Social Cognitive and Affective Neuroscience, 2017, 1594–1604

doi: 10.1093/scan/nsx090
Advance Access Publication Date: 11 July 2017
Original article

Subthalamic nucleus stimulation impairs emotional conflict adaptation in Parkinson's disease

Friederike Irmen,[1,2] Julius Huebl,[2] Henning Schroll,[2,3] Christof Brücke,[2] Gerd-Helge Schneider,[4] Fred H. Hamker,[3] and Andrea A. Kühn[1,2,5,6]

[1]Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin 10117 Germany, [2]Department of Neurology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin 10117, Germany, [3]Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin 10117, Germany, [4]Department of Computer Science, Chemnitz University of Technology, 09111 Chemnitz, Germany, [5]NeuroCure Cluster of Excellence, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin 10117, Germany, and [6]Deutsches Zentrum für Neurodegenerative Erkrankungen, 10117 Berlin, Germany

Correspondence should be addressed to Andrea A. Kühn, Department of Neurology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: andrea.kuehn@charite.de

Abstract

The subthalamic nucleus (STN) occupies a strategic position in the motor network, slowing down responses in situations with conflicting perceptual input. Recent evidence suggests a role of the STN in emotion processing through strong connections with emotion recognition structures. As deep brain stimulation (DBS) of the STN in patients with Parkinson's disease (PD) inhibits monitoring of perceptual and value-based conflict, STN DBS may also interfere with emotional conflict processing. To assess a possible interference of STN DBS with emotional conflict processing, we used an emotional Stroop paradigm. Subjects categorized face stimuli according to their emotional expression while ignoring emotionally congruent or incongruent superimposed word labels. Eleven PD patients ON and OFF STN DBS and eleven age-matched healthy subjects conducted the task. We found conflict-induced response slowing in healthy controls and PD patients OFF DBS, but not ON DBS, suggesting STN DBS to decrease adaptation to within-trial conflict. OFF DBS, patients showed more conflict-induced slowing for negative conflict stimuli, which was diminished by STN DBS. Computational modelling of STN influence on conflict adaptation disclosed DBS to interfere via increased baseline activity.

Key words: subthalamic nucleus; deep brain stimulation; emotional conflict; stroop model; Parkinson's disease

Introduction

The subthalamic nucleus (STN) is a key node in information processing during action selection receiving input via the hyperdirect and indirect pathway (Alexander and Crutcher, 1990; Nambu *et al.*, 2002). Its functional role has been related to centre surround inhibition and supression of motor output of the basal ganglia during movement selection (Mink, 2003). More recently, evidence for a role of the STN in response slowing related to conflicting input has emerged (Brittain *et al.*,). It is presumed that the STN pauses basal ganglia motor output in response to conflict until the appropriate motor plan is set

Received: 24 December 2016; **Revised:** 23 June 2017; **Accepted:** 30 June 2017

(Frank et al., 2007). However, the STN's conflict processing capacity goes beyond the motor domain. In fact, cumulative evidence points towards its role being a more general one, coordinating and weighing input from motor and non-motor brain regions to regulate behaviour (Aron and Poldrack, 2006; Frank and Claus, 2006; Baunez and Lardeux, 2011; Péron et al., 2013).

Subthalamic deep brain stimulation (DBS) has become a guideline therapy for advanced Parkinson's disease (PD) due to its high effectiveness in the control of motor symptoms and improvement in quality of life (Schüpbach et al., 2014). Despite its great therapeutic effect, clinical studies have revealed selective undesirable effects of STN DBS on cognition, behaviour and emotion (Mallet et al., 2007; Voon et al., 2008; Witt et al., 2008; Le Jeune et al., 2010; Maillet et al., 2016; Péron et al., 2013). In particular, STN DBS has been found to increase impulsive behaviour (Hälbig et al., 2009; Florin et al., 2013; Brandt et al., 2015), with conflict-induced slowing turning into conflict-induced speeding with DBS (Frank et al., 2007). This process has been formalized using computational models such as the drift diffusion model of decision making predicting impulsive behaviour in the face of conflict if STN inhibitory activity is disrupted (Cavanagh et al., 2011; Green et al., 2013; Obeso et al., 2014). In line with this, patients with STN DBS make more erroneous choices when their stimulator is turned on, for instance, in the Stroop task, where they have to suppress reading a word while naming its colour (Jahanshahi et al., 2000; Witt et al., 2004). Lower accuracy in such action selection tasks involving conflict provides evidence for impaired response inhibition during STN DBS suggesting a role of the STN in inhibitory executive control (Jahanshahi et al., 2015; Zavala et al., 2015). Further support derives from neuroimaging studies presenting a close functional link of the STN and frontal areas of higher cognitive function via the hyperdirect pathway (Nambu et al., 2002). Yet, the STN has recently been found to also receive input from areas processing affective stimulus contents such as the basolateral amygdala (Lambert et al., 2012) or the orbitofrontal cortex (Le Jeune et al., 2008). In fact, new evidence extends the role of the STN to presenting a central hub for multi-level integration of motor, cognitive and affective information (Accolla et al., 2016). In the affective domain, the STN may play a crucial role in the temporal coordination of cortical and subcortical co-activation that is the foundation to affective sensation (Péron et al., 2013). Behavioural data supporting this notion includes studies showing DBS-induced impairments of emotion recognition and expression, especially in the domain of unpleasant emotions (Le Jeune et al., 2008; Péron et al., 2010).

A crucial question yet unanswered is whether the STN modulates the integration of affective information in the motor output relative to a conflict signal. If the processing of conflicting affective input is impaired through STN DBS, the STN could be assumed to apply the braking signal during processing of emotional input, holding back motor output until the relevance of affective information could be checked.

