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Frontotemporal dementia patients exhibit deficits in predictive saccades

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Abstract
Prediction and time estimation are all but required for motor function in everyday life. In the context of eye movements, for instance, they allow predictive saccades and eye re-acceleration in anticipation of a target re-appearance. While the neural pathways involved are not fully understood, it is known that the frontal lobe plays an important role. As such, neurological disorders that affect it, such as frontotemporal (FTD) dementia, are likely to induce deficits in such movements. In this work, we study the performances of frontotemporal dementia patients in an oculomotor task designed to elicit predictive saccades at different rates, and compare them to young and older adults. Clear deficits in the production of predictive saccades were found in patients, in particular when the time between saccades was short (~500 ms). Furthermore, one asymptomatic C9ORF72 mutation bearer showed patterns of oculomotor behavior similar to FTD patients. He exhibited FTD symptoms within 3 years post-measure, suggesting that an impairment of oculomotor function could be an early clinical sign. Taken together, these results argue in favor of a role of the frontal lobe in predictive movements timing over short timescales, and suggest that predictive saccades in FTD patients warrant further investigation to fully assess their potential as a diagnostic aid.

Keywords Saccade · Prediction · Time processing · FTD · Predictive saccade · Timing · Frontotemporal dementia · C9ORF72 · Eye movements

1 Introduction

Frontotemporal Dementia (FTD) is an umbrella clinical term that designates a heterogeneous and complex group of neurodegenerative disorders (Bang et al. 2015; Bigio 2013; Laforce 2013), typically encompassing two broad categories according to the clinical presentation: behavioral variant FTD (bvFTD; Laforce 2013; Rascovsky et al. 2011) presenting with a frontal syndrome, and primary progressive aphasia (PPA) presenting with a language impairment, itself divided

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into three variants (Gorno-Tempini et al. 2011): semantic (svPPA, also known as semantic dementia), nonfluent/agrammatic (naPPA, also known as progressive nonfluent aphasia) and logopenic (lvPPA).

FTD mainly affects the frontal and anterior temporal lobes, as well as some subcortical structures (Garibotto et al. 2011; Laforce 2013; Landin-Romero et al. 2017; Zhang et al. 2013), and there is wide overlap between these areas and the ones responsible for the control of eye movements (Anderson and MacAskill 2013; Antoniades and Kennard 2015; Leigh and Kennard 2004). As such, several studies investigated the eye movements of FTD patients (Boxer et al. 2006; Boxer et al. 2012; Coppe et al. 2012; Garbutt et al. 2008; Henley et al. 2014; Meyniel et al. 2005) and highlighted abnormalities among several FTDs (including Progressive Supranuclear Palsy, Cortico Basal Degeneration, FTDtau).

In one of these studies (Coppe et al. 2012), FTD patients were asked to track a target moving at a constant velocity. Following a gap period of 300 ms, the target started to move at a constant velocity for a few hundred milliseconds, then, on ~75% of the trials, was blanked during 800 ms. Such blanking typically causes a decrease of smooth pursuit gain, which can be maintained at a plateau if the target is expected to reappear (Madelain and Krauzlis 2003; Orban de Xivry et al. 2008). In healthy and AD participants, several repetitions of this task elicited predictive reacceleration before the end of the blanking, showing that they had learned the timing of reapparition. On the contrary, FTD patients were shown to make no predictive eye acceleration in the same situation. Still, during the 300 ms blank that preceded target onset, they were able to elicit normal predictive acceleration. This prompted the authors to suggest an impairment of time estimation in FTD patients.

In this study, we investigate prediction and implicit time estimation in a varied population of FTD patients using a different type of eye movement, saccades, which are easier to process and analyse in a clinical setting. When the direction, amplitude and timing of the next target step are fully known, a healthy subject typically generates predictive behaviors within a few target presentations (*i.e.* predictive saccades), thereby reducing latencies to 0 or below (Findlay 1981; Shelhamer and Joiner 2003).

Because these saccades involve pathways that overlap with predictive smooth pursuit and timing (Fukushima et al. 2013; Krauzlis 2004, 2005; Lee et al. 2016b; Lukasova et al. 2018; Orban de Xivry and Lefèvre 2007), the deficits exhibited by FTD patients in Coppe et al. (2012) might transfer to this task. Therefore, we designed a protocol in which the time between two target steps is constant within a trial (of several steps), and increases from 500 ms to 700 ms and to 900 ms across several trials. Our initial hypothesis was that FTD patients would exhibit low performance in trials for which the time between two steps is 900 ms, longer than the 800 ms of blanking in Coppe et al. (2012), better performance at 500 ms, with 700 ms falling somewhere in-between.

2 Methods

2.1 Participants

Twenty-three patients (12 female) having been diagnosed with a form of FTD at the Memory and Cognition Clinics of the Saint Luc University Hospital (13), Erasme University Hospital (7) and Brugmann Hospital (2) accepted to participate in this study. Their eye movements were recorded, and one patient was excluded because of excessive data loss, leaving 22 patients. Their ages ranged from 51yo to 83yo (avg. 68.7yo, sd. 7.36yo). Based on clinical assessment, neuropsychological tests (*cf.* Coppe et al. 2012), and brain imagery (MRI, F-18 FDG PET scanner, Tc-99 m HMPAO or ECD brain scintigraphy), the patients were diagnosed by expert clinicians (AI, JCB, and KS) as presenting either behavioral frontotemporal dementia (bvFTD, 16 patients) or primary progressive aphasia (PPA, 6 patients). For the diagnosis, the revised diagnostic criteria were applied (Gorno-Tempini et al. 2011; Rascovsky et al. 2011). The severity of the symptoms was appreciated by the clinicians as mild or below (12 patients), moderate (7 patients) and severe (3 patients). In addition, we also recruited two participants (47 and 71yo) exhibiting the C9ORF72 (Gijselinck et al. 2012; Renton et al. 2011) gene mutation responsible for a majority of genetic FTD cases (autosomal dominant inheritance pattern), but with no behavioral or clinical symptoms of FTD at the time of measure. As these two patients may have a preclinical frontal involvement they were considered as another asymptomatic FTD subgroup.

All patients but one were followed-up by the same neurologists that made the initial diagnosis, and reexamined to validate it. Morphological and functional imaging deficits of all patients were evaluated by the same neurologist without information on the oculomotor performances of specific patients.

