Background: In Alzheimer disease (AD), tests of “first-order capabilities,” such as reaction time or motor ability, might measure central nervous system integrity or disability more reliably than those of abstract, conceptual, or cognitive behavior. Saccade system impairments are present in AD, but their sensitivity or specificity remains unevaluated.

Objectives: To determine sensitivity and specificity of saccade measures for AD, precise impairments in AD, and the relationship between dementia severity and saccade system function.

Design: Case-control study comparing saccade system function between patients and control subjects, including correlations between saccade system function and dementia severity in patients and standardized scores examining impairment in individual patients.

Setting: Neuropsychiatric research institute.

Participants: Two hundred forty-five healthy volunteers from the general population, and 35 patients with AD referred by memory clinics. Age- and sex-matched controls were compared with patients on random saccade (n=35), predictive saccade (n=11), and antisaccade (n=18) tasks.

Main Outcome Measures: Saccade latencies, velocities, and accuracies and antisaccade error rates. Sensitivity, specificity, and predictive positive and negative values were calculated using all control data.

Results: Patients had longer and more variable latencies, more hypometric and anticipatory random saccades, and higher antisaccade error rates (P<.01 for all comparisons). The antisaccade error rate correlated with dementia severity (Spearman r = -0.59, P = .02). Antisaccade measures were the most specific (0.70-0.90) and random saccade gain the most sensitive (0.87).

Conclusions: Despite AD group impairment, individual patients function within the control range, reducing the sensitivity and specificity of saccade measures for AD. Longitudinal evaluation may provide more reliable classification.

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SACCADE SYSTEM dysfunction relative to healthy control subjects has been reported in Alzheimer disease (AD), including increased latency, reduced peak velocity, deficient fixation, reduced accuracy, and increased antisaccade error rates. These often large differences suggest that examining measures of saccade system function as diagnostic markers for AD and for monitoring disease progression or assessing new treatment efficacy may be warranted. This theory is enhanced by our findings of slight or no effects of age and mood on simple saccade function in individuals older than 45 years without neurological, psychiatric, or systemic illnesses, although other studies report larger increases in latency and some hypometria with increasing age. In contrast, performance on many neuropsychological tests used to detect AD is affected dramatically by mood and age, as well as fatigue and low motivation, which are frequent in older people referred for assessment of questionable dementia.

Despite this potential, nearly all studies identifying saccade system dysfunction in AD compared small groups of patients with probable AD with small groups of healthy controls, without determining the capacity of saccade system measures to detect AD in individual patients. This may have arisen from the lack of sufficiently large normative databases to support valid comparisons of saccade variables from individual patients. Similarly, although various saccade system measures are considered impaired in AD, those identifying AD most reliably are unknown, and the possibility remains that saccade system impairment in AD is as heterogeneous as that observed on batteries.
of neuropsychological tests. Accordingly, to clarify the nature of saccade system impairment in AD, we compared horizontal saccades between a group of patients with probable AD and a large group of healthy older people. We also examined the relationship between saccade system function and dementia severity in AD to determine the capability of saccade system measures to monitor disease progression. Finally, we assessed the sensitivity and specificity of measures of saccade system function for the diagnosis of AD in individual patients.

METHODS

PARTICIPANTS

Thirty-five patients (15 male; mean±SD age, 70.9±9.4 years [range, 56-89 years]) meeting the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association criteria for dementia of the Alzheimer type were recruited through our clinic. Dementia severity was assessed using the Mini-Mental State Examination (MMSE). The control group was a pool of 245 healthy people (79 male; mean±SD age, 62.8±8.6 years [range, 44-85 years]) recruited from the general population from which age- and sex-matched subjects were selected for the first part of the study. No control subject met the criteria for dementia, scored less than 28 on the MMSE, scored less than the age-appropriate limit on the Short Blessed Test, showed the presence of 2 or more abnormal neurological signs on the Consortium to Establish a Registry for Alzheimer’s Disease neurologically examination, scored less than the age- and education-appropriate limit on any test of the Consortium’s neuropsychological battery, or had a history of or currently had hypertension, stroke, major vascular disorder, heart disease, head injury, epilepsy, diabetes mellitus, thyroid disease, major depressive or anxiety disorder, or other psychiatric illness. Additional exclusion criteria included the obligate use of antihypertensive, other cardiovascular, antidepressant, sedative, antipsychotic, anxiolytic, anticonvulsant, or anticoagulant medication or a history of alcohol or other drug abuse. Each control subject and patient or his or her caregiver gave informed consent. The institutional research and ethics committee approved the study.

