Inhibitory Control of Saccadic Eye Movements and Cognitive Impairment in Alzheimer's Disease

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Background: *This study examined the relationship of inhibitory control and measures of neuropsychological impairment in patients with early Alzheimer's disease (AD). Four specific questions were addressed: 1) Which error parameters of saccadic inhibition are sensitive to AD? 2) Which inhibitory deficits are related to cognitive measures of impairment? 3) Is the inhibitory impairment in AD dependent on the initiation of a volitional eye movement? 4) How do the effects of saccadic inhibitory control in AD relate to the normal effects of aging?*

Methods: *Eighteen patients with probable AD and two control groups (seventeen young, and eighteen old participants) completed a battery of neuropsychological tests and four saccadic eye movement paradigms: pro-saccade, NO-GO, GO/NO-GO and anti-saccade.*

Results: *Old controls generated increased inhibition errors in comparison to young controls in the GO/NO-GO paradigm. In comparison to old controls, AD generated normal saccades in the pro-saccade paradigm, but showed a higher proportion of inhibition errors in the NO-GO, GO/NO-GO and anti-paradigms. The frequency of uncorrected errors in the anti-saccade paradigm was positively correlated with cognitive measures of dementia.*

Conclusions: *AD patients have an impairment of inhibitory control and error-correction that exceeds the effects of normal aging and is related to the severity of dementia. However, the inhibitory impairment is not contingent on the interaction with a volitional saccade.*

Key Words: Anti-saccade, attention, cholinesterase inhibitors, dementia, GO/NO-GO, inhibition errors

Alzheimer's disease (AD) accounts for the largest proportion of patients with dementia. The diagnosis of AD rests on the exclusion of other causes as there are no specific pathophysiological or biological markers. It has traditionally been characterised as a degenerative disorder with the early impairment of short term memory progressing to the global impairment of cognition. More recently, there has been a growing interest in the role of attentional and executive functions in AD (Baddeley et al 2001; Daffner et al 1999; Parasuraman and Haxby 1993; Perry and Hodges 1999; Scinto et al 1994; Simone and Baylis 1997). The current study attempts to clarify the specific cognitive operations that are impaired in relation to visual attention using saccadic eye movements (SEM). It is widely accepted that future progress in the treatment of dementia will be heavily dependent on access to a reliable early marker of AD (Nestor et al 2004). A marker should be clearly sensitive to disease progression or severity and should be able to differentiate between the effects of normal aging and the disease. The technology should be readily applicable and inexpensive, if it is to be generally accessible. It is hoped that this work will contribute towards the evaluation of SEMs as a potential early marker of AD.

Patients with AD present a formidable challenge for neuropsychological research. The psychological complications of the disease make it difficult to distinguish any generic cognitive impairment from the secondary effects of the disorder. Experimental studies must address the inevitable uncertainties concerning the source of the poor performance in AD. Does poor performance reflect an inability to perform the task, a failure to comprehend the task, or simply a lack of motivation? In contrast to many of the traditional neuropsychological tasks, where performance is dependent on the sparing of verbal and manual skills, SEM paradigms are well adapted to studies of both clinical and nonclinical groups (Broerse et al 2001; Leigh and Kennard 2004). Two levels of saccadic control were distinguished in the present study: 1) Pro-saccades refer to the rapid refixations of the eye to a novel target where the parameters of the eye movement are primarily determined by properties of the stimulus. A pro-saccade, is an automatic response that is triggered directly towards a visible stimulus (although they are not fully formed reflexes since in healthy individuals the response can be inhibited); 2) Eye movements can also be elicited in response to higher order plans and intentions. The anti-saccade paradigm (Hallet 1978) demonstrates one example of this process. The objective is to avoid the new target with an eye movement towards the mirror-image position in the opposite hemifield. This requires the inhibition of a pro-saccade that would normally be generated in response to a novel visual target and the generation of a volitional saccade away from the target. A major feature of the paradigm is that it yields behavioral measures of 1) inhibitory control and 2) an implicit knowledge of the failure of inhibition. The eyes are inadvertently drawn towards the target on some trials, but this error is normally followed by a rapid corrective eye movement to the opposite hemifield (Crawford et al 1995a; Crawford et al 1995b). This corrective mechanism yields a behavioral demonstration of self-monitoring, that is supported by a network of frontal, parietal, and basal ganglia activity (Broerse et al 2001; Kennard et al 1994; Pierrot-Deseilligny 1991). Two forms of the anti-saccade inhibition errors can be distinguished: errors that are detected at some level and spontaneously corrected, and errors that remain uncorrected.

Abnormalities of eye movements in AD have been reported in a number of studies. Deficits of smooth pursuit eye movements include reduced gain (Fletcher and Sharpe 1986) and increased catch-up saccades (Hutton et al 1984), although there have been conflicting reports (Hutton et al 1981, 1984; Muller et al 1991). Hypometric saccades, prolonged saccade latencies (Fletcher and Sharpe 1986; Hershey et al 1983; Schewe et al 1999) and

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Table 1. Neuropsychiatric Performance on the Clinical and Cognitive Test Battery

	AD (n = 18)		OC (n = 18)				
	Mean	SD	Mean	SD	*df*	*f*	Significance
Age	77.8	4.8	75.2	3.8	1,34	3.14	.085
Education (years)	12.56	1.79	11.33	1.94	1,34	3.859	.058
MMSE Score	20.9	4.3	29.2	1.1	1,34	63.48	.0001[a]
ADAS Dementia Score	23.5	8.9	8.2	2.5	1,34	49.38	.0001[a]
Verbal Fluency	11.3	5.3	19.3	4.6	1,34	23.03	.0001[a]
Trail Making Form A (secs)[c]	80.0	33.6	42.7	14.9	1,33	18.43	.0001[a]
Trail Making Form B (secs)[b]	155.8	61.0	79.7	24.5	1,27	22.51	.0001[a]
Digit Span	13.6	4.3	17.3	3.6	1,34	7.79	.009
Spatial Span	9.1	3.1	13.4	2.6	1,34	20.80	.0001[a]
Gibson Spiral Maze Errors	15.2	14.0	5.4	2.7	1,34	8.60	.006
Day/Night Inhibition Task	18.8	1.8	19.8	.7	1,34	5.36	.027
Motor Perseveration	4.4	1.1	5.0	.0	1,34	4.62	.039
NART IQ	106.4	10.9	115.6	9.7	1,34	7.16	.011
GDS	2.4	2.0	1.1	1.2	1,34	5.43	.026
CDR	1.0	.6					
NPI	11.8	9.6					
ADFACS	14.6	9.0					