Two control groups of young or elderly healthy adults were also recruited, and their eye movements recorded. The first group, hereafter denoted as the young adults (YA) group, was composed of 25 participants (8 female) and ranged in age between 22yo and 38yo (avg. 27.6yo, sd. 4.19yo). The second group, hereafter denoted as the older adults (OA) group, was composed of 26 participants (16 female), ranging in ages from 53yo to 75yo (avg. 64.1, sd. 13.6yo – *cf.* Fig. 1c).

The general cognitive performance of the OA group was evaluated using the MMSE test (Folstein et al. 1975), and a minimal score of 27 (over 30) was set for inclusion in the study. No one was excluded.

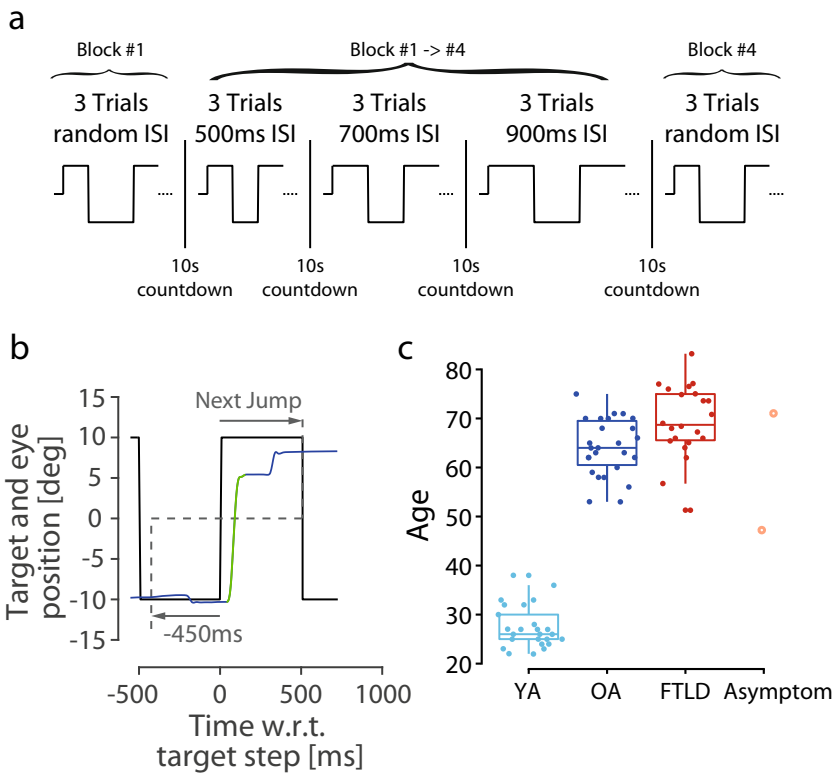

Fig. 1 Panel **a**: Overview of the protocol. Panel **b**: Criteria for valid saccades. The dashed lines indicate thresholds in time (vertical lines) and in space (horizontal lines). Panel **c**: Age Distribution

The procedures were approved by the Université catholique de Louvain Ethics Committee and in accordance with the Declaration of Helsinki. After full description of the experiment, participants gave informed consent before taking part in the experiment. For patients who assented to participating but lacked full capacity to consent, we received consent from a family member.

2.2 Behavioral testing

Participants were sat in a dark room, 151 cm from a 197 × 150 cm screen placed in front of them, spanning approximately 65° (horizontal) by 50° (vertical) of their visual field. Chin and forehead rests restrained their head movements. A cine8 Barco projector (Barco Inc., Kortrijk, Belgium) displayed stimuli at a refresh rate of 100 Hz while eye movements were recorded at 1000 Hz by an Eyelink 1000 (SR Research, Ottawa, Ontario, Canada). The display was handled by an in-house Matlab® (MathWorks®) toolbox, while Eyelink® interactions were handled by the Psychtoolbox (Kleiner et al. 2007).

Each trial began with an initial fixation, during which a yellow target dot (0.8° wide) was displayed in the center of the screen for a random duration between 500 and 1000 ms. After this, the target instantly jumped 10° to the left/right (pseudo-randomly distributed across blocks), then made 10 more 20° steps from one side of the screen to the other. The time between two steps (Inter Stimulus Interval - ISI) was either random (among 500, 700, 900, 1200 ms) – the random condition – or constant (among 500, 700, 900 ms) – the predictable condition – within a trial. Participants were instructed to keep looking at the displayed target to the best of their abilities.

Trials were always presented in groups of 3 with the same ISI condition (random/500/700/900). There were 4 blocks, which always contained the 3 × 3 trials of the predictable condition in the same ascending order (*cf.* Fig. 1a). In addition, the first block started with an additional 3 random trials, and, for 50 of the participants (~65%), another 3 random trials were included at the end of the last block. Calibration targets were presented at the start of every block.

Finally, there were mandatory breaks: after each trial, a countdown was displayed (5 s between trials, increased to 10 s every 3 trials) and the participants were instructed to stay still while resting their eyes by looking downward or blinking. After each block, participants were free to take a break. The duration of an experiment was around 12 min.

2.3 Data processing

Data were processed using Matlab® and R (R Core Team 2018). Missing values in the eye position data were considered blinks and removed (along with safety margins of up to the first local minimum of vertical eye movement on each side of the blink). Eye position signals were low-pass filtered at

48 Hz, and eye velocity and acceleration were obtained using a central difference algorithm on a ± 10 ms interval.

We detected saccade onsets and offsets by using a simple 500°/s^2 threshold on eye acceleration.

2.4 Criteria for saccades selection

To match participant's saccades with the relevant target steps, we used a few criteria (*cf.* Fig. 1b): 1) Saccade onset within 450 ms before the step, up to the next step (500–1200 ms after); 2) The saccade must cross the middle of the screen; 3) The amplitude must be at least 25% of the target step size. If several saccades met those criteria, the earliest saccade was chosen.

2.5 Saccade features

For each valid saccade, we computed its latency with respect to the associated target step, as defined by the time (in milliseconds) between the onset of the saccade and the target step. Saccades were categorized as predictive if their latency was lower than 80 ms (with respect to the target step), and reactive otherwise.

