

**Human subthalamic nucleus-medial frontal cortex theta phase coherence is involved in conflict and error related cortical monitoring.**

**Baltazar Zavala**<sup>1,2</sup>, **Huiling Tan**<sup>1,3</sup>, **Keyoumars Ashkan**<sup>4</sup>, **Thomas Foltynie**<sup>5</sup>, **Patricia Limousin**<sup>5</sup>, **Ludvic Zrinzo**<sup>5</sup>, **Kareem Zaghloul**<sup>2</sup>, **Peter Brown**<sup>1,3</sup>

1. Nuffield Department of Clinical Neurology, University of Oxford John Radcliffe Hospital, Oxford, OX3 9DU, UK
2. Surgical Neurology Branch, National Institutes of Health, 10 Center Drive, 3D20, Bethesda, MD 20814, USA
3. Medical Research Council Brain Network Dynamics Unit at the University of Oxford, Mansfield Road, OX1 3TH, UK
4. Department of Neurosurgery, King's College Hospital, Kings College, London, SE5 9RS, UK
5. Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, London, WC1 3BG, UK

Running title: STN-frontal cortex coherence during conflict and errors.

Word count: Abstract (238), Introduction (503), Discussion (1499).

Number of Tables: 1

Number of Figures: 4

Corresponding author:

Peter Brown

Professor of Experimental Neurology

Nuffield Department of Clinical Neurology

University of Oxford

Level 6, West Wing

John Radcliffe Hospital, OX3 9DU

Tel: 01865 231858

peter.brown@ndcn.ox.ac.uk

**Acknowledgments**

B.Z. is supported by the National Institutes of Health Oxford-Cambridge fellowship. T.F. and L.Z. are funded by the Department of Health National Institute for Health Research UCL Biomedical Research Center, The Monument Trust, and Parkinson's Appeal for Deep Brain Stimulation. P.B. and H.T. are funded by the Medical Research Council, and P.B. further funded by the Department of Health National Institute for Health Research Oxford Biomedical Research Centre.

## **Abstract**

The medial prefrontal cortex (mPFC) is thought to control the shift from automatic to controlled action selection when conflict is present or when mistakes have been recently committed. Growing evidence suggests that this process involves frequency specific communication between the mPFC and the subthalamic nucleus (STN), which is the main target of deep brain stimulation (DBS) for Parkinson's disease. Key in this hypothesis is the finding that DBS disrupts the relationship between mPFC theta (4-8 Hz) oscillations and conflict related reaction time slowing, resulting in impulsivity. In order to test whether theta band coherence between the mPFC and the STN underlies adjustments to conflict and to errors, we simultaneously recorded mPFC and STN electrophysiological activity while DBS patients performed an arrowed flanker task. These recordings revealed increased theta phase coherence between the two sites soon after conflicting arrows were displayed, but before a response was executed. Increased phase coherence was also observed on the trials that occurred after an error was committed, suggesting that mPFC-STN connectivity may also play a role in error related adjustments in behavior. Interestingly, the phase coherence we observed occurred before increases in theta power, implying that the theta phase and power may play different roles during cortical monitoring. Finally, we showed that pre-stimulus differences in STN theta power were related to the reaction time on a given trial, which may help adjust behavior based on the probability of observing conflict during a task.

## **Introduction**

Being able to execute tasks quickly and accurately is a key skill. Equally as important, however, is the ability to dynamically alter the amount of time dedicated to a task based on the task's difficulty and based on previous performance. One area of the brain implicated in speed-accuracy trade off, particularly in scenarios that require a quick action in the face of conflict, is the medial prefrontal cortex (mPFC, Botvinick et al., 2001, 2004; Ridderinkhof et al., 2004). mPFC activity is not only higher for high conflict tasks (Botvinick et al., 2004), it is also directly correlated to the reaction time during conflict (Cavanagh et al., 2011; Cohen and Cavanagh, 2011). The mechanisms by which the mPFC is able to rapidly and dynamically alter behavior, however, are still unclear.

There is growing evidence suggesting that rapidly conducting hyperdirect inputs from the mPFC to the subthalamic nucleus (STN) allow the mPFC to alter the activity of motor networks and thus increase the amount of evidence that is needed to select an action during conflict (Zavala et al., 2015b). Both the subthalamic nucleus (STN) (Fumagalli et al., 2011; Brittain et al., 2012; Zavala et al., 2013, 2014, 2015a) and the mPFC (Cavanagh et al., 2011, 2012; Cohen and Cavanagh, 2011) show similar increases in theta (4-8 Hz) band activity during conflict, and deep brain stimulation of the STN for Parkinson's diseases disrupts the relationship between mPFC theta and "evidence threshold" (Cavanagh et al., 2011; Ratcliff and Frank, 2012), resulting in impulsivity (Frank et al., 2007; Coulthard et al., 2012; Green et al., 2013).

Recently, a direct link between mPFC and STN oscillatory activity was established as the theta activity of the mPFC was shown to drive that of the STN in a dot motion discrimination task that involved gradual increases in conflict (Zavala et al., 2014). Whether or not this mechanism also underlies abrupt onsets of conflict, as well as how the phase coherence between the two sites relates to the theta phase resets that are associated with rapid stimulus onsets (Cavanagh et al., 2012; Zavala et al., 2013), remains unknown.