PROCEDURE

Horizontal random saccades, predictive saccades, and antisaccades were recorded in controls and patients in a dark, acoustically sealed room using the differential limbus infrared reflectance technique (IRIS; Skalar Medical BV, DeHis, the Netherlands; bandwidth direct current to 100 Hz [−3 dB down]) according to the method described in detail elsewhere. Data were sampled at 1 kHz. Subjects, with their chins supported, were seated 1 m away from a polyester film screen on which the experimental stimuli of green central fixation circles (luminance, 8.3 cd/m²) were back-projected. Stimuli subtended 0.2° of visual angle and were sampled at 1 kHz. Subjects, with their chins supported, were required to follow the target as it made these 30° excursions. The response from the central stimulus to the first peripheral target was excluded from analysis. For the first part of the study, data from 11 patients (mean±SD age, 70.9±9.4 years [range, 56-89 years]) were compared with data from 11 age- and sex-matched control subjects from the larger pool of 245 subjects (mean±SD age, 68.7±7.3 years [range, 58-77 years]) (t = -0.33, P = .74).

In the antisaccade test of 40 trials, subjects were required to generate a saccade to a symmetrical location in the opposite hemifield to a suddenly appearing laser target occurring pseudorandomly at plus or minus 4° or 8° of a central green fixation point. Targets were shown for 2500 milliseconds and the central fixation point for a pseudorandomly variable time of 2000 to 2500 milliseconds. For the first part of the study, data from 18 patients (mean±SD age, 71.9±10.2 years [range, 56-89 years]) were compared with data from 18 age- and sex-matched control subjects from the larger pool of 245 subjects (mean±SD age, 70.4±9.0 years [range, 55-86 years]) (t = 0.46, P = .67).

All patients and controls completed a full battery of tests as a practice trial. Saccade latency and latency SD were measured for all saccade tests. Velocity, gain (amplitude of initial saccade divided by amplitude of target), and number of hypometric (<85% of target size) and hypermetric (>115% of target size) random and predictive saccades were measured or counted. Two measures of fixation ability were also counted: the number of anticipatory saccades (nonvisually guided saccades generated before target onset or with latencies <100 milliseconds, random and predictive saccades only) and the number of saccades made in the wrong direction (before or after target onset, random saccades only). Patients performed the antisaccade test after the random saccade test to minimize the probability of making wrong direction saccades in the random saccade test. The antisaccade latency and latency SD are reported for correct antisaccades only, that is, those made initially in the direction opposite to the target. The antisaccade error rate was calculated as the number of incorrect antisaccades as a proportion of the total number of valid trials for each subject. Excluded from analysis were trials in which fixation on the central stimulus was not maintained for at least 200 milliseconds before its offset in the random saccade and antisaccade tests.

SACCADE TESTS

In the random saccade test of 50 trials, a red central fixation point was shown and then extinguished after a pseudorandomly variable delay between 1400 and 2400 milliseconds. Simultaneously, a peripheral target stimulus of 2000 milliseconds’ duration was shown pseudorandomly at plus or minus 5°, 7.5°, 10°, 12.5°, or 15° of the central point on the horizontal meridian. After target offset, the central stimulus was shown again to begin the next trial. Subjects were instructed to follow the stimuli quickly and accurately with their eyes. Ten targets at each possible amplitude were shown. Data were averaged across target amplitudes. For the first part of the study, data from all 35 patients (mean±SD age, 70.9±9.4 years [range, 56-89 years]) were compared with data from 35 age- and sex-matched control subjects from the larger pool of 245 subjects (mean±SD age, 69.8±8.2 years [range, 56-86 years]) (t = -0.53, P = .59).

In the predictive saccade test of 30 trials, the red central stimulus was shown for 2000 milliseconds, then removed, and a peripheral target stimulus shown at −15° for 2000 milliseconds, followed by a target at plus or minus 15° for 2000 milliseconds. This target sequence was repeated 14 times. Subjects were required to follow the target as it made these 30° excursions. The response from the central stimulus to the first peripheral target was excluded from analysis. For the first part of the study, data from 11 patients (mean±SD age, 69.8±8.0 years [range, 58-80 years]) were compared with data from 11 age- and sex-matched control subjects from the larger pool of 245 subjects (mean±SD age, 68.7±7.3 years [range, 58-77 years]) (t = 0.57, P = .57).

