Saccade Abnormalities in Autopsy-Confirmed Frontotemporal Lobar Degeneration and Alzheimer Disease

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Background: Deficits in the generation and control of saccades have been described in clinically defined frontotemporal dementia (FTD) and Alzheimer disease (AD).

Objective: To determine the saccade abnormalities associated with autopsy-defined cases of frontotemporal lobar degeneration (FTLD) and of AD, because clinical FTD syndromes can correspond to a number of different underlying neuropathologic FTD and non-FTD diagnoses.

Design: An infrared eye tracker was used to record visually guided saccades to 10° targets and antisaccades in subjects with autopsy-confirmed FTD and subjects with autopsy-confirmed AD, a mean (SE) of 35.6 (10.0) months prior to death, and age-matched normal controls. Twelve subjects with FTD had an FTLD–TAR DNA-binding protein 43 pathology, 15 had an FTLD-tau pathology, and 1 subject showed an FTLD–fused in sarcoma protein pathology. Receiver operating curve statistics were used to determine the diagnostic value of the oculomotor variables. Neuroanatomical correlates of oculomotor abnormalities were investigated using voxel-based morphometry.

Setting: Memory and Aging Center, Department of Neurology, University of California, San Francisco.

Participants: A total of 28 subjects with autopsy-confirmed FTD, 10 subjects with autopsy-confirmed AD, and 27 age-matched normal controls.

Results: All subjects with FTD or AD were impaired relative to normal controls on the antisaccade task. However, only FTLD-tau and AD cases displayed reflexive visually guided saccade abnormalities. The AD cases displayed prominent increases in horizontal saccade latency that differentiated them from the FTD cases. Impairments in velocity and gain were most severe in individuals with progressive supranuclear palsy but were also present in other tauopathies. By using vertical and horizontal saccade velocity and gain as our measures, we were able to differentiate patients with progressive supranuclear palsy from other patients. Vertical saccade velocity was strongly correlated with dorsal midbrain volume.

Conclusion: Decreased visually guided saccade velocity and gain are suggestive of underlying tau pathology in FTD, with vertical saccade abnormalities most diagnostic of progressive supranuclear palsy.

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ate with a single molecular pathology, whereas others may be associated with one or more pathologies. For example, semantic dementia and FTD-ALS usually predict FTLD-TDP pathology at autopsy, whereas progressive nonfluent aphasia and PSPs most often reflect FTLD-tau pathology.  

Despite our improved understanding of the molecular underpinnings of FTD, there are currently no effective treatments. New agents that specifically target tau have begun to enter human clinical trials, increasing the importance of early accurate prediction of underlying pathology in patients with FTD syndromes. Abnormalities in the control of eye movements are frequently observed in FTD and are useful diagnostically in differentiating clinical FTD syndromes from each other as well as from Alzheimer disease (AD). We previously found that, although most clinical FTD syndromes were impaired in the voluntary control of saccades and smooth pursuit eye movements, clinical syndromes with predicted FTLD-tau pathology, including PSPs and CBDS, displayed relatively specific and severe abnormalities in visually guided (reflexive) saccades. We reasoned that such saccade abnormalities might be useful diagnostically in identifying FTD cases with underlying tau pathology during life. However, because clinical CBDS often corresponds to other non–FTLD-tau pathology diagnoses, including AD, at autopsy, and PSP pathology is found in a variety of clinical syndromes, including individuals who present with bvFTD or with CBDS, the utility of using saccade measurements to identify FTLD-tau pathology would need to be evaluated in FTD cases with autopsy-confirmed diagnoses. Therefore, the goals of our study were to (1) determine the saccade abnormalities associated with autopsy-confirmed FTD as compared with AD and (2) determine the ability of saccade abnormalities to differentiate FTLD-tau from FTLD-TDP and AD during life.

# METHODS

## NOMENCLATURE

We use the acronym FTD to refer to the following clinically defined syndromes: semantic dementia, CBDS, progressive nonfluent aphasia, PSPs, and bvFTD. We use the acronym FTLD to refer to the following neuropathologically defined syndromes: FTLD-tau pathology, FTLD-TDP pathology, and FTLD-FUS pathology, and to the following diagnoses: CBD, Pick disease, and PSP. Subjects with AD met the National Institute on Aging–Reagan Institute criteria for high likelihood AD.

