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Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease

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Frontotemporal lobar degeneration (FTLD) often overlaps clinically with corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), both of which have prominent eye movement abnormalities. To investigate the ability of oculomotor performance to differentiate between FTLD, Alzheimer's disease, CBS and PSP, saccades and smooth pursuit were measured in three FTLD subtypes, including 24 individuals with frontotemporal dementia (FTD), 19 with semantic dementia (SD) and six with progressive non-fluent aphasia (PA), as compared to 28 individuals with Alzheimer's disease, 15 with CBS, 10 with PSP and 27 control subjects. Different combinations of oculomotor abnormalities were identified in all clinical syndromes except for SD, which had oculomotor performance that was indistinguishable from age-matched controls. Only PSP patients displayed abnormalities in saccade velocity, whereas abnormalities in saccade gain were observed in PSP > CBS > Alzheimer's disease subjects. All patient groups except those with SD were impaired on the anti-saccade task, however only the FTLD subjects and not Alzheimer's disease, CBS or PSP groups, were able to spontaneously self-correct anti-saccade errors as well as controls. Receiver operating characteristic statistics demonstrated that oculomotor findings were superior to neuropsychological tests in differentiating PSP from other disorders, and comparable to neuropsychological tests in differentiating the other patient groups. These data suggest that oculomotor assessment may aid in the diagnosis of FTLD and related disorders.

Keywords: oculomotor; frontotemporal lobar degeneration; corticobasal syndrome; progressive supranuclear palsy; Alzheimer's disease

Abbreviations: CBD = corticobasal degeneration; CBS = corticobasal syndrome; CDR = clinical dementia rating; FTLD = frontotemporal lobar degeneration; FTD = frontotemporal dementia; PA = progressive non-fluent apahasia; PSP = progressive supranuclear palsy; ROC = receiver operating characteristic; SD = semantic dementia; TIV = total intra-cranial volume; UPDRS = Unified Parkinson's Disease Rating Scale

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Introduction

Eye movement abnormalities are sensitive markers of neurological disease and are useful in the differential diagnosis of a variety of clinical neurological syndromes (Leigh and Kennard, 2004). Prominent eye movement abnormalities have been described in corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) (Vidailhet *et al.*, 1994; Rottach *et al.*, 1996; Rivaud-Pechoux *et al.*, 2000), and are useful for diagnosing these disorders and differentiating them from each other as well as other neurodegenerative diseases (Litvan *et al.*, 1996*a*, 1997; Leigh and Riley, 2000). CBS and PSP are clinically, genetically and pathologically related to frontotemporal lobar degeneration (FTLD), a common cause of dementia in individuals with disease onset at ages <65 (Boeve *et al.*, 2003; Boxer and Miller, 2005; Cairns *et al.*, 2007; Kertesz *et al.*, 2007). However, it is not known to what extent CBS- and PSP-related oculomotor abnormalities are present in FTLD,

or whether such findings can differentiate FTLD from CBS, PSP or Alzheimer's disease.

FTLD comprises three core clinical dementia syndromes, a behavioural and dysexecutive (or frontal) variant called frontotemporal dementia (FTD), and two forms of primary progressive aphasia, a temporal lobe variant, also called semantic dementia (SD), and a progressive non-fluent apahasia (PA) (Neary *et al*., 1998). Diagnosis of each of the FTLD clinical syndromes relies mainly on the identification of a combination of progressive behavioural and neuropsychological impairments and the exclusion of others. In contrast, the presence of oculomotor abnormalities is a core diagnostic feature of PSP (Litvan *et al*., 1996*a*). Although CBS is associated with oculomotor abnormalities that are distinct from PSP (Leigh and Riley, 2000), such findings do not constitute core diagnostic criteria for this syndrome (Boeve *et al*., 2003). Instead, most clinical CBS criteria rely on the presence of atypical Parkinsonism, cortical signs and cognitive impairments. Like FTLD, clinical research criteria for Alzheimer's disease are primarily based on the presence of progressive cognitive and functional deficits (McKhann *et al*., 1984).

CBS and PSP display prominent visually guided saccade abnormalities, including increased saccade latency in CBS and decreased saccade velocity and gain in PSP (Steele *et al*., 1964; Rebeiz *et al*., 1967; Vidailhet *et al*., 1994; Rottach *et al*., 1996). Consistent with the overlapping cognitive and behavioural features of CBS and PSP with FTLD, FTLD variants with frontal lobe damage are similarly impaired to PSP patients in their ability to withhold visually guided (reflexive) saccades on the anti-saccade task (Meyniel *et al*., 2005; Boxer *et al*., 2006*a*). Two of the core clinical FTLD syndromes, FTD and PA, are associated with abnormalities in voluntary saccades and smooth pursuit, however visually guided (reflexive) saccades are relatively normal (Boxer *et al*., 2006*a*). Increased latency, decreased spatial accuracy and impaired ability to control the initiation of saccades, as well as decreased smooth pursuit gain have been described in Alzheimer's disease (Hutton *et al*., 1984; Fletcher and Sharpe, 1986; Currie *et al*., 1991; Moser *et al*., 1995; Shafiq-Antonacci *et al*., 2003; Mosimann *et al*., 2004; Crawford *et al*., 2005; Boxer *et al*., 2006*a*). In this regard, the oculomotor abnormalities in Alzheimer's disease are similar to what has been described for CBS, but there have been no direct comparisons between these disorders.

Complicating the comparison of oculomotor features between CBS, PSP and FTLD are the overlapping molecular pathologies identified at autopsy in all three groups. Most clinically diagnosed cases of FTLD are found to have protein deposits that stain for the proteins tau or ubiquitin (FTLD-U) in different patterns (Cairns *et al*., 2007). Depending on the reported pathological series, there are approximately equal percentages of both types of molecular pathology found at autopsy in clinically diagnosed FTD cases (Forman *et al*., 2006; Josephs *et al*., 2006*b*), whereas most SD cases are associated with FTLD-U pathology (Davies *et al*., 2005). As classically described, both corticobasal degeneration [CBD; the autopsy finding first described in association with CBS (Rebeiz *et al*., 1967)] and PSP are associated with tau deposition (in different patterns), and most clinically diagnosed cases of PA are also found to have CBD or PSP pathology at autopsy (Josephs *et al*., 2006*a*). Less commonly, clinical FTD cases may also be associated with CBD- or PSP-type pathology at autopsy (Josephs *et al*., 2006*b*) and conversely FTLD-U pathology may be associated with clinical oculomotor abnormalities similar to PSP (Paviour *et al*., 2004). Thus, if the clinical oculomotor features of CBS and PSP predict tau deposition at autopsy, it would be expected that similar oculomotor abnormalities should be detected in FTLD cases with tau deposition, particularly PA, but also a significant proportion of FTD cases.

The goal of this study was to directly compare the oculomotor abnormalities associated with CBS, PSP, FTLD and Alzheimer's disease, and to investigate the ability of oculomotor measurements to differentiate these syndromes. Given the similarities between autopsy findings in CBS, PSP and FTLD we hypothesized that the characteristic oculomotor features of CBS and PSP would also be present in FTLD. Since oculomotor function is less sensitive to language or limb motor impairments than traditional neuropsychological tests, we hypothesized that eye movements would be superior to neuropsychological tests in diagnosing the clinical syndromes with the most profound oculomotor impairments.

Materials and Methods

Subjects

All subjects were evaluated at the University of California, San Francisco Memory and Aging Center and gave informed consent to participate in the experimental procedures. For demented individuals who could not give informed consent because of their degree of cognitive impairment, a surrogate consenting procedure was used. First, subjects' capacity to consent was evaluated using a standard assessment protocol. In subjects without capacity to consent who assented to participation, a family member or caregiver gave consent for that subject to participate. Further details regarding the UCSF Surrogate Consenting procedure may be found on the UCSF Institutional Review Board (IRB) website: http://www.research.ucsf.edu/chr/Guide/chrCogImp.asp. All aspects of the study were approved by the UCSF IRB.

Subjects underwent neurological examination, neuropsychological testing and brain MRI scans within 3 months of eye movement evaluation and were categorized as control, FTLD, Alzheimer's disease, CBS or PSP subjects. FTLD subjects met criteria of Neary *et al.* (1998) for FTD, SD or PA.