AD, Alzheimer's Disease; OC, Old controls; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; NART, National Adult Reading Test; CDR, Clinical Dementia Rating Scale; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; ADFACS, Alzheimer's Disease Functional Assessment and Change Scale. [a]Significant after Bonferroni adjustment alpha level .0038. Complete data for [b]11 patients and [c]17 patients.

disorganized visual scanning (Lueck et al 2000; Mosimann et al 2004; Rosler et al 2000) have also been noted. However, an early observation suggesting that pro-saccade latencies might prove to be a reliable index of dementia severity (Pirozzolo and Haunsch 1981) was not confirmed (Hershey et al 1983). Scinto and colleagues (Scinto et al 1994) noted deficits in the generation of visually-guided saccades in patients with AD which they attributed to an attentional, rather than to an oculomotor source. However, two consistent impairments of saccades have emerged from AD research: (1) A high frequency of saccadic intrusions during attempted fixation (e.g. Schewe et al 1999), and (2) visual capture by the target on anti-saccade trials (Abel et al 2002; Currie et al 1991; Fletcher and Sharpe 1986; Shafiq-Antonacci et al 2003). Interestingly, inhibition errors in the anti-saccade paradigm were predicted by measures of dementia severity (Abel et al 2002; Currie et al 1991; Shafiq-Antonacci et al 2003).

However, an unresolved issue concerns the functional source of the inhibitory impairment in AD. One recent theory (Reuter and Kathmann 2004) has suggested that, with reference schizophrenia, inhibitory impairment reflects the cognitive loading in the preparation of the volitional anti-saccade. According to this view, the failure of behavioral inhibition is caused by an impairment of volition, not of inhibition. The critical idea is that the additional cognitive load, imposed by the mechanisms of volitional control, reduces attentional capacity which results in the attentional capture of the target and an incorrect pro-saccade (Mitchell et al 2002; Reuter and Kathmann 2004; Roberts et al 1994; Stuyven et al 2000). Alternatively, performance in AD may be subject to direct effects on cognition and behavior of defective inhibitory control and error-monitoring. In order to determine whether any inhibitory impairment in AD is contingent on the additional cognitive load of volitional control we tested patients in a series of saccadic paradigms; pro-saccade, anti-saccade, NO-GO and GO/NO-GO. An important feature of the NO-GO and the GO/NO-GO paradigms was that they required the inhibition of a prepotent saccade in the 'NO-GO' phase. However, in contrast to the anti-saccade paradigm, which specified a voluntary saccade away from the target, the GO/NO-GO paradigm specified a saccade directly towards to the target in the 'GO' phase. If the requirement to initiate a volitional saccade is the source of the inhibitory impairment in AD, then inhibitory performance should improve in the GO/NO-GO paradigm since the volitional component is reduced, relative to the anti-saccade paradigm. If however, the primary deficit is one of inhibitory control then the change in the volitional component should have no effect on the degree of impairment.

A growing number of researchers have recognized the importance of discriminating the effects of AD from those of normal aging within a single research design (Baddeley et al 2001; Perry and Hodges 1999; Solfrizzi et al 2002). It is preferable to conduct this discrimination using a within-subjects design to avoid the confounding factors that can characterize cross-study comparisons (Baddeley et al 2001). Therefore, in this work we conducted an analysis of spatial and temporal parameters of the SEMs in ADs and two groups of healthy controls: a 'young' control (YC) and an 'old' age-matched control (OC) group. In order to examine any relationships with dementia severity, the AD patients and OC group also completed a battery of neuropsychological tests.

In summary, the current study addressed four principal questions: (1) Which parameters of saccadic inhibition are sensitive to AD? (2) Which inhibitory deficits are related to cognitive measures of impairment? (3) Is the inhibitory impairment in AD dependent on initiation of a volitional eye movement? (4) How do the effects of saccadic inhibitory control in AD relate to the normal effects of aging?

Methods and Materials

Participants

The patient group consisted of 18 patients (see Table 1) with early dementia (mean age = 77.8 years; 13 males, 5 females) who satisfied the criteria for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) for probable AD. Patients were recruited from the Memory Clinic of the Directorate of Old Age

Psychiatry, Lytham Hospital, Lancashire Hospitals Trust. We recruited patients with mild dementia who were most likely to complete the tests.

Details of cognitive status are shown in Table 1. All patients underwent a detailed clinical history, physical/neurological examination and routine investigations: hemoglobin, full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, blood glucose, thyroid function tests, serum vitamin B12 and folate, serology for syphilis and urinalysis. Computerized tomography (CT) scans were obtained for eight patients. Ten patients were taking cholinesterase inhibitors: galantamine (3), rivastigmine (4), donepezil (3). Patients with acute physical symptoms, focal cerebral lesions, history of neurological disorder strokes, cerebrovascular disease, neurodegenerative disease, alcoholism or a systemic disorder were excluded from the study. Two groups of healthy participants were recruited: a group of 17 young participants (mean age = 23.8 years; 8 males, 9 females) and a group of 18 old participants (mean age = 75.2 years; 8 males, 10 females). No participant with a psychiatric or focal neurological disorder was included. All age-matched control participants underwent a detailed neuropsychological assessment. Any control who scored less than 27 on the Mini Mental State Examination (MMSE) (Folstein et al 1975) or more than 12 on the Alzheimer's Disease Assessment Scale Cognitive Test (ADAS), (Dahalke et al 1992) was excluded. All participants were screened for visual acuity using the Snellen's chart and for visual neglect with the line bisection task (Schenkenberg et al 1980). Written informed consent was obtained from all participants after a detailed description of the study, which was approved by the Blackpool, Wyre, and Fylde Local Research Ethics Committee.

