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Error signals in the subthalamic nucleus are related to post-error slowing in patients with Parkinson's disease

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ABSTRACT

Error monitoring is essential for optimizing motor behavior. It has been linked to the medial frontal cortex, in particular to the anterior midcingulate cortex (aMCC). The aMCC subserves its performance-monitoring function in interaction with the basal ganglia (BG) circuits, as has been demonstrated in patients suffering from BG lesions or from Parkinson's disease (PD). The subthalamic nucleus (STN) has been assumed an integrative structure for emotional, cognitive and motor processing. Error-related behavioral adaptation such as post-error slowing has been linked to motor inhibition involving activation of an inhibitory network including the STN. However, direct involvement of the STN in error monitoring and post-error behavioral adjustment has not yet been demonstrated.

Here, we used simultaneous scalp electroencephalogram (EEG) and local field potential (LFP) recordings from the BG in 17 patients undergoing deep brain stimulation (DBS) for PD to investigate error-related evoked activity in the human STN, its relation to post-error behavioral adjustment and the influence of dopamine during the performance of a speeded flanker task.

We found an error-related positive deflection (STN-Pe) in the STN-LFP 260–450 msec after error commission. Importantly, the STN-Pe amplitude was larger in trials with post-error slowing compared to trials with post-error speeding. There was no overall effect of dopamine on error processing. Subgroup analysis revealed a higher error rate (ER) in younger patients with earlier disease onset ON medication compared to OFF medication (and vice versa in the older patient group), which was associated with modulatory effects

Abbreviations: ON/OFF, with/without dopaminergic medication.

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of the early cortical error-related negativity (ERN) and late STN-Pe. The late error-related STN-Pe that is associated with post-error reaction time (RT) adjustments supports the notion that post-error slowing is implemented by motor inhibition involving the STN. Further, the modulation of behavioral performance by dopaminergic therapy depending on patients' age may suggest a dopamine overdose effect in patients with earlier onset of PD.

1. Introduction

What happens if one plays a wrong note in a piano concert? Detection of action errors entails a cascade of consequences affecting autonomic, emotional, and cognitive processes aimed at remediating the error, optimizing future behavior, and adjusting motivation (Ullsperger, Danielmeier, & Jocham, 2014). A typical behavioral adjustment seen after errors is the slowing of reaction times (RTs) on subsequent trials, known as post-error slowing (Danielmeier & Ullsperger, 2011; Rabbitt, 1966). Recently, post-error slowing has been suggested to be part of more complex orienting reflex (Sokolov, 1963) elicited by the salience of the error (Notebaert et al., 2009). This orienting reflex, comprising autonomic, affective, and motor responses to a motivationally salient event such as an error (Hajcak, McDonald, & Simons, 2003; Wessel, Danielmeier, & Ullsperger, 2011), can be interpreted as an emotional reaction as defined by Péron, Fruhholz, Verin, and Grandjean (Péron, Fruhholz, Verin, & Grandjean, 2013). The entailed RT prolongation has been shown to result not only from errors but also from other motivationally salient events such as (valence-free) novel action outcomes (Wessel, Danielmeier, Morton, & Ullsperger, 2012). Several theoretical accounts suggest that post-error slowing results from motor inhibition or a decrease in corticospinal excitability (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Danielmeier & Ullsperger, 2011; Dutilh et al., 2012). This notion has found indirect support by functional and diffusion imaging studies (Danielmeier, Eichele, Forstmann, Tittgemeyer, & Ullsperger, 2011; King, Korb, von Cramon, & Ullsperger, 2010).

Performance monitoring and resulting adaptation relies on a large network of cortical and subcortical structures, including frontal and temporal areas (Rusnakova, Daniel, Chladek, Jurak, & Rektor, 2011), as well as the thalamus, the basal ganglia (BG), and the nucleus accumbens (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Munte et al., 2007; Seifert, von Cramon, Imperati, Tittgemeyer, & Ullsperger, 2011). The central structure in this network is the posterior mesial frontal cortex, in particular the anterior midcingulate cortex (aMCC) (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Ullsperger et al., 2014), which is the putative generator of an event-related brain potential (ERP) associated with errors in speeded RT tasks, the error-related negativity (ERN; Debener et al., 2005; Falkenstein, Hohnsbein, & Hoormann, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN peaks around 50–100 msec after the erroneous response and has a frontocentral distribution over the scalp. It is followed by the error positivity (Pe; Falkenstein et al., 1990), which can be divided into an early frontocentral positivity and a later, more sustained positive wave at centroparietal electrodes. The ERN seems to reflect the objective evidence for a mistake, whereas the Pe appears to code the accumulating subjective error evidence leading to conscious error perception (Steinhauser & Yeung, 2010; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010; Wessel & Ullsperger, 2011). Error-related activity of the posterior mesial frontal cortex reflected in hemodynamic functional magnetic resonance imaging signals as well as the ERN and early Pe have been shown to correlate with post-error slowing on subsequent trials (Debener et al., 2005; Gehring et al., 1993; Kerns et al., 2004; Wessel et al., 2011). The amplitude of the error signal in the posterior mesial frontal cortex predicted the reduction of the functional magnetic resonance imaging signal in primary motor cortex on post-error trials (Danielmeier et al., 2011), which in turn correlated with post-error slowing (Danielmeier et al., 2011; King et al., 2010). Moreover, diffusion imaging data suggest that white matter integrity, as reflected in fractional anisotropy beneath posterior mesial frontal cortex affecting a network triangulating pre-supplementary motor cortex, right inferior frontal gyrus, and the subthalamic nucleus (STN) is related to post-error slowing. This network has been previously associated with motor inhibition (Aron, Behrens, et al., 2007; Aron, Durston, et al., 2007) which supports the notion that post-error slowing reflects a general motor inhibition process triggered by errors or, more broadly, by salient action-related events.

Here we address the role of the STN, a key structure of the BG, in error processing and test the hypothesis that the STN contributes to error-driven adaptation, in particular post-error slowing. The STN has a tripartite structure with overlapping functional zones for motor, cognitive, and affective processing that receive direct inputs from widespread cortical areas via the hyperdirect pathway (Lambert et al., 2012; Nambu, Tokuno, & Takada, 2002). Accumulating evidence renders the STN a strong candidate for a coordinating structure of adaptive motor, cognitive, and emotional functions (Péron et al., 2013). While the involvement of the striatum in performance monitoring has been demonstrated in patients with focal lesions and degenerative BG diseases (Beste, Saft, Andrich, Gold, & Falkenstein, 2006; Falkenstein et al., 2001; Ullsperger & von Cramon, 2006), direct evidence for an involvement of the STN in these functions is still sparse. Direct recordings of local field potentials (LFP) from electrodes inserted for deep brain stimulation (DBS) in patients with Parkinson's disease (PD) revealed feedback-related STN activity differentiating correct and incorrect responses in a movement timing task (Brown et al., 2006) which was modulated by the motivational state (Kühn et al., 2008). Interestingly, the strongest STN response was associated with the