Another outstanding question centers around the important role the mPFC seems to play in across-trial adaptations to the level of conflict or to errors (Kerns et al., 2004; Ridderinkhof et al., 2004; Danielmeier and Ullsperger, 2011). mPFC theta activity seems to interact with areas of the dorsolateral prefrontal cortex (DLPFC) following high conflict and error trials, which may be related to the respective speeding and slowing of reaction times on subsequent trials (Kerns et al., 2004; Hanslmayr et al., 2007; Cavanagh et al., 2009). Whether or not these interactions also involve the STN remains an open question, but a link is suggested by studies showing error related activity in the STN (Brown et al., 2006; Zavala et al., 2013; Bastin et al., 2014; Cavanagh et al., 2014; Siegert et al., 2014). Here, we address these questions by simultaneously recording electrophysiological activity from the mPFC and STN while DBS patients performed an Eriksen flanker task.

## **Methods**

### *Subjects and task.*

All subjects gave their written informed consent to take part in the study, which was approved by the appropriate local ethics committees. Thirteen subjects (13 males; mean disease duration, 10 years; mean age, 56 years; age range, 42–69 years) underwent bilateral implantation of DBS electrodes into the STN, as a prelude to high-frequency stimulation for the treatment of advanced PD. Only two patients had been diagnosed as having an impulse control disorder. Techniques to target and implant electrodes in the STN have previously been described (Foltynie and Hariz, 2010). Lead location was confirmed with intraoperative stereotactic MRI at University College London Hospital and with immediate postoperative stereotactic computed tomography at the remaining centers. Effective stimulation was confirmed intraoperatively in patients operated at King's College Hospital and the Oxford University Hospitals Trust. The permanent quadripolar electrode used was model 3389 (Medtronic Inc., Minneapolis, USA) featuring four cylindrical contacts. Electrode extension cables were externalized through the scalp to enable recordings before connection to a subcutaneous DBS pacemaker, implanted in a second operation up to 7 d later. Clinical details of the patients are available in Table 1. The mean percentage improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) following treatment with levodopa was  $64.4 \pm 4.5\%$  ( $p < 0.001$ , paired t-test) across subjects, indicating good responsiveness to levodopa in our study participants.

Patients performed an arrow version of the flanker task (Eriksen and Eriksen, 1974)

while receiving their regular medication 3–6 d after electrode implantation. The task was identical to one we have previously used (Zavala et al., 2013), a schematic of which is shown in Figure 1A. Each trial began with a black screen containing a white fixation dot in the middle of the screen, which subtended a visual angle of  $\approx 1^\circ$ . Five hundred milliseconds before the arrows were shown, the dot changed from white to gray to prepare the test subject for the imperative cue. Either congruent ( $> > > >$ ) or incongruent ( $< < > < <$ ) arrows (visual angle  $\approx 3^\circ$  per arrow) were then briefly shown and replaced with the white fixation dot after 200 ms. The subjects had 2 more seconds in which to respond (2.2 s total possible window for a response) before the fixation dot changed from white to gray again to signal the next trial. Correct responses were indicated by a button press in the hand corresponding to the direction of the middle arrow. The ratio of incongruent trials to congruent trials was 2:1. Subjects underwent two 60-trial blocks.

Two of the subjects showed significantly higher error rates than the other 11 subjects (error rate across all trials = 27.7% and 27.8% for the two outlier subjects and  $8.5 \pm 1.1\%$  for the 11 other subjects,  $p < 0.001$ , unpaired t-test) and were therefore excluded prior to any of the analysis. Further justification for excluding these two subjects stems from their reaction time distributions, which showed no significant difference between low and high conflict trials ( $p > 0.05$ , unpaired t-test). All other subjects did exhibit a significant within subject difference. In one of the retained subjects, recordings were only accessible from one STN, therefore the total number of STNs included in the analysis was 21. Data from two of the participants (cases 1 and 2) were also included in our previously published work (Zavala et al., 2013), although that work did not include mPFC theta connectivity, which is the main focus of this paper.

#### *LFP data recording and analysis of power.*

STN LFPs were recorded from the DBS electrodes. Simultaneously, continuous scalp EEG was recorded from frontal, central and parietal electrodes over the midline (Fz, Cz and Pz; International 10-20 System). More lateral electrodes were prohibited by surgical wounds and dressings in this patient group. All signals were sampled at 2048 Hz, bandpass filtered between 0.5 and 500 Hz, and amplified using a TMSi Porti and its respective software (TMS International). Monopolar recordings were subsequently converted off-line to a bipolar montage between adjacent contacts (three bipolar channels per STN side and two bipolar channels for the EEG recordings: Fz-Cz and Pz-Cz) to limit the effects of volume conduction from distant sources. Before further analysis, LFP data were filtered between 1 and 500 Hz and down-sampled to 1000 Hz.

Data were analyzed using custom-written Matlab (MathWorks) scripts. Any trials with reaction times  $> 1.5$  s (including no response trials) or  $< 300$  ms were not included in the analysis ( $< 1\%$ ). For the comparison of correct low conflict and high conflict trials, all incorrect responses were excluded. For the comparison of high

conflict error trials to high conflict correct trials, a reaction time matched subset of the correct trials was used. For each incorrect high conflict trial, one reaction time matched trial was randomly chosen from all of the correct high conflict trials that had a reaction time within 30 ms of the incorrect trial. Any incorrect trial that did not have a correct trial that was within 30 ms was excluded from the analysis. Subjects with fewer than 5 errors were not included in this analysis ( $n = 2$ ). The average number of error trials for the 9 subjects that were included in the error analysis was  $8 \pm 0.8$  trials. For the analysis shown in figure 3, the correct trials that followed error trials were compared to the correct trials that followed the reaction time matched set of correct trials. The average number of trials used for this analysis was  $6 \pm 0.9$  trials for the post error trials and  $6.1 \pm 0.8$  for the post reaction time matched correct trials. These numbers were slightly lower than the number of error trials and reaction time matched correct trials because a few subjects had consecutive errors or errors that occurred at the end of a block. The post error trials and the post reaction time matched correct trials had a similar proportion of high conflict trials that was consistent with the 2:1 ratio of high to low conflict trials that was used in the task ( $63.5 \pm 8.1\%$  for the post error trials and  $64.3 \pm 4.3\%$  for the post reaction time matched correct trials,  $p=0.85$ , paired t-test).