Eye Tracking Recordings

Horizontal SEMs were recorded monocularly using an 'ExpressEye' (Optom, Freiburg, Germany) infra-red scleral reflection system, with a temporal resolution 1 msec and spatial resolution of .1°. The system allows for ±15° field of view. The stimulus array consisted of a central fixation point within an unfilled .75° × .75° central square, and a peripheral target that was projected at ±4° in the horizontal plane. These stimuli were generated by a head-mounted laser projected onto a white tangential screen at 57 cm. The laser output was .2 mW, with a wavelength of 635 nm. The luminance of the stimuli was 66.37 cd/m^2. The head-mounted lasers restricted the effects of head movement, which were also restrained using an adjustable head and chin rest. The system sampled at 1000 Hz, with a minimum bandwidth of 0-250 Hz.

The experiments were conducted in a darkened room in the oculomotor laboratory at Lytham Hospital. The tasks were conducted in separate blocks. The blocks consisted of 24 pro-saccade trials, 24 anti, 10 NO-GO, 10 GO/NO-GO-Right and 10 GO/NO-GO-Left trials. Each block was preceded by a set of 5 practice trials. The sequence of these paradigms began with the pro-saccade, followed by the NO-GO, GO/NO-GO and ended with the anti-saccade. The procedure began with the pro-saccade paradigm for two reasons: 1) this design avoided the previously reported carry-over effects from the anti-saccade paradigm (Roberts et al 1994); 2) A pilot study revealed that patients with dementia were more compliant when they were first exposed to the least demanding task.

Target Paradigms

Pro-Saccade Paradigm. At the beginning of each trial a central fixation point was illuminated for 1000 msec within the central square. This central square remained visible throughout all the trials, and in all the experimental conditions of this study. The central fixation point was then extinguished for the remainder of the trial. The screen was immediately blanked for a 200 msec period (i.e. GAP) before a peripheral target was presented for 2000 msec. An inter-trial interval of 1200 msec then elapsed, during which only the central square was visible, before the central fixation point was presented to signal the next trial. Participants were instructed to direct their gaze, as quickly and as accurately as possible, to the newly illuminated target and then to return to the central square.

GO/NO-GO Paradigm. A central fixation point was illuminated for 1000 msec at the beginning of each trial and the participant was asked to fixate on it. The central fixation point was then switched off, followed by a 200 msec 'GAP.' At the termination of the 'GAP' period a peripheral target was presented for 700 msec, while the central fixation point remained off. The next trial commenced after an interval of 1200 msec during which only the central square was presented. Three versions of this paradigm examined the ability to maintain central attention and to ignore a target that was presented in the left, right or both visual fields. A) NO-GO: Participants were instructed to ignore the target light and to maintain fixation at the centre of the screen for the duration of the trial. B) GO-RIGHT/NO-GO-LEFT: Participants were instructed to 'look' at the targets that were presented in the right visual field, but to suppress eye movements to all targets in the left field. C) GO-LEFT/NO-GO-RIGHT: Participants were required to 'look' at the targets that were presented in the left field but to suppress eye movements to all targets in the right field.

Anti-Saccade Paradigm. The target conditions of the anti-saccade paradigm were identical to the pro-saccade paradigm described above. However, here participants were instructed to 'look' towards a position in space, equally distant but in the opposite direction from the peripheral stimulus, as quickly and as accurately as possible (see Figure 1A).

In order to familiarize the patients with the procedures, a 'bedside' manual demonstration of pro-saccade and anti-saccade eye movements was administered before any testing. All participants were required to verbalize the appropriate instructions for each paradigm before the practice trials.

Measurement of Saccadic Parameters

The start and end of a saccade was initially detected at the point at which the eye velocity crossed 30°/sec threshold. An experienced eye movement researcher confirmed all saccades interactively.

Various sources of errors were distinguished in the pro- and anti-saccade paradigms. Anticipatory errors were defined as SEMs with a latency less than 80 msec after the target was presented. Errors of omission, consisted of those trials where a participant failed to generate an SEM to the target. In order to examine the specific process of self-monitoring, we distinguished between the inhibition errors that were corrected and uncorrected. "Inhibitions errors" were defined as the combined sum of both corrected and uncorrected errors. "Uncorrected inhibition errors," consisted of the trials in which the eye was captured inappropriately by the target, but the errors were not followed by an error-corrective saccade (see Figure 1B). 'Corrected inhibition errors' were defined as errors that were subsequently corrected with an eye movement into the opposite hemifield (see Figure 1C). The primary saccade amplitudes and latencies were measured in the pro-saccade and anti-saccade paradigms. Additionally, for the anti-saccade paradigm we mea-

