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Eye movement deficits in X-linked dystonia-parkinsonism are related to striatal degeneration

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ABSTRACT

Background: X-linked dystonia-parkinsonism (XDP) is characterized by the unique transition of dystonia to parkinsonism and striatal degeneration. Slowing of saccades on clinical examination has been taken as suggestive of a progressive supranuclear palsy (PSP) phenotype.
Objectives: To elucidate whether eye movement abnormalities in XDP patients reflect striatonigral impairment or deficits in the brainstem saccade generator as present in PSP.
Methods: Eye movements of 18 male XDP patients from the Philippines and 16 ethnically and age-matched, healthy control participants were analyzed and the results related to morphometric frontostriatal changes.
Results: There was moderate saccade hypometria in XDP but velocity of visually guided saccades was normal. XDP patients showed an increased antisaccade error rate which correlated with the reduction of (i) the volume of the pallidum and putamen as well as (ii) the volume and cortical thickness in dorsolateral prefrontal cortex. Amplitude of memory-guided saccades was smaller and latency prolonged. Horizontal smooth pursuit eye movements were impaired.
Conclusions: Oculomotor abnormalities in XDP resemble those of patients with the Parkinsonian type of multiple system atrophy and - to a lesser degree - Parkinson's disease, but are not compatible with PSP. They indicate striatal impairment and may represent preclinical signs of the parkinsonian stage of XDP. The increasing failure of response inhibition in the antisaccade task with increasing striatal atrophy may indicate an endophenotype for striatal degeneration. Dorsolateral prefrontal degeneration can be inferred from the failure in initiating antisaccades, prolonged latency of memory-guided saccades and the reduction of dorsolateral prefrontal volume and cortical thickness.

1. Introduction

X-linked dystonia-parkinsonism (XDP) is an inherited neurodegenerative adult-onset and progressive movement disorder characterized by the unique transition of rapidly generalizing dystonia and the development of parkinsonian features within a few years [1].

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Thereby it may serve as a basal ganglia model disease with the evolution of dystonia to parkinsonism in later disease stages due to a circumscribed striatal pathology. The disease is highly prevalent in a specific region in the Philippines (Panay Island) and affects worldwide approximately 1000 men. Neurodegeneration in XDP involves functional [2,3] and structural [4,5] decline of the striatum. Volume loss was found bilaterally in caudate nucleus, putamen and pallidum. In accordance with this finding,^{123}iodobenzamide (IBZM) single-photon emission computed tomography (SPECT) showed reduced post-synaptic tracer uptake in the caudate nucleus and putamen of symptomatic XDP patients [2] indicating deficient postsynaptic dopaminergic nigrostriatal pathways. Deficient post-synaptic dopaminergic transmission is also found in multi-system atrophy and progressive supranuclear palsy (PSP) in which eye movement abnormalities clearly differ from those in idiopathic Parkinson's disease (PD). In contrast to PD, the hallmark of PSP is slowing of saccades indicating a disorder of brainstem saccadic burst neurons.

Moreover, based on clinical-ophthalmological observations of XDP patients with slowing of saccades and a limited oculomotor range, a PSP-like syndrome has been suggested with presumed involvement of brainstem structures [6]. However, (i) eye movements in XDP have not yet been systematically recorded, and (ii) neuronal loss of brainstem neurons has never been described in histopathological *post-mortem* studies.

Parkinsonian syndromes can be distinguished from healthy controls by eye movement analysis, i.e. pro- and antisaccades as well as smooth pursuit eye movements (see below and Table 1) [7]. Therefore, one may expect eye movement abnormalities in XDP to resemble those of parkinsonian syndromes, e.g. in multiple system atrophy with predominant parkinsonism (MSA-P) based on striatal degeneration, or PD, based on the clinical phenotype in later stages of the disease. Both, multiple system atrophy (MSA) and XDP are associated with an imbalance of striosome and matrix functions [8]. Upon post mortem studies, the striosome is thought to be predominantly involved in the early, dystonic phase of XDP [5] whereas the opposite is the case in early MSA-P with predominant matrix pathology [9].

In XDP, degeneration of the striosomal compartment of the striatum is supposedly associated with decreased GABAergic inhibition of the substantia nigra (SN) in the dystonic phase of XDP. Hence, nigral disinhibition may give rise to subsequent activity changes of the striatum, thalamus [3] and colliculus superior (SC), a crucial structure in saccade generation [10].

Deficient dopaminergic nigro-striatal transmission, e.g. in Parkinson's disease, usually leads to interrupted smooth pursuit eye movements (SPEM), high distractability in anti-saccade tasks and saccade hypometria [7]. When compared with other Parkinsonian syndromes, PD patients show mild impairment of the suppression of visually guided saccades in the antisaccade task. Abnormal error rates in antisaccades have also been suggested to be a potential predictor of progression in PD [11] which has not been tested in XDP yet.

Table 1
Oculomotor performance in Parkinsonian syndromes + XDP.

Oculomotor system	Direction	Parameter	PD	PSP	MSA	XDP
Pro- saccades	Horizontal	Latency	=	= /↑	= /↑	=
		Gain	↓	↓	↓	↓
		Velocity	=	↓↓	=	=
	Vertical	Latency	=	= /↑	= /↑	↑
		Gain	↓	↓↓	↓	↓
		Velocity	=	↓↓	=	=
Anti-saccades	Horizontal	Error rate	= /↑	↑↑	=	↑
Smooth pursuit	Horizontal	Gain	↓	↓	↓	↓
	Vertical	Gain	↓	↓	↓	=

↓↓: strongly reduced; ↓: reduced; = : equal; ↑: increased; ↑↑: strongly increased. Assessment of PD, PSP and MSA according to Leigh and Zee [15, p. 918f] and XDP (this study).

The aims of this study were therefore to characterize eye movement behavior in XDP patients by quantitative recordings and to relate behavioral changes to volumetric abnormalities obtained by MR volumetry.