The instantaneous theta power and phase of the bipolar LFP and EEG signals were calculated by bandpass filtering each trial's raw signal between 4 and 8 Hz and applying the Hilbert transform. Each trial was analyzed from 0.75 s before to 2 s after arrow onset for the cue-aligned analysis, from 1.5 s before to 1.5 s after the response for the response-aligned analysis, and from 2 s before to 0 s before arrow onset for the analysis of the pre-stimulus period (figure 4). A 1 s buffer on either side was used when calculating phase and power to eliminate any edge effects. Any trial with a clear artifact in any of the LFP or EEG channels was discarded.

To assess differences in power between low and high conflict trials, the following approach was used. First, the mean power in each bipolar recording for each trial type was calculated by averaging the power time series across trials. This method produced a time series for low and high conflict trials for each of the three bipolar contacts on each STN electrode and the two bipolar EEG contacts. Each time series was then normalized to the mean power of that channel recorded during a "baseline" period of all trials in the full second leading up to the warning cue onset ( $t=-1.5$  to  $-0.5$ , relative to the arrow onset). Finally, all three STN bipolar contacts were averaged together before being averaged across all STN electrodes. Averaging across all the contact pairs in a given electrode was performed so as to avoid selection bias, and support for this strategy comes from that fact that our previous studies have not allowed us to assess regional difference in STN reactivity based on LFP biomarkers (Zavala et al., 2013, 2014). To assess the statistical significance of any difference between low and high conflict trials, the across electrode average was repeated 1000 times with the low and high conflict labels of each electrode's average data randomly assigned during each permutation. The p value of each time point was found by comparing the actual mean difference to the distribution of the

1000 permutations. The p values were then corrected for multiple comparisons using exceedence mass testing (Maris and Oostenveld, 2007). Exceedence mass testing involves integrating the excess mass of suprathreshold clusters in the spectrogram and recording the largest per iteration. The top 5% of this distribution then determined the corrected threshold for time series-wise significance. When performing other comparisons (i.e., high conflict errors vs high conflict correct, post high conflict errors vs post high conflict correct, fast-high conflict vs slow-high conflict), the same procedure was repeated using the relevant trial groups. Throughout all of our analyses, exceedence mass testing was used to correct for multiple comparisons whenever the difference in a continuous time series between two conditions was assessed. This allowed us to take into account when adjacent points were significant, whereas more traditional methods of correction such as Bonferroni or false discovery rate assume that all time points are independent measurements. When only individual, non-continuous values were compared between trial types, more traditional parametric statistics (i.e. t-tests and ANOVAs) were used.

To assess the single-trial correlation between reaction time and normalized power changes, the normalized theta power of each trial was averaged across the 1.25 s time period leading up to the warning cue onset and correlated with the reaction time in that trial. The resulting correlation coefficients (positive and negative coefficients derived using Spearman's correlation) were then averaged across the STN sides and a two-tailed, one-sample t-test was performed to determine whether the mean correlation was significantly different from zero across subjects.

#### *Intertrial phase consistency (ITPC)*

To analyze the theta phase consistency across trials, the inter trial phase consistency (ITPC, sometimes also called inter trial phase clustering; Cohen and Gulbinaite, 2014) was found in at each time point by projecting the phase at time  $t$  for each trial onto the complex plane, averaging across trials, and taking the absolute value. Using this formulation, an ITPC( $t$ ) value of 0 would mean there is a uniform distribution of phase across trials at time  $t$ , and a value of 1 would mean that the phase at time  $t$  is identical for each trial. ITPC values were calculated separately for low and high conflict trials. In order to prevent the 2:1 high to low conflict trial ratio from affecting our results, the high conflict trials were down-sampled for each subject to match the number of low conflict trials. 1000 down-sampled ITPC time series were calculated for each subject's high conflict trials, and the average of the down-sampled values was used for each subject. The low conflict and the down-sampled high conflict ITPC time series were then normalized to the "baseline" ITPC value recorded during the full second leading up to the presentation of the warning cue onset ( $t=-1.5$  to  $-0.5$ , relative to the arrow onset). Randomly drawn subsets of all the trials were used to calculate the baseline 1000 times, with the number of trials used for each baseline calculation equal to the number of low conflict trials (and the number of down-sampled high conflict trials). An identical procedure was used when comparing error trials to correct trials, with the only

exception being that the number of trials used to calculate the baseline was equal to the number of error trials.

To assess the statistical differences between conditions, the low and high conflict normalized ITPC values were first calculated for each bipolar signal and averaged across all three bipolar contact pairs of each STN electrode. The resulting values were then averaged across electrodes and the difference between the two trial types was compared to 1000 permuted differences generating by permuting each electrode's average values prior to finding the across-electrode average. The p value at each point was calculated using the distribution of the 1000 permuted values and corrected for multiple comparisons at a significance level of 0.05 using exceedence mass testing.