Alzheimer's disease subjects met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's disease (McKhann *et al*., 1984). All PSP patients met the National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy criteria for probable PSP (Litvan *et al*., 1996*a*). Briefly, these include

(i) a gradually progressive disorder with onset at the age of 40 years or later; and (ii) vertical supranuclear gaze palsy and prominent postural instability within the first year of disease onset. A probable diagnosis of CBS required the following features: (i) a slowly progressive course; (ii) asymmetric limb or axial rigidity, present without reinforcement; (iii) aphasia, visuospatial impairment or neglect or apraxia; and (iv) dystonia, myoclonus, cortical sensory loss or alien limb phenomenon (Boeve *et al.*, 2003). To verify that CBS subjects had Parkinsonism typical of other clinical CBS case series (Schneider *et al.*, 1997; Kompoliti *et al.*, 1998; Boeve *et al.*, 1999, 2003; Boxer *et al.*, 2006*b*), we measured Unified Parkinson's Disease Rating Scale (UPDRS) motor scores. As expected, CBS patients had higher ($P < 0.001$, *t*-test) Unified Parkinson's Disease Rating Scale (UPDRS) motor scores (mean ± standard deviation: 29.7 ± 3.4; $n = 9$) than Alzheimer's disease patients (3.9 ± 2.8; $n = 13$).

Control subjects had no neurological complaints, normal neurological and neuropsychological examinations, and clinical dementia rating (CDR) scores of 0 (Morris, 1993), except for one control subject with a CDR score of 0.5 but normal performance on neuropsychological tests. Our subject population contained 27 control, 23 FTD, 18 SD, six PA, 27 Alzheimer's disease, 16 CBS and nine PSP subjects. Autopsy confirmed diagnoses were available in five FTD subjects (four FTLD-U; one Pick's disease), five PSP subjects (all PSP) and one PA subject (CBD) (Cairns *et al.*, 2007).

Eye movement recordings

Subjects were seated on a cushioned chair with their heads stabilized using padded chin and forehead rests, and a head strap. Stimuli were viewed binocularly in a dark room, and the two-dimensional movements of the right eye were measured using the Fourward Technologies (Buena Vista, VA, USA) Generation 6.1 Dual Purkinje Image Eye Tracker. The spatial resolution of the eye tracker was 1 min of arc with a temporal resolution of 1 ms. The automatic optical staging (auto stage) and focus servo of the tracker were disabled to avoid introducing head position artefacts into the eye position data. The eye position signal was low-pass filtered with a cut-off at 330 Hz, and voltages proportional to eye velocity were obtained by differentiating the eye position signals with an analogue circuit. The circuit differentiated signal content up to 25 Hz and rejected signals of higher frequencies. Data were stored for off-line analysis.

Targets consisted of white spots of 0.1° visual angle presented on a large analogue oscilloscope (model A12-63; Xytron, Sylmar, CA, USA) that was driven by digital-to-analogue outputs from a digital signal processing board in a Pentium computer. The monitor was 80 cm from the subject and subtended a visual angle of 30° horizontally by 24° vertically. The eye position signals were calibrated at the beginning of each recording session by having subjects fixate stationary targets at known horizontal and vertical eccentricities.

Oculomotor paradigms

The following three paradigms were performed in all subjects and in the same chronological sequence: prosaccades, smooth pursuit, anti-saccades. Each paradigm was conducted as a series of trials separated by inter-trial intervals of 1000–2000 ms. The task instructions were given by the experimenter before each of the paradigms and subjects were asked whether they understood the instructions. If the subject did not understand the instructions they were repeated and demonstration trials were shown. Subjects determined the rest period between paradigms and the overall duration of the experiment was in the range of 30–45 min.

Prosaccade trials consisted of randomly interleaved 5 and 10° targets presented up, down, left or right of a central fixation point. Each trial began with illumination of a central fixation spot for 1000 ms. When the fixation light was extinguished, targets appeared either immediately (overlap condition) or after a 200-ms gap (gap condition, horizontal 10° trials only). The eccentric target remained illuminated for 1000 ms. Subjects were instructed to look at the central fixation point while it was illuminated, then to look as quickly and as accurately as possible at the eccentric target. At least seven responses were recorded for each stimulus in each direction. There were no differences between subject groups ($P > 0.1$, ANOVA) in the percentage of trials with adequate quality data for analysis in any direction. The mean ± standard deviation percentage of analysable trials ranged from 78.2 ± 25% for 10° downward saccades to 84.4 ± 20% for 10° leftward saccades.

Smooth pursuit eye movements were evaluated in blocks of trials that delivered step-ramp target motion (Rashbass, 1961) in each of four directions (up, down, left or right). Each pursuit trial began when a fixation spot was presented in the centre of the screen for 1200–1900 ms. The spot then underwent a step displacement of 5° and a smooth ramp motion towards the position of fixation for 600 ms at 20° per second or 1200 ms at 10° per second. Subjects were instructed to follow the target as accurately as possible. Each target was presented 10–15 times.

Anti-saccade trials began with the illumination of the central fixation point for 1000 ms. The central fixation point was then replaced by a minus sign for 1000 ms. After a 200-ms gap, targets appeared 10° to the right or left and remained illuminated for 1000 ms. Subjects were given instructions to 'look away from the target that appears on the side at the corresponding spot on the other side of the fixation point, and if you make a mistake try to correct yourself.' The minus sign before the appearance of the lateral target served as a reminder to look in the direction opposite to the target stimulus. Responses to at least 18 anti-saccade trials were recorded in each direction. There were no differences ($P > 0.05$, ANOVA) in the percentage of analysable anti-saccade trials between subject groups.

Data analysis

All data were analysed interactively offline. For saccades, a cursor was moved along each individual trial and the following marks were made: (i) the point in position and time where the saccade began; (ii) the point in position and time where the first eye movement ended; and (iii) the final eye position. Saccade latencies were computed as the duration of the interval from the appearance of an eccentric target to the onset of the first eye movement. Saccade first gains were computed as the difference in eye position between fixation and the end of the first movement. Sacccade end gains were computed as the difference in eye position between fixation and the final eye position for the trial. To minimize the contribution of lens shift artefacts from the Purkinje tracker (Deubel and Bridgeman, 1995), mean saccadic velocity was estimated as the initial change in eye position (first gain) divided by the duration of the initial saccade. Analysis of selected data showed the same effects, but higher values, in measurements of peak eye velocity obtained by differentiation

of the eye position record. Saccades with latencies below 80 ms and/or amplitude below 1° were rejected.

Data analysis for pursuit trials began with the removal of rapid deflections (due to saccades) from the eye velocity traces. A cursor was moved along each eye velocity trace and the start and end of each rapid deflection was marked. These deflections were then excised and the intervening velocity points were estimated using a linear interpolation algorithm. The responses to identical stimuli were aligned on the onset of target motion and the mean and standard deviation of eye velocity were calculated at each sample point.

The mean eye velocity responses were used to estimate latency, initial eye acceleration and two estimates of gain for each target direction. The latency to onset of pursuit was defined as the time at which the amplitude of eye velocity was >3 SD from the baseline velocity during fixation. The average eye acceleration for the first 100 ms of pursuit was determined by calculating the difference between eye velocity 100 ms after pursuit onset and eye velocity at the initiation of pursuit, divided by 100 ms. Peak gain was computed as the average of 10 points either side of the maximum eye velocity divided by the target speed. Finally, we calculated the mean gain as the average eye velocity for the period the target was moving divided by the target speed.

Anti-saccades were marked in a similar way to prosaccades. A cursor was moved along each trial and three points were marked: (i) the point in position and time where the saccade began; (ii) the position where the first eye movement ended; and (iii) the final eye position. Responses were considered to be successful anti-saccades if the first eye movement after target onset had an amplitude >3° and was in the opposite direction from the target. Anti-saccade corrections were recorded as anti-saccades that occurred within 500 ms of the initial erroneous prosaccade.

