

- Training classification accuracy: The percentage of correctly classified subjects in the training set.
- Testing classification accuracy: The percentage of correctly classified subjects in the test set.
- Sensitivity: The percentage of correctly classified patients.
- Specificity: The percentage of correctly classified controls.

In this evaluation, the testing classification accuracy will be the main indicator for the strength of the classifiers. The training data accuracy was used to assess generalisation of the classifiers. Finally, the sensitivity and specificity were used to determine the proportion of subjects per class that were classified correctly.
Chapter 3. Novelty Preference in Patients with Alzheimer’s Disease

In the visual paired comparison task, the differences between the fixation time on novel images and images that were previously seen (repeated images) are used to assess novelty preference [27]. As discussed in Chapter 1, novelty preference is associated with implicit memory [34] and therefore differences between fixation times on novel and repeated images can serve as a physiological marker of the implicit memory. In this chapter, novelty preference is assessed with a new method. The new method uses two pairs of novel and repeated images (in contrast to one pair of images in the standard test) so that subjects have more flexibility in the manner that they can shift attention between images. Also, the use of more images allows for the presentation of different types of images into the subject’s peripheral vision, which affect visual scanning parameters such as the length of fixations [54]. The new method uses several visual scanning parameters (not only fixation time) to quantify differences in visual scanning behaviour (VSB) on novel and repeated images. In the tests that are described in this chapter, the number of slides between the first (novel) and second presentations (repeated) are not fixed (this is in contrast with the standard method) to mask the purpose of the test and enables observations regarding the length of time (and distractions) over which novelty preference can be maintained.

The VSB parameters are divided into three groups. The first group consists of basic eye movement parameters that include: a) the number of fixations within an image; b) the average fixation duration; c) the average saccadic amplitude and d) the number of transitions between images. The first group of parameters is measured over the full duration of slide presentations. The VSB parameters in the second group are dependent on the order (sequence) in which the slides are scanned and include parameters that are associated with the first visit to an image (early processing) and parameters that are associated with later visits to the same image (late processing). The parameters studied are: a) fixations within an image; b) fixation durations and c) saccadic amplitudes. The third group includes parameters that are a composite of the basic parameters: a) fixation time and b) relative fixation time.

The VSB parameters were first studied with young controls that should demonstrate preference to novel images [55]. The study with young controls was used to characterise the effects of
novelty preference on VSB parameters when our new test is used. The study with young controls was followed by a study with patients with Alzheimer’s disease (AD) and elderly controls.

3.1 Study Design

The study design consists of describing the visual stimuli and participants.

3.1.1 Visual stimuli

Two types of slides were presented in this study: slides with four novel images (NN-slides) and slides with two novel and two repeated images. Slides with repeated images are referred to as “n-back” test slides where “n” is the number of slides between the first and second presentations of images that appear on both slides. Repeated images were presented in the same positions on the slides during the first and second presentations. The technical details of the visual stimuli were described in the Methods chapter (Section 2.1.1). As an example, the slides in Figure 3.1 were used to assess novelty preference when repeated images were presented after one slide (“1-back” test condition) or two slides (“2-back” test condition) following the presentation of the same images for the first time (“NN-slides”). For young controls, the test conditions were “1-back”, “5-back”, “10-back” and “15-back” and each test condition was repeated 12 times. For patients with AD and elderly controls, the test conditions were “1-back” and “2-back” and each test condition was repeated 16 times.
Figure 3.1 Example of the visual stimuli used to test novelty preference. Two of the four images in the NN-slides (slide with four novel images) were repeated in the “1-back” and the other two were repeated in the “2-back”. Slides have neutral images with similar complexities.
3.1.2 Participants

Thirty five patients with AD (age = 78.00 ± 7.87) and twenty two elderly controls (age = 71.65 ± 9.26) were recruited from the Alzheimer’s disease clinic at the Sunnybrook Health Sciences Centre (Ontario, Canada). Ten young healthy controls (age = 25.00 ± 5.30) were recruited at the University of Toronto. The following table shows the number of subjects who participated in the study:

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Subjects recruited</th>
<th>Subjects analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AD</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Elderly controls</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Young controls</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

As shown in Table 3.1, data from one patient with AD did not satisfy the data quality criteria (at least 50% of the slides have more than 70% of the gaze estimates within the boundaries of the images on each slide) for the study.

3.2 Novelty Preference in Young Controls

With young control we carried out studies to:

- Quantify differences between VSB parameters on novel and repeated images
- Quantify the effects of the test conditions (i.e., “1-back, “5-back”, “10-back” and “15-back”) on the differences between VSB parameters on novel and repeated images
- Quantify differences between the VSB parameters on novel images on slides with only novel images (“NN-slides”) and slides with novel and repeated images

3.2.1 Basic parameters of visual scanning behaviour

The eye-tracker’s gaze data provide the image coordinates of items that are viewed by the fovea (central vision). As VSB parameters are derived from this information, it is tempting to assume
that VSB parameters in our study are only affected by central processing. This is incorrect, as it is well known that VSB parameters such as fixation duration and saccadic amplitude are not only affected by the image that is being fixated on (viewed by central vision) but also by the surrounding images (viewed by peripheral vision) [54]. To quantify the effects of peripheral vision on the measured VSB parameters, we analysed the differences between VSB parameters on novel images in slides that include only novel images (“NN-slides”) and on novel images in slides that include two novel images and two repeated images (“n-back” slides). As there is no difference between the test conditions regarding images that are viewed by central vision, the differences between the VSB parameters on the novelty images in the “NN-slides” and the “n-back” test condition reflect the effects of peripheral vision on VSB. For the four different test conditions: “1-back”, “5-back”, “10-back” and “15-back” the basic VSB parameters on novel and repeated images were analysed and the data are summarised in Table 3.2.
Table 3.2 Basic parameters of VSB on the NN-slide, 1, 5, 10 and 15-back test conditions for young controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>NN-slides</th>
<th>1-back</th>
<th>5-back</th>
<th>10-back</th>
<th>15-back</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Novel</td>
<td>Repeated</td>
<td>Novel</td>
<td>Repeated</td>
<td>Novel</td>
</tr>
<tr>
<td>Number of fixations within an image (FWI)</td>
<td>5.301 ± 0.589</td>
<td>6.829 ± 1.241</td>
<td>3.551 ± 0.878 **</td>
<td>6.900 ± 1.495</td>
<td>3.659 ± 0.615 **</td>
</tr>
<tr>
<td>Average fixation duration (AFD) (msec)</td>
<td>505.798 ± 61.579</td>
<td>531.541 ± 102.207</td>
<td>413.579 ± 69.995 *</td>
<td>531.799 ± 102.392</td>
<td>455.272 ± 105.060 *</td>
</tr>
<tr>
<td>Average saccadic amplitude (ASA) (degrees)</td>
<td>1.910 ± 0.126</td>
<td>2.111 ± 0.285</td>
<td>1.838 ± 0.342</td>
<td>2.261 ± 0.335</td>
<td>1.817 ± 0.151*</td>
</tr>
<tr>
<td>Number of transitions between images (TBI)</td>
<td>2.360 ± 0.389</td>
<td>2.508 ± 0.599</td>
<td>2.046 ± 0.419*</td>
<td>2.575 ± 0.515</td>
<td>2.102 ± 0.466*</td>
</tr>
</tbody>
</table>

**p < 0.0001, * p < 0.05 significant differences between novel and repeated images for each test conditions**
The data were explored with descriptive analyses, which included the means and standard deviations of VSB parameters on the different image types (novel, repeated) for each test condition ("NN-slides", “1-back”, “5-back”, “10-back” and “15-back”). The parameters were first analysed using a mixed design repeated measures ANOVA [56]. If significant differences were found, planned paired comparisons (t-tests) were performed between novel and repeated images in the “1-back”, “5-back”, “10-back” and “15-back” test conditions. To test if VSB parameters on repeated images were similar to each other in the different test conditions, repeated measures ANOVA analysis with a within-subject factor of repeated images in “1-back”, “5-back”, “10-back” and “15-back” test conditions was performed. If significant differences were found, post-hoc paired comparisons (t-tests) with Bonferroni correction were used to determine significant differences between test conditions. Finally, to test if VSB parameters on slides with only novel images (NN-slide) were similar to VSB parameters on novel images that are viewed alongside repeated images, we used repeated measures AVOVA analysis with a within-subject factor of novel images for each test condition (“NN-slides”, “1-back”, “5-back”, “10-back” and “15-back”). Where significant differences were found, post-hoc paired comparisons (t-tests) with Bonferroni corrections were used to determine significant differences. Significances levels for all statistical tests were set to $p = 0.05$.  

**Number of fixations within an image**

Repeated measures ANOVA revealed significant differences between the number of fixations within images (FWI) for the test conditions ($F(8, 72) = 20.711$, $p = 0.001$, $\eta^2 = 0.697$). Paired t-test revealed significantly larger FWI on novel images compared to repeated images in the “1-back” ($t(9) = 5.11$, $p = 6.348 \times 10^{-4}$, $d = 3.050$), “5-back” ($t(9) = 5.10$, $p = 6.437 \times 10^{-4}$, $d = 2.835$), “10-back” ($t(9) = 3.95$, $p = 3.364 \times 10^{-3}$, $d = 2.313$) and “15-back” ($t(9) = 4.39$, $p = 1.751 \times 10^{-3}$, $d = 2.380$) test conditions. The data suggest that as the number of slides between the first and second presentation increases, the effects of novelty preference on the FWI are reduced (i.e., the FWI parameters on repeated images become more similar to novel images).

The FWI on repeated images in the “1-back”, “5-back”, “10-back” and “15-back” test conditions were marginally different ($F(3, 27) = 2.970$, $p = 5.0 \times 10^{-2}$, $\eta^2 = 0.248$). Post-hoc analysis revealed
only one marginally significant difference between the FWI on repeated images in the “15-back” and “1-back” test conditions (t(9) = 3.25, p = 6.0×10^{-2}, d = 0.830).

The FWI on novel images were significantly different between the five test conditions (F(4, 36) = 13.162, p = 1.0×10^{-6}, η^2 = 0.594). Post-hoc analysis showed that FWI on novel images in the “NN-slides” was significantly smaller than FWI on novel images in the “1-back” (t(9) = 4.92, p = 8.0×10^{-3}, d = 1.573), “5-back” (t(9) = 4.76, p = 1.0×10^{-2}, d = 1.407), “10-back” (t(9) = 3.92, p = 3.5×10^{-2}, d = 1.145) and “15-back” (t(9) = 4.76, p = 1.0×10^{-2}, d = 1.512) test conditions.

**Average fixation duration**

Repeated measures ANOVA revealed significant main effects between the average fixation duration (AFD) for the different test conditions (F(8, 72) = 7.015, p = 8.333×10^{-7}, η^2 = 0.438). Paired t-tests showed significant differences between the AFD on novel and repeated images for the following test conditions: “1-back” (t(9) = 4.74, p = 1.1×10^{-3}, d = 1.347), “5-back” (t(9) = 5.61, p = 3.3×10^{-4}, d = 0.738) and “10-back” (t(9) = 2.79, p = 2.1×10^{-2}, d = 0.881). No significant differences were found for the “15-back” test condition (t(9) = 0.03, p = 0.98, d = 0.007). The following plot shows the means of the AFDs on novel and repeated images for the different test conditions.
As shown in Figure 3.2, differences between the AFDs on novel and repeated images decreased as the number of slides between the first and second presentation increases.

When the AFD on novel images in each test condition were tested using repeated measures ANOVA, significant differences were found ($F(4, 36) = 4.283, p = 0.006, \eta^2 = 0.322$). Post-hoc analysis showed that the AFD on novel images in the “15-back” test condition was significantly smaller than the “NN-slide” ($t(9) = 4.25, p = 0.0215, d = 1.042$) and marginally significantly smaller than the “1-back” test condition ($t(9) = 3.57, p = 0.06, d = 1.061$). On the other hand, no significant differences were found between the AFD on repeated images in all test conditions ($F(3, 27) = 1.403, p = 0.263, \eta^2 = 0.135$).

In addition, the AFD on novel and repeated images in “NN-slides” and “1” to “15-back” were compared to that of the FWI and Pearson’s correlation tests showed no significant correlations were found between the parameters ($r(90) = 0.143, p = 0.178$).
Average saccadic amplitude

Repeated measures ANOVA showed significant differences between the average saccadic amplitude (ASA) for the different test conditions ($F(8, 72) = 3.778$, $p = 0.001$, $\eta^2 = 0.296$). Paired t-tests revealed significant differences between the ASA on novel and repeated images in the “5-back” test condition ($t(9) = 3.53$, $p = 6.5 \times 10^{-3}$, $d = 1.711$) and marginally significant differences in “1-back” test condition ($t(9) = 2.21$, $p = 0.055$, $d = 0.866$). The data from Table 3.2 show that for all test conditions the ASA is consistently smaller on repeated images compared to novel images.

There were no significant differences between the ASA on repeated images for the different test conditions ($F(3, 27) = 0.459$, $p = 0.713$, $\eta^2 = 0.049$). There were significant differences between the ASAs on novel images for the different test conditions ($F(4, 36) = 3.489$, $p = 0.017$, $\eta^2 = 0.279$). Post-hoc analysis showed that the ASA on novel images in “NN-slides” was significantly smaller than on novel images in the “5-back” ($t(9) = 4.02$, $p = 3.0 \times 10^{-3}$, $d = 1.386$) test condition.

VSB parameters that describe saccadic eye movements (e.g., ASA) are expected to be independent from VSB parameters that describe fixations (e.g., AFD) as these eye movements are controlled by two different control systems in the human brain. As expected, in all test conditions (“NN-slide”, “1-back”, “5-back”, “10-back” and “15-back”) the AFD and ASA were not significantly correlated (Pearson’s correlation, $r(90) = 0.130$, $p = 0.223$). However, the ASA and FWI were found to be significantly correlated ($r(90) = 0.591$, $p = 8.352 \times 10^{-10}$).

The number of transitions between images

Repeated measures ANOVA revealed significant differences between the number of transitions into images (TBI) for the different test conditions ($F(8, 72) = 7.590$, $p = 2.644 \times 10^{-7}$, $\eta^2 = 0.458$). Paired t-tests revealed significant differences between transitions into novel and repeated images for all the test conditions (“1-back”: $t(9) = 2.26$, $p = 5.0 \times 10^{-2}$, $d = 0.937$; “5-back”: $t(9) = 3.65$, $p = 5.3 \times 10^{-3}$, $d = 0.963$; “10-back”: $t(9) = 3.03$, $p = 1.4 \times 10^{-2}$, $d = 0.60$; “15-back”: $t(9) = 3.50$, $p = 6.7 \times 10^{-3}$, $d = 1.355$).