#### *Intersite phase coherence.*

The cortico:STN phase coherence (occasionally also referred to as inter-site phase clustering; Cohen and Gulbinaite, 2014) was calculated using the continuous time evolving methods we have previously used (Zavala et al., 2014) as outlined by Lachaux et al. (2002). Low- and high-conflict trials were analyzed separately, with the high conflict trial's phase coherence values being calculated 1000 times using a down-sampled data set (see ITPC section above). The difference between the instantaneous theta phase (projected on the complex plane) at time  $t$  in each bipolar STN contact and the theta phase at time  $t$  in the Fz-Cz channel was found at each time point. The phase difference values at time  $t$  were then averaged across trials and a sliding window was used to integrate across time (Lachaux et al., 2002). The width of the window was chosen to be 333 ms (2 cycles of a 6 Hz oscillation). The magnitude of the resulting average was then taken to generate the phase coherence. Each channel's time evolving phase coherence signal was then normalized by that channel's "baseline" phase coherence. The baseline was chosen in the same way as it was chosen for the ITPC analysis: calculating the mean phase coherence value (averaged across the full second before the warning cue onset) 1000 times for down-sampled sets of trials (equal in number to the number of low conflict trials) randomly chosen from all of the trials. The three resulting normalized time series generated for each of the three contacts in each STN were then averaged within each STN before averaging across STNs. Statistical significance was determined using permutation testing as outlined above. To calculate the Hilbert parietal cortex:STN phase coherence, the same analysis was done using the Pz-Cz bipolar electrode instead of the Fz-Cz electrode. An identical procedure was used when comparing error trials to correct trials, with the only exception being that the number of trials used to calculate the baseline was equal to the number of error trials.

## **Results**

### *Behavioral Effects*

Subjects performed an arrowed version of the Eriksen flanker task (figure 1a). This used the exact same configuration as our previous study, although that study did not simultaneously record EEG with STN LFPs (Zavala et al., 2013). Consistent with our previous results, patients were significantly slower during the high conflict condition relative to the low conflict condition (mean  $\pm$  SEM= 596 $\pm$ 24 ms vs 512 $\pm$ 19 ms,  $p < 0.001$ , paired t-test) and showed a significantly higher error rate during conflict (mean  $\pm$  SEM = 11.6 $\pm$ 1.5% vs 2.1 $\pm$ 1.2%,  $p < 0.01$ , paired t-test; figure 1a, inset). There was no slowing of reaction time in trials that followed an error ( $p > 0.05$ , paired t-test). There was also no Gratton effect on reaction time (Gratton et al., 1992): the reaction time of high conflict trials was not affected by the level of conflict in the previous trial, and the same was true for low conflict trials (ANOVA, within-subject repeated measures, current trial conflict x previous trial conflict: current trial conflict  $F = 87.2$ ,  $p < 0.001$ ; previous trial conflict  $F = 1.5$ ,  $p = 0.25$ ; interaction  $F = 0.04$ ,  $p = 0.84$ ).

#### *Conflict related difference in STN LFP and mesial frontal theta activity*

In agreement with the results we have previously reported, subjects demonstrated an increase in theta power in the STN LFP during the task, as well as a decrease in beta power (top panel Figure 1b). As most of the literature concerning cortical and subcortical conflict related networks implicates coupling in the theta band (Cavanagh et al., 2011, 2012; Zavala et al., 2013, 2014, 2015a), we focused our attention on this band. The bottom panel of figure 1b shows that during the task, the subjects showed a consistent increase in band-passed theta (4 to 8 Hz) LFP power in the STN LFP after onset of the warning cue (at  $t = -500$ ms), and this was followed by an even greater increase after onset of the arrows (at  $t = 0$ ms).

In order to explore the temporal evolution of theta band activity during the flanker task, we analyzed the theta power, theta inter-trial phase consistency (ITPC), and theta inter-site phase coherence in the STN LFP and in the mesial frontal EEG (figure 2). Consistent with our previous results, we showed that high conflict trials were associated with a higher increase in pre-response theta power in the STN LFP relative to the low conflict trials (figure 2a, top). During the 500 ms leading up to the response, the average theta power increase was 15.7  $\pm$  3.7% for low conflict trials and 21.4  $\pm$  4.6% for high conflict trials ( $p < 0.01$ , paired t-test). There was also a trend toward higher post response STN theta power during the period that followed high conflict trials but before onset of the warning cue for the next trial (see "Pre-stimulus correlates of behavior" section below). When we analyzed the mesial frontal theta power changes (figure 2a, bottom), we observed no significant conflict related differences. Surprisingly, the mesial frontal theta activity peaked after the response (mean peak time  $\pm$  SEM for all correct trials= 85.9 $\pm$ 78.6 ms relative to the response), which was significantly later than the STN theta power peak that occurred before the response (mean peak time  $\pm$  SEM for all correct trials = -58.4 $\pm$ 28.1 ms relative to the response,  $p < 0.05$ , paired t-test; relative to the cue these

values were  $770 \pm 82.5$  ms for the mesial frontal EEG and  $633.7 \pm 94.1$  ms for the STN LFP,  $p < 0.05$ , paired t-test).