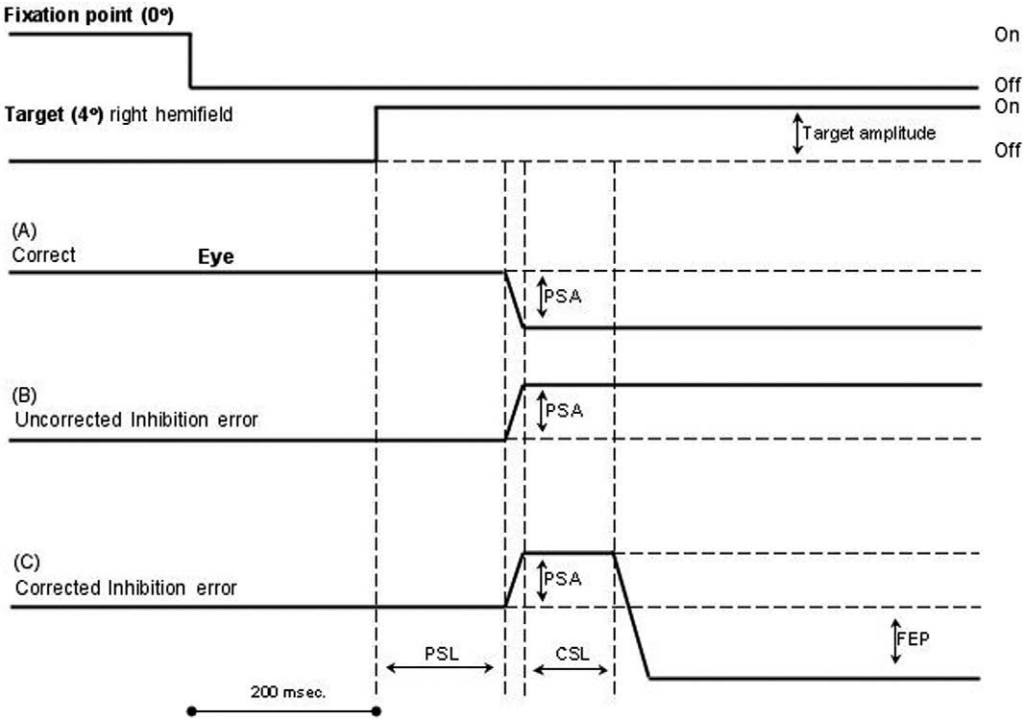

Figure 1. Responses in the anti-saccade task displaying the temporal and spatial characteristics of the visual stimulus. **(A)** Anti-saccade that was correctly directed into the opposite (i.e. left) hemifield. **(B)** An uncorrected inhibition error. A 'reflexive' movement takes the eye incorrectly towards the visual angle of the target. No corrective saccade is generated to correct this error. **(C)** Corrected inhibition error. The primary movement takes the eye incorrectly towards the target. This error is subsequently followed by a corrective movement to the opposite hemifield. PSA, Primary saccade amplitude; FEP, Final eye position amplitude; PSL, Primary saccade latency; CSL, Corrective saccade latency.

sured the latencies of any secondary error corrective saccades and the final eye positions (see Figure 1C). From the GO/NO-GO paradigm we extracted the proportion of saccades to the target that were falsely triggered in the NO-GO phase. Percentage scores were expressed as a proportion of all valid trials.

Neuropsychological Battery

Once the SEM experiments were complete, all patients and OCs returned to the laboratory within a two-week window to complete a neuropsychological test battery. These tests incorporated the Mini Mental State Examination (MMSE) (Folstein et al 1975), The European version of Alzheimer's Disease Assessment Scale Cognitive Test (ADAS), (Dahalke et al 1992) based on the Alzheimer's Disease Assessment Scale Cognitive Test (Rosen et al 1984), Clinical Dementia Rating Scale (CDR) (Hughes et al 1982), Neuropsychiatric Inventory (NPI) (Cummings et al 1994), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) (Galasko et al 1997), Geriatric Depression Scale (GDS) (Yesavage et al 1983), National Adult Reading Test (NART) (Nelson 1982), Verbal Fluency (Storandt et al 1984), Trail Making Form A and B (Reitan 1958), Digit Span from Wechsler Adult Intelligence Scale III (Wechsler 1997a), Spatial Span from Wechsler Memory Scale III (Wechsler 1997b), Day/Night Test to assess verbal response inhibition (Gerstadt et al 1994), Motor Perseveration (Golding 1989) and the Gibson Spiral Maze (Pattie and Gilleard 1987).

Results

Neuropsychological Tests

Table 1 shows the mean scores and standard deviations on the neuropsychological tests for the AD patients and OCs.

Demographic and Neuropsychological Analyses

Tests for homogeneity of variance were conducted using the Levene test using SPSS 11.5 (SPSS Inc., Chicago, Illinois). For variables that violated the assumption of homogeneity of variance, the data were submitted to nonparametric analyses. The Wilcoxon's Signed Ranks test was conducted for within-group analyses and the Kruskal Wallis test for between group analyses. Post-hoc comparisons for these nonparametric data were conducted using Tamhane's T2 for unequal variance. Parametric data were submitted to a one-way between groups analysis of variance (ANOVA). Subsequent analyses were confirmed with Bonferroni alpha adjustment and the Scheffe test was conducted for post-hoc comparisons.

As expected the ADs were impaired, relative to the OCs (see Table 1), on the following psychometric cognitive assessments: MMSE and ADAS (sub-tests: Recognition memory and Recall memory), Verbal Fluency, Trails Making A and B, Spatial Span (all p's $< .001$). The weaker group effects on errors on the Gibson Spiral Maze, Digit span tests and NART measure of pre-morbid IQ did not survive the stringent Bonferroni adjustment (Table 1). The GDS revealed one control and one patient with scores that fell within the 'mild' range of clinical depression.

Pro-Saccade Paradigm

The results of the pro-saccade analyses are presented in Table 2. Pro-saccade latencies of AD patients showed a small, nonsignificant mean increase of 16 msec in comparison to OCs. An ANOVA also revealed that the groups did not differ in the frequency of pro-anticipatory saccades. The nonparametric analyses showed a significant group effect for pro-omission errors

Table 2. Means, Standard Deviations, Group Comparisons For the Saccadic Eye Movement Data