The transitions into novel images were also shown to be significantly different between test conditions ($F(4, 36) = 5.981$, $p = 0.001$, $\eta^2 = 0.399$). Post-hoc analysis showed significant differences in the number of transitions into novel images between the “1-back” and the “15-
back” test conditions ($t(9) = 4.63$, $p = 0.012$, $d = 0.534$) and showed marginally significant
differences between the “NN-slides” and “15-back” ($t(9) = 3.60$, $p = 0.057$, $d = 0.899$). No
significant differences were found between the number of transition into repeated images for all
test conditions ($F(3, 27) = 1.097$, $p = 0.367$, $\eta^2 = 0.109$). The following plot shows the mean TBI
on novel and repeated images for the different test conditions.

![Graph showing transitions into novel and repeated images for five test conditions.]

Figure 3.3 The mean (± 1 standard errors of the mean) transitions into novel and repeated images for young controls for
the five test conditions (NN-slides, 1-back, 5-back, 10-back and 15-back).

As shown in Figure 3.3, the transitions into novel images (i.e., TBI on novel images) were
consistently higher than the transitions into repeated images (i.e., TBI on repeated images). The
TBI on novel images and repeated images were similar for all test conditions except for the TBI
on novel images in the “15-back” test condition (effect size, $d < 0.6$). It is not clear why the TBI
for the “15-back” condition is higher than those for “1-back”, “5-back” and “10-back” and the
observation is not consistent with the TBI on “NN-slides” (as “n” increases, VSB parameters on
novel images in test conditions supposed to converge to the values of VSB parameters on “NN-
slides”).
To provide more insights into the parameter TBI, we explored the transition probabilities between novel and repeated images. On each slide, there are four types of possible transitions between images; novel to novel, novel to repeated, repeated to novel and repeated to repeated. Each transition is defined by its starting and final states and the transition probabilities are defined by first calculating the number of transitions from the start state to the final state divided by the total number of transitions from the start state, and then multiplying the results by the probability of being in the start state. When the transitions between images were explored it was found that subjects exhibited less diagonal transitions between images (e.g., top left to bottom right) compared to horizontal and vertical transitions (horizontal: 0.500 ± 0.056; vertical: 0.392 ± 0.053; diagonal: 0.108 ± 0.034). Since images of the same type were always placed on the same row or column (this is due to an error in the preparation of the slides for young controls), young controls performed 89% of their transitions in either vertical or horizontal directions. Therefore, 44.5% of the transitions were between images of the same type (novel to novel or repeated to repeated). This implies that if transitions between images are independent of the image type, the expected novel to novel average transition probabilities (ATP) and repeated to repeated ATP will be approximately 44.5%, while novel to repeated ATP and repeated to novel ATP will be approximately 55.5%. The ATP for all test conditions are summarised in Table 3.3.

<table>
<thead>
<tr>
<th>Transition type</th>
<th>Mean ± standard deviation</th>
<th>Expected values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel to Novel</td>
<td>0.550 ± 0.092</td>
<td>0.445</td>
</tr>
<tr>
<td>Novel to Repeated</td>
<td>0.450 ± 0.092</td>
<td>0.555</td>
</tr>
<tr>
<td>Repeated to Novel</td>
<td>0.597 ± 0.087</td>
<td>0.555</td>
</tr>
<tr>
<td>Repeated to Repeated</td>
<td>0.403 ± 0.087</td>
<td>0.445</td>
</tr>
</tbody>
</table>

As shown in the table above, the ATP deviated from the expected values. Transition probabilities from either novel or repeated images to novel images were higher than expected under the assumption that transition probabilities are independent of image type. The inverse was correct for repeated images. Transition probabilities from either novel or repeated images to repeated images were lower than expected under the assumption that transition probabilities are
independent of image type was correct. The analysis demonstrates that regardless of the type of the image that the subject is currently fixating on (novel or repeated) subjects have biases towards novel images when they shift their attention to the next image.

3.2.2 Sequence dependent parameter of visual scanning behaviour

In the previous section, parameters that describe average VSB were described. Often, VSB changes throughout the viewing process and to capture such changes we analyse in this section the number of fixations within an image, average fixation duration and average saccadic amplitude when images on a slide are viewed for the first time (early processing) and at subsequent instances (later processing). The parameters are shown for all test conditions (“NN-slides”, “1-back”, “5-back”, “10-back” and “15-back”) in Table 3.4.
<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>NN-slides</th>
<th>1-back</th>
<th>5-back</th>
<th>10-back</th>
<th>15-back</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of fixations within image early processing (EFWI)</td>
<td>2.187 ± 0.464</td>
<td>2.438 ± 0.602</td>
<td>1.562 ± 0.271 **</td>
<td>2.262 ± 0.553</td>
<td>1.647 ± 0.283 **</td>
</tr>
<tr>
<td>Number of fixations within image late processing (LFWI)</td>
<td>2.459 ± 0.448</td>
<td>3.228 ± 0.971</td>
<td>1.936 ± 0.275 **</td>
<td>3.295 ± 0.972</td>
<td>1.948 ± 0.349 **</td>
</tr>
<tr>
<td>Fixation duration late processing (LFD) (msec)</td>
<td>544.964 ± 93.557</td>
<td>579.036 ± 120.230</td>
<td>485.260 ± 105.351</td>
<td>575.756 ± 123.445</td>
<td>453.469 ± 90.280 *</td>
</tr>
<tr>
<td>Saccadic amplitude early processing (ESA) (degree)</td>
<td>1.411 ± 0.123</td>
<td>1.606 ± 0.251</td>
<td>1.113 ± 0.156 **</td>
<td>1.511 ± 0.214</td>
<td>1.259 ± 0.257</td>
</tr>
<tr>
<td>Saccadic amplitude late processing (LSA) (degree)</td>
<td>1.824 ± 0.169</td>
<td>2.154 ± 0.350</td>
<td>1.563 ± 0.688</td>
<td>2.334 ± 0.441</td>
<td>1.837 ± 0.758</td>
</tr>
</tbody>
</table>

**p < 0.0001, *p < 0.05 significant differences between novel and repeated images for each test conditions**
Number of fixations within image during early and late processing

Repeated measures ANOVA showed significant differences between the number of fixations within an image during early processing (EFWI) for the various tests (F(8, 72) = 7.433, p = 3.608×10^{-7}, η^2 = 0.452). Planned t-tests showed that the EFWI was significantly larger on novel compared to repeated images in “1-back” (t(9) = 4.86, p = 8.951×10^{-4}, d = 1.875), “5-back” (t(9) = 3.89, p = 3.689×10^{-3}, d = 1.402), “10-back” (t(9) = 2.77, p = 2.169×10^{-2}, d = 1.291) and “15-back” (t(9) = 2.65, p = 2.640×10^{-2}, d = 0.994). However, no significant differences were found between the EFWI on novel images (F(4, 36) = 0.853, p = 0.501, η^2 = 0.087) in the different test conditions and between the EFWI on repeated images (F(3, 27) = 1.715, p = 0.187, η^2 = 0.160).

The number of fixations within an image during late processing (LFWI) was also shown to be significantly different between the test conditions (F(8, 72) = 11.299, p = 3.235×10^{-10}, η^2 = 0.557). Planned t-tests show that the LFWI on novel images was significantly larger than on repeated images in the “1-back” (t(9) = 4.88, p = 8.671×10^{-4}, d = 1.811), “5-back” (t(9) = 4.36, p = 1.821×10^{-3}, d = 1.844), “10-back” (t(9) = 3.92, p = 3.490×10^{-3}, d = 1.338) and “15-back” (t(9) = 2.51, p = 3.350×10^{-2}, d = 0.983) test conditions. Repeated measures ANOVA showed that the LFWI on novel images were significantly different (F(4, 36) = 4.193, p = 0.007, η^2 = 0.318). However, post-hoc analysis showed no significant differences between the LFWI on novel images and no significant differences were found in the LFWI on repeated images.

The data suggest that the effects of novelty preference on the number of fixations within images are distributed uniformly throughout the scanning sequence (i.e., early and late processing are affected in a very similar manner).

Fixation duration during early and late processing

Repeated measures ANOVA revealed significant differences between the average fixation durations on novel and repeated images during early processing (EFD, F(8, 72) = 2.734, p = 1.10×10^{-2}, η^2 = 0.233) and late processing (LFD, F(8, 72) = 4.780, p = 9.80×10^{-5}, η^2 = 0.347). Planned t-tests showed significantly larger EFDs on novel compared to the repeated images in only one test (1-back, t(9) = 2.56, p = 3.1×10^{-2}, d = 1.004). Planned t-tests also showed significant differences in LFDs between novel and repeated images in “5-back” (t(9) = 3.66, p =
5.2×10^{-3}, d = 1.131) and “10-back” (t(9) = 2.26, p = 5.0×10^{-2}, d = 0.983). The data suggest that novelty preference affect AFD more in late processing than in early processing. EFD and LFD on novel images and repeated images showed no significant differences between the test conditions.

**Saccadic amplitude during early and late processing**

When the average saccadic amplitude was analysed in the previous section, there were no significant differences between the saccadic amplitudes on novel and repeated images. When the average saccadic amplitude was analysed during early and late stages of processing, repeated measures ANOVA revealed significant differences between the test conditions for both early saccadic amplitude (ESA, F(8, 72) = 3.778, p = 9.53×10^{-4}, η^2 = 0.296) and late saccadic amplitude (LSA, F(8, 72) = 2.920, p = 7.037×10^{-3}, η^2 = 0.245). Paired t-test revealed significantly larger ESAs on novel images compared to repeated images in the “1-back” (t(9) = 8.67, p = 1.2×10^{-5}, d = 2.361) and marginally significant difference in 5-back (t(9) = 2.13, p = 6.2×10^{-2}, d = 1.065) test conditions. LSA was not found to be significantly different between novel and repeated images for any of the test conditions. The data suggest that differences between average saccadic amplitudes on novel and repeated images are more pronounced during the early phases of viewing.

Repeated measures ANOVA showed that ESA was not significantly different between the test conditions on novel or repeated images. LSA was significantly different for novel images (F(4, 36) = 5.134, p = 0.002, η^2 = 0.363) but post-hoc analysis showed no significant differences in the pair-wise comparisons.

**3.2.3 Composite parameters of visual scanning behaviour**

In this section, the product of two basic VSB parameters FWI and AFD was used to estimate the fixation times and the relative fixation times on novel and repeated images. The two parameters are shown for all test conditions (“NN-slides”, “1-back”, “5-back”, “10-back” and “15-back”) in Table 3.5.
Table 3.5 Composite parameters of VSB on the NN-slide, 1, 5, 10 and 15-back test conditions for young controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>NN-slides</th>
<th>1-back</th>
<th>5-back</th>
<th>10-back</th>
<th>15-back</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Novel</td>
<td>Repeated</td>
<td>Novel</td>
<td>Repeated</td>
</tr>
<tr>
<td>Fixation Time (FT) (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2437.484</td>
<td>3282.825</td>
<td>1477.497 ± 3249.866</td>
<td>1560.968 ± 454.648</td>
<td>3073.990 ± 525.184</td>
</tr>
<tr>
<td></td>
<td>± 65.340</td>
<td>± 434.227</td>
<td>± 454.648 **</td>
<td>± 344.839</td>
<td>± 428.863 **</td>
</tr>
<tr>
<td>Relative fixation time (RFT)</td>
<td>0.250 ±</td>
<td>0.346 ±</td>
<td>0.156 ±</td>
<td>0.341 ±</td>
<td>0.163 ±</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>0.049</td>
<td>0.046 **</td>
<td>0.045</td>
<td>0.039 **</td>
</tr>
</tbody>
</table>

** p < 0.0001, * p < 0.05 significant differences of the pairwise comparison test between novel and repeated images on the test conditions
Fixation time and relative fixation time

Repeated measures ANOVA showed significant differences between the fixation times (FT) for the different test conditions (F(8, 72) = 28.889, p = 1.396×10^{-19}, η² = 0.762). Planned paired comparison showed that the FT on the novel and repeated images were significantly different in the “1-back” (t(9) = 6.50, p = 1.1×10^{-4}, d = 4.061), “5-back” (t(9) = 7.14, p = 5.4×10^{-5}, d = 4.340), “10-back” (t(9) = 4.36, p = 1.8×10^{-3}, d = 2.684) and “15-back” (t(9) = 3.89, p = 3.7×10^{-3}, d = 2.426) test conditions. The differences between the FTs on novel and repeated images had large Cohen’s effect size values for all test conditions. Repeated measure ANOVA also showed significant differences in FTs on novel images between the test conditions (F(4, 36) = 13.699, p = 6.956×10^{-7}, η² = 0.604). Post-hoc analysis revealed that the FT on novel images in the “NN-slides” was significantly smaller than the FTs on novel images in the “1-back” (t(9) = 5.84, p = 2.476×10^{-3}, d = 2.723), “5-back” (t(9) = 7.15, p = 5.39×10^{-4}, d = 3.273) and “10-back” (t(9) = 4.03, p = 0.0299, d = 1.701) test conditions. Finally, significant differences were found in the FT on repeated images between the test conditions (F(3, 27) = 3.974, p = 0.018, η² = 0.306). Post-hoc analysis showed that the FT in the “1-back” test condition was significantly smaller than the FT in “15-back” (t(9) = 3.54, p = 0.0377, d = 0.722). The following plot shows the FTs in each test condition:
Figure 3.4 The mean (± 1 standard errors of the mean) fixation time for (AFD) for young controls for the five test conditions (NN-slides, 1-back, 5-back, 10-back and 15-back).

As shown in Figure 3.4, the means of the FTs on repeated/novel images increase/decrease when the time difference between the presentation of novel and repeated images increase. The graph shows that the increase/decrease is continuous and approximately linear. Even though in the study we did not get statistically significant differences between FTs on repeated/novel images unless there were large differences between the test conditions (e.g., “1-back” and “15-back”), it is very likely that the difference will become significant if we use more than 10 subjects (i.e., by reducing the standard error of the mean). As the differences between the FTs on novel and repeated images decrease when the number of slides between the first and second presentation of an image is increased, it is clear that if we want to maximise the differences, the number of slides between the first and second presentation should be minimised.

FTs on novel images that were presented alongside repeated images were significantly higher than FTs on slides that include only novel images (“NN-slides”). This observation clearly shows the effects of peripheral vision on the observed VSB parameters (parameters that are measured
by monitoring gaze position that is directly linked to central vision). The significant reduction in the FT on “NN-slides” is the result of reduction in the number of fixations within images (FWI), reduction in the average fixation duration (AFD) and reduction in the number of transitions into novel images (TBI).

The relative fixation times (RFT) were calculated as the proportion of the FTs on novel and repeated images on the slides. The RFT are very similar to the FT but they provide a normalised quantity per slide that supports comparisons between groups in the same study (young controls, patients with AD, etc.) and comparisons with data from other studies when different experimental protocols are used (i.e., presentation time and number of images).