We have previously shown that the presentation of the warning cue or of the target arrows consistently realigns the phases of ongoing STN LFP theta oscillations as indexed by ITPC (Zavala et al., 2013). Here we reproduce these results and show that a simultaneous increase occurs in the mesial frontal EEG. Both STN LFP and mesial frontal EEG ITPC increases were much higher for the cue aligned data than they were for the response aligned data, supporting our previous claim that the ITPC changes are evoked by stimulus onset. Notably, the STN LFP and mesial frontal EEG ITPC increases seemed to occur simultaneously, early during the trial (mean STN LFP ITPC peak time  $\pm$  SEM for all correct trials =  $257.6 \pm 49.8$  ms relative to the cue; peak time for medial frontal EEG ITPC =  $319.5 \pm 115.6$  ms,  $p > 0.6$ , paired t-test), and they both peaked significantly ( $p < 0.001$ , paired t-test) before the theta power increases described above. Though there were no significant, conflict related differences in the stimulus-triggered ITPC increase in either location, this may be because it is not the particular phase of the oscillation that is important at any given time in a trial, but rather the coherence of the phases between the STN LFP and mesial frontal EEG.

Consistent with the idea that coherent oscillations between two brain sites would allow behaviorally relevant information to flow from one site to the other (Fries, 2005), we observed higher pre-response theta phase coherence between the mesial frontal EEG and the STN LFP during the high conflict trials (figure 2c). Averaging across the first 500 ms following the cue showed a phase coherence value of  $20.0 \pm 7.1\%$  for the high conflict trials and a value of  $-2.4 \pm 7.8\%$  for the low conflict trials ( $p < 0.01$ , paired t-test). Likewise looking at the 500 ms leading up to the response showed higher phase coherence values for the high conflict condition relative to the low conflict condition ( $16.4 \pm 4.6\%$  vs  $-3.1 \pm 7.0\%$ ,  $p < 0.01$ , paired t-test). As a control, we also analyzed the theta band phase coherence between the STN LFP and EEG over the parietal cortex (Pz-Cz) and found no conflict related differences (data not shown). The conflict related increase in phase coherence was not secondary to ITPC differences, as neither the STN LFP nor mesial frontal EEG showed any significant differences in ITPC for low or high conflict trials over these periods. However, given that the stimulus onset induced a phase reset in both the STN LFP and the mesial frontal EEG for low conflict trials, it is interesting that these trials did not show any increases in phase coherence during the periods with elevated ITPC levels. This discrepancy, together with the fact that the phase consistency across trials is not uniform (average maximum un-normalized ITPC across all correct trials in all subjects =  $0.34 \pm 0.03$ , perfect inter trial phase alignments would have a value of 1) shows that there is some inconsistency in the exact phase to which both structures are aligning. Only during conflict did the two structures reset their phase in a way such that phase differences were sustained across time both within and across trials (see also Nigbur et al., 2012).

*Post Error related difference in STN LFP and mesial frontal EEG theta phase coherence*

Much of the literature concerning the mPFC focuses on the role this brain area might play in error monitoring and post error adaptations (Ridderinkhof et al., 2004; Danielmeier and Ullsperger, 2011). When we compared the theta band activity in the incorrect high conflict trials to the activity observed in a reaction time matched set of correct high conflict trials, we observed no differences in theta band power, ITPC, or phase coherence (data not shown). We also observed no differences in theta power or ITPC when we compared the correct trial that followed a high conflict incorrect trial to the correct trial that followed a reaction time matched high conflict correct trial (figure 3a,b). However, when we analyzed the phase coherence between the mesial frontal EEG and the STN LFP, we observed a significant, pre-response difference between the trials that followed errors and those that did not (figure 3c). Averaging across the 500 ms leading up to the response revealed significantly higher phase coherence in the trials that followed an error (post error coherence= $13.3\pm 6.8\%$ , post correct coherence = $-9.9\pm 4.4\%$ ,  $p<0.01$ , paired t-test), and averaging across the first 500 ms following the cue revealed a similar trend (post error coherence= $10.7\pm 6.3\%$ , post correct coherence = $-6.1\pm 4.2\%$ ,  $p<0.07$ , paired t-test). As a control, we also analyzed the theta band phase coherence between the STN LFP and the EEG over the parietal cortex (Pz-Cz) and found no error related differences (data not shown).

#### *Pre-stimulus correlates of conflict and behavior*

As the previous section highlighted that task related activity on one trial can be related to electrophysiological activity on the subsequent trial, we decided to further explore the post-response, pre-subsequent warning cue STN power differences reported in figure 2a. When we analyzed the pre-stimulus periods ( $t=-2000$  to  $0$  ms) that followed high and low conflict trials, we observed a significant difference in power approximately midway through this period (figure 4a). This difference did not reflect a “spill over” of the conflict related differences of the previous trial as there was a period in between the pre-response differences of the previous trial and the pre-stimulus differences on the subsequent trial in which the power had returned to baseline levels for both conditions. Moreover, when we median split high conflict trials into two populations based on whether they were in the fastest half or the slowest half of the high conflict trials, we observed significant differences in the pre-warning cue power levels between the fastest and slowest high conflict trials (figure 4b, bottom). During the 1.25 s that preceded the warning cue, the power level for the slowest high conflict trials was  $2.8\pm 0.7\%$  higher than the average baseline power observed during all trials, and the power level for the fastest high conflict trials was  $1.7\pm 0.6\%$  lower than the average baseline ( $p<0.01$ , paired t-test). This effect was not present during the low conflict trials (figure 4b, top), suggesting that the pre-stimulus differences only affect reaction time when the subsequent stimulus contains conflict. Further support for this claim stems from our finding that the pre-stimulus power levels significantly correlated with trial reaction time in the high conflict condition (mean  $R=0.10\pm 0.03$ ,  $p<0.05$ , one-sample t-test),

but not in the low conflict condition (mean  $R = -0.01 \pm 0.03$ ,  $p = 0.6$ , one-sample t-test; high vs low  $p < 0.05$ , paired t-test figure 4c).