The following hypotheses were tested:

(1) The *PSP hypothesis* [6] states slowing of saccades implying brainstem involvement in XDP.
(2) The *PD hypothesis,* driven by the late clinical phenotype, predicts moderately deficient smooth pursuit eye movements and mild saccade hypometria but normal latency, as found in PD patients with deficient nigro-striatal transmission.
(3) The *striosome hypothesis* states early prevailing striosome degeneration and predicts insufficient control of competing voluntary and automatic saccadic behavior (e.g., suppression of erroneous pro-saccades).
(4) The *matrix hypothesis* predicts oculomotor abnormalities seen in MSA-P, i.e. deficient smooth pursuit eye movements with catch-up saccades, moderate saccade hypometria, frequent fixation instabilities, gaze evoked and positional nystagmus [12] due to matrix pathology already existing in the dystonic phase of XDP.

2. Methods

Methods are reported in short, for details see e-Supplement.

2.1. Participants

The study included 18 male XDP patients from the Philippines and 16 age- and ancestry-matched, mutation-negative healthy control participants (Table 2). Apart from a video-recorded neurological examination, XDP patients were rated using the motor part of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) for dystonic symptoms and the Unified Parkinson's Disease Rating Scale (UPDRS, Part III) for Parkinsonian motor symptoms, and the Mini Mental State Examination (MMSE) for global cognitive function.

Healthy participants did not show oculomotor abnormalities on clinical examination and had no history of neurological or psychiatric diseases including dementia.

2.2. Oculomotor tasks

The participants performed four different oculomotor tasks: 1) reflexive pro-saccades horizontally and vertically, 2) sinusoidal smooth pursuit and 3) anti-saccades. 4) Memory-guided saccades towards memorized target locations.

2.3. Imaging analysis

The T1-weighted images of the whole brain were acquired at a 3 T MR Scanner using a fast field echo (FFE) 3D MPRAGE sequence. Details of general imaging processing are given elsewhere [2,4] and in e-Supplement.

Table 2
Demographic data.

	Group	Mean (± 1 SD)	Range	p (*t*-test)
Age	Patients (N = 18)	40.2 (7.1)	30–52	> 0.1
	Healthy controls (N = 16, 11 male)	37.1 (6.9)	29–53	
BFMDRS	Patients	51.0 (21.6)	3.5–85.0	
UPDRS III	Patients	36.8 (15.3)	5.0–62.0	
MMSE	Patients	25.0 (3.2)	21–30	
Disease duration	Patients	3.1 (1.5)	1.0–6.0	

2.4. Statistical analysis

Statistical analyses were performed using general linear model (ANOVA) and Student's t-tests. If not stated otherwise, subsequently reported values are means (± 1 standard error of mean).

3. Results

3.1. Clinical assessment of eye movements

Upon clinical oculomotor examination, XDP patients did neither show saccadic intrusions on attempted fixation nor gaze-evoked nystagmus. Fourteen patients had blepharospasm (ranging from 0.5 to 6 points on the Burke-Fahn-Marsden-Dystonia Scale). There was no lid lag or lid retraction visible and blink rate appeared low but still normal (without task: 8–12 blinks/min). Vertical and horizontal oculomotor range was full. There was some vertical hypometria of upward saccades and a lower frequency of saccades when patients were asked to perform rapid refixations between two stationary visible targets but also during externally guided target displacements. However, clinically, there was no fragmented (multistep) saccade hypometria. In the anti-saccade test, patients showed an increased error rate. Saccade velocity appeared normal. Smooth pursuit eye movements were mildly cogwheel in the horizontal plane. All investigated patients exhibited cervical dystonia but there was no vertical misalignment of the eyes.

All patients were in the dystonic phase of the disease (suppl. video 1). Five patients showed additional signs of Parkinsonism, i.e. dystonia and Parkinsonism (XDP-DP, suppl. video 2) and one patient with a very short disease duration had mild Parkinsonism and may belong to a small subgroup (~5%) with primary parkinsonism. We analyzed all dependent variables, compared XDP-DP patients with purely dystonic XDP-D patients, and found no difference between the groups (p always > 0.57) in all of the variables. Consequently, we kept the patient group as one.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.10.016.

3.1.1. Fixation

There was no group-related difference in the saccadic intrusion rate (> 2°; controls: 3.5° ± 1.2°; XDP: 4.1° ± 1.8°; $p > 0.5$), i.e. square-wave jerks could be ruled out to be present in XDP. There was no gaze-evoked or positional nystagmus.

3.1.2. Saccades

3.1.2.1. Horizontal pro-saccades. The ANOVA on gain (accuracy) of horizontal pro-saccades revealed a main effect of target amplitude ($F(2, 27) = 35.49$, $p < 0.001$) and group differences ($F(1,28) = 4.86$, $p = 0.036$) but no main effects of target direction or other interactions. Consequently, z-values were computed and data were aggregated over target amplitude and direction. A T-test showed a significant difference between groups ($T(32) = 3.175$, $p = 0.004$, Fig. 1A). Analyzing the latency of saccades there was a main effect of target amplitude ($F(2, 27) = 53.82$, $p < 0.001$) but no other main effects, interactions or group differences (Fig. 1B). A T-test on z-values revealed no differences between groups ($T(32) = 1.32$, $p = 0.21$). Thus, horizontal saccades were smaller in XDP patients but had normal latency.

3.1.2.2. Vertical pro-saccades. The ANOVA on accuracy of vertical saccades (gain) showed a main effect of target amplitude ($F(2, 28) = 22.04$, $p < 0.001$), a main effect of direction (up vs. down, $F(1, 29) = 32.74$, $p < 0.001$), an interaction of target amplitude x direction ($F(2, 28) = 7.44$, $p = 0.002$) and group differences ($F(1, 29) = 5.92$, $p = 0.021$). z-values were computed and aggregated over target amplitude. A subsequent ANOVA showed a main effect for direction ($F(1, 31) = 30.03$, $p < 0.001$) but no interaction of direction x group ($p > 0.5$) or group differences ($p = 0.092$). Latency of saccades showed a main effect of target amplitude ($F(2, 28) = 13.40$, $p < 0.001$), a trend for an interaction of target amplitude x direction ($F(2, 28) = 3.53$, $p = 0.052$) and group differences ($F(1, 29) = 5.66$, $p = 0.024$). z-values of latency revealed no effect of direction ($p > 0.42$) but group differences ($F(1, 31) = 8.78$, $p = 0.006$) (Fig. 1B). Thus, vertical upward saccades were smaller in both groups compared to downward saccades but showed no significant group-related difference, despite a trend. Latency of vertical pro-saccades was larger in XDP patients.