3.2.4 An alternative approach to data analysis

Until now, the analysis looked at differences between VSB parameters when all the image types (novel, repeated) appear on the same slide. Another option for data analysis is to look at the differences between VSB parameters when the same images appear for the first time (First-Time images) and the second time (Second-time images). In the terminology that was used in the analysis so far, first-time images are novel images (in the “NN-slide”) and second-time images are repeated images. An advantage of the alternative approach to data analysis is that VSB parameters for novel and repeated images are analysed with the same images, which should reduce the variability of the estimated VSB parameters. A disadvantage of the alternative approach is that it tends to reduce differences between visual scanning parameters on images of different types. For example, the FT on novel images in slides with four novel images (“NN-slides”) is significantly lower than the FTs on novel images that appear alongside repeated images (Table 3.5). In this example reductions in the FTs on repeated images in slides that include both novel and repeated images contribute to increases in the FTs on novel images in these slides.
The differences between the FTs on the first-time and second-time images were calculated for all the subjects and all test conditions. The mean difference for young controls for the alternative approach was 734.440 ± 358.255 msec. When the FTs were calculated by the method that was used throughout in previous sections (novel – repeated, when the images are on the same slide) the difference between novel and repeated images was: 1330.717 ± 444.488 msec. As expected, the alternative approach led to a lower mean difference between FTs on novel and repeated images (80% less) but also led to a lower standard deviation of the difference (25% less). Since the ratio of the mean difference in FTs to its standard deviation plays an important role in detection and classification of differences between VSB parameters, and this ratio is lower by 32% for the alternative method, VSB parameters in this chapter are estimated from visual scanning patterns on slides that include both novel and repeated images.

### 3.2.5 Discussion

In previous studies, the fixation time (FT) on novel images was generally used to quantify novelty preference and was shown to be longer on novel compared to repeated images [26][27]. Our data are consistent with this observation for all test conditions. Our data also show that the differences between the fixation times on novel and repeated images decrease as the number of

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**Figure 3.5** First-time images when all the images on the slide are novel and Second-time images when only the two bottom images on the slide are novel.
slides between the first and second presentation is increased. This observation is consistent with studies in older control subjects [57] who showed small, immediate and long term recency (i.e., pictures that were presented closer to the time of recall were remembered better) in free recall experiments in which pictures were presented for relatively long time periods (10 seconds). Even though the difference between the fixation times on novel and repeated images decreases as the number of slides between the first and second presentation increases there is no significant reduction in the ability to detect novelty preference when the novel and repeated images are separated by less than 10 slides (120 seconds).

We also found that the number of fixations within an image (FWI), average fixation duration (AFD), and number of transitions (TBI) are significantly larger on novel images than on repeated images (for one of the test conditions, the average saccadic amplitude (ASA) was also significantly larger on novel images than on repeated images). Further analysis showed that during both early and late processing, the number of fixations within an image (FWI) were significantly higher on novel images than on repeated images. On the other hand, significantly higher AFDs were found on novel compared to repeated images. When the analysis separated the early and late processing, the differences between novel and repeated images were found to be more prominent in late processing.

Even though the average saccadic amplitudes were generally higher on novel images than on repeated images, there was only one test in which there were statistically significant differences between them. Further analysis showed that differences between average saccadic amplitudes on novel and repeated images are more likely to occur during early processing rather than during late processing. The data suggest that during both early and late phases of viewing, the spatial extent of fixations on repeated images is lower compared to that on novel images.

For both novel and repeated images the average fixation durations and the average saccadic amplitudes are larger during late processing than during early processing. These observations suggest that during late processing subjects are more likely to explore areas of images that are spatially apart (larger average saccadic amplitudes) while paying more attention to details in these areas (longer average fixation times).
The study provides two separate indications for the importance of peripheral vision in determining visual scanning behaviour. The first indication is associated with the observation that all the VSB parameters (with the exception of number of fixations within an image during early processing) on novel images in the “NN-Slides” were significantly different from those on novel images in the “n-back” test conditions. The second indication is associated with the observation that the average transitional probabilities into novel images were higher than the average transitional probabilities into repeated images. As transitional probabilities between images are driven by peripheral vision, the bias is further indication for the role that peripheral vision is playing in enhancing the differences between the visual scanning behaviour on novel and repeated images.

3.3 Novelty Preference in Patients with AD and Elderly Controls

The results in the study with young controls provide insights into the expected behaviour of the VSB parameters when subjects are known to have novelty preference. In this section, we studied the VSB parameters in populations that might have diminished or no capacity for novelty preference. These populations include patients with AD and elderly controls. In this section we carried out studies to:

1. Quantify differences between VSB parameters on novel and repeated images
2. Quantify recency effects of the “1-back” and “2-back” test conditions on repeated images
3. Quantify the differences between VSB parameters in patients with AD and elderly controls

3.3.1 Basic parameters of visual scanning behaviour

Table 3.6 shows the means and standard deviations of the basic VSB parameters on novel and repeated images for the “1-back” and “2-back” test conditions for patients with AD and elderly controls. The basic VSB parameters on novel images for slides with only novel images (“NN-slides”) are also presented.
Table 3.6 Basic parameters of VSB on the NN-slide, 1 and 2-back test conditions for patients with AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NN-slides</td>
<td>1-back</td>
<td>2-back</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>Repeated</td>
<td>Novel</td>
</tr>
<tr>
<td>FWI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.397 ± 0.715</td>
<td>5.450 ± 0.851</td>
<td>4.968 ± 0.851 *</td>
</tr>
<tr>
<td>AFD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>422.793 ± 67.285</td>
<td>480.617 ± 117.107</td>
<td>424.683 ± 73.883 *</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.948 ± 0.388</td>
<td>2.003 ± 0.281</td>
<td>1.905 ± 0.290 *</td>
</tr>
<tr>
<td>TBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.237 ± 0.602</td>
<td>2.335 ± 0.721</td>
<td>2.229 ± 0.704 *</td>
</tr>
</tbody>
</table>

**p < 0.001, *p < 0.05 significant differences of the pairwise t-test between novel and repeated images on the test-condition**
The parameters were compared using a mixed design repeated measures ANOVA [56] to study the between-group differences (patients with AD, elderly controls) and the within-group differences in each test condition (“1-back”, “2-back”). If significant differences were found, planned paired comparisons (t-tests) were performed between the novel and repeated images in the “1-back” and “2-back” test condition. This was followed by planned paired comparisons between repeated images in the “1-back” and “2-back” test conditions. If significant diagnostic group × test conditions interactions were found, post-hoc paired comparisons (t-tests) with Bonferroni correction were used to determine significant differences in the VSB parameters on novel and repeated images between patients with AD and elderly controls.

**Number of fixations on images**

Repeated measures ANOVA showed significant main effect for test conditions (F(3, 162) = 38.224, p = 9.835×10⁻¹⁹, η² = 0.414) and significant test condition × diagnostic group interactions (F(3, 162) = 19.990, p = 4.490×10⁻¹¹, η² = 0.270). Planned paired comparisons revealed that a) elderly controls had significantly smaller FWI on repeated images compared novel images in the “1-back” (t(21) = 7.09, p = 5.402×10⁻⁷, d = 2.302) and “2-back” (t(21) = 4.93, p = 7.058×10⁻⁵, d = 1.584) test conditions, b) patients with AD also showed significantly smaller FWI on repeated compared to novel images in “1-back” (t(33) = 3.29, p = 2.380×10⁻³, d = 0.566) but not in “2-back” (t(33) = 0.48, p = 0.6344, d = 0.093), c) No significant differences were found between repeated images in “1-back” and “2-back” test conditions for elderly controls, d) significant differences with small effect size were found between repeated images in the “1-back” and “2-back” test condition for patients with AD (t(33) = 2.15, p = 3.862×10⁻², d = 0.300) and e) significant differences were found between patients with AD and elderly controls on novel images (t(54) = 3.585, p = 0.001, d = 0.975) for both “1-back” and “2-back” test conditions.

Patients with AD had significantly larger number of fixation on novel images than on repeated images. However, this bias was significantly smaller than that of elderly controls and young controls. In addition, the observation that FWI of patients with AD on repeated images in the “2-back” test condition was significantly smaller than the FWI in the “1-back” test condition might suggest that the effects of novelty preference on FWI in patients with AD is so weak that it disappears when the recency effects are reduced (i.e., the time between presentations is...
increased). Figure 3.6 shows the differences between FWI on novel and repeated images, for all test conditions, for patients with AD, elderly controls and young adults.

![Graph showing differences in fixation numbers between novel and repeated images for AD, elderly controls, and young controls](image)

**Figure 3.6** The mean (± 1 standard errors of the mean) difference between the number of fixations within an image (FWI) on novel and repeated images for patients with AD, elderly controls and young controls. A value of zero indicates no differences between the FWI on novel and repeated images.

All the groups exhibited some decrease in the difference between FWI on novel and repeated images as the number of slides between the first and second presentation increased. However, the rate of decline for young controls is much lower than the rate of decline for patients with AD and elderly controls.

**Average fixation duration**

Repeated measures ANOVA revealed significant differences in the average fixation duration (AFD) between the test conditions ($F(3, 162) = 10.884, p = 1.00 \times 10^{-6}, \eta^2 = 0.168$) but no significant interactions between the diagnostic groups and test conditions were found ($F(3, 162) = 0.484, p = 0.695, \eta^2 = 0.009$). Planned t-tests showed that: a) patients with AD exhibited significantly larger AFD on novel than on repeated images in the “1-back” test condition ($t(33) = 3.02, p = 4.9 \times 10^{-3}, d = 0.571$) but not in the “2-back” test conditions; b) for elderly controls AFD
was significantly larger on novel images than on repeated images in both the “1-back” \((t(21) = 3.79, p = 1.1 \times 10^{-3}, d = 0.849)\) and “2-back” test conditions \((t(21) = 3.60, p = 1.7 \times 10^{-3}, d = 0.643)\) and c) no significant differences in AFD were found on repeated images between the “1-back” and “2-back” test conditions for patients with AD and for elderly controls. Both patients with AD and elderly controls had longer AFDs on novel images than on repeated images. In the “1-back” test, patients with AD had significantly longer AFDs on novel images than on repeated images, which is an indication for the effects of novelty preference on AFD. However, as can be seen from the magnitude of the size-effects for the t-tests, this bias was smaller than that of elderly controls and young controls.

**Average saccadic amplitude**

Repeated measures ANOVA showed significant differences between the average saccadic amplitude (ASA) for the different test conditions for patients with AD and elderly controls \((F(3, 162) = 3.980, p = 0.009, \eta^2 = 0.069)\). Planned t-tests showed that significant differences between the ASAs on novel and repeated images in the “1-back” test condition for patients with AD \((t(33) = 2.46, p = 0.019, d = 0.342)\) and for elderly controls \((t(21) = 2.42, p = 0.025, d = 0.521)\). No significant differences were found between the ASAs on novel and repeated images in the “2-back” test conditions for both patients with AD and elderly controls.

**Number of transitions into images**

Repeated measures ANOVA showed significant main effects for the number of transitions into images (TBI) between the test conditions \((F(3, 162) = 9.087, p = 1.4 \times 10^{-5}, \eta^2 = 0.144)\) and significant test conditions \(\times\) diagnostic groups interactions \((F(3, 162) = 3.42, p = 0.0187, \eta^2 = 0.0596)\). Planned t-test showed that a) patients with AD had significantly more TBI into novel images than into repeated images in the “1-back” test condition \((t(33) = 2.33, p = 2.6 \times 10^{-2}, d = 0.150)\), b) elderly controls had significantly more TBI into novel images than into repeated images on both the “1-back” \((t(21) = 5.15, p = 4.2 \times 10^{-5}, d = 0.712)\) and “2-back” \((t(21) = 2.95, p = 7.7 \times 10^{-3}, d = 0.500)\) test conditions, c) no significant differences were found between patients with AD and elderly controls on novel \((t(54) = 1.52, p = 0.133, d = 0.413)\) and on repeated images \((t(54) = 0.3, p = 0.763, d = 0.0816)\), even when data from the two test conditions were averaged. Figure 3.7 shows the difference between the TBI into novel and repeated images.
Figure 3.7 The mean (±1 standard errors of the mean) difference between the number of transitions between images (TBI) on novel and repeated images for patients with AD, elderly controls and young controls.

To provide more insights into the parameter TBI, we explored the transition probabilities between novel and repeated images in a manner that is similar to the study of the average transition probabilities (ATP) in young controls. The ATP was calculated by taking the mean of the transitional probabilities in the “1-back” and “2-back” test condition.

Table 3.7 The average transitional probability of patients with AD and elderly controls for novel to novel, novel to repeated, repeated to novel and repeated to repeated

<table>
<thead>
<tr>
<th>Transition type</th>
<th>Mean ± standard deviation</th>
<th>Expected ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with AD</td>
<td>Elderly controls</td>
</tr>
<tr>
<td>Novel to Novel</td>
<td>0.316 ± 0.065</td>
<td>0.379 ± 0.076</td>
</tr>
<tr>
<td>Novel to Repeated</td>
<td>0.659 ± 0.043</td>
<td>0.621 ± 0.076</td>
</tr>
<tr>
<td>Repeated to Novel</td>
<td>0.666 ± 0.054</td>
<td>0.713 ± 0.052</td>
</tr>
<tr>
<td>Repeated to Repeated</td>
<td>0.308 ± 0.061</td>
<td>0.287 ± 0.052</td>
</tr>
</tbody>
</table>
In this test, images of the same type (novel or repeated images) were not confined into the same row or column. Pairwise comparisons showed that the ATP of patients with AD were not significantly different from the expected values (novel to novel: \( t(33) = 1.23, p = 0.229 \), novel to repeated: \( t(33) = 1.23, p = 0.229 \), repeated to novel: \( t(33) = 1.95, p = 0.0602 \), and repeated to repeated: \( t(33) = 1.95, p = 0.0602 \)). On the other hand, paired comparisons showed for elderly controls the ATP were significantly different from the expected values (novel to novel: \( t(21) = 2.83, p = 1.011 \times 10^{-2} \), novel to repeated: \( t(21) = 2.83, p = 1.011 \times 10^{-2} \), repeated to novel: \( t(21) = 4.19, p = 4.079 \times 10^{-4} \) and repeated to repeated: \( t(21) = 4.19, p = 4.079 \times 10^{-4} \)). The results showed that for patients with AD the shifts of attention between images were not affected by novelty preference, while elderly controls showed a preference for transitions into novel images. The results of the elderly controls were consistent with the results for young controls.

### 3.3.2 Sequence dependent parameters of visual scanning behaviour

Table 3.8 presents data regarding the number of fixations within an image, average fixation duration and the average saccadic amplitude when images on slides are viewed for the first time (early processing) and at subsequent instances (late processing). Data is presented for patients with AD and elderly controls for all test conditions: “1-back”, “2-back” and “NN-slides”.

