

Dysfunctions in striatal microstructure can enhance perceptual decision making through deficits in predictive coding

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Abstract An important brain function is to predict upcoming events on the basis of extracted regularities of previous inputs. These predictive coding processes can disturb performance in concurrent perceptual decision-making and are known to depend on fronto-striatal circuits. However, it is unknown whether, and if so, to what extent striatal microstructural properties modulate these processes. We addressed this question in a human disease model of striosomal dysfunction, i.e. X-linked dystonia-parkinsonism (XDP), using high-density EEG recordings and source localization. The results show faster and more accurate perceptual decision-making performance during distraction in XDP patients compared to healthy controls. The electrophysiological data show that sensory memory and predictive coding processes reflected by the mismatch negativity related to lateral prefrontal brain regions were weakened in XDP patients and thus induced less cognitive conflict than in controls as reflected by the N2 event-related potential (ERP). Consequently, attentional shifting (P3a ERP) and reorientation processes (RON ERP) were less

pronounced in the XDP group. Taken together, these results suggest that striosomal dysfunction is related to predictive coding deficits leading to a better performance in concomitant perceptual decision-making, probably because predictive coding does not interfere with perceptual decision-making processes. These effects may reflect striatal imbalances between the striosomes and the matrix compartment.

Keywords Sensory memory · Predictive coding · Striosomes · EEG · Basal ganglia · Perceptual decision making · X-linked dystonia parkinsonism

Introduction

One remarkable brain function is the ability to predict what is going to happen next on the basis of extracted regularities of previous inputs (Friston 2005; Vogel et al. 2015). This function is often termed predictive coding and refers to processes comparing top-down expectations to bottom-up inputs (Friston 2005). On a neurophysiological level, processes of predictive coding are reflected in the mismatch negativity (MMN), an event-related potential (ERP) (Näätänen and Winkler 1999; Doeller et al. 2003; Balde- weg et al. 2006; Garrido et al. 2009; Wacongne et al. 2012), which has been associated to reflect sensory memory processes (Näätänen et al. 2007). It is evoked by rare deviant stimuli in sequences of frequent stimuli and reflects residual variance between prediction and sensory information (Wacongne et al. 2012). Experimental and computational neuroscience approaches showed that striatal processes engaging striatal medium spiny neurons (MSNs) play a crucial role in sensory memory processes in the auditory (Beste et al. 2008, 2014; Tomkins et al. 2013) and

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the visual domain (Beste et al. 2011, 2012a; Arning et al. 2014).

An important organizational principle of the striatum is its modular organization into a striosome and matrix compartment (Gerfen 1989; Eblen and Graybiel 1995). The striosomes are small islands of neurons embedded and scattered throughout the matrix (Martin et al. 1993; Crittenden and Graybiel 2011). Recent lines of evidence suggest that reward prediction error signals are modulated by the integrity of the striosomes (Beste et al. 2017) and that the striosomes are important in reward-based decision making (Friedman et al. 2015). Also other evidences suggests that the striosomes receive strong input from mesencephalic dopaminergic neurons and in turn modulate dopaminergic transmission via direct inhibitory projections to dopaminergic neurons in the substantia nigra pars compacta (Prensa and Parent 2001; Fujiyama et al. 2011; Watabe-Uchida et al. 2012), which underlines a possible role of these structures for processes related to reward prediction error signaling. Interestingly, the MMN and hence sensory memory processes show close similarities to processes thought to rely on a minimization of prediction errors (Garrido et al. 2009; Rentzsch et al. 2015). This makes it likely that sensory memory processes are also affected by striosomal functioning.

In the current study, we examine the role of the striosomes for sensory memory in a human model disease, X-linked dystonia parkinsonism (XDP) (Lee et al. 2011; Weissbach et al. 2015) that is characterized by predominant striosomal neurodegeneration in early disease stages with the basal ganglia matrix being much less affected (Goto et al. 2005; Lee et al. 2011; Weissbach et al. 2015). XDP is putatively caused by genetic alterations forming an XDP haplotype, located in a region on the X chromosome that includes the *TAF1* gene (Makino et al. 2007; Domingo et al. 2015). XDP in early disease stages is, therefore, a suitable disease model to examine the relevance of the striosomes for predictive coding processes in humans. We test these processes using event-related potentials (ERPs) and source localization analyses. If the functional integrity of the striosomes is critical for these processes to unfold, it is likely that these processes will be dysfunctional, resulting in a smaller MMN in XDP.