3.1.3. Saccade peak velocity

For horizontal saccades, peak velocity did not differ between groups ($T(32) = 1.71$, $p = 0.097$, Fig. 1C). For vertical saccades (up/down) there was a main effect of direction ($F(1, 31) = 6.49$, $p = 0.016$, Fig. 1D) but no interaction of direction x group ($p > 0.8$) and no main effect of group ($p > 0.6$). Thus, the main sequence of both groups did not differ, i.e. there was no saccadic slowing.

3.1.4. Memory-guided saccades

Patients showed an increased latency of the first saccade (418.3 ms) compared to healthy participants (320.4 ms, $T(25) = 2.31$, $p = 0.029$). The initial saccade amplitude to memorized target location was significantly smaller in patients (0.37) compared to healthy participants (0.76, $T(25) = 3.74$, $p = 0.001$). There were no differences in unwanted reflexive saccades towards the flashed target location during the memorization phase ($p = 0.115$). The number of valid trials was non-significantly smaller in patients (43%) compared to healthy participants (65%, $p = 0.058$).

3.1.5. Smooth pursuit eye movements

Performance on smooth pursuit differed significantly between groups for horizontal movements ($F(1, 31) = 12.76$, $p = 0.001$) but not for vertical movements ($F(1, 31) = 1.78$, $p = 0.19$, Fig. 2A). Reduced velocity gain necessitated catch up-saccades to reach target velocity (Fig. 2B). We hardly found any anticipatory saccades which necessitated back up saccades.

3.1.6. Anti-saccades

Patients showed higher error rates (42.7% ± 5.4) in the anti-saccade paradigm compared to healthy subjects (24.2% ± 3.1; $T(28) = 2.95$, $p = 0.007$) (original recordings in Fig. 3A and B; group data in Fig. 3C).

3.2. Correlation of oculomotor and brain volumetric data with behavioral scores

Five XDP participants had to be excluded from the MRI analysis due to movement artefacts. Total volume of the putamen ($p < 0.0001$), caudate nucleus ($p < 0.0001$) and pallidum ($p < 0.003$) were smaller bilaterally (data from both sides pooled as there was no significant side difference), compared to healthy controls, as previously reported [2,4,13]. The anti-saccade error rate in XDP patients increased significantly with the reduction of total volume of the putamen bilaterally ($r = -.725$, $p = 0.008$; $df = 10$) and the pallidum ($r = -0.583$, $p = 0.037$; $df = 11$) (Fig. 3 D,E). There was an additional trend for a correlation of anti-saccade error rate with volume reduction of the caudate nucleus ($r = -0.534$, $p = 0.074$; $df = 10$).

Cortical thickness and volume were analyzed for the dorsolateral prefrontal cortex (DLPFC) to prove the *a-priori* hypothesis that the increased antisaccade error rate in XDP is related to deficient prefrontal inhibition on striatal neurons. As there were no significant differences across sides, data were pooled for both sides. Cortical thickness of the DLPFC was smaller in XDP patients compared to healthy controls (3.69 mm ± 0.11 mm vs. 3.28 mm ± 0.08 mm, $p < 0.0074$). The volume of the DLPFC showed a significant reduction of 9.7% in XDP

