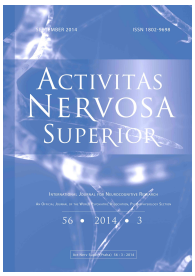

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REVIEW ARTICLE

DEEP BRAIN STIMULATION IN SCHIZOPHRENIA

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Abstract

Deep brain stimulation (DBS) has successfully advanced treatment options of putative therapy-resistant neuropsychiatric diseases. Building on this strong foundation more and more mental disorders in the stadium of therapy-resistance are considered as possible indications for DBS. Especially schizophrenia with its associated severe and difficult to treat symptoms is gaining attention. This attention demands critical questions regarding the assumed mechanisms of DBS and its possible influence on the supposed pathophysiology of schizophrenia. Here we synoptically compare current approaches and theories of DBS and discuss the feasibility of DBS in schizophrenia as well as the transferability from other psychiatric disorders successfully treated with DBS. For this we consider recent advances in animal models of schizophrenic symptoms, results regarding the influence of DBS on dopaminergic transmission as well as data concerning neural oscillation and synchronization. In conclusion the use of DBS for some symptoms of schizophrenia seems to be a promising approach, but the lack of a comprehensive theory of the mechanisms of DBS as well as its impact on schizophrenia might void the use of DBS in schizophrenia at this point.

Key words: *Deep brain stimulation; Schizophrenia; Translational medicine; Neural oscillations*

1. INTRODUCTION

Since the first application of 'deep brain stimulation' (DBS) in the late 1980s, the electrical stimulation of basal ganglia has become a routine treatment of movement disorders (Benabid et al., 1987). DBS is delivered via electrodes usually implanted in both brain hemispheres. These electrodes emit short-lasting, balanced pulses of constant frequency and defined voltage. In so doing, DBS is thought to attenuate clinical symptoms by balancing dysfunctional networks in neuropsychiatric disorders.

Until today, DBS has been delivered to more than 50,000 individuals suffering from idiopathic Parkinson's disease, essential tremor, and dystonia, respectively (Deuschl et al., 2006; Kupsch et al., 2006; Schuurman et al., 2000). Outcome studies have demonstrated a large

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effect-size, but overall few and well-tolerated side effects. The best evidence refers to idiopathic Parkinson's disease, where bilateral stimulation of the nucleus subthalamicus (STN) yields significant benefits regarding both, symptom burden and quality of life (Deuschl et al., 2006). It has to be considered, however, that the accidental stimulation of limbic parts of the STN often leads to behavioral and psychological side effects. These effects might be occasionally almost pleasant, e. g., yielding *euthymia* in formerly depressed patients, but are in general grave in inducing hypomania or severe depression (Skuban, et al., submitted).

Since 2000, DBS has been applied and evaluated in psychiatric disorders in stages of illness beyond responsiveness to standard treatments (Nuttin et al., 1999; Vandewalle et al., 1999). Until today, a considerable number of investigations have demonstrated beneficial clinical effects of DBS in depression, obsessive-compulsive disorder (OCD), and Tourette's syndrome, respectively. Hence, DBS has become an approved treatment option in OCD under the humanitarian device exemption, and current discussions aim to extend its therapeutic scope even further (Kuhn et al., 2010). Besides others, current approaches address addiction due to psychotropic substances and Alzheimer's disease, both representing disorders of great socioeconomic relevance (Kuhn et al., submitted; Kuhn et al., 2007; Laxton et al., 2010). However, all studies comprised a not neglectable number of non-responders.

The story of success told by DBS suggests its application in individuals suffering from otherwise treatment resistant paranoid schizophrenia, despite issues regarding the precarious history of neurosurgery in this disorder (see (Huys et al., submitted) for overview). Further objections exist regarding possible delusional misapprehension of the DBS procedure. However, case reports of successful DBS of the globus pallidus internus in schizophrenia patients suffering from tardive dyskinesia did not support these objectives (Trottenberg et al., 2005; Damier et al., 2004).

Schizophrenia apparently warrants advanced treatment options. Although research in the last decades significantly improved the prognosis of schizophrenia, its course is still largely heterogeneous. A considerable number of individuals suffer from long-lasting impairments due to persistent positive, negative, and cognitive symptoms, respectively (Cipriani, Boso & Barbui, 2009; Kirkpatrick et al., 2006; van Os & Kapur, 2009). Regarding the causes of disability in the lifespan, schizophrenia is located within the top ten (Wittchen et al., 1992; Perala et al., 2007). The subjective quality of life is substantially diminished (Skantze, 1998; Pinikahana et al., 2002). In an Australian investigation patients complained of reduced capacity of self supply (35.3%) and housekeeping (50.0%), impaired social functioning (61.2%), and reduced capacity to maintain partnership (48.4%) (Castle & Morgan, 2008). Current clinical research aims to evaluate if this long-term functional impact of schizophrenia depends on adequate treatment in the initial stages of illness. Incomplete remission of symptoms, however, has been demonstrated to promote precarious outcomes (Andreasen et al., 2005; Lambert et al., 2010).

Independent of these points substantiating the need of further improvement of schizophrenia treatment, DBS must be discussed in terms of a risk-benefit ratio. Side effects of DBS represent a collection of three types: (1) harm due to neurosurgery, (2) technical issues, and (3) side effects due to the stimulation itself. Most severe are intracerebral hemorrhages, occurring in 0.2 to 5%, and infectious brain disease, occurring in 2 to 25% (Krack et al., 2003). Technical problems, e. g., lead fracture, are overall declining and amounted to 8%/electrode/year in 2002 (Oh et al., 2002). The stimulation itself may lead to side effects, e. g., double vision or dysarthria, depending on the brain structure targeted by DBS. However, side-effects due to stimulation are reversible. Effects on psychopathology and behavior are intensely investigated (Müller & Christen, 2011). In this regard, current data are not sufficient to draw any conclusions.

The present paper aims to evaluate if both, the technical and the pathophysiological knowledge is currently sufficient to make DBS a treatment option in schizophrenia. To this end, it is evaluated if any feature in the pathophysiology of schizophrenia is known today that requires a therapeutic mechanism provided by DBS. The paper is arranged in four sections, each dealing with a distinct hypothesis putatively justifying DBS application in schizophrenia.

2. FIRST APPROACH: FUNCTIONAL LESIONING

In December 1986, the modern technique of DBS was introduced by the neurosurgeon Benabid and the neurologist Pollak in Grenoble/France (Benabid et al., 1987). They treated a patient who suffered from bilateral tremor and had benefit from unilateral thalamotomy. A second thalamothomy, however, was prohibited by the known risks of this procedure. Thus, Benabid and Pollak decided to only functionally inhibit the contralateral thalamus by electrical stimulation, which yielded imminent remission of the tremor.

With regard to pathophysiology, DBS has been thought to induce a 'functional lesion' (McIntyre et al., 2004). In this context, the so called 'network inhibition' achieved by DBS was hypothesized to represent a collection of particular neuronal effects: (1) reinforcing afferent inhibitory neurons, (2) inhibition of excitatory afferents, and (3) depolarization-block of ion channels in close proximity to the active electrodes (Dostrovsky et al., 2000; Beurrier et al., 2001). This hypothesis of functional neuronal inhibition is consistent with the observation of immediate and reversible effects of DBS on 'Parkinson-plus' symptoms, e. g., tremor. Adopting this model, Nuttin (Nuttin et al., 1999) and Visser-Vandewalle (Vandewalle et al., 1999), who had chosen to treat OCD and Tourette syndrome with DBS, targeted to anatomical structures which had been already identified with thalamotomies or capsulotomies and led to remarkable success.

Schizophrenia, although not yet fully elucidated in terms of neurobiology, is certainly not caused by a single brain damage or a localized brain deficit. The dysfunctional network presumably underlying schizophrenia which needs to be considered is only partly understood. The disappointing results of ablative stereotactic procedures in schizophrenia also support these assumptions. A recent meta-analysis demonstrated that more than 170 individuals have been treated with ablative procedures (mainly cingulotomy and callosotomy, respectively). The clinical benefit in schizophrenia however lagged markedly behind the success achieved by DBS in other psychiatric disorders (Leiphart & Valone, 2010). Thus, no valid expertise regarding putative anatomical targets in schizophrenia can be drawn from previous neurosurgical approaches.

In contrast to particular symptoms of schizophrenia the model of functional lesions appears to be more sensible. The results of investigations employing transcranial magnetic stimulation (TMS) seem to do so, as well. TMS is a non-invasive procedure to deliver magnetic currents (2 tesla, 250 μsec) through the scull, thereby inducing electric currents in the targeted brain volume (approximately 2 cm^3). Repetitive stimulations yield either excitatory or inhibitory effects. TMS of ