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# Predictive coding and adaptive behavior in patients with genetically determined cerebellar ataxia—A neurophysiology study

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ABSTRACT

Genetically determined cerebellar ataxias (CA) are a heterogeneous group of disorders with progressive decline of cerebellar functions. The cerebellum influences internal forward models that play a role in cognitive control, but whether these processes are dysfunctional in CA is unclear. Here, we examined sensory predictive coding processes and response adaptation in CA and healthy controls (HC) using behavioral tests with concomitant EEG recordings. $N = 23$ patients and $N = 29$ age- and sex-matched HC were studied. Sensory prediction coding was tested with an auditory distraction paradigm and error-related behavioral adaptation with a visual flanker task. As neurophysiological markers we studied different event-related potentials: the P3a for orientation of attention; the N2 and the error-related negativity (ERN) for cognitive adaptation processes/consequences of response errors; error-related positivity (Pe) for error-awareness; the mismatch negativity (MMN) for sensory predictive coding; and reorientation negativity (RON) for reorientation after unexpected events. Overall reaction times were slower in patients compared to HC, but error rates did not differ. Both in patients and HC, P3a amplitudes were larger in distraction trials, but the P3a amplitude was smaller in patients compared to HC. The MMN as well as behavioral and EEG-correlates of response adaptation (ERN/N2) did not differ between groups, while the Pe was attenuated in patients. During sensory predictive coding, RON amplitudes were significantly larger in HC compared to patients. In HC, but not in patients, RON amplitudes were also larger in deviant compared to frequent trials. Processes generating internal forward models are largely intact in genetically determined CA, whereas updating of mental models and error awareness are disturbed in these patients.

| | |
|---|---|
| ACC | anterior cingulate cortex |
| BFMDS | Burke–Fahn–Marsden Dystonia Rating Scale |
| CA | cerebellar ataxia |
| EQ5D | Euro Quality of Life-5-Dimensions scale |
| ERN | error-related negativity |
| HC | healthy control |
| INAS | inventory of non-ataxia signs |
| MMN | the mismatch negativity |
| MoCA | Montreal Cognitive Assessment |
| NHPT | 9-Hole-Peg-Test |
| Pe | error-related positivity |
| RON | reorientation negativity |
| SARA | Scale for the Assessment and Rating of Ataxia |
| XDP | X-linked dystonia parkinsonism |

## 1. Introduction

Genetically determined cerebellar ataxias (CA) are a heterogeneous

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**Table 1**
Clinical characteristics of the study population.

SARA: Scale for the Assessment and Rating of Ataxia (Weyer et al., 2007), INAS: inventory of non-ataxia signs (Jacobi et al., 2013), BFMDS: Burke–Fahn–Marsden Dystonia Rating Scale (Burke et al., 1985); NHPT: 9-Hole-Peg-Test of the dominant hand (the best trial is given) (Schmitz-Hubsch et al., 2008), the PATA repetition rate, EQ5D: Euro Quality of Life-5-Dimensions scale (Brooks, 2013), MoCA: Montreal Cognitive Assessment.

| | | Age (in years) | Disease duration (in years) | SARA score | INAS count | BFMDS score | NHPT (best trial, in seconds) | PATA rate | EQ5D health score | MOCA score |
|---|---|---|---|---|---|---|---|---|---|---|
| HC $N$ = 29, 12 male | mean | 43.2 | n/a | 0.57 | n/a | 0.88 | 16.2 | 28.2 | 87.5 | 27.2 |
| | SD | 12.4 | n/a | 0.48 | n/a | 0.81 | 1.45 | 4.6 | 12.5 | 2.0 |
| | range | 22.0–72.0 | n/a | 0–1.5 | n/a | 0–2.5 | 14.1–19.4 | 19.0–41.0 | 50.0–100.0 | 23–30 |
| Patients $N$ = 23, 10 male | mean | 51.0 | 9.3 | 12.8 | 5.1 | 5.2 | 29.8 | 21.7 | 70.9 | 26.8 |
| | SD | 11.4 | 7.7 | 5.0 | 2.0 | 5.3 | 8.5 | 4.5 | 21.0 | 3.6 |
| | range | 22.0–74.0 | 0.4–32.0 | 4.75–23.0 | 2.0–10.0 | 0–20.5 | 17.9–47.1 | 14.0–32.0 | 35.0–100.0 | 19–30 |
| SCA1 $N$ = 7, 2 male | mean | 46.9 | 5.4 | 11.5 | 5.9 | 4.1 | 27.2 | 22.4 | 72.3 | 27.1 |
| | SD | 6.2 | 5.1 | 5.8 | 2.6 | 3.3 | 8.6 | 5.4 | 21.5 | 3.0 |
| | range | 39.0–58.0 | 0.4–13.0 | 5.0–23.0 | 4.0–10.0 | 1.0–9.25 | 18.7–45.1 | 17.0–32.0 | 41.0–100.0 | 22.0–30.0 |
| SCA2 $N$ = 2, 2 male | mean | 49.0 | 6.0 | 11.1 | 3.0 | 2.1 | 25.4 | 21.0 | 86.0 | 30.0 |
| | SD | 5.7 | 1.4 | 1.2 | 1.4 | 0.9 | 7.8 | 2.8 | 5.7 | 0.0 |
| | range | 45.0–53.0 | 5.0–7.0 | 10.3–12.0 | 2.0–4.0 | 1.5–2.75 | 19.9–30.9 | 19.0–23.0 | 82.0–90.0 | 30.0–30.0 |
| SCA3 $N$ = 4, 1 male | mean | 52.5 | 11.5 | 13.3 | 5.7 | 6.8 | 26.1 | 23.5 | 61.9 | 28.8 |
| | SD | 6.6 | 13.8 | 7.1 | 3.1 | 8.1 | 7.4 | 4.4 | 34.7 | 1.5 |
| | range | 47.0–62.0 | 2.0–32 | 4.75–22.0 | 3.0–9.0 | 0–18.5 | 17.9–35.8 | 20.0–29.0 | 30.0–100.0 | 27.0–30.0 |
| SCA6 $N$ = 6, 2 male | mean | 60.2 | 12.3 | 14.4 | 5.0 | 3.6 | 32.6 | 19.8 | 77.0 | 25.3 |
| | SD | 9.4 | 7.4 | 5.5 | 1.3 | 2.9 | 9.8 | 3.4 | 13.5 | 4.2 |
| | range | 53.0–74.0 | 3.0–23.0 | 6.5–20.5 | 4.0–7.0 | 0.5–7.5 | 20.3–47.1 | 14.0–23.0 | 60.0–90.0 | 19.0–29.0 |
| SCA7 $N$ = 1, female | | 69.0 | 14.0 | 11.3 | 6.0 | 20.5 | 34.8 | 16.0 | 40.0 | 22.0 |
| SCA17 $N$ = 1, male | | 49.0 | 6.0 | 12.5 | 5.0 | 5.5 | 41.0 | 17.0 | 70.0 | 20 |
| SCA28 $N$ = 1, male | | 37.0 | 17.0 | 14.0 | 4.0 | 2.8 | 28.8 | 27.0 | 60.0 | 28 |
| AOA2 $N$ = 1, male | | 22.0 | 7.0 | 15.0 | 4.0 | 8.3 | 39.9 | 27.0 | 80.0 | 30 |