## Discussion

The results we present here corroborate previous findings concerning the potentially crucial roles of theta oscillations and of the STN during conflict (Cavanagh et al., 2011; Zavala et al., 2013, 2014). Our results also provide several novel insights concerning the relationships between the STN and cognitive control. High conflict trials demonstrated higher theta phase coupling between the mesial frontal EEG and the STN, and these differences occurred early in the trial before any power differences took place. Furthermore, error trials were followed by increased phase coherence between the two sites on the subsequent trial. Finally, pre-stimulus differences in STN theta power correlated with the reaction time of the subsequent trial, but only when that trial contained conflict. These data help explain why disruption of this network by DBS may influence behaviors such as impulsivity during conflict and suggest the hitherto untested hypothesis that DBS may also interfere with some of the behavioral adjustments that take place when mistakes are committed.

Prior to further discussing the significance of our results, it is important to discuss some of the limitations in this study. First and foremost, this study was, out of necessity, conducted in patients with Parkinson's disease. Nevertheless, the patients performed the task on their regular medication in an attempt to reproduce "normal" basal ganglia activity to the greatest extent possible. Further evidence supporting the generalizability of our findings stems from the fact that the subjects included in the analysis showed relatively fast reaction times (about 500ms on average for low conflict trials) and conflict slowed reaction times as in healthy subjects. The second limitation of this study is the low number of errors that we were able to record per subject. Low trial counts may be the reason why we were unable to reproduce previous conflict or error related differences in mPFC theta power (Cavanagh et al., 2012; Cohen and van Gaal, 2014). However, ours is not the only study that has failed to show these differences when averaging across trials (Cohen and Cavanagh, 2011).

### *Conflict related STN theta power and phase play separate roles within a trial*

Despite the above caveats, we believe our data allow us to make some inferences regarding theta band interactions between the mPFC and the STN. The importance of mPFC-STN theta connectivity was previously suggested by a study showing that DBS to the STN disrupts the relationships between mPFC theta power and conflict related changes in reaction time (Cavanagh et al., 2011). To our knowledge, however, only one study has directly shown increased coherence between the mPFC and the STN during conflict (Zavala et al., 2014). The latter study used a gradually adapting dot motion task to show that trials containing slow increases in conflicting information were associated with increased mPFC-STN coherence and of mPFC

drive of STN theta activity. Here, we have reproduced the increase in mPFC-STN phase coherence using the flanker task, which involves rapid onset conflict and ITPC increases. In contrast to the phase coherence, though, we did not observe any conflict related differences in ITPC during the task. This suggests that only when phases realign in a way that produces a specific and sustained phase difference between the two structures does activity in the two structures become coherent (Fries, 2005; Nigbur et al., 2012). The finding may also help explain previous contradictory results between studies showing task related differences in ITPC in the mPFC (Cavanagh et al., 2012) and STN (Zavala et al., 2013), and others that do not (Cohen and Cavanagh, 2011; Nigbur et al., 2012; Zavala et al., 2014). It is the relative phase difference between mPFC and STN activities that is important, not the absolute phase in each.

The rapid conflict onset paradigm we used here also allows us to make claims regarding the relative timing of theta activity. One unexpected finding in our data was that STN LFP theta power increases actually occurred before those of the mesial frontal EEG. Indeed, the mesial frontal theta increase peaked after the response. Given that we have previously shown that mesial frontal oscillations drive those in the STN during conflict, this finding would seem paradoxical. A potential resolution is provided by the phase of the theta oscillations. Unlike the theta power increases, both the mesial frontal EEG and the STN LFP ITPC increases occurred at the same time, early during the trial, and it was these time periods that were associated with increased mesial frontal-STN coherence. The late increases in mesial frontal and STN theta power may therefore reflect other activity unrelated to whether or not conflict is present. Indeed, a recent study by Cohen and Van Gaal (2014) showed that increases in mesial frontal theta power are associated with EMG detected “partial” errors. Interestingly, theta power differences between correct trials and partial error trials did not take place until after the partial error began. In light of these findings, we propose that *early* (phase coherence) changes in mesial frontal-STN theta coupling may be responsible for delaying all responses only during conflict trials, while *late* (power) changes in theta band activity may be responsible for suppressing only the incorrect response during all trials. This hypothesis may help explain why low conflict trials also show a late increase in STN theta power as well as a late increase in mesial frontal-STN phase coherence. According to this interpretation, the higher increases in theta power that occur late during high conflict trials may reflect a greater drive needed to inhibit the incorrect response due to a stronger activation of that response by the flanking arrows. Still, it must be stressed that the evidence we have presented is correlative in nature, and causality remain to be established.

#### *STN theta activity also plays a role across trials*

Another key finding we report is that mesial frontal-STN connectivity seems to be involved in post error monitoring, which is thought to be one of the core mPFC functions (Ridderinkhof et al., 2004; Danielmeier and Ullsperger, 2011). Error trials are associated with increased mPFC BOLD activity and theta power (Carter et al.,

1998; Kerns et al., 2004; Cavanagh et al., 2009, 2012). Furthermore, mPFC theta power is thought to underlie post error slowing (Rabbitt, 1966), either by interactions with DLPFC (Kerns et al., 2004; Hanslmayr et al., 2007; Cavanagh et al., 2009; Cohen and Cavanagh, 2011; Cohen and van Gaal, 2014) or by adjusting the excitability of the motor cortex following errors (Danielmeier et al., 2011). Here, we show that the STN provides a path by which mPFC theta oscillations might influence the excitability of the motor cortex following errors and thus potentially allow for error-related behavioral adjustments. Nevertheless, in our paradigm there was no slowing of reaction time in trials that followed an error, perhaps because of our use of an inter trial interval that is too long for post error slowing in healthy subjects (Jentsch and Dudschig, 2009; Danielmeier and Ullsperger, 2011) or possibly because mesial frontal-STN connectivity might be impaired in our patient group, either as a function of PD or due to temporary stun effects at the level of the STN following surgery (Mann et al., 2009).