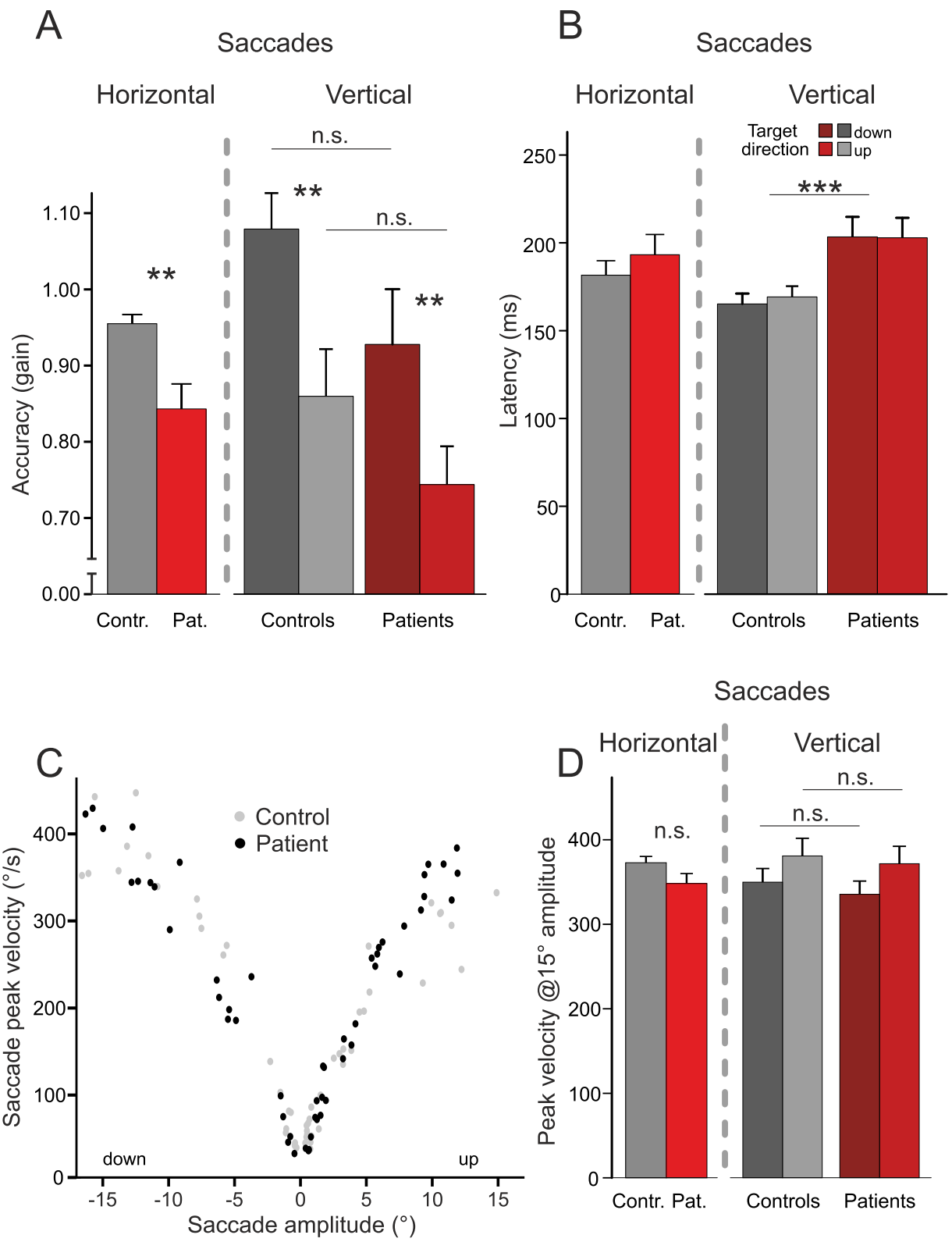

Fig. 1. Amplitude (A) gain (ratio of eye to target amplitude) and latency (B) of visually guided saccades are shown for horizontal and vertical saccades separately for XDP patients and healthy age-matched control subjects. XDP patients showed smaller horizontal saccade amplitude (hypometria) and prolonged latency for vertical saccades. (C) shows amplitude-velocity ratio (main sequence) of vertical saccades in a control subject and XDP patient. Main sequence of both horizontal and vertical saccades did not differ between groups (D). ** = $p < 0.01$, *** = $p < 0.001$.

($10.02\,cm^3 \pm 0.27$ vs. $11.10\,cm^3 \pm 0.32\,cm^3$ in controls, $p < 0.0188$). In contrast, there was no group-related difference in cortical thickness and volume in the cuneus which was taken as control region. The volume of the DLPFC (Fig. 3F) was negatively correlated with the antisaccade error rate (Pearson $r = -0.662$, $df = 10$, $p = 0.019$) but not with other oculomotor parameters. DLPFC volume reduction was not correlated with the volume in putamen ($r = 0.505$; $p = 0.0781$) or caudate nucleus ($r = 0.581$; $p = 0.0374$). Cortical

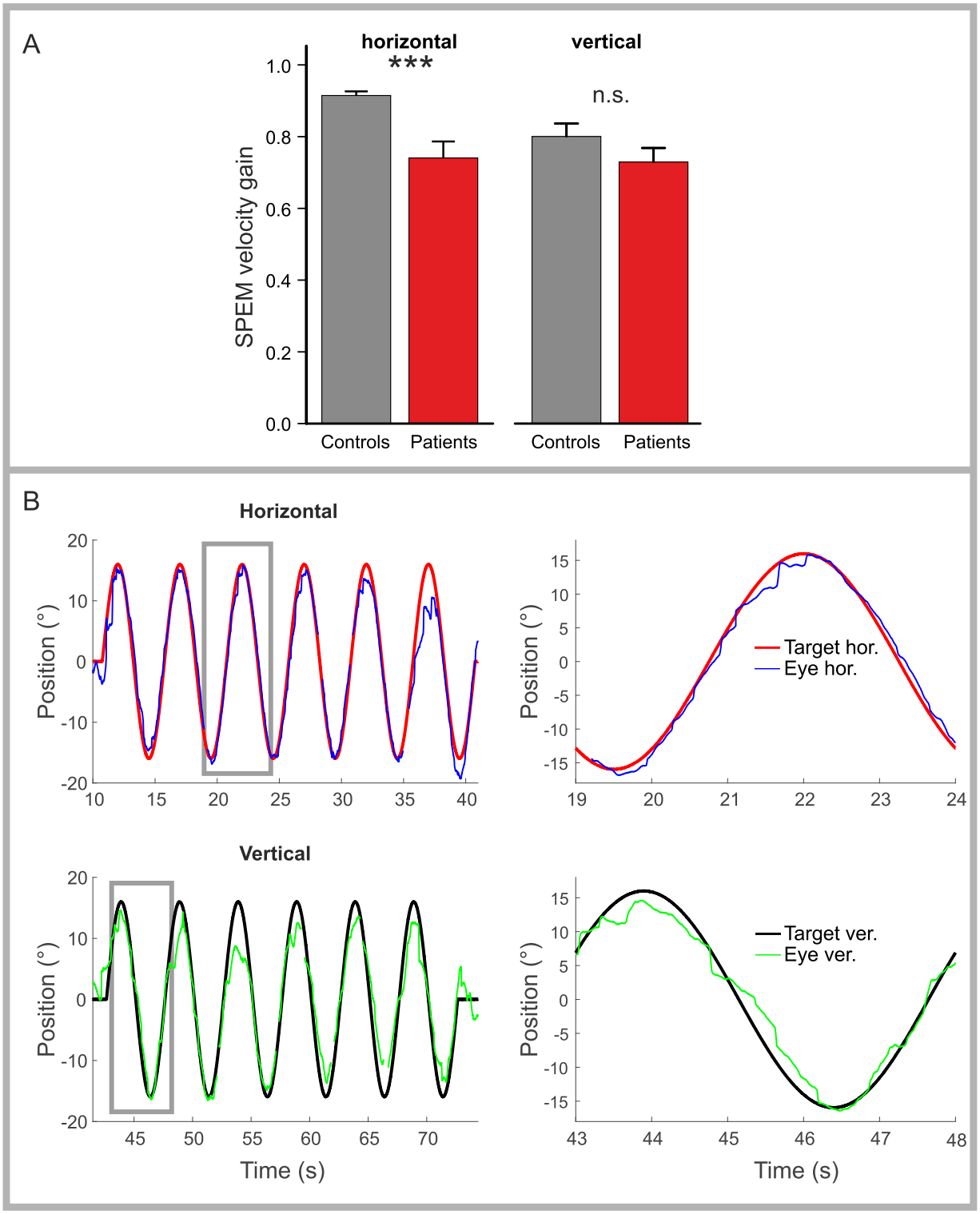

Fig. 2. Horizontal (left) and vertical (right) smooth pursuit eye movements gain (eye/target position, ± 16°; 0.2 Hz) is shown for XDP patients (red) and healthy age-matched control subjects (grey) (**A**). XDP patients showed smaller horizontal SPEM gain. Individual eye position traces (°) of an XDP patient with decreased horizontal (0.71) and vertical (0.59) smooth pursuit gain (**B**). Magnified view on example in grey box. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

