



## Altered brain activation in a reversal learning task unmasks adaptive changes in cognitive control in writer's cramp



Kirsten E. Zeuner<sup>a,\*</sup>, Arne Knutzen<sup>a</sup>, Oliver Granert<sup>a</sup>, Simone Sablowsky<sup>a</sup>, Julia Götz<sup>a</sup>, Stephan Wolff<sup>b</sup>, Olav Jansen<sup>b</sup>, Dirk Dressler<sup>c</sup>, Susanne A. Schneider<sup>a</sup>, Christine Klein<sup>d</sup>, Günther Deuschl<sup>a</sup>, Thilo van Eimeren<sup>a</sup>, Karsten Witt<sup>a</sup>

<sup>a</sup>Department of Neurology, Kiel University, Germany

<sup>b</sup>Department of Radiology and Neuroradiology, Kiel University, Germany

<sup>c</sup>Movement Disorders Section, Department of Neurology, Hannover Medical School, Germany

<sup>d</sup>Institute of Neurogenetics, University of Lübeck, Germany

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### ABSTRACT

Previous receptor binding studies suggest dopamine function is altered in the basal ganglia circuitry in task-specific dystonia, a condition characterized by contraction of agonist and antagonist muscles while performing specific tasks. Dopamine plays a role in reward-based learning.

Using fMRI, this study compared 31 right-handed writer's cramp patients in reward-based learning of a probabilistic reversal-learning task. All subjects chose between two stimuli and indicated their response with their left or right index finger. One stimulus response was rewarded 80%, the other 20%. After contingencies reversal, the second stimulus response was rewarded in 80%. We further linked the DRD2/ANKK1-Taqla polymorphism, which is associated with 30% reduction of the striatal dopamine receptor density with reward-based learning and assumed impaired reversal learning in A+ subjects.

Feedback learning in patients was normal. Blood-oxygen level dependent (BOLD) signal in controls increased with negative feedback in the insula, rostral cingulate cortex, middle frontal gyrus and parietal cortex ( $p_{FWE} < 0.05$ ). In comparison to controls, patients showed greater increase in BOLD activity following negative feedback in the dorsal anterior cingulate cortex (BA32). The genetic status was not correlated with the BOLD activity.

The Brodmann area 32 (BA32) is part of the dorsal anterior cingulate cortex (dACC) that plays an important role in coordinating and integrating information to guide behavior and in reward-based learning. The dACC is connected with the basal ganglia-thalamo-loop modulated by dopaminergic signaling. This finding suggests disturbed integration of reinforcement history in decision making and implicate that the reward system might contribute to the pathogenesis in writer's cramp.

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### 1. Introduction

Writer's cramp, the most common focal task specific dystonia, is characterized by dystonic co-contraction during writing (Hallett, 2006). Abnormalities in the striatal dopamine system may contribute to the pathophysiology. One aspect is that D<sub>2</sub>/D<sub>3</sub> receptor availability is reduced. This has been detected in several dopaminergic positron emission tomography (PET) studies with focal dystonias (Karimi et al., 2011) including writer's cramp (Horstink et al., 1997; Berger et al., 2007), cervical (Naumann et al., 1998) and facial dystonia (Perlmutter et al., 1997; Horie et al., 2009) and spasmodic dysphonia (Simonyan et al., 2013). Consistent with those previous studies, C-raclopride

binding to D<sub>2</sub>/D<sub>3</sub> receptors was reduced in patients with writer's cramp at rest in the bilateral striatum and in the contralateral caudate nucleus during tapping; a finding that has been attributed to a possible defect in receptor turnover or an abnormal D<sub>2</sub>-like receptor expression (Berman et al., 2013).

The striatum connects with the premotor and prefrontal cortex or the rostral cingulate zone. These areas are presumably also associated with striatal dopamine release and are involved in tasks that require dopamine (Cools et al., 2002; Jocham et al., 2009a; Mell et al., 2009) such as reward based learning and decision making (Cools et al., 2002, 2007; Peterson et al., 2009). A paradigm to investigate reward-based learning and decision making is reversal learning (Cools et al., 2002; Jocham et al., 2009a). In this task a specific response is rewarded. After a number of trials the contingencies are reversed and the alternative stimulus is rewarded (Cools et al., 2002; Jocham et al., 2009a). Patients with Parkinson's disease demonstrated normal functioning of initial

\* Corresponding author at: Department of Neurology, Kiel University, Arnold Heller Straße 3, Haus 41, 24105 Kiel, Germany.

E-mail address: [k.zeuner@neurologie.uni-kiel.de](mailto:k.zeuner@neurologie.uni-kiel.de) (K.E. Zeuner).

acquisition (Cools et al., 2006), but impaired reversal learning (Peterson et al., 2009) which may be suggestive of ventral striatum dysfunction.

Furthermore, there are reports indicating that the DRD2/ANKK1-Taqla polymorphism, especially the A1 allele is associated with 30% reduction of the striatal receptor density (Thompson et al., 1997; Pohjalainen et al., 1998; Ritchie and Noble, 2003; Kadota et al., 2010). Ventral regions of the caudate nucleus, the putamen and the prefrontal cortex are vulnerable to diminished D<sub>2</sub> receptor density (Noble et al., 1997; Bertolino et al., 2010; Stelzel et al., 2010). Pre-existing studies demonstrated that the performance in a probabilistic reversal-learning task was changed in subjects, who carried the DRD2/ANKK1-Taqla polymorphism (Frank and Hutchison, 2009; Jocham et al., 2009a). A1 + carriers showed numerically better positive, but worse negative learning (Frank and Hutchison, 2009), displayed difficulties in maintaining the newly rewarded response after change of contingencies and switched their response more frequently (Jocham et al., 2009a).