We employed an emotional Stroop paradigm previously established by Etkin et al. (2006), using positive and negative facial expressions and superimposed congruent (non-conflicting) or incongruent (conflicting) emotion words. In healthy individuals, conflict monitoring, i.e. the recognition that perceptual input is conflicting, induces automatic slowing of reaction times (Stroop effect) due to the recruitment of cognitive control applied to inhibit the influence of irrelevant information on performance (Botvinick et al., 2001). Etkin et al. (2006) found such conflict-related slowing to be present for conflicting emotional face stimuli with emotion word stimuli superimposed, irrespective of valence. Further, conflict-related slowing in one trial primed conflict adaptation, i.e. faster responses, in a following conflict trial. This paradigm thus allows assessing reaction time slowing in conflict trials as compared to no-conflict trials (reactive or within-trial conflict adaptation), and furthermore, reaction time adjustments from one conflict trial to the next (proactive or across-trial conflict adaptation).

A unique tool to directly modulate STN activity comes in patients with severe PD treated with STN DBS, in whom the stimulator can be switched ON and OFF. We used this approach to differentially test our hypothesis that STN DBS would interfere with emotional conflict adaptation. We predicted the Stroop effect to be equally strong in healthy controls and PD patients OFF DBS and to drop ON DBS due to the interference of DBS with physiological STN activity during conflict monitoring. Moreover, we simulated potential mechanisms by which DBS may interrupt emotional conflict processing in the STN using an adapted version of the renown Stroop model introduced by Cohen et al. (1990) and Botvinick et al. (2001).

Materials and methods

Patients

We included 11 patients (two females; mean age 62 ± 6.4 years) with idiopathic PD (disease duration 11.5 ± 4.2 years) who have undergone functional neurosurgery for subthalamic DBS. Details of surgery and electrode placement have been described previously (Huebl et al., 2011). Post-operative electrode placement within the STN was corroborated via T2-weighted magnetic resonance imaging. Furthermore, effective stimulation was indexed by a significant decrease in postoperative United PD Rating Scale-III motor score (% reduction 57.55 ± 17.58, ON vs. OFF paired t-test $P < 0.01$) and a significant reduction of levodopa daily dose (LEDD) (% reduction 61.42 ± 26.80, ON *vs* OFF paired t-test $P < 0.01$). All patients and healthy controls gave written informed consent for participating in the study. The local ethics committee approved all parts of the study in accordance with the declaration of Helsinki. Table 1 provides an overview of the patient demographics and clinical data. Major cognitive or affective disorders were ruled out prior to surgery by neuropsychological and neuropsychiatric assessment (as in Huebl et al., 2011). Depression scores [Beck Depression Inventory (BDI)] were assessed only in the ON DBS state. Patients had none or mild clinically relevant depressive symptoms (BDI scores <19 indicate minimal or moderate depressive symptoms). At the time of the study in comparison to the preoperative state, BDI scores were decreased (cases 1, 2, 7, 9 and 10) or unchanged (cases 5, 6 and 8) in all but in one (case 4) patient. Furthermore, none of the patients had difficulties recognizing facial expressions on an early processing level as indexed by a normal score in the Benton Facial Recognition Test (Benton, 1990).

Healthy controls

We included an age- and gender-matched control group of 11 subjects (two females; mean age 63.5 ± SD 7.4 years). The healthy controls denied any history of neurological or psychiatric disease and were not under influence of any medication that would affect their cognitive or affective state. Subjects had a mean BDI of 3.0 ± SD 3.9 indicating minimal depressivity and all passed the Benton Facial Recognition Test without

Table 1. Patients sample demographic and clinical characteristics

Case/sex	Age	Disease duration	BDI prior to surgery	BDI time of study	Benton FRT	UPDRS-III score : OFF DBS	UPDRS-III score: ON DBS	LEDD pre-OP	LEDD post-OP	Contacts used for continuous STN DBS
1/f	50	6	5	1	49	40	13	1175	600	L:-1;+2 R: -1;+2
2/m	69	20	15	9	45	56	16	1260	400	L:-1 R:-1
3/m	64	7	–	–	39	45	23	1250	200	L:-1 R: -2: -3
4/m	65	12	8	14	–	30	7	1450	240	L:-1;-3 R:-1;-3
5/m	60	7	0	0	49	23	19	900	800	L:-0 R:-0
6/m	69	10	4	4	–	30	8	1400	0	L:-1 R:-1
7/m	66	14	3	1	43	34	14	1400	600	L:-1 R:-1
8/f	63	14	17	17	39	28	18	1080	140	L:-1 R:-1
9/m	56	15	13	6	39	44	11	750	300	L:-2;-3 R: -1
10/m	70	14	14	7	43	30	14	600	500	L:-0;-1 R:-1;-2
11/m	53	7	–	–	41	40	18	1100	450	L:-1;-2 R:-1;-2
M (s.d.)	62 (6.4)	11.5 (4.2)	8.7 (5.8)	6.5 (5.6)	43 (3.8)	36.4 (9.1)	14.6 (4.6)	1124.09 (263.32)	384.54 (224.23)	

M (s.d.), Mean (s.d.), disease duration in years, Benton FRT, Benton Facial Recognition Test, UPDRS-III, United PD rating scale. Part III, motor evaluation.

indication of impaired recognition of faces (mean score 46.5 ± SD 3.2). No indication of cognitive impairment was present as indicated by the Montreal Cognitive Assessment test (mean score 27.0 ± 1.4). All subjects had normal or corrected-to-normal vision acuity, were fluent in German and naïve to the hypotheses of the study.

Paradigm and conditions

PD Patients performed the behavioural task in two experimental sessions, ON and OFF DBS, in a pseudo-randomized order. After switching off the DBS device, patients waited for 30 minutes before starting (or continuing) the task. Patients were on their usual antiparkinsonian medication that was stable during the two test sessions. Healthy controls underwent the experimental procedure only once. One experimental session took about 20 minutes.