group of disorders, that can be inherited in an autosomal dominant, autosomal recessive, X-linked fashion, or through maternal mitochondrial inheritance (Jayadev and Bird, 2013). Clinically, they are characterized by progressive loss of cerebellar functions resulting in increasing deficits of limb coordination, oculomotor abnormalities, dysarthia, gait and balance problems and variable combinations of extra-cerebellar signs including, for instance, other movement disorders and spasticity. Many subtypes are also associated with cognitive decline (Coarelli et al., 2018). However, the cognitive profile of CA is still a matter of debate and the evidence is inconclusive (Coarelli et al., 2018; Giocondo and Curcio, 2018). This is particularly the case with respect to cognitive control functions (Diamond, 2013; Donchin and Timmann, 2019). Cognitive control is an umbrella term encompassing the ability to extract regularities from the past to predict future events and to adapt behavior. There is evidence that cognitive control processes are disturbed in patients with cerebellar dysfunctions (Peterburs and Desmond, 2016) supporting the notion that the cerebellum is important for the processing of 'internal forward models' (Ito, 2008; Wolpert et al., 1998) and hence the prediction and processing of sensory events (Bellebaum and Daum, 2011; Kotz et al., 2014) and adaptive behavior (Peterburs and Desmond, 2016). There is further evidence from neuroimaging studies that the cerebellum contributes to post-error processing mainly engaging the prefrontal cortex and the anterior cingulate cortex (ACC) supposedly via cerebello-thalamo-cortical projections (Ide and Li, 2011; Strick et al., 2009). As a neurophysiological correlate of error-processing, the error-related negativity (ERN) generated in the ACC is associated with the (conscious and subconscious) processing of performance errors (Falkenstein et al., 1991; Gehring et al., 2018; Ullsperger et al., 2014) while the error-related positivity (Pe) that has a centro-parietal distribution, is related to more conscious aspects of error processing including error monitoring (Beste et al., 2008; Falkenstein et al., 2000; Hoffmann and Beste, 2015; Overbeek et al., 2005). In this context Peterburs et al. (2013, 2012) reported altered processing of correct and erroneous saccades but preserved performance accuracy in an anti-saccade task in patients with cerebellar lesions. Moreover, this group of researchers found that ERN amplitudes were reduced in these patients, while Pe amplitudes were increased suggesting that compensatory mechanisms led to preserved performance. Interestingly, in contrast to patients with cerebellar lesions, Pe amplitudes in patients with cerebellar degeneration did not differ from those in healthy controls in another study (Peterburs et al., 2015).

In the current study, we examined whether patients with CA have deficits in the ability to extract regularities from the past to predict future events and to adapt behavior, i.e. we studied cognitive control processes, in which internal forward models play a role. If these processes are indeed under cerebellar control, they should also be dysfunctional in CA patients. We used two behavioral paradigms, (i) to assess sensory predictive coding processes and (ii) to determine cognitive adaptation to response conflict and error with concomitant EEG recordings. This approach has been shown to detect even subtle variations in processes and performance in patients with diseases predominantly affecting the basal ganglia (Beste et al., 2018, 2017a, 2017b, 2017c) that are interconnected directly and through multiple cortical areas with the cerebellum (Bostan et al., 2010; Hoshi et al., 2005; Middleton, 2000; Middleton and Strick, 2000; Mori et al., 2016). The approach taken is therefore expected to be sensitive to show possible deficits in CA. On the EEG level, the intensity of processing has been linked to the amplitude of the P3a (Kok, 2001; Verleger et al., 2017), an event-related potential (ERP) that has also been linked to the updating of expectancies (Donchin, 1981). Sensory predictive coding is reflected in the mismatch negativity (MMN) (Baldeweg et al., 2006; Doeller et al., 2003; Garrido et al., 2009; Näätänen et al., 2014; Näätänen and Winkler, 1999; Wacongne et al., 2012) associated with sensory memory processes (Näätänen et al., 2007). The MMN is followed by the reorienting-negativity (RON) - a correlate of attentional re-orienting processes to the primary task after being distracted (Beste et al., 2008; Escera and Corral, 2007; Schröger and Wolff, 1998). Possible deficits in sensory predictive coding in CA patients should be reflected in (i) longer response times in CA patients than controls, whenever predictions have been violated, and (ii) decreased MMN compared to healthy controls. Re-orienting processes (as elicited by the RON) should not be affected in CA patients. Cognitive adaptation processes can emerge as a consequence of a perceived conflict between response alternatives (Botvinick et al., 2001), or as a consequence of response errors (Rabbitt, 1966). At the behavioral level, deficits during

these processes should lead to (iii) increased response times whenever there is conflict between response alternatives, and less adaptation of response times after errors. At the neurophysiological level, the N2 and the ERN component (Ullsperger et al., 2014) reflect these processes, and deficits should be mirrored by (iv) respective amplitude reductions.