Importantly, this may, however, confer behavioral advantages: it is known that violations of predictions in sensory memory disrupt performance in concurrent perceptual decision making (Schröger and Wolff 1998); i.e. deviations in the pitch of a tone can impair the ability to discern the duration of this tone. It follows that striosomal dysfunction may lead to performance advantages because impaired sensory memory processes will interfere less with perceptual decision making. This may be reflected by a lack of modulation in the N2 ERP between

interfering and non-interfering trials, because the N2 is modulated by cognitive conflicts (Folstein and Van Petten 2008; Wolff et al. 2016; Stock et al. 2016; Bluschke et al. 2017). The MMN is followed by the P3a reflecting a shift of attention from the primary task (tone length judgment) to the distracting deviance in the pitch of the tone (Escera and Corral 2007). Thereafter, processes of attentional reorientation occurs redirecting attention towards task-relevant aspects (Schröger et al. 2000). These are reflected by the reorienting negativity (RON) ERP component (Schröger and Wolff 1998; Berti and Schröger 2001). Given expected dysfunctions in sensory memory and the resulting smaller effect of the distractor stimuli in XDP, these processes (i.e. P3a and RON) are also likely affected in these patients.

Materials and methods

XDP patients and control participants

The study was approved by local ethics committees in Lübeck, Germany, and Manila, Philippines. All patients were genotyped using blood DNA to confirm the presence of the genetic changes associated with XDP (Domingo et al. 2015). $N = 21$ XDP patients were recruited from Manila, Philippines. Two of the patients had to be excluded from the data analysis due to quality issues in the neurophysiological recordings. Details on the cohort of the remaining $N = 19$ patients, including their medications, are shown in Table 1.

All patients were in their earlier disease stages and stable on their current medication of clonazepam or biperiden as treatment for dystonia. No other medications than those listed in Table 1 were administered. After obtaining informed consent, all patients underwent detailed neurological examination and clinical motor scoring using the Burke–Fahn–Marsden dystonia score and Parts II (Activities of Daily Living) and III (Motor) of the Unified Parkinson's Disease Rating Scale (UPDRS). All patients showed components of dystonia and parkinsonism of varying degrees (Lee et al. 1991). Regression analyses (see further below) shows that medication did not affect the results of the study. Two patients previously underwent insertion of deep brain stimulation (DBS) leads (of the globus pallidus internus bilaterally) and were under continuous stimulation at the time of investigation (bipolar stimulation, 3.0–4.0 V, pulse width of 60–90 μ s, and frequency of 130 Hz). The DBS patients did not bias the effects in the study (see analysis below). Along with the patients, age-matched male Filipino controls were recruited, who were not taking any medication.

Table 1 Clinical data of XDP patients

	XDP (entire group)	XDP patient 1 with DBS	XDP patient 2 with DBS 2
<i>N</i>	19		
Age at examination	46.00 (7.94)	45	46
Age of disease onset	41.43 (4.91)	33	38
Disease duration	4.56 (4.28)	8	8
Burke–Fahn–Marsden dystonia score	20.96 (13.73)	36.5	6.5
UPDRS (activities of daily living)	13.81 (10.06)	36	0
UPDRS (motor)	24.81 (17.85)	25	5
UPDRS (total)	38.62 (26.01)	61	5
Medications clonazepam	1.12 mg (1.35) range 0–3 mg	1 mg	
Biperiden	0.66 mg (1.77) range 0–6 mg	1 mg	6 mg
Levodopa	100 mg (138) range 0–400 mg	100 mg	300 mg

Mean and standard deviations are given for the XDP patient group as a whole

Task

The task used is identical to that employed in previous studies in basal ganglia diseases (Beste et al. 2008, 2014). It was introduced by Schröger and Wolff (1998). Briefly, patients and controls were presented tones at three different pitches (1000, 1100, 900 Hz) for either 400 or 200 ms. One pitch (i.e. 1000 Hz) served as the standard tone and was presented in 80% of the trials. The other pitches were presented at a frequency of 10% each. The subjects were asked to respond with their thumb and indicate, whether the tone was short (right button press) or long (left button press). Variations in the pitch of the tone thus served as distraction. The primary task was a judgment of tone duration (perceptual decision making task) that was superimposed by a sensory memory component because the frequently presented standard tone establishes an expectation/prediction of what is going to happen next; i.e. processes comparing top-down expectations to bottom-up inputs are initiated.

EEG recording and analysis

The EEG was recorded from 60 Ag/AgCl electrodes arranged in equidistant positions (500 Hz sampling rate). Electrode impedances were kept below 5 k Ω and the data were filtered offline (0.5–20 Hz, 48 db/oct; notch filter at 60 Hz) before a manual inspection of the data was conducted. During this step, technical artifacts were removed. Periodically recurring artifacts (horizontal and vertical eye movements and blinks), as well as muscle artifacts were corrected for using an independent component analysis (Infomax algorithm) in the next step. Components that reveal horizontal and vertical eye movements, blinks and