In the antisaccade test of 40 trials, subjects were required to generate a saccade to a symmetrical location in the opposite hemifield to a suddenly appearing laser target occurring pseudorandomly at plus or minus 4° or 8° of a central green fixation point. Targets were shown for 2500 milliseconds and the central fixation point for a pseudorandomly variable time of 2000 to 2500 milliseconds. For the first part of the study, data from 18 patients (mean±SD age, 71.9±10.2 years [range, 56-89 years]) were compared with data from 18 age- and sex-matched control subjects from the larger pool of 245 subjects (mean±SD age, 70.4±9.0 years [range, 55-86 years]) (t = 0.46, P = .67).

All patients and controls completed a full battery of tests as a practice trial. Saccade latency and latency SD were measured for all saccade tests. Velocity, gain (amplitude of initial saccade divided by amplitude of target), and number of hypometric (<85% of target size) and hypermetric (>115% of target size) random and predictive saccades were measured or counted. Two measures of fixation ability were also counted: the number of anticipatory saccades (nonvisually guided saccades generated before target onset or with latencies <100 milliseconds, random and predictive saccades only) and the number of saccades made in the wrong direction (before or after target onset, random saccades only). Patients performed the antisaccade test after the random saccade test to minimize the probability of making wrong direction saccades in the random saccade test. The antisaccade latency and latency SD are reported for correct antisaccades only, that is, those made initially in the direction opposite to the target. The antisaccade error rate was calculated as the number of incorrect antisaccades as a proportion of the total number of valid trials for each subject. Excluded from analysis were trials in which fixation on the central stimulus was not maintained for at least 200 milliseconds before its offset in the random saccade and antisaccade tests,
Table 1. Results of Independent Samples t Tests Between Patients and Control Subjects*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Patients</th>
<th>Mean Difference‡</th>
<th>t Test</th>
<th>Cohen d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Random saccade (n = 35)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>274.00 (39.34)</td>
<td>333.26 (91.72)</td>
<td>59.26</td>
<td>-3.51‡</td>
<td>0.83 (L)</td>
</tr>
<tr>
<td>Latency SD</td>
<td>69.73 (23.00)</td>
<td>141.22 (74.92)</td>
<td>71.49</td>
<td>-5.38‡</td>
<td>1.29 (L)</td>
</tr>
<tr>
<td>Velocity</td>
<td>342.33 (58.62)</td>
<td>368.76 (76.75)</td>
<td>26.43</td>
<td>-1.61</td>
<td>0.38 (M)</td>
</tr>
<tr>
<td>Gain</td>
<td>0.99 (0.21)</td>
<td>0.91 (0.19)</td>
<td>-0.08</td>
<td>1.58§</td>
<td>0.005 (S)</td>
</tr>
<tr>
<td>Hypometric</td>
<td>7.02 (5.96)</td>
<td>10.77 (8.85)</td>
<td>-3.75</td>
<td>-2.43 (M)</td>
<td>0.58 (M)</td>
</tr>
<tr>
<td>Hypermetric</td>
<td>4.05 (4.53)</td>
<td>3.51 (4.81)</td>
<td>-0.74</td>
<td>0.67 (S)</td>
<td>0.16 (S)</td>
</tr>
<tr>
<td>Wrong direction</td>
<td>0.85 (1.26)</td>
<td>1.14 (1.78)</td>
<td>0.29</td>
<td>-0.77</td>
<td>0.18 (S)</td>
</tr>
<tr>
<td>Anticipations</td>
<td>2.80 (3.86)</td>
<td>5.54 (6.41)</td>
<td>2.74</td>
<td>-2.16 (M)</td>
<td>0.51 (M)</td>
</tr>
<tr>
<td><strong>Predictive saccade (n = 11)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>251.07 (38.66)</td>
<td>312.41 (64.11)</td>
<td>61.34</td>
<td>-2.71 (L)</td>
<td>1.15 (L)</td>
</tr>
<tr>
<td>Latency SD</td>
<td>71.38 (18.98)</td>
<td>93.92 (61.78)</td>
<td>22.54</td>
<td>-1.15 (M)</td>
<td>0.49 (M)</td>
</tr>
<tr>
<td>Velocity</td>
<td>551.10 (99.58)</td>
<td>518.76 (118.45)</td>
<td>32.34</td>
<td>0.69</td>
<td>0.29 (S)</td>
</tr>
<tr>
<td>Gain</td>
<td>0.94 (0.10)</td>
<td>0.83 (0.16)</td>
<td>-0.11</td>
<td>1.76</td>
<td>0.82 (L)</td>
</tr>
<tr>
<td>Anticipations</td>
<td>5.00 (3.52)</td>
<td>6.45 (4.92)</td>
<td>1.45</td>
<td>-0.79</td>
<td>0.33 (M)</td>
</tr>
<tr>
<td><strong>Antisaccade (n = 18)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>480.11 (93.21)</td>
<td>752.13 (478.13)</td>
<td>272.02</td>
<td>-2.36 (L)</td>
<td>0.79 (L)</td>
</tr>
<tr>
<td>Latency SD</td>
<td>96.22 (46.44)</td>
<td>228.25 (187.01)</td>
<td>132.03</td>
<td>-2.88‡</td>
<td>0.96 (L)</td>
</tr>
<tr>
<td>Error rate</td>
<td>31.44 (15.36)</td>
<td>55.88 (32.74)</td>
<td>24.44</td>
<td>-2.86</td>
<td>0.95 (L)</td>
</tr>
</tbody>
</table>