thickness of the DLPFC was negatively correlated with antisaccade error rate (Pearson r = −0.838, df = 10, p = 0.0007; Fig. 3G) but not with any other oculomotor parameter (saccade latency, SPEM), i.e., DLPFC thickness was smaller with higher antisaccade error rates. None of the oculomotor parameters correlated with general behavioral scores (UPDRS III, BFMDRS motor, MMSE) or disease duration (p always > 0.05). There were no significant correlations between smooth pursuit eye movement gain and brain volume changes in putamen, pallidum or caudate nucleus.

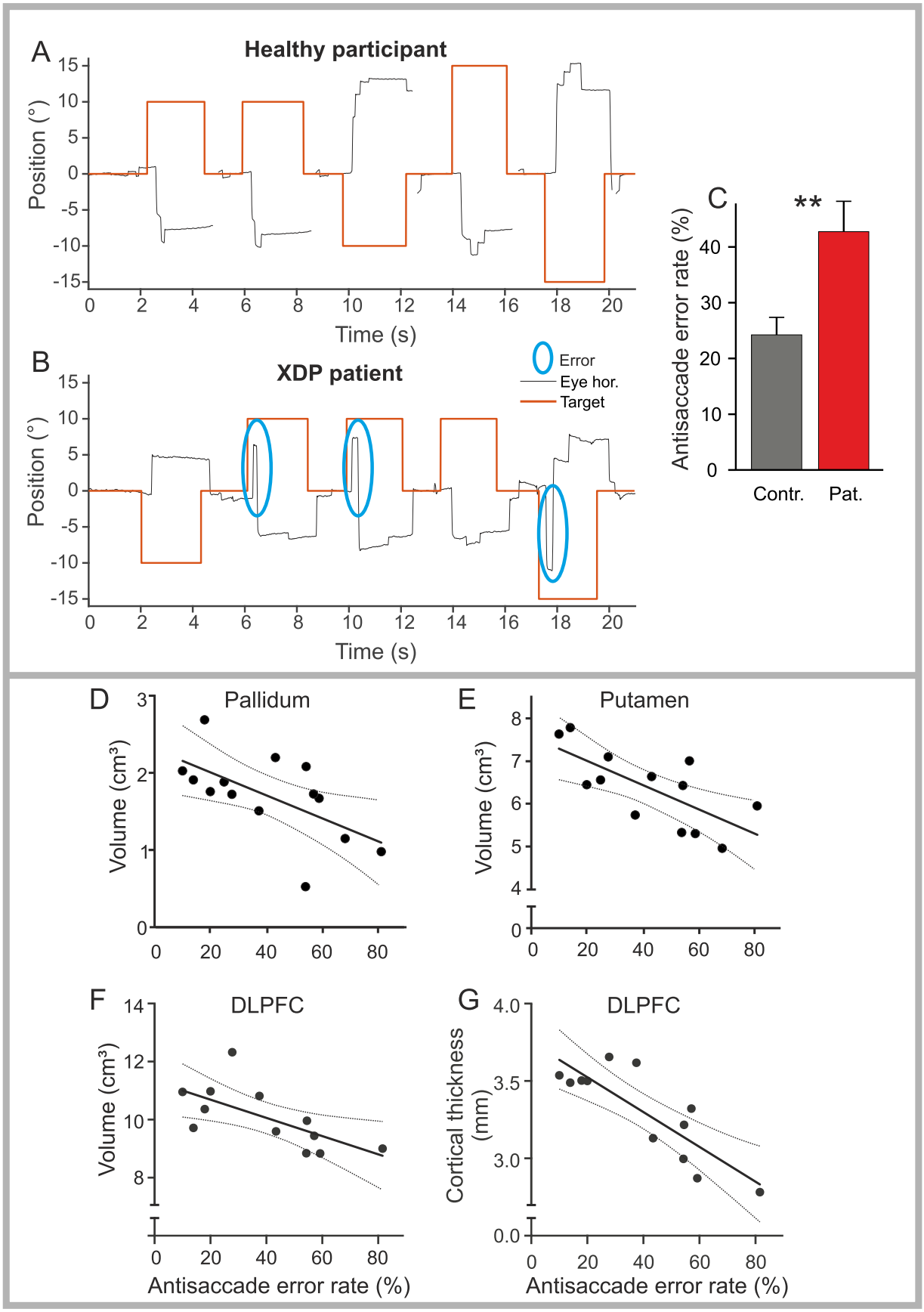

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Fig. 3. Antisaccades. Individual eye position traces (grey) of a healthy control person (*upper row*) and a XDP patient (*middle row*) are displayed for the antisaccade paradigm. While the healthy control (**A**) correctly exerts saccades opposite to the target direction (red) the XDP patient (**B**) often cannot suppress making reflexive saccades towards the target (blue circles, error). *Lower row*: XDP patients showed a significantly increased antisaccade error rate (AER) in (**C**) which increased with volume reduction in pallidum (**D**), putamen (**E**) and DLPFC (**F**). Cortical thickness in DLPFC was smaller in XDP patients and correlated with antisaccade error rate (**G**). ** = $p < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

Our XDP patients showed oculomotor abnormalities which are not compatible with PSP, only in part in line with those of PD patients [7] but more so with those found in multiple system atrophy (MSA) patients with predominant parkinsonism (MSA-P) [14]. Table 1 synoptically shows the results of the XDP patients and compares these with those of patients with PD, MSA and PSP.