## 2. Methods

### 2.1. Patients and controls

A total of $N = 25$ patients with genetically determined CA (see Table 1) and $N = 30$ sex- and age-matched (+/− 5 years) healthy controls (HC) were recruited for this study. After written informed consent to participate, all subjects underwent a standardized study protocol including (i) medical and family history for neurological, medical and/or psychiatric conditions, (ii) genetic diagnoses, and (iii) a detailed neurological examination following a standardized video protocol. The clinical evaluations were based on video recordings and were carried out by two independent investigators, one blinded to clinical diagnosis (JFB), and one un-blinded (ST). Both examiners were experienced in the use of the applied scales. To measure the severity of ataxia and non-ataxia symptoms, we used the Scale for the Assessment and Rating of Ataxia (SARA) (Weyer et al., 2007), the inventory of non-ataxia signs (INAS) (Jacobi et al., 2013), the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDS) (Burke et al., 1985), the PATA repetition rate (a 10 s timed speech task where subjects are asked to repeat the syllables "PATA" as quickly and clearly as possible; performed twice) (Schmitz-Hubsch et al., 2008), the 9-Hole-Peg-Test of the dominant hand (NHPT) (Schmitz-Hubsch et al., 2008), the EuroQol-5-Dimensions scale (with a visual analogue scale for subjectively perceived health status with a grade ranging from 0 = the worst possible health status to 100 = best possible health status (EQ5D) (Brooks, 2013), and the Montreal Cognitive Assessment (MOCA). Two patients had to be excluded from the analyses due to their inability to complete the study (1 with spinocerebellar ataxia (SCA) type 3, 1 with SCA6) resulting in 23 patients ($N = 7$ SCA1, $N = 2$ SCA2, $N = 4$ SCA3, $N = 6$ SCA6, $N = 1$ SCA7, $N = 1$ SCA17, $N = 1$ SCA28, $N = 1$ AOA2) with genetically determined CA (Table 1). One HC was excluded from further analyses due to an incidental finding of dystonia. Patients and HC with task performance below chance level were excluded from further analyses. All participants underwent the same examination setup and experimental paradigms. The study was approved by the Ethics Committee of the University of Lübeck, Germany (AZ 16-068).

### 2.2. Experimental paradigms

For sensory prediction coding, a "distraction paradigm" was used as in previous studies examining predictive coding processes (Beste et al., 2017c; Beste et al., 2008; Schröger and Wolff, 1998): tones were presented at three different frequencies (1000 Hz, 1100 Hz, 900 Hz) and two different lengths (400 ms, 200 ms). The standard tone (1000 Hz) occurred with a probability of 80%, the deviant tones (1100 Hz, 900 Hz), serving as distractors, occurred with 10% probability each. Regardless of tone frequency, the participants had to react with their index fingers whether the tone was of short (left response key, 50% of the trials) or long (right response key, 50% of the trials) duration. The paradigm consisted of 6 blocks with 100 trials each. The inter-trial interval was 1200 ms. Button presses in an interval below 200 ms after target stimuli were discarded. Three patients (1 SCA3, 1 SCA17, 1 SCA6) performed below chance level and were therefore excluded from further analyses yielding a total of $n = 20$ patients and $n = 29$ HC for this paradigm. For error-related behavioral processes, we used an established flanker task (Beste et al., 2017a; Chmielewski et al., 2014): the flanker (vertically arranged triangles pointing either to the left or right) preceded a centrally presented target stimulus (also a triangle pointing to the left or right) with a stimulus asynchrony of 200 ms. Target and flanker stimulus were displayed together for 300 ms. Compatible and incompatible trials corresponded to arrowheads of flankers and the target pointing in the same or opposite directions, respectively. Flanker and target arrows were switched off simultaneously. Time pressure was created by asking the subjects to respond within 450 ms. In trials with reaction times exceeding this time, a feedback stimulus tone (1000 Hz, 60 dB SPL) was given; this stimulus had to be avoided by the subjects. These trials were not excluded from further analyses. Inter-trial intervals were jittered between 900 and 1300 ms after response key presses. The experiment consisted of 4 blocks. Compatible (67%) and incompatible trials (33%) were presented pseudo-randomly (pseudo-randomized sequence consisting of 24 trials, 16 compatible/8 incompatible trials, repeated 10 times). A total of 480 trials were tested. The analyses reported here are limited to the pseudo-randomized blocks 2 and 4, yielding a total of 240 trials. The chance level was calculated using binomial methods: Two HC and three patients (1 SCA3, 1 SCA6, and 1 SCA28 patient) had less than 20 correct trials in the incompatible condition (after EEG preprocessing) and were therefore excluded from further analyses yielding a total of $N = 20$ patients and $N = 27$ HC in the flanker task.