	AD		OC		YC		ANOVA/Nonparametric Analyses				Post hoc Contrasts	
Saccade parameters	Mean	SD	Mean	SD	Mean	SD	*df*	χ^2	*F*	Sig.	Disease AD vs OC	Age OC vs YC
Pro-Saccade Latency (msecs)	225	49	209	32	202	29	2,50		1.711	.191	.427[b]	.890[b]
Pro-Saccade Amplitude (degs)	3.0	.6	3.2	.8	3.9	.4	2,50		10.39	.0001[d]	.684[b]	.005[b,e]
Pro-Omission Errors (%)	4.7	9.7	6.5	11.5	.0	.0	2	8.57		.014[a]	.940[c]	.085[c]
Pro-Anticipatory Saccades (%)	2.1	5.1	4.5	6.0	1.0	2.4	2,50		2.372	.104	.353[b]	.115[b]
NO-GO Inhibition Errors (%)	32.5	25.9	10.6	12.1	4.1	6.2	2	19.69		.0001[a,d]	.01[c,e]	.160[c]
GO/NO-GO Inhibition Errors (%)	66.3	24.1	36.6	24.1	7.3	24.6	2	28.04		.0001[a,d]	.01[c,e]	.001[c,e]
Anti-Primary Saccade Latency (msecs)	331	121	293	45	244	38	2	11.36		.003[a,d]	.544[c]	.004[c,e]
Anti-Primary Saccade Amplitude (degs)	3.5	2.5	4.2	1.6	3.9	1.4	2,49		.709	.497	.500[b]	.893[b]
Anti-Inhibition Errors (%)	53.4	23.6	18.4	13.4	10.8	9.3	2	27.22		.0001[a,d]	.0001[c,e]	.167[c]
Anti-Uncorrected Errors (%)	25.4	22.4	2.5	7.0	1.0	1.8	2	21.32		.0001[a,d]	.002[c,e]	.749[c]
Anti-Omission Errors (%)	10.4	12.0	5.8	12.6	1.2	2.4	2	8.86		.012[a]	.606[c]	.382[c]
Anti-Anticipatory Saccades (%)	5.3	6.0	2.6	5.0	3.6	7.5	2,50		0.86	.430	.440[b]	.904[b]
Anti-Corrective Saccade Latency (msecs)	500	112	365	84	327	74	2,43		14.81	.0001[d]	.001[b,e]	.561[b]
Anti-Final Eye Position (degs)	3.6	1.6	4.1	2.1	4.6	2.9	2,43		.868	.427	.807[b]	.791[b]

AD, Alzheimer's disease; OC, Old controls; YC, Young controls; ANOVA, analysis of variance.
[a]Kruskal Wallis Test for non-parametric data.
[b]Post-hoc comparisons using Sheffe test.
[c]Tamhane's T2 for unequal variance.
[d]Significant after Bonferroni alpha adjustment.
[e]Significant at $p < .01$ level.

($\chi^2 = 8.57$, $df = 2$, $p < .014$) due to the better performance of the YCs in comparison to both OCs and ADs, who did not differ from each other. However, this group effect did not survive the Bonferroni alpha adjustment. There was a significant effect of group on pro-saccade amplitudes ($F(2,50) = 10.39$, $p < .0001$). Post-hoc Scheffe comparisons revealed that the pro-saccade amplitudes of the YCs were significantly larger (and more accurate) than the ADs and OCs, who did not differ from each other. Analyses of the medication effects on saccadic eye parameters were conducted by contrasting the 10 patients on anti-dementia medication (mean duration = 102 days, SD = 76) and the 8 unmedicated AD patients. There were no significant effects of medication group on any parameter of the pro-saccades ($F(1,16) < 2.9$, $p > .103$, ns).

NO-GO Paradigm

In comparison to the YCs and OCs, ADs generated 20-30% more NO-GO inhibition errors ($\chi^2 = 19.69$, $df = 2$, $p < .0001$; see Table 2). Post-hoc comparisons (OCs vs. YCs) revealed a significant AD versus OC group effect but no effect of normal aging on the frequency of NO-GO inhibition errors.

GO/NO-GO Paradigm

A task analysis comparing the performance in the GO/NO-GO Left versus GO/NO-GO Right revealed no main effect of the paradigm or group by paradigm interaction, therefore for each group these results were combined and submitted to a one-way between-groups nonparametric analysis. In the GO/NO-GO paradigm there was a significantly higher frequency of inhibition errors for ADs compared to OCs (mean difference = 29.7%) and between YCs and OCs ($\chi^2 = 28.04$, $df = 2$, $p < .0001$, see Table 2). There were no significant effects of medication group on inhibition errors in the NO-GO or GO/NO-GO paradigms ($F(1,16) < 1.7$, $p > .2$, ns).

Anti-Saccade Paradigm

Table 2 reveals a significant effect of group membership on anti-inhibition errors ($\chi^2 = 27.22$, $df = 2$, $p < .0001$) and anti-uncorrected errors ($\chi^2 = 21.32$, $df = 2$, $p < .0001$). Figure 2 shows the distribution of reaction times for correct saccades, corrected error saccades and uncorrected error saccades for the ADs and controls in the anti-saccade task. There was a similar distribution of correct anti-saccades and corrected errors for the ADs and OCs. However, the AD group was distinguished from the controls by a marked early peak (125–150 msec) in the distribution of uncorrected anti-saccades. These data reveal that the uncorrected errors have characteristic short latencies, close to the express-saccade range, and provides further evidence that the AD group was frequently unable to inhibit short latency saccades in this task.

Interestingly, an unexpected fall in the mean inhibition error rate for ADs in the anti-saccade paradigm (54%) in comparison to their level of inhibition errors in the GO/NO-GO paradigm (66.3%) did not reach significance ($Z = -1.807$, $p = .071$). In comparison to the OCs (mean = 2.5%), the ADs (mean = 25.4%) generated a higher proportion of anti-saccade errors that were uncorrected. The frequencies of uncorrected anti-saccades in the OCs and YC groups (mean = 1%) showed no effect of normal aging. In comparison to the OCs, the AD patients required an average of 135 msec longer to trigger an anti-corrective saccade ($F(2,43) = 14.81$, $p < .001$). Post-hoc comparisons (OCs vs. YCs) yielded no effect of normal aging on anti-corrective saccade latency. There was a strong overall group effect on anti-primary saccade latencies ($\chi^2 = 11.36$, $df = 2$, $p = .003$). Post hoc analyses revealed that in comparison to OCs, the YC group had significantly faster anti-saccade latencies (Table 2). The mean final eye positions of anti-saccades did not differ significantly between groups ($F(2,43) = .868$, $p = .427$, ns).