4.1. Normal velocity of saccades

Contrary to the hypothesis (#1) posed by a related study [6] we did not find slowing of saccades. Therefore it is highly unlikely that neurodegeneration in XDP extends to the mesencephalic rostral interstitial nucleus of the medial longitudinal fascicle which contains the vertical saccade burst neurons usually affected in PSP.

4.2. Hypometria of visually guided saccades

Why do saccades undershoot the target in XDP? To promote pro-saccades, projections from the prefrontal cortex activate the caudate nucleus (CN) via the direct cortico-subcortical pathway. The CN sends inhibitory projections to the substantia nigra pars reticularis (SNr) for evoking saccades. The SNr in turn sends inhibitory projections to the SC. Activation of the direct oculomotor pathway thus gives rise to a decreasing activity of the GPi/SNr and a subsequent disinhibition of the SC due to the decreasing inhibitory SNr input. The SC itself is a crucial area in triggering voluntary and visually guided saccades as it receives direct projections from the frontal and parietal cortex (e.g. frontal eye field, FEF; dorsolateral prefrontal cortex, DLPFC) and indirect projections via the basal ganglia circuit [15].

Saccade hypometria in our XDP patients resembles hypometria in PD [16] and MSA-P patients [14]. In contrast to PD, neurodegeneration in MSA-P involves the striatum, predominantly the posterior putamen and caudate nucleus [14,17] which is also functionally [2,3] and pathologically [4] affected in XDP. Thus, saccade hypometria in XDP may likely be related to mechanisms similar to MSA-P [18]. Unlike XDP, however, neurodegeneration in MSA-P reveals a preferential loss of the matrix compartment relative to the striosome [19]. The matrix medium spiny neurons (MSNs) are the input structures of the classical direct and indirect basal ganglia pathway and project to the GPi or SNr. Normally, the direct striatonigral (caudate-to-SNr) pathway promotes saccades while the indirect pathway suppresses saccades [15]. As caudate degeneration is clearly present in XDP [2], both the direct and indirect pathway are probably affected in this disorder. In early XDP there is predominant pathology of striosomes and a dopaminergic striatal excess is supposed to be related to an imbalance of the direct and indirect pathway in favor of the direct pathway. As this would functionally result in SC disinhibition, the direct pathway must already be concomitantly compromised in this phase of the disease to turn the basal ganglia output balance of SNr towards a net SC inhibition. As a result, the disinhibited SNr increases its inhibitory control on SC making initiation of saccades more difficult and provoking saccade hypometria. Thus, saccade hypometria in early XDP indicates considerable degeneration of the matrix compartment which has previously been shown to be affected largely in the Parkinsonian phase of XDP [5]. Thus, our results may point towards a Parkinsonian endophenotype of XDP long before parkinsonism becomes an obvious clinical feature.

4.3. Increased error of antisaccades

The most striking finding in our XDP patients was a significant increase of AER. It possibly reflects the failure of the basal ganglia to appropriately contribute to the initiation of self-guided movement by a release of the target structure from tonic inhibition, the SC [20]. This mechanism is particularly critical for movements based on stored or remembered signals that are not currently available as incoming sensory inputs, i.e., anti-saccades.

There are several ways by which striatal degeneration in XDP comes into play here. First, degeneration of direction-specific neuronal CN activity weakens the capacity of voluntary saccadic signals (anti-saccades) to override automatic (visual reflexive) responses. Second, matrix pathology may result in altered SNr and SC activity. Third, striosomal degeneration in XDP involves fronto-striatal projections [21] and thereby accounts for the elevated AER. Finally, increased AER in XDP might come from decreased direct prefrontal inhibition of SC [22]. This is supported by the increasing AER with the reduction of cortical volume and thickness in DLPFC.

Additional evidence of deficient prefrontal cortex inhibition comes from the patients' memory-guided saccades (MGS). MGS are largely controlled by basal ganglia loops. They are more affected in PD than reflexive visually guided saccades [18] as they are voluntarily, i.e. internally guided saccades. Increased latency of MGS and a decrease in their accuracy, as found in our XDP participants, can be observed in prefrontal cortex lesions, i.e. of the dorsolateral prefrontal cortex (DLPFC), e.g. due to a visuospatial working memory deficit.

4.4. Impaired smooth pursuit eye movements (SPEM)

XDP patients showed reduced velocity gain of SPEM during tracking. The magnitude of SPEM impairment is in line with that found in PD patients [23,24], monogenetic parkinsonian syndromes, e.g. *Parkin* mutations (PARK2) [25], and MSA-P patients [24].

Our paradigm provided a predictable slowly moving target which has been found to elicit anticipatory saccades in PD patients while MSA patients rather use catch-up saccades due to decreased SPEM velocity gain [24]. In our XDP patients we largely found catch-up but hardly anticipatory saccades during SPEM resembling SPEM behavior in MSA-P [24].

SPEM impairment in XDP may be related to the following control circuit: Neurons in CN, receiving SPEM-related projections from the frontal eye field [26], and pallidum [27], are active during SPEM. The GP controls SPEM by feedback projections to the FEF [28] and inhibitory projections to the SNr. SNr stops firing during SPEM while microstimulation in SNr elicits suppression of pursuit responses [29]. Patients with bilateral lesions in the putamen, which degenerates in XDP [2] and MSA-P patients [18], show deficits in the anticipation of target motions [30]. This may have contributed to impaired SPEM in our XDP patients. Thus, SPEM deficits in XDP and MSA-P might share similar disease mechanisms. Alternatively, an extradopaminergic mechanism could have caused lower SPEM gain which is related to deficient DLPFC inhibition on striatal SPEM neurons.