Neuropsychological battery

Subjects were administered a comprehensive neuropsychological battery that measures multiple domains of cognition (Table 1). Tests of general cognition and functional abilities included the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) and the CDR (Morris, 1993). Verbal memory was evaluated using the California Verbal Learning Test – Mental Status (CVLT-MS) (Delis *et al.*, 2000) (total of trials one through four and the 10-min delayed recall trial). Visual memory was assessed using the 30-min delayed recall trial of the Wechsler Memory Scale – Visual Reproductions (Wechsler, 1997). The longest correct backward digit span (Wechsler, 1997) was used as a measure of working memory. Language was assessed using a 15-item Boston Naming Test (Kaplan *et al.*, 1983), and measures of verbal fluency included phonemic fluency (number of D words in 1 min) and category

Table 1 Demographic and neuropsychological results

	Controls	FTD	SD	PA	AD	CBS	PSP
Demographics							
n	27	24	19	6	28	15	10
Age	65.0 ± 1.5	**57.4 ± 1.7**	60.3 ± 1.3	64.5 ± 3.0	59.8 ± 1.4	62.7 ± 2.0	65.5 ± 1.3
Duration (years)	–	4.2 ± 1.0	5.3 ± 0.7	4.8 ± 0.5	4.7 ± 0.5	3.4 ± 0.4	3.3 ± 0.6
Gender (m/f)	10/17	16/8	10/9	1/5	17/11	6/9	8/2
Education	17.2 ± 0.5	19.1 ± 3.5	15.9 ± 0.7	16.3 ± 1.2	15 ± 0.6	14.9 ± 0.7	16.8 ± 1.1
General							
MMSE	29.7 ± 0.4	**23.5 ± 7.5**	**21.7 ± 7.3**	25.2 ± 3.5	**19.5 ± 5.3**	**19.8 ± 7.7**	26.8 ± 2.6
CDR total	0.0 ± 0.1	**1.1 ± 0.4**	**0.8 ± 0.3**	0.5 ± 0.3	**0.8 ± 0.2**	**0.9 ± 0.6**	**1.2 ± 0.5**
CDR box score	0.5 ± 0.1	**6.6 ± 2.4**	**4.5 ± 2.1**	1.9 ± 1.4	**5.4 ± 1.5**	**4.9 ± 3.4**	**6.8 ± 2.1**
Memory							
CVLT trials 1–4 (max. 36)	29.9 ± 4.3	**18.8 ± 9.1**	**13.1 ± 9.4**	22.0 ± 7.9	**13.8 ± 5.2**	**14.9 ± 7.0**	22.7 ± 4.1
CVLT 10' recall (max. 9)	7.6 ± 1.8	**3.6 ± 3.1**	**1.8 ± 2.7**	5.8 ± 1.2	**1.1 ± 1.4**	**3.1 ± 3.1**	5.3 ± 1.2
WMS Vis recall (scaled)	14.5 ± 2.9	**7.7 ± 4.0**	**7.4 ± 3.6**	11.6 ± 4.9	**4.3 ± 1.5**	**6.6 ± 3.7**	**9.4 ± 1.1**
Mod. Rey recall (max. 17)	13.3 ± 0.5	**7.5 ± 1.2**	**8.0 ± 1.3**	12.0 ± 0.3	**2.9 ± 0.7**	**5.4 ± 1.4**	**7.9 ± 0.5**
Language							
BNT (max. 15)	14.6 ± 0.7	11.7 ± 4.4	**4.1 ± 4.8**	11.0 ± 1.5	**11.2 ± 3.6**	**10.7 ± 5.2**	11.3 ± 5.0
Animals/min.	24.1 ± 5.3	**12.6 ± 7.3**	**6.2 ± 5.7**	**8.0 ± 3.7**	**8.2 ± 4.7**	**10.2 ± 5.7**	**9.9 ± 3.0**
D-words/min.	15.2 ± 4.1	**8.4 ± 5.9**	**7.3 ± 8.6**	**5.3 ± 4.3**	**7.8 ± 6.7**	**7.9 ± 4.2**	**5.9 ± 1.8**
Visuospatial							
VOSP (max. 10)	9.3 ± 1.0	7.7 ± 2.2	9.7 ± 0.5	10.0 ± 0.0	**5.6 ± 2.8**	**5.4 ± 3.6**	7.1 ± 2.0
Beery copy (max. 16)	15.0 ± 1.0	12.8 ± 2.8	14.7 ± 1.5	12.2 ± 4.2	**7.0 ± 5.5**	**5.8 ± 5.2**	9.5 ± 3.2
Block Design	12.7 ± 2.8	**8.2 ± 4.1**	10.6 ± 3.4	9.5 ± 1.3	**4.0 ± 3.4**	**4.6 ± 3.5**	**5.9 ± 2.1**
Mod. Rey copy (max. 17)	16.3 ± 0.1	14.8 ± 0.7	16.0 ± 0.3	14.2 ± 2.3	**8.4 ± 1.2**	**8.1 ± 1.7**	11.8 ± 0.7
Executive							
Digits backward	5.4 ± 1.3	**3.6 ± 1.4**	4.6 ± 1.5	**2.8 ± 0.8**	**3.0 ± 1.3**	**2.6 ± 1.3**	**3.1 ± 0.8**
Stroop interference (scaled)	12.3 ± 1.4	**6.1 ± 4.6**	**6.5 ± 4.4**	**1.5 ± 0.7**	**1.8 ± 1.6**	**4.1 ± 3.7**	**2.7 ± 2.4**
Trails (lines/min)	33.9 ± 12.9	32.2 ± 63.7	24.9 ± 13.8	17.0 ± 16.0	**4.4 ± 6.9**	**4.3 ± 5.3**	4.8 ± 2.4

Bold values indicate $P < 0.05$ vs. control, ANOVA with Tukey *post hoc*. FTD = Frontotemporal dementia; SD = semantic dementia; PA = progressive nonfluent aphasia; AD = Alzheimer's disease; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; MMSE = Mini Mental State Exam; CDR = Clinical Dementia Rating; CVLT = California Verbal Learning Test; WMS = Wechsler Memory Scale; BNT = modified Boston Naming Test; VOSP = Visual Object Spatial Perception battery.

fluency (number of animals in 1 min). The Number Location condition from the Visual Object Spatial Perception battery (VOSP) (Warrington and James, 1991), the WAIS-III Block Design (Wechsler, 1997) and a modified Beery Test of Visual-Motor Integration (Beery, 1997), which requires subjects to copy eight figures, and copy of a simplified version of the Rey–Osterrieth figure, were used to assess visuospatial abilities. Executive function was assessed using Stroop (Interference condition, scaled score) from the Delis–Kaplan Executive Function System (D-KEFS) (Delis *et al.*, 2001) and a modified Trailmaking test (number of correct lines per minute) (Kramer *et al.*, 2003).

Lobar brain volumes

MRI scans were obtained on a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, NJ, USA) at the San Francisco VA Magnetic Resonance Unit, as described in a previous report (Rosen *et al.*, 2002). 3D T_1-weighted scans (MP-RAGE) were used for generating lobar volumes. Lobar volumes were generated using the BRAINS2 software package [Mental Health – Clinical Research Center at the University of Iowa (Magnotta *et al.*, 2002)]. Briefly, the T_1-weighted images were spatially normalized so that the inter-hemispheric fissure was aligned vertically in the axial and coronal views and the line connecting the anterior and posterior commissures was horizontal in the sagital view, and re-sampled to 1.0 mm^3 voxels. Next, the outermost boundaries of the cortex, as well as the anterior and posterior commissure, were identified to warp the Talairach grid (Tailarach and Tournoux, 1988) onto the current brain. The T_2- and PD-weighted images were then realigned to the spatially normalized T_1-weighted image using an automated image registration programme (Woods *et al.*, 1992). A brain mask was generated using a previously trained artificial neural network, and lobar volumes were then calculated using an automated Talairach-based method of regional classification (Magnotta *et al.*, 2002). Finally, the lobar volumes were normalized to correct for differences in overall head size: the absolute lobar volume was multiplied by the average total intracranial volume (TIV) of all subjects and then divided by the individual's TIV.

Statistics

In the first stage of our analysis, we compared demographic, neuropsychological and eye movement measures between diagnostic groups using chi-square tests for categorical measures and ANOVA with Tukey *post hoc* statistics for continuous measures. In the second stage of our analysis, we identified the single eye movement or neuropsychological measure that best distinguished between pairs of diagnostic groups using recursive partitioning (classification and regression trees) (Breiman *et al.*, 1984).

We focused on single variables since many of the diagnostic groups were small and the initial trees contained just a single split. The recursive partitioning analyses identified the single variables that minimized misclassification between groups. We identified the single 'best' oculomotor and neuropsychological variables and constructed receiver operating characteristic (ROC) curves (Hanley and McNeil, 1982) to assess their ability to differentiate groups of interest. We measured the area under each ROC curve and compared them using chi square statistics (DeLong *et al.*, 1988). These comparisons assessed whether the 'best' oculomotor and neuropsychological variables differed in their ability to differentiate the groups.

For all tests, significance was accepted at the $P<0.05$ level. We carried out the statistical analyses using routines in SPSS (version 14.0, Chicago, IL, USA), Stata (version 10, College Station, TX, USA) and R (R Development Core Team. 1999. R: A language and environment).

