Dramatic impairment of prediction due to frontal lobe degeneration

Sébastien Coppe, Jean-Jacques Orban de Xivry, Demet Yüksel, Adrian Ivanoiu and Philippe Lefèvre

J Neurophysiol 108:2957-2966, 2012. First published 5 September 2012;
doi: 10.1152/jn.00582.2012

J Neurophysiol 108: 2957–2966, 2012.
First published September 5, 2012; doi:10.1152/jn.00582.2012.

Dramatic impairment of prediction due to frontal lobe degeneration

Sébastien Coppe,[1,2]* Jean-Jacques Orban de Xivry,[1,2]* Demet Yüksel,[2,3] Adrian Ivanoiu,[2,4] and Philippe Lefèvre[1,2]

[1]*ICTEAM, Université catholique de Louvain, Louvain-La-Neuve, Belgium;* [2]*Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium;* [3]*Ophthalmology Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium; and* [4]*Department of Neurology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

Submitted 6 July 2012; accepted in final form 4 September 2012

Coppe S, Orban de Xivry JJ, Yüksel D, Ivanoiu A, Lefèvre P. Dramatic impairment of prediction due to frontal lobe degeneration. *J Neurophysiol* 108: 2957–2966, 2012. First published September 5, 2012; doi:10.1152/jn.00582.2012.—Prediction is essential for motor function in everyday life. For instance, predictive mechanisms improve the perception of a moving target by increasing eye speed anticipatively, thus reducing motion blur on the retina. Subregions of the frontal lobes play a key role in eye movements in general and in smooth pursuit in particular, but their precise function is not firmly established. Here, the role of frontal lobes in the timing of predictive action is demonstrated by studying predictive smooth pursuit during transient blanking of a moving target in mild frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) patients. While control subjects and AD patients predictively reaccelerated their eyes before the predicted time of target reappearance, FTLD patients did not. The difference was so dramatic (classification accuracy >90%) that it could even lead to the definition of a new biomarker. In contrast, anticipatory eye movements triggered by the disappearance of the fixation point were still present before target motion onset in FTLD patients and visually guided pursuit was normal in both patient groups compared with controls. Therefore, FTLD patients were only impaired when the predicted timing of an external event was required to elicit an action. These results argue in favor of a role of the frontal lobes in predictive movement timing.

eye movements; frontotemporal dementia; Alzheimer's disease; frontal lobes; frontal eye field

PREDICTION IS A CORNERSTONE of human motor function. It is used to improve the perception of a moving object (Orban de Xivry and Lefèvre 2007; Barnes 2008), to avoid the slippage of a handheld object during its transport (Flanagan and Wing 1997), or to anticipate the consequences of one's own actions (Blakemore et al. 2000). In the present study, we focus on predictive mechanisms active during smooth pursuit eye movements that are normally used to overcome sensorimotor delays (Carl and Gellman 1987).

Predictive smooth pursuit eye movements are especially highlighted when the fixation cue disappears for a few hundred milliseconds before target motion onset (anticipatory pursuit; Barnes 2008; Barnes and Asselman 1991, 1992; Barnes et al. 1987; Boman and Hotson 1988, 1989; Kowler 2011; Kowler and Steinman 1979a, 1979b, 1981) or when the target transiently disappears from the visual environment (Barnes 2008; Becker and Fuchs 1985; Mitrani and Dimitrov 1978). In this case, smooth pursuit eye movements are maintained in the absence of visual feedback through predictive mechanisms.

During this blanking period, smooth pursuit eye velocity decreases to a plateau value (Becker and Fuchs 1985; Orban de Xivry et al. 2006, 2008) and is compensated for by saccades (Orban de Xivry et al. 2006, 2009). Moreover, if the duration of the blanking period is predictable, a predictive eye reacceleration takes place before target reappearance (Bennett and Barnes 2003, 2004; Churchland et al. 2003; Orban de Xivry et al. 2006). This predictive reacceleration is scaled to upcoming target velocity (Bennett and Barnes 2004; Orban de Xivry et al. 2006). It is present in experiments where target velocity at reappearance changes from trial-to-trial but can be anticipated from the preblanking period (Bennett et al. 2007). When the same target motion is used in consecutive trials, it takes three trials to build up an appropriate predictive reacceleration (Bennett et al. 2010). In contrast, such a predictive reacceleration is absent when the duration of the blanking period is unknown (Orban de Xivry et al. 2008).

Three lines of evidence highlight the implication of the frontal lobes in predictive smooth pursuit in humans (Sharpe 2008). First, fMRI studies found changes in activation during predictive smooth pursuit in the frontal eye fields (FEF), the supplementary motor area (SMA), including supplementary eye fields (SEF), and the dorsolateral prefrontal cortex (DLPFC) (Schmid et al. 2001; Lencer et al. 2004; Nagel et al. 2006, 2007). Second, anticipatory and visually guided smooth pursuit eye movements are impaired in stroke patients when frontal areas are damaged (Morrow and Sharpe 1995; Heide et al. 1996; Lekwuwa and Barnes 1996). Third, disrupting FEF activity by transcranial magnetic stimulation impairs predictive pursuit whereas disrupting the SEF affects the phase around the time of target direction reversal (Gagnon et al. 2006; Nyffeler et al. 2008).

In monkeys, the role of the FEF and SEF subregions of the frontal lobes in smooth pursuit is still much debated and three hypotheses have been presented. Based on recordings of FEF neurons during target blanking, Ferrera and colleagues suggested that the FEFs contain an internal motion representation (Barborica and Ferrera 2003, 2004; Xiao et al. 2007). Based on smooth pursuit perturbation, Tanaka and Lisberger (2001, 2002) identified FEF neuron responses consistent with a gain controller for visually guided pursuit. Finally, the behavior of FEF neurons during visually guided and anticipatory smooth pursuit might also be consistent with a role of FEF in timing representation (de Hemptinne et al. 2008; Schoppik et al. 2008; Li and Lisberger 2011). One goal of this study was therefore to

* S. Coppe and J.-J. Orban de Xivry contributed equally to this study.

Address for reprint requests and other correspondence: P. Lefèvre, Av. G. Lemaitre, 4 B-1348 Louvain la Neuve, Belgium (e-mail: philippe.lefevre@uclouvain.be).

investigate which function of the pursuit system will be impaired by the degeneration of the frontal lobes of human brain.

To do so, we compare the predictive abilities of frontotemporal lobar degeneration (FTLD) patients to those of age-matched control subjects and Alzheimer's disease (AD) patients. Previous studies have shown that a subset of FTLD patients performed significantly worse during an antisaccade task (Meyniel et al. 2005; Boxer et al. 2006; Garbutt et al. 2008) and exhibited a lower eye velocity during the steady-state pursuit (Boxer et al. 2006; Garbutt et al. 2008). Some FTLD patients could also present larger saccade latencies and smaller visually guided saccade velocity and gain (Boxer et al. 2012; Burrell et al. 2012). FTLD is a neurodegenerative disorder that is associated with degeneration of the frontal and/or anterior temporal lobes with relative sparing of more posterior cortical regions. The FEF and the SMA are among the first areas impaired by this neurodegenerative process (Broe et al. 2003). In contrast, the frontal lobes of AD patients are relatively spared at the early stage of the disease (Nelson et al. 2009; Aries et al. 2010; Vemuri et al. 2011). Therefore, the comparison of the predictive tracking behavior of FTLD and AD patients will highlight the importance of the integrity of the frontal lobes in the control of predictive smooth pursuit.

MATERIALS AND METHODS

Participants. Eye movements of 14 patients (three females) with mild FTLD were recorded. They were between 49 and 82 yr old (mean = 62.9 yr, standard deviation = 5.9 yr). FTLD patients were diagnosed according to their presentation as behavioral and dysexecutive frontotemporal dementia (FTD), semantic dementia (SD), or progressive nonfluent aphasia (PA). All subjects met criteria of Neary et al. (1998) for FTD (8), SD (2), or PA (4). Two FTD patients also showed signs of motor neuron disease (MND), a well-known association (Bak and Hodges 2001; Lomen-Hoerth et al. 2002; Lillo and Hodges 2009). Diagnosis was supported by clinical assessment, neuropsychological evaluation, magnetic resonance imaging, functional imagery (F-18 FDG PET scanner, Tc-99m HMPAO or ECD brain scintigraphy), and, in six patients, by cerebrospinal fluid (CSF) biomarkers assay. One FTD patient carried a mutation in the progranulin (GRN) gene (Chen-Plotkin et al. 2011), and another FTD patient associated with motor neuron disease has a familial history (genetic assessment ongoing).