We adapted the emotional Stroop task used by Etkin *et al.* (2006). The stimulus set consisted of black and white photographs of happy and sad faces taken from the 2D Facial Emotional Stimuli dataset (Erwin *et al.*, 1992). The faces were superimposed with the German words for 'joy' [Freude] or 'grief' [Trauer] in prominent red letters (Figure 1). Stimuli could thus be non-conflicting (congruent) if the valence of facial expression and the word would match (e.g. 'joy' and a happy face) or conflicting (incongruent) if the valence would differ (e.g. 'joy' and sad face). During the analysis, similar to Gyurak *et al.* (2011), we referred to a conflict trial that was primed by a previous conflict trial as 'high across-trial conflict adaptation trial' (Figure 1). Conversely, we referred to a conflict trial that was preceded by a no-conflict trial as 'low across-trial conflict adaptation trial'.

The face stimuli were organized in two sets of 36 face stimuli, with an equal number in each condition: happy congruent, happy incongruent, sad congruent and sad incongruent. Stimuli occurred in a pseudo-randomized order, with the maximum repetition for a category being set to three. The stimulus duration was 1 second and the inter-stimulus interval was jittered between 3 and 4 seconds, during which a black screen with a white fixation cross in the centre was shown. Subjects were seated in a chair facing a 15″ laptop screen at approximately 60 cm distance. They were instructed to react to sad or happy facial expressions with a left or right button press. The assignment of button valence was pseudo-randomized across patients (7 out of 11 patients and controls pressed right for joy and left for grief). After task completion, subjects were presented the emotional task stimuli for a classification of sad and happy faces without superimposed emotion words. All patients and controls correctly classified all emotional face expressions.

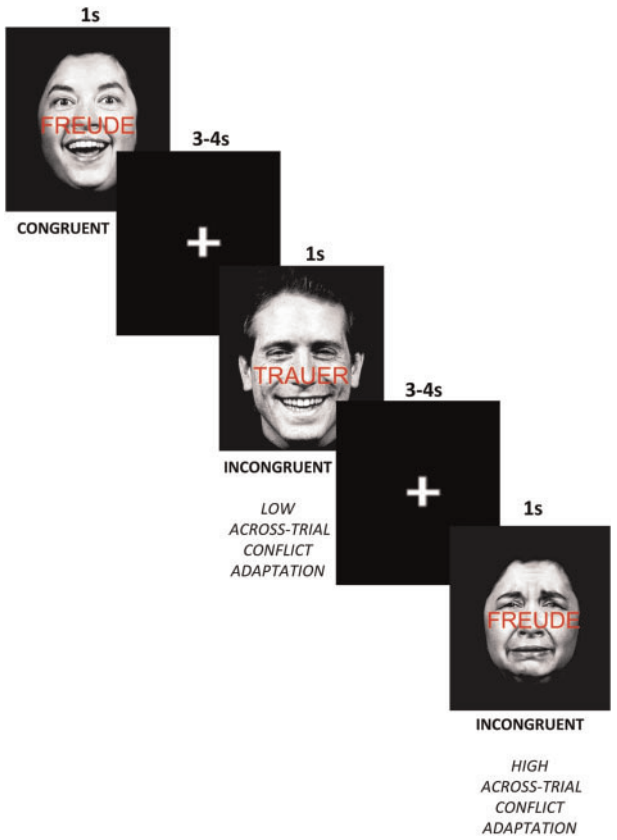

Fig. 1. Emotional Stroop paradigm. Stimuli were presented for 1 second, followed by a black screen with a white fixation cross presented for a jittered interval of 3–4 seconds.

Statistical analyses

Trials with reaction time outliers were excluded using the Thompson Tau test (rejection limit at 0.05) taking into account

the standard deviation and average of the data (Anbarasi, 2011). Thompson Tau provides a statistically determined rejection zone that labels outliers beyond the limit. For the reaction time analysis, error trials, i.e. trials in which the response button did not match the facial expression, were excluded. Normal distribution of the reaction time data was checked with Kolmogorov Smirnov test to ensure validity of parametric testing. Intra-group reaction times changes between ON and OFF DBS test sessions were analysed using a multifactorial repeated measures analysis of variance (ANOVA) using MATLAB (The Mathworks, Natwick, MA, USA) and SPSS (IBM SPSS Statistics; IBM Corporation, Chicago, IL, USA).

To compare the patient group ON and OFF DBS with the control group, reaction times of each patient (RT_X) were standardized subtracting the mean reaction times of the control group ($RT_{controls}$) and dividing by the control group's standard deviation. The standardized mean reaction times (RTx.*std*) for each subject of the patient group thus described how far the subject's mean laid from the mean of the control group.

$$RTx.std = (RT_X – mean(RT_{controls}))/SD(RT_{controls})$$

For ANOVA I (Stroop effect), we computed the difference (delta) of conflict and no-conflict trials to describe the Stroop effect for trials with negative and positive valence. The standardized mean Stroop effect ON *vs* OFF DBS in trials with negative *vs* positive valence was compared using a repeated-measures ANOVA with the factors group (ON *vs* OFF DBS) and valence (positive *vs* negative). We tested for significance of the intercept, to see if the mean of both groups differed from the mean of the control group. Using post hoc tests we tested the mean Stroop effect of patients ON DBS, OFF DBS against zero to establish which groups differed from the control group.

To compare the effect of across-trial conflict adaptation (ANOVA II) between PD patients ON and OFF DBS and healthy controls, we standardized patients' reaction times in high *vs* low conflict adaptation trials to the control group. We then computed the delta of low and high across-trial conflict adaptation trials of positive and negative valence and compared them in a repeated-measures ANOVA in the same was as in ANOVA I.

