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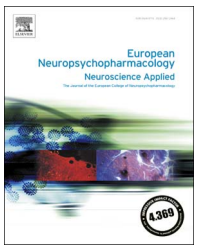

Deep brain stimulation of the subthalamic nucleus in obsessive-compulsive disorder: Neuroanatomical and pathophysiological considerations

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Abstract
Obsessive-compulsive disorder (OCD) is among the most disabling chronic psychiatric disorders and has a significant negative impact on multiple domains of quality of life. For patients suffering from severe refractory OCD, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been applied. Reviewing the literature of the last years we believe that through its central position within the cortico-basal ganglia-thalamocortical circuits, the STN has a coordinating role in decision-making and action-selection mechanisms. Dysfunctional information-processing at the level of the STN is responsible for some of the core symptoms of OCD. Research confirms an electrophysiological dysfunction in the associative and limbic (non-motor) parts of the STN. Compared to Parkinson's disease patients, STN neurons in OCD exhibit a lower firing rate, less frequent but longer bursts, increased burst activity in the anterior ventromedial area, an asymmetrical left-sided burst distribution, and a predominant oscillatory activity in the δ-band. Moreover, there is direct evidence for the involvement of the STN in both checking behavior and OCD symptoms, which are both related to changes in

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electrophysiological activity in the non-motor STN. Through a combination of mechanisms, DBS of the STN seems to interrupt the disturbed information-processing, leading to a normalization of connectivity within the cortico-basal ganglia-thalamocortical circuits and consequently to a reduction in symptoms. In conclusion, based on the STN's strategic position within cortico-basal ganglia-thalamocortical circuits and its involvement in action-selection mechanisms that are responsible for some of the core symptoms of OCD, the STN is a mechanism-based target for DBS in OCD.

1. Introduction

In the last decades the interest in neuromodulation therapies for psychiatric disorders, such as obsessive-compulsive disorder (OCD), has increased due to the advances in the field of deep brain stimulation (DBS). OCD is among the most disabling chronic psychiatric disorders and has a significant negative impact on multiple domains of quality of life (Blomstedt et al., 2013; Hou et al., 2010; Mallet et al., 2008). Even after state-of-the-art psychotherapeutic and pharmacological treatments, approximately 10–20% of patients do not respond sufficiently to treatment (De Koning et al., 2012; Temel et al., 2012). For the most treatment-resistant OCD patients, DBS has resulted in a substantial relief of key symptoms (Greenberg et al., 2010; Kisely et al., 2014; Nuttin et al., 1999).

The rationale for the current use of DBS for OCD is based on findings from both clinical and experimental studies, suggesting an involvement of abnormal functioning of cortico-basal ganglia-thalamocortical circuits (Blomstedt et al., 2013; Hamani and Temel, 2012; Temel et al., 2012). The main target areas for DBS for OCD are the ventral capsule/ventral striatum (VC/VS), the nucleus accumbens (NAc) with the involvement of the bed nucleus of the stria terminalis, the anterior limb of the internal capsule (ALIC), and the subthalamic nucleus (STN) (Alonso et al., 2015; Barcia et al., 2014; Blomstedt et al., 2013; Kisely et al., 2014). In this review we will focus on the latter target.

The STN as a surgical target for OCD has recently been introduced and the therapeutic effects are promising (Chabardes et al., 2013; Mallet et al., 2008). The STN is a key structure in the basal ganglia in which motor, cognitive and limbic projections come together (Alexander and Crutcher, 1990; Alexander et al., 1986; Temel et al., 2005). It is like a crossroad in which different modalities of behavior are being processed (Mallet et al., 2007). The present review aims to shed light on the functional role of the STN in the pathophysiology of OCD, by integrating neuroanatomical and pathophysiological findings.

2. Obsessive-compulsive disorder

OCD is characterized by the repeated occurrence of obsessions and/or compulsions that are recognized as excessive, inappropriate or unreasonable, causing marked distress, and significantly interfere with daily functioning (Blomstedt et al., 2013). Obsessions are defined as intrusive, repetitive and distressing thoughts, images, or impulses that can cause anxiety or distress. Compulsions can take the form of repetitive, stereotyped, or ritualized overt behaviors or covert mental acts, both of which perform a neutralization function in order to reduce distress, to weaken an obsession, or to prevent some feared outcome (Mallet et al., 2008; Schruers et al., 2005). According to epidemiological studies, the prevalence of OCD in the general population and across countries has been estimated at approximately 1–3% (Thomsen, 2013).

The treatment of OCD is based on assessment of the severity of OCD, age, and the presence of comorbid disorders (Schruers et al., 2005; Thomsen, 2013). Conventional treatments include psychoeducation, reduction of psychosocial stress, cognitive behavioral therapy (CBT) and/or pharmacotherapy (Mallet et al., 2008; Schruers et al., 2005; Thomsen, 2013). Selective serotonin reuptake inhibitors (SSRIs) are the first choice of medication in OCD (Sayyah et al., 2013; Schruers et al., 2005). However, the response to treatment can take months and high dosages are often required for good efficacy (Brakoulias, 2014; Pallanti and Quercioli, 2006). Moreover, up to 60% of OCD patients do not respond to treatment with SSRIs (Dold et al., 2013; Pallanti and Quercioli, 2006; Sayyah et al., 2013).

3. Deep brain stimulation

In DBS, electrical current is delivered to specific locations in the brain through permanently implanted electrodes (Hamani and Temel, 2012). Because of its adjustable stimulation parameters, DBS therapy can be tailored for individual patients (Greenberg et al., 2010). DBS is a treatment option only for OCD patients who have failed to respond to: (1) three treatment attempts with SSRIs, including clomipramine for at least 10–12 weeks at the maximum doses; (2) augmentation with a neuroleptic; and, (3) a minimum of 16–20 sessions of CBT (Blomstedt et al., 2013; Mallet et al., 2008).

To date more than 100 patients with refractory OCD have received DBS in one of the following targets: the VC/VS; the inferior thalamic peduncle; the NAc; the ALIC; the medial forebrain bundle (Coenen et al., 2016); and, the STN (see Alonso et al. (2015), Blomstedt et al. (2013), Kisely et al. (2014), Lapidus et al. (2013)). The STN is a well-known target for DBS in patients with early and advanced Parkinson's disease (PD) (Deuschl et al., 2006; Odekerken et al., 2013). The interest for the STN as a potential target for DBS in OCD came from case observations. In two patients with

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