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<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NN-slides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-back</td>
<td>2-back</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>Repeated</td>
</tr>
<tr>
<td>EFWI</td>
<td>2.517 ± 0.706</td>
<td>2.410 ± 0.799</td>
</tr>
<tr>
<td>LFWI</td>
<td>2.233 ± 0.414</td>
<td>2.317 ± 0.487</td>
</tr>
<tr>
<td>EFD</td>
<td>393.778 ± 54.303</td>
<td>444.902 ± 101.966</td>
</tr>
<tr>
<td>LFD</td>
<td>426.167 ± 89.261</td>
<td>487.775 ± 162.119</td>
</tr>
<tr>
<td>ESA</td>
<td>1.197 ± 0.375</td>
<td>1.460 ± 0.322</td>
</tr>
<tr>
<td>LSA</td>
<td>1.857 ± 0.378</td>
<td>1.944 ± 0.419</td>
</tr>
</tbody>
</table>

**p < 0.001, *p < 0.05 significant differences of the pairwise t-test between novel and repeated images on the test-condition**
Number of fixations within an image during early and late processing

Repeated measures ANOVA showed significant main effects between the various test conditions for the number of fixations within an image during early processing (EFWI, F(3, 162) = 18.552, p = 2.146×10^{-10}, η² = 0.256) and showed significant test conditions × group interactions (F(3, 162) = 7.239, p = 1.38×10^{-4}, η² = 0.118). Planned paired t-tests showed significant differences in EFWI between novel and repeated images in the “1-back” test condition for patients with AD (t(33) = 2.31, p = 2.703×10^{-2}, d = 0.191) and elderly controls (t(21) = 6.29, p = 3.099×10^{-6}, d = 1.090). In the “2-back” test condition, only the EFWI on elderly controls were found to be significantly different between novel and repeated images (t(21) = 4.30, p = 3.173×10^{-4}, d = 0.949). In addition, significant differences were found in the EFWI between patients with AD and elderly controls on repeated images (t(54) = 2.414, p = 0.019, d = 0.657) but not on novel images (t(54) = 0.153, p = 0.877, d = 0.0416).

Significant differences between the test conditions were also found in the number of fixations within an image during late processing (LFWI, F(3, 162) = 6.752, p = 2.60×10^{-4}, η² = 0.115) and in the diagnostic group × test condition interactions (F(3, 162) = 0.392, p = 0.01, η² = 0.07). Planned t-test showed that only elderly controls showed significant differences between the LFWI on novel and repeated in the “1-back” (t(21) = 5.22, p = 3.583×10^{-5}, d = 1.350) and “2-back” test conditions (t(21) = 2.07, p = 5.128×10^{-2}, d = 0.675). In addition when data from both test conditions were combined significant differences between patients with AD and elderly controls were found on repeated images (t(54) = 2.065, p = 0.045, d = 0.562) but not on novel images (t(54) = 1.442, p = 0.115, d = 0.392). The data suggest that for both patients with AD and elderly controls, the effects of novelty preference on the number of fixations within an image occur throughout the duration of scanning.

Fixation duration during early and late processing

Repeated measures ANOVA showed significant main effects for fixation duration during early processing (EFD) between test conditions, for patients with AD and elderly controls (F(3,162) = 13.545, p = 6.264×10^{-8}, η² = 0.201) and no significant diagnostic group × test condition interactions (F(3, 162) = 0.242, p = 0.867, n = 0.004). Planned paired comparison showed
significant differences in the EFD between the novel and repeated images for a) patients with AD in the “1-back” test conditions \((t(33) = 2.98, p = 5.4 \times 10^{-3}, d = 0.585)\) and b) elderly controls in the “1-back” \((t(21) = 3.57, p = 1.8 \times 10^{-3}, d = 0.775)\) and “2-back” test conditions \((t(21) = 5.08, p = 5.0 \times 10^{-5}, d = 0.766)\).

Mauchly’s test indicated that fixation duration during late processing (LFD) for all test conditions violated the assumption of sphericity \(\chi^2(5) = 20.840, p = 0.001\), and the degree of freedom were corrected using Greenhouse-Geisser estimates of sphericity \(\varepsilon = 0.775\). Repeated measures ANOVA revealed significant differences in LFDs between test conditions \((F(2.326, 120.956) = 3.239, p = 0.024, \eta^2 = 0.059)\) but no significant diagnostic group × test condition interactions \((F(2.326, 120.956) = 1.509, p = 0.214, \eta^2 = 0.028)\) were found. Planned t-test showed no significant differences between fixation duration on novel or repeated images during late processing.

The data suggest that for both patients with AD and elderly controls the effects of novelty preference on fixation duration occur primarily during early processing of images rather than during late processing.

**Saccadic amplitude during early and late processing**

Repeated measures ANOVA showed significant main effects for saccadic amplitude between test conditions during early processing (ESA, \(F(3, 162) = 2.939, p = 8.779 \times 10^{-7}, \eta^2 = 0.172\)), and significant diagnostic group × test conditions interactions \((F(3, 162) = 2.939, p = 0.035, \eta^2 = 0.052)\). Repeated measures ANOVA did not show significant differences in saccadic amplitude between test conditions during late processing (LSA, \(F(3, 141) = 0.552, p = 0.648, \eta^2 = 0.012\)).

The reasons for the decrease in the degrees of freedom for LSA was because several subjects did not make saccadic eye movements within images after all the images were seen (i.e., they only performed one fixation in an image on subsequent visits). Paired t-tests showed that patients with AD had significantly larger ESA in the “1-back” test on novel images \((t(33) = 2.32, p = 2.7 \times 10^{-2}, d = 0.354)\), while elderly controls had significantly larger ESA on novel images during both the “1-back” \((t(21) = 4.14, p = 4.6 \times 10^{-4}, d = 1.011)\) and “2-back” \((t(21) = 3.38, p = 3.0 \times 10^{-3}, d = 1.003)\). However, the ESA was not found to be significantly different between patients with AD.
and elderly controls on novel (t(54) = 0.52, p = 0.608, d = 0.141) and repeated images (t(54) = 1.655, p = 0.102, d = 0.450).

For patients with AD, the differences between saccadic amplitudes on novel and repeated images during early processing are much smaller than the differences for elderly controls and young controls (based on the magnitudes of the size-effects for the t-tests). The data suggest that for both patients with AD and elderly controls, the effects of novelty preference on saccadic amplitude occur primarily during early processing rather than during late processing of images.

### 3.3.3 Composite parameters of visual scanning behaviour

The following table shows the fixation time and relative fixation time on novel and repeated images for all test conditions: “NN-slides”, “1-back” and “2-back” for patients with AD and elderly controls.
Table 3.9 Composite parameters of VSB on NN-slides, 1, and 2-back images for patients with AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
<th>NN-slides</th>
<th>NN-slides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-back</td>
<td>2-back</td>
<td>1-back</td>
<td>2-back</td>
</tr>
<tr>
<td></td>
<td>Novel</td>
<td>Repeated</td>
<td>Novel</td>
<td>Repeated</td>
</tr>
<tr>
<td>FT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2214.171 ± 192.720</td>
<td>2453.061 ± 403.507</td>
<td>2064.457 ± 308.942**</td>
<td>2451.049 ± 404.060</td>
<td>2130.962 ± 356.920*</td>
</tr>
<tr>
<td>RFT</td>
<td>0.250 ± 0.000</td>
<td>0.276 ± 0.031</td>
<td>0.234 ± 0.027**</td>
<td>0.276 ± 0.031</td>
</tr>
</tbody>
</table>

**p < 0.001, *p < 0.05 significant differences of the pairwise t-test between novel and repeated images on the test-condition
**Fixation time**

Repeated measures ANOVA showed significant differences between the fixation times (FT) for the different test conditions (F(3, 162) = 63.481, p = 3.419×10^{-27}, \eta^2 = 0.540) and significant test condition × diagnostic group interactions (F(3, 162) = 16.422, p = 2.293×10^{-9}, \eta^2 = 0.233).

Planned paired comparisons showed that a) patients with AD had significantly longer FTs on novel images than on repeated images in the “1-back” (t(33) = 4.84, p = 3.0×10^{-5}, d = 1.081) and in the “2-back” (t(33) = 2.40, p = 2.2×10^{-2}, d = 0.611) test conditions, b) elderly controls had significantly longer FTs on novel images than on repeated images in the “1-back” (t(21) = 8.21, p = 5.5×10^{-8}, d = 2.847) and in the “2-back” (t(21) = 5.87, p = 8.0×10^{-6}, d = 2.091) test conditions, c) significant differences were found in the FT between patients with AD and elderly controls on novel (t(54) = 2.563, p = 0.013, d = 0.697) and on repeated (t(54) = 4.838, p = 1.1×10^{-5}, d = 1.316) images. Even though both groups had significant differences between the fixation times on novel and repeated images, elderly controls had much larger differences (see effect-sizes of the t-tests) than patients with AD.

As expected, the results of the statistical analysis of the relative fixation times (RFT) were very similar to those obtained for the fixation time (FT). The expected values for RFT is 0.25 if all the images were viewed equally. T-tests showed that patients with AD had significantly different RFTs on both novel and repeated images in the “1-back” (Novel: t(33) = 4.93, p = 2.26×10^{-5}; Repeated: t(33) = 3.414, p = 0.0017) and only novel images in the “2-back” (Novel: t(33) = 3.168, p = 0.033). Repeated images in the “2-back” test conditions were not viewed significantly different from the expected value (t(33) = 1.23, p = 0.227). Elderly controls were also found to exhibit significantly different RFTs compared to the expected value in the “1-back” (Novel: t(21) = 8.756, p = 1.87×10^{-8}; Repeated: t(21) = 8.34, p = 4.192×10^{-8}) and “2-back” (Novel: t(21) = 6.828, p = 9.45×10^{-7}; Repeated: t(21) = 5.540, p = 1.692×10^{-5}) test conditions.

The following plot (Figure 3.8) shows the differences between the RFTs on novel and repeated images for young controls, elderly controls and patients with AD.
A one-way ANOVA with between-subject factors of diagnostic group (patients with AD, elderly controls, young controls) and the difference in RFTs in the “1-back” test conditions (the only test condition for which we have data for the three groups) showed significant main effects ($F(2, 63) = 21.485, p = 7.689 \times 10^{-8}$). Post-hoc analysis with Bonferroni correction showed significant differences between the three diagnostic groups (young controls vs elderly controls: $p = 0.011$, young controls vs patients with AD: $p = 1.528 \times 10^{-7}$, elderly controls vs patients with AD: $p = 6.72 \times 10^{-5}$).

3.3.4 Discussion

The results in this section shows that fixation times (FT), number of fixations within an image (FWI), average fixation duration (AFD), average saccadic amplitudes (ASA) and the number of transitions (TBI) are significantly longer/larger on novel images than on repeated images for both patients with AD and elderly controls. Further analysis showed that differences between the AFD and ASA on novel and repeated images are mainly due to differences in the early stages of processing (i.e., processing that are associated with the first visit to an image) whereas the differences in the FWI occurs over the full duration of slide presentation.
Even though patients with AD demonstrated biases to novel images in several VSB parameters, these biases tend to be much smaller than those observed in elderly controls. For some of the parameters (e.g., average fixation duration) these biases disappear when the time and the number of slides between the presentations of novel and repeated images increase. The average transition probabilities (ATP) of patients with AD showed no significant differences from the expected values whereas the ATP of young adults and elderly controls showed significant preference towards novel images. On the other hand, the relative fixation times of elderly patients with AD were significantly different (with the exception of repeated images in “2-back”) from the expected value. Since the ATP is presumed to be a process of peripheral vision and RFT is presumed to be a process of peripheral and central vision, this may suggest that novelty preference may affect the two processes differently.

For all parameters, biases of the VSB parameters towards novel images were largest for young controls and smallest for patients with AD. The results suggest that the effects of novelty preference on VSB parameters are reduced by age and by Alzheimer’s disease (patients with AD show less affects than elderly controls).

The analysis in this section showed that with our novel testing paradigm, we can measure significant differences between the visual scanning behaviour of patients with AD and elderly controls when these two groups view slides of novel and repeated images. The analysis identified several VSB parameters that help to quantify these differences and in the next section we will explore the use of these parameters in classifiers that are designed to separate patients with AD from elderly controls.

3.4 Using Novelty Preference to Differentiate between Patients with AD and Elderly Controls

3.4.1 Parameter selection

The results in the previous section showed significant differences between patients with AD and elderly controls for the following VSB parameters: FWI, TBI, EFWI, LFWI, ESA, FT and RFT. These VSB parameters capture differences in the effects of novelty preference on visual scanning behaviour of patients with AD and elderly controls. For all of the above VSB parameters, the differences between the magnitudes of the parameters for novel images and
repeated images indicate the effects of novelty preference on these parameters. When the
difference is zero, it indicates no bias towards novel images (no indication that novelty
preference affects this VSB parameter). In this section we will study how the effects of novelty
preference, as measured by these differences, can be used as potential inputs to classifiers that
differentiate between the two groups.

The difference in the VSB parameters on novel and repeated images that showed significant
differences between patients with AD and elderly controls are shown in Table 3.10 (ΔFWI, ΔTBI, ΔEFWI, ΔLFWI, ΔESA, ΔFT and ΔRFT).

Table 3.10 The mean and standard error of the mean of the differences between VSB parameters on novel and repeated images for patients with AD and elderly controls

<table>
<thead>
<tr>
<th>VSB Parameters</th>
<th>Patients with AD</th>
<th>Elderly Controls</th>
<th>Paired t-test between groups and effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-back</td>
<td>2-back</td>
<td>1-back</td>
</tr>
<tr>
<td>ΔFWI</td>
<td>0.4819 ± 0.8537 **</td>
<td>0.1003 ± 1.2187 **</td>
<td>2.0904 ± 1.3831 **</td>
</tr>
<tr>
<td>ΔTBI</td>
<td>0.1068 ± 0.2673 *</td>
<td>0.006 ± 0.3164 *</td>
<td>0.2864 ± 0.2610 *</td>
</tr>
<tr>
<td>ΔEFWI</td>
<td>0.1503 ± 0.3939 **</td>
<td>0.1965 ± 0.583*</td>
<td>0.696 ± 0.531**</td>
</tr>
<tr>
<td>ΔLFWI</td>
<td>0.1261 ± 0.608*</td>
<td>-0.0468 ± 0.5904*</td>
<td>0.5628 ± 0.5058*</td>
</tr>
<tr>
<td>ΔESA</td>
<td>0.125 ± 0.3130 *</td>
<td>0.081 ± 0.3721</td>
<td>0.3158 ± 0.3578 *</td>
</tr>
<tr>
<td>ΔFT</td>
<td>388.604 ± 468.130 **</td>
<td>223.357 ± 543.6154 **</td>
<td>1020.5 ± 583.305 **</td>
</tr>
<tr>
<td>ΔRFT</td>
<td>0.0422 ± 0.0512 **</td>
<td>0.0243 ± 0.0605 **</td>
<td>0.1174 ± 0.0639 **</td>
</tr>
</tbody>
</table>

** p < 0.001, * p < 0.05 significant differences between patients with AD and elderly controls (paired t-test)
The table above shows the group differences when patients with AD and elderly controls look at novel and repeated images. The asterisks indicate the significance levels of the paired t-tests between patients with AD and elderly controls in the “1-back” and “2-back” test conditions. The ΔFWI showed the largest effect size (d = 1.508) between patients with AD and elderly controls.