Twelve AD patients (three females) participated in the same experiment. They were between 58 and 85 yr old (mean = 67.3 yr, standard deviation = 7.3 yr). Diagnosis of AD followed the NINCDS-ADRDA criteria (McKhann et al. 1984). All AD patients underwent neuropsychological assessment and structural and functional brain imaging. In 10 AD patients, the diagnosis was corroborated by specific biomarkers assessment: either a CSF analysis showing pathological levels of tau protein and/or amyloid beta42 or a 18F-flutemetamol amyloid imaging PET scanner displaying senile plaques in the brain (Vandenberghe et al. 2010). The positivity of CSF and/or imaging biomarkers in the AD patients supported the diagnosis in mild cases when the Mini-Mental State Examination (MMSE) was above the classical threshold of 24/30 (Jack et al. 2011).

All patients were followed-up by the same neurologist that made the diagnosis initially (A. Ivanoiu) and were reexamined 6 mo after the eye recording to validate the diagnosis. The morphological and functional imaging deficits were recorded by the same neurologist (A. Ivanoiu) who was unaware of the oculomotor performances of the patients.

Sixteen age-matched control subjects (four females) participated in the same experiment as control (CTRL) subjects. They were between 55 and 83 yr old (mean = 64.3 yr, standard deviation = 4.3 yr).

Data of one FTLD patient (from FTD subgroup), one AD patient, and one CTRL subject were excluded based on their abnormal visually guided pursuit performance (see *Data analysis*). We analyzed the data from 13 FTLD patients, 11 AD patients, and 15 CTRL subjects. The patient demographics as well as their disease related characteristics are summed up in Table 1. Magnetic resonance imaging and functional imagery (F-18 FDG PET scan) of two typical patients (*patients FTLD5* and *AD9*) are shown in Fig. 1.

All procedures were approved by the Université catholique de Louvain Ethics Committee and were in agreement with the Declaration of Helsinki. All participants gave their informed consent before participating in the experiment.

Neuropsychological testing. Patients performed a standard battery of neuropsychological tests that measures several domains of cognition. The scores of these tests are presented in Table 2 for each patient. In short, AD patients were in general more amnesic but less impaired at language tests than FTLD patients. However, executive tests yielded comparable results in FTLD and AD patients.

This Table 2 includes verbal tests (e.g., word fluencies) but also tests of executive function: the Luria Series Test (nonverbal visuo-spatial test) and the TMT Test (no verbal production; Table 2). General cognitive performance was evaluated using the MMSE (Folstein et al. 1975). Language was assessed using the LEXIS Graded Naming test as well as a Semantic Fluency (animals in 2 min) and Phonemic Fluency (P-words in 2 min) Tests (de Partz et al. 2001). Visuo-spatial processing assessment included the Clock Drawing Test (Rouleau et al. 1992) and the "Praxis" part of the CERAD battery (Morris et al. 1988), which consisted in drawing four simple shapes. Executive functions were assessed using verbal fluency tests (see above, de Partz et al. 2001), a variant of "Luria's Graphical or Alternating Sequences Test," which consisted in copying iteratively some series of geometric forms (local battery, unpublished) and using the "Trail Making Test." Long-term memory assessment was completed by using the "Doors Test" of the "Doors and People Test" (Baddeley et al. 1994) and the French adaptation of the RL/RI 16 items test (Grober and Buschke 1987; Van der Linden et al. 2004).

Stimuli. All trials started with an initial fixation during which a yellow dot (diameter of 0.8°) was visible on one side of horizontal meridian of the screen (between 25 and 15° of eccentricity) for 1,000 ms (Fig. 2). The stimulus disappeared for 300 ms (gap period) and then immediately started to move toward the center at constant velocity for 2,000 ms. After 600 ms, the target transiently disappeared for 800 ms and then reappeared for an additional 600 ms period (test trials). The direction (leftward or rightward) and the velocity of the target (10, 15, or 20°/s) were kept constant within a block but changed randomly across blocks. The duration of the block (between 20 and 25 trials) was adjusted for each subject to reduce fatigue effects. To minimize sequence effects, the order in which the blocks were received was randomized across subjects. The subjects were instructed to follow the dot even when it was blanked. Each subject or patient performed between 8 and 12 blocks, so there were at least 30 test trials per subject per target velocity. There was a 2-min break between two consecutive blocks to keep the subjects alert and concentrated.

During the first two trials as well as three other trials of each block, the target was continuously visible (control trials) to reinforce the continuous movement of the target. The visually guided smooth pursuit gain was measured in these trials. Except the first two, the control trials were randomly inserted in the block but were always followed by at least three test trials.

Apparatus and data analysis. Subjects were seated in a dimly lit room with their head restrained by a chin rest and a forehead rest. They faced a 1.5-m distant tangent screen that spanned 40° of their visual field. Stimuli were projected onto the screen with a cine8 Barco projector (refresh rate: 100 Hz; Barco). Eye movements were recorded at 1,000 Hz using an Eyelink 1000 (SR Research, Ottawa, Ontario, Canada). A calibration was performed at the beginning of each block.

Table 1. *Demographics and imagery characteristics of the patients*

Patients	Age	Educ	Gend	Type	D Dur	Morphological Impairment	Functional Impairment
FTLD Patients							
FTLD1	59	9	M	SD	50	Temporal pole L, frontal L	Temporal, fronto-lateral and parietal L
FTLD2	63	18	M	FTD$	19	Temporo-polar R	Frontal medial, orbital and temporal poles R
FTLD3	59	20	M	PA	25	Normal	Fronto-lateral, inferior and SMA L
FTLD4	60	18	M	FTD	30	Fronto-insular R	Bifrontal; temporo-polar R
FTLD5	58	12	M	FTD	24	Bifrontal	Bifrontal; temporo-parietal R
FTLD6	69	18	M	SD	24	Bitemporo-polar L	Temporal L
FTLD7	73	12	F	PA	40	Diffuse atrophy	Bifrontal; premotor, temporal and parietal R
FTLD8	66	18	F	FTD	42	Bifrontal (basal) and subcortical	Bifrontal
FTLD9	82	20	M	PA	60	Diffuse atrophy	Frontal lateral premotor L
FTLD10	55	18	M	FTD$	12	Diffuse atrophy	Frontal L
FTLD11	49	10	F	PA	16	Temporal L	Temporal L
FTLD12	63	12	M	FTD	50	Vertex and para hippo L	Frontal L
FTLD13	62	18	M	FTD	48	Frontal dorso-lateral and inferior L	Bitemporal
Mean	62.9	15.6	10/3		33.8		
AD Patients							
AD1	58	9	M	/	48	Quite normal	Superior parietal L
AD2	60	20	F	/	30	Slight diffuse and medial temporal	Parietal L
AD3	63	15	M	/	20	Slight diffuse and medial temporal	Parietal and lateral temporal R
AD4	68	15	M	/	18	Slight diffuse and medial temporal L	Bilateral superior parietal
AD5	59	18	M	/	62	Slight bi-temporal atrophy	Parietal and posterior temporal R
AD6	79	14	M	/	66	Diffuse and medial temporal atrophy	Posterior temporal R
AD7	63	20	F	/	50	Medial temporal atrophy	Parietal and posterior temporal R
AD8	74	15	M	/	39	Slight bi-temporal atrophy	Posterior temporal R
AD9	85	15	M	/	72	Medial temporal atrophy	Medial temporal and anterior and posterior cingulate cortex
AD10	71	16	F	/	60	Slight diffuse and medial temporal	Posterior temporal L
AD11	61	18	M	/	42	Slight diffuse and medial temporal	Parietal and posterior temporal L
Mean	67.3	15.9	8/3		46		

Educ, education (in yr); Gend, gender; Type, syndrome for frontotemporal lobar degeneration (FTLD) patients; FTD, frontotemporal behavioral subtype; SD, semantic dementia subtype; PA, progressive aphasia subtype; $, FTD patients with motor neuron disease; D Dur, disease duration (in months) from the first symptoms observed by the patient (or his/her family) until the moment of the eye assessment; AD, Alzheimer's disease. Morphological and functional imaging deficits are based on the visual appreciation of the neurologist who was unaware of the oculomotor performances of the patients. For impairments: L, left; *R*, right.