Planned comparisons were adjusted with Bonferroni correction. In the reported comparisons of mean reaction times, *P* values regarding reaction times are results of paired two-sided *t*-tests for ON and OFF DBS group comparisons. Corrected *P*-values are classified significant on a 5% level. Cohen's d (*d*) and eta-squared (η^2) were used for calculation and report of effect sizes.

Computational simulations

To investigate the computational mechanisms behind patients' altered Stroop effects, we implemented a well-established computational model that consists of five modules, each containing one to three processing units (Figure 2; Botvinick *et al.*, 2001). Processing units are interconnected via connection weights that allow for the spread of activity between units. Two sensory modules, related to the processing of face and word stimuli, respectively, are activated by input stimuli according to trial types. Each sensory module contains three processing units related to the processing of negative, positive and neutral stimuli, respectively, in line with the original model (Botvinick *et al.*, 2001). These sensory modules compete for controlling the activities of a response module that selects the model's response in each given trial (i.e. negative *vs* positive).

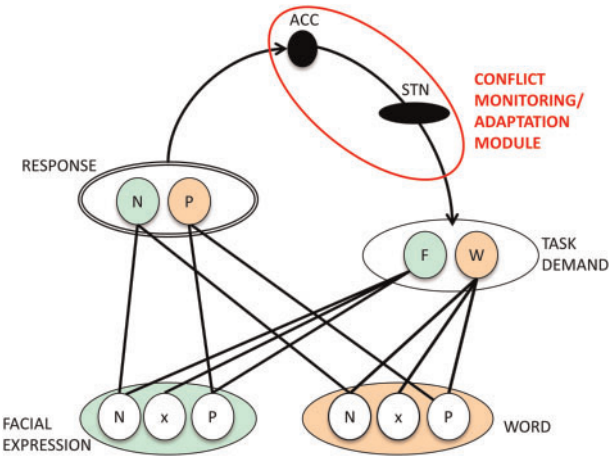

Fig. 2. Computational model of STN involvement in emotional conflict monitoring and adaptation. Small circles represent units, large ovals represent modules. Arrows represent unidirectional connections while lines represent bidirectional connections. P represents positive stimulus features, N represents negative features. x represents the assumed representation of features of neutral valence. F: Facial expression naming; W: Word naming.

The task demand module represents the task set according to which the response is to be selected (containing the units word naming and face identification). The task-relevant face identification unit of this module receives direct external input in each trial representing the explicit instruction that subjects should respond to faces, not to word stimuli. In addition, the word naming and the face identification units are bi-directionally connected with the sensory face module and the sensory word module, respectively. This means that they both receive bottom-up inputs from these sensory modules and modulate the activities of these modules in a top-down manner. Finally, the units of the task demand module receive top-down inputs from a conflict-processing module, consisting of the anterior cingulate cortex (ACC) and the STN. The ACC receives a conflict signal from the response module (representing the amount of conflict between the two response units) and forwards it to the STN, which then modulates the activities in the task demand module.

Botvinick *et al.* (2001) assumed the conflict module to be closely related to the ACC, which is known to project to the STN (Botvinick *et al.*, 2004; Lambert *et al.*, 2012). We propose that as conflict monitoring and adaptation module it contains both, the ACC and the STN (Figure 2). This assumption does not alter the model's dynamics, but allowed us to investigate a potential role of STN DBS in Stroop dynamics.

We reproduced all model equations for the healthy-state model exactly as implemented in the original publication by Botvinick *et al.* (2001). This was done to ensure comparability of our results with previous publications and to avoid overfitting of the model to our findings. All model equations are reported in Supplementary Methods. Botvinick *et al.* (2001), however, did not define a Parkinsonian version of the model so that we had to specify, in which respects such a Parkinsonian model would differ from the healthy state. Based on our empirical results, PD was implemented by changing the connection weights between the task demand module and the sensory word module. These connections specify the amount of interference that incongruent words produce (i.e. the extent of the Stroop effect). Specifically, we increased the bidirectional weight between the

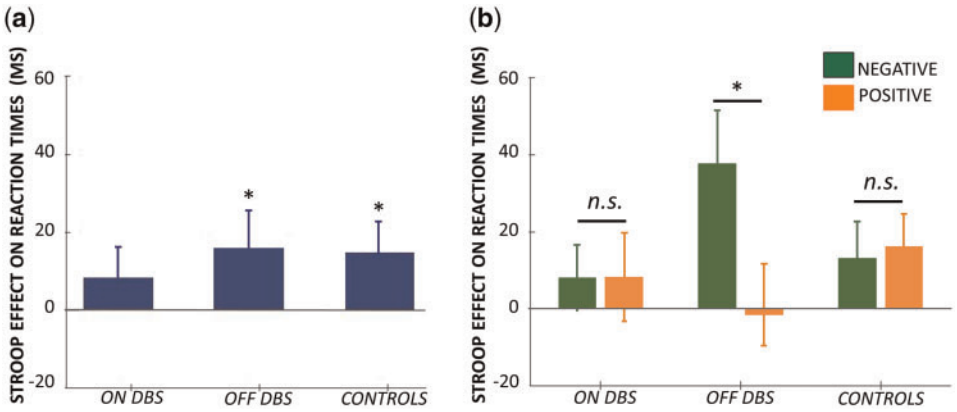

Fig. 3. Emotional Stroop effect on reaction times. (a) Over both valences, the Stroop effect of reaction times (delta of conflict – no conflict trials) is significantly different from zero in PD patients OFF DBS and healthy controls. No such difference is present ON DBS. (b) PD patients OFF DBS show a strong Stroop effect only for conflicting negative stimuli whereas no valence difference is found ON DBS and in healthy controls. Mean reaction times and standard error of the mean (SEM) are displayed (*$P < 0.05$).

sensory positive word unit and the word processing unit from 4.0 to 4.15 and reduced the bidirectional weight between the sensory negative word unit and the word processing unit from 4.0 to 3.85. Thereby, the model would reproduce increased Stroop effects in PD for negative faces and decreased Stroop effects of positive faces. The magnitude of changes was determined via manual fitting.