3.4.2 Baseline classifier of patients with AD and elderly controls

The standard measure of novelty preference is to use the RFT on novel compared to repeated images (i.e., ΔRFT) [58]. The following table shows the classification results of patients with AD and elderly controls using a Maximum a Posterior (MAP) classifier with ΔRFT data from the “1-back”, “2-back” test conditions:

<table>
<thead>
<tr>
<th>VSB Parameters</th>
<th>Training</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔRFT: 1-back</td>
<td>0.821</td>
<td>0.853</td>
<td>0.773</td>
<td>0.821</td>
</tr>
<tr>
<td>ΔRFT: 2-back</td>
<td>0.731</td>
<td>0.735</td>
<td>0.773</td>
<td>0.731</td>
</tr>
<tr>
<td>ΔRFT: average 1 and 2-back</td>
<td>0.821</td>
<td>0.853</td>
<td>0.773</td>
<td>0.821</td>
</tr>
</tbody>
</table>

The data from the “1-back” test condition, achieved high sensitivity (0.853) and test accuracy (0.821). The performance of the base line classifier (MAP) with ΔRFT data from the “2-back” condition had similar specificity and slightly worse sensitivity compared to the classifier from the “1-back” condition (0.773). Figure 3.9 shows the ΔRFT for individual participants in the “1-back” and “2-back” conditions. As expected, individual patients with AD tend to have smaller differences between their RFTs on novel and repeated images compared to elderly controls. In addition, both patients with AD and elderly controls show larger ΔRFTs in the “1-back” test condition compared to the “2-back” test condition (the data are below a line with a slope of 1) which can explain the increased sensitivity of the classifier with data from the “1-back” test condition. When the ΔRFTs in the “1-back” and “2-back” test conditions were averaged the classifier results were similar to the results obtained with data from the “1-back” test condition. The classifier results with the averaged data were used as a baseline classifier.
3.4.3 Classification of patients with AD and elderly controls using a single VSB parameter

As was shown at the beginning of this section, the parameter ΔFWI best characterizes differences in VSB between patients with AD and elderly controls. Figure 3.10 shows a scatter plot of the number of fixations within image (FWI), for individual subjects (patients with AD and elderly controls), for the two test conditions (“1-back” and “2-back”). Notice the close resemblance of Figure 3.9 and Figure 3.10.
Figure 3.10 The difference between the number of fixations within an image on novel and repeated images in the 1-back and 2-back test condition.

Figure 3.10 suggests that even though individual results in the “1-back” and “2-back” are highly correlated ($r(56) = 0.593, p = 1 \times 10^{-6}$) the recency effects are clearly shown (the points are below a line with a slope of 1). This suggests that on average, subjects tend to have higher ΔFWIs in the “1-back” condition compared to the “2-back” condition. The FWIs in the two test conditions (“1-back” and “2-back”) were used as a feature space for the following classifiers; MAP (baseline), voting, averaging, logistic regression, naïve Bayes, discrete adaboost and real adaboost.
### Table 3.12 The results of the FWI classifiers for patients with AD and elderly controls

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Training</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.821</td>
<td>0.853</td>
<td>0.773</td>
<td>0.821</td>
</tr>
<tr>
<td>Voting</td>
<td>0.804</td>
<td>0.911</td>
<td>0.634</td>
<td>0.804</td>
</tr>
<tr>
<td>Averaging</td>
<td>0.804</td>
<td>0.794</td>
<td>0.818</td>
<td>0.804</td>
</tr>
<tr>
<td>Logistic regression</td>
<td>0.804</td>
<td>0.882</td>
<td>0.590</td>
<td>0.768</td>
</tr>
<tr>
<td>Naïve Bayes</td>
<td>0.750</td>
<td>0.882</td>
<td>0.545</td>
<td>0.750</td>
</tr>
<tr>
<td>Adaboost</td>
<td>1</td>
<td>0.791</td>
<td>0.724</td>
<td>0.769</td>
</tr>
<tr>
<td>Real adaboost</td>
<td>0.875</td>
<td>0.912</td>
<td>0.818</td>
<td>0.875</td>
</tr>
</tbody>
</table>

As shown in Table 3.12, real adaboost provides better classification accuracies compared to the baseline classifier (MAP classifier using the average ΔRFTs of “1-back” and “2-back” test conditions) while the performances of all other classifiers were inferior to that of the baseline classifier. For all classifiers, the sensitivity (classifying patients with AD correctly) was higher compared to specificity (classifying elderly controls correctly), which suggests that the results of the patients with AD are confined to a smaller area in the observation space than those of elderly controls. The differences between the training and testing accuracies of logistic regression and adaboost may suggest that these two classifiers are over fitting the data.

### 3.4.4 Classification of patients with AD and elderly controls using two VSB parameters

Using more than one VSB parameter (in addition to the ΔFWI) may provide better classification results. To improve the performance of the classifier we try to select a VSB parameter that captures the difference in the effects of novelty preference on visual scanning behaviour of patients with AD and elderly controls and at the same time is not correlated with the ΔFWI. Pearson’s correlation coefficients between ΔFWI and ΔTBI, ΔEFWI, ΔLFWI, ΔESA and ΔRFT (ΔFT was omitted due to the similarities to ΔRFT) for data from both the “1-back” and “2-back” test conditions, for patients with AD and elderly controls, were computed and the results are shown in Table 3.13:
Table 3.13 Correlation between the parameters and the FWI

<table>
<thead>
<tr>
<th>VSB parameters</th>
<th>Correlation between parameters and the ΔFWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTBI</td>
<td>$r = 0.782$</td>
</tr>
<tr>
<td>ΔEFWI</td>
<td>$r = 0.551$</td>
</tr>
<tr>
<td>ΔLFWI</td>
<td>$r = 0.504$</td>
</tr>
<tr>
<td>ΔESA</td>
<td>$r = 0.328$</td>
</tr>
<tr>
<td>ΔRFT</td>
<td>$r = 0.911$</td>
</tr>
</tbody>
</table>

As shown in Table 3.13, differences in early saccadic amplitudes (ESA) are the least correlated with ΔFWI. ΔFWI and ΔESA in the “1-back” and “2-back” test conditions were used to classify patients with AD and elderly controls. The results are shown in the table below.

Table 3.14 Classification of patients with AD and elderly controls using ΔFWI and ΔESA

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Training</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.821</td>
<td>0.853</td>
<td>0.773</td>
<td>0.821</td>
</tr>
<tr>
<td>Voting</td>
<td>0.893</td>
<td>0.971</td>
<td>0.773</td>
<td>0.893</td>
</tr>
<tr>
<td>Averaging</td>
<td>0.821</td>
<td>0.823</td>
<td>0.818</td>
<td>0.821</td>
</tr>
<tr>
<td>Logistic regression</td>
<td>0.929</td>
<td>0.941</td>
<td>0.818</td>
<td>0.893</td>
</tr>
<tr>
<td>Naive Bayes</td>
<td>0.917</td>
<td>0.941</td>
<td>0.818</td>
<td>0.893</td>
</tr>
<tr>
<td>Adaboost</td>
<td>1</td>
<td>0.941</td>
<td>0.863</td>
<td>0.910</td>
</tr>
<tr>
<td>Real Adaboost</td>
<td>0.929</td>
<td>0.941</td>
<td>0.818</td>
<td>0.893</td>
</tr>
</tbody>
</table>

Table 3.14 shows that the test accuracies for all the classifiers, other than “Averaging”, were larger compared to the base line classifier. Adaboost showed the best performance that achieved very high sensitivity (94.1%, 32/34 patients with AD were classified correctly) and specificity (86.3% 19/22 elderly controls were classified correctly). When the input space for the classifiers included only ΔFWI, the highest sensitivity and specificity were (91.2% 31/34 and 81.8 18/22),
respectively. This suggests that the use of uncorrelated VSB parameters improves the performance of the classifier.

3.5 Discussion

Remembering new events and facts often become more difficult with age and almost impossible for patients with AD [59]. The effects of aging and disease on memory performance can be measured directly on tasks that explicitly require subjects to recall or recognise information (explicit or declarative memory tasks) or indirectly on tasks that measure changes in speed, accuracy, or response bias due to previous exposure to a stimulus (implicit memory tasks) [31]. In this chapter we studied the effects of novelty preference (an implicit memory task) on VSB parameters in young controls, patients with AD and elderly controls. The effects of novelty preference on VSB parameters in older healthy subjects were reduced when compared with the effects on young adults (effects of aging) but were larger than the effects of novelty preference on patients with AD. These results are somewhat inconsistent with the results of previous studies where no difference in the responses of priming tasks were found between of elderly controls and patients with AD (for review see [36]). When results from a variety of priming tasks were reviewed (word-stem completion etc.) the results regarding impaired performance in patients with AD were ambiguous. 21 of the 63 reviewed studies found impaired memory performance in patient with AD when compared with aging healthy individuals while 42 studies did not find such impairment. Our data add objective evidence for the deleterious effect of AD on memory performance. It is very likely that the results from priming studies [36] suffer from low reliability and sensitivity as they require substantial cooperation and participation from subject. Our methodology does not require much effort or cooperation from the subjects and therefore the effects of novelty preference can be measured with high reliability and sensitivity.

Previous studies showed that differences in fixation times on novel and repeated images could be used to measure of novelty preference [58]. In this study we showed that a large number of VSB parameters, including differences in fixation durations, saccadic amplitudes, the number of fixations within images and the number of transition between images can also be used to measure novelty preference. When two of these parameters: a) the difference between the number of fixations on novel and repeated images and b) the difference between the average saccadic amplitudes on novel and repeated images during early processing were used by an
adaboost classifier, patients with AD could be differentiated from the elderly controls with high sensitivity (94.1%) and specificity (86.3%).

The methodology that was described in this chapter improves the sensitivity and reliability of detecting memory impairment. Measures of novelty preference at varying stages of AD may provide insight on the degradation of memory. The early stages or prior to (mild cognitive impairment) onset of AD is associated with changes in cognitive performance [58]. The ability to detect memory impairment more accurately might support early detection of subjects who are likely to suffer from AD to aid the future planning of the patient and the evaluation of possible pharmaceutical treatment [17].
Chapter 4. Apathy and Visual Scanning Bias in Patients with Alzheimer’s Disease

Apathy is defined as emotional indifference, diminished motivation and disinterest [7] and is common in patients with AD [8]. Previous studies showed that biases in visual scanning behaviour can be used to quantify emotional preferences [40], motivation and interest [44]. In this chapter we test the hypothesis that emotional indifference reduces differences between VSB when images with different emotional contents are viewed. To test the hypothesis we studied VSB parameters in apathetic patients with Alzheimer Disease (AD-AP) and compared their VSB to that of patients with AD and elderly controls. Participants were presented with two sets of slides. In the first set, participants looked at slides with images that vary in attractiveness/pleasantness (valence) but have similar excitability (arousal). In the second set, participants looked at slides with images that vary in both attractiveness/pleasantness and excitability. The second set provides a method to study both valence and arousal in a continuum which was previously not assessed as subjects were either presented with emotionally pleasant or emotionally unpleasant images alongside neutral images.

The VSB parameters were divided into three groups. The first group includes parameters that characterise basic eye movement a) number of fixations within an image; b) average fixation duration; c) average saccadic amplitude and d) number of transitions between images. The second group consists of VSB parameters that are associated with early processing (the first visit) and late processing (subsequent visits). The parameters include: a) number of fixations within images; b) fixation duration and c) saccadic amplitude. Finally, the third group includes composite VSB parameters: a) fixation time and b) relative fixation time.

4.1 Study Design

The visual stimuli and participants are described in this section.

4.1.1 Visual stimuli

Two types of slides were presented; slides with two social and two dysphoric images (images on each slide had large differences in valances and similar arousals) and slides with one social, one dysphoric and two neutral images (images on each slide had large differences in arousals and
valances). For the slides with two social and two dysphoric images, the images were selected from the International Affective Picturing system (IAPS). IAPS is a database consisting of images of different emotional contents which are normalised for complexity [60]. Images in the IAPS database were rated based on valence (high valence: attractive or pleasant, low valence: aversive or unpleasant) [61] and arousal (high arousal: exciting, low arousal: calm) [60]. Images in the slides with one social, one dysphoric and two neutral images were not selected from the IAPS database however they were rated using the same criteria that was used to rate images from the IAPs database. The following table describes the images used in the study (social, dysphoric and neutral) based on the IAPS rating scale.

<table>
<thead>
<tr>
<th>Image Type</th>
<th>Valence</th>
<th>Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social</td>
<td>High (greater than 5.5)</td>
<td>Medium (4 - 6)</td>
</tr>
<tr>
<td>Dysphoric</td>
<td>Low (less than 4.5)</td>
<td>Medium (4 - 6)</td>
</tr>
<tr>
<td>Neutral</td>
<td>Medium (4 - 6)</td>
<td>Low (1 - 4)</td>
</tr>
</tbody>
</table>

Each slide set had 16 slides and examples of one slide from each type of slide are shown in Figure 4.1:

Figure 4.1 An example of the slides used in this section; the left consist of 2 social and 2 dysphoric images and the right consists of 1 social, 1 dysphoric and 2 neutral images.
Images on the slides with two social and two dysphoric images are referred to as the images in the “valence” test condition. Images on slides with one social, one dysphoric and two neutral images are referred to as images in the “valence arousal” test condition.

4.1.2 Participants

The participants in this study included 35 patients with AD that were recruited from the Alzheimer’s disease clinic at the Sunnybrook Health Science Centre (Ontario, Canada). Of the 35 patients with AD, 16 patients were apathetic (NPI-apathy > 4 and NPI-depression < 4, age = 78.56 ± 6.74). In this section, apathetic patients with AD are referred to as patients with AD-AP and patients with only AD are referred to as “patients with AD” (NPI-apathy < 4 and NPI-depression < 4, age = 77.50 ± 8.92). In addition, 22 elderly controls (age = 71.65 ± 9.26) participated in the study.

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Number recruited</th>
<th>Number with usable data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AD-AP</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Patients with AD</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Elderly controls</td>
<td>22</td>
<td>21</td>
</tr>
</tbody>
</table>

As shown in Table 4.2, one patient with AD and one elderly control did not satisfy the data quality criteria (at least 50% of the slides have more than 70% of the gaze estimates within the boundaries of the images on each slide) for the study.