Eye movements were low-pass filtered at 45 Hz. Velocity and acceleration signals were obtained from position signals using a central difference algorithm on a ±10-ms interval. Saccade onset and offset were detected using a 500°/s^2 acceleration threshold. Those saccades were removed from the smooth eye velocity trace (see details in de Brouwer et al. 2002). In such a block design, three trials are required before predictive behavior can be exhibited (Bennett et al. 2010). Therefore, the test trials were divided into early (first three test trials, also identified as P1) and late trials (remaining test trials). The late trials were further divided into three periods P2 (first five of them), P3 (next five ones), and P4 (remaining trials: between 5 and 10 trials).

In test trials, we measured the residual pursuit gain as the mean smooth pursuit velocity averaged over a 50-ms period centered at 500 ms after target disappearance, divided by target velocity. The same measure was extracted in control trials as a proxy of the visually guided smooth pursuit gain. All patients and subjects had a visually guided pursuit gain >0.85, except three people (one FTLD patient, one AD patient, and one CTRL subject) that had a pursuit gain <0.6. These subjects were excluded from further analyses.

In test trials, the predictive smooth pursuit reacceleration was measured as the slope of the linear fit for the smooth velocity trace between 100 ms before target reappearance and 50 ms after this reappearance, i.e., before any influence of the visual feedback.

A "heat map" of saccade endpoints during blanking was computed for each participant to analyze the saccadic behavior. The saccade endpoint was estimated as the position of the eye when eye acceleration decreased below a 500°/s^2 threshold. To build the heat map, each saccade endpoint was represented by a 3D-Gaussian curve. The height of each Gaussian for one participant was equal to $1/x$, with x equal the total number of saccades elicited by this participant during the blanking periods. The y-coordinate of the center of the Gaussian curve was the horizontal position of the saccade endpoint, and the x-coordinate of the center of the Gaussian curve was the time of saccade offset. The heat map for one participant was obtained by summing up all Gaussians together. The heat map for one population was constructed as the intersubject average of the individual heat maps. Saccades were tagged as predictive if they ended at least 200 ms after target blanking whereas earlier saccades were tagged as visually guided because they were likely triggered before target blanking (Orban de Xivry et al. 2009).

An analysis of the interaction between saccades and pursuit was also performed. To do so, both the saccadic eye displacement (SAD, sum of predictive saccade amplitudes) and smooth eye displacement (SED, integral of smooth eye velocity during the blanking) were obtained and normalized by the target displacement during the blanking. The relationship between SAD and SED was quantified by the slope of the linear fit between the two variables (using the function "robustfit" in Matlab).

For the statistical analyses, data were collapsed across directions because none of the studied parameters were influenced by the direction of target motion. ANOVA was performed on intrasubject mean of the different parameters with group as between-subject factor and velocity as within-subject factors. Tukey's post hoc test was used to evaluate one-to-one differences. Statistical analyses were performed with Statistica (Statsoft, Tulsa, OK).

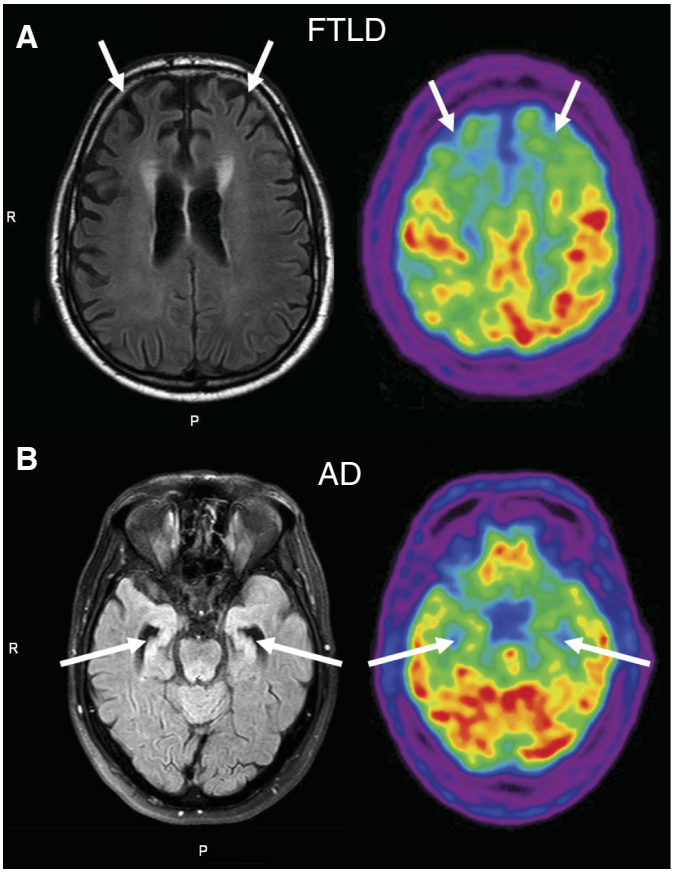

Fig. 1. Typical brain imaging of FTLD and AD patients. Magnetic resonance imaging and functional imagery (F-18 FDG PET scan) of one typical frontotemporal lobar degeneration (FTLD) patient, with frontal lobes impairment (*A*, *patient FTLD5*), and of one typical Alzheimer's disease (AD) patient, with medial temporal lobe impairment (*B*, *patient AD9*).

RESULTS

Visually guided and predictive smooth pursuit. In control trials (target continuously visible), the performance of the smooth pursuit response was comparable across groups (Fig. 3*A*, dashed traces). This indicates that visually guided pursuit was normal in FTLD and AD patients in early course of the disease compared with age-matched control subjects [ANOVA: main effect of group on visually guided smooth pursuit gain: $F(2,36) = 0.81$, $P = 0.57$]. In test trials, when the target was blanked, subjects continued to track the target with the same eye velocity for another 100 ms before it decreased exponentially towards a plateau level. During the first three test trials of each block (early test trials), eye velocity continued to decay slowly until 100 ms after target reappearance, i.e., when visual feedback of target motion became available and elicited a visually guided reacceleration (Fig. 3*A*, solid traces). In these trials, subjects from all groups exhibited a similar behavior.

In the late test trials (all test trials except the first three, i.e., periods P2 to P4), the decay in eye velocity was similar to the one observed during the early trials for all groups. However, 200 ms before target reappearance, subjects from the CTRL and AD groups increased their eye velocity and exhibited a positive predictive reacceleration (Fig. 3*B*, blue and green traces, respectively). In contrast, FTLD patients failed to reaccelerate predictively (Fig. 3*B*, red trace). Rather, eye reacceleration was prompted by the visual feedback of the target after its reappearance, similarly to what happened in the early trials (~100 ms after target reappearance).

Oculomotor performance was quantified by the measure of pursuit gain 500 ms into the blanking period to assess the decay in eye velocity and by the eye acceleration at the end of the blanking period to assess the predictive reacceleration. The between-group differences were analyzed over the course of the block (periods P1 to P4, see MATERIALS AND METHODS) and for the late trials only (P2 to P4 merged together).

As illustrated in Fig. 4, pursuit gain 500 ms into the blanking period was very similar across groups [Fig. 4*A*; ANOVA, main effect of group: $F(2,144) = 1.27$, $P = 0.38$] and did not evolve over the course of the blocks [ANOVA, main effect of period: $F(3,144) = 0.29$, $P = 0.83$]. Moreover, there was no between-group difference in residual velocity when it was measured from 400 to 600 ms. Comparison of the individual data from all subjects (Fig. 4*B*) revealed that the residual pursuit gain was quite variable across subjects but had a similar range for all three groups {Fig. 4*B*: CTRL: [0.31, 0.87]; FTLD: [0.33, 0.87]; AD: [0.26, 0.86]; ANOVA, main effect of group: $F(2,36) = 0.17$, $P = 0.85$}.

In contrast, the evolution of the predictive reacceleration from P1 to P4 differed across the populations [Fig. 4*C*, ANOVA, groups by periods interaction: $F(6,144) = 4.6$, $P = 0.00027$]. This interaction was observed for the three different target velocities separately [ANOVA, groups by periods interaction: 10°/s: $F(6,144) = 3.6$, $P = 0.0021$; 15°/s: $F(6,144) = 6.2$, $P < 0.00001$; 20°/s: $F(6,144) = 4.5$, $P = 0.0003$]. Initially, as noted in Fig. 3*A*, the acceleration around the time of target reappearance was negative (no evidence of predictive reacceleration for P1) and similar across groups [ANOVA, $F(2,36) = 0.97$, $P = 0.39$]. However, this acceleration became positive from P1 to P2 for the CTRL and AD groups (P1 vs. P2 Tukey's post hoc: CTRL: $P = 0.000018$; AD: $P = 0.000023$) but not for the FTLD group ($P = 0.99$). For the controls and AD patients, this predictive reacceleration did not improve further and was maintained until the end of the block. For the FTLD group, the acceleration around the time of target reappearance never became positive, even at the end of the blocks. Therefore, during late trials, predictive reacceleration was significantly higher in CTRL and AD groups than in the FTLD group [ANOVA, $t(26)=23.7$, $P < 0.00001$; and $t(22)=10.8$, $P = 0.003$]. This effect is significant for each target velocity separately (10°/s: $P < 0.00001$ and $P = 0.005$; 15°/s: $P < 0.00001$ and $P < 0.00001$; and 20°/s: $P < 0.00001$ and $P = 0.00003$).