While it has been shown empirically that STN DBS reduces the activation of STN somata, presumably via activation of neighbouring inhibitory neurons, and at the same time directly excites STN neurons' axons (Agnesi *et al.*, 2013; Dorval *et al.*, 2008, 2010), the physiological relevance of these two effects is yet unknown. We here used the computational model by Botvinick *et al.* (2001) to investigate, whether each of these effects alone or in combination could reproduce the empirically observed effects of STN DBS on Stroop dynamics. To this end, we simulated the DBS ON condition in three versions, testing the following sets of assumptions:

i. STN inputs from the ACC were divided in magnitude by 2.0 to simulate DBS induced inhibition of STN neurons' somata. Additionally, the STN's baseline activity was increased from 0.0 to 3.0 to simulate DBS induced activation of STN neurons' axons.
ii. Again, STN inputs from the ACC were divided by 2.0. However, the baseline was not increased (i.e. axons were not assumed to be activated).
iii. The STN's baseline activity was increased to 3.0, while inputs from the ACC were not reduced (i.e. somata were not assumed to be inhibited).

We ran our simulations for a total of 72 trials per simulated subject (18 trials for each condition in random order, but precluding more than three identical trials in a row), in line with the original paradigm. Eleven subjects were simulated for each subject group. The model's Stroop effects on reaction time were fitted to empirical results by linear regression (as previously done by Botvinick *et al.*, 2001), estimating a single increment and offset parameter across four conditions. These conditions comprised the two face emotion conditions times two subject groups (i.e. healthy control subjects and patients OFF stimulation). The stimulation ON group was left out from the fitting procedure, since our goal was to compare the effects of different stimulation settings for this condition (precluding the possibility to arrive at a single set of fitted parameters). Thus, we fit the model for the other two conditions and then used the resulting parameters for all conditions.

Results

Emotional Stroop effect (within-trial conflict adaptation)

ANOVA I revealed a significant main effect of group, $F_{1,10} = 5.022$, $P = 0.049$, $\eta^2 = 0.201$, suggesting that the Stroop effect on reaction times ON DBS differed from the Stroop effect OFF DBS. Comparing the unstandardized Stroop effect in either group irrespective of valence, against zero revealed that conflict-induced slowing was significant in PD patients OFF DBS (mean Stroop effect of 17.96 ms), $t(10) = 2.006$, $P = 0.05$, $d = 0.605$, and in healthy controls (mean Stroop effect of 15.75 ms), $t(10) = 2.245$, $P = 0.045$, $d = 0.677$, but not in PD patients ON DBS (mean Stroop effect of 8.19 ms), $t(10) = 1.01$, $P = 0.35$, $d = 0.304$ (Figure 3A). Furthermore we found a significant interaction of valence and group, $F_{1,10} = 10.025$, $P = 0.01$, $\eta^2 = 0.334$, indicating that the group difference between ON and OFF was influenced by trial valence. In post hoc paired *t*-tests, trials with positive *vs* negative valence differed significantly from one another OFF DBS, $t(10) = 3.52$, $P = 0.005$, $d = 1.123$, but not ON DBS, $t(10) = 0.02$, $P = 0.97$, $d = 0.007$, or in healthy controls $t(10) = 0.34$, $P = 0.74$, $d = 0.108$. Specifically, there was a larger Stroop effect for negative than positive trials OFF DBS leading to significantly longer reaction times if the target stimulus (face) was negative and the superimposed word was positive or faster if the target stimulus (face) was positive and the superimposed word was negative, respectively (Figure 3B). Since the intercept test was non-significant, the mean patients response ON and OFF DBS did not differ from the mean of the control group, $F_{1,10} = 0.099$, $P = 0.759$, $\eta^2 = 0.005$. There were no significant correlations of the Stroop effect in either valence with disease duration, age, United PD Rating Scale III motor scale or medication intake (LEDD at time of study).

Across-trial conflict adaptation

Reaction time slowing in conflict trials has previously been described as being dependent on trial-to-trial adaptation of cognitive control, irrespective of valence. In ANOVA II, we found neither a main effect of group, $F_{1,10} = 2.61$, $P = 0.13$, $\eta^2 = 0.115$, or valence, $F_{1,10} = 0.149$, $P = 0.708$, $\eta^2 = 0.007$ nor the interaction of the two, $F_{1,10} = 1.634$, $P = 0.23$, $\eta^2 = 0.076$, to be significant. These results indicate that neither group nor valence influenced reaction time differences between high and low across-trial conflict adaptation trials. The intercept test was non-significant, $F_{1,10} = 3.374$, $P = 0.1$, $\eta^2 = 0.144$, indicating the mean of ON and OFF

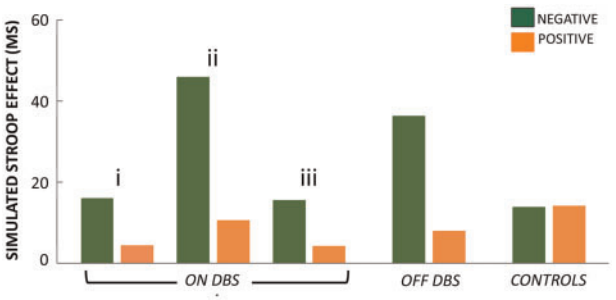

Fig. 4. Results of computational modelling of STN DBS interference with the Stroop effect. STN DBS is modelled with (i) a reduction in inputs from the ACC to the STN and increased STN baseline outputs, (ii) a reduction in STN inputs, and (iii) a reduction in STN outputs.