## SUBJECTS

All subjects with autopsy-confirmed FTD or with autopsy-confirmed AD as of December 2010 (n=38) from a larger series of clinically diagnosed patients with FTD reported previously and 27 age-matched normal controls were enrolled. All subjects were evaluated at the University of California, San Francisco, and gave informed consent to participate in the experimental procedures. An additional group of 50 clinically diagnosed subjects with FTD were used for the neuroimaging analysis only (eTable 1, http://www.archneurol.com). All aspects of our study were approved by the institutional review board of the University of California, San Francisco.

## CLINICAL DIAGNOSES

Subjects underwent clinical evaluations and magnetic resonance imaging within 3 months of an eye movement evaluation and were categorized as having AD, semantic dementia, PSPs, CBDS, or bvFTD as normal controls. At the time of assessment, all subjects with FTD met the criteria of Neary et al10 for semantic dementia, progressive nonfluent aphasia, or bvFTD; the National Institute of Neurological Disorders and Stroke–Society for PSP criteria for probable PSP22; or the criteria for CBDS as described in Garbutt et al.20 Normal controls had normal neurological and neuropsychological examinations and had clinical dementia rating (CDR) scores of 0. Subjects with AD met the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association probable criteria.24

## AUTOPSY-DEFINED GROUPS

For group analyses, subjects with FTLD were subdivided by underlying neuropathology into 1 of 4 groups: (1) FTLD-TDP pathology (type 1, 2, or 3; n=12); (2) PSP (n=8); (3) CBD (n=4); (4) Pick disease (n=2) or FTD and parkinsonism linked to chromosome 17 (FTDP-17; n=1); and (5) AD (n=10). The subjects with Pick disease and those with an FTDP-17 pathology were combined on the basis of having similar saccade abnormalities. One subject had a diagnosis of FTLD-FUS pathology (eTable 2) and was excluded from the group analyses but used in the neuroimaging and receiver operating characteristic (ROC) curve analyses.

## NEUROPATHOLOGICAL ANALYSIS

Autopsies were performed at the University of California, San Francisco, or at the University of Pennsylvania, according to standard protocols.

## EYE MOVEMENT RECORDINGS

Two-dimensional movements of the right eye were measured using the Fourward Technologies Generation 6.1 Dual Purkinje Image Eye Tracker as described previously. Targets were 0.1° bright spots presented on a large analog oscilloscope at a viewing distance of 80 cm.

## OCULOMOTOR PARADIGMS

Reflexive, visually guided (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 milliseconds. When the fixation light was extinguished, targets appeared either immediately (overlap condition) or after a 200-millisecond gap (gap condition). The eccentric target remained illuminated for 1000 milliseconds. A blank screen interval of 1000 milliseconds occurred between trials. At least 7 responses were recorded for each stimulus in each direction. Only the 10°-overlap data were analyzed.

Antisaccade trials began with illumination of the central fixation point for 1000 milliseconds. After a 200-millisecond gap, targets appeared 10° to the right or left and remained illuminated for 1000 milliseconds. 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.” Responses to at least 18 antisaccade trials were recorded in each direction.
SACCADE PARAMETERS

Saccade latencies were computed as the duration from the appearance of an eccentric target to the onset of the first eye movement (Figure 1A). First gains were computed as the difference in eye position between fixation and the end of the first movement. End gains were computed as the difference in eye position between fixation and the final eye position for the trial. Antisaccade responses were considered to be correct if the first eye movement after target onset had an amplitude greater than 3° and was in the opposite direction from the target.