There was a small overall effect of group on the frequency of anti-saccade omissions in AD patients which did not survive the Bonferroni alpha adjustment ($\chi^2 = 8.86$, $df = 2$, $p = .012$). AD patients on medication revealed a trend towards an increase in anti-saccade latencies (mean = 374 msec, SD = 70) compared to the unmedicated group mean (270 msec, SD =

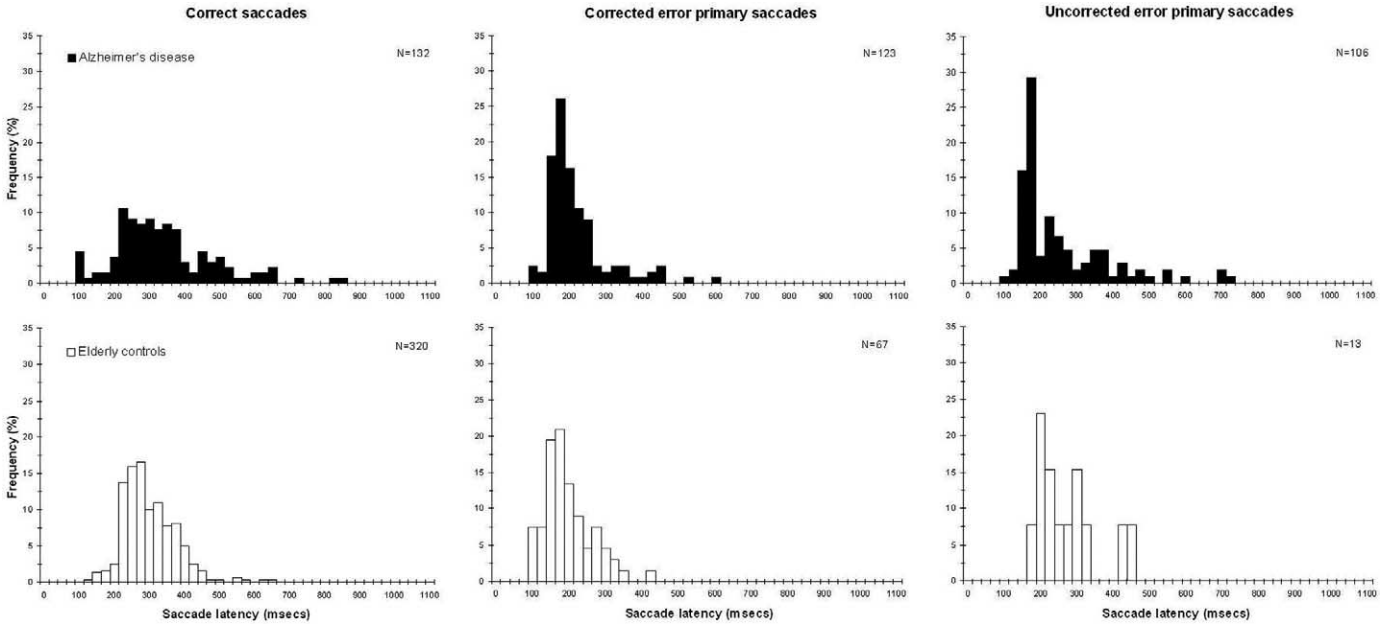

Figure 2. Frequency distributions of latencies for correct anti saccade, corrected error anti-saccades and uncorrected errors. Upper panels show data from patients with Alzheimer's disease, lower panels show data for the elderly control group.

44), but the effect was not statistically reliable ($F(1,16) = 3.542$, $p < .079$, ns). There were no other effects of medication group on any parameter in the anti-saccade paradigm ($F(1, 16) = 2.2$, $p > .162$, ns).

Correlations of Cognitive Tests and the Correction of Saccadic Inhibition Errors

Correlations (Pearson) of saccadic parameters and cognitive performance for the OCs and patients with AD are shown in Table 3. In comparison to other saccadic parameters, the frequency of anti-uncorrected errors ('Anti-UCE') showed a consistent correlation with the measures of dementia severity. These data revealed that the relationships were largely specific to the AD group, and were obtained predominantly in connection with the uncorrected anti-saccades. Uncorrected errors were most highly correlated with the ADAS and MMSE dementia scores, Trails A and Spatial span. These correlations remained significant when age was introduced as a covariate. The scatter plot in Figure 3 shows the relationship of error corrections in AD and cognitive scores on the ADAS ($r = .653$, $p = .003$). Note that

Table 3. Correlations (Pearson) of Cognitive and Anti-Saccade Performance Measures

		Error Parameters					Correct Saccade Parameters	
		Anti-UCE (%)	Anti IE (%)	Omissions (%)	Anticipations (%)	Corrective Saccade latency (msecs)	Primary Latency (msecs)	Primary Amplitude (degs)
MMSE Score	AD	−.644[b]	−.196	−.431	.331	.093	−.506[a]	.237
	OC	.002	−.226	.368	−.189	.137	.137	.076
ADAS Score	AD	.653[b]	.341	.315	.056	.036	.022	−.234
	OC	−.115	.202	−.213	−.144	−.556[a]	−.34	−.213
NART IQ	AD	−.383	−.424	−.052	.144	.162	−.216	−.096
	OC	.005	.053	.221	.208	−.075	.068	−.163
Verbal Fluency	AD	−.536[a]	−.203	−.377	.011	.424	−.425	.148
	OC	−.018	.002	−.276	.257	−.397	−.268	−.287
Digit Span Total	AD	−.415	−.269	−.183	.214	.059	−.128	.31
	OC	−.248	−.372	.54[a]	−.364	.469	.019	−.013
Spatial Span Total	AD	−.65[b]	−.192	−.349	.145	−.061	−.515	.172
	OC	.245	.112	−.273	.151	−.487	−.302	−.05
Gibson Spiral Maze: Errors	AD	.128	−.236	.115	−.283	.586	.283	−.201
	OC	−.065	−.017	−.198	.179	−.434	−.128	−.418
Trails A Time (secs)	AD	.825[b]	.454	−.024	.03	.227	.373	−.168
	OC	.395	.251	.136	−.252	.213	.105	.011
Trails B Time (secs)	AD	.356	−.144	.543	.009	.055	.031	.099
	OC	−.081	.116	.106	−.4	.41	.13	−.016