Results

Demographics

The FTD patient group was significantly younger than the control group ($P=0.01$), but there was no significant difference in age between the patient groups (Table 1). There was also no significant difference in disease duration, gender or education between patient groups. All patients, except the PA group, were significantly different from controls on the CDR total score and sum of boxes score ($P<0.001$). Mean MMSE scores were lower in FTD, SD, Alzheimer's disease and CBS groups than controls ($P<0.001$), however, there were no significant differences in MMSE score between controls, PA and PSP patients.

Memory

Short-term memory impairments were observed in all patient groups relative to controls. The FTD, SD, Alzheimer's disease and CBS groups had lower scores on both the California Verbal Learning Test (CVLT) learning and delayed recall trials than controls ($P<0.001$ for both). Alzheimer's disease individuals also recalled fewer words after the 10-min delay than FTD, PA and PSP subjects ($P<0.02$). All patient groups except PA scored lower relative to controls on recall of the Wechsler Memory Scale visual reproductions ($P<0.011$). Alzheimer's disease individuals were more impaired on this measure than all other patients ($P<0.045$) except CBS ($P=0.311$).

Language

All patient groups were significantly impaired on language measures relative to controls. SD, Alzheimer's disease and CBS individuals scored lower ($P<0.05$) relative to controls on a 15-item version of the Boston Naming Test (BNT). SD patients named fewer pictures than all other subject groups on the BNT ($P<0.004$). Verbal fluency measures (D-words or animals per minute) were impaired in all patient groups relative to controls ($P<0.001$ for animals, $P<0.04$ for D-words).

Visuospatial function

Visuospatial function was most impaired in Alzheimer's disease and CBS. Both groups had lower scores relative to controls on the number location task from the Visual Object Spatial Perception (VOSP) test ($P<0.001$), modified Rey–Osterrieth figure copy ($P<0.01$) and copy of the Beery Visual Motor Integration figures ($P<0.04$). Other patient

groups' performance was not significantly different from controls on these measures. On the WAIS-III block design task, the FTD, Alzheimer's disease, CBS and PSP groups had lower performance relative to controls ($P<0.011$).

Executive function

Backward digit span was reduced in all patient groups except SD relative to controls ($P<0.003$). Performance on the Stroop interference task was impaired in all patient groups relative to controls ($P<0.003$), however only the Alzheimer's disease and CBS subjects generated fewer lines than controls on the D-KEFS Trails ($P<0.021$).

Visually guided saccades

Examples of three successive upward, 10° saccades from a representative subject from each patient group are shown in Fig. 1. As a group, SD and PA patients showed no deficits in visually guided (pro-) saccades to single targets as compared to controls (Fig. 2). As compared to controls, FTD patients displayed mildly hypometric saccades, that is the gains of the first saccade towards targets that appeared 5° up or down or 10° left or right of the central fixation point were smaller ($P=0.013$ for vertical 5° overlap, $P=0.038$ for horizontal 10° gap; Supplementary Tables S1 and S2).

Alzheimer's disease patients showed increased latency of all saccades compared to controls ($P=0.001$ for horizontal 10° overlap, $P<0.001$ for vertical 10° overlap, $P=0.002$ for horizontal 5° overlap, $P<0.001$ for vertical 5° overlap, $P=0.047$ for horizontal 10° gap). Vertical saccade latency was also increased as compared to FTD and SD patients ($P<0.04$). Vertical, but not horizontal saccades were hypometric relative to controls ($P=0.028$).

Like Alzheimer's disease patients, CBS individuals displayed increased saccade latencies in the vertical ($P<0.001$) direction and a trend towards increased latency in the horizontal ($P=0.067$) direction as compared to controls. There was a decrease in the first gain of vertical saccades to 5° and 10° targets compared to controls and all patient groups ($P<0.015$) except PSP patients who had lower vertical saccade gains than CBS.

Of all the patient groups, PSP subjects' saccades were the most different from controls and showed abnormalities in almost all aspects of visually guided saccade function. In these individuals, latency for vertical 10° and 5° saccades was increased compared to controls ($P<0.001$), FTD and SD patients ($P<0.003$).

PSP patients displayed dramatically decreased saccade velocity as compared to controls ($P<0.001$) and all other patient groups ($P<0.007$) for 10° saccades. In the 5° horizontal condition, differences in velocity only reached significance as compared to SD, Alzheimer's disease and CBS patient groups (Supplementary Table S2). First gains were reduced for all saccades in PSP patients compared to controls and other patient groups ($P<0.001$ for all). The end gain was also decreased compared to controls for horizontal and vertical 10° overlap and vertical 5° overlap saccades ($P=0.001$ for horizontal 10° overlap, $P<0.001$ for vertical 10° overlap, $P<0.001$ for vertical 5° overlap). End gain for horizontal and vertical 10° overlap and vertical 5° overlap saccades was also decreased compared to all other patient groups (except horizontal 10° overlap saccades compared to PA patients).

Smooth pursuit

Smooth pursuit of step-ramp targets (Rashbass, 1961; Rottach *et al.*, 1996) travelling at 10 or 20° per second was impaired in the Alzheimer's disease, FTD and PSP patient groups. Mean vertical pursuit traces for a target moving upward at 20° per second from representative

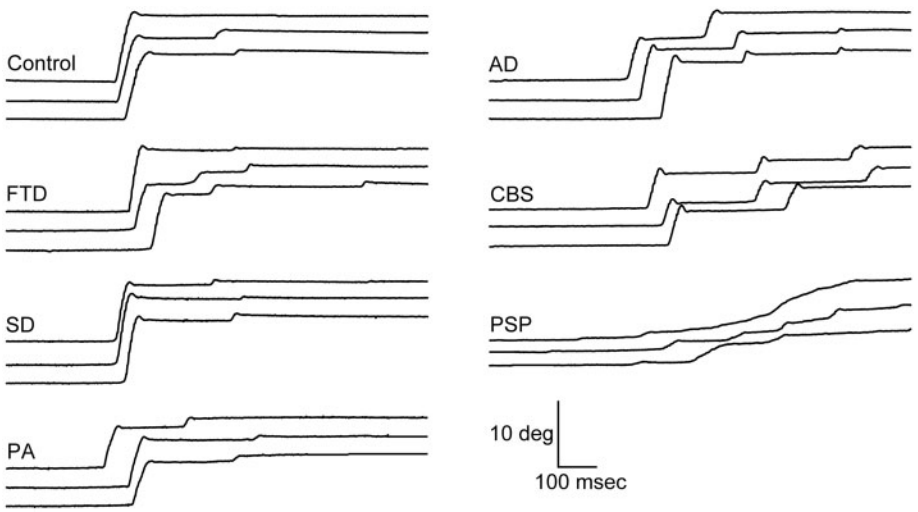

Fig. 1 Upward saccade examples. Eye position versus time traces showing three representative, successive 10° upward saccades in a control subject and a patient from each of the diagnostic groups.