VOXEL-BASED MORPHOMETRY

Magnetic resonance imaging scans were obtained on a 1.5-T Magnetom VISION system (Siemens) as described in a previous report.26 Three-dimensional T1-weighted scans (magnetization-prepared rapid-acquisition gradient echo) were used for analyses. Voxel-based morphometric images were preprocessed and statistically analyzed with the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm), using standard procedures as described previously.15 We used an analysis of covariance, controlling for total intracranial volume, age, and sex, to investigate the brain structure correlates of saccade abnormalities in the subjects with autopsy-confirmed FTLD plus an additional 30 subjects with clinically diagnosed FTLD (eTable 2). At the voxel level, a statistical threshold of P < .05, corrected for multiple comparisons (familywise error), was used.

STATISTICAL ANALYSIS

We used χ² analysis or analysis of variance, along with Tukey or Sidak post hoc statistics, for comparisons of demographic, neuropsychological, and eye movement measures among the neuropathologically diagnosed groups. For the analyses of oculomotor findings, we controlled for differences in disease severity at the time of assessment by including the CDR Sum of Boxes (CDR-SB) score as a covariate in the analyses of variance. The diagnostic value of oculomotor findings was analyzed using ROC curve statistics. To control for differences in disease severity, in ROC analyses, we used the residual values from linear regressions of CDR-SB scores and the oculomotor values of interest. Significance was accepted at the P < .05 level. Analyses were performed using SPSS version 17.0 (SPSS Inc).

Figure 1. Examples of upward saccades and fixation abnormalities. Plots of eye position vs time are presented for 3 successive upward saccades to 10° targets for the following individuals: a normal control, which shows intervals for subsequent saccade measurements, including latency, velocity (slope of eye position vs time), and first and end gains (A); a subject with clinical corticobasal degeneration syndrome (CBD) with a frontotemporal lobar degeneration–TAR DNA-binding protein 43 pathology (B); a subject with clinical CBD with CBD pathology (C); a subject with the behavioral variant of clinical frontotemporal dementia with Pick disease pathology (D); a subject with clinical progressive supranuclear palsy syndrome (PSP) with PSP pathology (E); and a subject with clinical Alzheimer disease (AD) with AD pathology (F). Examples of fixation abnormalities in horizontal eye position vs time traces are presented for the following individuals: the same subject with CBD (C) who had macrosaccadic oscillations (G) and a subject with PSP with PSP pathology (H).
Subjects With Autopsy-Confirmed Diagnoses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NC (n = 27)</th>
<th>Subjects With FTLD-TDP (n = 12)</th>
<th>Subjects With PSP (n = 8)</th>
<th>Subjects With CBD (n = 4)</th>
<th>Subjects With Pick/FTDP-17 (n = 3)</th>
<th>Subjects With AD (n = 10)</th>
<th>F Value*</th>
<th>P Value*</th>
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<tbody>
<tr>
<td>Sex, No. of subjects</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Education, mean (SE), y</td>
<td>17.4 (0.5)</td>
<td>15.8 (0.7)</td>
<td>16.3 (1.3)</td>
<td>17.5 (1.6)</td>
<td>15.3 (1.8)</td>
<td>15.4 (1.3)</td>
<td>F1,10 = 1.05</td>
<td>.40</td>
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<tr>
<td>Age at testing, mean (SE), y</td>
<td>66.8 (1.6)</td>
<td>64.7 (2.2)</td>
<td>66.9 (1.5)</td>
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<td>60.4 (2.7)</td>
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<td>Disease duration, mean (SE), y</td>
<td>NA</td>
<td>5.53 (1.14)</td>
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<td>Months prior to autopsy, mean (SE)</td>
<td>NA</td>
<td>27.4 (5.3)</td>
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<td>.06</td>
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</table>

Abbreviations: AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; bvFTD, behavioral variant frontotemporal dementia; CBSD, corticobasal degeneration syndrome; CDR, Clinical Dementia Rating; CDR-SB, CDR Sum of Boxes; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; NA, not available; NC, normal controls; Pick/FTDP-17, Pick disease or FTD and parkinsonism linked to chromosome 17; PNFA, progressive nonfluent aphasia; PSPS, progressive supranuclear palsy syndrome; ROC, receiver operating characteristic; SD, semantic dementia.

a For the overall analysis of variance.

b For the overall χ² analysis or analysis of variance.

c P < .05 for comparison with NC.

d P < .05 for comparison with subjects with FTLD associated with insoluble deposits of the TAR DNA-binding protein 43.

e P < .05 for comparison with subjects with PSP, using a post hoc Tukey test.

f One subject with FTLD related to deposition of the fused in sarcoma protein who had bvFTD at the time of assessment and who was included in the ROC curve and imaging analyses is not shown. Details regarding this subject are shown in eTable 2.