### 2.3. EEG recording and analyses

EEG was recorded from 32 Ag-AgCl electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, Fz, Cz, Pz, FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, FCz, T3, T4, T5, T6, FT9, FT10, A1, A2) at standard scalp positions with a sampling rate of 512 Hz. To monitor ocular artifacts, vertical (vEOG) and horizontal (hEOG) electrooculogram were recorded. The reference electrodes were initially located at the left and right mastoids. All electrode impedances were kept $<5$ kΩ. Data were analyzed offline using BrainVision Analyzer 2.1.0 (Brain Products GmbH, Gilching, Germany). After downsampling to 256 Hz, a bandpass filter ranging from 0.5 to 20 Hz (48 dB/oct) and an additional notch filter (50 Hz) were applied, followed by manual inspection of the data to remove technical artifacts. After re-referencing to the average reference, an independent component analysis (ICA, infomax algorithm) for correction of ocular, muscular, and cardiac artifacts was performed. For the distraction paradigm, the segmentation created epochs of −500 ms to 1500 ms relative to stimulus onset. Only correct trials were included in this segmentation. The segmentation was followed by an automatic artifact rejection for central electrodes: C3, C4, CP1, CP2, CP5, CP6, Cz, F3, F4, FC1, FC2, FC5, FC6, FCz, Fz, P3, P4, Pz (gradient 80 μV/ms; value difference >100 μV/250 ms; amplitude < −100 μV or >100 μV/250 ms; activity >0.5 μV/200 ms) and baseline correction (−200 to 0 ms). As neurophysiological markers we studied different event-related potentials: (i) P3a for orientation of attention, (ii) mismatch negativity (MMN)/reorientation negativity (RON) for sensory predictive coding and reorientation after unexpected events, and (iii) the N2 and the error-related negativity (ERN) for cognitive adaptation processes/consequences of response errors. The MMN was measured as the difference waves of deviant minus standard ERP (Näätänen et al., 2014). Mean activities for ERP components were calculated from separate electrode sites and time intervals: MMN (FCz, 105–145 ms), P3a (CP1, 375–415 ms, CP2 360–400 ms), and RON (FCz, 430–530 ms). For the flanker paradigm, data obtained on correctly and incorrectly completed trials were segmented separately into epochs relative to target (−500 to 1500 ms) and response onset (−500 ms to 900 ms). After performing the segmentation, an automatic artifact rejection was applied (value difference >100 μV/250 ms; amplitude < −100 μV or >100 μV/200 ms; activity >0.2 μV/100 ms). To analyze target-related ERP components, the baseline correction (−500 ms to −300 ms) was followed by further segmentations for compatible and incompatible trials. Mean activities for ERP components were calculated from separate electrode sites and time intervals: Target-N2 (FCz, compatible 290–310 ms, incompatible 270–290 ms; Cz, both 280–300 ms), Target-P3 (compatible CP1/CP2, 360–400 ms, incompatible CP1/CP2

380–420 ms), Target-P1 (P4, 105–125 ms), Target-N1 (P4, 190–210 ms), Flanker-P1 (P4, −115 to −95 ms), and Flanker-N1 (P4, −65 ms to −45 ms). To analyze response-related ERP components the error-related-negativity (ERN, mean activity between 33–53 ms; FCz), correct-related-negativity (CRN, 25–45 ms; FCz) and error-related positivity (Pe, mean activity between 105–360 ms; Cz) were extracted from erroneous trials of both conditions after baseline-correction (−205 to −5 ms). Averages of stimulus- and response-locked ERPs were computed for both tasks on individual subject levels, followed by grand averages above groups (patients vs. HC). The data were quantified at the single-subject level. Electrode sites for ERPs were chosen with regards to where they had largest negativity (N1, N2, MMN, RON) and positivity (P3a, CRN, Pe), respectively, within the expected time frames. The time windows for mean amplitudes were defined through peak detection +/- 10 ms (N1, P1, N2, ERN), +/- 20 ms (P3a, MMN) and for the whole amplitude width (RON, Pe) in grand averages of HC.

### 2.4. Statistical analyses

The clinical, behavioral and neurophysiological data were analyzed using mixed-effects ANOVAs with "condition" as within-subject factors (distraction: frequent vs. deviant; flanker: compatible vs. incompatible) and "group" (HC vs. patient) as between-subject factors. Post-hoc tests were corrected for multiple comparisons (Bonferroni). Bayesian statistics were used to further elucidate the absence of significant "group x condition" interactions, based on sums-of-squares data from the ANOVA (Masson, 2011; Wagenmakers, 2007). With this approach, a graded level of evidence was obtained regarding which model, i.e. null hypothesis (no effect present) vs. alternative hypothesis (effect is present), is more strongly supported by the data (supplementary Table A) (Masson, 2011; Wagenmakers, 2007). The means and standard errors of the means are given for descriptive statistics. For correlations between symptom severity (indicated by disease duration, SARA, BFMDRS, and INAS scores) and measures of interests in the distraction task (accuracy, P3a deviant/frequent, MMN, RON) and flanker task (accuracy, P3a compatible/incompatible, N2, ERN, CRN, Pe) we used Pearson-correlations and applied Bonferroni corrections for multiple comparisons.

## 3. Results

### 3.1. Clinical characterization

The clinical data of the patients and HCs are given in Table 1. As the interrater reliability was high for the SARA (Cronbach's alpha = 0.984) and BFMDS scores (Cronbach's alpha = 0.966), we calculated the mean values for the rating scales of both raters.

### 3.2. Predictive coding and reorientation (distraction task)

Descriptive values for the behavioral data and summary data for the extracted ERPs are given in Fig. 1. The ANOVA revealed main effects of reaction time (RT) for "group" ($F(1,47) = 13.3$, $p = .001$) and "condition" ($F(1,47) = 85.91$, $p < .001$) with slower RT in patients (733 +/ −16 ms) vs. HC (658 +/ −13 ms). No interaction of "group x condition" was found ($F(1,47) = 0.99$, $p = .325$), which was supported by the Bayesian analysis revealing a probability of the null hypothesis of p(H0|D) = 0.81, corresponding to a Bayes Factor (BF01) of 4.2 in favor of the null hypothesis. Accuracy of responses did not differ between groups ($F(1,47) = 0.99$, $p = .323$) and conditions ($F(1,47) = 3.24$, $p = .078$) and there was no interaction of factors ($F(1,47) = 1.12$, $p = .295$, BF01 = 3.9). For details of the Bayes statistics see supplementary Table A. Taken together, overall RT were slower in patients compared to HC, and slower in patients and HC for deviant tones. There were no group differences with respect to the distractor.