Abbreviations: L, large; M, medium; S, small.

*Data are given as mean (SD) unless otherwise indicated. Note that mean and random saccade velocities are significantly lower than predictive saccade velocities for patients (n = 11, t = -15.83, P < .001) and controls (n = 245, t = -23.89, P < .001) as they are averaged across 5 target amplitudes, whereas predictive saccades are made to 30° target jumps only.

†Mean difference is the subtraction of the mean control score from the mean patient score.

‡P < .001.

§P < .05.

||P < .01.

DATA ANALYSIS

1. Group means (patients vs control subjects) for random, predictive, and antisaccade variables were compared using independent samples t tests with separate variance estimates. Table 1 gives the results and a measure of effect size for each comparison (Cohen d).

2. The relationship between dementia severity, measured by the MMSE, and random saccade and antisaccade function was examined using Spearman rank correlations (Table 2). A reliable statistical analysis of the relationship between the MMSE score and predictive saccade function was not possible because of insufficient predictive saccade and matching MMSE data. Patients were selected who completed an MMSE test on the same day as a random saccade test (n = 32; mean ± SD age, 68.7 ± 9.8 years [range, 48-85 years]; mean ± SD MMSE score, 17.1 ± 7.4 [range, 4-26]) or an antisaccade test (n = 14; mean ± SD age, 69.7 ± 11.3 years [range, 53-83 years]; mean ± SD MMSE score, 21.3 ± 4.8 [range, 12-26]). The sample size for this test was smaller than for the random saccade test because most patients were incapable of executing correct antisaccades in the severe stage of their illness.

3. To determine the extent to which saccadic impairments could identify individual patients, the performance of each patient on each saccade variable in Table 1 was expressed as a standard score of the entire pool of 245 subjects. Scatterplots of the individual z scores were generated for each variable (Figure 1). Each scatterplot shows the mean control z values of zero and plus or minus 1.96 to define the upper and lower fifth percentile scores of the entire pool of control subjects. The association of saccade impairment and disease presence or absence was quantified with measures of sensitivity, specificity, predictive positive value, and predictive negative value for each variable (Table 3). Presence of impairment was defined as a test score in the abnormal range; abnormal range was defined as outside the 95% confidence interval of the complete control data. Absence of impairment was defined as a test score within the 95% confidence interval.

RESULTS

1. Random, predictive, and antisaccade latencies were prolonged significantly and had greater variability (measured by the SD) in the patients, who also had significantly higher frequencies of anticipatory and hypometric random saccades, lower random saccade gain, and higher antisaccade error rates, than control subjects. Latencies and latency SDs of all 3 saccade types, and the antisaccade error rate, had the largest effect sizes. Others have previously reported lower gain to predictable amplitude and timing targets than to targets with random timing only in both patients and controls. For our random and predictive tests, this was observed in con-
trols (n=245; t=4.04, P<.001) but not in patients (n=11, t=0.74, P=.47).

2. A significant and negative moderate correlation between the antisaccade error rate and the MMSE score was observed in patients (r=-0.59, P=.02) (Figure 2). The MMSE score did not correlate significantly with any other saccade variable.

