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Testing different paradigms to optimize antidepressant deep brain stimulation in different rat models of depression

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ABSTRACT

Deep brain stimulation (DBS) of several targets induces beneficial responses in approximately 60% of patients suffering from treatment-resistant depression (TRD). The remaining 40% indicate that these stimulation sites do not bear therapeutic relevance for all TRD patients and consequently DBS-targets should be selected according to individual symptom profiles. We here used two animal models of depression known to have different genetic backgrounds and behavioral responses: the therapy-responsive Flinders sensitive line (FSL) and the therapy-refractory congenitally learned helpless rats (cLH) to study symptom-specific DBS effects i) of different brain sites ii) at different stimulation parameters, and iii) at different expressions of the disease. Sham-stimulation/DBS was applied chronic-intermittently or chronic-continuously to either the ventromedial prefrontal cortex (vmPFC, rodent equivalent to subgenual cingulate), nucleus accumbens (Nacc) or subthalamic nucleus (STN), and effects were studied on different depression-associated behaviors, i.e. anhedonia, immobility/behavioral despair and learned helplessness. Biochemical substrates of behaviorally effective versus ineffective DBS were analyzed using in-vivo microdialysis and post-mortem high-performance liquid chromatography (HPLC). We found that i) vmPFC-DBS outperforms Nacc-DBS, ii) STN-DBS increases depressive states, iii) chronic-continuous DBS does not add benefits compared to chronic-intermittent DBS, iv) DBS-efficacy depends on the disease expression modeled and iv) antidepressant DBS is associated with an increase in serotonin turnover alongside site-specific reductions in serotonin contents. The reported limited effectiveness of vmPFC DBS suggests that future research may consider the specific disease expression, investigation of different DBS-targets and alternative parameter settings.

1. Introduction

Major depressive disorder (MDD) is the leading cause of impairment worldwide (World Health Organization, 2012). Despite the wide range of existing therapeutic interventions up to 30% of patients remain therapy-refractory, even after a combination of treatments (Warden et al., 2007). Deep brain stimulation (DBS) constitutes an effective tool to therapeutically modulate pathological neural activity (Davis et al., 1997) and has been promoted as an alternative intervention for treatment-resistant depression (TRD, usually defined as non-responsiveness to at least four different antidepressant treatments, including psychotherapy, medication, and electroconvulsive therapy, each given at adequate duration and dosages; Mayberg et al., 2005) (Anderson et al., 2012;

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Mayberg et al., 2005). Meanwhile a number of DBS targets has been investigated and varying response rates defined as percentage of patients with at least a 50% reduction in depression rating scales have been reported for all targets tested: subgenual cingulate (Cg25; 29–63% responders) (Holtzheimer et al., 2012; Lozano et al., 2008, 2012; Mayberg et al., 2005; Puigdemont et al., 2012), anterior limb of the capsula interna (53%) (Malone et al., 2009), medial forebrain bundle (MFB; 85%) (Schlaepfer et al., 2013), nucleus accumbens (Nacc)/ventral striatum (25% (Dougherty et al., 2015) and 45% (Bewernick et al., 2010, 2012; Schlaepfer et al., 2008)), lateral habenula and inferior thalamic peduncle (one patient was investigated for each target, both were found to be effective, Sartorius et al., 2010; Jiménez et al., 2005). Promising results yielded by Nacc/ventral striatum- and Cg25-DBS in open-label trials failed to be replicated unequivocally in multicenter, prospective, randomized trials, indicating that to date the support of the application of DBS in TRD by high-quality clinical data is limited (Morishita et al., 2014; Dougherty et al., 2015; Crowell et al., 2015). Further, the fact that about 40% of patients remain depressed after DBS suggests that there might not be just one optimal stimulation target for all TRD patients, but that site and parameters should be selected according to the individual symptom profile (Hamani et al., 2014; Morishita et al., 2014). To assess superiority of one simulation target over another within a specific symptom profile, broad-based comparative studies on homogeneous patient groups are required. Given the heterogeneity of MDD patients, this represents a major challenge in the clinical situation. Controlled animal experimental approaches may however circumvent this problem.

Studies applying DBS in rats report antidepressant effects for DBS to the ventromedial prefrontal cortex (vmPFC, rodent analogue of Cg25, Hamani et al., 2010a,b; Rea et al., 2014), Nacc (Gersner et al., 2010), MFB (Edemann-Callesen et al., 2015), ventral tegmental area (VTA, Gazit et al., 2015) and lateral habenula (LHb, Meng et al., 2011). Most of these investigations however have been carried out in naïve rats or in single animal models of depression. The comparison of antidepressant-like DBS effects in animal models with distinct behavioral phenotypes is still lacking.