For the P3a amplitudes, the ANOVA revealed main effects for "group" ($F(1,46) = 5.34$, $p = .025$) and "condition" ($F(1,46) = 7.16$, $p = .01$), but no interaction of "group x condition" ($F(1,46) = 0.096$, $p = .758$, p(H0|D) = 0.87, BF01 = 6.6). The amplitude of the P3a was smaller in patients (0.12 +/ −0.82μV) compared to HC (0.78 +/ −1.42μV). Both in patients and HC, P3a amplitudes were larger in deviant trials (Fig. 1B). The MMN amplitudes did not differ between groups ($t(46) = 0.79$, $p = .431$; patients −0.24 +/ −0.30 μV vs. HC −0.32 +/− 0.39 μV). The ANOVA for the RON amplitudes revealed a main effect of "condition" ($F(1,46) = 11.88$, $p = .001$) and a "group x condition" interaction ($F(1,46) = 9.88$, $p = .003$), but no effect of group ($F(1,46) = 0.02$, $p = .877$). Post-hoc tests showed a significant effect of "condition" on the RON in HC ($t(27) = 4.77$, $p < .001$) but not in patients ($t(19) = 0.22$; $p = .826$), with mean amplitudes (before calculating the RON) being more negative in deviant (−0.87 +/−2.34 μV) vs. frequent (−0.33 +/−0.38 μV) trials in HC but not in patients (deviant −0.69 +/−1.10 μV vs. frequent −0.67 +/−1.15 μV). Overall, RON amplitudes (Fig. 1C) were larger in HC (−0.54 +/− 0.6) compared to patients (−0.025 +/−0.5, $t(46) = 3.143$, $p = .003$).

In patients, there was an inverse correlation between MMN and response accuracy (Pearsons $r = −0.613$, $p = .004$, after Bonferroni $p = .036$). The following correlation coefficients were high, but were not significant following Bonferroni correction for multiple testing: Ataxia severity measured with the SARA correlated inversely with response accuracy (Pearsons $r = −0.578$, $p = .008$; after Bonferroni $p = .072$), SARA correlated with the RON amplitude ($r = 0.447$, $p = .048$; after Bonferroni $p = .432$), and disease duration correlated inversely with response accuracy ($r = −0.447$, $p = .048$ after Bonferroni correction $p = .432$).

### 3.3. Behavioral adaptation processes (flanker task)

Descriptive values for the behavioral data and average ERP data are given in Fig. 2. The ANOVA of reaction times showed a main effect for "group" ($F(1,45) = 18.74$, $p < .001$) and "condition" ($F(1,45) = 545.08$, $p < .001$), with slower responses in patients (450 +/ −15 ms) compared to HC (367 +/ −13 ms) and in incompatible (455 +/ −11 ms) compared to compatible trials (362 +/ −9 ms), but no "group x condition" interaction ($F(1,45) = 0.51$, $p = .481$, p(H0|D) = 0.84, BF01 = 5.3). Response accuracy differed between conditions ($F(1,45) = 158.22$, $p < .001$), but the ANOVA did neither reveal main effects of "group" ($F(1,45) = 0.14$, $p = .714$), nor a "group x condition" interaction ($F(1,45) = 3.59$, $p = .064$, p(H0|D) = 0.53, BF01 = 1.1). Compatibility effects ( = difference of RT incompatible – RT compatible) did not differ between groups ($t(45) = 0.711$, $p = .481$). For post-error slowing the ANOVA showed main effects for "group" ($F(1,45) = 18.58$, $p < .001$) and "condition" ("RT posthit" vs "RT posterror") ($F(1,45) = 13.03$, $p = .001$) but no interaction effect of "group" x "condition" ($F(1,45) = 0.049$ $p = .826$, p(H0|D) = 0.87, BF01 = 6.7), i.e. post error slowing was present in both groups and did not differ between groups. Also, differences of RTs of erroneous and correct trials after correct hits ("RT posterror" minus " RT posthit") did not differ between patients (20.4 +/−55.2 ms) and HC (23.0 +/−25.4 ms, $t(45) = −0.22$; $p = .074$).

For the P3a, the repeated measures ANOVA revealed a main effect of "group" ($F(1,44) = 4.61$, $p = .037$) but not "condition" ("compatible" vs. "incompatible") ($F(1,44) = 2.69$, $p = .108$) and also no interaction effect ($F(1,44) = 0.30$, $p = .58$, p(H0|D) = 0.85, BF01 = 5.8), i.e. the P3a was larger in HC than in patients, but did not differ between compatible (HC 3.46 +/−2.95 μV vs. patients 1.93 +/ −1.62 μV) compared to incompatible trials (HC 3.22 +/−3.60 μV vs. patients 1.44 +/−1.64 μV). Target-N2 amplitudes in compatible ($t(44) = −0.26$, $p = .790$) and incompatible ($t(44) = 0.21$, $p = .836$) trials did not differ between groups. In addition, there were no group differences for the ERN ($t(44) = 1.49$, $p = .141$) or the CRN ($t(44) = −0.81$, $p = .419$) (Fig. 2E). There were also no group differences of ERN−CRN difference waves in the ERN time window at electrode FCz (t