Interindividual variability of reacceleration during all late trials was very low within groups (Fig. 4*D*). All subjects from the control group ($n = 15$) exhibited a positive reacceleration around the time of target reappearance. Only one from the AD group ($n = 11$) did not (*patient AD2*). Moreover, the excluded control subject and AD patient also showed a predictive reacceleration. In contrast, only two of the FTLD patients ($n = 13$) showed signs of predictive reacceleration (*patients FTLD6* and *FTLD2*). The excluded FTLD patient did not reaccelerate predictively. There was no difference in predictive reacceleration between the three FTLD subgroups.

Given the very small overlap in predictive reacceleration across groups, the absence of predictive reacceleration could be considered as a potential biomarker for FTLD. This biomarker has a sensitivity of 85% (=11/13). Its specificity between CTRL and FTLD is 100% (=15/15) and between AD and FTLD is ~91% (10/11). Sensitivity and specificity mea-

Table 2. *Neuropsychological results for all patients*

Patients	MMSE	Da MM	Da NP	Den, %	Se Fl	Ph Fl	Clock (/8)	CER (/11)	Luria (/32)	TMT Ti (B-A)	TMT Er (B-A)	Doors (/24)	RL/RI16 Sum of 3 Trials (/48)	RL/RI16 Delayed Recall (/16)
FTLD1	27	5	5	0.47	11	83	6	10	30	45	0	21	15	5
FTLD2	28	0	0	0.68	19	7	7	11	26	50	0	17	17	6
FTLD3	24	2	2	0.85	7	6	7	10	27	87	0	15	25	12
FTLD4	28	1	1	0.93	31	12	3	9	20.5	58	0	18	23	10
FTLD5	29	0	0	0.82	29	15	7	9	23	108	3	16	30	14
FTLD6	21	3	3	0.13	10	3	7	11	31	41	0	17	9	2
FTLD7	27	0	11	0.86	15	5	6	10	/	/	/	/	/	/
FTLD8	22	0	7	0.84	19	20	5	9	20	344	6	16	26	10
FTLD9	27	2	2	0.66	8	4	3	9	19	90	1	8	16	6
FTLD10	28	5	5	0.79	21	5	7	10	27	204	4	12	24	12
FTLD11	24	0	0	0.34	8	4	1	7	6	285	6	13	20	7
FTLD12	24	4	4	0.84	28	14	7	8	25	59	0	5	8	2
FTLD13	30	3	3	0.9	27	14	8	10	29	51	0	21	22	5
AD1	27	4	4	0.91	20	21	6	10	31	56	1	12	10	6
AD2	24	2	2	0.92	25	19	8	11	30.5	37	0	12	5	3
AD3	26	3	15	0.89	21	22	8	10	31	62	0	12	6	2
AD4	22	6	6	0.92	25	13	5	10	28.5	88	1	13	3	1
AD5	28	2	30	0.85	18	20	7	6	19.5	95	1	11	6	3
AD6	28	0	20	0.81	14	7	8	10	22.5	261	5	12	9	2
AD7	23	5	5	0.88	28	17	5	9	15	402	7	9	3	0
AD8	27	9	9	0.78	22	9	7	9	21.5	42	1	7	13	5
AD9	27	1	12	0.84	29	12	8	11	16.5	69	2	16	10	5
AD10	25	0	16	0.94	36	17	7	9	27.5	85	0	14	13	2
AD11	24	4	4	0.80	24	21	5	8	20.5	209	0	17	8	2
MEAN FTLD	25.9	1.9	3.3	**0.70**	17.7	**9.5**	5.7	9.4	23.7	118	1.7	14.9	**18.8**	**7.6**
MEAN AD	25.5	3.3	11	**0.87**	24.4	**16.2**	6.7	9.4	25.7	125	1.6	12.3	**7.8**	**2.7**

MMSE, Mini Mental State Examination (/30); Da MMSE, number of months between MMSE and eye recording; Da NP, number of months between neuropsychological examination and eye recording; Den, Denomination task (2 variants of the task: /64 for individuals older than 60 years and /80 for younger individuals. Performance is reported as percentage of correct response); Se Fl, Semantic Fluency (number of animals in 2 min); Ph Fl, Phonemic Fluency (number of P-words in 2 min); Clock, Clock Test (/8); CER, Praxis part of CERAD battery (drawing 4 simple shapes; /11); LURIA, variant of "Luria's graphical or alternating sequences test" (/32); TMT Ti, Trail-Making Test Time (Time of Part B – Time of Part A); TMT Er, Trail-Making Test Errors (number of errors in Part B – number of errors in Part A); Doors, sum of the 2 sets of 12 doors (/24); RL/RI16, French adaptation of Grober and Buschke (1987) task with 3 learning trials of 16 items including a support at encoding phase by semantic category cueing. Among the different scores available we considered free recall 1–3 (/48) and free recall after 20 min (last column, /16). Underlined results are considered pathological (results inferior to 2 standard deviations away from healthy controls mean, weighted by age and education of each patient). Numbers in parenthesis represent maximum possible score for each test when relevant. Patient FTLD7 did not conclude all tests. The 2 last lines show mean results for FTLD group and for AD group. Bold indicates significant difference between the 2 groups (ANOVA with Tukey post hoc, $P < 0.05$).

sures are improved if the subjects that were excluded because of low visually guided pursuit gain are included in the analysis. Sensitivity becomes 86% (12/14). Specificity between CTRL and FTLD remains at 100%. Specificity between AD and FTLD increases to 92% (11/12). In contrast, the neuropsychological data did not separate FTLD patients from AD patients as accurately as the predictive reacceleration (Table 2). As expected, AD patients were in general more amnesic but less impaired at language tests than FTLD patients. However, the variability across patients was quite high. In addition, the executive tests were comparable across the two groups of patients.

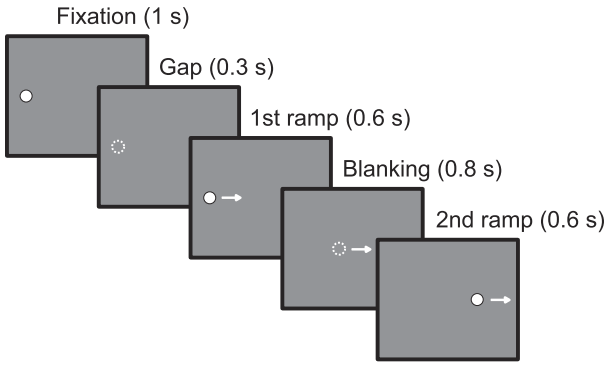

Fig. 2. Test trials used in the experiments. A yellow target was projected on a black screen. After one second, a 300-ms gap period preceded target motion onset. Then, target moved at a constant velocity for 2 s. Target was visible the first 600 ms and then was blanked for 800 ms (test trials). Target was visible again the last 600 ms of the trial. Target velocity (10, 15, or 20°/s) and direction (from *left* to *right*, as illustrated, or from *right* to *left*) were randomly chosen in the beginning of a block, and were kept constant into the block.

Predictive smooth pursuit before target motion onset. The absence of predictive reacceleration in the FTLD group could be due either to the inability to elicit any predictive action or to the inability to know when the target will reappear. Indeed, in absence of timing information, no predictive reacceleration is observed (Orban de Xivry et al. 2008). In the present experiment, predictive mechanisms could also be observed during the 300-ms gap period that took place immediately before target motion onset. In this case, the extinction of the fixation cue elicited anticipatory smooth eye movements in the absence of visual motion signals. On average, smooth eye velocity reached 21% of target velocity by the time of target motion onset. This percentage did not differ across the groups [ANOVA, $F(2,36) = 0.15$, $P = 0.86$]. Therefore, the ability to elicit predictive smooth pursuit before target motion was comparable across groups.