In summary, the causes of impaired dopaminergic neurotransmission remain unclear and could be related to either increased or decreased endogenous dopamine release as well as changes in D<sub>2</sub>/D<sub>3</sub> receptors availability. Assuming that in patients with writer's cramp dopaminergic neurotransmission might be abnormal, the activity during a reversal learning task should be altered in dopamine innervated areas in these patients. Therefore, we conducted this study in patients with writer's cramp using fMRI during a reversal learning task and hypothesized that BOLD activity is abnormal in the striatum, the prefrontal cortex and the rostral cingulate zone in response to negative feedback during task performance. We further investigated the DRD2/ANKK1-Taqla polymorphism and assumed that reversal learning would be particularly impaired in those subjects, who carried the A + allele.

## 2. Methods

### 2.1. Patients and controls

Thirty-one patients with writer's cramp (16 women) with a mean age of  $51.0 \pm SD 13.1$  years (range: 24–78 years) and a mean disease duration of  $13.6 \pm SD 8.7$  years were comprised in the fMRI study. Thirty-five age-matched healthy individuals (17 women) with a mean age of  $49.7 \pm SD 8.8$  (range: 25–68 years) served as controls. Eleven patients (3 women, age  $53.6 \pm SD 8.8$ ) and eighteen controls (7 women, age  $47.6 \pm SD 9.4$ ), assigned to the A + group, participated.

Patients and controls were right-handed (laterality quotient: patients  $92.1 \pm SD 9.8$ , range: 62.5–100; controls  $88.4 \pm SD 10.5$ , range: 68.4–100) according to the Oldfield handedness test (Oldfield, 1971). The handedness test was not performed in patients P108 and P125.

The diagnosis of writer's cramp was established by medical history and standard neurological examination including a writing test of the right, affected hand. The last botulinum toxin injection was performed at least three months before inclusion. Exclusion criteria comprised any other neurological or psychiatric disorder, musicians and professional typists.

All participants gave written informed consent before the study. The study was conducted in full accordance to the Declaration of Helsinki and had been approved by the local ethics committee in Kiel.

#### 2.1.1. Clinical assessment of writer's cramp

Patients were videotaped while writing the German sentence "Die Wellen schlagen hoch" ("The waves are surging high") ten times, and the severity analyzed from the video segments (face not shown) using the Writer's Cramp Rating Scale (WCRC) (Wissel et al., 1996). A higher total WCRC score (with a maximum score of 30 points) implies more severe dystonic signs during handwriting.

The Arm Dystonia Disability Scale (ADDS) contains seven items that estimate the impairment of manual skills reported by patients. A score of 100% indicates normal motor function. The final score represents

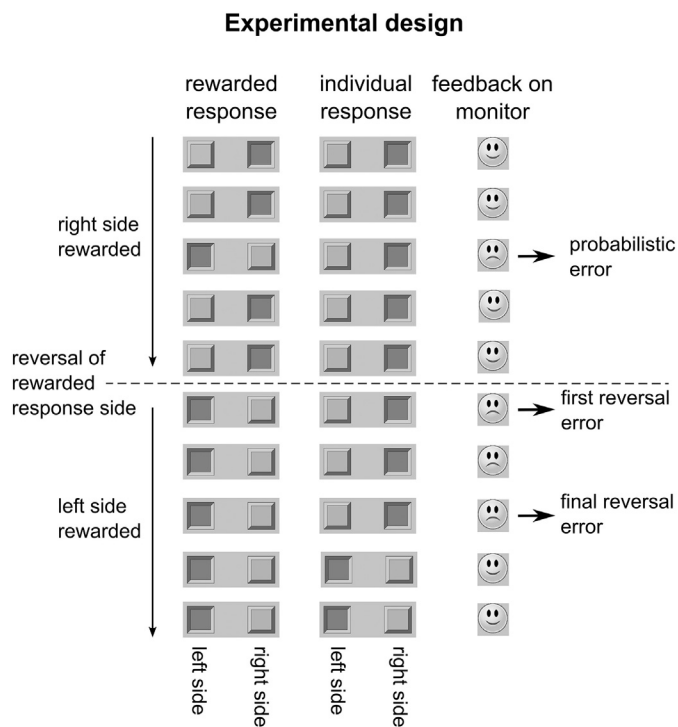
the percentage of normal manual activity. Therefore, a lower ADDS score denotes more severe functional impairment (Fahn, 1989).

### 2.2. Genetic analyses

The DRD2/ANKK1-Taqla polymorphism can be differentiated into the A1/A1, the A1/A2 and A2/A2 genotypes. In our study, participants were divided into two groups according to their genotype. The examiners and subjects were blinded with respect to the genotype. Genotyping of the DRD2/ANKK1-Taqla was performed by Sanger sequencing. The genetic analysis was performed first and subjects were selected according to the DRD2/ANKK1-Taqla polymorphism.