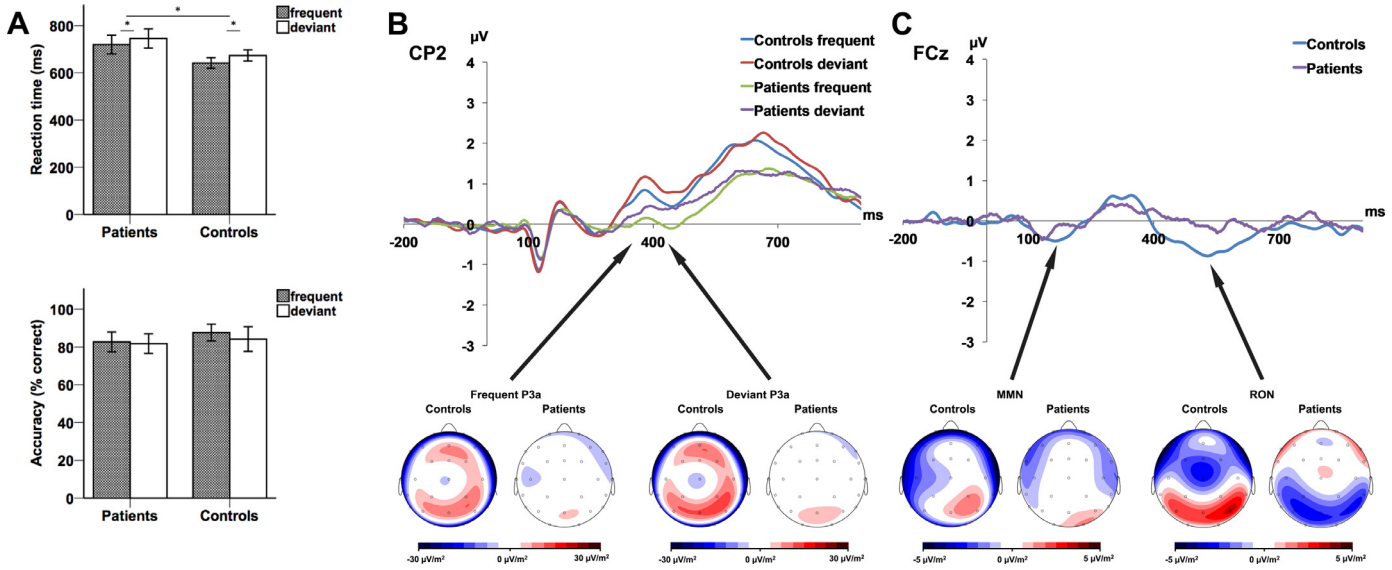


**Fig. 1.** Behavioral and ERP data in the distraction task. (A) Reaction times and accuracy (percentage of correct answers) in patients and healthy controls are given for frequent (grey) and deviant trials (white bar). Data are mean +/− standard error of the mean. Statistically significant differences are marked with [*]. (B) The P3a waves for frequent (controls blue and patients green) and deviant tones (controls red, patients purple) at the electrode CP2. (C) The mismatch negativity (MMN) and reorienting negativity (RON) are shown for controls (blue) and patients (purple) at the electrode FCz. The MMN and RON were measured as the difference waves (deviant minus frequent). Scalp topographies are shown for P3a of frequent and deviant tones, MMN and RON. Time point zero denotes the time point of stimulus presentation. Scalp topographies are given of the respective ERP-components for time intervals specified in 2.3 of the methods section. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(44) = 1.8, $p$ = .077) (Fig. 2F). In contrast, the Pe amplitude was larger in HC than in patients (HC 3.0+/−2.6 μV vs. patients 0.91 +/−2.2μV; t(44) = −2.89, $p$ = .006). The ANOVAs of the remaining early ERPs are summarized in the supplementary Table B. Correlations of clinical parameters with behavioral and ERP data in patients showed an inverse correlation of Pe amplitudes with the BFMDS ($r$ = −0.68, $p$ = .001; after Bonferroni $p$ = .011), indicating that patients with more severe dystonic symptoms had smaller Pe amplitudes. Further, the amplitudes of Pe and P3a for incompatible trials showed a high correlation coefficient, but this did not withstand Bonferroni correction for multiple testing ($r$ = 0.486; $p$ = .03; after Bonferroni $p$ = .33). In HC, we found correlations of the incompatible N2 and P3 amplitudes for compatible ($r$ = 0.66, $p$ < .001, after Bonferroni $p$ = .003) and incompatible ($r$ = 0.67; $p$ < .001, after Bonferroni $p$ = .002) trials. Other correlations did not withstand the Bonferroni corrections, even though they showed high correlation coefficients for N2 and ERN amplitudes ($r$ = 0.48, $p$ = .014; after Bonferroni $p$ = .154), as well as a high inverse correlation coefficient for the incompatible N2 and Pe ($r$ = −0.47; $p$ = .016, after Bonferroni $p$ = .176). Not surprisingly, P3 amplitudes of compatible and incompatible trials were highly correlated in patients ($r$ = 0.74; $p$ < .001) and HC ($r$ = 0.88, $p$ < .001).

## 4. Discussion

In the current study, we examined cognitive control processes in CA with a focus on mechanisms important for the ability to extract regularities from the past to predict future events and to adapt behavior. The rationale was that there is evidence that the cerebellum influences internal forward models. In the first paradigm, we examined sensory predictive coding processes, in the second, error-related behavioral adaptation processes that also depend on processing of predictions and prediction errors.

While CA patients revealed a general slowing in reaction times, the neurophysiological correlate of predictive coding, the MMN (Baldeweg et al., 2006; Doeller et al., 2003; Garrido et al., 2009; Näätänen et al., 2014; Näätänen and Winkler, 1999; Wacongne et al., 2012) did not differ from HCs. This was corroborated by a Bayesian data analysis and strongly suggests that CA patients are not more distracted than HC by deviant (i.e. prediction-violating) sensory information. Therefore, the data clearly show that predictive coding processes are largely intact in CA. This is a surprising finding because cerebellar dysfunction is expected to alter these processes that contribute to 'internal forward models', which in turn likely depend on cerebellar functions (Ito, 2008; Wolpert et al., 1998; Blakemore et al., 2001; Blakemore and Sirigu, 2003; Fellows et al., 2001). Corroborating evidence for the interpretation that forward model processing is intact in genetically determined CA comes from the obtained data of error-related behavioral adaptation. In fact, there was no group difference in the ERN and related behavioral processes of post-error slowing. The ERN is known to reflect a reward prediction error signal (Holroyd and Coles, 2002) that also includes processes of forward model planning (Holroyd and Coles, 2002; Smout et al., 2019). Taken together, MMN and ERN data suggest that the examined groups of genetically determined CA do not show alterations in overarching mechanisms related to the processing of internal forward models.