other muscle artifacts were visually identified by means of recurrent similar waveforms and by the scalp topography. Components reflecting the above-mentioned artifacts were discarded. To measure the MMN, P3a and the RON, the EEG time-series were epoched in segments from –200 till 800 ms after the stimulus onset. Within these epochs, an automated artifact rejection procedure was applied: Rejection criteria included a maximum voltage step of more than 80 μ V/ms, a maximal value difference of 100 μ V in a 250 ms interval or activity below 0.5 μ V in a period of 200 ms. After this, a current source density (CSD) transformation was applied to re-reference the data (Nunez and Pilgreen 1991). Such current source density transformation eliminates the reference potential from the data and thereby serves as a spatial filter facilitating the identification of electrodes that have to be analyzed for the different ERP components. Then, a baseline correction was applied from –200 until 0 ms (i.e. time point of stimulus presentation). To measure the MMN, P3a and RON, difference waves were calculated (distractor minus standard ERPs) (Kujala et al. 2007). In these difference waves, the MMN was defined as the most negative peak between 100 and 250 ms. The P3a was defined as the most positive peak between 250 and 600 ms and the RON as the most negative peak between 500 and 800 ms post-stimulus presentation. In these time windows the peaks were detected and the mean amplitude in the interval \pm 20 ms around this peak was quantified. This choice of electrodes and time windows for peak quantification were further statistically validated using the established methods (Mückschel et al. 2014). For each ERP component, a search interval, during which the component is maximal, was defined. Within each of these search intervals, the mean amplitude was extracted for all 60 electrodes including the interpolated reference

electrode. Each electrode was subsequently compared against the average of all other electrodes using Bonferroni-correction for multiple comparisons (critical threshold $p = .0007$). Only electrodes that showed significantly larger mean amplitudes (i.e. negative for N-potentials and positive for P-potentials) than the remaining electrodes were selected. This validation procedure revealed the same electrode position as in the visual inspection.

Source localization and analysis

Source localization analyses were carried out using sLORETA [standardized low resolution brain electromagnetic tomography; (Pascual-Marqui 2002)]. Several EEG/fMRI and EEG/TMS studies underline the validity of the sources estimated using sLORETA (Sekihara et al. 2005; Dippel and Beste 2015). sLORETA provides a single linear solution to the inverse problem (Pascual-Marqui 2002; Marco-Pallarés et al. 2005; Sekihara et al. 2005). It partitions the intracerebral volume into 6239 voxels at 5 mm spatial resolution before calculating the standardized current density at each voxel in a realistic head model using the MNI152 template. Voxels with significant differences ($p < .01$, corrected for multiple comparisons) contrasted between groups were located in the MNI-brain. Obtained voxel-based sLORETA images for the different calculated contrasts between groups and conditions were calculated using the sLORETA-built-in voxel-wise randomization tests with 2000 permutations, based on statistical non-parametric mapping (SnPM).

Statistics

The data was analyzed using mixed effects ANOVAs, in which the factor “condition” (standard vs. deviant) was included as within-subject factor and the factor “group” as between-subject factor. For the neurophysiological data, an additional within-subject factor “electrode” was included where appropriate. Greenhouse–Geisser correction was applied for all tests and post hoc tests were Bonferroni-corrected. All data included in the analyses were tested for normal distribution using Kolmogorov–Smirnov tests (all $z < 0.8$; $p > .3$). For the descriptive statistics, the mean and the standard deviation (SD) are given.

Results

Behavioral and neurophysiological data in the entire sample

For the accuracy (rate of response errors) the ANOVA revealed a main effect “condition” [$F(1,36) = 73.13$;

$p < .001$; $\eta_p^2 = .670$] showing that fewer errors were committed in standard ($7.36\% \pm 2.37$) than in deviant trials ($12.34\% \pm 4.15$). The main effect “group” [$F(1,36) = 25.06$; $p < .001$; $\eta_p^2 = .410$] showed that the XDP patients committed fewer errors ($8.29\% \pm 4.95$) than the controls ($11.42\% \pm 2.45$). The interaction “condition \times group” was also significant [$F(1,36) = 25.22$; $p < .001$; $\eta_p^2 = .412$]. Post-hoc tests revealed no group difference in error rates on trials with standard tones [$t(36) = -0.27$; $p > .7$], but on trials with deviant tones [$t(36) = -6.56$; $p < .001$]. In the latter, the error rate was lower in XDP patients (9.31 ± 2.26) compared to controls (15.36 ± 3.32) (refer Fig. 1a). A post hoc power analysis revealed that the obtained power in the interaction was above 95%.

For the reaction times (RTs), the ANOVA revealed a main effect “condition” [$F(1,36) = 28.49$; $p < .001$; $\eta_p^2 = .442$] showing that RTs were longer on deviant ($651 \text{ ms} \pm 86$) than on standard trials ($568 \text{ ms} \pm 85$). The main effect “group” [$F(1,36) = 4.39$; $p = .043$; $\eta_p^2 = .109$] showed that RTs were longer in controls ($632 \text{ ms} \pm 114$) than in XDP patients ($588 \text{ ms} \pm 65$). Importantly, there was an interaction “condition \times group” [$F(1,36) = 9.69$; $p = .004$; $\eta_p^2 = .212$]. Post-hoc tests showed that there was no group difference in RTs in trials

