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

Trevor J. Crawford, Steve Higham, Ted Renvoize, Julie Patel, Mark Dale, Anur Suriya, and Sue Tetley

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

From the Mental Health and Neural Systems Research Unit (TJC, SH, ST), Department of Psychology, Lancaster University, Lancaster; Department of Old Age Psychiatry (TR, JP, AS), Lytham Hospital, Lytham; Fleetwood Hospital (MD), Fleetwood, United Kingdom.

Address reprint requests to Dr. Trevor J. Crawford, The Mental Health and Neural Systems Research Unit, Department of Psychology, Lancaster University, Lancaster, LA1 4YF, United Kingdom; E-mail: t.crawford@lancaster.ac.uk.

Received July 28, 2004; revised October 25, 2004; revised December 20, 2004; accepted January 11, 2005.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2005.01.017

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