### 2.3. Probabilistic response reversal learning task

The probabilistic response reversal task was based on previous studies (Cools et al., 2002; Jocham et al., 2009a). Two identical squares were presented on the right and left side of a fixation cross. The subjects selected one of the squares and pressed the corresponding button with their right or left index finger. One of the squares was rewarded with a smiling face in 80% of the trials, while in 20% a sad face was presented despite of a correct response. After 14–18 blocks the contingencies changed and the other response was rewarded in 80% (Fig. 1). All participants were recompensed with 10 cents after a correct response, while 5 cents were subtracted following an incorrect response. Gains, losses and a balance sheet were shown on the screen after each decision and the money paid at the end of the scanning session. A previous training session included two blocks of task trials with one reversal. The experiment lasted 26.1 min and consisted of 348 trials of 4.5 s in total, 21 blocks with 20 contingency reversals (310 trials) and randomly interspersed 38 null trials. The interval between the presentation of the fixation cross and



**Fig. 1.** Experimental design: this was an event-related design, in which the individuals chose between two identical stimuli right and left side and indicated their response with their index finger of the hand corresponding to the side of the stimulus. The first column indicates the rewarded response, the middle column the answer of the individual. One stimulus response side was rewarded with a smile in 80%, the other in 20%. If the answer was incorrect, a sad face appeared. After 14–18 trials, the contingencies reversed, and the other stimulus response side was rewarded in 80%. The light gray squares indicate that the button was not pressed, while the dark gray square reflects the pressed button.

the squares (remained on the screen for 1.4 s) were jittered between 0 and 2.2 s. Following the response, the corresponding button changed its color and was displayed for 0.1 s followed by the feedback (smiling/sad face) of 0.8 s. No answer was acknowledged with a sad face and a 5 cents loss. A reversal error occurred with a previously correct response after a contingency change indicating a negative feedback for a wrong answer. The final reversal error was predefined for the last reversal error before shifting to the new, correct response (Cools et al., 2002; Jocham et al., 2009a).

#### 2.4. MRI data acquisition

Functional images were acquired at the Kiel University hospital using a 3 T whole-body MRI scanner (Achieva; Philips, Best, the Netherlands) equipped with an 8-channel head coil. An fMRI system (Invivo, Gainesville, FL, USA) provided with E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) was used for stimulus presentation and response recording.

We performed a whole-brain echo planar imaging (EPI) to measure regional changes in the blood oxygen level-dependent (BOLD) signal. The EPI sequence consisted of 635 volumes with 38 axial slices acquired parallel to the anterior–posterior plane with the following acquisition parameters: Slice thickness 3.0 mm, inter-slice gap of 0.3 mm, TR 2500 ms; TE 36.4 ms; FOV  $216 \times 216 \times 125.1 \text{ mm}^3$ ; matrix  $64 \times 64$ ; flip angle  $90^\circ$ . The resulting voxel size was  $3.38 \times 3.38 \times 3.29 \text{ mm}^3$ .

For normalization to the Montreal Neurological Institute (MNI) standard space and radiological diagnostics a 3-dimensional (3D) T1-weighted gradient echo MRI scan with sagittal volume excitation was acquired from each participant with the following parameters: TR 7.8 ms; TE 3.6 ms; TI 800 ms; flip angle  $8^\circ$ ; FOV  $160 \times 240 \times 240 \text{ mm}^3$ ; 160 slices with an image matrix and a scan resolution of  $240 \times 224$  voxels and a reconstruction matrix of  $256 \times 256$  voxels yielding in final voxel size of  $1 \times 0.94 \times 0.94 \text{ mm}^3$ .

#### 2.5. Analysis of imaging data

Data preprocessing and statistical analysis was done with SPM8 (Release V4010) software (<http://www.fil.ion.ucl.ac.uk/spm/>) and Matlab 7.11.0 (MathWorks Inc., Natick Massachusetts, USA).

#### 2.6. Image preprocessing

For spatial normalization of the images to the MNI standard space, the SPM8 segmentation algorithm was applied to the individual T1-weighted images. The functional EPI images were registered to their pre-aligned mean using the SPM two pass realignment procedures to compensate movement effects. We co-registered the mean image of the realigned EPI images to the corresponding individual T1-weighted image and used the concatenated transformation from this co-registration and the normalization from the T1-segmentation step to write normalized versions of the EPI images (re-sliced with a resolution of  $2 \times 2 \times 2 \text{ mm}$ ). This procedure optimized spatial normalization, because the complex nonlinear spatial normalization functions were determined from the high-resolution T1-weighted structural image and not from the EPI images with lower resolution and less contrast.

Finally, a smoothing filter with a Gaussian kernel of 8 mm full-width half-maximum (FWHM) was applied to the normalized EPI images to reduce residual anatomical differences and implement the Gaussian random field theory in further statistical analysis.

### 3. Statistical analysis

#### 3.1. Probabilistic reversal learning task

The two-sample t-test was used to evaluate differences of the baseline data. In a second analysis, the comparison of the behavioral data

between the different genetic groups (A+ controls and A– controls; A+ patients and A– patients) was performed using a one-way ANOVA. Group comparison to test for the A+/A– distribution between patients and controls was performed with the chi-square test. A p-value  $< 0.05$  was considered significant.

#### 3.2. Functional magnetic resonance image analysis (fMRI)

We used a first-level fMRI event related model (Cools et al., 2002; Jocham et al., 2009a). All negative and positive feedbacks were modeled at feedback onset. The following events were analyzed: 1. Positive feedback to correct responses (positive feedback). 2. Negative feedback to correct responses (probabilistic error). 3. Reversal error after the contingency had changed. 4. Final reversal error with the last incorrect before the new, correct response. 5. Negative feedback that is not captured by the previous event types (remaining negative feedback events). We added six additional movement variables (3 translation and 3 rotation parameters) from the realignment procedure to compensate for residual movement-related artifacts. The first-level model included four different types of negative feedbacks in our experiment. To access the individual general BOLD effect on negative feedbacks we calculated a weighted mean over all negative feedback parameter estimates. The weighted mean was implemented by adjusting the contrast weights individually according to the number of events within each event type. This calculation ensured that each event contributed equally to the final contrast image used in the subsequent group analysis and allowed us to compare the estimate to the positive feedback parameters.