Finally, we observed that high conflict trials were followed by elevated STN LFP theta power levels in the baseline period before the subsequent trial, and that the reaction time in high conflict trials positively (albeit, weakly) correlated with that trial's baseline theta power. Interestingly, the baseline theta levels did not seem to influence low conflict trial reaction time, which is in line with studies showing that some theta activity only correlates with behavior during conflict (Cavanagh et al., 2011; Oehrns et al., 2014). Though our results are consistent with the posited braking effect of conflict related STN theta activity, they are in disagreement with what would be expected in the context of the Gratton effect (Gratton et al., 1992). That said, our paradigm elicited no Gratton effect on reaction time here or previously (Zavala et al., 2013), which may be related to impaired congruency sequence effects in PD (Rustamov et al., 2013).

### *Conclusion*

We have investigated the mechanisms by which communication between brain regions may rapidly influence behavior. However, the picture presented is likely to be incomplete, as many studies have shown that mPFC-DLPFC interactions are also related to within trial conflict processing and across trial adjustments to conflict and errors (Kerns et al., 2004; Hanslmayr et al., 2007; Cavanagh et al., 2009; Nigbur et al., 2012; Cohen and van Gaal, 2014; Oehrns et al., 2014). Nevertheless, our study suggests that theta synchronization between cortical and subcortical structures may play a role in conflict and error related adaptations. Though disruption of this theta activity by either DBS (Cavanagh et al., 2011) or dopaminergic medication (Rodriguez-Oroz et al., 2011) has been shown to influence impulsivity, it remains to be determined if DBS affects across trial adjustments in behavior or whether other disorders involving impaired decision making and poor impulse control demonstrate altered theta activity in these networks (Fitzgerald et al., 2005; van Meel et al., 2007).

## References

- Bastin J, Polosan M, Benis D, Goetz L, Bhattacharjee M, Piallat B, Krainik A, Bougerol T, Chabardès S, David O (2014) Inhibitory control and error monitoring by human subthalamic neurons. *Transl Psychiatry* 4:e439.
- Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. *Psychol Rev* 108:624–652.
- Botvinick MM, Cohen JD, Carter CS (2004) Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci* 8:539–546.
- Brittain J-S, Watkins KE, Joundi RA, Ray NJ, Holland P, Green AL, Aziz TZ, Jenkinson N (2012) A Role for the Subthalamic Nucleus in Response Inhibition during Conflict. *J Neurosci* 32:13396–13401.
- Brown P, Chen CC, Wang S, Kühn AA, Doyle L, Yarrow K, Nuttin B, Stein J, Aziz T (2006) Involvement of human basal ganglia in offline feedback control of voluntary movement. *Curr Biol* 16:2129–2134.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998) Anterior Cingulate Cortex, Error Detection, and the Online Monitoring of Performance. *Science* 280:747–749.
- Cavanagh JF, Cohen MX, Allen JJ (2009) Prelude To And Resolution of an Error: EEG Phase Synchrony Reveals Cognitive Control Dynamics During Action Monitoring. *J Neurosci* 29:98–105.
- Cavanagh JF, Sanguinetti JL, Allen JJB, Sherman SJ, Frank MJ (2014) The Subthalamic Nucleus Contributes to Post-error Slowing. *J Cogn Neurosci* 26:2637–2644.
- Cavanagh JF, Wiecki TV, Cohen MX, Figueroa CM, Samanta J, Sherman SJ, Frank MJ (2011) Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. *Nat Neurosci* 14:1462–1467.
- Cavanagh JF, Zambrano-Vazquez L, Allen JJB (2012) Theta lingua franca: A common mid-frontal substrate for action monitoring processes. *Psychophysiology* 49:220–238.
- Cohen MX, Cavanagh JF (2011) Single-trial regression elucidates the role of prefrontal theta oscillations in response conflict. *Front Percept Sci* 2:30.
- Cohen MX, Gulbinaite R (2014) Five methodological challenges in cognitive electrophysiology. *Neuroimage* 85 Pt 2:702–710.
- Cohen MX, van Gaal S (2014) Subthreshold muscle twitches dissociate oscillatory neural signatures of conflicts from errors. *NeuroImage* 86:503–513.