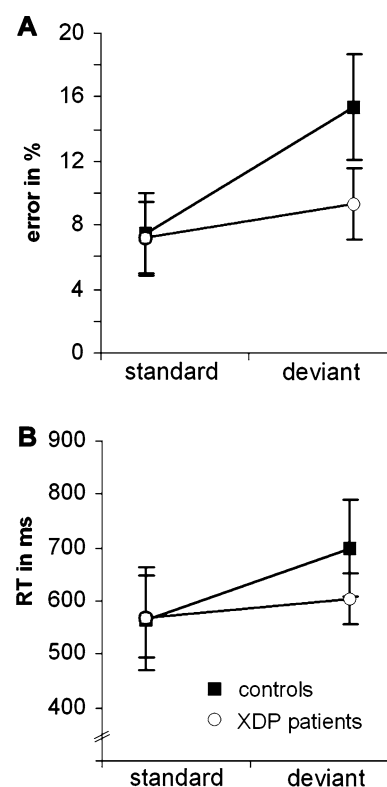


Fig. 1 Error rates (a) and reaction times (RTs) in milliseconds (b) in standard and deviant trials in the XDP patient group (white circles) and the control group (black squares). Mean and SD are given

with standard tones [$t(36) = 0.15$; $p > .8$], but in trials with deviant tones [$t(36) = -3.86$; $p < .001$]. In the latter, XDP patients had faster RTs ($605 \text{ ms} \pm 48$) than controls ($698 \text{ ms} \pm 92$) (refer Fig. 1b).

The MMN, the P3a and the RON are shown in Fig. 2.

The MMN as well as the P3a showed a left-sided maximum (cf. Beste et al. 2008) and were most pronounced at electrode FC3 both in XDP patients and the control group as validated using the statistical procedure outlined in the methods section. MMN amplitudes were larger (more negative) in controls (-8.42 ± 2.41) than in XDP patients (-4.95 ± 2.87) [$t(36) = 4.03$; $p < .001$]. The sLORETA analysis suggests that this is due to activation differences in the left inferior frontal gyrus, which is in line with the literature (Garrido et al. 2009). The same picture emerged for the P3a that was also larger in controls (14.39 ± 3.92) than XDP patients (9.03 ± 2.53) [$t(36) = -5.02$; $p < .001$]. The RON showed a right-sided maximum (cf. Beste et al. 2008) with largest amplitudes at electrode F2 in both groups as validated using the procedure outlined above. The RON was larger (more negative) in controls (-14.31 ± 4.42) than XDP patients (-7.47 ± 2.18) [$t(36) = 6.11$; $p < .001$]. There were no group differences as regards latency of the MMN, P3a and RON (all $t < 0.9$; $p > .3$).

Together, the pattern of behavioral and neurophysiological data suggests that deviations in the pitch of a tone do not disrupt performance to judge the length of this tone in the XDP group. This is supported by an analysis of the N2 ERP component on standard and deviant trials. The N2 has been shown to be enlarged when cognitive conflicts arise (Folstein and Van Petten 2008). For the N2 amplitudes, the ANOVA revealed an interaction “condition x group” [$F(1,36) = 7.54$; $p = .009$; $\eta_p^2 = .173$] with post hoc tests showing that the N2 was larger on deviant trials in controls (-12.23 ± 2.77) than in XDP patients (-8.88 ± 2.29) [$t(36) = 4.05$; $p < .001$], whereas no such effect was observed for standard trials [$t(36) = 0.05$; $p > .9$] (refer Fig. 2).

Two of the XDP patients received bilateral deep brain stimulation of the globus pallidus. Their clinical data are shown in Table 1. To probe whether deep brain stimulation had an effect, we used single-case t statistics (Crawford and Garthwaite 2012) to compare the two XDP patients with deep brain stimulation to the cohort of XDP patients with no stimulation. The descriptive behavioral and neurophysiological data of these patients is shown in Table 2.

The single-case t statistics revealed that behavioral or neurophysiological parameter did not differ between the 2 XDP patients with deep brain stimulation and the remaining group of XDP patients (all $t < 1.20$; $p > .2$). Importantly, the pattern of results did also not change when the remaining sample of XDP patients (i.e. without the two