At the group level, the following three event-related BOLD differences were studied between:

- negative and positive feedbacks (Jocham et al., 2009a),
- final reversal and reversal errors (Jocham et al., 2009a),
- final reversal errors and correct responses (Cools et al., 2002).

All feedback types included button-press events. Thus, calculating the differences ensured that motor related activations were compensated.

We examined each of these BOLD differences by specifying three separate group-level models:

- A one-sample t-test model based on the controls to understand the BOLD signal changes in the healthy “normal” brain.
- A two-sample t-test model with the patient and control group to test for disease specific activation differences.
- A two-sample t-test model with the genetic groups A– and A+ to test for gene specific activation differences.

Finally, this procedure resulted in nine separate models, namely A0, A1, A2, B0, B1, B2, C0, C1 and C2. Based on previous studies (Ridderinkhof et al., 2004; van Veen et al., 2004; Jocham et al., 2009b) a small volume correction was applied for the anterior cingulate cortex (ACC; BA 32) and the basal ganglia (putamen and pallidum) (Seger and Cincotta, 2005; Kadota et al., 2010; Wu et al., 2010; Berman et al., 2013; Zeuner et al., 2015) to test for differences between negative and positive feedbacks (models A0, A1, A2).

The following additional factorial design was conducted (Analysis A4) to examine the event and group specific effects in the BA32 region: groups (4 levels: PAT (A+), PAT (A–), CON (A+) and CON (A–)), event type (2 levels: pos. and neg. feedback), subject (number of subjects levels) to model subject dependency between positive and negative feedback conditions.

#### 3.3. Threshold of significance for fMRI

We applied a family-wise error (FWE) correction for multiple comparisons (with  $p_{\text{FWE}} < 0.05$ ) at the whole brain level and with a reduced number of comparisons (small volume correction) within our dopamine associated volume of interest (BA32 as defined in the Brodmann atlas shipped within mricon software, see <http://www.>

mccauslandcenter.sc.edu/MRIcro/mricron) and the basal ganglia (putamen and globus pallidus as defined in the AAL atlas, see <http://www.cyceron.fr/index.php/en/plateforme-en/freeware>) (Tzourio-Mazoyer et al., 2002).

## 4. Results

### 4.1. Clinical data of writer's cramp patients

Two controls were excluded, because of insufficient quality of the MRI scans. The mean WCERS score was  $9.4 \pm 4.9$  (range 3–22), while the ADDS averaged  $60.7 \pm 13.0$  (range 26–81). Details of the patients' characteristics are given in Table 1.

### 4.2. DRD2/ANKK1-Taqla polymorphism

The genetic analysis was performed first and subjects were selected according to the DRD2/ANKK1-Taqla polymorphism. Finally, 18 A+ positive, 17 A− controls, 11 A+ and 20 A− writer's cramp patients were included. Three different haplotypes could be identified: A1/A1 (patients  $n = 0$ , controls  $n = 1$ ), A2/A2 (patients  $n = 20$ , controls  $n = 17$ ), and A1/A2 (patients  $n = 11$ , controls  $n = 17$ ). A1/A1 and A1/A2 were considered as A+ subjects, because the A1/A1 subtype is only present in 3% of healthy Caucasians, while A2/A2 was defined as the A− group (Cools et al., 2002; Jocham et al., 2009a). A group comparison between patients and controls showed no significant differences in terms of the A+/A− status, ( $\chi^2 = 1.7$ ,  $p = 0.2$ ).

### 4.3. Behavioral data of the probabilistic reversal-learning task

Patients and controls earned similar monetary gain (patients  $13.15 \pm 1.76$  Euros; controls  $12.74 \pm 1.41$  Euros;  $F = 1.11$ ;  $P = 0.30$ ). The number of reversal errors (patients  $40.35 \pm 17.48$ ; controls

$49.66 \pm 22.52$ ;  $F = 3.45$ ;  $P = 0.07$ ) and changes after positive (patients  $3.74 \pm 5.47$ ; controls  $4.69 \pm 6.92$ ;  $F = 0.37$ ;  $P = 0.54$ ) or negative (patients  $56.42 \pm 22.47$ ; controls  $51.40 \pm 26.05$ ;  $F = 0.69$ ;  $P = 0.41$ ) feedback were comparable ( $p > 0.05$  for all comparisons). The probability in percent to switch after a positive feedback (patients  $2.10\% \pm 3.00$ ; controls  $2.63\% \pm 3.81$ ;  $F = 0.39$ ;  $P = 0.54$ ) or to stay with the previous response (patients  $96.19\% \pm 2.89$ ; controls  $95.86\% \pm 4.01$ ;  $F = 0.15$ ;  $P = 0.70$ ) after the final reversal error showed no differences. Both groups received a similar number of positive (patients  $184.32 \pm 11.25$ ; controls  $181.57 \pm 9.43$ ;  $F = 1.11$ ;  $P = 0.30$ ) or negative feedbacks (patients  $122.16 \pm 9.47$ ; controls  $125.46 \pm 9.32$ ;  $F = 2.03$ ;  $P = 0.16$ ). The reaction times after negative (patients  $497.80 \pm 83.30$ ; controls  $490.87 \pm 83.01$ ;  $F = 0.11$ ;  $P = 0.74$ ) and positive (patients  $499.05 \pm 84.57$ ; controls  $494.39 \pm 85.67$ ;  $F = 0.06$ ;  $P = 0.80$ ) feedback showed no differences between the groups. The genetic subgroups within patients and controls displayed no behavioral differences ( $p > 0.05$  for all comparisons).