4.4.1. Limitations

Three XDP patients were on medication using levodopa. Although some patients report a minor relief using levodopa, their movement disorders do not show a clear response to dopaminergic drugs. Therefore, XDP patients on levodopa do not have phases with good

(ON) or poor (OFF) states, comparable to MSA. Furthermore, Hood et al. [31] showed that levodopa slows prosaccades and improves antisaccades. Our results reflect the opposite: XDP patients had a normal prosaccade peak velocity and abnormal antisaccade error rates. Consequently, we do not assume the abnormal oculomotor behavior to be caused by levodopa.

5. Conclusion

None of the patients' recordings provided evidence for saccade slowing resembling PSP (hypothesis 1 disproved). In several aspects, our XDP patients' oculomotor abnormalities resemble those of patients with MSA-P and - to a lesser degree – PD (hypotheses 4 and 2, Table 1). We suggest that abnormalities in pro-saccades and smooth pursuit eye movements of our XDP patients are precursor signs of the parkinsonian stage of the disease. The increasing failure of response inhibition (antisaccade task) and prolonged saccade latencies could support extranigral parkinsonism (hypothesis 3). This inhibition failure was closely related to volumetric striatal atrophy and reduction of cortical thickness in DLPFC. This deficient inhibition of automatic response behavior in the antisaccade task may indicate a sensitive endophenotype for striatal and of DLPFC degeneration in XDP and possibly striosomal decline.

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Authors' roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

A.S.: 1A-C, 2A-C, 3B
H.H.: 1B, 2B-C.
I.H.: 1B,C.
J.P.: 1B, 2B-C.
A.D.: 1B,C.
R.L.R.: 1B, 3B
R.D.G.J.: 1B, 3B
C.C.D.: 1B, 3B
C.K.: 1A-C, 3B
N.B.: 1A-C, 2C, 3B
C.H.: 1A-C, 2A,C, 3A,B.

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R.D.G.J.: Advisory Boards: Lundbeck Phils., Torrent Phils.; Honoraria: Philippine offices of Allergan, Lundbeck, Medichem, Medtronic, Natrapharm, Sun, Torrent; Grants: Collaborative Center for XDP (CCXDP), MGH.

C.C.D.: no disclosures.

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Appendix A. Supplementary data

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References

[1] R.L. Rosales, X-linked dystonia parkinsonism: clinical phenotype, genetics and therapeutics, J. Move. Dis. 3 (2) (2010) 32–38, https://doi.org/10.14802/jmd.10009.
[2] N. Bruggemann, R.L. Rosales, J.L. Waugh, A.J. Blood, A. Domingo, M. Heldmann, R.D. Jamora, A. Munchau, T.F. Munte, L.V. Lee, I. Buchmann, C. Klein, Striatal dysfunction in X-linked dystonia-parkinsonism is associated with disease progression, Eur. J. Neurol. (2017), https://doi.org/10.1111/ene.13256.
[3] A. Weissbach, T. Baumer, R. Rosales, L.V. Lee, N. Bruggemann, A. Domingo, A. Westenberger, R.D. Jamora, C.C. Diesta, V. Brandt, V. Tadic, S. Zittel, C. Klein, A. Munchau, Neurophysiological fingerprints of X-linked dystonia-parkinsonism: a model basal ganglia disease, Movement Dis.: Off. J. Movement Dis. Soc. 30 (6) (2015) 873–875, https://doi.org/10.1002/mds.26224.
[4] N. Bruggemann, M. Heldmann, C. Klein, A. Domingo, D. Rasche, V. Tronnier, R.L. Rosales, R.D. Jamora, L.V. Lee, T.F. Munte, Neuroanatomical changes extend beyond striatal atrophy in X-linked dystonia parkinsonism, Park. Relat. Disord. 31 (2016) 91–97, https://doi.org/10.1016/j.parkreldis.2016.07.012.