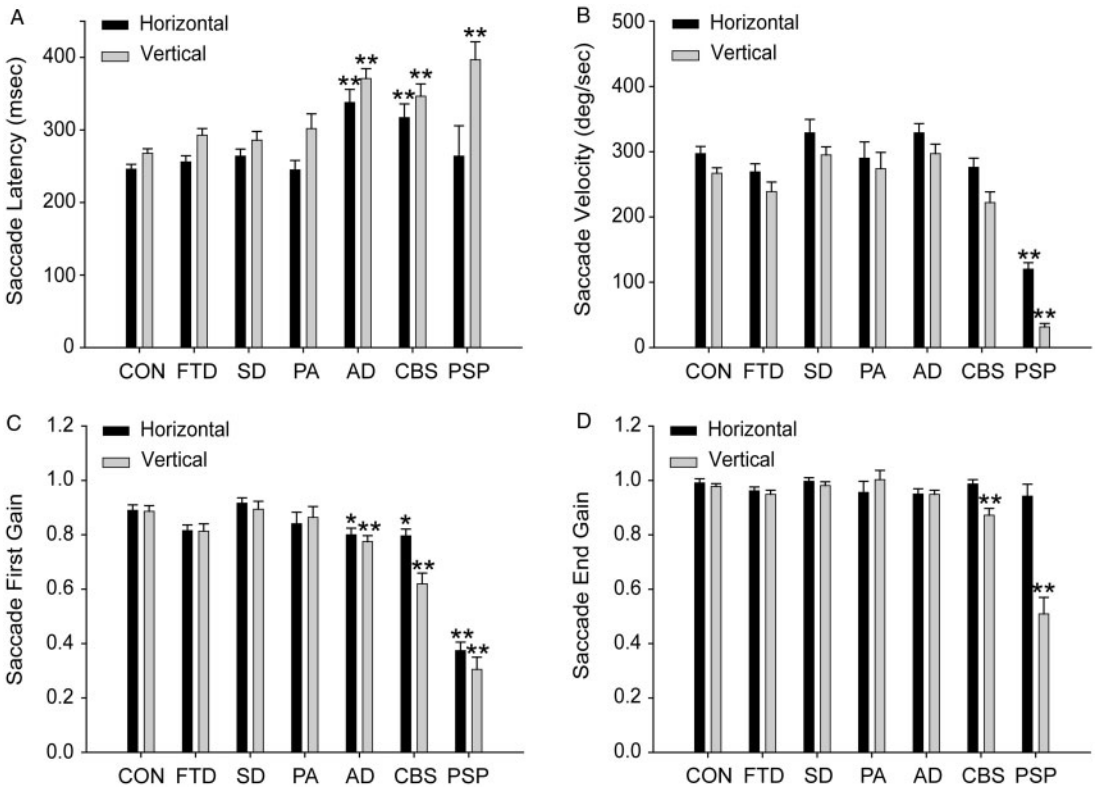

Fig. 2 Bar graphs summarizing the saccade behaviour under overlap conditions of controls (CON) and all the patient groups. Targets moved 10°. In all graphs, black and grey bars show responses to horizontal and vertical targets respectively. Error bars show standard errors across subjects within each group. Asterisks indicate effects that were statistically significant relative to controls ($P < 0.05$, ANOVA, Tukey *post hoc*). Double asterisks indicate $P < 0.005$ relative to controls. (**A**) Saccade latencies, (**B**) Saccade slope velocity, (**C**) First gain of saccades, (**D**) End gain of saccades.

individuals from each group are shown in Fig. 3. In CBS, there was a non-significant trend towards lower initial acceleration of smooth pursuit in the vertical direction ($P = 0.057$). There were no significant smooth pursuit abnormalities in the SD and PA patients for horizontal and vertical smooth pursuit targets moving at 20° per second and 10° per second (Fig. 4, Supplementary Tables S3 and S4).

FTD patients displayed multiple abnormalities in horizontal 20° per second pursuit compared to controls. Compared to controls the FTD group had reduced mean and peak gains and initial acceleration ($P = 0.008$ for mean gain, P 0.004 for peak gain, P 0.044 for initial acceleration). Mean and peak gains were also reduced in the FTD group compared to the SD group for horizontal pursuit targets at 20° per second.

Alzheimer's disease patients had impaired pursuit compared to controls and SD patients. Latency was increased for targets moving vertically at 10° per second ($P = 0.013$) and mean and peak gains were reduced in Alzheimer's disease subjects compared to controls for horizontal and vertical targets moving at 20° per second (peak gain $P < 0.01$ for horizontal; $P < 0.02$ for vertical). Mean and peak gains were also reduced in Alzheimer's disease patients compared to SD patients for horizontal and

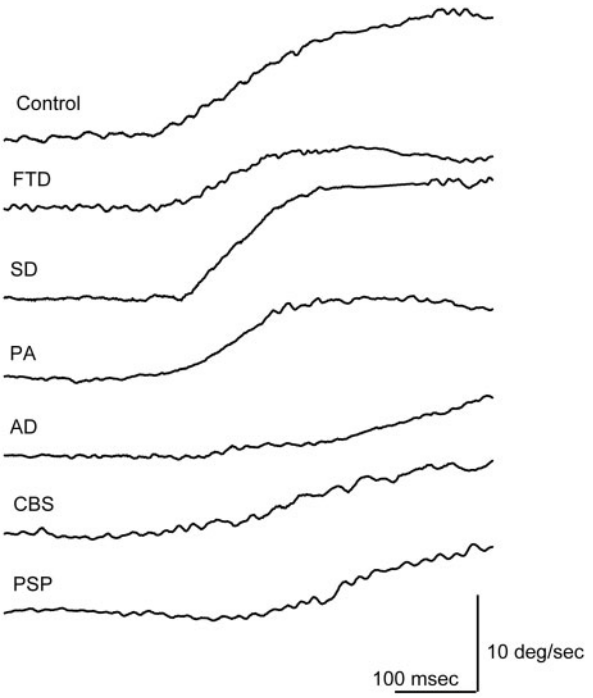

Fig. 3 Average vertical eye velocity traces for a control subject and a patient from each of the diagnostic groups. Target motion was 20°/s upward. Traces are an average of at least eight trials.

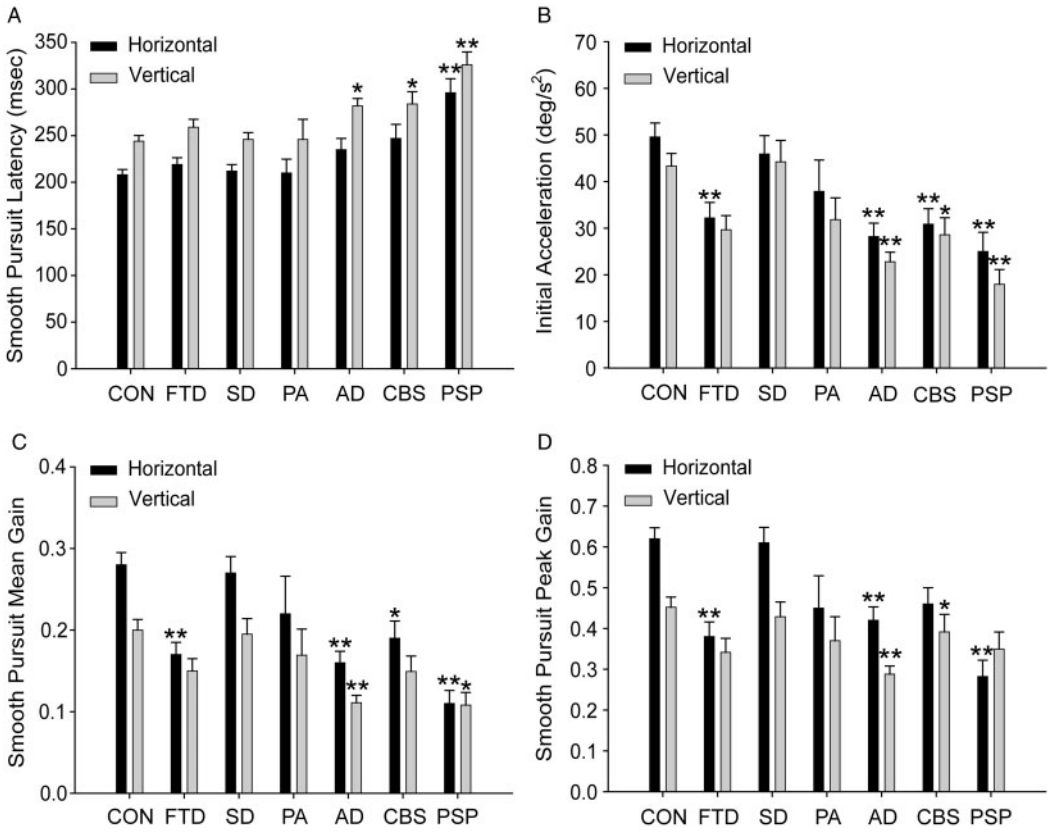

Fig. 4 Bar graphs summarizing the pursuit behavior of controls (CON) and all the patient groups. Target velocity was 20°/s. In all graphs, black and grey bars show responses to horizontal and vertical targets respectively. Error bars show SEs across subjects within each group. Asterisks indicate effects that were statistically significant relative to controls ($P < 0.05$ ANOVA, Tukey *post hoc*). Double asterisks indicate $P < 0.005$ relative to controls. (**A**) Smooth pursuit latencies, (**B**) Initial eye acceleration of smooth pursuit, (**C**) Mean gain of smooth pursuit, (**D**) Peak gain of smooth pursuit.

vertical targets at 20° per second (except peak gain to a 20° per second vertically moving target). Initial acceleration was reduced in Alzheimer's disease patients in all directions and at both target speeds ($P < 0.003$ for horizontal; $P < 0.005$ for vertical 10 and 20° per second pursuit). Initial acceleration in Alzheimer's disease patients was lower than SD patients for 20° per second horizontal and vertical pursuit and 10° per second vertical pursuit ($P < 0.05$).