### 4.4. Functional imaging results of the probabilistic reversal-learning task

#### 4.4.1. Response to positive or negative feedback

The control group (Analysis A0) demonstrated an increased BOLD response to negative feedback (neg. feedback  $>$  pos. feedback) in the right middle cingulum (BA32), right supplementary motor area (SMA), bilateral insula, dorsolateral prefrontal cortex right, bilateral parietal inferior cortex and the right precuneus (Table 2, Fig. 2A). BOLD response to positive exceeded the response to negative feedback (pos. feedback  $>$  neg. feedback) in the anterior prefrontal cortex, left frontal gyrus pars triangularis, posterior cingulum, bilateral temporal area, bilateral hippocampus and finally the right superior occipital gyrus of the visual area (Table 2, Fig. 2B).

In writer's cramp patients responses to neg. feedback  $>$  pos. feedback yielded in higher BOLD activation in the middle cingulum bilateral (BA-

**Table 1**  
Clinical data of patients with writer's cramp.

Patient ID	Age (y)	Symptom duration (y)	Type of writer's cramp	Last injection (months)	Duration BoNT treatment (y)	Total ADDS score (%)	Total WCERS score
P101	69	9	c	4	8	60	10
P103	52	7	s	14	0.25	72.85	6
P105	68	7	s	3	3.75	81.43	19
P106	49	10	c	n.a.	n.a.	68.57	5
P107	43	9	c	60	3	64.29	22
P108	36	11	s	n.a.	n.a.	55.71	8
P109	27	13	c	n.a.	n.a.	72.35	10
P110	60	14	s	n.a.	n.a.	51.43	6
P111	39	12	s	n.a.	n.a.	55.71	17
P112	36	3	c	17	0.7	42.85	7
P113	54	6	c	n.a.	n.a.	51.43	5
P114	53	14	c	36	0.25	55.71	5
P115	56	14	s	5	10	60	10
P117	70	15	c	n.a.	n.a.	68.57	13
P118	52	21	c	120	2	55.71	11
P120	58	25	c	72	0.25	60	5
P121	42	10	c	96	0.5	55.71	11
P122	59	13	c	120	0.5	51.43	6
P123	68	25	c	132	0.5	25.71	8
P124	50	17	c	96	3	42.85	8
P125	55	4	c	18	3	81.43	5
P126	45	30	c	3	3.5	68.57	5
P127	51	19	c	3	4	72.86	3
P128	57	34	c	10	2	34.29	12
P129	42	22	s	6	1	68.57	11
P130	60	7	s	60	0.25	77.14	3
P131	29	1	s	n.a.	n.a.	68.57	11
P132	78	6	c	4	3	68.57	5
P133	24	1	s	n.a.	n.a.	68.57	11
P134	59	31	c	n.a.	n.a.	51.43	20
P135	41	11	s	n.a.	n.a.	68.57	13
Mean	51.0	13.6	11 simple	44.0	2.5	60.7	9.4
SD	13.1	8.7	19 complex	46.3	2.6	13.0	4.9

Legend: ADDS = Arm Dystonia Disability Scale; WCERS = Writer's Cramp Rating Scale; BoNT = Botulinum Neurotoxin, s = simple writer's cramp, c = complex writer's cramp.



**Table 2**

BOLD differences between responses to negative and positive feedback in patients and controls. Table lists peak locations of the statistical t-map with  $p < 0.05$  after correction for multiple comparisons (FWE) for the whole brain.