In addition, we computed peak velocity as the maximum eye velocity reached between the onset and the offset of the saccades. The gain of saccades was computed as the ratio between the amplitude of the saccade and the distance between the eye and the target towards which the saccade is headed (even if it has not appeared yet).

All further analyses were conducted on saccades from the 4th target step of each trial on, therefore setting aside the first 3, to ensure that participants had time to learn the current ISI.

2.6 Statistical analyses

In order to measure the ability of participants to anticipate target steps of different ISIs, we concentrated our analyses on saccades latency. Depending on participants or ISIs, reactive and predictive behaviors were present in different amounts. Therefore, the distribution of latencies was assumed non-normal, and potentially multi-modal. Given this, the typical performance of each participant was characterized by computing median latencies, using the Harrell-Davis method (Harrell and Davis 1982).

Group comparisons were made on individual medians, on the interquartile range, and on the differences between medians in the predictable and random trials, using robust trimmed-means t-tests and one-way ANOVA (factor group) or two way mixed-design ANOVAs (within factor ISI, between factor group) provided by the R package WRS2 (Mair and Wilcox 2018), using 20% trimmed means and 2000 bootstrap samples (Field and Wilcox 2017).

These tests compare central tendencies on the basis of 20% trimmed means (by removing 20% of data on each side of the median), which makes them more robust to most non-normality problems and outliers (Field and Wilcox 2017). The trimmed means t-test used was *yuenbt*, which uses a bootstrap procedure to sample each group with replacement nboot times and apply the t-test on each, then outputs a *p* value and a confidence interval based on the results, as well as the difference between the groups M_{diff}. The one-way ANOVA used was *t1waybt*, which uses a percentile-t bootstrap to perform a heteroscedastic one-way ANOVA to test the hypothesis of equal trimmed means. It outputs a F-value F_t, as well as a bootstrapped p value. Post-hoc corresponding to this anova are provided by *mcppb20*, which again performs a bootstrap to evaluate the hypothesis of equal trimmed means between 2 groups, outputting $\widehat{\psi}$, the difference between the groups, a 95% confidence interval, and a bootstrapped p value. Finally, the two-way mixed-design used the function *bwtrimbt* of the packages WRS2 and WRS (Wilcox 2017), which produce a F-value and bootstrapped *p*-values for each main and interaction effect.

Significant main effects and interactions were further explored using simple effect analyses based on robust t-tests, correcting p-values with the Holm-Bonferroni method to account for multiple comparisons.

Furthermore, we used linear discriminant analysis to build a linear classifier of OA and FTD participants, so as to predict the group to which asymptomatic participants are most likely to belong. For that, we used the function *lda*, from the R package MASS. The training variables were the corrected saccades latencies medians for each predictable ISI (difference between predictable and reactive conditions), as well as the overall percentage of predictive saccades.

Finally, we did not further investigate differences between sub-groups of patients (based on disease severity of sub-type of FTD), because of our relatively low number of patients and the absence of significant differences between them in preliminary analyses.

3 Results

Participants made saccades to track target steps grouped in trials of 11 steps, with either constant (predictable) or random ISIs (*cf.* Fig. 1a). The design encouraged predictive saccades in all predictable trials.

Eye position traces of a few representative participants are shown in Fig. 2 (random ISI not shown). As can be seen in Fig. 2a, the YA participant's saccades tended to closely match target steps, while the OA participant's saccades (panel B) had more variable and more anticipative saccade onsets. FTD patients (panel C and D) also exhibited more variability than YA

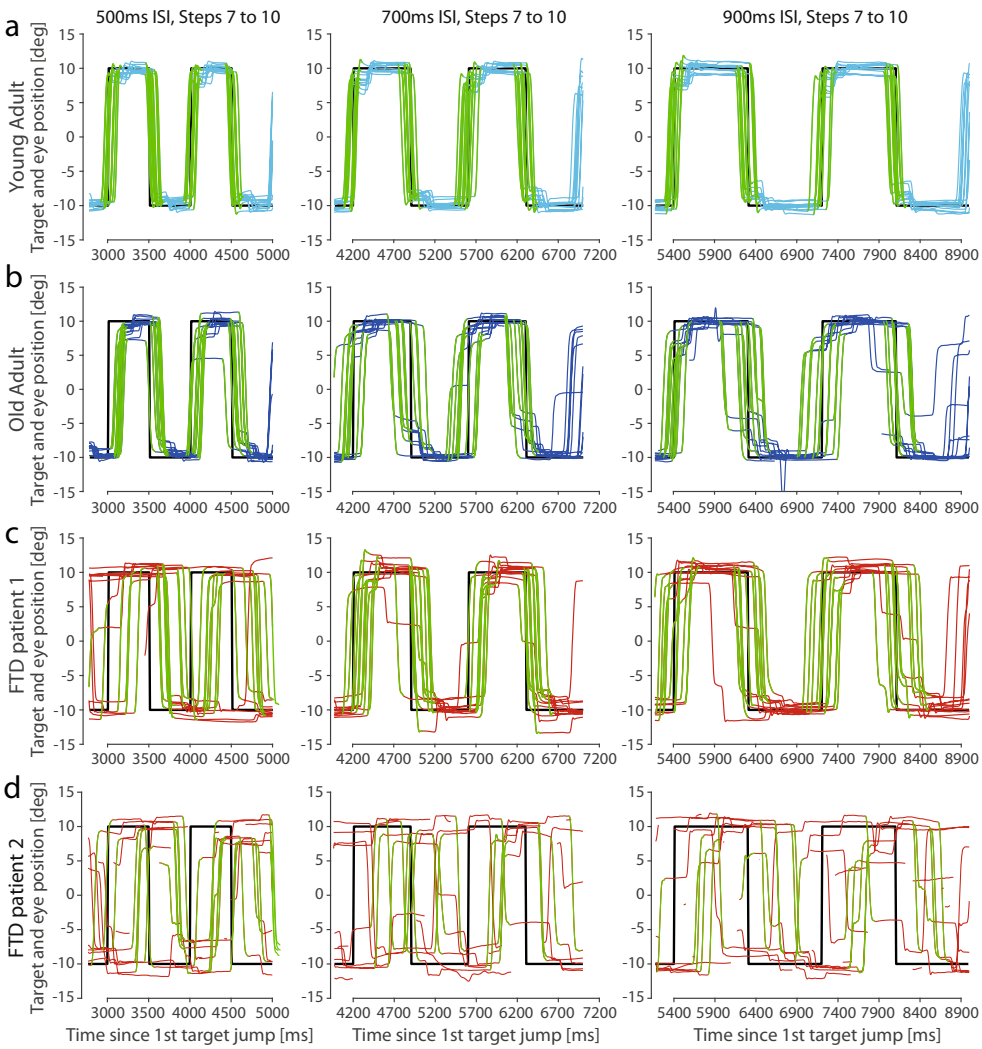

Fig. 2 Traces corresponding to steps 7 to 10 of predictable trials for typical participants from all groups, with FTD being represented by 2 such participants

in saccade latencies, but did not make as much predictive saccades as either YA or OA, in particular with an inter-stimulus interval of 500 ms. In addition, FTD patients sometimes failed to initiate saccades altogether. For some patients (such as the FTD patient 2 of Fig. 2c), this variability and reactive behavior were also seen at longer ISIs, with latencies reaching 500 milliseconds.

A broader view of the evolution of saccadic latencies within trials, allowing comparisons between groups and ISIs, is shown in Fig. 3. In trials of predictable ISIs, control participants exhibited a rapid decrease of saccadic latencies across target steps, typically going from reactive to predictive behavior within 1 to 3 steps (*cf.* 1st row and first 3 columns of the 2nd row of Fig. 6). In contrast, in trials of random ISIs (*cf.* "ISI random" in Fig. 6), this decrease in latency was much smaller and control participants made mainly reactive saccades with latencies over 80 ms, as well as a few predictive ones.

Overall, FTD patients exhibited much more difficulties to produce predictive saccades.

Some patients were able to perform the task, exhibiting similar patterns of a rapid decrease of latency across the first 3 steps of predictable ISIs. However, at all ISIs there were some patients unable to generate predictive saccades (grey dotted lines over the 80 ms threshold in Fig. 3), which was rarely observed in control groups. The 500 ms ISI was the most striking condition, as most of the FTD patients were unable to generate predictive saccades during it, to the extent that it appears almost undistinguishable from the random ISI condition. During random ISI trials, patients showed behavior similar to controls, although their between-subject variability appeared higher.

3.1 Group differences in saccade latencies during random ISIs trials

Unless otherwise specified, the saccades considered from this section onwards are saccades from the 4th target step onwards, to ensure that participants have had enough time to learn the current ISI.

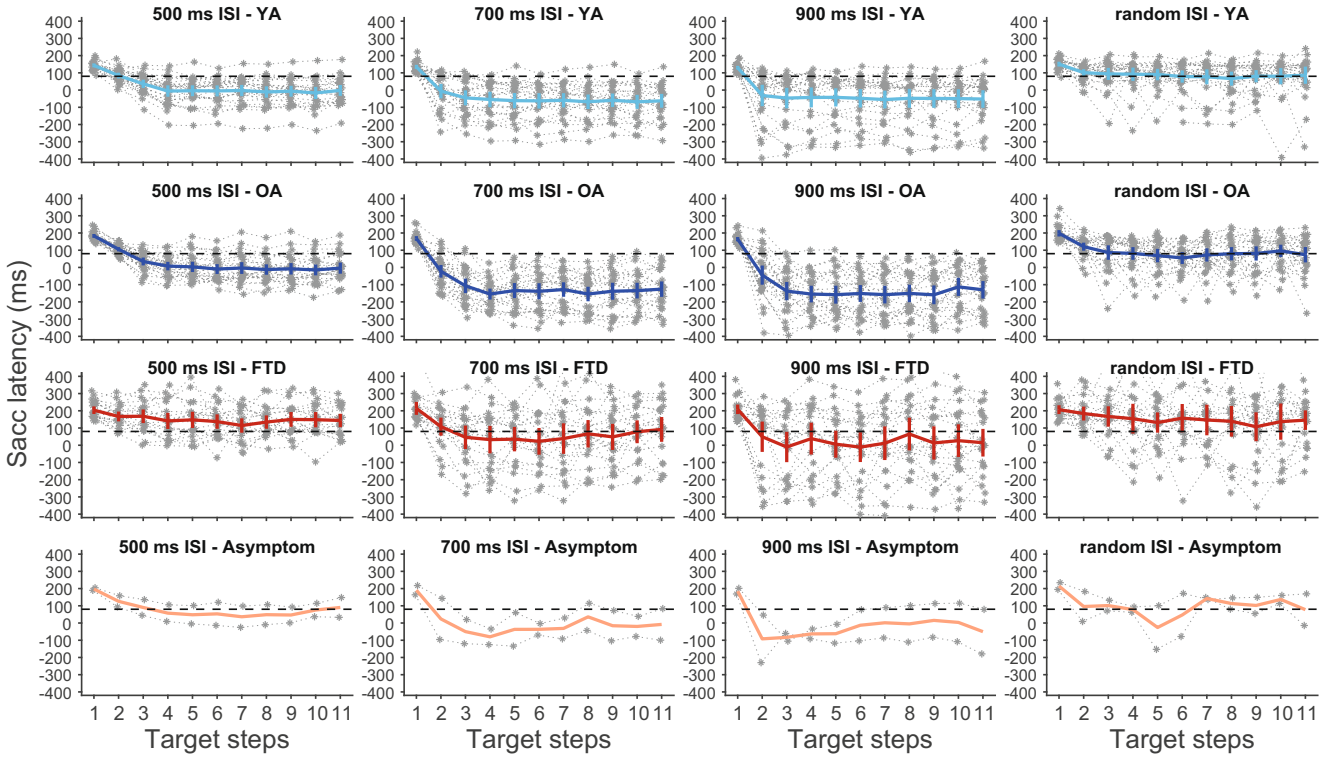

Fig. 3 Median latencies across target steps. Connected grey dots are individual medians across trials and blocks, and colored error bars show the median of individual medians. The dashed lines mark the prediction threshold at 80 ms

In random ISIs trials, since target steps were unpredictable, valid saccades tended to be reactive – although inter-individual variability was high (*cf.* Fig. 4). The 20% trimmed means of saccadic latencies were lowest for the YA group, followed by the OA and the FTD groups (*cf.* Table 1). Group-level comparisons of individual median latencies showed a