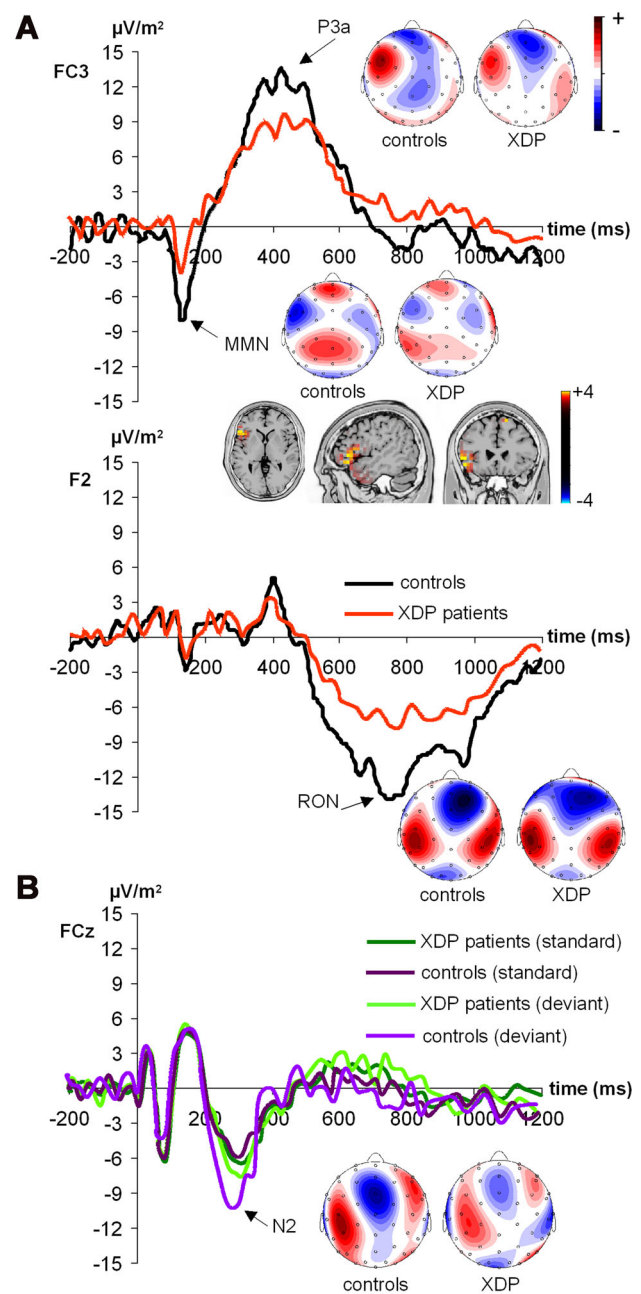


Fig. 2 **a** Event-related potentials showing the MMN and P3a component at electrode FC3 and the RON component at electrode F2. *Black curves* denote the ERPs for the control group, *red curves* for the XDP patient group. Time-point zero denotes the time-point of stimulus presentation. The scalp topography plots show the topography at the maximal amplitude of each ERP component. In the scalp topography plots negativity is shown in *blue* and positivity in *red*. The sLORETA plots show activation differences for the MMN (critical t values) between groups (corrected for multiple comparisons using SnPM) in the left inferior frontal gyrus. **b** Event-related potentials showing the N2 on standard and deviant trials

XDP patients with DBS) was compared to the healthy control group. For the accuracy data, there was still an interaction “condition x group” [$F(1,34) = 19.21$;

Table 2 Behavioral and neurophysiological data in the two XDP patients receiving DBS compared to the remaining XDP patients

	XDP group ($N = 17$)	DBS 1	DBS 2
Error % standard	7.06 (2.30)	9	9
Error % deviant	9.06 (2.25)	12	11
RT standard (ms)	570 (81)	587	561
RT deviant (ms)	601 (49)	633	648
MMN amplitude ($\mu\text{V}/\text{m}^2$)	-4.96 (3.04)	-5.23	-4.58
P3a amplitude ($\mu\text{V}/\text{m}^2$)	9.01 (2.47)	12.08	6.26
RON amplitude ($\mu\text{V}/\text{m}^2$)	-7.63 (2.21)	-5.56	-5.48
N2 amplitude deviant ($\mu\text{V}/\text{m}^2$)	-7.73 (2.77)	-6.85	-6.99
N2 amplitude standard ($\mu\text{V}/\text{m}^2$)	-8.95 (2.42)	-7.96	-8.73

Mean and standard deviations are given for the group of remaining $N = 17$ XDP patients

$p < .001$; $\eta_p^2 = .430$]. Post-hoc tests revealed no group difference in error rates on trials with standard tones [$t(34) = -0.33$; $p > .6$], but on trials with deviant tones [$t(34) = -5.44$; $p < .001$]. In the latter, the error rate was lower in XDP patients compared to controls. Similarly, there was an interaction “condition x group” for the RT data [$F(1,34) = 8.55$; $p = .003$; $\eta_p^2 = .255$]. Post-hoc tests showed that there was no group difference in RTs in trials with standard tones [$t(34) = 0.10$; $p > .8$], but in trials with deviant tones [$t(34) = -3.99$; $p < .001$]. In the latter, XDP patients had faster RTs than controls. For the neurophysiological data it is shown that the amplitudes of the MMN, the P3a and the RON were all smaller in XDP patients than in controls [all $t(34) > 3.99$; $p < .005$]. Also for the N2 ERP-component it is shown that XDP patients showed a smaller in N2 for deviant trials than controls [$t(34) = 3.85$; $p < .001$], whereas no difference was evident for standard trials [$t(34) = 0.15$; $p > .8$]. This analysis clearly shows that the effects are still the same compared to the entire group of XDP patients.