As with saccades, smooth pursuit deficits were most severe in PSP patients. Compared to controls, PSP patients had longer latencies to horizontal and vertical 20° per second targets and horizontal 10° per second targets ($P = 0.001$ for horizontal and vertical 20° per second pursuit, $P = 0.003$ for horizontal 10° per second pursuit). Between patient groups, PSP patients had longer latencies to initiation of pursuit to horizontal 20° per second targets than FTD and SD patients and longer latencies to vertical 20° per second targets than FTD, SD and PA patients. Compared to controls and SD patients, the mean and peak gains of pursuit to horizontal targets moving at 20° per second and 10° per second were reduced in PSP patients (mean gain $P = 0.002$, peak gain $P = 0.003$ for 20° per second horizontal pursuit; mean gain $P = 0.001$, peak gain $P < 0.001$ for 10° per second horizontal pursuit). Initial acceleration in PSP patients was reduced horizontally and vertically to both target speeds in PSP patients compared to controls ($P = 0.040$ for 20° per second horizontal targets, $P = 0.010$ for 20° per second vertical targets, $P = 0.001$ for 10° per second horizontal targets, $P = 0.034$ for 10° per second vertical targets). The initial acceleration of PSP patients was also reduced compared to SD patients.

Anti-saccades

The anti-saccade task requires a subject to suppress a visually guided saccade to an eccentrically appearing target, and instead generate a saccade in the opposite direction. FTD, PA, Alzheimer's disease, CBS and PSP patients all made fewer correct anti-saccades compared to controls ($P < 0.001$ for FTD, Alzheimer's disease, CBS and PSP patients, $P = 0.020$ for PA patients) (Fig. 5). Anti-saccade responses in SD patients were not significantly different from controls. FTD, Alzheimer's disease, CBS and PSP patients also made significantly fewer correct responses than SD patients ($P < 0.001$ for Alzheimer's disease, CBD and PSP patients; $P = 0.018$ for FTD patients). PSP patients generated the fewest correct anti-saccade responses, and in

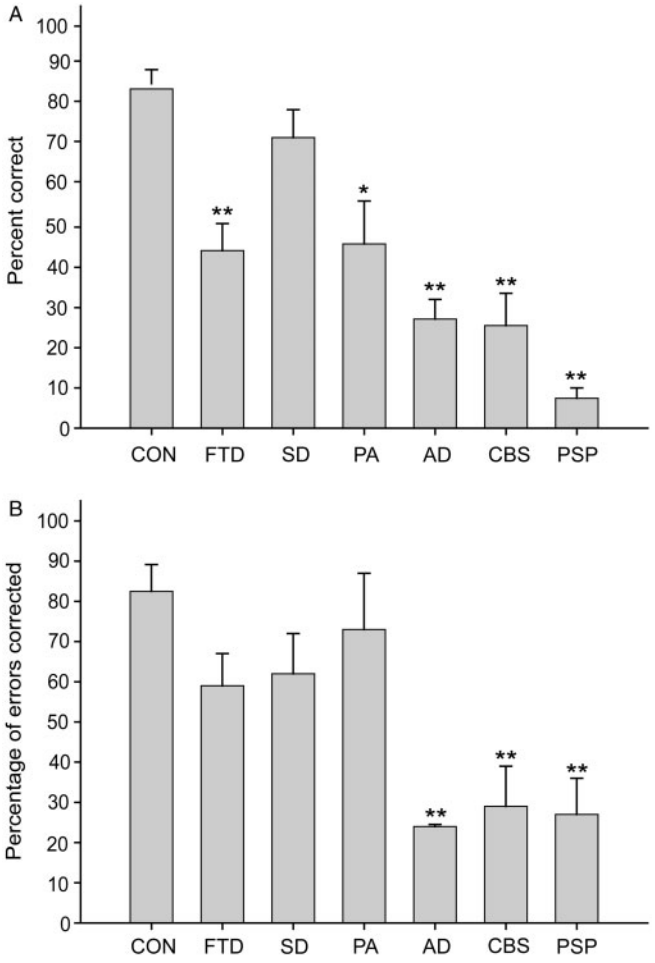

Fig. 5 Bar graphs summarizing the antisaccade behavior of controls (CON) and all the patient groups. In all graphs the bars show the responses to horizontal targets and the error bars show standard errors across subjects within each group. Asterisks indicate effects that were statistically significant relative to controls ($P < 0.05$, ANOVA, Tukey *post hoc*). Double asterisks indicate $P < 0.005$ relative to controls. (**A**) Percentage of correct antisaccades, (**B**) Percentage of errors that were corrected which was calculated by: number of trials that were corrected/number of error trials × 100.

addition to being different to controls and SD patients, this group also made fewer correct responses compared to FTD patients ($P = 0.022$). There were no differences in anti-saccade latencies between any of the groups (Supplementary Table S5).

All the patient groups were able to spontaneously correct a proportion of anti-saccade errors indicating that the subjects understood the task. However, Alzheimer's disease, CBS and PSP patients corrected a lower proportion of errors as compared to controls ($P < 0.001$ for Alzheimer's disease and CBS patient groups, $P = 0.004$ for PSP patients). Alzheimer's disease patients corrected the lowest proportion of errors and the proportion of errors corrected in these patients was smaller than in FTD, SD and PA patients ($P < 0.05$). The addition of self-corrected errors to the percentage of correct anti-saccade responses in each group did not alter the differences in anti-saccade performance between groups.

Comparison of neuropsychological and oculomotor variables for group differentiation

Table 2 summarizes the differences in oculomotor performance between each of the patient groups and the normal control subjects as identified using ANOVA. To identify which of these oculomotor abnormalities were most valuable for differentiating the patient groups, we constructed nine binary diagnostic comparisons involving the CBS, PSP, FTD, Alzheimer's disease and SD groups based on common diagnostic dilemmas encountered in the clinic (Table 3). The best single oculomotor and neuropsychological variables for each comparison were identified using recursive partitioning (classification and regression trees), a non-parametric, multivariate method. Separate trees were constructed for oculomotor and neuropsychological variables. The best variables were then plotted on the same ROC curve and the area under the curve (AUC) values were directly compared to assess whether one measure was superior to the other for differentiating the groups.

Figure 6 shows examples of ROC curves for the differentiation of PSP subjects from all other patients, and the SD patients from the Alzheimer's disease patients. For the PSP versus all other patients differential (Fig. 6A), the comparison of AUCs revealed that the best oculomotor measure (upward 10° saccade velocity) was superior to the best neuropsychological measurement (Trails time) in differentiating the two groups ($P < 0.0001$, Chi Square; Table 3). In contrast, examination of AUC values for the SD versus Alzheimer's disease comparison (Fig. 6B) revealed that the best oculomotor variable (the percentage of correct anti-saccade responses with self corrected errors) was similar to the best neuropsychological variable (the VOSP score) in terms of ability to distinguish these two diagnostic groups ($P = 0.518$; Table 3). For all other diagnostic comparisons, oculomotor performance was similar to neuropsychological tests in differentiating subject groups.

Comparison of CBS and Alzheimer's disease groups

Both the Alzheimer's disease and CBS groups had markedly elevated saccade latencies and obtained lower scores relative to controls on all neuropsychological measurements of visuospatial function, including the Beery Figure Copy, modified Rey–Osterrieth figure copy and VOSP number localization task (Table 1). Since both Alzheimer's disease (Thompson *et al.*, 2003; Boxer *et al.*, 2003*b*; Du *et al.*, 2007) and CBS (Groschel *et al.*, 2004; Boxer *et al.*, 2006*b*) are associated with damage to extra-striate visual cortical

Table 2 Summary of oculomotor abnormalities by patient group

	Horizontal saccades	Vertical saccades	Horizontal pursuit	Vertical pursuit	Antisaccade correct responses	Antisaccade spontaneous error correction
FTD	↓ First gain	NS	↓↓ Gain ↓↓ Acceleration	↓ Acceleration	↓↓	NS
SD	NS	NS	NS	NS	NS	NS
PA	NS	NS	NS	NS	↓↓	NS
AD	↑↑ Latency ↓ First gain	↑↑ Latency	↓↓ Gain ↓↓ Acceleration	↑ Latency ↓↓ Gain ↓↓ Acceleration	↓↓	↓↓
CBS	↑ Latency ↓ First gain	↑↑ Latency ↓↓ End gain	↓↓ Gain ↓↓ Acceleration	↑ Latency ↓↓ Acceleration	↓↓	↓↓
PSP	↓ First gain ↓↓ Velocity	↑↑ Latency ↓↓ Gain ↓↓ Velocity	↑↑ Latency ↓↓ Gain ↓↓ Acceleration	↑↑ Latency ↓ Gain ↓↓ Acceleration	↓↓	↓↓

NS = not significantly different from controls; ↓ = mildly decreased compared to controls; ↓↓ = moderate-severely decreased; ↑ = mildly increased; ↑↑ = moderate-severely increased.