Anti-IE, Anti-inhibition errors; Anti-UCE, Anti-uncorrected error; AD, Alzheimer's Disease ($n = 18$); OC, Old controls ($n = 18$).
[a] $p < .05$.
[b] Significant with Bonferroni adjustment alpha level $p < .005$.

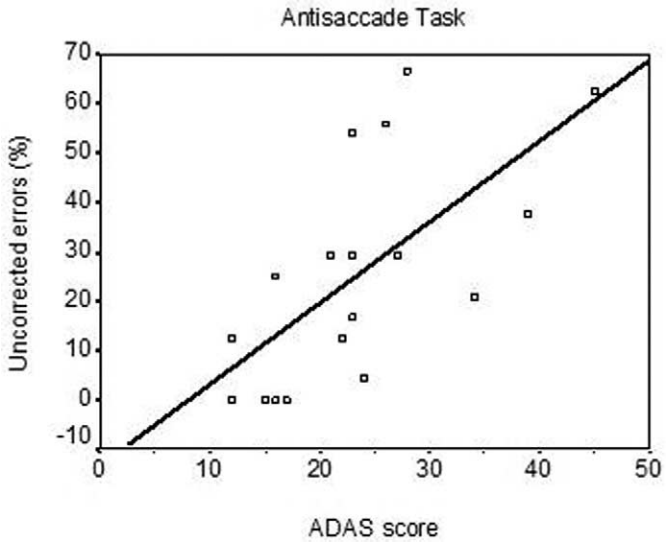

Figure 3. Relationship of uncorrected errors in the anti-saccade task with cognitive impairment in patients with probable Alzheimer's disease. ADAS, Alzheimer's disease assessment scale.

there was no significant correlation of inhibition errors with the premorbid estimate of IQ in the NART ($r = -.383$, $p = .117$, ns). These data were submitted to multiple regression analysis to determine the relative contribution of these variables to error performance. The multiple regression analyses included stepwise forward and backward entry methods for the predictors to confirm the reliability of the analyses. These analyses revealed that the best predictor of uncorrected errors was the Trails A task, followed by ADAS scores. In contrast the best predictors for inhibition errors was spatial span and MMSE ($r^2 = .465$).

Discussion

Various types of anti-saccade errors were distinguished in this study: anticipations, omissions and inhibition errors (separated into corrected and uncorrected inhibition errors). The principle abnormality in AD was a striking increase in inhibitory errors together with a marked reduction in corrective saccades after the eye had moved inadvertently towards the target. The AD patients yielded a 10-fold increase in the proportion of anti uncorrected errors (mean = 25.4%) in comparison to OCs (mean = 2.5%). The proportion of uncorrected errors correlated with the severity of cognitive impairment as measured by the ADAS (see Table 2). These data support previous studies (Abel et al 2002; Currie et al 1991; Shafiq-Antonacci et al 2003) showing that patients with AD display increased inhibition errors during the anti-saccade paradigm, and provide reassurance that these uncorrected errors are characteristic of both medicated and unmedicated patients. Uncorrected errors were also correlated with cognitive scores on the MMSE, Verbal Fluency and Spatial Span tests. When the AD patients were able to correct their errors in the anti-saccade paradigm, they were slow (average increase >130 msec) in comparison to OCs.

Distinguishing the Effect of Healthy Aging from Alzheimer's Disease

The pro-saccadic parameters including latency, omissions, anticipations and uncorrected errors showed little effect of aging or AD. It should be noted that no member of the YC group generated a pro-omission error, although this error was also infrequent in the OCs and ADs. However, the principal effect of aging on pro-saccades was on the amplitude. The YC group generated larger and more accurate saccades in comparison to the AD patients and the OCs. This suggests that pro-saccades become less accurate in elderly individuals, but are not specifically impaired in AD.

Inhibition errors in the GO/NO-GO paradigm revealed an effect of normal aging that differed quantitatively, but not qualitatively, from that of AD. AD patients generated approximately 30% more inhibition errors than the OCs, who themselves generated approximately 30% more inhibition errors than the YCs. These inhibition errors demonstrated that AD patients and the OCs had a substantial problem of inhibitory control. However, it is important to note that this inhibitory deficit does not directly reflect an impairment of volitional saccades (Reuter and Kathmann 2004). The anti-saccade paradigm uniquely required a volitional saccade 'away' from the target in addition to the inhibition of a pro-saccade. In contrast, the GO/NO-GO paradigm required only a pro-saccade or the inhibition of a pro-saccade. If the requirement to initiate a volitional saccade was the critical factor in the inhibitory impairment in AD, then the GO/NO-GO paradigm would have been expected to yield a weaker inhibitory deficit in comparison to the anti-saccade paradigm. On the contrary, the increase of 12.9% in the frequency of inhibition errors for the AD group in GO/NO-GO paradigm, in comparison to the anti-saccade paradigm, demonstrated that the impairment of inhibitory control was not contingent on the initiation of a volitional anti-saccade. However, it is important to note that performance in the GO/NO-GO task is also subject to a high cognitive load, due to the rule about task spatial contingencies. Performance also depends on the ability to switch between inhibitory and movement modes on a trial-by-trial basis. These demands may contribute to the high error rates in this task. Yet, the evidence that AD patients also produced significantly more inhibition errors than the OCs in the less demanding NO-GO task demonstrates that the AD impairment was not dependent on the competing demand of a volitional saccade. In the NO-GO task, there was no reliable difference in the mean inhibition errors of the OC and YC groups. Thus the weaker attention demanding nature of the NO-GO paradigm revealed some preservation of inhibitory capacity in the OCs, but not in the AD group. These results provide converging evidence that the inhibitory deficit in AD cannot be explained by an attentional loading effect of volitional saccades, but may reflect direct degenerative effects on inhibitory control.