RESULTS

SUBJECT DEMOGRAPHICS

When grouped by pathologic diagnosis, patient groups were comparable in age, sex, disease duration, and time to autopsy. Autopsies showed that 15 subjects with FTD had FTLD-tau pathology, 12 had FTLD-TDP pathology, and 1 patient had FTLD-FUS pathology; the clinical research diagnoses at the time of oculomotor assessment are shown in Table 1. All groups except the PSP group were impaired relative to normal controls with regard to the Mini-Mental State Examination score. The subjects in the CBD and Pick disease/FTDP-17 groups were more impaired than the subjects in the FTLD-TDP and PSP groups (P < .05, determined by use of analysis of variance with Tukey post hoc statistics). The CDR² and CDR-SB scores were higher in the CBD, PSP, and Pick disease groups than in the FTLD-TDP group (P < .05).

QUALITATIVE ABNORMALITIES IN VISUALLY GUIDED SACCADES

Examples of 10° upward saccades (Figure 1) demonstrate the differences in vertical saccade performance among the pathologic groups. Subjects with FTLD-TDP and 3 of 4 subjects with CBD displayed visually guided saccades that were indistinguishable from those of normal controls (Figure 1A and B). In contrast, the fourth subject with CBD, who presented with classic CBSDs, showed abnormalities that included increased latency, decreased velocity, and decreased gain, as well as occasional macrorraccadic oscillations (Figure 1C and H). One of the subjects with Pick disease displayed decreased saccade velocity and gain (Figure 1D) compared with the more severely decreased saccade velocity and gain seen in a subject with PSP (Figure 1E). The subjects with PSP also exhibited occasional square-wave jerks (Figure 1G).

GROUP COMPARISONS OF REFLEXIVE, VISUALLY GUIDED SACCADES

Both horizontal (F6,59 = 3.90; P = .003; Figure 2A) and vertical saccade latency (F6,59 = 6.59; P < .001) differed among groups. All group comparisons controlled for disease severity at the time of oculomotor assessment (Table 1) by including the CDR-SB score as a covariate. Post hoc tests revealed that subjects with AD had increased horizontal saccade latencies relative to subjects with FTLD-TDP pathology (P = .007) and subjects with PSP (P = .04). Vertical saccade latencies were increased in both subjects with AD and subjects with PSP com-
pared with normal controls and subjects with FTLD-TDP pathology (*P* < .01 or †P < .05 for comparison with normal controls (NC) and subjects with frontotemporal lobar degeneration associated with insoluble deposits of the TAR DNA-binding protein 43 (TDP). The saccade parameter of antisaccade performance (D) is also expressed as mean (SEM) values, with *P* < .01 or †P < .05 for comparison with NC. The error bars indicate SEM. CBD indicates subjects with corticobasal degeneration; Pick/FTDP-17, subjects with Pick disease or with FTD and parkinsonism linked to chromosome 17; and PSP, subjects with progressive supranuclear palsy.

**ANTISACCADE PERFORMANCE**

Performance on the antisaccade task also revealed differences among groups (*F*$_{6,55}$ = 9.47; *P* < .001; Figure 2D). The antisaccade task involves suppression of a visually guided saccade and generation of a voluntary saccade in the opposite direction. Post hoc test results showed that the FTLD-TDP, Pick disease/FTDP-17, PSP, and AD groups all had significantly lower percentages of correct antisaccade trials than did normal controls (*P* < .03), with a trend (*P* = .07) toward worse performance in the CBD group as well. As a measure of the ability to self-correct antisaccade errors, the total (correct and self-corrected errors) antisaccade score also differed among groups (*F*$_{6,55}$ = 7.09; *P* < .001), with the FTLD-TDP, Pick disease/FTDP-17, PSP, and AD groups performing worse than normal controls (*P* < .02).