DBS data did not differ from the mean of the control group. Across-trial conflict adaptation was present in PD patients OFF and ON DBS and healthy controls to a similar extend, however, bearing in mind a limited number of subjects in our study.

Accuracy

Similar to Etkin *et al.* (2006), we found overall error rates to be relatively low in our sample with >99% mean accuracy in all conditions. Due to the low percentage of errors, we refrained from further analysis and discussion.

Computational results

We fitted the model by Botvinick *et al.* (2001) to the results of the healthy control group and of the stimulation OFF group as detailed in Materials and methods. Resulting Stroop effects for these two subject groups well reproduced empirically observed Stroop effects (Figure 4). For the healthy control condition, our simulations reproduced equally sized Stroop effects for negative and positive faces. For the Parkinsonian stimulation OFF condition, moreover, simulation results reproduced the observation that Stroop effects were stronger for negative than for positive faces.

As previously detailed by Botvinick *et al.* (2001), Stroop effects in this model result from increased competition between negative and positive response units (causing longer reaction times) when comparing incongruent to congruent trials. In the healthy condition, Stroop effects are of equal size for negative and positive faces as there is no bias in the original model. For simulating the results of PD patients, based on our experimental results, we expected positive words to interfere more strongly with negative faces in the PD conditions than in the healthy condition and negative words to interfere less strongly. As a consequence, our simulations reproduced a stronger Stroop effect for negative faces than for positive faces.

To investigate how STN DBS affects Stroop dynamics, we tested three different sets of assumptions with different modulation of STN input/output dynamics. In our simulations, we found that an increased baseline activity of the STN well reproduced the empirical results of PD patients ON stimulation irrespective of any reduction in inputs (Figure 4). In contrast, we found that a reduction in inputs to the STN did not reproduce findings.

Discussion

In this study, we assessed the influence of STN DBS on emotional conflict processing in patients with PD using an emotional Stroop paradigm introduced by Etkin *et al.* (2006). In this task, subjects needed to label face stimuli according to their emotional expression (negative or positive) while ignoring a superimposed emotion word congruent or incongruent to the facial expression. Because reading is automatized (Stroop, 1935), labelling a facial expression that is incongruent to the superimposed word should elicit cognitive control to suppress response to the word stimulus which in turn would slow down reaction times (Etkin *et al.*, 2006). Such conflict-related reaction time slowing is classified as being implicit, thus it requires no conscious awareness (Gyurak *et al.*, 2011). Our main result shows that ON DBS, PD patients did not slow down their reactions in trials where a conflict signal should have been detected. This implicates a defect in within-trial conflict adaptation induced through STN DBS. This finding is in line with growing evidence indicating interference of STN DBS with conflict processing and respective slowing of motor responses (Frank *et al.*, 2007; Brittain *et al.*, 2012; Green *et al.*, 2013; Zavala *et al.*, 2015, 2016; Herz *et al.*, 2016).

Previous studies had found no or even contrary effects of DBS on the traditional Stroop effect in PD patients (Jahanshahi *et al.*, 2000; Schroeder *et al.*, 2002; Witt *et al.*, 2004). However, this conflicting evidence likely relates to methodological differences in the applied paradigm: The above-mentioned studies assessed differences in total completion time of a colour-word Stroop versus a control task. In this study, we were interested in the direct reaction time differences between congruent and incongruent trials that are likely modulated by STN activity; defining the Stroop effect as trial-by-trial reaction time slowing due to recruitment of cognitive control (Botvinick *et al.*, 2001; Etkin *et al.*, 2006). Our study furthermore differs by design, as we controlled for confounding continuous stimulation effectiveness by waiting 30 minutes after switching off the DBS device before starting the task, which Schroeder *et al.* (2002) did not. Moreover, one may argue that the emotional Stroop paradigm inherently differs from the traditional colour-word Stroop task as facial expressions may, at least subtly, also be processed automatically. The evidence on processing hierarchy of faces and words is however inconsistent (Dolan and Vuilleumier, 2003; Beall and Herbert, 2008; Ovaysikia *et al.*, 2011). Yet, it cannot be ruled out that the emotional Stroop task manifests through neural resources beyond the network engaged in the traditional colour-word Stroop task.

Interestingly, we found stimulus valence to affect emotional conflict processing in PD patients OFF DBS. In particular, we found conflict-induced reaction time slowing to be much more prominent for negative conflict stimuli. That is, in PD patients OFF DBS, if a negative facial expression was superimposed with a positive word, the interference was significantly stronger than if a positive facial expression was superimposed with a negative word. This finding is evidence for a valence bias affecting conflict-induced reaction time slowing in PD patients OFF DBS. In PD patients ON DBS and healthy controls, such difference was absent resembling the findings by Etkin *et al.* (2006).

Previous research has indicated that STN DBS surgery may cause alterations in the ability to recognize emotions, especially regarding negative emotions such as fear, sadness, anger and disgust (Biseul *et al.*, 2005; Drapier *et al.*, 2008; Péron *et al.*, 2010). Our data suggest that active stimulation in the STN area

modulates the affective bias that is present OFF DBS and reduces the interference of positive words with negative facial expressions leading to a reduced slowing of reaction times during negative emotional conflict trials.

It is worthwhile considering this DBS-induced change to occur along with the clinical improvement of the affective mood state. Psychiatric signs of PD often include emotional blunting, apathy and depression (Maillet *et al.*, 2016), possibly relating to a higher degree of modulation of alpha oscillatory activity in the STN (Huebl *et al.*, 2011). STN DBS has been found to elevate the current subjective mood, facilitating emotional experience and improving emotional memory similar to the effect of dopaminergic replacement medication (Schneider *et al.*, 2003). By altering the current affective state, STN DBS may interact with affective biases on attention and memory in PD (Gray and Tickle-Degnen, 2010), which have been described to be present in negative affective states (Gotlib *et al.* 2004; Beck *et al.*, 2012). Continuous STN DBS may thus adjust a selective attention or working-memory bias towards negative and away from positive information that is present in PD patients OFF DBS. This could occur independent of the presence of moderate or severe depressive symptoms as it was the case in our cohort although one limitation is that we did not obtain the BDI score separately ON and OFF DBS.