4.2 Visual Scanning Biases in the Valence Test Condition

The VSB parameters on images in the “valence” test condition were first used to test for emotional preferences for “sad” (low valence) or “social” (high valence) images. In this section, we quantified differences between VSB parameters on social and dysphoric images for patients with AD-AP, AD and elderly controls.
4.2.1 Basic parameters of visual scanning behaviour

Table 4.3 shows the means and standard deviations of the basic VSB parameters in the “valence” test condition for patients with AD-AP, AD and elderly controls. The VSB parameters are shown in two separate columns, one for social images and one for dysphoric images.

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social</td>
<td>Dysphoric</td>
<td>Social</td>
</tr>
<tr>
<td>Number of fixations within an image (FWI)</td>
<td>5.191 ± 0.974</td>
<td>5.138 ± 0.690</td>
<td>4.977 ± 0.918</td>
</tr>
<tr>
<td>Average fixation duration (AFD) (msec)</td>
<td>479.843 ± 59.644</td>
<td>484.842 ± 75.958</td>
<td>507.249 ± 167.960</td>
</tr>
<tr>
<td>Average saccadic amplitude (ASA) (degrees)</td>
<td>1.970 ± 0.248</td>
<td>2.189 ± 0.255</td>
<td>2.084 ± 0.288</td>
</tr>
<tr>
<td>Number of transitions between images (TBI)</td>
<td>1.920 ± 0.392</td>
<td>1.862 ± 0.442</td>
<td>1.953 ± 0.695</td>
</tr>
</tbody>
</table>

The mean and standard deviations of the VSB parameters were compared using a mixed design repeated measures ANOVA with a between-group difference of diagnostic group (patients with AD-AP, patients with AD, elderly controls) and a within-group difference of image types (social, dysphoric). If significant differences were found, planned paired comparisons (t-tests) were performed between the VSB parameter on social and dysphoric images for patients with AD-AP, AD and elderly controls. If significant image type × diagnostic group interactions were found, planned t-tests were performed between the VSB parameters of patients with AD-AP and patients with AD on social and dysphoric images. Significances levels for all statistical tests were set to $p = 0.05$.

**Number of fixations within an image**

Repeated measure ANOVA showed no significant main effects in the number of fixations with an image (FWI) between social and dysphoric images for patients with AD-AP, patients with AD and elderly controls ($F(1, 53) = 1.462, p = 0.232, \eta^2 = 0.027$). Patients with AD-AP and patients
with AD showed very similar FWI on social images compared to dysphoric images. Elderly controls showed a tendency to have higher FWI on social images compared to dysphoric images.

**Average fixation duration**

The average fixation duration (AFD) did not show significant differences between the image types in the “valence” test condition (F(1, 53) = 2.405, p = 0.127, \( \eta^2 = 0.043 \)). Although no significant differences were found, the AFDs on dysphoric images were lower than on social images for patients with AD and elderly controls whereas the AD-AP had similar AFDs on social and dysphoric images.

**Average saccadic amplitude**

Repeated measure ANOVA showed significant main effect between the average saccadic amplitudes (ASA) on social and dysphoric images (F(1, 53) = 22.222, p = 1.8\times10^{-5}, \( \eta^2 = 0.295 \)) however no significant image type \( \times \) diagnostic group interactions were found. Planned t-test showed that the ASA on social and dysphoric images were significantly different for patients with AD-AP (\( t(15) = 2.95, p = 4.599\times10^{-3} \)) and elderly controls (\( t(21) = 3.52, p = 8.98\times10^{-4} \)) and marginally significance for patients with AD (\( t(17) = 1.757, p = 0.0833 \)). The ASA was lower on the social compared to dysphoric images for all diagnostic groups.

**Number of transitions between images**

Repeated measure ANOVA showed significant main effects for the number of transitions between images (TBI), between the social and dysphoric images (F(1, 53) = 11.285, p = 0.001, \( \eta^2 = 0.176 \)) as well as significant image type \( \times \) diagnostic group interactions (F(1, 53) = 6.274, p = 0.004, \( \eta^2 = 0.191 \)). The planned t-tests showed that: a) elderly controls had significantly different TBIs on social and dysphoric images (\( t(21) = 5.138, p = 4.0\times10^{-6}, d = 0.793 \)) while patients with AD and patients with AD-AP had similar TBIs on social and dysphoric images. Planned t-tests showed no significant differences between the TBI of patients with AD-AP and patients with AD.

**4.2.2 Sequence dependent parameters of visual scanning behaviour**

Table 4.4 presents the sequence dependent VSB parameters in the “valence” test condition.
Table 4.4 Sequence dependent parameters of VSB in the valence test condition for patients with AD-AP, AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social</td>
<td>Dysphoric</td>
<td>Social</td>
</tr>
<tr>
<td>Number of fixations within an image during early processing (EFWI)</td>
<td>2.857 ± 0.978</td>
<td>2.940 ± 0.764</td>
<td>2.691 ± 0.646</td>
</tr>
<tr>
<td>Average number of fixations within an image during late processing (LFWI)</td>
<td>2.846 ± 0.988</td>
<td>2.877 ± 0.549</td>
<td>2.783 ± 0.798</td>
</tr>
<tr>
<td>Fixation duration during early processing (EFD) (msec)</td>
<td>448.817 ± 69.065</td>
<td>489.692 ± 92.525</td>
<td>454.340 ± 111.863</td>
</tr>
<tr>
<td>Fixation duration during late processing (LFD) (msec)</td>
<td>543.319 ± 86.845</td>
<td>499.960 ± 95.851</td>
<td>644.122 ± 119.754</td>
</tr>
<tr>
<td>Saccadic amplitude during early processing (ESA) (degrees)</td>
<td>1.403 ± 0.371</td>
<td>1.421 ± 0.372</td>
<td>1.439 ± 0.313</td>
</tr>
<tr>
<td>Saccadic amplitude during late processing (LSA) (degrees)</td>
<td>1.909 ± 0.166</td>
<td>2.151 ± 0.348</td>
<td>2.083 ± 0.416</td>
</tr>
</tbody>
</table>

Number of fixations during early and late processing

Repeated measures ANOVA showed no significant differences between social and dysphoric images in the number of fixations during early (EFWI, F(1, 53) = 0.147, p = 0.703, η² = 0.003) and late processing (LFWI, F(1, 53) = 0.166, p = 0.686, η² = 0.003). However, the data from Table 4.4 show a small tendency for the differences between early and late processing to be smaller for patients with AD-AP than for the other groups. The difference between the early and late processing in the FWI (ΔEL-FWI) for each image type of each diagnostic group is shown.

Table 4.5 The difference in the number of fixations within image during early processing compared to late processing

<table>
<thead>
<tr>
<th>Image type</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social</td>
<td>-0.00114 ± 0.809</td>
<td>0.0924 ± 0.878</td>
<td>0.211 ± 0.587</td>
</tr>
<tr>
<td>Dysphoric</td>
<td>-0.0631 ± 0.915</td>
<td>0.308 ± 0.697</td>
<td>0.116 ± 0.763</td>
</tr>
</tbody>
</table>
The planned t-tests showed no significant differences between patients with AD-AP and patients with AD for ΔEL-FWI on social images \((t(32) = 0.346, p = 0.731)\) or for the ΔEL-FWI on dysphoric images \((t(32) = 1.30, p = 0.203)\).

**Fixation duration during early and late processing**

No significant differences were found in the fixation duration during early processing between social and dysphoric images in the “valence” test conditions \((F(1, 53) = 2.405, p = 0.127, \eta^2 = 0.043)\). However, during late processing significant differences were found between the fixation durations (LFD) on social and dysphoric images \((F(1, 53) = 5.245, p = 0.026, \eta^2 = 0.09)\). No significant diagnostic group \(\times\) image type interactions were found in the LFD. Planned pairwise comparison suggest that only patients with AD had significantly different LFD on social and dysphoric images \((t(17) = 2.34, p = 0.023, d = 0.497)\).

**Saccadic amplitude during early and late processing**

Repeated measures ANOVA showed no significant main effects in the average saccadic amplitude during early processing (ESA) \((F(1. 53) = 0.130, p = 0.720, \eta^2 = 0.002)\). However, significant main effects were found in the average saccadic amplitude during late processing (LSA) \((F(1. 53) = 8.095, p = 0.006, \eta^2 = 0.132)\). Planned pairwise comparison showed marginally significant differences in LSA between social and dysphoric images in patients with AD-AP \((t(15) = 1.96, p = 0.053, d = 0.0049)\).

### 4.2.3 Composite parameters of visual scanning behaviour

The basic parameters of VSB were used to obtain the composite parameters: fixation time and relative fixation time. These composite parameters are shown for patients with AD-AP, AD and elderly controls on social and dysphoric images.
Table 4.6 Composite parameters of VSB in the valence test condition for patients with AD-AP, AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social</td>
<td>Dysphoric</td>
<td>Social</td>
</tr>
<tr>
<td>Relative fixation time (RFT)</td>
<td>0.269 ± 0.062</td>
<td>0.265 ± 0.031</td>
<td>0.266 ± 0.072</td>
</tr>
</tbody>
</table>

**Fixation time**

The fixation times on social and dysphoric images in the “valence” test condition were not significantly different from each other (F(1, 53) = 2.665, p = 0.109, η² = 0.048). Similarly, the relative fixations times were not significantly different from each other (F(1, 53) = 2.249, p = 0.140, η² = 0.041). Even though no significant differences in fixation times were found, the smallest differences were observed for patients with AD-AP.

**4.2.4 Discussion**

The results in this section showed that in the “valence” test condition, the VSB parameters were not significantly different between patients with AD-AP, AD and elderly controls. Elderly controls demonstrated larger differences between VSB parameters on dysphoric and social images (significant differences for TBI, ASA, AFD and FWI) than patients with AD (significant differences for ASA and AFD) and patients with AD-AP (significant differences for ASA). Consistent with our hypothesis, the difference between the fixation times on social and dysphoric images were smaller for patients with AD-AP than for the other two groups. As there were no significant differences between the VSB parameters of the three diagnostic groups, the VSB parameters in the “valence” test condition do not provide physiological markers that can be used to separate between apathetic and non-apathetic patients.
4.3 Visual Scanning Behaviours in the Valence Arousal Test Condition

The data in the previous section suggest that of the three diagnostic groups, patients with AD-AP had the smallest differences in VSB parameters when slides with images of high and low valances were viewed. Even though this observation is consistent with the hypothesis of emotional indifference, the data from all three groups are not statistically different. In this section, we analyse VSB on slides that include images with different arousals and valences to test the emotional indifference hypothesis. The image set includes images with high arousals (social, dysphoric) and low arousals (neutral images). Note that social/dysphoric images have high/low valances while neutral images have valances that are neither high not low.

4.3.1 Basic parameters of visual scanning behaviour

Table 4.7 presents data of the basic parameters in the valence arousal test condition. The data is presented for patients with AD-AP, patients with AD and elderly controls on social, dysphoric and neutral images.

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social</td>
<td>Dysphoric</td>
<td>Neutral</td>
</tr>
<tr>
<td>FWI</td>
<td>6.152 ± 1.757</td>
<td>6.600 ± 1.266</td>
<td>4.001 ± 0.860</td>
</tr>
<tr>
<td>AFD</td>
<td>463.623 ± 87.752</td>
<td>483.110 ± 75.458</td>
<td>468.123 ± 97.851</td>
</tr>
<tr>
<td>ASA</td>
<td>2.265 ± 0.299</td>
<td>2.340 ± 0.387</td>
<td>1.718 ± 0.193</td>
</tr>
<tr>
<td>TBI</td>
<td>2.074 ± 0.445</td>
<td>2.225 ± 0.532</td>
<td>1.951 ± 0.437</td>
</tr>
</tbody>
</table>
The data was explored using repeated measures ANOVA with a between-group difference of diagnostic group (patients with AD-AP, patients with AD, elderly controls) and a within-group difference of image types (social, dysphoric, neutral). If significant differences were found, planned paired comparisons (t-tests) were performed to test the differences between: a) social and neutral images and b) dysphoric and neutral images for patients with AD-AP, patients with AD and elderly controls. If significant image type × diagnostic group interactions were found, planned t-tests were performed between the VSB parameters of the patients with AD-AP and patients with AD on social, dysphoric and neutral images. Significance level for all statistical tests were set to p = 0.05.

**Number of fixations within an image**

Repeated measures ANOVA indicated significant main effects in the number of fixations within an image (FWI) on social, dysphoric and neutral images for patients with AD, AD-AP and elderly controls (F(2, 106) = 62.03, p = 1.458×10⁻¹⁸, η² = 0.539). However, no significant image type and diagnostic group interactions were found (F(2, 106) = 1.360, p = 0.253, η² = 0.049). Planned paired comparisons showed that a) the FWIs on social images were significantly larger than on neutral images for patients with AD-AP (t(15) = 4.29, p = 6.389×10⁻⁴, d = 1.555), patients with AD (t(17) = 7.74, p = 5.660×10⁻⁷, d = 2.642) and elderly controls (t(21) = 7.48, p = 2.376×10⁻⁷, d = 2.393) and b) the FWIs on dysphoric images were significantly larger than on neutral images for patients with AD-AP (t(15) = 5.67, p = 4.446×10⁻⁵, d = 2.401), patients with AD (t(17) = 6.05, p = 1.302×10⁻⁵, d = 1.531) and elderly controls (t(21) = 6.08, p = 4.937×10⁻⁶, d = 1.961).

The results showed that, all the groups had significantly larger FWI on images with high arousals (social, dysphoric) compared to images of low arousals (neutral). When the FWI on social and neutral images were compared, patients with AD-AP showed smaller differences (effect size d = 1.555) than patients with AD (d = 2.642) and elderly controls (d = 2.393). On the other hand, when the FWI on dysphoric and neutral images were compared, patients with AD-AP exhibited larger differences (d = 2.401) compared to the patients with AD (d=1.531) and elderly controls (d = 1.961). Even though all groups show significant differences between the number of fixations within high and low arousal images (note that the high arousal images are also more complex)
AD-AP patients showed the smallest differences (this is consistent with the emotional indifference hypothesis).

**Average fixation duration**

Repeated measures ANOVA showed that the average fixation duration (AFD) was not significantly different between the image types (F(2, 106) = 2.467, p = 0.09, η² = 0.044). Table 4.7 showed that the differences in AFDs between social and dysphoric images were higher for patients with AD and elderly control than patients with AD-AP.

**Average saccadic amplitude**

Significant main effects were found in the average saccadic amplitude (ASA) between social, dysphoric and neutral images (F(2, 106) = 112.479, p = 6.212×10⁻²⁷, η² = 0.680). No significant diagnostic group × image type interactions were found (F(2, 106) = 0.906, p = 0.464, η² = 0.033). Planned paired comparisons showed that the ASA on social images were significantly larger than the ASA on neutral images for patients with AD-AP (t(15) = 5.946, p = 6.138×10⁻⁷, d = 3.07), patients with AD (t(17) = 7.82, p = 7.373×10⁻¹⁰, d = 3.79) and elderly controls (t(21) = 9.56, p = 1.2695×10⁻¹², d = 4.63). Also, the ASAs on dysphoric images were significantly larger than the ASA on neutral images for patients with AD-AP (t(15) = 6.222, p = 2.695×10⁻⁷, d = 3.21), patients with AD (t(17) = 8.653, p = 2.771×10⁻¹¹, d = 4.19) and elderly controls (t(21) = 9.105, p = 5.279×10⁻¹², d = 4.41).