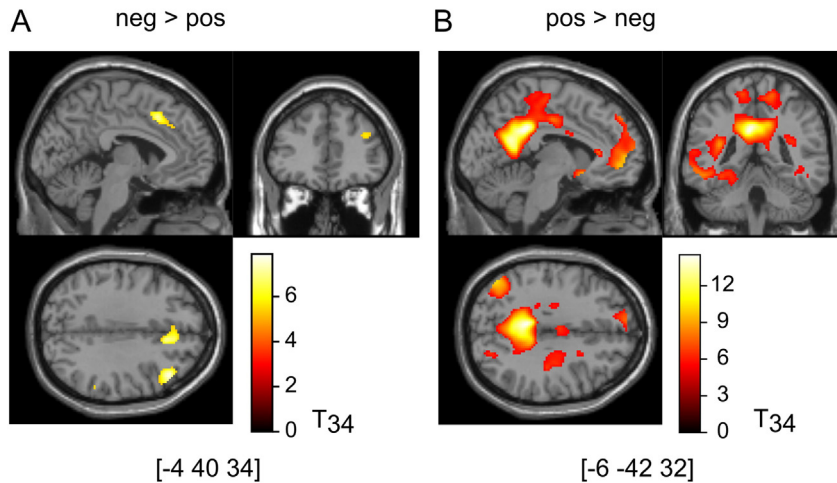
Region	Left hemisphere				Right hemisphere			
	MNI peak coordinate			T-value	MNI peak coordinate			T-value
	x	y	z		x	y	z	
Controls, negative feedback > positive feedback								
Cingulum middle (BA32), bilateral					8	26	38	7.89
SMA (BA6), bilateral					6	12	52	7.62
DLPFC (BA9, BA10, BA45, BA46)	−36	50	8	6.83	42	30	32	7.73
Parietal inferior cortex (BA40)					54	−44	38	6.35
Insula (BA48, BA47)	−34	18	4	6.35	32	24	2	5.55
Precuneus (BA7)					10	−66	54	5.97
Controls, positive feedback > negative feedback								
Cingulum posterior (BA23)	−6	−42	32	14.53				
Anterior prefrontal cortex (BA10)	0	54	4	10.82				
Hippocampus (BA20)	−30	−10	−14	5.34	26	−16	−18	9.49
Rolandic operculum (BA48)					50	−28	24	5.96
Frontal gyrus pars triangularis (BA45)	−46	32	8	8.36				
Temporal medial (BA21)	−56	−4	−14	6.93				
Temporal inferior (BA20)					50	−46	−12	5.84
Temporal superior (BA22)					64	−20	8	7.20
Occipital superior (BA18, BA19)					22	−80	36	6.50
Patients, negative feedback > positive feedback								
Cingulum middle (BA32), bilateral					4	34	38	7.83
SMA (BA6), bilateral	−6	14	48	7.45				
Insula (BA48, BA47)	−30	22	0	8.83	30	24	−2	6.86
DLPFC (BA10, BA46)	−32	48	12	5.58	40	34	28	5.63
Patients, positive feedback > negative feedback								
Precuneus (BA23, BA30)	−6	−54	16	8.76				
Cingulum posterior (BA23)	−4	−44	30	7.1	10	−50	24	8.12
Subgenual cingulate (BA25)					8	10	−14	8.39
Anterior prefrontal cortex (BA10)	−6	64	20	6.87				
Hippocampus (BA20)	−30	−16	−18	7.97	30	−12	−20	7.99
Temporal inferior (BA20)	−56	−52	−4	7.49				
Temporal superior (BA22)	−54	−10	−12	6.62				
Middle temporal gyrus (BA39)	−42	−64	22	9.03				
Rolandic operculum (BA48)					36	2	14	6.09

SMA = supplementary motor area; DLPFC = dorsolateral prefrontal cortex; bilateral = cluster extends to both hemispheres.

32), SMA bilateral, the insula bilateral and the dorsolateral prefrontal cortex ( $p_{FWE} = 0.05$ ) (Table 2). After positive feedback (pos. feedback > neg. feedback) areas with enhanced BOLD signal included

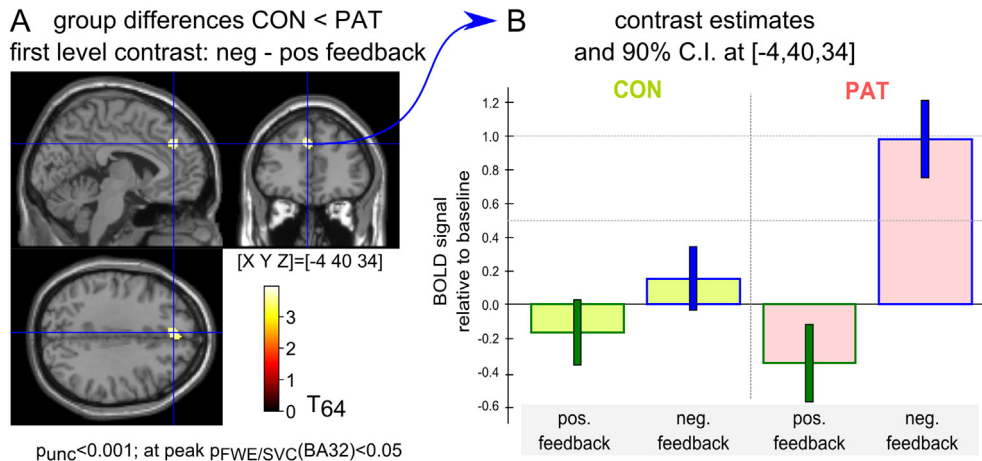
the posterior cingulum, the precuneus, the hippocampus bilateral, right anterior prefrontal cortex (BA10), temporal inferior and superior, the middle temporal gyrus (BA39), and the rolandic operculum

**BOLD response to feedback in healthy controls**



**Fig. 2.** The contrasts between negative and positive feedback are shown. Panel A: In panel A the effect to negative > positive feedback in controls is illustrated. BOLD increase ( $p_{FWE} < 0.05$ ) occurred in the right middle cingulum (8, 26, 38), supplementary motor area right (6, 12, 52) the insula bilateral (right: 32, 24, 0; left: −34, 18, 4), the bilateral dorsolateral prefrontal cortex (right: 42, 30, 32; left: −36, 50, 8), the precuneus on the right (10, −66, 54) and the inferior parietal cortex right (54, −44, 38). Panel B: The BOLD activity in the contrast positive > negative feedback is demonstrated. Controls exhibited an increase ( $p_{FWE} < 0.05$ ) in the posterior cingulum (BA 23) (6, −42, 32), the bilateral hippocampus (right: 26, −16, −18; left: −10, 26, −14), the left pars angularis of the frontal gyrus (−46, 32, 8), the temporal areas (BA 20–22) (right: 50, −46, −12; left: 64, −20, 8) and finally the right superior occipital cortex (22, −80, 36).