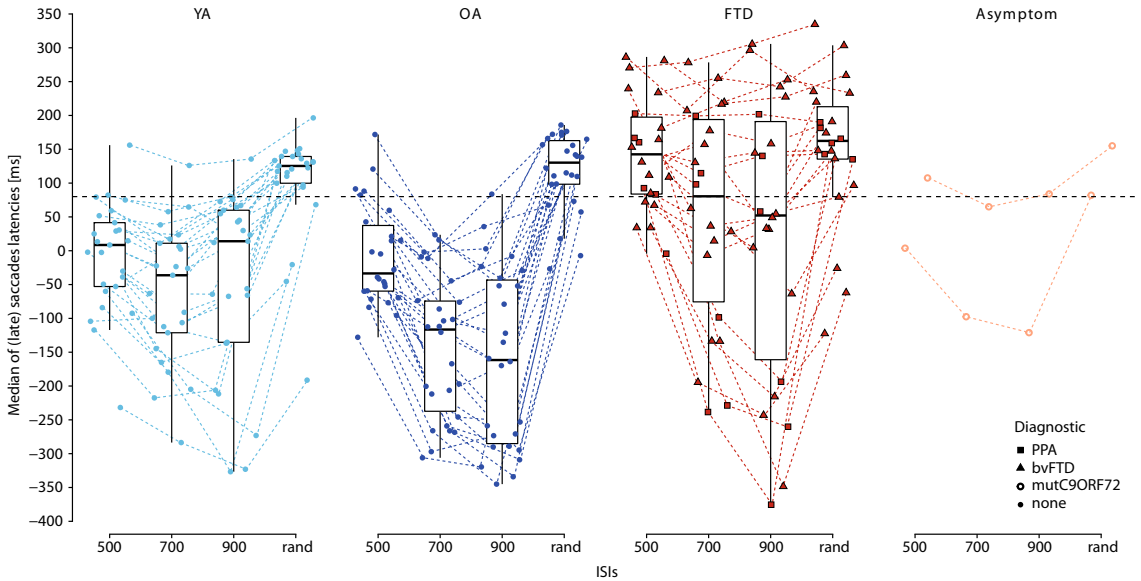

Fig. 4 Median latencies in predictable and random ISI conditions. Dots, square and triangles connected by dotted lines are individuals. The dashed line marks the prediction threshold at 80 ms. PPA: Progressive Primary Aphasia, bvFTD: behavioral variant of FTD. mutC9ORF72: asymptomatic carrier of the C9ORF72 mutation

significant difference between groups ($F_t(2,23.49) = 3.149$, $p_{boot} = .047$). However, simple effect tests could not highlight significant differences between pairs of groups: not between YA and OA ($\hat{\psi} = -7$ ms, CI = [−39.36,25.11], $p = .586$), or YA and FTD ($\hat{\psi} = -43.68$ ms, CI = [−86.59,15.73], $p = .061$), nor OA and FTD ($\hat{\psi} = -36.68$ ms, CI = [−82.73,30.34], $p = .115$).

3.2 FTD patients have higher latencies in shorter predictable ISIs

As shown in Fig. 4, median latencies in both control groups were well below 80 ms in all predictable ISIs. However, the FTD group had comparatively higher latencies, notably in the 500 ms ISI, in which 75% of patients had medians latencies over 80 ms.

Comparing the median latencies across groups and (predictable) ISIs showed significant main effects of group ($F(2,26.64) = 8.81$, $p = 0.0045$), ISI ($F(2,28.7) = 24.64$, $p < 0.0001$), and an interaction group x ISI ($F(4,26.61) = 6.03$, $p = 0.012$). Simple effect tests showed significant differences at the 500 ms ISI, between YA and FTD ($M_{diff} = -141.32$, CI = [−195.17, −87.48], $Y_t = -5.26$, $p_{corr} < 0.0001$), and between OA and FTD ($M_{diff} = -158.62$, CI = [−213.76, −103.45], $Y_t = -5.69$, $p_{corr} < 0.0001$); at the 700 ms ISI between the OA and FTD groups ($M_{diff} = -216.43$, CI = [−334.36, −98.49], $Y_t = -3.91$, $p_{corr} = 0.007$); and at the 900 ms ISI between YA and OA ($M_{diff} = -154.93$, CI = [59.76, 250.10], $Y_t = 3.35$, $p_{corr} = 0.021$).

3.3 FTD patients make less predictive saccades

Because of large differences in latencies between participants, as well as prior research suggesting overall higher latencies in FTD patients (Burrell et al. 2012), we compared the ability to generate predictive saccades using the difference between the predictable and random ISI conditions. As can be seen in Fig. 5, the FTD group had lower levels of differences compared to the control groups, meaning that, even accounting for higher latencies, patients made less predictive saccades.

Comparing these differential latencies confirmed significant main effects of group ($F(2,27.73) = 21.41$, $p < 0.0001$) and ISI ($F(2,33.85) = 33.78$, $p < 0.0001$), as well as a significant interaction group x ISI ($F(4,27.32) = 7.83$, $p = 0.0002$).

Post-hoc with robust t-tests showed significant differences between the OA and FTD groups at all ISIs ($p < .005$), while the differences between YA and FTD or OA were significant ($p < .005$) for all ISIs except for the differences between YA and OA at the 500 ms ISI ($M_{diff} = 21.89$, CI = [−21.46,65.23], $Y_t = 1.05$, $p_{corr} = 0.583$), and between YA and FTD at the 900 ms ISI ($M_{diff} = -22.54$, CI = [−87.3588, 42.2734], $Y_t = -0.664$, $p_{corr} = 0.583$).