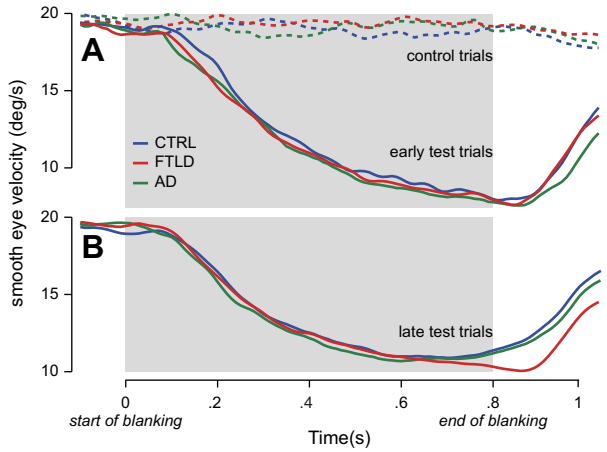

Fig. 3. Average smooth pursuit velocity of FTLD patients (red traces), of AD patients (green traces), and of control (CTRL) subjects (blue traces). *A*: eye velocity profiles for the control (dashed traces) and early test trials (solid traces; first three trials of each block). *B*: eye velocity profile for the late test trials, i.e., all test trials except the first three. Grey area represents the blanking period for the test trials. Darker areas represent the periods where the residual pursuit gain and the predictive reacceleration were measured for the test trials. Target was moving rightward at 20°/s.

Predictive saccades. The absence of predictive reacceleration for FTLD patients could be explained by a difference in strategy. Indeed, rather than tracking the target during the blanking period, FTLD patients could focus on the position of the target at its reappearance. Following this assumption, saccade endpoints should differ across the groups by being closer to the position of the target at its reappearance for the FTLD group. However, a difference in saccade endpoint was not observed (Fig. 5). In Fig. 5, eye positions at the end of the saccades are represented in function of time with the red color corresponding to places where saccade endpoints were often observed and the blue colored areas representing places where very few saccades landed. Most predictive saccades landed ahead of the target (red colored areas are located above the white line). Importantly, this feature was present for all three groups and the distribution of predictive saccades did not differ across the groups (Fig. 5). For instance, position error was similar across the three groups at the end of the first and second predictive saccades [ANOVA, first saccade: $F(2,36) = 0.82$, $P = 0.49$; second saccade: $F(2,36) = 1.03$, $P = 0.59$]. Therefore, the strategy appeared comparable across groups.

Interaction between saccades and pursuit. During blanking of the target, the amplitude of the saccades is adjusted to the level of the eye velocity decay on a trial-to-trial basis (e.g., Fig. 6*A*). A difference in modulation of the saccadic amplitude by the smooth pursuit performance across populations would highlight a deficit in internal representation of target motion as this modulation depends on where the target is during the blanking period. This modulation is revealed by the strong correlation between the SED (how much smooth pursuit moved the eyes) and the SAD (how much the saccades moved the eyes) during the blanking period (see MATERIALS AND METHODS). The SED is predominantly determined by the eye velocity decay and not by the predictive reacceleration, which happened too late to largely influence the smooth eye displacement. The correlation between SED and SAD is illustrated for a typical FTLD patient in Fig. 6*A*. This plot shows that the intertrial variability of the smooth eye displacement during the blanking was quite high (variability along the *x*-axis) but that the saccades largely compensated for this variability. Indeed, in trials during which the smooth eye displacement was small, saccadic displacement was large (Fig. 6*A*, *point*

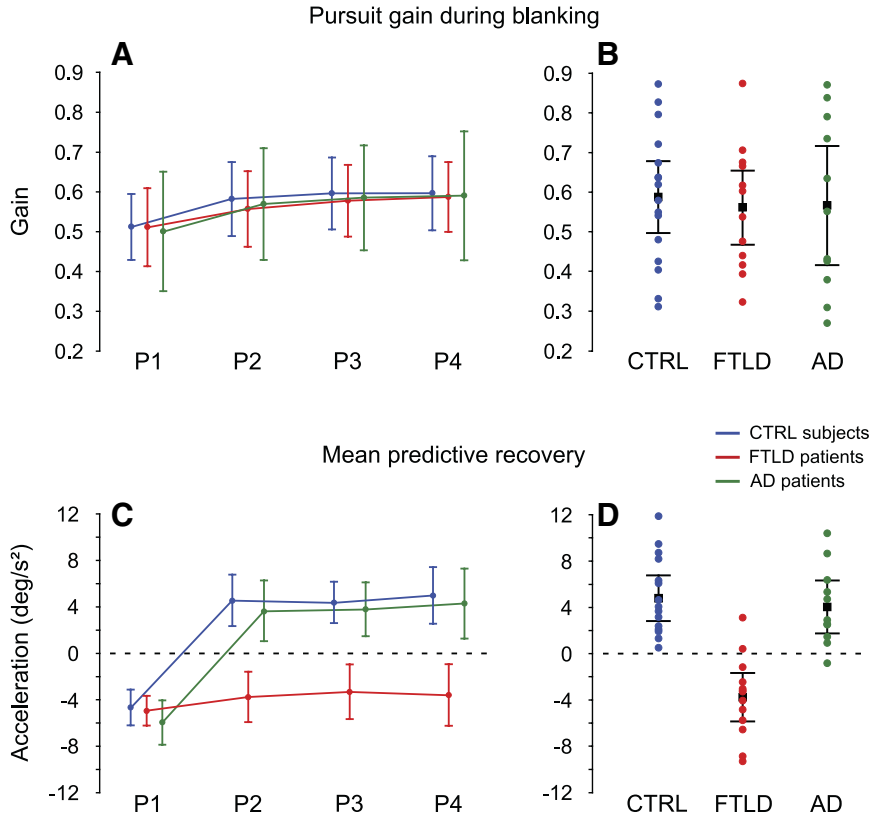

Fig. 4. Predictive behavior analysis. *A*: evolution of the residual pursuit gain during blanking through trials for FTLD patients (red traces), CTRL subjects (blue traces), and AD patients (green traces) within the blocks (P1 to P4). *B*: residual pursuit gain during blanking for the "late trials" (P2 to P4). All patients and subjects are represented separately with a dot. *C*: evolution of the predictive reacceleration within the blocks for the three groups. *D*: predictive reacceleration for the three groups and individual subjects. In *B* and *D*, each point represents the average for one subject across the three target velocities. Spreads represent the 95% confidence intervals.

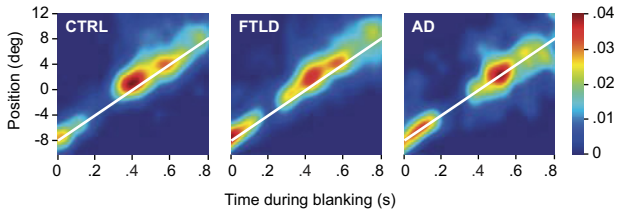

Fig. 5. "Heat map" of the position of the saccade endpoints versus time during the blanking of the target (0ms corresponds to target blanking onset). *A*: CTRL subjects; *B*: FTLD patients; *C*: AD patients. White lines represent target position. Color scales represent the probability that a saccade triggered during the blanking period lands on a point. Target velocity was 20°/s.

1). In contrast, when the smooth eye displacement was large, the saccadic displacement was reduced (Fig. 6*A*, *point 2*). In both cases, the synergy between saccades and pursuit allowed the eyes to be close to the target at its reappearance (target position corresponds to the dashed trace). To quantify the synergy between saccades and pursuit, the slope of the linear fit performed on the SED-SAD relationship (solid trace) was used. Perfect synergy would correspond to a slope of −1. In the experiment, the synergy between saccades and pursuit did not differ across groups [Fig. 6*B*; ANOVA, $F(2,36) = 0.56$, $P = 0.57$] and did not differ from the ideal slope for each group separately (*t*-tests, CTRL: $P = 0.84$; FTLD: $P = 0.23$; AD: $P = 0.4$).

DISCUSSION

In the present study, the smooth pursuit response of mild FTLD patients during a visually guided and a predictive tracking task was compared with the performance of control subjects and mild AD patients. All groups had normal visually guided pursuit responses. During the blanking, eye velocity dropped in all groups to a "plateau level." After some practice, eye velocity increased before target reappearance in control subjects and AD patients but failed to recover predictively in FTLD patients. All other measures of oculomotor performance during the blanking period were similar across the groups. For instance, the ability to elicit anticipatory action before target motion onset and to maintain an accurate internal representation of target motion during the blanking was comparable across groups. These results suggest that subtle and specific oculomotor deficiencies are present in the early course of FTLD. This impairment in predictive reacceleration is a potential biomarker of early stage of FTLD, which can help the clinician in the early differential diagnosis between neurodegenerative disorders. This also highlights the role of the frontal lobes in prediction.

