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Review

Deep brain electrophysiological recordings provide clues to the pathophysiology of Tourette syndrome

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ABSTRACT

Although ample evidence suggests that high-frequency deep brain stimulation (DBS) is an effective therapy in patients with Tourette syndrome (TS), its pathophysiology and the neurophysiological mechanisms underlying these benefits remain unclear. The DBS targets mainly used to date in TS are located within the basal ganglia-thalamo-cortical circuit compromised in this syndrome: the medial and ventral thalamic nuclei, which are way stations within the circuit, the globus pallidus and the nucleus accumbens. Neuronal activity can be electrophysiologically recorded from deep brain structures during DBS surgery (intraoperative microrecordings) or within few days after DBS electrode implantation (local field potentials, LFPs). Recordings from the thalamus in patients with TS showed that the power in low-frequency oscillations (2–15 Hz) was higher than power in high frequency oscillations (<45 Hz) and that activity in gamma band (25–45 Hz) increases when patients' clinical status improved. Effective thalamic DBS for tic reduction seems to increase high frequency band oscillations (25–45 Hz). The same oscillatory pattern persists after DBS for 1 year, therefore showing that in TS DBS does not induce persistent neuroplastic changes in the neural activity in the stimulated structures. Neurophysiological recordings from deep brain structures suggest that tics originate not from the cortex but from neuronal dysfunction in deep brain structures such as the thalamus and globus pallidus. In conclusion, DBS can induce its beneficial effects in TS by modulating specific neural rhythms in the cortico-basal ganglia thalamic network. DBS could reduce tics related increased low-frequency activity by shifting the basal ganglia-thalamic oscillation power to higher frequencies.

Contents

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1. Introduction

When patients with Tourette syndrome (TS) are refractory to behavioral (Kurlan, 2010; Verdellen et al., 2011), pharmacological (Goetz et al., 1987; Leckman et al., 1991; Porta et al., 2008; Pringsheim and Marras, 2009; Sallee et al., 1997; Scahill et al., 2001) and invasive non surgical treatment (botulinum toxin injections) (Kwak et al., 2000; Simpson et al., 2008), a viable emerging option is deep brain stimulation (DBS) (Ackermans et al., 2010, 2008a,b; Giannicola et al., in press; Houeto et al., 2005; Muller-Vahl et al., 2011; Porta et al., 2012b; Servello et al., 2010; Visser-Vandewalle, 2007; Visser-Vandewalle et al., 2003, 2006). To deliver DBS, multipolar-electrodes are implanted in deep brain target structures and then connected to a subcutaneous pulse generator delivering high-frequency (130–150 Hz) electrical stimulation. Because TS is a complex syndrome that is supposed to involve the whole thalamo-cortico-basal ganglia network (Albin and Mink, 2006; Draganski et al., 2010; Groenewegen et al., 2003; Mink, 2001a; Saka and Graybiel, 2003; Segawa, 2003; Worbe et al., 2012), several subcortical targets have been proposed for patients with TS: the medial and ventral thalamic nuclei, globus pallidus internus (GPi) and nucleus accumbens (NA) (Burdick et al., 2010; Cannon et al., 2012; Martinez-Fernandez et al., 2011; Neuner et al., 2010; Okun et al., 2012; Servello et al., 2010; Visser-Vandewalle et al., 2003; Welter et al., 2008).

Useful neurophysiological information on the pathophysiology of TS comes from activity in target brain structures recorded through electrodes implanted for intraoperative monitoring during DBS surgery or through the DBS electrodes after DBS surgery. This article reviews the few studies on electrical activity recorded from deep brain structures in patients with TS and reports original neurophysiological data from patients seen by our group (studied after their informed consent and local institutional review board approval).

2. Neural activity recorded from deep brain structures in TS

Obeso et al. (1981) and Karp et al. (1996) showed that no premotor EEG potentials preceded simple motor tics in TS, suggesting that they originate not from the cortex but from elsewhere in the brain. Hence, neural activity recorded from deep brain structures in TS could help in understanding the pathophysiology of TS.

During DBS surgery exploratory microelectrodes are used to record the activity in single neurons from deep brain structures to electrophysiologically characterize the target point for the final DBS electrode implantation. Besides serving clinical purposes, microrecordings also provide a powerful research tool to correlate anatomical data with the neuronal firing pattern (Mrakic-Sposta et al., 2008; Priori et al., 2003).

After DBS surgery the electrodes for DBS are accessible for electrophysiological recordings from the target structure and signals reflect the overall activity from specific neuronal networks (Brown and Williams, 2005; Giannicola and Priori, 2012; Priori et al., 2004, 2012; Rosa et al., 2012a,b).

