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

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

[a]Department of Neurology, Kiel University, Germany
[b]Department of Radiology and Neuroradiology, Kiel University, Germany
[c]Movement Disorders Section, Department of Neurology, Hannover Medical School, Germany
[d]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 to 35 controls 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-TaqIa 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.

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_2/D_3 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_2/D_3 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_2-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 (K.E. Zeuner).

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

Furthermore, there are reports indicating that the DRD2/ANKK1-TaqIa 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_2 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-TaqIa 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_2/D_3 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-TaqIa 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 ± SD 13.1 years (range: 24–78 years) and a mean disease duration of 13.6 ± SD 8.7 years were comprised in the fMRI study. Thirty-five age-matched healthy individuals (17 women) with a mean age of age 49.7 ± SD 8.8 (range: 25–68 years) served as controls. Eleven patients (3 women, age 53.6 ± SD 8.8) and eighteen controls (7 women, age 47.6 ± SD 9.4), assigned to the A + group, participated.

Patients and controls were right-handed (laterality quotient: patients 92.1 ± SD 9.8, range: 62.5–100; controls 88.4 ± 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 (WCRS) (Wissel et al., 1996). A higher total WCRS 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-TaqIa 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-TaqIa was performed by Sanger sequencing. The genetic analysis was performed first and subjects were selected according to the DRD2/ANKK1-TaqIa 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

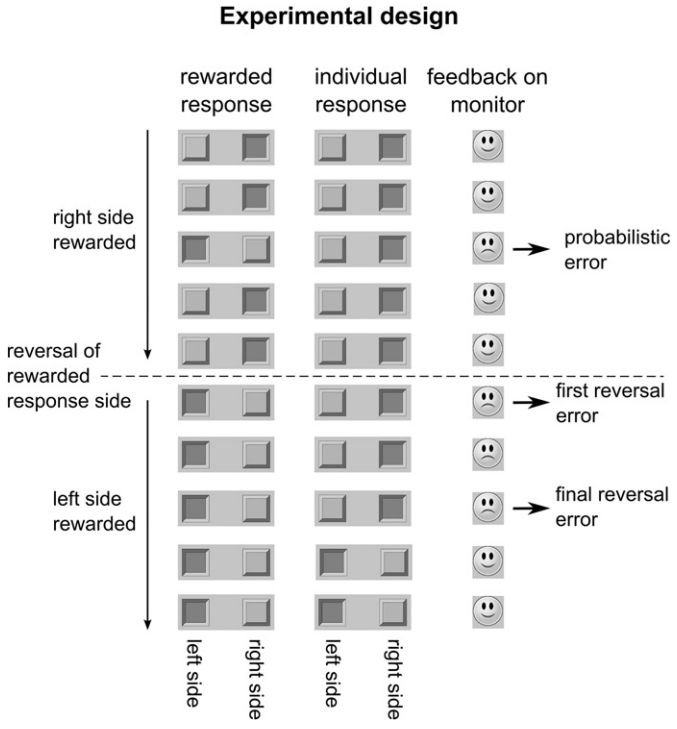

Fig. 1. Experimental design: this was an event-related design, in which the individuals chose between two identical stimuli right and left side and indicated their response with their index finger of the hand corresponding to the side of the stimulus. The first column indicates the rewarded response, 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 was rewarded in 80%. The light gray squares indicate that the button was not pressed, while the dark gray square reflects the pressed button.