To examine whether the heterogeneous medication profile (refer Table 1) affected the results in the XDP group, regression analyses were conducted. These showed that there were no correlations between doses of different medications and behavioral and neurophysiological parameters (all $F < 0.89$; $p > .4$ and all $\beta < .031$; $p > .4$). Therefore, the medication profile of the patients is unlikely to have modulated the effects obtained.

There were also no correlations with clinical parameters, such as BFMD or disease duration (all $r < .155$; $p > .3$).

Behavioral and neurophysiological data in patients with mild parkinsonism

The above analyses showing better task performance and an altered neurophysiological pattern in XDP patients compared to healthy controls suggests that these patients were less distracted by deviant stimuli. Given preferential striosomal dysfunction in XDP (Goto et al. 2005),

distraction as tested here may be attributed to the integrity of the striosomes. However, the results by Goto et al. (2005) shows that neurodegeneration in XDP patients with prominent parkinsonism is less specific affecting both striosomal and matrix compartments and probably neocortical parts (Brüggemann et al. 2016).

Since the UPDRS motor score was ~ 24.81 , parkinsonism may have biased the effects. Therefore, we analyzed $N = 5$ XDP with a low UPDRS score of 4.5 (3.5) and a BFM score of 12.3 (5.11), i.e. a patient subgroup characterized primarily by dystonia but not parkinsonism. Figure 3a shows the behavioral data and Fig. 3b the neurophysiological data of the different XDP subgroups in comparison to healthy controls.

Wilcoxon tests revealed that the subgroup did not differ from the control group in RTs in standard trials ($600 \text{ ms} \pm 113$) ($Z = -0.19$; $p > .8$), but showed faster RTs than controls in deviant trials ($585 \text{ ms} \pm 36$) ($Z = -2.03$; $p = .020$). Similarly, the error rate was not different to controls in standard trials ($5.4\% \pm 2.07$) ($Z = -1.59$; $p = .15$), but was lower than in controls in deviant trials ($9.0\% \pm 0.71$) ($Z = -3.34$; $p < .001$). Compared to controls, also the MMN was smaller in this subgroup (-6.02 ± 3.34) ($Z = -2.10$; $p = .015$). The same was the case for the P3a (8.89 ± 3.67) ($Z = -2.50$; $p = .006$) and also the RON (-7.01 ± 3.52) ($Z = -2.70$; $p = .003$). Also, the N2 on deviant trials was smaller in this subgroup (-9.04 ± 0.69) than in controls ($Z = -2.31$; $p = 0.21$). The pattern observed in the XDP subgroup showing mild parkinsonism is, therefore, comparable to the pattern observed in the entire sample of XDP patients.

Discussion

In the current study, we examined the relevance of striosomal processes for perceptual decision-making and sensory memory processes in a human disease model of striosomal dysfunction, XDP. The behavioral results shows