2.1. Thalamus

Recordings from microelectrodes in the thalamic nuclei during DBS surgery typically disclose the so called burst firing. We recorded from ventralis oralis/centromedian-parafascicular (Vo/CM-Pf) nucleus of the thalamus in anaesthetized patients with TS ($n = 7$) (with no tics during recordings) a burst firing pattern with an interburst interval ranging between 0.12 and 0.40 s (within the low-frequency range 2.5–8 Hz) (Fig. 1) (Marceglia et al., 2010). The low-frequency thalamic neuronal burst firing

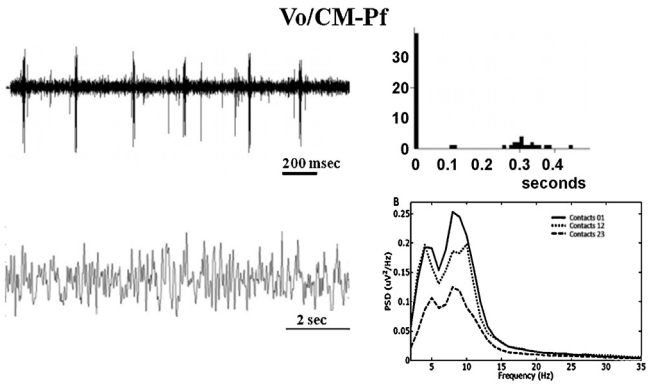

Fig. 1. Neural activity and local field potentials (LFPs) recorded from ventralis oralis/centromedian-parafascicular (Vo/CM-Pf) (from Marceglia et al., 2010, with permission). Top: the left panel shows a segment recorded from a representative neuron displaying oscillatory burst firing activity; the right panel shows the interspike interval (ISI) histogram for the same representative neuron. Note that the burst interval ranging between 0.12 and 0.40 s (within low-frequency range 2.5–8 Hz). Below: the left panel shows raw Vo/CM-Pf LFPs; the right panel shows the power spectral density (PSD) for Vo/CM-Pf LFPs captured from macroelectrode contacts 0–1, 1–2 and 2–3. Patients had no tics during LFP recordings. Note that Vo/CM-Pf LFP activity oscillates predominantly at low-frequencies (2–15 Hz).

can, however, be found in other neurological disorders: in anaesthetized patients with epilepsy ($n = 5$) burst firing intervals range between 0.17 and 0.36 s in the anterior nucleus (AN) (Hodaie et al., 2006), in awake patients with neurogenic pain, tinnitus, abnormal movements, epilepsy and certain neuropsychiatric disorders (obsessive-compulsive disease, endogenous depression and psychosis) ($n = 104$) the interburst interval ranges between 0.17 and 0.39 s in medial thalamic targets (Jeanmonod et al., 1996). In conclusion, whether the neuronal bursting patterns in thalamic nuclei of TS patients is specific or is common to other neurological disorders (Jeanmonod et al., 1996; Llinas et al., 2005) awaits an answer from future research.

Further important neurophysiological information came from LFP oscillations studied after surgery from definitive DBS macroelectrodes. LFP recordings from Vo/CM-Pf in awake patients with TS ($n = 7$) at rest (with no tics during recordings) were characterized by alpha (8–13 Hz) and low-frequency activity (2–7 Hz) without oscillations in the beta-band (20–35 Hz) (Fig. 1). Thalamic low-frequency LFP oscillations in TS are also in line with basal ganglia LFP findings in other hyperkinetic conditions such as dyskinesias (Alonso-Frech et al., 2006; Foffani et al., 2005) and dystonia (Marceglia et al., 2007; Silberstein et al., 2003). Conversely, exaggerated beta oscillations (11–30 Hz) have been related to hypokinesia in Parkinson's disease (PD) (Brown and Eusebio, 2008; Priori et al., 2004). Therefore increased low-frequency activity and decreased thalamic beta activity in patients with TS would unbalance the system and ultimately contribute to the pathophysiology of tics and, possibly, of other hyperkinetic disorders. Interestingly, low-frequency activity could correlate with the clinical phenotype: thalamic LFPs recorded from a patient with TS who had few tics but a severe obsessive-compulsive disorder (OCD) (Fig. 2, personal observation) showed remarkably fewer low-frequency oscillations than LFPs recorded in patients with severe tics (Fig. 1). This correlation between electrophysiological and clinical data is in line with resting state neuroimaging studies showing that tic complexity correlates with dysfunction in the sensorimotor and associative networks whereas the severity of OCD and other behavioral TS symptoms are associated with dysfunction in the associative and limbic networks (Worbe et al., 2012).

Increased gamma activity (25–45 Hz) recorded from CM in awake patients with TS ($n = 5$) correlates with tic improvement after DBS (Maling et al., 2012). The same study showed that short-term