**DIAGNOSTIC VALUE OF SACCADE ABNORMALITIES**

Saccade parameters differed among groups, which indicates that abnormalities could be diagnostically useful. Receiver operating curve statistics were used to determine the diagnostic value of saccade abnormalities in differentiating patients with autopsy-confirmed FTLD from
patients with autopsy-confirmed AD patients (n = 38). Horizontal saccade latency, but not other measures, differentiated AD from all FTLD cases (area under the curve, 0.807; P = .01). A variety of saccade parameters differentiated subjects with PSP from all other patients, with vertical saccade velocity and both vertical and horizontal first gains being most effective (P < .001; Table 2). When all subjects with FTLD-tau pathology were combined, horizontal saccade velocity and first gain were best (P < .01) able to differentiate this group (n = 15) from the non–tau FTLD and AD cases (n = 22).

ANATOMICAL CORRELATES OF DECREASED VERTICAL SACCADE VELOCITY

We investigated the neuroanatomical correlates of the saccade parameters that best differentiated the FTD groups using voxel-based morphometry. At the whole-brain level, vertical saccade velocity was correlated with brain volume in the dorsal midbrain white matter in the vicinity of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF; coordinates x, y, z, respectively, in Montreal Neurological Institute standard brain: 2, −18, −4; P = .03, familywise error–corrected; Figure 3A). No other brain regions were correlated with vertical saccade velocity, even when we used a lower statistical threshold (P < .10, corrected), nor were any other oculomotor variables that differentiated the groups correlated with brain volume. The slowest vertical saccades and the lowest volumes were in the subjects with PSP and in the subject with Pick disease (Figure 3B). In the riMLF region, subjects with PSP had smaller brain volumes than did normal controls and subjects with FTLD-TDP pathology (P < .001; Figure 3C). In the vicinity of the riMLF, subjects with CBD also showed atrophy compared with normal controls (P = .001) and subjects with FTLD-TDP pathology (P = .03).

We investigated the saccade abnormalities found in cases of autopsy-confirmed FTD and in cases of autopsy-confirmed AD, and we found distinctive abnormalities in FTLD cases with underlying tau pathology and in AD cases. Although all subjects with FTD or AD were impaired in their ability to inhibit visually guided saccades on the antisaccade task, the reflexive, visually guided saccades of the subjects with FTLD-TDP pathology were indistinguishable from those of normal controls. Subjects with PSP had the most severe visually guided saccade abnormalities, with greater involvement of vertical rather than horizontal saccades. These abnormalities included elevated latency, decreased velocity, and decreased gains. Unexpectedly, other cases of FTLD-tau pathology, including one subject with Pick disease and another with FTDP-17, also had similar saccade abnormalities, although, in these cases, the abnormalities were more prominent in the horizontal rather than vertical plane. In contrast, the subjects in the AD group displayed increased saccade latencies compared with the subjects in the other groups. Consistent with these findings, using visually guided saccade velocity and gain as our measures, we found that we were able to differentiate subjects with PSP from all other patients and to differentiate subjects with FTLD-tau pathology from subjects with a non–FTLD-tau pathology, whereas, using horizontal saccade latency as our measure, we were able to differentiate subjects with AD from subjects with FTLD, all at a mean of more than 2.5 years prior to death. The parameter best able to differentiate subjects with PSP from all other subjects, vertical saccade velocity, was also strongly correlated with dorsal midbrain volume in the vicinity of the riMLF, and cases with FTLD-tau pathology were atrophied relative to normal controls and cases with FTLD-TDP pathology in this region. This suggests a potential neuroanatomical basis for the differences that we measured in visually guided saccades (ie, damage to the brainstem oculomotor network is more severe in FTLD-tau than in FTLD-TDP).