What FTLD tells us about the smooth pursuit system. Primate studies have suggested that the FEF could play a critical role in the maintenance of the internal representation of target motion during a blanking period (Barborica and Ferrera 2003, 2004; Xiao et al. 2007), in the gain control mechanisms of visually guided pursuit (Tanaka and Lisberger 2001, 2002), and in the timing representation during smooth pursuit (Schoppik et al. 2008; Li and Lisberger 2011).

The present results suggest that mild degeneration of the frontal lobes affects the timing function first. Indeed, while FTLD patients had an impaired predictive reacceleration, their dynamic internal representation of target motion was not impaired, as assessed either by the endpoint of predictive saccades or by the synergy between saccades and pursuit during the blanking periods. Neither was there an impairment of the gain control mechanism as assessed by the gain of visually guided pursuit.

However, the ability of eliciting anticipatory eye movements was still present in FTLD patients as they were able to elicit them before target motion onset (i.e., during the initial gap period). In this case, the disappearance of the fixation point could act as a "go signal" for all subjects, which could help them to anticipate target motion onset. In contrast, the long blanking period with the absence of go cue prevented them to reaccelerate predictively.

Interestingly enough, this impairment is not present in mild AD patients, which reflects the particular involvement of the frontal lobes in predictive reacceleration. Indeed, frontal lobes are deteriorated early in the degeneration process in FTLD patients but are relatively spared during the early stages of the AD (Nelson et al. 2009; Aries et al. 2010; Vemuri et al. 2011). To the best of our knowledge, the importance of the frontal lobes for the timing of predictive behavior has not been demonstrated previously, neither in human nor in animal studies.

The FEF and SEF might have a predominant role in eliciting predictive reacceleration at the appropriate time for the four following reasons. First, they are involved in timing representation during smooth pursuit eye movements (Schoppik et al. 2008). Second, neural learning emerges in FEF during an oculomotor task that involves learning the timing of a change in target direction (Li and Lisberger 2011). Third, the timing of anticipatory pursuit is reflected in SEF neurons (de Hemptinne et al. 2008). Finally, the observed deficit in predictive reacceleration in mild FTLD can be associated with the early impairment of both FEF and SEF in FTLD (Broe et al. 2003).

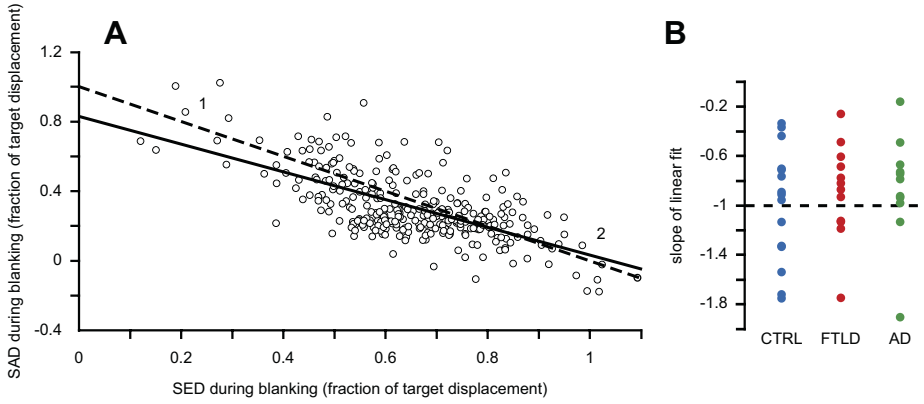

Fig. 6. Saccade-pursuit interactions. *A*: saccadic eye displacement (SAD) during blanking vs. smooth pursuit eye displacement (SED) during blanking, for a typical FTLD patient (*patient FTLD5*). These displacements were normalized by the target displacement during blanking. Each dot represents one trial. All trials are displayed, merging all velocities and directions together. Continuous line represents the linear fit and has a slope of −0.89. Dashed line represents the optimal compensation, with slope equal to −1. *B*: mean slope of the linear fits for individual subjects. Each point represents the average for one subject across the three target velocities.

Alternatively, the absence of predictive reacceleration might also reflect a network disruption rather than damage to a specific brain area. Changes in connectivity among brain areas occur early in neurodegenerative disorders (Seeley et al. 2009; Pievani et al. 2011). In FTLD, this connectivity change is especially marked in the frontal lobes in FTLD patients (Zhou et al. 2010). Predictive smooth pursuit relies on the connectivity between frontal areas more heavily during target blanking than during visually guided tracking (Ding et al. 2009). Therefore, this reliance on brain connectivity might explain why FTLD results in a subtle deficit, different from those seen in focal lesions (Morrow and Sharpe 1995; Heide et al. 1996; Lekwuwa and Barnes 1996). However, it is surprising that the interaction between the saccadic and pursuit systems was not strongly affected given that it probably also relies on the interaction between several areas (Krauzlis 2004, 2005; Orban de Xivry and Lefèvre 2007).

The observed deficit might be linked to general time estimation impairment in frontal lobe patients. Indeed, the frontal lobes have been involved in several timing tasks (Lewis and Miall 2003a; Buhusi and Meck 2005; Koch et al. 2009). For instance, patients with frontal lesions are impaired in time estimation (Harrington et al. 1998; Mimura et al. 2000; Koch et al. 2002). However, this deficit is predominant for tasks in the range of seconds but not at the millisecond time scale (Mangels et al. 1998; Jones et al. 2004). Likewise, a timing deficit has been reported in one FTLD patient with time interval in the range of seconds (Wiener and Coslett 2008). Moreover, AD patients also exhibit some deficits in time estimation tasks (Caselli et al. 2009; Rueda and Schmitter-Edgecombe 2009), even at the millisecond time scale. The existence of different timing mechanisms for automatic and cognitively controlled tasks (Lewis and Miall 2003b) might explain why AD patients are impaired in cognitively controlled estimation tasks but not in automatically controlled tasks (our task).

What predictive smooth pursuit tells us about FTLD. FTLD patients are difficult to differentiate from AD patients in the early stages of the disease (Hampel et al. 2010; Hu et al. 2011; Shaw et al. 2007). The diagnosis criteria of FTLD should be supported by brain imaging (Piguet et al. 2011), which is the case for every FTLD and AD patients included in the present study. Indeed, classical executive tests used in clinic are not always able to distinguish the groups at an early stage. In the present study, even the executive tests used (Luria and TMT, see MATERIALS AND METHODS) do not show differences between the groups. Indeed, the aphasic subgroup of FTLD (6 patients) is not supposed to be impaired for this kind of test and not all behavioral FTD patients show deficits on formal executive tests at an early stage. In some cases, the executive impairment is purely behavioral, especially when the lesions are localized in the inferior and medial part of the frontal lobes (Gregory et al. 1999). Conversely, some mild AD patients may show deficits on tests such as Luria and TMT for different reasons, including incipient visuo-spatial deficits and forgetting the wording. In contrast, our task was very sensitive to subtle deficits present in early stage FTLD patients.

Based on predictive smooth pursuit measurements, we differentiated FTLD patients from AD patients and controls. All of the 15 controls and 10 out of 11 of the mild AD patients exhibited a predictive reacceleration before target reappearance while only 2 out of the 13 FTLD patients were able to do so. This dramatic impairment of mild FTLD patients on a very particular aspect of a smooth pursuit task compared with healthy controls and mild AD patients highlights the potential of this oculomotor task to isolate a cheap and efficient biomarker for FTLD.

Finally, it is important to highlight that the deficit of predictive acceleration is present in a very early phase of the FTLD when the usual measures of smooth pursuit are still normal. This contrasts with earlier studies (Boxer et al. 2006; Garbutt et al. 2008) with later stage FTLD patients (disease duration of 60 vs. 30 mo in this study) who already had impaired visually guided smooth pursuit and with patients with focal lesions in the frontal lobes (Morrow and Sharpe 1995; Heide et al. 1996; Lekwuwa and Barnes 1996). Longitudinal follow-up will need to evaluate whether the gain of the visually guided smooth pursuit or any other characteristics of the oculomotor performance could be used to assess the stage of FTLD.