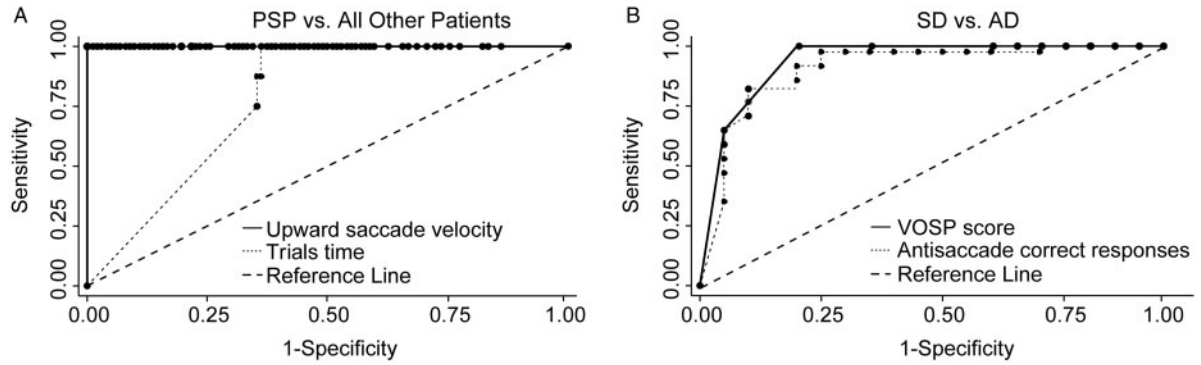

Fig. 6 Receiver operating characteristic (ROC) curves comparing best oculomotor and neuropsychological variables. (**A**) Comparison of the best oculomotor variable from the recursive partitioning analysis (upward saccade velocity) versus the best neuropsychological variable (time to complete the modified trails task) for differentiating PSP from all other patients. (**B**) Comparison of the best oculomotor variable (percentage correct antisaccade responses) versus best neuropsychological variable (number localization task from VOSP battery) for differentiating SD from AD group.

Table 3 Comparison of oculomotor and neuropsychological variable for group differentiation

Comparison	Oculomotor		Neuropsychology		Comparison	
	Model	AUC	Model	AUC	χ^2	*P*
PSP vs. Not PSP	Upward saccade velocity (10 deg)	1.0	Trails time	0.78	30.1	<0.0001
PSP vs. CBS	Horizontal saccade gain (10 deg)	1.0	Trails correct	0.83	3.9	0.048
PSP vs. FTD	Horizontal saccade gain (10 deg)	0.99	Modified Rey copy	0.85	3.65	0.056
SD vs. AD	Antisaccade correct + corrections	0.89	VOSP	0.94	0.42	0.518
SD vs. Not SD	Antisaccade correct + corrections	0.80	BNT	0.83	0.39	0.532
CBS vs. AD	Down saccade velocity (10 deg)	0.76	CVLT recall	0.64	1.24	0.266
FTD vs. SD	Antisaccade correct responses	0.74	BNT	0.84	0.66	0.265
CBS vs. Not CBS	Antisaccade correct + corrections	0.73	Beery	0.76	0.13	0.717
FTD vs. Not FTD	Vertical saccade latency (10 deg)	0.64	Trails correct	0.72	0.67	0.415

AUC = Area under curve from receiver operating characteristic (ROC) curve analysis; 'Not' refers to all other patients (no controls), see legend to Table 1 for additional abbreviations.

structures and visuospatial function is correlated with brain volume in the extra-striate cortical regions in Alzheimer's disease (Boxer *et al.*, 2003*a*), we hypothesized that saccade latency may also be correlated with atrophy of visual cortical regions, regardless of clinical syndrome. To test this hypothesis, lobar (frontal, temporal, parietal and occipital) brain volumes, corrected for total intra-cranial volume to control for differences in head size, were correlated with

Table 4 Mean regional brain volumes

	L Frontal	R Frontal	L Temporal	R Temporal	L Parietal	R Parietal	L Occipital	R Occipital
Control	180.2 ± 17.7	189.5 ± 17.4	106.0 ± 6.0	106.9 ± 4.7	110.4 ± 10.3	113.7 ± 9.8	52.9 ± 6.1	51.8 ± 4.2
FTD	158.3 ± 21.6	164.2 ± 23.4	102.2 ± 9.4	99.1 ± 12.6	106.4 ± 7.9	106.4 ± 8.6	55.8 ± 5.2	49.7 ± 4.7
SD	164.4 ± 18.9	186.4 ± 14.7	82.7 ± 11.5	96.6 ± 8.9	104.9 ± 7.4	113.9 ± 8.1	51.4 ± 5.0	50.4 ± 5.4
PA	153.0 ± 11.6	173.0 ± 10.7	100.5 ± 11.3	105.1 ± 6.9	99.8 ± 10.4	107.9 ± 10.6	51.5 ± 5.2	50.7 ± 5.9
AD	167.0 ± 17.2	178.3 ± 13.4	98.7 ± 8.6	100.4 ± 6.8	97.2 ± 10.3	100.1 ± 9.2	48.2 ± 5.1	46.0 ± 4.8
CBS	158.2 ± 12.6	169.7 ± 16.0	95.3 ± 7.6	96.5 ± 5.9	99.2 ± 5.9	99.0 ± 9.4	51.0 ± 3.9	46.2 ± 4.5
PSP	177.2 ± 13.8	185.3 ± 13.8	104.4 ± 6.5	102.4 ± 7.0	108.8 ± 9.0	109.2 ± 8.5	53.9 ± 5.2	49.6 ± 6.4
$P < 0.05$					AD < Con	AD < Con		
Tukey *post hoc*	FTD < Con PA < Con CBS < Con	FTD < Con FTD < SD FTD < PSP	SD < All CBS < Con	SD < Con CBS < Con	CBS < Con AD < SD AD < PSP	CBS < Con AD < SD CBS < SD	AD < SD	CBS < Con AD < Con

Mean ± SD lobar brain volumes (normalized to total intracranial volume) for each subject group. Group ANOVA values were significant ($P < 0.02$) for all brain regions. Group differences identified using a Tukey *post hoc* analysis are shown in the bottom panel.

Table 5 Saccade latency—brain volume correlations

	L Frontal	R Frontal	L Temporal	R Temporal	L Parietal	R Parietal	L Occipital	R Occipital
Horizontal latency	0.024	−0.108	−0.091	−0.307**	−0.229*	−0.279*	−0.430**	−0.282*
Horizontal latency (gap)	−0.010	−0.101	−0.192	−0.321**	−0.256*	−0.256*	−0.419**	−0.221*
Vertical latency	0.041	−0.082	−0.019	−0.146	−0.182	−0.267*	−0.355**	−0.277*
Antisaccade latency	0.041	0.054	−0.144	−0.131	−0.097	−0.082	−0.135	−0.042

Pearson correlation coefficients are shown for the relationship of mean 10 degree saccade latencies to lobar brain volumes (normalized to total intracranial volume). *$P < 0.05$, **$P < 0.005$ ($n = 90$).

mean 10° horizontal (overlap or 200 ms gap conditions), vertical and anti-saccade latencies. As expected, the Alzheimer's disease and CBS groups had smaller parietal and occipital lobe volumes than the control and SD groups (Table 4), and correlations were identified for the three visually guided saccade variables, but not for anti-saccade latency (Table 5). As predicted, the strongest correlations between saccade latency and brain volume were observed in the visual cortical regions, including the bilateral parietal and occipital lobes and right temporal lobe. No correlations were identified between frontal cortex volume and saccade latency.