On the other hand, we found decreased Pe amplitudes in CA indicating that the error-awareness of patients is altered. Interestingly, the Pe amplitude appears to be inversely correlated with dystonia severity, i.e. that patients with more severe dystonic symptoms have a less pronounced Pe. Traditionally, dystonia has been considered a sign of basal ganglia dysfunction (Berardelli et al., 1998). However, a number of studies have also suggested a role of the cerebellum in the pathophysiology of dystonia, but this continues to be a contentious issue (Bologna and Berardelli, 2018). On the basis of the data available, we cannot decide with certainty whether the relation between Pe amplitudes and dystonia, which was overall mild in the patients we studied, might be indicative of cerebellar or (subtle) basal ganglia pathology, or both.

Our main finding of intact processing of internal forward models differs from previous reports of patients with cerebellar pathology, particularly with respect to error-related behavioral adaptation (Peterburs and Desmond, 2016). In fact, some findings from saccade-related efference copy processing in patients with cerebellar and thalamic lesions (Peterburs et al., 2013, 2012) and processing of correct

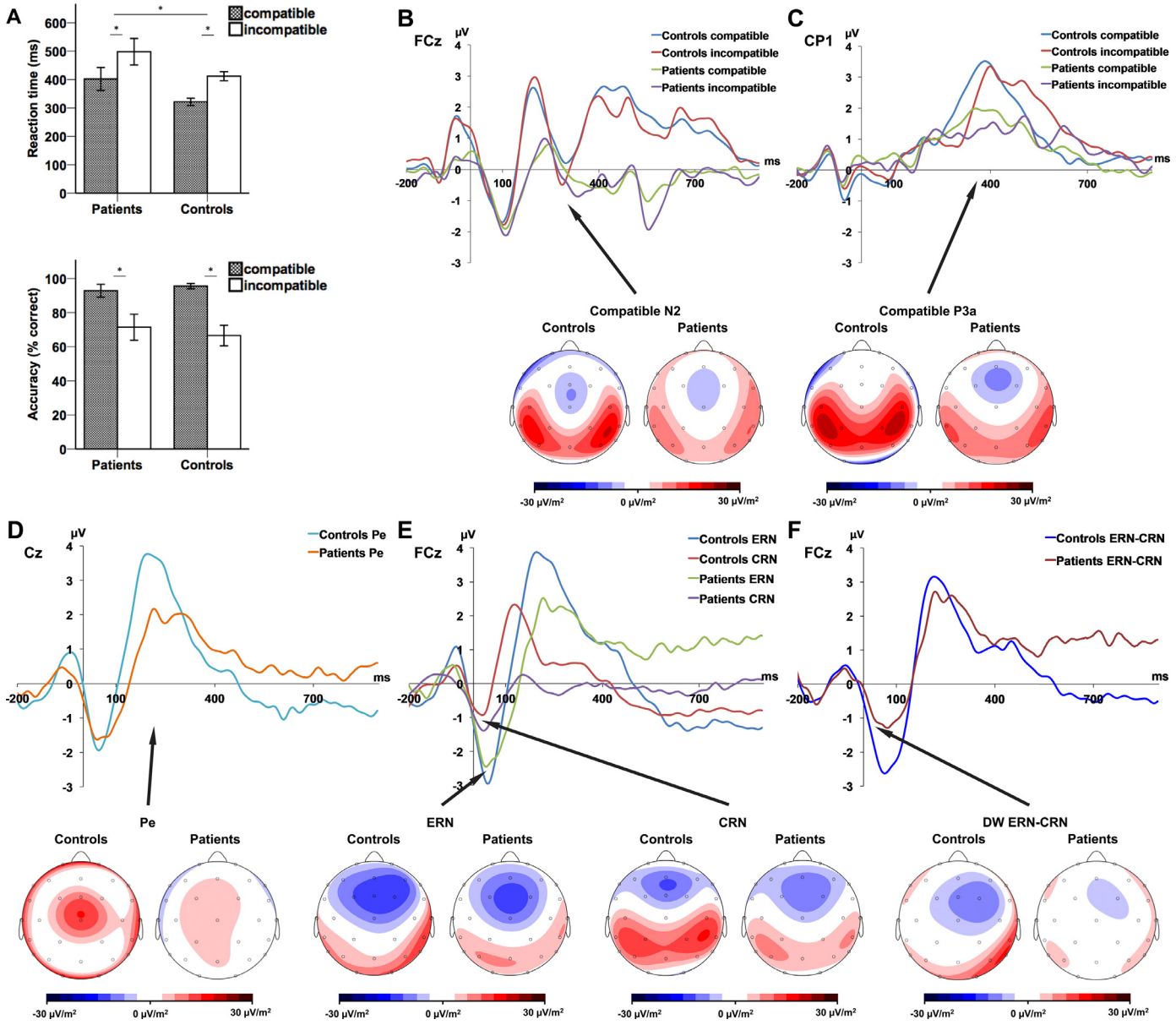


**Fig. 2.** Behavioral and ERP data in the flanker task. (A) Reaction times and accuracy (percentage of correct answers) for compatible (grey bars) and incompatible (white bars) trials in the flanker task in patients and controls. Data are mean +/− standard error of the mean. Statistically significant differences are marked with [*]. (B) Target-N1 and -N2 extracted from FCz. (C) target-P3a extracted from CP1 for compatible (controls blue, patients green) and incompatible trials (controls red, patients purple). (D) Pe extracted from Cz (controls light blue, patients orange). (E) ERN (controls blue, patients green) and CRN (controls red, patients purple) at the electrode FCz from stimulus-locked waves. (F) Difference waves showing the ERN−CRN difference at electrode FCz. Time point zero denotes the time point of the target stimulus presentation in (B) and (C) and of the response in (D) and (E). Scalp topographies are given of the respective ERP-components for time intervals specified in 2.3 of the methods section. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and erroneous saccades in patients with cerebellar degeneration (Peterburs et al., 2015) indicated that error rates were increased and ERN was reduced in these patients. Interestingly, this group of researchers observed an increase of Pe amplitude in patients with focal cerebellar lesions but not in patients with degenerative cerebellar disease (Peterburs et al., 2015), concluding that the increased Pe in patients with focal lesions might reflect a compensatory mechanism for altered error monitoring as evident in a reduced ERN. Furthermore, volume loss of the cerebellum was reported to be associated with a reduced ERN (Peterburs et al., 2015). In the context of cerebellar involvement in cognitive control, a meta-analysis (Stoodley and Schmahmann, 2009) reported that the cerebellar lobules VI, VIIb and Crus I are involved in executive function task that were known to predominantly activate frontal areas and the cingulate cortex. It is, however, important to consider that previous studies predominantly examined patients with cerebellar lesions due to stroke or following surgery and therefore addressed sequelae of abrupt dysfunctions of cerebellar circuits. In contrast, genetically determined CA are a group of slowly progressive diseases due to neurodegeneration, where compensation and progression are evolving at the same time. Therefore, adaptive processes at a system level compensating for molecular defects that are present since neural development (Harding et al., 2017) need to be considered and might explain why error awareness was altered while predictive coding and error-related behavioral adaption processes were normal in our group of patients.

This complex neurophysiological pattern in genetically determined progressive neurodegenerative diseases is not unprecedented. Predictive coding processes have been shown to be useful markers of