- Coulthard EJ, Bogacz R, Javed S, Mooney LK, Murphy G, Keeley S, Whone AL (2012) Distinct roles of dopamine and subthalamic nucleus in learning and probabilistic decision making. *Brain* 135:3721–3734.
- Danielmeier C, Eichele T, Forstmann BU, Tittgemeyer M, Ullsperger M (2011) Posterior Medial Frontal Cortex Activity Predicts Post-Error Adaptations in Task-Related Visual and Motor Areas. *J Neurosci* 31:1780–1789.
- Danielmeier C, Ullsperger M (2011) Post-error adjustments. *Front Psychology* 2:233.
- Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, Taylor SF (2005) Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry* 57:287–294.
- Foltynie T, Hariz MI (2010) Surgical management of Parkinson's disease. *Expert Rev Neurother* 10:903–914.
- Frank MJ, Samanta J, Moustafa AA, Sherman SJ (2007) Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism. *Science* 318:1309–1312.
- Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci* 9:474–480.
- Fumagalli M, Giannicola G, Rosa M, Marceglia S, Lucchiari C, Mrakic-Spota S, Servello D, Pacchetti C, Porta M, Sassi M, Zangaglia R, Franzini A, Albanese A, Romito L, Piacentini S, Zago S, Pravettoni G, Barbieri S, Priori A (2011) Conflict-dependent dynamic of subthalamic nucleus oscillations during moral decisions. *Soc Neurosci* 6:243–256.
- Gratton G, Coles MGH, Donchin E (1992) Optimizing the use of information: Strategic control of activation of responses. *J Exp Psychol Gen* 121:480–506.
- Green N, Bogacz R, Huebl J, Beyer A-K, Kühn AA, Heekeren HR (2013) Reduction of Influence of Task Difficulty on Perceptual Decision Making by STN Deep Brain Stimulation. *Curr Biol* 23:1681–1684.
- Hanslmayr S, Pastötter B, Bäuml K-H, Gruber S, Wimber M, Klimesch W (2007) The Electrophysiological Dynamics of Interference during the Stroop Task. *J Cogn Neurosci* 20:215–225.
- Jentsch I, Dudschig C (2009) Why do we slow down after an error? Mechanisms underlying the effects of posterror slowing. *Q J Exp Psychol* 62:209–218.

- Kerns JG, Cohen JD, MacDonald AW, Cho RY, Stenger VA, Carter CS (2004) Anterior Cingulate Conflict Monitoring and Adjustments in Control. *Science* 303:1023–1026.
- Lachaux J-P, Lutz A, Rudrauf D, Cosmelli D, Le Van Quyen M, Martinerie J, Varela F (2002) Estimating the time-course of coherence between single-trial brain signals: an introduction to wavelet coherence. *Neurophysiol Clin Neurophysiol* 32:157–174.
- Mann JM, Foote KD, Garvan CW, Fernandez HH, Jacobson CE, Rodriguez RL, Haq IU, Siddiqui MS, Malaty IA, Morishita T, Hass CJ, Okun MS (2009) Brain penetration effects of microelectrodes and DBS leads in STN or GPi. *J Neurol Neurosurg Psychiatry* 80:794–797.
- Maris E, Oostenveld R (2007) Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods* 164:177–190.
- Nigbur R, Cohen MX, Ridderinkhof KR, Stürmer B (2012) Theta dynamics reveal domain-specific control over stimulus and response conflict. *J Cogn Neurosci* 24:1264–1274.
- Oehrns CR, Hanslmayr S, Fell J, Deuker L, Kremers NA, Lam ATD, Elger CE, Axmacher N (2014) Neural Communication Patterns Underlying Conflict Detection, Resolution, and Adaptation. *J Neurosci* 34:10438–10452.
- Ratcliff R, Frank MJ (2012) Reinforcement-based decision making in corticostriatal circuits: mutual constraints by neurocomputational and diffusion models. *Neural Comput* 24:1186–1229.
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The Role of the Medial Frontal Cortex in Cognitive Control. *Science* 306:443–447.
- Rodriguez-Oroz MC, López-Azcárate J, Garcia-Garcia D, Alegre M, Toledo J, Valencia M, Guridi J, Artieda J, Obeso JA (2011) Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. *Brain* 134:36–49.
- Rustamov N, Rodriguez-Raecke R, Timm L, Agrawal D, Dressler D, Schrader C, Tacik P, Wegner F, Dengler R, Wittfoth M, Kopp B (2013) Absence of congruency sequence effects reveals neurocognitive inflexibility in Parkinson's disease. *Neuropsychologia* 51:2976–2987.
- Siebert S, Herrojo Ruiz M, Brücke C, Huebl J, Schneider G-H, Ullsperger M, Kühn AA (2014) Error signals in the subthalamic nucleus are related to post-error slowing in patients with Parkinson's disease. *Cortex J Devoted Study Nerv Syst Behav*.

- Van Meel CS, Heslenfeld DJ, Oosterlaan J, Sergeant JA (2007) Adaptive control deficits in attention-deficit/hyperactivity disorder (ADHD): the role of error processing. *Psychiatry Res* 151:211–220.
- Zavala B, Brittain J-S, Jenkinson N, Ashkan K, Foltynie T, Limousin P, Zrinzo L, Green AL, Aziz T, Zaghoul K, Brown P (2013) Subthalamic Nucleus Local Field Potential Activity during the Eriksen Flanker Task Reveals a Novel Role for Theta Phase during Conflict Monitoring. *J Neurosci* 33:14758–14766.
- Zavala B, Damera S, Dong JW, Lungu C, Brown P, Zaghoul KA (2015a) Human Subthalamic Nucleus Theta and Beta Oscillations Entrain Neuronal Firing During Sensorimotor Conflict. *Cereb Cortex*:bhv244.
- Zavala B, Zaghoul K, Brown P (2015b) The subthalamic nucleus, oscillations, and conflict. *Mov Disord* 30:328–338.
- Zavala BA, Tan H, Little S, Ashkan K, Hariz M, Foltynie T, Zrinzo L, Zaghoul KA, Brown P (2014) Midline Frontal Cortex Low-Frequency Activity Drives Subthalamic Nucleus Oscillations during Conflict. *J Neurosci* 34:7322–7333.