GRANTS

This work was supported by the Fonds National de la Recherche Scientifique, Fondation pour la Recherche Scientifique Médicale, Belgian Program on Interuniversity Attraction Poles initiated by the Belgian Federal Science Policy Office, Actions de Recherche Concertées (French community, Belgium), an internal research grant (Fonds Spéciaux de Recherche) of the Université Catholique de Louvain, and European Space Agency of the European Union. J.-J. Orban de Xivry is supported by the Brains Back to Brussels Program from the Brussels Region (Belgium).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: S.C., J.-J.O.d.X., D.Y., A.I., and P.L. conception and design of research; S.C. performed experiments; S.C. and J.-J.O.d.X. analyzed data; S.C., J.-J.O.d.X., D.Y., A.I., and P.L. interpreted results of experiments; S.C. and J.-J.O.d.X. prepared figures; S.C. and J.-J.O.d.X. drafted manuscript; S.C., J.-J.O.d.X., D.Y., A.I., and P.L. edited and revised manuscript; S.C., J.-J.O.d.X., and P.L. approved final version of manuscript.

REFERENCES

Aries MJH, Le Bastard N, Debruyne H, Van Buggenhout M, Nagels G, De Deyn PP, Engelborghs S. Relation between frontal lobe symptoms and dementia severity within and across diagnostic dementia categories. *Intern J Geriatr Psychiatry* 25: 1186–1195, 2010.

Baddeley A, Emslie H, Nimmo-Smith I. *Doors and People Test*. Bury St Edmunds, UK: Thames Valley Test Comp., 1994.

Bak TH, Hodges JR. Motor neurone disease, dementia and aphasia: coincidence, co-occurrence or continuum? *J Neurol* 248: 260–270, 2001.

Barborica A, Ferrera VP. Estimating invisible target speed from neuronal activity in monkey frontal eye field. *Nat Neurosci* 6: 66–74, 2003.

Barborica A, Ferrera VP. Modification of saccades evoked by stimulation of frontal eye field during invisible target tracking. *J Neurosci* 24: 3260–3267, 2004.

Barnes GR. Cognitive processes involved in smooth pursuit eye movements. *Brain Cogn* 68: 309–326, 2008.

Barnes GR, Asselman PT. The mechanism of prediction in human smooth pursuit eye movements. *J Physiol* 439: 439–461, 1991.

Barnes GR, Asselman PT. Pursuit of intermittently illuminated moving targets in the human. *J Physiol* 445: 617–637, 1992.

Barnes GR, Donnelly S, Eason RD. Predictive velocity estimation in the pursuit reflex response to pseudo-random and step displacement stimuli in man. *J Physiol* 389: 111–136, 1987.

Becker W, Fuchs AF. Prediction in the oculomotor system: smooth pursuit during transient disappearance of a visual target. *Exp Brain Res* 57: 562–575, 1985.

Bennett SJ, Barnes GR. Human ocular pursuit during the transient disappearance of a visual target. *J Neurophysiol* 90: 2504–2520, 2003.

Bennett SJ, Barnes GR. Predictive smooth ocular pursuit during the transient disappearance of a visual target. *J Neurophysiol* 92: 578–590, 2004.

Bennett SJ, Orban de Xivry JJ, Barnes GR, Lefèvre P. Target acceleration can be extracted and represented within the predictive drive to ocular pursuit. *J Neurophysiol* 98: 1405, 2007.

Bennett SJ, Orban de Xivry JJ, Lefèvre P, Barnes GR. Oculomotor prediction of accelerative target motion during occlusion: long-term and short-term effects. *Exp Brain Res* 204: 493–504, 2010.

Blakemore SJ, Wolpert D, Frith C. Why can't you tickle yourself? *Neuroreport* 11: R11–6, 2000.

Boman DK, Hotson JR. Stimulus conditions that enhance anticipatory slow eye movements. *Vision Res* 28: 1157–1165, 1988.

Boman DK, Hotson JR. Motion perception prominence alters anticipatory slow eye movements. *Exp Brain Res* 74: 555–562, 1989.

Boxer AL, Garbutt S, Rankin KP, Hellmuth J, Neuhaus J, Miller BL, Lisberger SG. Medial versus lateral frontal lobe contributions to voluntary saccade control as revealed by the study of patients with frontal lobe degeneration. *J Neurosci* 26: 6354–6363, 2006.

Boxer AL, Garbutt S, Seeley WW, Jafari A, Heuer HW, Mirsky J, Hellmuth J, Trojanowski JQ, Huang E, Dearmond S, Neuhaus J, Miller BL. Saccade abnormalities in autopsy-confirmed frontotemporal lobar degeneration and Alzheimer disease. *Arch Neurol* 69: 509–517, 2012.

Broe M, Hodges JR, Schofield E, Shepherd CE, Kril JJ, Halliday GM. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology* 60: 1005–11, 2003.

Buhusi CV, Meck WH. What makes us tick? Functional and neural mechanisms of interval timing. *Nat Rev Neurosci* 6: 755–765, 2005.

Burrell JR, Hornberger M, Carpenter RHS, Kiernan MC, Hodges JR. Saccadic abnormalities in frontotemporal dementia. *Neurology* 78: 1816–1823, 2012.

Carl JR, Gellman RS. Human smooth pursuit: stimulus-dependent responses. *J Neurophysiol* 57: 1446–1463, 1987.

Caselli L, Iaboli L, Nichelli P. Time estimation in mild Alzheimer's disease patients. *Behav Brain Funct* 5: 32, 2009.

Chen-Plotkin AS, Martinez-Lage M, Sleiman PMA, Hu WT, Greene R, Wood EM, Bing S, Grossman M, Schellenberg GD, Hatanpaa KJ, Weiner MF, White CL, Brooks WS, Halliday GM, Kril JJ, Gearing M, Beach TG, Graff-Radford NR, Dickson DW, Rademakers R, Boeve BF, Pickering-Brown SM, Snowden J, van Swieten JC, Heutink P, Seelaar H, Murrell JR, Ghetti B, Spina S, Grafman J, Kaye JA, Woltjer RL, Mesulam M, Bigio E, Lladó A, Miller BL, Alzualde A, Moreno F, Rohrer JD, Mackenzie IRA, Feldman HH, Hamilton RL, Cruts M, Engelborghs S, De Deyn PP, Van Broeckhoven C, Bird TD, Cairns NJ, Goate A, Frosch MP, Riederer PF, Bogdanovic N, Lee VMY, Trojanowski JQ, Van Deerlin VM. Genetic and clinical features of progranulin-associated frontotemporal lobar degeneration. *Arch Neurol* 68: 488–497, 2011.

Churchland MM, Chou IH, Lisberger SG. Evidence for object permanence in the smooth-pursuit eye movements of monkeys. *J Neurophysiol* 90: 2205–2218, 2003.

de Brouwer S, Missal M, Barnes GR, Lefèvre P. Quantitative analysis of catch-up saccades during sustained pursuit. *J Neurophysiol* 87: 1772–1780, 2002.

de Hemptinne C, Lefèvre P, Missal M. Neuronal bases of directional expectation and anticipatory pursuit. *J Neurosci* 28: 4298–4310, 2008.

de Partz M, Bilocq V, De Wilde V, Seron X, Pillon A. *LEXIS: Tests Pour l'Evaluation des Rroubles Lexicaux Chez la Personne Aphasique*. Marseille, France: Solal, 2001.

Ding J, Powell DK, Jiang Y. Dissociable frontal controls during visible and memory-guided eye-tracking of moving targets. *Hum Brain Mapp* 30: 3541–3552, 2009.

Flanagan JR, Wing AM. The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. *J Neurosci* 17: 1519–28, 1997.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198, 1975.

Gagnon D, Paus T, Grosbras MH, Pike GB, O'Driscoll GA. Transcranial magnetic stimulation of frontal oculomotor regions during smooth pursuit. *J Neurosci* 26: 458–466, 2006.

Garbutt S, Matlin A, Hellmuth J, Schenk AK, Johnson JK, Rosen H, Dean D, Kramer JH, Neuhaus J, Miller BL, Lisberger SG, Boxer AL. Oculomotor function in frontotemporal lobar degeneration, related disorders and Alzheimer's disease. *Brain* 131: 1268–1281, 2008.

Gregory CA, Serra-Mestres J, Hodges JR. Early diagnosis of the frontal variant of frontotemporal dementia: how sensitive are standard neuroimaging and neuropsychologic tests? *Neuropsychiatry Neuropsychol Behav Neurol* 12: 128–135, 1999.

Grober E, Buschke H. Genuine memory deficits in dementia. *Dev Neuropsychol* 3: 13–36, 1987.

Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, Herholz K, Bokde ALW, Jessen F, Hoessler YC, Sanhai WR, Zetterberg H, Woodcock J, Blennow K. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. *Nat Rev Drug Discov* 9: 560–574, 2010.

Harrington DL, Haaland KY, Knight RT. Cortical networks underlying mechanisms of time perception. *J Neurosci* 18: 1085–1095, 1998.