disease processes in other neurodegenerative diseases, for instance in Huntington's disease (HD) it was shown that clinically symptomatic HD patients had higher MMN and RON amplitudes, shorter latencies and better behavioral performance (lower error rates, shorter RTs) compared to HC and pre-symptomatic gene mutation carriers (Beste et al., 2014; Beste et al., 2008). This surprising finding of supra-normal performance in a disease typically presenting with profound cognitive impairment was interpreted as a sign of increased glutamatergic transmission due to the disease process. This has also been corroborated by computational studies (Beste et al., 2014; Tomkins et al., 2013). In another basal ganglia model diseases, X-linked dystonia parkinsonism (XDP) characterized by predominant striosomal degeneration or microstructural alterations of medium spiny neurons, error-related behavioral adaptation processes (displayed by an attenuated ERN amplitude) but not response inhibition functions were found to be altered (Beste et al., 2017a, 2017b; Beste and Saft, 2014). Differences in the ERN between XDP and healthy controls were a result of activation differences in the subgenual and pregenual ACC (Beste et al., 2017a), which receives strong input from the striosomal compartment of the striatum. This led to the conclusion that dysfunctions in error-related behavioral adaptation and related neurophysiological changes in the ACC reflect an indirect effect of striosomal dysfunction, leading to disturbances in fronto-striatal circuits.

With respect to spinocerebellar ataxias it has been suggested that cerebellar functions involved in error-based processes show a decline, while reward-based processes predominantly mediated by the basal ganglia show a concomitant upregulation in early disease stages (Donchin and Timmann, 2019). Reward-prediction error-based basal ganglia processes are important for predictive coding (Beste et al., 2014; Beste et al., 2008; Tomkins et al., 2013; Wacongne et al., 2012) and error-related behavioral adaptation (Holroyd and Coles, 2002; Ullsperger et al., 2014). Thus, basal ganglia circuits engaged in error processing and predictive coding may compensate for dysfunctional cerebellar contributions to these processes.

On the other hand, the frontal P3a, a marker of attentional shifting and updating of a mental model, and the RON, a correlate of attentional re-orienting processes to the primary task after being distracted (Escera and Corral, 2007; Schröger and Wolff, 1998), were both abnormal in our CA patients. These processes are largely mediated by dorsolateral and orbitofrontal areas receiving inputs from the basal ganglia via the ventro-anterior and the dorso-medial regions of the thalamus (Alexander et al., 1986; Lindsay and Storey, 2017). Disruptions of these pathways also lead to impaired set shifting. The latter has in fact been reported in patients with degenerative CAs (Lindsay E and Storey E, 2017; Maruff et al., 1996; Pereira et al., 2017). It is thus possible that these circuits are primarily affected in the disease process, so that deficits of attention and set shifting are more sensitive markers for cognitive dysfunctions in CA than predictive coding and error related behavioral adaptation.

Our study has limitations. Although the study population comprised genetically confirmed CA patients the study population was not homogeneous. Patients had a wide range of disease duration (0.4–32 years) and symptom severity (SARA mean range 4.75–23). Also, while some subtypes of CA have a relatively “pure” cerebellar disease (e.g. SCA6), there is a diverse pattern of extracerebellar involvement in others (e.g. SCA3, SCA17). Neuroimaging illustrating cerebellar pathology was not regularly acquired in the patients we studied and was not taken into account for the analyses and interpretation of our data. Even if imaging had been performed systematically in all patients normal structural imaging of, for instance, basal ganglia, in a given patient would not have ruled out microstructural involvement of these nuclei. To address the relevant issue of extra-cerebellar involvement, we extended our clinical analyses by including subitems of the INAS as surrogate parameters for symptoms indicative of extra-cerebellar pathology including spasticity, rigidity and resting tremor. A sub-analysis of these parameters revealed that only a few patients had such symptoms and these were generally mild (supplementary Table C). This makes it unlikely that extra-cerebellar pathology was a crucial factor in the sample we studied.

## 5. Conclusions

Taken together, CA patients studied here displayed preserved sensory prediction and error processing, whereas error awareness, orientation of attention and reorientation after disruption of attention were abnormal, so that in CA patients processes generating internal forward models *per se* are not dysfunctional but rather the updating of mental models.

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## Declaration of Competing Interest

The authors do not have any conflict of interest.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102043.

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