Discussion

We directly compared horizontal and vertical oculomotor performance in three FTLD clinical syndromes, Alzheimer's disease, CBS and PSP and evaluated the ability of oculomotor findings to differentiate patient groups. Significant oculomotor abnormalities were identified in all patient groups except for SD, which had oculomotor performance that was indistinguishable from age-matched controls. In all subjects, both visually guided saccade and smooth pursuit abnormalities were more prominent in the vertical than horizontal plane. Only PSP patients displayed abnormalities in saccade velocity, whereas abnormalities in saccade gain were observed in PSP > CBS > Alzheimer's disease subjects. All patient groups except SD were impaired on the anti-saccade task, however only the FTLD (FTD, SD and PA) subjects and not Alzheimer's disease, CBS and PSP, were able to spontaneously self-correct erroneous prosaccades as well as controls. ROC statistics revealed that oculomotor assessments were superior to neuropsychological tests for differentiating PSP from other diagnoses, and comparable to neuropsychological tests in differentiating the other patient groups. These data suggest that oculomotor assessments, particularly of vertical saccades and anti-saccades, may be useful for the differential diagnosis of clinical dementia syndromes.

Diagnostic value of clinical oculomotor abnormalities

Multiple oculomotor abnormalities were identified in all of the patient groups except PA and SD. However, measurements of vertical and horizontal saccade velocity and gain as well as the percentage of correct anti-saccade responses were most useful for differentiating the patient groups (Fig. 6 and Table 3).The most dramatic oculomotor impairments were observed in PSP, involving almost all aspects of saccade and smooth pursuit function. In this respect, our findings are similar to previously published descriptions of PSP-associated oculomotor abnormalities. (Vidailhet *et al.*, 1994; Rottach *et al.*, 1996; Rivaud-Pechoux *et al.*, 2000) Unlike these reports, we found increased latency of saccade initiation in the vertical plane in our PSP

subjects. This increased latency might be explained by differences in the definition of saccade onset used here as opposed to other studies. Consistent with the central role of oculomotor abnormalities in the diagnosis of PSP, the vertical saccade gain and velocity (data not shown) measurements were superior to neuropsychological tests for differentiating these patients from CBS, FTD and the other patient groups.

Importantly, the lack of measurable oculomotor impairments in the SD group was useful for differentiating these patients from other patient groups, particularly the Alzheimer's disease subjects who had similar neuropsychological deficits to the SD subjects in most cognitive domains (aside from visuospatial function). Normal performance on the anti-saccade task was able to differentiate SD patients from Alzheimer's disease, FTD and the other patient groups, particularly when the percentage of self-corrected errors was included in the anti-saccade score (Fig. 6).

Although oculomotor and neuropsychological values were similar in CBS and Alzheimer's disease, downward saccade velocities were able to differentiate the CBS from the Alzheimer's disease subjects (Table 3). Both Alzheimer's disease and CBS patients had increased latency of saccades, prominent impairments in smooth pursuit and impaired performance on the anti-saccade task relative to controls. These results are consistent with previous descriptions of oculomotor abnormalities in Alzheimer's disease (Hutton *et al.*, 1984; Fletcher and Sharpe, 1986; Currie *et al.*, 1991; Moser *et al.*, 1995; Abel *et al.*, 2002; Shafiq-Antonacci *et al.*, 2003; Crawford *et al.*, 2005; Boxer *et al.*, 2006*a*) and CBS (Vidailhet *et al.*, 1994; Rottach *et al.*, 1996; Rivaud-Pechoux *et al.*, 2000, 2007). The fact that the increased saccade latency in our series was less prominent than that previously reported (Rivaud-Pechoux *et al.*, 2000) for CBS may have reflected differences in the visually guided saccade paradigm that we used. We measured saccades to 5 and 10° targets, whereas others studied larger amplitude saccades (25°).

Oculomotor impairments were also able to differentiate FTD from other patient groups, but there was a non-significant trend towards better diagnostic differentiation of FTD patients using neuropsychological measures than oculomotor variables. FTD patients displayed slightly hypometric horizontal saccades but were otherwise similar to controls in their ability to perform visually guided saccades. As compared to controls, FTD patients had decreased gain and initial acceleration of horizontal pursuit as well as decreased vertical pursuit acceleration. FTD patients were impaired in their ability to withhold a visually guided saccade on the anti-saccade task, but were not significantly impaired relative to controls in the frequency with which they self-corrected erroneous prosaccades on the anti-saccade task. These results are consistent with previous studies of anti-saccade abnormalities in FTD as compared to PSP (Meyniel *et al.*, 2005), as well as saccade and smooth pursuit abnormalities in FTD as compared to other FTLD subtypes and Alzheimer's disease (Boxer *et al.*, 2006*a*).

Clinical and anatomical correlates of oculomotor impairments

Our findings suggest that oculomotor impairments reflect the anatomical patterns of brain damage associated with neurodegenerative syndromes. The patient groups that were found to have brain atrophy involving the frontal and parietal lobes (FTD, PA, Alzheimer's disease and CBS in Table 2) which contain the frontal and parietal eye fields (Pierrot-Deseilligny *et al.*, 2004) displayed deficits in the initiation and suppression of saccades and smooth pursuit, but normal saccade velocities. PSP subjects, who have prominent atrophy of the brainstem oculomotor regions, (Groschel *et al.*, 2004; Boxer *et al.*, 2006*b*) displayed additional deficits in saccade velocity and end gain. In contrast, SD patients had no measurable differences in oculomotor function from controls, despite having cognitive impairments that were comparable to the other patient groups (Table 1) and prominent atrophy that spared the frontal and parietal lobes (Table 4). Oculomotor impairments, including increased saccade latency and a reduced ability to self-correct anti-saccade errors were most similar in Alzheimer's disease and CBS, the two clinical syndromes that were also found to have volume loss in the parietal and occipital lobes (Table 4). Consistent with these findings, visually guided saccade latencies, which were prominently increased in these groups, correlated with parietal and occipital lobe volumes (Table 5). The correlation between saccade latency and volume of visual cortical regions is similar to focal lesion studies from stroke patients which have demonstrated increased saccade latency with lesions involving the right parietal lobe (Pierrot-Deseilligny *et al.*, 1991). Although we did not identify a correlation between anti-saccade latency and lobar brain volume a previous study demonstrated correlations between regional frontal lobe grey matter volume and anti-saccade performance in FTLD and Alzheimer's disease (Boxer *et al.*, 2006*a*) suggesting that other structural neuroimaging methods might be more sensitive to oculomotor function–brain volume correlations than those used here.

A limitation of this study was that the majority of our subjects did not have autopsy-confirmed diagnoses. Nonetheless, our results have implications for the ability of oculomotor findings to predict the molecular pathology associated with these clinical dementia syndromes. Previous studies have indicated that downward gaze palsy is strongly predictive of a diagnosis of PSP (with tau protein deposition) at autopsy (Litvan *et al.*, 1996*b*). Most clinically diagnosed PA patients are found to have PSP or CBD pathology at autopsy (Hodges *et al.*, 2004; Josephs *et al.*, 2006*a*) (and the one patient in our series that went to autopsy had CBD), however the PA group's eye movements

did not display the increased saccade latency classically associated with CBS or the saccade velocity and gain changes seen in PSP (Rivaud-Pechoux *et al.*, 2000). Most SD cases are associated with FTLD-U pathology at autopsy (Davies *et al.*, 2005), and there are approximately equal percentages of both FTLD-U and tau pathology found in clinically diagnosed FTD cases (Forman *et al.*, 2006; Josephs *et al.*, 2006*b*). Unlike the SD group, however, we identified prominent oculomotor abnormalities in our FTD group, including in two subjects who were found to have FTLD-U pathology at autopsy.

Taken together, these data suggest that clinical FTLD syndromes associated with FTLD-U pathology may have no oculomotor abnormalities (as in SD), abnormalities in smooth pursuit and anti-saccades (as in FTD) or even findings similar to PSP (Paviour *et al.*, 2004). Similarly, tau pathology may be associated with clinical oculomotor features of decreased saccade velocity and gain (as in PSP), increased saccade latency (as in CBS) or more subtle deficits in anti-saccade control and smooth pursuit (as in PA). While further studies are clearly needed to confirm these hypotheses, at a minimum our data suggest that caution should be exercised when attempting to predict the FTLD-related molecular pathology from isolated clinical oculomotor findings, except in PSP.

Conclusion

Oculomotor assessment is a component of most standard neurological examinations. While many of the eye movement variables described in this study require the use of an eye tracker for accurate measurement, the findings that were found to be most useful for differentiating groups (saccade gain and velocity and anti-saccade performance) can be appreciated at the bedside. Although further studies will be necessary to determine the utility of bedside oculomotor testing relative to laboratory measurements, the results suggest examination of eye movements can provide important diagnostic information when attempting to differentiate CBS, PSP, FTLD and Alzheimer's disease.

Supplementary material

Supplementary material is available at *Brain* online.

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