In the present study we used two animal models of depression known to have different genetic backgrounds and behavioral responses: the therapy-responsive Flinders sensitive line (FSL) (Overstreet and Russell, 1982; Overstreet, 1993) and the therapy-refractory congenitally learned helpless rats (cLH) (Henn and Vollmayr, 2005). FSL rats were selectively bred for hypersensitivity to a cholinergic agent and have been found to display several depressive-like symptoms, such as passive stress coping, reduced appetite, elevated REM sleep, stress-induced anhedonia, as well as HPA axis and neuropeptide Y system dysregulations (Overstreet and Wegener, 2013). These symptoms are responsive to antidepressant treatment, making the FSL an attractive model for translational depression research (Overstreet et al., 1995). cLH rats were selectively bred according to their susceptibility to helpless behavior after inescapable stress exposure, resulting in a congenitally learned helpless phenotype. Neither anti-depressive agents nor electroconvulsive therapy antagonize these behavioral peculiarities (Sartorius et al., 2007), making cLH an appealing model for TRD. Using these models we studied symptom-specific DBS effects i) of different brain sites ii) at different stimulation parameters, and iii) at different expressions of the disease. We applied sham-stimulation/DBS chronic-intermittently or chronic-continuously to either the vmPFC, Nacc or subthalamic nucleus (STN), and studied the effects on different depression-associated behaviors, i.e. anhedonia, immobility/behavioral despair and learned helplessness. In addition, we analyzed biochemical substrates of behaviorally effective versus ineffective/depressogenic DBS using in-vivo microdialysis and post-mortem high-performance liquid chromatography (HPLC).

2. Methods and materials

2.1. Animals

A total of 234 male rats (own breeding, 280–310 g) were used (Fig. S1). Experiments were conducted in phenotypic (FSL; n = 96 and cLH; n = 20) rats. Parallel experiments conducted in controls (Flinders resistant line (FRL; n = 98) and congenitally non helpless rats (cNLH; n = 20)) served to follow on unspecific DBS effects not related to depression pathology (Fig. S1).

2.2. Experimental design

We first assessed effects of chronic-intermittent DBS of i) the vmPFC, ii) the Nacc and iii) the STN on core symptoms of depressive disorders such as anhedonia, behavioral despair and learned helplessness. vmPFC and Nacc constitute the mostly implanted targets in clinical trials of depression while the STN was chosen as additional control site, as STN-DBS has been shown to induce symptoms of depression in Parkinson patients (Castrioto et al., 2014; Temel et al., 2006) and respective animal models (Temel et al., 2007). FSL and control rats were randomly divided into the following groups: sham-stimulation (with electrodes in the STN, Nacc, or vmPFC), STN-DBS, Nacc-DBS, and vmPFC-DBS (Figure S1A) with electrodes implanted into the respective targets. One week after surgery chronic-intermittent DBS treatment, as usually performed in animal experimental setups (Hamani et al., 2010a,b; Rea et al., 2014; Edemann-Callesen et al., 2015) and behavioral testing began with 2–3 days in between tests. Sham groups were connected to the stimulation system, but received no DBS. Thereafter, FSL rats that underwent either sham-stimulation (n = 10), STN-DBS (n = 9), or vmPFC-DBS (n = 10) were subjected to accumbal in-vivo microdialysis to measure short-term biochemical DBS-effects. As in patients, DBS is delivered continuously over a period of years if not life-long, in the second experiment we used chronic-continuous DBS to assess whether antidepressant effects could be maximized with a stimulation protocol more closely resembling the clinical situation. FSL/controls were divided into the following groups: sham-stimulation (with electrodes in the Nacc or vmPFC), Nacc-DBS and vmPFC-DBS (Figure S1C). Electrodes were connected to a (dummy-)microstimulator (Ewing et al., 2013a,b), carried in rodent jackets (Harvard Apparatus GmbH, Germany) to which rats had been previously habituated (Figure S1B). One week after surgery, chronic-continuous DBS treatment was initiated and sustained for 16 consecutive days. Behavioral testing was conducted as in experiment one (Figure S1C). Brains of FSL animals treated with chronic-continuous vmPFC- and sham-stimulation were processed for post-mortem HPLC to measure long-term biochemical DBS effects. In the third experiment, we applied the DBS protocol (stimulation target and parameters) in cLH rats that yielded the best antidepressant response in the first two experiments. Accordingly, electrodes were implanted into the vmPFC of cLH/cNLH rats. Sham-stimulation/DBS and behavioral testing procedures were conducted according to experiment one (Figure S1D). Upon completion of every experiment, electrode and guide cannula placements were confirmed in cresyl violet stained sections.

2.3. Surgery

Stereotactic implantations were performed under subcutaneous (s.c.) general anesthesia: fentanyl (0.005 mg/kg, Janssen-Cilag, Germany), midazolam (2 mg/kg, Hameln, Germany) and medetomidine dihydrochloride (0.135 mg/kg, Elanci Animal Health,