We were also interested in whether STN DBS would alter across-trial conflict adaptation. Conflict adaptation is adjusted based on contextual information: conflict detected in one trial triggers up-regulation of selective attention in anticipation of the next trial (Botvinick *et al.*, 2001). This trial-to-trial regulation of top-down control determines that response times are faster in a conflict trial that was cued by a previous conflict trial (high across-trial conflict adaptation) than in a conflict trial where the previous trial elicited no conflict (low across-trial conflict adaptation) (Etkin *et al.*, 2006). We found across-trial adaptation of top-down control to be present in all three groups equally, suggesting that STN DBS does not interfere with context-based adjustment of cognitive control in this task. However, we cannot rule out that STN DBS may inhibit the regulatory interplay of cognitive control regions in response to conflict. Our restricted sample size and the comparatively long inter-stimulus interval that we had to use for patients to be able to complete the task in an OFF DBS often severe bradykinetic state may have limited the observability of the effect. Future studies should use a different design focussing specifically on across-trial conflict adaptation to rule out potential disturbances induced through STN DBS.

Taken together, our findings indicate an interference of STN DBS with reaction time slowing in response to emotional conflict (within-trial conflict adaptation), but not with across-trial conflict adaptation. These results will be discussed further with regard to the dissociation of anatomical substrates guiding conflict monitoring and adaptation processes.

Neural networks of emotional conflict adaptation

Electrophysiological and neuroimaging studies suggest a partial dissociation of within-trial and across-trial conflict adaptation networks in the brain (MacDonald *et al.*, 2000; Carter and van Veen, 2007). Conflict-related slowing (within-trial conflict adaptation) has largely been attributed to follow activity of the dorsal-caudal ACC (Botvinick *et al.*, 2001, 2004; Botvinick and Cohen, 2014). In other words, during response preparation, conflicting environmental demands are automatically detected in the dorsal-caudal ACC engaging cognitive control to direct attention towards the relevant and away from irrelevant stimulus features (Egner and Hirsch, 2005). Evidence for this notion derives from studies using the classic colour-word Stroop paradigm (Botvinick *et al.*, 2004) as well as the emotional Stroop paradigm (Etkin *et al.*, 2006). The ACC seems thus to engage in monitoring of both non-emotional and emotional conflicting input (Egner *et al.*, 2008) specifying adaptive adjustments to be implemented by regulative structures such as the STN (Shenhav *et al.*, 2013).

For effective across-trial emotional conflict adaptation, it is the interplay of the ACC, PFC and amygdala that seems to be particularly important for the regulation of cognitive control (Etkin *et al.*, 2011). To minimize resource costs, cognitive control needs to adapt to contextual affective information, so that, once engaged, resolving subsequent conflicting emotional input requires less attention and less cognitive control (Kerns *et al.*, 2004; Egner and Hirsch, 2005; Walsh *et al.*, 2011). There is evidence for a pathway through which the rostral-ventral ACC exhibits inhibitory control over the amygdala to constrain the amygdalar response triggered by emotional distracters (Bush *et al.*, 2000; Egner *et al.*, 2008). On the other hand, strong associative white matter tracts link the rostral-ventral ACC with the PFC (Heilbronner and Haber, 2014) allowing for conflict-related information transfer to elicit adjustment of control resources (Keedwell *et al.*, 2016). Effective adaptation to emotional conflict seem thus to be dependent on a successful link between the ACC, prefrontal and amygdalar regions. In order to understand the role of the STN in emotional conflict processing, it is thus vital to focus on its connection with the abovementioned structures.

Out of its previously demarcated functional divisions (limbic-anterior, associative-mid, sensorimotor-posterior) (Joel and Weiner, 1997; Karachi *et al.*, 2005; Lambert *et al.*, 2012; Accolla *et al.*, 2016), it is the anterior STN that holds direct connections to emotion networks. The confirmed presence of associative tracts to and from the ACC, the basolateral amygdala, the internal globus pallidus and anterior hippocampi (Lambert *et al.*, 2012; Péron *et al.*, 2015) highlight the putative involvement of the STN in emotion processing, albeit direct evidence for emotional conflict processing in the STN is to date still sparse. However, there is evidence for the STN to be involved in processing of both affective content and conflicting perceptual input.

Direct recordings of neuronal activity from the STN during an emotional picture-viewing task have confirmed its role in processing affective content (Kühn *et al.*, 2005; Brücke *et al.*, 2007; Huebl *et al.*, 2011). Clinical studies with PD patients using STN DBS have reported occasional emotional disturbances such as hypomania, mirthful laughter or crying (Krack *et al.*, 2001; Mallet *et al.*, 2007; Wojtecki *et al.*, 2007). It could be assumed that DBS interferes with information integration from emotional processing structures such as the ACC, PFC and amygdala in the STN (Péron *et al.*, 2013); however, a clear deduction of STN contribution requires more research evidence.

Regarding the processing of conflicting perceptual input, plenty of evidence suggests that the STN modulates the integration of prefrontal conflict signals into the motor response (see Zavala *et al.*, 2015 for review). Holding a gateway position, the STN responds to mPFC conflict signals by slowing down action initiation until action tendencies are weighted based on accumulating evidence (Frank *et al.*, 2007). This capacity to slow down responses is crucial to avoid errors and premature responses and the underlying mPFC-STN interplay has been suggested to be modulated by a temporary increase of low-frequency oscillation

synchrony between the two regions (Cavanagh *et al*., 2011; Brittain *et al*., 2013; Zavala *et al*., 2014; Herz *et al*., 2016; Zénon *et al*., 2016). During DBS, this interplay is disturbed resulting in more erroneous and impulsive choices (Frank *et al*., 2007; Herz *et al*., 2016). Extending these assumptions to emotional conflict processing, it is likely that DBS would interfere with synchronization of STN and mPFC activity, on the one hand, and the integration of emotion-related signals of ACC and amygdala in the STN gateway signal, on the other hand. We aimed to provide a computational approach to verify the involvement of the STN in emotional conflict processing by applying the distinguished Stroop model (Botvinick *et al*., 2001) on emotional content.

An adapted Stroop model of emotional conflict processing

The model by Botvinick *et al*. (2001) explains the emergence of Stroop effects by increased competition between response units for incongruent as compared to congruent trials. Applied to the emotional Stroop task, responses are fast and correct in congruent trials, where congruent face and word information adds up, while in incongruent trials, incongruent face and word information competes for access to the model's response units, requiring more time to select the correct response. Stroop effects (i.e. differences in reaction times between congruent and incongruent trials) are thus directly related to the 'strength' (i.e. saliency) of word stimulus in incongruent trials. The model thus explains stronger Stroop effects for negative faces and weaker Stroop effects for positive faces in PD patients OFF stimulation by an increased saliency of positive words and a decreased saliency of negative words in these patients. These results suggest that, other than might have been expected, non-stimulated PD patients' attention is more strongly captured by positive words than by negative words.

DBS is empirically known to directly alter pathological as well as task-related physiological activity (Garcia *et al*., 2003; Chen *et al*., 2006). During the colour-word Stroop task, automatized responses in incongruent trials are held back by momentary increases in STN beta activity (Brittain *et al*., 2012). Taken together with its interference with conflict-related oscillations detailed above, such suppression of spontaneous STN activity well explains the disruptive impact of DBS on performance in tasks comparing high *vs* low conflict scenarios such as our paradigm.

On a mechanistic level, DBS has been shown to both increase the outputs of targeted brain structures (i.e. to directly activate axons) and to reduce the influence of inputs to these structures (i.e. to de-activate somata; Dorval *et al*., 2008; 2010; Agnesi et al, 2013). With our simulations, we showed that the former of these effects, but not the latter, explains how STN DBS affects Stroop dynamics in PD patients: Our model suggests that the DBS-induced activation of STN axons is more important for explaining DBS effects on Stroop dynamics than the reduction of STN inputs from the ACC. However, the two effects might not be fully independent due to boundary effects. Frank *et al*. (2007) stressed this via computational simulations in a different model. They showed that changes in STN baseline activity can disrupt task-related cortical inputs to the STN to such an extent that PD patients become impaired in their ability to slow down with conflicting decisions.

The original model by Botvinick *et al*. (2001) has been subject to criticism mainly directed towards its primary focus on the ACC. The neural network guiding conflict monitoring and adaptation is likely more extensive including along ACC also the pre-supplementary motor area (pre-SMA) (Nachev *et al*., 2007; Kouneiher *et al*., 2009; Roberts and Husain, 2015) and other cortical and subcortical regions supplying information leveraged by dorsal ACC (dACC) to maximise the expected value of control (Shenhav *et al*., 2013). In this context, the STN is counted to the regulatory structures effecting the control adjustments estimated by dACC (Cavanagh *et al*., 2011; Shenhav *et al*., 2013). Our model does not make this distinction between dACC as estimating and STN as implementing control structure and future development of computational models should aim to disentangle the hierarchical interplay of dACC and STN conflict signals in emotional conflict processing.

Overall, our findings suggest that STN DBS does not re-establish normal Stroop functioning in PD patients, but induces a different physiological state that results from increased output of the STN conflict unit.

Limitations

This study has a few limitations. First of all, we cannot exclude the influence of secondary confounding variables on performance. Between-patients variations in electrode placement could have influenced the results. However, post-operative imaging and a good clinical effect verified correct electrode placement (Huebl *et al*., 2011). Moreover, between-patients variations in disease progress and degree of dopaminergic denervation could have influenced cognitive abilities. Yet, we found no correlation of the Stroop effect with clinical parameters such as disease duration or LEDD indicating their potential influence to be insignificant. Furthermore, within-patient variations in dopamine blood level could have impacted performance unnoticed, as we did not test subjects OFF their medication. However, in the tested patients, dopaminergic medication remained unchanged during each 20-minute test session and the applied randomized order of ON and OFF DBS test sessions controlled for this confound. Further, subjects performed the task with a mean accuracy of >99%, which precluded further analysis of error processing. It is likely that due to (i) the stimulus material which only included 100% correct emotional faces of joy and fear (not morphed faces that would have had a higher threshold of recognition) and (ii) the comparatively long stimulus display times used variations in accuracy could not be recorded as effectively. Finally, we did not find an effect of STN DBS on across-trial conflict adaptation, which may also be influenced by the long stimulus interval and limited number of subjects.

Conclusion

This study provides evidence for an interference of STN DBS with emotional conflict adaptation. Hereby, STN DBS regulates an emotional performance bias in PD patients that is present OFF stimulation. Specifically, STN DBS may reduce the impact of emotional conflict on the motor response leading to a respective lack of reaction time slowing ON DBS in conflicting trials. The results of our computational simulations suggest that it is the elevation of baseline activity induced by DBS and not the reduction of task-related activity within the STN caused by reduced inputs from the ACC that alter conflict processing.

Funding

This work was supported by the German research Foundation [DFG, grant KU2261/6-1 and KFO 247]. F. Irmen

was supported by a doctorate scholarship of the Berlin School of Mind and Brain, Humboldt-Universität zu Berlin.

Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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