3. Moderate to high sensitivity was demonstrated by all random saccade variables except the numbers of hypermetric and wrong direction saccades, and by all predictive saccade variables except the number of anticipations; moderate sensitivity was demonstrated by the antisaccade error rate. Random and predictive saccade gains, latencies, and latency SDs were the most sensitive variables. Antisaccade variables, especially the latency and latency SD, were the most specific for classifying control subjects, with the antisaccade error rate producing the best balance between sensitivity and specificity. All variables had low positive predictive value and high negative predictive value, denoting that abnormal scores are poorly related to the presence of AD but that normal scores are highly related to being a control subject. Although the saccadic function of patients was commonly in the “normal range,” the presence of abnormal scores was not specific to AD; similarly, normal scores could not indicate control status perfectly.

### Table 2. Spearman Nonparametric Correlations With Pairwise Missing Data Deletion Between the MMSE Score and Saccade Variable Measured in Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valid No. of Patients</th>
<th>Spearman r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random saccade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>32</td>
<td>0.10</td>
</tr>
<tr>
<td>Latency SD</td>
<td>31</td>
<td>-0.16</td>
</tr>
<tr>
<td>Velocity</td>
<td>32</td>
<td>0.30</td>
</tr>
<tr>
<td>Gain</td>
<td>31</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypometric</td>
<td>32</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypermetric</td>
<td>32</td>
<td>-0.03</td>
</tr>
<tr>
<td>Wrong direction</td>
<td>32</td>
<td>-0.16</td>
</tr>
<tr>
<td>Anticipations</td>
<td>32</td>
<td>-0.18</td>
</tr>
<tr>
<td>Antisaccade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>13</td>
<td>-0.36</td>
</tr>
<tr>
<td>Latency SD</td>
<td>10</td>
<td>-0.53</td>
</tr>
<tr>
<td>Error rate</td>
<td>14</td>
<td>-0.59*</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination.

*P<.05.

**Figure 1.** Scatterplots of individual patient z scores for random saccade (A), predictive saccade (B), and antisaccade (C) variables. Each plot has the mean control value of z=0 marked by the solid vertical line and the 5th and 95th percentiles of the control distribution marked by the left and right broken lines, respectively. Scores above the 95th percentile are considered abnormal according to the control data distribution for all variables except the random and predictive saccade velocities, for which scores below the 5th percentile are abnormally slow, and the random and predictive saccade gains, for which scores above the 95th percentile indicate abnormally large saccades and scores below the 5th percentile indicate abnormally small saccades compared with the target size.

Comparisons between the large control group and patients with AD in this study have confirmed the findings among patients of increased saccadic latency, reduced gain, and higher antisaccade error rates reported previously. However, they failed to confirm an increased velocity in patients with AD in the random or predictive saccade test. Patients also made significantly more hypermetric and wrong direction saccades, and predictive saccade variables except the number of anticipations; moderate sensitivity was demonstrated by the antisaccade error rate. Random and predictive saccade gains, latencies, and latency SDs were the most sensitive variables. Antisaccade variables, especially the latency and latency SD, were the most specific for classifying control subjects, with the antisaccade error rate producing the best balance between sensitivity and specificity. All variables had low positive predictive value and high negative predictive value, denoting that abnormal scores are poorly related to the presence of AD but that normal scores are highly related to being a control subject. Although the saccadic function of patients was commonly in the “normal range,” the presence of abnormal scores was not specific to AD; similarly, normal scores could not indicate control status perfectly.

**Comment**

In summary, saccade latency is prolonged in AD independent of the predictability of target timing and amplitude and regardless of the behavioral test goal (looking toward a target in the random and predictive saccade tests, or away from it in the antisaccade test). However, the magnitude of the lengthening depends on the test stimulus arrangement and behavioral requirement. The largest difference in saccade latency between patients and controls occurred in the antisaccade test and the smallest difference in the random saccade test, as reflected in the measures of effect size given in Table 1. The varying differences in saccade latency across the 3 tests may reflect the degree of difficulty of each test or the amount of learning required to perform each particular test. For example, the antisaccade test, requiring suppression of a reflexive saccade to a target followed by the generation of a nonvisually guided saccade to the opposite location, is the most difficult, creating the largest difference, and the predictive saccade test, requiring spatial and tem-
poral information to be learned, has the next largest difference.

Although impaired performance on cognitively demanding tasks such as the antisaccade test has been demonstrated in AD, the present results confirm that the generation of primarily reflexive responses by the saccade network, such as those elicited by the random saccade task, is also impaired. The overall increase in saccade reaction time, independent of the response-eliciting test, is consistent with literature showing increased motor and sensory processing time in AD and may reflect a global processing speed deficit in AD. Positron emission tomography and magnetic resonance imaging technology has shown that, in humans, the control of basic and complex types of eye movements uses distributed neural processing networks that include prefrontal, cingulate, striate, extrastriate, and parietal cortex and subcortical structures such as caudate, substantia nigra, and superior colliculus, as well as cerebellar areas. However, it is unclear at this stage whether the broad impairment in saccadic function observed herein in patients could simply reflect the diffuse cortical damage that characterizes AD (affecting regulatory descending signals) or disruptions to specific areas such as the frontal eye fields, or a combination of these factors.