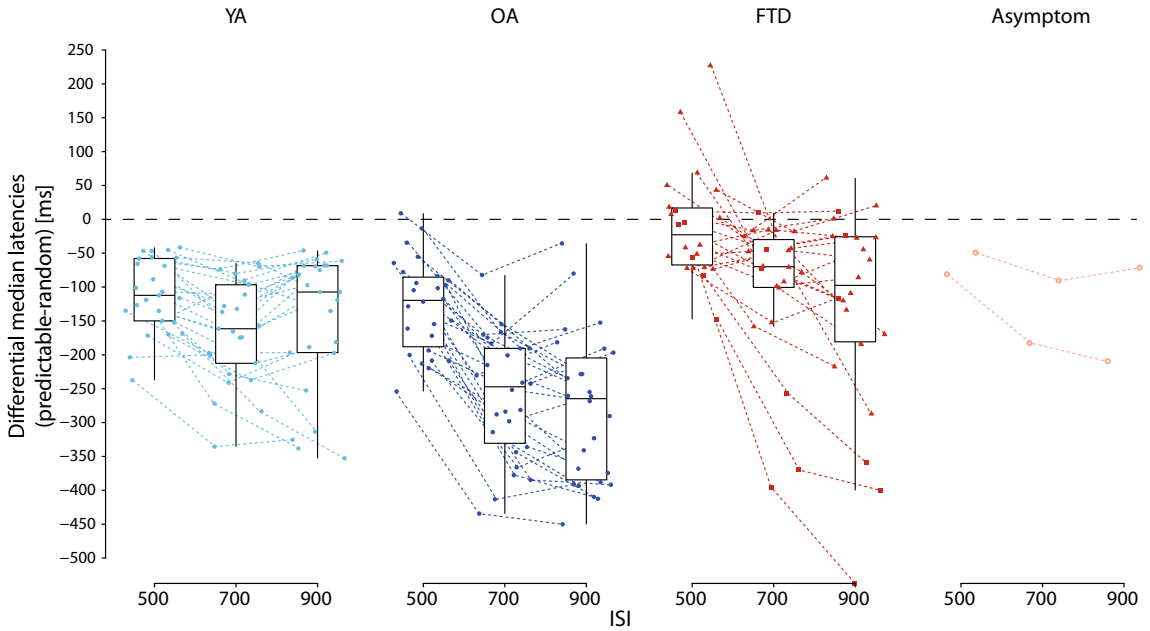

Fig. 5 Differences between median latencies in predictable and random ISI conditions. Connected dots, square and triangles are individuals

3.3.1 The variability of saccade latencies did not significantly differ between OA and FTD

We evaluated individual variability using interquartile ranges, for each predictable ISI, and compared groups using robust two way mixed-design ANOVA with group and ISI factors. This revealed main effects of group ($F(2,26.18) = 10.89$, $p = 0.0004$) and ISI ($F(2,23.55) = 57.66$, $p < 0.0001$), as well as an interaction group x ISI ($F(2,25.74) = 3.94$, $p = 0.0126$). The main effect of the group appeared to be mainly driven by the YA group, as post-hocs with robust t-tests only showed significant differences at the 900 ms ISI between YA and OA ($M_{diff} = -75.84$, CI = [−113.97, −37.7], $Y_t = -2.49$, $p_{corr} = 0.0045$), as well as between YA and FTD ($M_{diff} = -107$, CI = [−161.06, −52.94], $Y_t = -4.3$, $p_{corr} = 0.012$).

The same two-way mixed-design ANOVA, when limited to the OA and FTD groups, similarly found no group effect ($p > 0.1$) or interaction group x ISI ($p > 0.1$), although the main effect of ISI remained ($p < 0.0001$).

3.4 Rate of valid and predictive saccades was lower in FTD patients

In addition to their difficulties to produce predictive saccades, patients also made less valid saccades overall. In Fig. 6, we show the overall percentages of valid saccades (x-axis) and compare it to the percentages of valid saccades that were predictive (y-axis), for three different contexts. As can be seen at a glance, the rate of valid saccades was very high (>94%) in control groups for all contexts, while it was systematically lower in FTD patients. Table 1 gives a group overview of the data in Fig. 6.

This lack of valid saccades stemmed mainly from two of the selection criteria (*cf.* Methods): no saccade within latency thresholds, and no crossing of the center (which tended to overlap with the criterion on amplitude), in similar proportions.

As such, the higher rate of valid saccades of FTD patients in the first steps (Fig. 6a) is consistent with its lower amplitude (10°).

In the random ISI condition (Fig. 6b), both control groups had high levels of valid saccades, while FTD patients had significantly lower levels, with an average of 74.4% of valid saccades ($\chi^2(2) = 261.47$, $p < .0001$), with high inter-individual variability.

In the predictable ISI conditions (Fig. 6c), control participants had no trouble doing the task, with over 94% of valid saccades in both groups, and a strong tendency to make predictive saccades (>78%). Although individual variation was high, this was more difficult for FTD patients, with a group average of 70% of valid saccades ($\chi^2(2) = 2822$, $p < .0001$), and less predictive saccades (*cf.* Table 1 and Fig. 6).

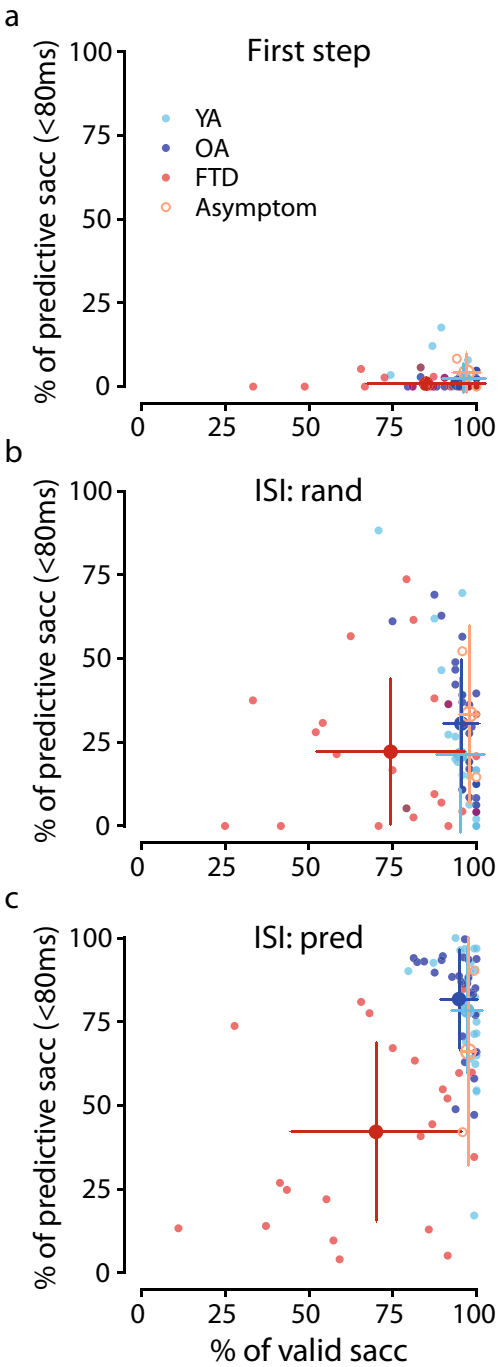

Fig. 6 Percentages of valid saccades (X-axis), and percentage of valid saccades that are predictive (Y-axis), for the first target steps (panel **a**), the random ISI steps (panel **b**), and the predictable ISI steps (panel C). Small dots are individuals, large dots averages across groups, and error bars indicate standard deviations