The difference between the ASA on social and neutral images is larger (effects size) for patients with AD and elderly controls compared to patients with AD-AP. The same trends were observed for the difference between the ASAs on dysphoric and neutral images.

**Number of transitions between images**

Repeated measures ANOVA showed significant main effects in the number of transitions between images (TBI) between social, dysphoric and neutral images (F(2, 106) = 10.573, p = 6.5×10⁻⁵, η² = 0.166), however no significant diagnosis group × image type interactions were found (F(2, 106) = 1.721, p = 0.151, η² = 0.061). Planned paired t-tests showed that a) patients with AD-AP have significantly larger TBIs towards dysphoric images than towards neutral
images (t(15) = 2.15, p = 0.039, d = 0.564) and b) elderly controls have significantly larger TBI towards social images compared to neutral images (t(21) = 5.56, p = 9.00 \times 10^{-6}, d = 1.068).

4.3.2 Sequence dependent parameters of visual scanning behaviour

In Table 4.8, sequence dependent VSB parameters on social, dysphoric and neutral images in the “valence-arousal” test condition were described for patients with AD-AP, patients with AD and elderly controls. The parameters include: number of fixations per visit; fixation duration and saccadic amplitude during early and late processing.

### Table 4.8 Sequence dependent parameters of VSB in the valence arousal test condition for patients with AD-AP, AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social</td>
<td>Dysphoric</td>
<td>Neutral</td>
</tr>
<tr>
<td>EFWI</td>
<td>3.276 ± 1.007</td>
<td>3.327 ± 0.801</td>
<td>2.057 ± 0.586</td>
</tr>
<tr>
<td>LFWI</td>
<td>2.870 ± 0.837</td>
<td>2.959 ± 0.614</td>
<td>2.216 ± 0.728</td>
</tr>
<tr>
<td>EFD</td>
<td>455.686 ± 96.808</td>
<td>471.917 ± 84.945</td>
<td>439.006 ± 88.192</td>
</tr>
<tr>
<td>LFD</td>
<td>501.606 ± 104.461</td>
<td>529.943 ± 94.366</td>
<td>482.315 ± 133.678</td>
</tr>
<tr>
<td>ESA</td>
<td>1.696 ± 0.529</td>
<td>1.723 ± 0.409</td>
<td>0.844 ± 0.361</td>
</tr>
<tr>
<td>LSA</td>
<td>1.971 ± 0.479</td>
<td>2.287 ± 0.443</td>
<td>1.715 ± 0.415</td>
</tr>
</tbody>
</table>
Number of fixations during early and late processing

The number of fixations during early processing (EFWI) was found to be significantly different between the social, dysphoric and neutral images \( (F(2, 106) = 65.665, p = 2.8025 \times 10^{-19}, \eta^2 = 0.553) \) however, no significant diagnostic group \( \times \) image type interactions were found \( (F(2, 106) = 0.989, p = 0.417, \eta^2 = 0.036) \). Planned t-test showed that a) patients with AD-AP had significantly higher EFWI on social compared to neutral images \( (t(15) = 5.46, p = 3.95 \times 10^{-7}, d = 1.480) \) and dysphoric compared to neutral images \( (t(15) = 6.99, p = 8.4693 \times 10^{-7}, d = 1.809) \); b) patients with AD had significantly higher EFWI on social compared to neutral images \( (t(17) = 8.59, p = 3.6299 \times 10^{-10}, d = 1.743) \) and dysphoric compared to neutral images \( (t(17) = 4.95, p = 7.0 \times 10^{-6}, d = 1.293) \) and c) elderly controls had significantly higher EFWI on social compared to neutral images \( (t(21) = 6.55, p = 1.5401 \times 10^{-7}, d = 1.556) \) and dysphoric compared to neutral images \( (t(21) = 5.92, p = 2.8824 \times 10^{-7}, d = 1.526) \).

The number of fixations during late processing (LFWI) was found to be significantly different between social, dysphoric and neutral images \( (F(2, 106) = 32.110, p = 1.380 \times 10^{-11}, \eta^2 = 0.382) \) however no significant diagnostic group \( \times \) image type interactions were found \( (F(2, 106) = 1.390, p = 0.243, \eta^2 = 0.051) \). Planned t-test showed that a) patients with AD-AP had significantly higher LFWI on dysphoric compared to neutral images \( (t(15) = 3.23, p = 0.015, d = 1.104) \); b) patients with AD had significantly higher LFWI on social compared to neutral images \( (t(17) = 2.49, p = 1.00 \times 10^{-6}, d = 0.933) \) and dysphoric compared to neutral images \( (t(17) = 2.80, p = 0.01, d = 0.825) \) and c) elderly controls had significantly higher LFWI on social compared to neutral images \( (t(21) = 5.62, p = 3.0 \times 10^{-6}, d = 1.849) \) and dysphoric compared to neutral images \( (t(21) = 4.17, p = 176 \times 10^{-6}, d = 1.389) \).

The EFWI and LFWI showed similar trends to the FWI, which suggests that differences in the number of fixations within images are distributed throughout the course of viewing the slides.

Fixation duration during early and late processing

Repeated measures ANOVA showed significant differences in the fixation duration during early (EFD) processing between the image types \( (F(2, 106) = 6.647, p = 0.002, \eta^2 = 0.111) \), however no significant diagnostic group \( \times \) image type interactions were found. No significant differences
were found in the fixation duration during late processing (F(2, 106) = 2.996, p = 0.054, η² = 0.054). Planned t-test showed that: a) patients with AD had significantly larger EFD on social compared to neutral images (t(17) = 1.98, p = 0.008, d = 0.577) and dysphoric compared to neutral images (t(17) = 2.61, p = 0.001, d = 0.584); b) elderly controls had significantly larger EFD on dysphoric compared to neutral images (t(21) = 4.03, p = 0.031, d = 0.720).

When the average fixation durations through the whole viewing period were compared (Table 4.8) no significant differences between the AFD on social, dysphoric and neutral images were found for any of the groups. This may suggest that the differences in the average fixation duration occur mainly during early processing. In addition, the fact that patients with AD-AP did not have significantly larger EFD on dysphoric or social images compared to neutral images is consistent with the hypothesis of emotional indifference. Analysis of the differences between EFD on dysphoric/social and neutral images may provide a method to differentiate between patients with AD-AP and the other diagnostic groups.

**Saccadic amplitude during early and late processing**

The average saccadic amplitude during early processing (ESA) was found to be significantly different between the images types (F(2, 106) = 106.634, p = 4.179×10⁻²⁶, η² = 0.668) however no significant diagnostic group × image type interactions were found (F(2, 106) = 0.676, p = 0.610, η² = 0.025). Planned t-tests showed that a) the ESAs on social images were significantly larger than on neutral images (patients with AD-AP: (t(15) = 7.22, p = 2.953×10⁻⁶, d = 1.881); patients with AD: (t(17) = 9.73, p = 2.326×10⁻⁶, d = 2.492); elderly controls (t(21) = 10.70, p = 5.843×10⁻¹⁰, d = 2.007)); b) the ESAs on dysphoric images were significantly larger than on neutral images (patients with AD-AP: (t(15) = 6.92, p = 4.874×10⁻⁶, d = 2.280); patients with AD: (t(17) = 7.03, p = 2.016×10⁻⁶, d = 2.026); elderly controls (t(21) = 8.44, p = 3.440×10⁻⁸, d = 2.065)).

The average saccadic amplitude during late processing (LSA) was found to be significantly different between the images types (F(2, 106) = 33.737, p = 5.0996×10⁻¹², η² = 0.393). Significant diagnostic group × subject interactions were also found (F(2, 106) = 2.508, p = 0.046, η² = 0.088). However, post-hoc analysis failed to show significant differences between the diagnostic groups. Planned t-tests showed that elderly controls had significantly different LSA
on social compared to neutral images (t(21) = 7.86, p = 8.848×10⁻⁸, d = 1.696) while such differences were not found for AD or AD-AP patients. Patients with AD-AP, AD and elderly controls had significantly larger LSA on dysphoric compared to neutral images (patients with AD-AP: (t(15) = 5.10, p = 0.001, d = 1.331); patients with AD: (t(17) = 5.06, p = 5.10×10⁻⁴, d = 1.230); elderly controls: (t(21) = 3.26, p = 9.89×10⁻⁴, d = 1.115)).

4.3.3 Composite parameters of visual scanning behaviour

The following section explores the composite VSB parameters (fixation time and relative fixation time) on social, dysphoric and neutral images in the valence arousal test condition. The data for the diagnostic groups (patients with AD-AP, AD and elderly controls) and image types are provided in Table 4.9.

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social</td>
<td>Dysphoric</td>
<td>Neutral</td>
</tr>
<tr>
<td>FT</td>
<td>2773.968 ± 759.646</td>
<td>3023.477 ± 546.755</td>
<td>1807.259 ± 576.413</td>
</tr>
<tr>
<td>RFT</td>
<td>0.310 ± 0.081</td>
<td>0.341 ± 0.067</td>
<td>0.201 ± 0.054</td>
</tr>
</tbody>
</table>

Fixation time

Repeated measure ANOVA showed significant differences between the fixation times (FT) on social, dysphoric and neutral images (F(2, 106) = 36.058, p = 1.132×10⁻¹², η² = 0.405). However no significant diagnostic group × image type interactions were found (F(2, 106) = 1.411, p = 0.235, η² = 0.051). Planned t-tests showed that all diagnostic groups had significantly larger FTs on social compared to neutral images (patients with AD-AP: (t(15) = 3.88, p = 1.483×10⁻³, d = 1.434); patients with AD (t(17) = 4.28, p = 5.079×10⁻⁴, d = 1.631); elderly controls (t(21) = 6.14, p = 4.354×10⁻⁶, d = 1.961)) and dysphoric compared to neutral images (Patients with AD-AP: (t(15) = 4.94, p = 1.765×10⁻⁴, d = 2.165); patients with AD (t(17) = 6.39, p = 6.752×10⁻⁶, d = 1.933); elderly controls (t(21) = 5.50, p = 1.856×10⁻⁵, d = 1.736)). The relative fixation times
(RFT), which are the normalized FTs on social, dysphoric and neutral images provided very similar results to those obtained for the FTs.

4.3.4 Discussion

The VSB parameters in the “valence arousal” test condition were not significantly different between the diagnostic groups. However, some differences between patients with AD-AP and the other two groups were observed when social and dysphoric images were compared to neutral images. When such comparisons were made, the differences between several VSB parameters (number of fixations within an image, average saccadic amplitude, number of fixations within an image during early and late processing, fixation duration during early processing, saccadic amplitude during early and late processing and the fixation time) were smaller for patients with AD-AP. This observation is consistent with the emotional indifference hypothesis. Differences between VSB parameters on social/dysphoric and neutral images are explored.

4.4 Visual Scanning Parameters to Characterise Apathy in Alzheimer’s Disease

Even though differences between VSB parameters when participants view images with different emotional contents were consistently smaller for the AD-AP patients, no significant diagnostic group × image type interactions were found in the “valence” and “arousal-valence” test conditions. It is possible that differences between the groups are masked by noise from nuisance parameters that increase the variance of the observed data for each group but are not relevant for the assessment of emotional preferences. For example, if subjects have longer or shorter fixations on both low and high arousal images it is not relevant to the assessment of emotional indifferences, but it affects the variance of the estimated average fixation duration of each group and therefore reduces the ability to differentiate between the groups. In this section, we explored methods to reduce effects of nuisance parameters when subjects look at images with different emotional contents. Since the purpose of this section is to explore how VSB parameters can be used to detect significant statistical differences between patients with AD-AP and patients with AD, the statistical analysis in this section will use only two groups (AD-AP and AD). In addition to simplify the problem, only the basic VSB parameters were analysed in this section.
4.4.1 Differences between visual scanning parameters on social and neutral images and between dysphoric and neutral images

The differences in the VSB parameters between social and neutral images and between dysphoric and neutral images for patients with AD-AP, patients with AD and elderly controls are presented in Table 4.10 (the data for elderly controls are presented for completeness). The data was explored by using planned t-tests between patients with AD-AP and patients with AD. Table 4.10 also shows the results of the planned t-tests that are displayed within the brackets of the columns for patients with AD-AP.

Table 4.10 Difference between VSB parameter on social and neutral images and between dysphoric and neutral images for patients with AD-AP, AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social -neutral</td>
<td>Dysphoric -neutral</td>
<td>Social -neutral</td>
</tr>
<tr>
<td>∆FWI</td>
<td>2.151 ± 2.003 (p = 0.149)</td>
<td>2.599 ± 1.833 (p = 0.577)</td>
<td>3.086 ± 1.691</td>
</tr>
<tr>
<td>∆AFD</td>
<td>-4.501 ± 94.956 (p = 0.155)</td>
<td>14.987 ± 93.324 (p = 0.226)</td>
<td>128.625 ± 354.014</td>
</tr>
<tr>
<td>∆ASA</td>
<td>0.547 ± 0.375 (p = 0.304)</td>
<td>0.622 ± 0.396 (p = 0.172)</td>
<td>0.673 ± 0.405</td>
</tr>
<tr>
<td>∆TBI</td>
<td>0.123 ± 0.375 (p = 0.714)</td>
<td>0.275 ± 0.512 (p = 0.433)</td>
<td>0.172 ± 0.393</td>
</tr>
</tbody>
</table>

The results of Table 4.10 were compared to the results obtained when the same parameters were computed directly (i.e., without taking the differences). The results of the t-tests between patients with AD-AP and patients with AD using the ∆FWI between social and neutral images was t(32) = 1.477, p = 0.149. Compared to using the FWI on social images directly (t(32) = 1.138, p = 0.264), the ∆FWI showed larger differences between the group. Table 4.10 suggests that the differences between VSB parameters on social and neutral images or dysphoric and neutral images tend to be smaller in patients with AD-AP compared to patients with AD. However, none
of the parameters provided significant differences between the groups. In the next section, relative parameters were explored to reduce the nuisance parameters between slides.

4.4.2 Differences between relative visual scanning parameters on social and neutral images and between dysphoric and neutral images

Although each slide is presented for the same duration, the number of eye-position estimates for each slide is not a constant. This is mainly due to imperfect eye-tracking performance. When parameter such as the average fixation time on images is calculated, slides with larger number of eye-position estimates will contribute more to the average than slides with smaller number of eye-position estimates. These unequal contributions increase the standard error of the means calculated per subject. Relative parameters are expected to reduce the noise associated with non-uniform tracking performance. For example the previously calculate relative fixation time (RFT) represents the proportion of fixation time on each image and is calculated by:

\[
RFT_{i,s} = \frac{FT_{i,s}}{\sum_{j=1}^{4} FT_{j,s}}
\]

where \( FT_{i,s} \) is the fixation time on image \( i \) on slide number \( s \).