Heide W, Kurzidim K, Kömpf D. Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain* 119: 1951–1969, 1996.

Hu WT, Trojanowski JQ, Shaw LM. Biomarkers in frontotemporal lobar degenerations–progress and challenges. *Prog Neurobiol* 95: 636–648, 2011.

Jack CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 7: 257–262, 2011.

Jones CRG, Rosenkranz K, Rothwell JC, Jahanshahi M. The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation. *Exp Brain Res* 158: 366–372, 2004.

Koch G, Oliveri M, Caltagirone C. Neural networks engaged in milliseconds and seconds time processing: evidence from transcranial magnetic stimulation and patients with cortical or subcortical dysfunction. *Philos Trans R Soc Lond B Biol Sci* 364: 1907–1918, 2009.

Koch G, Oliveri M, Carlesimo GA, Caltagirone C. Selective deficit of time perception in a patient with right prefrontal cortex lesion. *Neurology* 59: 1658–1659, 2002.

Krauzlis RJ. Recasting the smooth pursuit eye movement system. *J Neurophysiol* 91: 591–603, 2004.

Krauzlis RJ. The control of voluntary eye movements: new perspectives. *Neuroscientist* 11: 124–137, 2005.

Kowler E. Eye movements: the past 25 years. *Vision Res* 51: 1457–1483, 2011.

Kowler E, Steinman RM. The effect of expectations on slow oculomotor control. I. Periodic target steps. *Vision Res* 19: 633–646, 1979a.

Kowler E, Steinman RM. The effect of expectations on slow oculomotor control. II. Single target displacements. *Vision Res* 19: 633–646, 1979b.

Kowler E, Steinman RM. The effect of expectations on slow oculomotor control-III. Guessing. *Vision Res* 21: 191–203, 1981.

Lekwuwa GU, Barnes GR. Cerebral control of eye movements. II. Timing of anticipatory eye movements, predictive pursuit and phase errors in focal cerebral lesions. *Brain* 119: 491–505, 1996.

Lencer R, Nagel M, Sprenger A, Zapf S, Erdmann C, Heide W, Binkofski F. Cortical mechanisms of smooth pursuit eye movements with target blanking. An fMRI study. *Eur J Neurosci* 19: 1430–6, 2004.

Lewis PA, Miall RC. Brain activation patterns during measurement of sub- and supra-second intervals. *Neuropsychologia* 41: 1583–1592, 2003a.

Lewis PA, Miall RC. Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. *Curr Opin Neurobiol* 13: 250–255, 2003b.

Li JX, Lisberger SG. Learned timing of motor behavior in the smooth eye movement region of the frontal eye fields. *Neuron* 69: 159–169, 2011.

Lillo P, Hodges JR. Frontotemporal dementia and motor neurone disease: overlapping clinic-pathological disorders. *J Clin Neurosci* 16: 1131–1135, 2009.

Lomen-Hoerth C, Anderson T, Miller BL. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 59: 1077–1079, 2002.

Mangels JA, Ivry RB, Shimizu N. Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. *Brain Res* 7: 15–39, 1998.

McKhann GM, Drachman D, Folstein MF, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-

ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34: 939–944, 1984.

Meyniel C, Rivaud-Pechoux S, Damier P, Gaymard B. Saccade impairments in patients with fronto-temporal dementia. *J Neurol Neurosurg Psychiatry* 76: 1581–1584, 2005.

Mimura M, Kinsbourne M, O'Connor M. Time estimation by patients with frontal lesions and by Korsakoff amnesics. *J Int Neuropsychol Soc* 6: 517–528, 2000.

Mitrani L, Dimitrov G. Pursuit eye movements of a disappearing moving target. *Vision Res* 18: 537–9, 1978.

Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull* 24: 641–652, 1988.

Morrow MJ, Sharpe JA. Deficits of smooth-pursuit eye movement after unilateral frontal lobe lesions. *Ann Neurol* 37: 443–451, 1995.

Nagel M, Sprenger A, Nitschke M, Zapf S, Heide W, Binkofski F, Lencer R. Different extraretinal neuronal mechanisms of smooth pursuit eye movements in schizophrenia: an fMRI study. *Neuroimage* 34: 300–309, 2007.

Nagel M, Sprenger A, Zapf S, Erdmann C, Kömpf D, Heide W, Binkofski F, Lencer R. Parametric modulation of cortical activation during smooth pursuit with and without target blanking an fMRI study. *Neuroimage* 29: 1319–1325, 2006.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert MS, Boone K, Miller BL, Cummings JL, Benson DF. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 51: 1546–1554, 1998.

Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. *J Neuropathol Exp Neurol* 68: 1–14, 2009.

Nyffeler T, Rivaud-Pechoux S, Wattiez N, Gaymard B. Involvement of the supplementary eye field in oculomotor predictive behavior. *J Cogn Neurosci* 20: 1583–1594, 2008.

Orban de Xivry JJ, Bennett SJ, Lefèvre P, Barnes GR. Evidence for synergy between saccades and smooth pursuit during transient target disappearance. *J Neurophysiol* 95: 418–427, 2006.

Orban de Xivry JJ, Missal M, Lefèvre P. A dynamic representation of target motion drives predictive smooth pursuit during target blanking. *J Vis* 8: 6.1–13, 2008.

Orban de Xivry JJ, Lefèvre P. Saccades and pursuit: two outcomes of a single sensorimotor process. *J Physiol* 584: 11–23, 2007.

Orban de Xivry JJ, Missal M, Lefèvre P. Smooth pursuit performance during target blanking does not influence the triggering of predictive saccades. *J Vis* 9: 7.1–16, 2009.

Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB. Functional network disruption in the degenerative dementias. *Lancet Neurol* 10: 829–843, 2011.

Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. *Lancet Neurol* 10: 162–172, 2011.

Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain Cogn* 18: 70–87, 1992.

Rueda AD, Schmitter-Edgecombe M. Time estimation abilities in mild cognitive impairment and Alzheimer's disease. *Neuropsychology* 23: 178–188, 2009.

Schmid A, Barnes GR, Rees G, Frith CD. An fMRI study of anticipation and learning of smooth pursuit eye movements in humans. *Neuroreport* 12: 1409–1414, 2001.

Schoppik D, Nagel KI, Lisberger SG. Cortical mechanisms of smooth eye movements revealed by dynamic covariations of neural and behavioral responses. *Neuron* 58: 248–260, 2008.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 62: 42–52, 2009.

Sharpe JA. Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. *Brain Cogn* 68: 241–254, 2008.

Shaw LM, Korecka M, Clark CM, Lee VMY, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov* 6: 295–303, 2007.

Tanaka M, Lisberger SG. Regulation of the gain of visually guided smooth-pursuit eye movements by frontal cortex. *Nature* 409: 191–194, 2001.

Tanaka M, Lisberger SG. Role of arcuate frontal cortex of monkeys in smooth pursuit eye movements. I. Basic response properties to retinal image motion and position. *J Neurophysiol* 87: 2684–2699, 2002.

Vandenberghe R, Van Laere K, Ivanoiu A, Salmon E, Bastin C, Triau E, Hasselbalch S, Law I, Andersen A, Korner A, Minthon L, Garraux G, Nelissen N, Bormans G, Buckley C, Owenius R, Thurfjell L, Farrar G, Brooks DJ. 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Ann Neurol* 68: 319–329, 2010.

Van der Linden M, Coyette F, Poitrenaud J, Kalafat M, Calicis F, Wyns C, Adam S. L'épreuve de rappel libre/rappel indicé à 16 items (RL/RI-16). In: *L'évaluation des Troubles de la Mémoire: Présentation de Quatre Tests de Mémoire Episodique (Avec Leur Etalonnage)*. Marseille, France: Solal, 2004, p. 25–47.

Vemuri P, Simon G, Kantarci K, Whitwell JL, Senjem ML, Przybelski SA, Gunter JL, Josephs KA, Knopman DS, Boeve BF, Ferman TJ, Dickson DW, Parisi JE, Petersen RC, Jack CR. Antemortem differential diagnosis of dementia pathology using structural MRI: Differential-STAND. *Neuroimage* 55: 522–531, 2011.

Wiener M, Coslett HB. Disruption of temporal processing in a subject with probable frontotemporal dementia. *Neuropsychologia* 46: 1927–1939, 2008.

Xiao Q, Barborica A, Ferrera VP. Modulation of visual responses in macaque frontal eye field during covert tracking of invisible targets. *Cereb Cortex* 17: 918–928, 2007.

Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner MW, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain* 133: 1352–1367, 2010.