Table 1 Saccadic performance in different contexts. Percentages of valid saccades are relative to the total number of steps, while the percentage of predictive saccades is relative to the number of valid saccades

Group	Overall % valid Mean, [sd]	% predictive Mean, [sd]	Latency 20 trimmed mean, [95%CI]
First step			
YA	96.2%, [6.4]	2.5%, [4.4]	136.05 ms, [128.22, 143.89]
OA	94.4%, [6.6]	1.1%, [1.7]	169.85 ms, [161.15, 178.55]
FTD	84.9%, [17.7]	0.9%, [1.8]	190.64 ms, [165.03, 216.25]
Random ISI			
YA	95.3% [7.2]	21.2% [23.2]	123.58 ms, [111.64, 135.51]
OA	95.5% [5.3]	30.6% [19.2]	130.58 ms, [106.59, 154.56]
FTD	74.4% [22.1]	22.2% [21.8]	167.26 ms, [130.51, 204]
Predictable ISI			
YA	97.3%, [4.6]	78.3%, [18.9]	−20.8 ms, [−47.6, 6]
OA	94.8%, [5.6]	81.8%, [14.9]	−94.9 ms, [−132.4, −57.6]
FTD	70%, [25.3]	41.7%, [26.9]	104.7 ms, [68.9, 140.37]

In addition to these lower rates of valid saccades, FTD patients made significantly more blinks per second than OA ($M_{diff} = 0.082$, CI = [0.036, 0.128], $Y_t = 3.71$, $p_{corr} = 0.002$), with a 20% trimmed mean of 0.11 blinks per second [0.066, 0.15]. While most patients made less than 0.2 blinks per second, 4 of them made more, with averages of 0.34, 0.36, 0.4 and 0.68 (patients #18, 5, 2 and 12, *cf.* Suppl. Table 1).

All of the patients exhibiting overall percentages of valid saccades below 50% (3 patients: #7, 8 and 10 *cf.* Suppl. Table 1), or who blinked a lot (4 patients), were classified as 'moderate' or 'severe' on the disease severity scale.

3.5 Classification of 2 asymptomatic C9ORF72 mutation carriers

Because we only had access to 2 asymptomatic participants, it was not relevant to perform statistical comparisons between them and the other groups. Still, one of the two asymptomatic participants (A2) performed consistently outside of the group confidence interval of OA, and within the group CI of FTD patients (*cf.* Table 2, for two representative measures).

Furthermore, we decided to compare their performance by training a linear classifier on the OA and FTD groups (see Methods), bearing in mind that this analysis would not be generalizable beyond our data due to the small training sample and therefore lack of cross-validation.

The resulting classifier had an accuracy of 0.917 (95% CI = [0.800, 0.977]), a sensitivity of 0.864 and a specificity of 0.962 (with FTD being the positive class). The resulting posterior probabilities for the OA, FTD and asymptomatic participants are shown in Fig. 7. As can be seen, 1 OA and 3 FTD participants were misclassified, while one of the two asymptomatic participants (A2) was classified as FTD, with a posterior probability of 0.747. Furthermore, the 3 FTD patients classified as 'OA' by the algorithm were classified as 'mild' on the disease severity scale (patients n° 6, 21 and 22, *cf.* Suppl. Table 1).

4 Discussion

In this study, we show evidence that, as a group, FTD patients made significantly less predictive saccades than OA controls during a predictive saccade task. In a more reactive task, however, they exhibited moderately higher latencies (~40 ms) without the difference reaching significance.

Table 2 Comparison of saccadic performance of asymptomatic participants with the FTD and OA groups

Group	Overall % predictive 20% trimmed mean, 95% CI	Differential latency, 500 ms ISI 20% trimmed mean, 95% CI
FTD	17.02% [5.58, 28.46]	−22.43 ms [−57.79, 12.93]
OA	80.53% [73.56, 87.51]	−127.97 ms [−162.48, −93.46]
Asymptomatic		
A1	85.42%	20%trMean: −81.14 ms
A2	25.83%	20%trMean: −49.13 ms

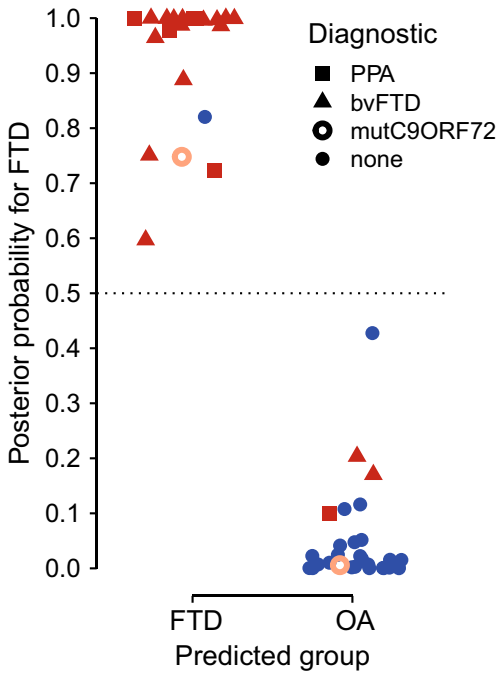

Fig. 7 Posterior probability of being FTD, and predicted group of the participants, based on a linear classifier. Color and shape give the actual group and the associated diagnostic, respectively

4.1 FTD patients exhibit deficits in predictive saccades

The lower rates of predictive saccades in FTD patients were linked to two main causes.

First, FTD patients struggled to initiate saccades on time and made more hypometric ones, resulting in fewer valid saccades. The lower rate of saccade initiation could be explained by a lack of engagement (apathy being a common symptom of FTD), attention deficits leading to increases in blink rate and duration (McIntire et al. 2014) but also lesions in the basal ganglia (Leigh and Kennard 2004; Stuphorn 2015), which can be present in FTD (Landin-Romero et al. 2017). Hypometric horizontal saccades have been previously documented in bvFTD and are related to contralateral lesions in the FEFs (Boxer et al. 2012; Douglass et al. 2018).