The relative values of the basic parameters are shown in Table 4.11.

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social-neutral</td>
<td>Dysphoric-neutral</td>
<td>Social-neutral</td>
</tr>
<tr>
<td>( \Delta RFWI )</td>
<td>0.106 ± 0.096 (p = 0.123)</td>
<td>0.129 ± 0.089 (p = 0.442)</td>
<td>0.160 ± 0.107 (p = 0.040)</td>
</tr>
<tr>
<td>( \Delta RAFD )</td>
<td>0.011 ± 0.042 (p = 0.183)</td>
<td>0.020 ± 0.035 (p = 0.298)</td>
<td>0.046 ± 0.037 (p = 0.058)</td>
</tr>
<tr>
<td>( \Delta RASA )</td>
<td>0.080 ± 0.056 (p = 0.023*)</td>
<td>0.094 ± 0.072 (p = 0.077)</td>
<td>0.132 ± 0.131 (p = 0.044)</td>
</tr>
<tr>
<td>( \Delta RTBI )</td>
<td>0.024 ± 0.045 (p = 0.745)</td>
<td>0.037 ± 0.057 (p = 0.563)</td>
<td>0.029 ± 0.028 (p = 0.038)</td>
</tr>
</tbody>
</table>
The results of Table 4.11 show that the differences between patients with AD-AP and patients with AD were larger for the relative difference in the number of fixations within images (ΔRFWI) and for the relative difference in the average saccadic amplitude (ΔRASA) compared to the results in Table 4.10. In addition, the ΔRASA on social and neutral images was significantly different between patients with AD-AP and patients with AD (t(32) = 2.388, p = 0.023). The ΔRASA between social and neutral images for patients with AD-AP, patients with AD and elderly controls is shown in Figure 4.2:

![Figure 4.2](image-url)

Figure 4.2 The mean (±1 standard error of the mean) differences between relative average saccadic amplitude (RASA) on social and neutral images for patients with AD-AP, patients with AD and elderly controls.

As shown in Figure 4.2 the ΔRASA is smaller for patients with AD-AP compared to both patients with AD and elderly controls. Previous studies have shown that subjects’ saccadic amplitude on an image varies depending on the complexity of the image [62]. Therefore, the ΔRASA could be normalising the effects of varying image complexities. In the next section, we
explored methods to normalise the VSB parameters by the average scanning behaviours of all subjects.

### 4.4.3 Image normalisation of visual scanning parameters

To normalize VSB parameters for each image, the average scanning behaviour on an image is subtracted from the measured VSB parameter for each subject and the result is divided by the standard deviation of the VSB parameter. This method transforms VSB parameters for different image types (social, dysphoric, neutral) into a normalised space. The image normalization procedure was carried out on the relative VSB parameters. The relative VSB parameters were normalised by Algorithm 4.1.

**Algorithm 4.1: Normalisation by the average scanning behaviours**

1. **Calculate the mean and standard deviation for each image**
   - For all diagnostic groups
     - For each image (i) and each VSB parameter (j)
       - Find the expected value ($E\{VSBij\}$) and the standard deviation ($\sigma\{VSBij\}$)
   
2. **Normalise the VSB parameter by the expected value and standard deviation**
   - For each participant
     - For each image (i) and each VSB parameter (j):
       - Calculate:
         $$VSB_{Nij} = \frac{VSB_{ij} - E\{VSB_{ij}\}}{\sigma\{VSB_{ij}\}}$$

The means and standard deviations of the relative VSB parameters for each image were calculated from the data of all the subjects (approximately the same number of participants from each group). VSB parameters on each image were then normalised using the Algorithm 4.1 (the results are denoted by a subscript N e.g., $RFWI_N$). Table 4.12 showed that the normalisation by average scanning behaviours increased the difference between patients with AD-AP and patients with AD. The $\Delta RFWI_N$ and $\Delta RASA_N$ between social and neutral images provided the largest differences between the groups. The $\Delta RFWI_N$ shows a tendency between patients with AD-AP and patients with AD and is shown in Figure 4.3.
Table 4.12 VSB parameters after normalisation by the average scanning behaviours on social minus neutral and dysphoric minus neutral for patients with AD-AP, AD and elderly controls

<table>
<thead>
<tr>
<th>VSB parameter</th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Social -neutral</td>
<td>Dysphoric -neutral</td>
<td>Social -neutral</td>
</tr>
<tr>
<td>ΔRFWI&lt;sub&gt;N&lt;/sub&gt;</td>
<td>-0.210 ± 0.636 (p = 0.110)</td>
<td>0.036 ± 0.612 (p = 0.618)</td>
<td>0.156 ± 0.662</td>
</tr>
<tr>
<td>ΔRAFD&lt;sub&gt;N&lt;/sub&gt;</td>
<td>-0.199 ± 0.405 (p = 0.131)</td>
<td>-0.067 ± 0.419 (p = 0.320)</td>
<td>0.182 ± 0.905</td>
</tr>
<tr>
<td>ΔRASA&lt;sub&gt;N&lt;/sub&gt;</td>
<td>-0.222 ± 0.307 (p = 0.009)</td>
<td>-0.171 ± 0.481 (p = 0.08)</td>
<td>0.146 ± 0.443</td>
</tr>
<tr>
<td>ΔRTBI&lt;sub&gt;N&lt;/sub&gt;</td>
<td>-0.051 ± 0.474 (p = 0.749)</td>
<td>0.075 ± 0.631 (p = 0.502)</td>
<td>0.007 ± 0.551</td>
</tr>
</tbody>
</table>

Figure 4.3 The mean (±1 standard error of the mean) difference between RFWIs on social and neutral images for patients with AD-AP, patients with AD and elderly controls.
The $\Delta$RASA$_N$ between social and neutral images was found to be significantly different between patients with AD-AP and patients with AD ($t(32) = 2.779$, $p = 0.009$). $\Delta$RASA$_N$ between dysphoric and neutral images was found to show a tendency to be different between AD-AP and AD patients ($t(32) = 1.805$, $p = 0.08$). Figure 4.4 show the data of $\Delta$RASA$_N$ between social and neutral images:

![Graph showing mean difference between RASA on social and neutral images for patients with AD-AP, patients with AD, and elderly controls.](image)

Figure 4.4 The mean ($\pm$1 standard error of the mean) difference between RASAn on social and neutral images for patients with AD-AP, patients with AD and elderly controls.

The method of normalisation by average scanning behaviour on each image increased the differences between the patients with AD-AP and patients with AD. In the context of measuring apathetic responses (i.e., diminished differences between images with different content and complexities), one expects that the normalised parameters will be larger for patients with AD-AP on neutral images and smaller on social and dysphoric images so that when the difference between the normalised parameters (social compared to neutral and dysphoric compared to
neutral) is calculated it will be negative for patients with AD-AP and positive for patients with AD.

4.4.4 Number of transitions between images with high and low arousals

A previous study conducted by Koehler et al. [63] suggested that in a free viewing task, subjects moves towards the most salient regions rather than continuously stay within those regions (i.e. saliency attracts attention from other region). In our study, social and dysphoric images have more salient regions than neutral images and he effects of saliency may be diminished in apathetic patients. To test this hypothesis the relative number of transitions towards images with high (social and dysphoric) from low (neutral) arousal images (denoted as RTBIS) was calculated. The results are shown in the Table 4.13 below:

Table 4.13 The relative number of transitions towards images with high from low arousal for patients with AD-AP, patients with AD and elderly controls

<table>
<thead>
<tr>
<th></th>
<th>Patients with AD-AP</th>
<th>Patients with AD</th>
<th>Elderly controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTBIS</td>
<td>0.3579 ± 0.0475</td>
<td>0.3724 ± 0.0376</td>
<td>0.3720 ± 0.0415</td>
</tr>
</tbody>
</table>

The following plot shows from the results of the RTBIS from Table 4.13:

![Figure 4.5 The mean (±1 standard error of the mean) relative number of transitions towards images with high arousals from images with low arousal (RTBIS) for patients with AD-AP, patients with AD and elderly controls.](image-url)
As shown in Figure 4.5, patients with AD and elderly controls have larger RTBIS compared to patients with AD-AP. Planned paired t-tests were performed between patients with AD-AP and patients with AD however, no significant differences were found (t(32) = 0.997, p = 0.326).

4.4.5 Relationships between the identified parameters

Patients with AD-AP and patients with AD were found to exhibit differences in three parameters: $\Delta$RFWI$_N$ between social and neutral images, $\Delta$RASA$_N$ between social and neutral images and RTBIS. Multiple Pearson’s test was used to study the correlation between the parameters. The test showed that $\Delta$RFWI$_N$ was significantly correlated to the $\Delta$RASA$_N$ ($r(34) = 0.703$, $p = 3.0 \times 10^{-7}$). However, RTBIS was not significantly correlated to $\Delta$RFWI$_N$ ($r(34) = -0.02$, $p = 0.909$) nor $\Delta$RASA$_N$ ($r(34) = -0.073$, $p = 0.681$). Since significant differences were found between the $\Delta$RASA$_N$ (t(32) = 2.779, $p = 0.009$) of patients with AD-AP and patients with AD and there was no correlations between the $\Delta$RASA$_N$ and RTBIS, the $\Delta$RASA$_N$ and the RTBIS were selected as weak indicators of apathy in AD.

4.5 Discussion

In Chapter 4, we studied VSB parameters that are likely to be affected by emotional indifference, diminished motivation and disinterest, which are common symptoms in apathetic patients. Emotional indifference was studied by exploring VSB parameters on images with high and low arousals. The data suggest that VSB parameters of apathetic patients are consistent with the expected behaviour of subjects that demonstrate emotional indifference. When differences between the VSB parameters of patients with AD-AP and patients with AD were transformed to a normalised space, the relative average saccadic amplitude and the number of transitions between images with low arousals to images with high arousals were identified as uncorrelated weak indicators of apathy. Individually, the parameters cannot be used to robustly classify patients with apathy from non-apathetic patients, but it is possible that several weak indicators can be combined to create a robust indicator for apathy in patients with AD.
Chapter 5. Conclusion and Future Direction

The major contributions of the thesis are summarized in this section. The possible future direction is also listed.

5.1 Summary

5.1.1 Improvements to the analysis of visual scanning behaviour (VSB)

The analysis of VSB parameters was automated and generalised. Software applications were designed and developed to automatically collect and calculate large sets of VSB parameters and to rapidly assemble VSB parameters from different tests and studies. The software to analyse data was optimised for flexible selection of VSB parameters and hypothesis testing.

5.1.2 Development of novel VSB parameters

Novel parameters to describe the spatial distribution of fixations were developed. The parameters include measurements such as saccadic amplitudes, scan-path length and the dispersion of fixations within an image. Sequential analysis of VSB introduced sets of parameters that describe cortical processes that are associated with either early or late processing of visual information.

5.1.3 Characterisation of novelty preference by VSB parameters

A novel paradigm to assess novelty preference in patients with AD was developed. The paradigm compares VSB parameters on novel images and images that were previously seen to determine novelty preference (bias towards novel images). Patients with AD, elderly controls and young controls showed biases towards novel images. Significant differences between VSB parameters of subjects in different age groups (young controls and elderly controls) and different diagnostic groups (elderly controls and patients with AD) were found. In addition, when the delays between the first and second presentation of repeated images increased, the differences between the VSB parameters on repeated images and novel images were reduced. Our data suggest that patients with AD demonstrated some bias towards novel images (significantly smaller than that of elderly controls). Based on research that links novelty preference and implicit memory these data might suggest that patients with AD might retain some limited capacity to perform tasks that require implicit memory.
5.1.4 Methods that use VSB parameters to classify patients with AD from elderly controls

Using the relative fixation time on novel images, a baseline classifier that was used to separate patients with AD from elderly controls achieved accuracy of 82%. Using the number of fixations within an image with the real adaptive boosting algorithm, classification accuracy increased to 87.5%. Using the number of fixations within an image and saccadic amplitude during early processing with the adaptive boosting algorithm classification accuracy increased to 91%.

5.1.5 Characterisation of apathy in AD by VSB parameters

The VSB of apathetic patients with AD (patients with AD-AP) showed less variability than that of patients with AD when images with different arousals were viewed. Specifically, patients with AD-AP were found to have smaller differences between the number of transitions into images with low and high arousals and between the amplitudes of saccades on images with low and high arousals.

5.2 Future Work

5.2.1 Characterisation of novelty preference in patients with mild cognitive impairment

Patients with mild cognitive impairment (MCI) are characterised by declining memory capabilities and/or cognitive abilities. MCI is a recognised risk factor of AD, where individuals progress towards AD at the rate of 10-15% a year [64]. During the early stages, MCI is often asymptomatic and patients often only seek medical attention when noticeable declines in their cognitive states are observed. Therefore an objective measure to detect subtle cognitive changes may be beneficial to the patients [65].

Previous studies showed that the visual paired comparison (VPC) task can be used to distinguish between patients with MCI and elderly controls with high accuracy [58]. In addition, parameters of VSB during the VPC task were used as an early predictor for dementia [32]. The novel paradigm developed to assess novelty preference (a variant of the standard VPC task) in patients with AD can be applied to patients with MCI. To measure subtle declines in the subjects’ cognitive functions, varying delays between the first and second presentation of the repeated
images could be used. Novelty preference (as measured by the techniques described in this thesis) at variable delays can be used to build a profile of the subject’s cognitive capabilities. Using variable delays one can explore capabilities associated with attention, executive functions and memory.

Accurate assessment of the severity of cognitive impairment in patients with MCI may assist in the clinical assessment of these patients. In addition, detecting subtle changes in cognitive capabilities in MCI may provide avenues to study the neuropathology of the illness and thus pharmaceutical treatments for patients with MCI.

5.2.2 Using multiple tests to develop a physiological marker for apathy in AD

In this thesis, we found that Alzheimer patients with apathy (AD-AP) tended to view images more uniformly. Even though this behaviour was very consistent for different types of images, the differences between the VSB parameters of patients with AD-AP and patients with AD were small. However, since apathy encompasses many symptoms, one can explore VSB parameters from several tests associated with apathy to build a better classifier (i.e., a strong classifier that is built by a combination of weak classifiers).

Previous studies have correlated apathy in schizophrenia with eye-movement parameters during a smooth pursuit task [66] and Daffner et al. suggested that patients with AD-AP should demonstrate diminished novelty preference [67]. The novel paradigm that was developed in this thesis may be augmented by other tests to provide parameters for several weak classifiers that can be combined to create a robust classifier for patients with AD-AP.
References


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