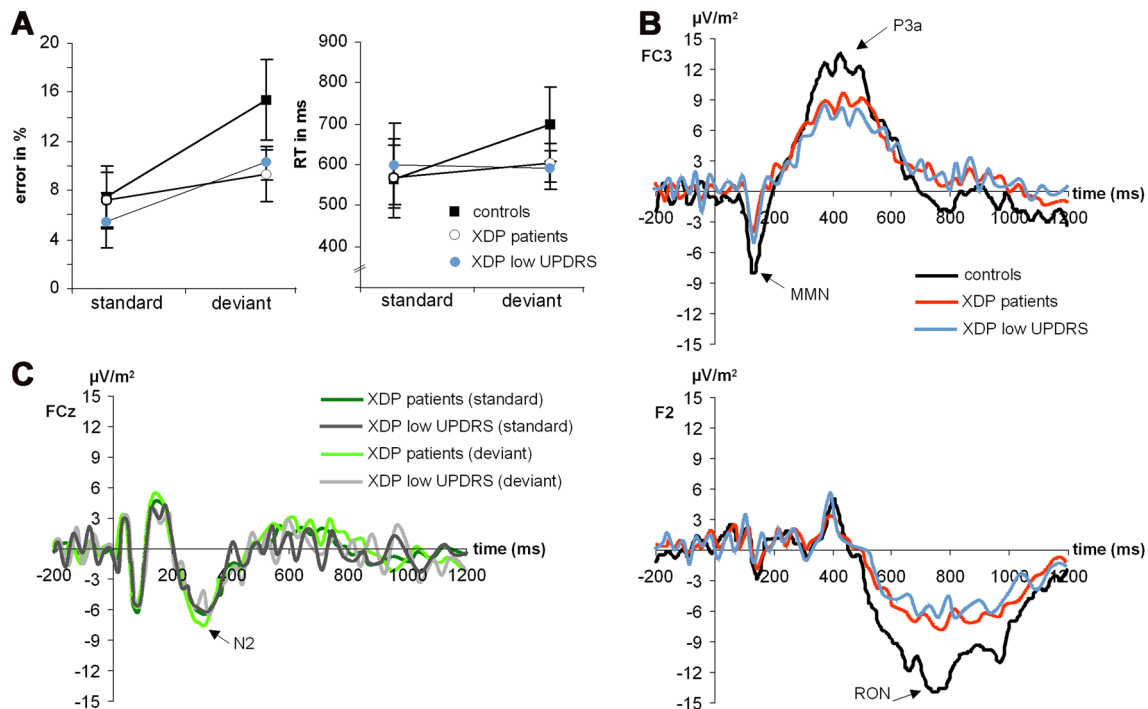


Fig. 3 **a** Behavioral data (error rates and RTs) in the subgroup of $N = 5$ XDP patients with mild parkinsonism, i.e. low UPDRS scores (blue circles), in comparison to the entire sample of XDP patients (white circles) and the entire sample of healthy controls (black circles). **b** Event-related potentials showing the MMN and P3a component at electrode FC3 and the RON component at electrode F2 for the subgroup of $N = 5$ XDP patients with mild parkinsonism (blue

lines) in comparison to the entire sample of XDP patients (red lines) and the entire sample of healthy controls (black lines). **c** Event-related potentials showing the N2 on standard and deviant trials for the entire sample of XDP patients (green shadings) and the subgroup of $N = 5$ XDP patients with mild parkinsonism (gray shadings) for standard and deviant trial types

that compared to healthy controls, XDP patients are less distracted by tones with deviant pitches in the primary task examined (i.e. judgment of the length of the presented tones). There was less response slowing and also a smaller reduction of accuracy when XDP patients were confronted with the distracting pitches of the tones compared to healthy controls. XDP patients therefore had an advantage in perceptual decision-making processes compared to controls suggesting that striosomal dysfunction is associated with better perceptual decision-making processes, when distracting information can interfere with this process. A post hoc power analysis revealed that the obtained power in the interaction was above 95% showing that a high power was achieved. This shows that the study is sufficiently powered to derive reliable conclusions.

The neurophysiological data show that the MMN as a functional correlate of sensory memory processes (Näätänen et al. 2007) was smaller in XDP patients than in controls. The source localization analysis suggests that this was due to activation differences in the left inferior frontal gyrus, which is well in line with the existing literature on the source of the MMN (Garrido et al. 2009). Since the MMN reflects processes of predictive coding (Näätänen and Winkler 1999; Doeller et al. 2003; Baldeweg et al.

2006; Näätänen et al. 2007; Garrido et al. 2009; Wacongne et al. 2012) showing close similarities to processes minimizing prediction errors (Garrido et al. 2009; Rentzsch et al. 2015) the results are in line with other recent evidence showing that behavioral adaptation processes depending on reward prediction errors are modulated by the striosomes (Beste et al. 2017). As a corollary, this suggests that sensory memory and predictive coding processes are modulated by the striosomes.

The P3a and the RON were also smaller in XDP patients than in controls suggesting that (1) shifts of attention from the primary task (tone length judgment) to the distracting deviance in the pitch of the tone (Escera and Corral 2007) are weaker and (2) that processes associated with the redirection of attention towards task-relevant aspects (Schröger et al. 2000) are likewise less pronounced. This is very likely an effect of dysfunctional sensory memory processes in XDP leading to smaller effects of auditory distractors on the primary task (i.e. judgment of the tone length). This is also supported by the analysis of the N2 data showing a larger N2 and hence probably a stronger cognitive conflict in deviant trials in controls than XDP patients. The data analysis further shows that the pattern of results was stable regardless of whether the entire sample

of XDP patients was analyzed or only a subgroup of XDP patients with mild parkinsonism. Since XDP patients with mild parkinsonism have predominant striosomal dysfunction (Goto et al. 2005) and show the same experimental effects compared to the control group in the current study, one can conclude that the effects observed are attributable to striosome processes and are unlikely to be biased by the affection of other brain areas in later stages of this disease. Similarly, the regression analyses shows the results are unlikely to be biased by the drug intake of the patients. The analysis of the patients with deep brain stimulation also revealed that deep brain stimulation does not alter the effects, since there were no differences between patients with deep brain stimulation and patients without deep brain stimulation. The analyses, therefore, show that the effects reported are very stable. Apparently, striosomal dysfunction can turn into a paradoxical benefit for perceptual decision-making processes under distraction. This may be the case because distractive features of the stimuli do not interfere with the primary and concurrent perceptual decision making-task, as supported by the findings in the N2 data.

In conjunction with other studies using this task in diseases affecting the striatum, our results provide novel insights into the functioning of the striatum for sensory memory and predictive coding processes and provide hints towards the neural mechanisms underlying the observed paradoxical gains in perceptual decision-making processes under distraction in conditions of striosomal dysfunction.