Second, as a group, FTD patients had significantly higher latencies than the OA group in the predictive task for the shorter ISIs, therefore making less predictive saccades. Even after accounting for individual differences in latencies, patients still differed from older controls by having significantly smaller differences between latencies in the predictive and reactive conditions. While the only study of predictive saccades in FTD, more specifically bvFTD, did not highlight such differences (Douglass et al. 2018), it tested an ISI of 1000 ms while we tested several sub-second ISIs, and involved younger participants.

The lesional patterns of the brain structures involved in eye movement control might explain the predictive saccades differences we highlighted. Cortical lesions in the FEF could explain both reactive latencies and saccade hypometry (Leigh and Kennard 2004), while lesions to the SEF or DLPFC would explain the reactive latencies without affecting saccade amplitude (Gaymard et al. 1998; Nyffeler et al. 2008; Pierrot-Deseilligny et al. 2003). In addition, impairments to subcortical timing-related areas, including the putamen and cerebellum (Hove et al. 2013; Lee et al. 2016b), have also been documented in FTD (Henley et al. 2014; Landin-Romero et al. 2017).

Still, while both subtypes (bvFTD and PPA) exhibited deficits, inter-individual variability was high, with some patients exhibiting normal behavior and others being unable to make predictive saccades. This might be due to the inherent variability of the localization of neurodegenerative lesions in FTD, the degree of brain damage in specific eye-movements related areas, or the presence of unknown subcategories within our population (such as their underlying neuropathology).

4.2 Is this a deficit in timing?

Our initial hypothesis stated that we expected an impairment in the timing of FTD patients, particularly for the longest ISIs.

Our results do not fully support this hypothesis, as, while some FTD patients exhibited timing impairment, it either did not increase with ISI or was worse at the shortest ISI. Furthermore, the variability of individuals latencies did not significantly differ between OA and FTD groups.

A first alternative hypothesis, unrelated to time processing, is that 500 ms is too short an interval for most FTD patients to elicit predictive saccades. While predictive saccades in the sub-second range are typically regarded as simple tasks, because they could be encoded as a rhythmic movement in the basal ganglia or the cerebellum (Lee et al. 2016a), such a behavior might first require processing in cortical areas. As such, FTD patients might come short because of an accumulation of small delays due to degeneration in prefrontal areas implicated in temporal processing and predictive saccades (Lewis and Miall 2003; Lukasova et al. 2018).

Our second hypothesis is directly related to the processing of time by the brain, which is a complex mechanism that is still not well understood (Merchant et al. 2013). Still, the existence of a centralized clock mechanism is now regarded as less probable than an intrinsic timing ability of cortical networks, at least for short intervals (Burr and Morrone 2006; Merchant et al. 2013). The sub-seconds predictable ISIs that were used in this study certainly fall under that category. As such, instead of an accumulation of delays suggested in the previous hypothesis, patients might exhibit small damage to the cortical sub-network responsible for the processing of timing, such that they are limited in their ability to measure small intervals of time, or that they consistently over-estimate it, causing them to initiate the saccade too late.

4.3 Older adults tend to anticipate more in longer ISI trials

There were significant differences in the saccadic behaviors of YA and OA. While their saccadic latencies did not differ in the random condition and in the 500 ms and 700 ms predictable ISIs, they significantly differed in their differential latencies (the difference between their latencies in the predictable and random condition) in the 700 ms and 900 ms ISIs. Looking at the differences between the predictable ISIs, it is apparent that OA exhibited more anticipative latencies with increasing ISIs, in a way consistent with a history effect of the first ISI on the next ones (Shelhamer and Joiner 2003).

Our interpretation is that OA relied more on their memory of the previous ISI timing, therefore initiating predictive saccades much earlier than necessary. This might be a strategy deployed by the participants in order to compensate limitations in their processing of time (Turgeon et al. 2016), their greater variability, or the symptoms of a greater weight given to memory rather than sensory inputs. In contrast, most of YA had latencies that were almost constant across predictable ISIs. As a consequence of these differences between OA and YA, FTD patients are more similar to YA at the 900 ms ISI, because at this ISI OA anticipate the step by around 150 ms, while YA are around 0 ms, approximately matching the FTD group latency.

4.4 Performance of C9ORF72 mutation carrier suggests preclinical deficit

The two asymptomatic participants carrying the C9ORF72 mutation exhibited qualitatively different behaviors in predictable trials. The younger of the two (A1) made predominantly predictive saccades at all predictable ISIs, while the older one (A2) made mostly reactive saccades. Furthermore, even when correcting for latency in the random condition, the latter's behavior appeared more similar to FTD patients than to the older controls, while the former was undistinguishable from the controls.

A more extensive comparison with the FTD and OA groups, using a linear classifier, reached similar conclusions by classifying A2 as FTD and A1 as OA. Incidentally, of those two participants, only A2 began exhibiting symptoms 3 years after his participation. While limited in scope by our small sample, this suggests that preclinical oculomotor deficits may exist in FTD, and that it could be worthwhile to regularly assess the oculomotor performance of C9ORF72 mutation carriers.

4.5 Limitations of the study

In this study, we did not have perfectly matched FTD and OA groups, with an average age difference of 4.6 years, which could affect the latency of the saccades (Irving et al. 2006). Furthermore, our sample of FTD patients was not sufficiently large for comparisons across subtypes. Finally, we did not know the underlying neuropathies of our FTD group, some of which might be more predisposed to some types of eye movement deficits than others (Boxer et al. 2012).

5 Conclusion

In conclusion, we show that FTD patients of both subtypes bvFTD and PPA exhibited difficulties to make predictive saccades. Furthermore, we found no positive correlation between the ISI duration and the prediction deficit, suggesting that this deficit is not a global impairment of time processing.

We believe that predictive saccades with sub-seconds ISIs, in particular around 500 ms, can be a promising tool to evaluate the integrity of reactive and predictive pathways in FTD and possibly provide diagnostic aid. Future studies could investigate larger populations of patients, and complement predictive saccades with real-time functional imagery to identify the brain structures involved in the deficits.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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