[5] S. Goto, L.V. Lee, E.L. Munoz, I. Tooyama, G. Tamiya, S. Makino, S. Ando, M.B. Dantes, K. Yamada, S. Matsumoto, H. Shimazu, J. Kuratsu, A. Hirano, R. Kaji, Functional anatomy of the basal ganglia in X-linked recessive dystonia-parkinsonism, Ann. Neurol. 58 (1) (2005) 7–17, https://doi.org/10.1002/ana.20513.
[6] D.D. Esmaili, R.A. Shubin, C.H. Waters, A.A. Sadun, Eye movement abnormalities in a case of X-linked dystonia-Parkinsonism (lubag), J. Neuro Ophthalmol.: Off. J. North Am. Neuro-Ophthalmol. Soc. 24 (2) (2004) 188–189.
[7] M. Gorges, H.P. Muller, D. Lule, E.H. Pinkhardt, A.C. Ludolph, J. Kassubek, The association between alterations of eye movement control and cerebral intrinsic functional connectivity in Parkinson's disease, Brain imaging and behavior 10 (1) (2016) 79–91, https://doi.org/10.1007/s11682-015-9367-7.
[8] J.R. Crittenden, A.M. Graybiel, Basal Ganglia disorders associated with imbalances in the striatal striosome and matrix compartments, Front. Neuroanat. 5 (2011) 59, https://doi.org/10.3389/fnana.2011.00059.
[9] S. Goto, A. Hirano, Inhomogeneity of the putaminal lesion in striatonigral degeneration, Acta Neuropathol. 80 (2) (1990) 204–207.
[10] D.P. Munoz, B.C. Coe, Saccade, search and orient–the neural control of saccadic eye movements, Eur. J. Neurosci. 33 (11) (2011) 1945–1947, https://doi.org/10.1111/j.1460-9568.2011.07739.x.
[11] C.A. Antoniades, N. Demeyere, C. Kennard, G.W. Humphreys, M.T. Hu, Antisaccades and executive dysfunction in early drug-naive Parkinson's disease: the discovery study, Movement Dis.: Off. J. Movement Dis. Soc. 30 (6) (2015) 843–847, https://doi.org/10.1002/mds.26134.
[12] T. Anderson, L. Luxon, N. Quinn, S. Daniel, C. David Marsden, A. Bronstein, Oculomotor function in multiple system atrophy: clinical and laboratory features in 30 patients, Movement Dis.: Off. J. Movement Dis. Soc. 23 (7) (2008) 977–984, https://doi.org/10.1002/mds.21999.
[13] H. Hanßen, M. Heldmann, R.L. Rosales, A. Domingo, A. Münchau, T. Bäumer, D. Rasche, V. Tronnier, T.F. Münte, C.L.V. Lee, C. Klein, N. Brüggemann, Severe striatal and pallidal atrophy in early disease stages of X-linked dystonia-parkinsonism, Mov. Disord. 31 (suppl 2) (2016).
[14] Y. Terao, H. Fukuda, S. Tokushige, S. Inomata-Terada, A. Yugeta, M. Hamada, Y. Ichikawa, R. Hanajima, Y. Ugawa, Is multiple system atrophy with cerebellar ataxia (MSA-C) like spinocerebellar ataxia and multiple system atrophy with parkinsonism (MSA-P) like Parkinson's disease? - a saccade study on pathophysiology, Clin. Neurophysiol.: Off. J. Int. Fed. Clin. Neurophysiol. 127 (2) (2016) 1491–1502, https://doi.org/10.1016/j.clinph.2015.07.035.
[15] R.J. Leigh, D.S. Zee, The Neurology of Eye Movements 5ed, Oxford University Press, New York, 2015.
[16] M. Gorges, E.H. Pinkhardt, J. Kassubek, Alterations of eye movement control in neurodegenerative movement disorders, J. ophthalmol. 2014 (2014) 658243, https://doi.org/10.1155/2014/658243.
[17] G.K. Wenning, F. Tison, Y. Ben Shlomo, S.E. Daniel, N.P. Quinn, Multiple system atrophy: a review of 203 pathologically proven cases, Movement Dis.: Off. J. Movement Dis. Soc. 12 (2) (1997) 133–147, https://doi.org/10.1002/mds.870120203.
[18] Y. Terao, H. Fukuda, Y. Ugawa, O. Hikosaka, New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: a clinical review, Clin. Neurophysiol.: Off. J. Int. Fed. Clin. Neurophysiol. 124 (8) (2013) 1491–1506, https://doi.org/10.1016/j.clinph.2013.01.021.
[19] K. Sato, R. Kaji, S. Matsumoto, S. Nagahiro, S. Goto, Compartmental loss of striatal medium spiny neurons in multiple system atrophy of parkinsonian type, Movement Dis.: Off. J. Movement Dis. Soc. 22 (16) (2007) 2365–2370, https://doi.org/10.1002/mds.21732.
[20] O. Hikosaka, R.H. Wurtz, Modification of saccadic eye movements by GABA-related substances. II. Effects of muscimol in monkey substantia nigra pars reticulata, J. Neurophysiol. 53 (1) (1985) 292–308.
[21] C. Beste, M. Muckschel, R. Rosales, A. Domingo, L. Lee, A. Ng, C. Klein, A. Munchau, Striosomal dysfunction affects behavioral adaptation but not impulsivity-Evidence from X-linked dystonia-parkinsonism, Movement Dis.: Off. J. Movement Dis. Soc. 32 (4) (2017) 576–584, https://doi.org/10.1002/mds.26895.
[22] C. Condy, S. Rivaud-Pechoux, F. Ostendorf, C.J. Ploner, B. Gaymard, Neural substrate of antisaccades: role of subcortical structures, Neurology 63 (9) (2004) 1571–1578.
[23] C. Helmchen, J. Pohlmann, P. Trillenberg, R. Lencer, J. Graf, A. Sprenger, Role of anticipation and prediction in smooth pursuit eye movement control in Parkinson's disease, Movement Dis.: Off. J. Movement Dis. Soc. 27 (8) (2012) 1012–1018, https://doi.org/10.1002/mds.25042.
[24] E.H. Pinkhardt, J. Kassubek, S. Sussmuth, A.C. Ludolph, W. Becker, R. Jurgens, Comparison of smooth pursuit eye movement deficits in multiple system atrophy and Parkinson's disease, J. Neurol. 256 (9) (2009) 1438–1446, https://doi.org/10.1007/s00415-009-5131-5.
[25] B. Machner, C. Klein, A. Sprenger, P. Baumbach, P.P. Pramstaller, C. Helmchen, W. Heide, Eye movement disorders are different in Parkin-linked and idiopathic early-onset PD, Neurology 75 (2) (2010) 125–128.
[26] D.M. Cui, Y.J. Yan, J.C. Lynch, Pursuit subregion of the frontal eye field projects to the caudate nucleus in monkeys, J. Neurophysiol. 89 (5) (2003) 2678–2684, https://doi.org/10.1152/jn.00501.2002.
[27] A. Yoshida, M. Tanaka, Neuronal activity in the primate globus pallidus during smooth pursuit eye movements, Neuroreport 20 (2) (2009) 121–125, https://doi.org/10.1097/WNR.0b013e32831af055.
[28] K. Fukushima, J. Fukushima, T. Warabi, G.R. Barnes, Cognitive processes involved in smooth pursuit eye movements: behavioral evidence, neural substrate and clinical correlation, Front. Syst. Neurosci. 7 (2013) 4, https://doi.org/10.3389/fnsys.2013.00004.
[29] M.A. Basso, J.J. Pokorny, P. Liu, Activity of substantia nigra pars reticulata neurons during smooth pursuit eye movements in monkeys, Eur. J. Neurosci. 22 (2) (2005) 448–464, https://doi.org/10.1111/j.1460-9568.2005.04215.x.
[30] A.I. Vermersch, R.M. Muri, S. Rivaud, M. Vidailhet, B. Gaymard, Y. Agid, C. Pierrot-Deseilligny, Saccade disturbances after bilateral lentiform nucleus lesions in humans, J. Neurol. Neurosurg. Psychiatry 60 (2) (1996) 179–184.
[31] A.J. Hood, S.C. Amador, A.E. Cain, K.A. Briand, A.H. Al-Refai, M.C. Schiess, A.B. Sereno, Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 78 (6) (2007) 565–570, https://doi.org/10.1136/jnnp.2006.099754.