For instance, it has been shown that Huntington's disease (HD) patients also show a better performance in perceptual decision making in the same task as used here, i.e. they are also less distracted by deviant stimuli and show superior performance in perceptual decision making (Beste et al. 2008). However, importantly, this was associated with larger MMN (i.e. sensory memory and predictive coding processes) compared to controls. The gain of function in HD was interpreted as being caused by increased NMDA receptor-related cortico-striatal neural transmission (Beste et al. 2008) representing a prominent pathogenic mechanism in HD (Beal and Ferrante 2004; Okamoto et al. 2009; Milnerwood et al. 2010) which has also been implicated in other paradoxically enhanced cognitive processes in HD (Beste et al. 2012b, 2015). This interpretation has been supported in later studies including computational models on response selection mechanisms in the striatum (Tomkins et al. 2013; Beste et al. 2014) and is well in line with findings showing that increased glutamatergic neural transmission leads to larger MMN and thus presumably increased sensory memory and predictive coding processes (Javitt et al. 1996; Kreitschmann-Andermahr et al. 2001; Umbricht et al. 2002; Kujala et al. 2007; Beste et al. 2012b). Currently, there is no evidence pointing

to an altered glutamatergic neural transmission in XDP. However, in light of striosomal pathology in XDP (Goto et al. 2005), the constellation of reduced MMN amplitudes, along with better behavioral performance in these patients, suggests that in addition to altered glutamatergic neurotransmission, the structural integrity of the striosomal basal ganglia network is an important determinant of sensory memory processes. At first sight, this appears to be at odds with insights gained from computational modelling (Tomkins et al. 2013; Beste et al. 2014), because these models, together with experimental data, suggest that both factors, a dysfunctional MSN network and increased glutamatergic neural transmission, are prerequisites to foster performance and cognitive subprocesses involved in sensory memory and perceptual decision-making. Importantly, previous computational approaches and experimental studies referred to non-selective damage of the MSN network integrity; i.e. of both striosomes and the matrix compartments (Beste et al. 2014).

Combined data from the current and the previous studies suggests that the balance and mutual influence between the matrix and the striosomes during superimposed processes of sensory memory and perceptual decision-making is critical. In fact, striosomes can exchange information with the surrounding matrix (Crittenden and Graybiel 2011), because of interneurons located at compartmental borders (Saka et al. 2002; Miura et al. 2007). This in turn enables the striosomes to exert control over behaviors driven by the surrounding sensorimotor and associative parts of the matrix (Crittenden and Graybiel 2011). In the current study, disease-related damage to the striosomes very likely compromises striosomal influence on the surrounding matrix. This will reduce interferences with processes possibly engaging the matrix. It is plausible that because of damage to the striosomes sensory memory and predictive coding processes are impaired, and therefore, do not interfere with perceptual decision-making process related to the judgment of tone length mediated by the matrix. It is likely that the matrix, largely unaffected in early disease stages of XDP (Goto et al. 2005), is involved in perceptual decision making because these processes are concerned with how humans choose an appropriate action during the detection, discrimination, or categorization of sensory information (Summerfield and Tsetsos 2012). Perceptual decision making processes thus refer to sensorimotor processes that have been shown to involve the matrix (Crittenden and Graybiel 2011). In healthy controls, the striosomal compartment is fully functional and can, therefore, interfere with matrix processes. As a result, sensory memory processes may interfere with perceptual decision-making processes and task performance deteriorates compared to XDP patients. Clearly, the above-outlined mechanisms on an altered balance between striosome and matrix compartments are hypothetical. Future studies should

investigate this issue of striosome-matrix interaction in detail. Doing so, it may be relevant to investigate patients with multiple system atrophy (MSA) with predominantly parkinsonian features (MSA-P). This is because it was suggested that in MSA-P there is selective loss of matrix medium spiny neurons in early stages of the disease (Sato et al. 2007; Crittenden and Graybiel 2011). Comparing XDP patients and MSA-P patients may shed light on striosome-matrix interactions. Moreover, electrophysiological studies in animals may be important. Yet, regarding the effects of superimposed sensory memory processes and perceptual decision-making it is also important to note that inferior frontal regions have been shown to be involved in perceptual decision making (Sherman et al. 2016). Since inferior frontal regions seems to be involved in this task and are shown to be differentially modulated between XDP patients and controls (refer results from the sLORETA analysis), it is also possible that inferior frontal regions play an important role for regarding the effects of superimposed sensory memory processes and perceptual decision-making.

From the current data, it cannot be decided whether the effects observed are due to an unsuccessful “storing” of the information about experienced regularities or whether this is this a problem affecting a recall phase that signals irregularities, or both. If predictive signaling is compromised by striosomal dysfunctions, incorrect learning would result in vague predictions about the future so that irregularities would not be registered as such. On the other hand the acquisition of possible regularities might not be compromised, so that the effect might be entirely caused by dysfunction in recognizing a mismatch.

In summary, the study shows that sensory memory or predictive coding processes and their impact on perceptual decision making processes are a function of the basal ganglia striosomes. Intriguingly, the results show that a dysfunction of the striosomes leads to better performance in perceptual decision-making. This is likely the case because sensory memory and predictive coding cannot fully unfold and are therefore, do not interfere with perceptual decision making processes. These effects are putatively caused by changes in the functional balance between the striosomes and the matrix compartment.

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