In the present study, increasing dementia severity measured by the MMSE was related to higher antisaccade error rates but to no other saccade measure, a finding that replicates an earlier observation of this relationship. This finding is not irreconcilable given that the MMSE does not evaluate visuospatial processing or eye movement control; impaired random saccade ability may simply be an independent measure of cerebral degeneration. In contrast, the higher cognitive processing required to generate antisaccades, primarily mediated by the prefrontal cortex, could more closely parallel the cortical resources drawn on when responding to MMSE questions, especially because patients with AD appear to recruit frontal and prefrontal cortical areas in a compensatory manner for processes normally controlled by parietal and temporal areas in normal controls. Consequently, although the antisaccade error rate seems to be the only index with potential use for monitoring rates of disease progression or assessing treatment response, the possible independence of other abnormal saccade measures to cognitive test performance may in fact provide superior use in this context if shown to progressively deteriorate over time, given their continuous scales and greater precision of measurement. Nevertheless, some studies have observed significant relationships between cross-sectional measures of saccade latency and disease severity, while others have not. Most studies did not include patients with all levels of disease severity, possibly causing these discrepant results. For ex-
ample, in the study by Hershey and colleagues, 80% of the reported MMSE scores were between 17 and 19 out of a possible 30. Although rarely evaluated, disease severity has also been related to the number of intrusive saccades and fixation duration, while saccade gain is reportedly unrelated to disease severity in AD.

The present study included patients with disease severity ranging from mild to severe, but no relationship was found between dementia severity and any random saccade variable, including latency. Assessment of the significant relationship between disease severity and antisaccade error rate was limited, however, by patients with MMSE scores less than 12 being unable to perform the task (Figure 2). Hence, any potential application for the antisaccade error rate in tracking disease progression or monitoring the effects of therapeutic intervention will be limited to the mild, moderate, and less severe phases of the disease when defined by the MMSE score.

Despite the differences in mean group performance given in Table 1, individual patients functioned within the normal range, reducing the sensitivity and specificity of these measures to classify AD. Figure 1 and Table 3 demonstrate that no saccade measure could classify AD with 100% sensitivity and specificity. However, there is no behavioral measure that can classify AD with 100% sensitivity and specificity, and definitive diagnosis can only be made after death. The probability that any given control sample may be contaminated by cases apparently unrelated to disease severity in AD.

Although cross-sectional measurements of the antisaccade performance cannot identify AD in individual cases, despite the reliable and robust differences between patients and healthy adult controls, performance on any single measure of saccade or antisaccade performance cannot identify AD in individual cases. Although cross-sectional measurements of the antisaccade error rate are related to dementia severity in groups of patients, it remains to be tested whether repeated measures of saccade variables deteriorate progressively in individual patients. If this occurs, indexes such as the rate of change in function should be examined to determine any improved sensitivity and specificity over single cross-sectional measurements.

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Author contributions: Study concept and design (Ms Shafiq-Antonacci, Dr Maruff and Currie, and Mr Masters); acquisition of data (Ms Shafiq-Antonacci and Drs Maruff and Currie); analysis and interpretation of data (Ms Shafiq-Antonacci and Dr Maruff); drafting of the manuscript (Ms Shafiq-Antonacci and Drs Maruff and Currie); critical revision of the manuscript for important intellectual content (Ms Shafiq-Antonacci, Dr Maruff, and Mr Masters); statistical expertise (Ms Shafiq-Antonacci and Dr Maruff); obtained funding (Drs Maruff and Currie and Mr Masters); administrative, technical, and material support (Ms Shafiq-Antonacci, Drs Maruff and Currie, and Mr Masters); study supervision (Drs Maruff and Currie and Mr Masters).

Corresponding author and reprints: Bussana Shafiq-Antonacci, BA AppSc (Hons), Neuropsychology Research Laboratory, Alzheimer’s Disease Research Group, The Mental Health Research Institute of Victoria, Locked Bag 11, Parkville, Victoria 3052, Australia (e-mail: rantonacci@mhrri.edu.au).

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of demographic variables on a neuropsychological battery for use in healthy age- 