The data from the GO/NO-GO and anti-saccade paradigms, when considered together, may reveal distinctive deficits of both inhibitory and volitional saccadic control in the AD group. In addition to the increase in inhibition errors, AD patients also demonstrated a trend towards increased latencies of the anti-primary (i.e. volitional) saccades (AD = 331 msec, OC = 293 msec, YC = 244 msec), although there was a large variability within the ADs in comparison to the control groups (see Table 2). The evidence that AD patients generated a higher frequency of uncorrected inhibition errors, and also required more time to correct these errors, may reflect a distinct deficit in the volitional control of anti-saccades.

Can the AD Data be Explained by Poor Patient Motivation or Task Comprehension?

A number of factors suggest that any difficulties of task compliance cannot provide a satisfactory account of these data. First, all ADs received a set of practice trials to confirm that they could

produce a series of appropriate SEMs. Second, the profile of saccadic impairments revealed that ADs performed normally on several of the pro-saccade and anti-saccade parameters. Inhibitory control and error-correction were primarily impaired, but the ADs responded efficiently on every measure of performance in the pro-saccade condition, a task that required selective attention and a precisely programmed eye movement to the visual target. In contrast, they generated a high frequency of inhibition errors in the less demanding NO-GO paradigm. Note that, since the majority of AD patients were in the early stages of the dementia (mean CDR = 1, see Table 1), they were able to fully cooperate with the saccadic and neuropsychological investigation.

Another possibility is that the AD group may have gradually failed to retain the task set during the course of a block of trials, which could account for their increased rate of uncorrected errors. One piece of evidence that would be consistent with the idea of memory loss, would be evidence of deterioration in performance within test sessions. Therefore we conducted an analysis of the frequency of inhibition errors in the first and second halves of the anti-saccade task to determine whether there was evidence of a deterioration in AD performance within a test. This analysis revealed that the mean uncorrected inhibition error rate during the first half (52.8%) did not differ in the second half (53.7%) of the test ($t(17) = -.21$, $p = .833$, ns). Similarly, a pair-wise correlation analysis revealed that the error rates were highly correlated across the two halves of the test ($r = .72$, $p < .001$). These results demonstrate that AD error rates did not change across the test and undermines the idea that inhibition errors were attributable to progressive memory loss during the experiment.

Neural Correlates of Error Correction

A number of recent studies have suggested that the anterior cingulate and prefrontal cortex play an important role in the monitoring of self-generated errors (Carter et al 1998; Gehring et al 1993; Ito et al 2003; Kiehl et al 2000; Rushworth et al 2003). Electrophysiological studies have distinguished between two sources of error processing; firstly, an early error-related negativity signal is thought to reflect internal information regarding an error, perhaps derived from an efference signal. A second slow error-related positivity signal gives rise to the conscious awareness of an error (Nieuwenhuis et al 2001). Studies of healthy individuals have revealed that the explicit knowledge of an error on the anti-saccade trials frequently escapes conscious awareness (Mockler and Fischer 1999; Nieuwenhuis et al 2001) even when these errors are followed by a large error-correcting saccade. However, there is good evidence that individuals are more likely to adjust a behavioral response after an error is detected (Rabbitt 1967). This provides empirical support for the idea that some knowledge of an error is crucial for the development of remedial action and will lead to the reduction of subsequent errors in performance.

Studies reflect a growing view that the anterior cingulate plays an important role in the signaling of behavioral errors and/or response conflicts. Schizophrenic patients generate a high proportion of inhibition errors in the anti-saccade paradigm, and functional (Crawford et al 1996; Paus et al 1993; Sweeney et al 1996) and volumetric (Ettinger et al 2004) brain imaging studies have linked the anterior cingulate to inhibitory control in this task. However, in contrast to schizophrenia, patients with AD show relatively few error-correction saccades, which suggests that patients with early AD may have a dysfunction of the neural circuitry for error-monitoring. Evidence from single unit recordings in monkey revealed that the underlying neural network of error monitoring includes the supplementary eye fields (Stuphorn et al 2000) although human fMRI data also implicates the presupplementary area (Curtis and D'Esposito 2003).

Conclusions

A failure in error-monitoring may be related to a number of cognitive and behavioral problems that are commonly associated with Alzheimer's disease. The evidence from this study reveals that the failure of error correction in AD is related to a set of executive control operations. The failures of error correction provided the most reliable oculomotor index of dementia severity in AD and distinguished it from the normal effects of aging. Oculomotor tests are easy to perform and can be conducted when verbal or manual skills are impoverished. Therefore this methodology may be particularly useful in studies of dementia, by providing a convenient measure of cognitive performance in clinical drug trials and patient management.

Munoz and colleagues (Munoz and Wurtz 1992; Munoz and Wurtz 1993a; Munoz and Wurtz 1993b) described neurones in the rostral pole of the superior colliculus that were active during visual fixation but were inhibited during an SEM. These neurones were reciprocally connected to movement neurones with the complimentary property of discharging during an SEM but produced inhibition during a fixation. Neurones with similar characteristics have also been identified in the frontal eye fields (Segraves and Goldberg 1987). This leaves open the idea that the failure of ADs to correct an erroneous saccade could also reflect an inability to disengage fixation from the stimulus due to a failure in the inhibition of the fixation neurones. In future work, we plan to explore the idea that AD patients may experience a failure in the mechanism for releasing visual fixation from the current visual stimulus.

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