These findings extend our previous work that suggested that visually guided saccades are normal in patients with underlying FTLD-TDP pathology, particularly in individuals with semantic dementia who often display enhanced visual talent. Moreover, similar to previous reports based on clinically diagnosed patients that included PSP, the subjects with autopsy-confirmed PSP in our study had the most severe vertical saccade impairments. Although clinically diagnosed CBDS has pre-

### Table 2. Diagnostic Value of Saccade Parameters From Receiver Operating Curve Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subjects With PSP vs Subjects With FTLD or AD</th>
<th>Subjects With FTLD-Tau Pathology vs Subjects With FTLD or AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC, Mean (SE)</td>
<td>P Value</td>
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<tr>
<td>Horizontal latency</td>
<td>0.506 (0.110)</td>
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<tr>
<td>Vertical latency</td>
<td>0.833 (0.075)</td>
<td>.012</td>
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<tr>
<td>Horizontal velocity</td>
<td>0.921 (0.047)</td>
<td>&lt;.001</td>
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<tr>
<td>Vertical velocity</td>
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<td>&lt;.001</td>
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<tr>
<td>Horizontal first gain</td>
<td>0.991 (0.012)</td>
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<tr>
<td>Horizontal end gain</td>
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<tr>
<td>Vertical end gain</td>
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<td>&lt;.001</td>
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<tr>
<td>Antisaccade correct</td>
<td>0.513 (0.150)</td>
<td>.92</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; AUC, area under the curve; FTLD, frontotemporal lobar degeneration; PSP, progressive supranuclear palsy.

*Mean (SE) AUC values are shown for the specified contrasts.
viously been associated with severe alterations in saccade latency and gain, we found that only 1 of the 4 subjects with autopsy-confirmed CBD had visually guided saccade abnormalities. These results are similar to a recent clinicopathologic CBD series that noted oculomotor findings in only approximately 20% of subjects, mainly late in the course of disease. We found that the subjects with AD displayed prominent increases in saccade latency. Because CBDS is known to be pathologically heterogeneous, with some clinically defined series containing a large percentage of subjects with pathologic AD, we suggest that previous descriptions of increased latency in CBDS may have largely reflected cases with underlying AD pathology. In the present study, the subject with CBD with abnormal visually guided saccades also experienced macrosaccadic oscillations (Figure 1F), a finding not previously described in CBDS or CBD. Although we did not quantify these fixation abnormalities, such findings might also help to identify FTD cases with underlying tau pathology.

Supranuclear gaze palsy and variably decreased saccade velocity have been reported in autopsy-confirmed ALS and clinically diagnosed FTD-ALS, however, we found no evidence of decreased saccade velocity in the 6 subjects with pathologically confirmed FTLD-ALS studied herein. Because saccade abnormalities in ALS have been closely associated with bulbar-onset cases, the lack of such abnormalities in our subjects may reflect the fact that none of our FTLD-ALS cases had bulbar-onset disease. The visually guided saccade abnormalities that we observed in our subjects with PSP are similar to those described in a previous case of autopsy-confirmed PSP, as well as in other clinical PSP series. The present study extends these observations to a series of subjects with autopsy-confirmed PSP who presented with PSP. Previous studies have inferred that damage to the riMLF and related structures explained vertical saccade impairments in PSP based on experiments with monkeys coupled with human postmortem data in individuals with vertical saccade palsy or PSP. We provide direct experimental support for models implicating damage to the riMLF and nearby structures as the cause of vertical saccade slowing in PSP, through the strong correlation between saccade velocity and dorsal midbrain volume that we quantified (Figure 3), and its severe atrophy in living subjects with PSP at the time they...
Because PSP can present with a frontal lobe dementia,17 we have demonstrated in previous studies,16,28,42 the increased saccade latency in AD is likely related to the prominent involvement of the dorsal parietal lobe in these cases.

We found that, by using saccade gain and velocity as our measures, we were able to differentiate PSP cases from other FTD syndromes (Table 2). These saccade abnormalities constitute the supranuclear gaze palsy observed at the bedside in patients with PSP, and thus our findings are consistent with previous studies16,28,43 that determined that gaze palsy is an effective criterion for differentiating PSP from other neurodegenerative diseases. Because PSP can present with a frontal lobe dementia,17 the measurement of saccade velocity and gain may be useful diagnostically in identifying cases of clinical FTD with underlying PSP or other tau pathology.

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