## BOLD responses in BA32 to pos. and neg. feedback



**Fig. 3.** Panel A. Differences between patients with writer's cramp and controls are shown a threshold of  $p < 0.001$  uncorrected. The cross hair was positioned in the dorsal ACC at the peak position in the statistical map which was tabulated after applying the small volume correction for the anterior cingulate cortex (BA 32). BOLD contrast was increased ( $x, y, z = -4, 40, 34$ ;  $P_{FWE} < 0.05$ ) in patients compared to controls for negative feedbacks (neg. feedback > pos. feedback). Panel B: Boxplot is shown to illustrate that the BOLD signal increase in patients with writer's cramp after negative feedback occurred, because the BOLD signal slightly decreased in both groups after positive feedback and in controls minimal after negative feedback. In contrast, negative feedback induced in patients a clear increase in BOLD signal. As a result the analyzed group difference (negative minus positive feedback) showed a strong signal increase in patients.

(Table 2). There were no group differences between patients and controls in BOLD activity following negative or positive feedback after applying the FWE correction for the voxels of the whole brain.

Reducing the correction to a small volume in the dorsal ACC (BA32) (Ridderinkhof et al., 2004; Jocham et al., 2009b; van der Veen et al., 2011) and the basal ganglia (putamen and pallidum) patients showed a significant increased BOLD signal ( $x, y, z = -4, 40, 34$ ;  $T = 3.97$   $P_{FWE, BA32} = 0.029$ ) for negative (neg. feedback > pos. feedback) feedback (Analysis A1; Fig. 3A) only in the dorsal ACC and not in the basal ganglia. This effect in the dorsal ACC occurred, because the BOLD signal slightly decreased in both groups after positive feedback. Negative feedback induced only a minimal increase of BOLD signal in controls, whereas in patients this increase was much more pronounced. The result of the difference negative–positive feedback aroused from a stronger BOLD signal increase in patients (Fig. 3B) to negative feedbacks. This effect was not based on genetic disparities (Analyses A3 and A4).

### 4.4.2. Responses to final reversal compared to reversal error

With the second part we estimated whether reversal errors specifically caused increased BOLD signal (Jocham et al., 2009a). In controls (Analysis B0), the final reversal error induced more ( $P_{FWE} < 0.05$ ) BOLD signal change bilaterally in the precentral region, the SMA, postcentral on the right, and the left inferior parietal lobe adjacent to the postcentral gyrus (Table 3, Supplemental Material). There were no differences between patients and controls (Analysis B1) or the genetic subgroups (Analysis B2).

### 4.4.3. Response to positive feedback after final reversal error

The third part concentrated on the contrast of the BOLD responses to final reversal errors and those to positive feedback (Cools et al., 2002) to examine behavioral change to the newly relevant pattern. In controls (Analysis C0), BOLD responses to final reversal errors exceeded BOLD responses to positive feedback in the bilateral insula and SMA, the medial frontal gyrus, postcentral, precentral bilateral, the left superior frontal gyrus (Table 4, Supplemental Material). Again, there were no differences between controls and patients (Analysis C1) or the genetic subgroups A+ and A- (Analysis C2).

## 5. Discussion

This is the first study that investigated a reward-based learning task in patients with writer's cramp and linked the behavioral results and the BOLD activity with DRD2/ANKK1-Taqla polymorphism. We expected that the BOLD activity is altered in dopamine-related areas such as the striatum, the prefrontal cortex and the rostral cingulate zone during this dopamine associated reversal-learning task. We further hypothesized impaired reversal learning particularly in those subjects who carried the A+ allele of the DRD2/ANKK1-Taqla polymorphism.

Consistent with the literature (O'Doherty et al., 2003; Ridderinkhof et al., 2004) positive feedback induced an elevated BOLD signal predominantly in the posterior cingulum, in the ventrolateral prefrontal and the orbitofrontal cortex. The ventrolateral prefrontal cortex responds to reward delivery (Schultz et al., 2000; Kirsch et al., 2003; Albrecht et al., 2014), is involved in monetary reward (Liu et al., 2007) and active during learning-related visual associative tasks (Passingham et al., 2000). The activity of the orbitofrontal cortex after positive feedback in our study may be associated with monitoring the reward value (Pochon et al., 2002). The same area is important for updating and evaluating recent consequences of a decision making process (Daw et al., 2006; Kovach et al., 2012). The function of the posterior cingulate cortex is in the context of reward-based decision making (Bush et al., 2002; McClure et al., 2004; van Veen et al., 2004). In contrast, the dorsolateral prefrontal cortex (BA9, BA10, BA45, BA46) showed greater BOLD signal in controls after negative feedback. The dorsolateral prefrontal cortex seems to be involved in updating the expectation of reward (Ridderinkhof et al., 2004) and has been shown to be active during reversal errors (Mitchell et al., 2008) and unexpected negative feedback (Xue et al., 2013) in previous studies. It seems to be important in correcting responses via inhibition of prior incorrect responses (Ghahremani et al., 2010).

### 5.1. Anterior cingulum

The main finding of our study was a significant increased neural activity in writer's cramp patients after negative feedback in the dorsal ACC (BA32), but not in the basal ganglia. Area BA32 is usually referred to as the dorsal anterior cingulate region or paracingulate cortex extending into the cingulate sulcus. The dorsal ACC plays an important

role in coordinating and integrating information to guide behavior. Functions that have been ascribed to this area include detecting error signals, action selection, encoding rewards, motor preparation and response and evaluating motivation (Bush et al., 2000, 2002; Holroyd and Coles, 2002). This region is also involved in emotional processing (Mohanty et al., 2007). Emotion plays a crucial role in risk-based decision making (Xu et al., 2013) and anxiety is also positively correlated with dorsal ACC activation (Straube et al., 2009). Depression and anxiety affect quality of life in patients with different types of focal dystonia (Pekmezovic et al., 2009). As pointed out, the dorsal ACC has heterogeneous functions, but one possibility is that increased BA32 activity associated with negative feedback might reflect a heightened sensitivity to negative stimuli in patients with dystonia. Our study was not focused on investigating depression or anxiety in writer's cramp patients, but this aspect should be considered in the future.

Previously, negative feedback was also associated with an increased response in the rostral cingulate zone (RCZ), a region that is identical to the dorsal/rostral ACC (Ridderinkhof et al., 2004). The elevated activity to negative feedback in the RCZ was accompanied by a dopamine release dip in the striatum (Holroyd and Coles, 2002). The enhanced BOLD signal in the RCZ possibly reflected the need for behavioral adjustment to other brain regions involved in action selection (Bush et al., 2002; Cools et al., 2002; Ridderinkhof et al., 2004; Jocham et al., 2009a; Mell et al., 2009; Mies et al., 2011). A negative outcome of a gambling task (Gehring and Willoughby, 2002) resulted in an even more increased BOLD signal of the medial frontal ACC region if it was associated with a monetary loss (Taylor et al., 2006). In summary, it is conceivable that in accordance with the findings of those prior studies, the BOLD signal enhancement in area BA32 of our study reflect disturbed integration of reinforcement history in our patient group.

An additional aspect is that the dorsal ACC is interconnected to the striatum, the lateral prefrontal and parietal cortex. It is considered a cortical target of the dopaminergic innervated cortical-basal ganglia-thalamic circuit (Obeso et al., 2008). Tasks with dorsal ACC involvement such as reward-based decision making or learning and performing novel, non-automatic activities are dopamine associated (Bush et al., 2002). PET studies showed reduced tracer binding to D<sub>2</sub>/D<sub>3</sub> receptors (Berman et al., 2013), but it is not clear whether abnormal dopaminergic neurotransmission or dysfunctional receptor availability can be attributed to those findings. Especially since we did not find any abnormal neural activity in the striatum, we can only speculate that disturbed striatal dopamine turnover in dystonic patients possibly lead to an elevated BOLD signal in BA32. This area is important for the integration of reward related behavior (Bellebaum et al., 2008), updating for decision making (Schultz, 2007, 2013) and fine tuning of upcoming behavior (Mies et al., 2011; Özyurt et al., 2012). The behavioral outcome in writer's cramp patients showed no significant differences to the control group, but it is worth mentioning that patients performed even slightly better than controls in regard to reversal errors. Although not significant, patients showed 20% (on average 40.35 vs. 49.66) less reversal errors than controls. Thus, one possible explanation is that the BOLD signal increase in BA32 in our study reflects compensatory mechanisms to finally reach the same behavioral results as controls.

## 5.2. Basal ganglia

Positive feedback has been shown to be associated with activation in the ventral striatum (Nieuwenhuis et al., 2005; Marco-Pallares et al., 2007) particularly in individuals with the DRD2/ANKK1-Taqla polymorphism (Jocham et al., 2009a). The BOLD signal increase in the bilateral putamen of the A – group in our study ( $p_{unc} < 0.001$ ) was not significant after FWE correction. Therefore the data did not confirm the previous effect (Jocham et al., 2009a) of the DRD2/ANKK1-Taqla polymorphism status on the BOLD activity in the putamen. Age seems to alter the function of the ventral striatum in response to probability rewards (Witt et al., 2006; Schmitt-Eliassen et al., 2007; Mell et al., 2009). One possible

explanation for the negative findings in this study may be the average age in patients ( $51.0 \pm SD 13.1$  years) and controls ( $49.7 \pm SD 8.8$  years) who were about twenty years older compared to the younger age in former studies (20–32 years; Jocham et al., 2009a, 19–31 years Marco-Pallares et al., 2007). As a result, it is conceivable that due to a diminished response in the striatum, differences between patients/controls and the genetic subgroups could not be determined.

On the other hand, our finding may be plausible, because abnormalities in reversal learning and reduced striatal BOLD activity had been predominantly demonstrated for patients with striatonigral degeneration such as in Parkinson's disease (Cools et al., 2007; Peterson et al., 2009) and following basal ganglia lesions (Bellebaum et al., 2008). The imbalance of the dopaminergic system in dystonia is different from other neurodegenerative diseases. These previous studies suggest that dystonic patients exhibit altered dopamine function rather than dopamine depletion as it is the case other neurodegenerative conditions such as Parkinson's disease. Hence, dopamine release is not reduced to a level that might be visible as an abnormal BOLD response in such a task.

## 6. Conclusion

Patients with writer's cramp, irrespective of their genetic status, performed similarly to controls, in a reversal-learning task that is sensitive for dopamine signaling in the ventral striatum. However, they showed increased BOLD activity in response to negative feedback in the dorsal anterior cingulum (BA32). This area has several different functions including cognition, emotion and motor preparation/response. It is also important for the integration of reward related behavior and updating for decision making. These findings may indicate a disturbed integration of reinforcement history or a possible compensatory phenomenon in dopamine related neural systems to attain similar behavioral results as controls. A possible conclusion is that the reward system contributes to the pathogenesis of dystonia.

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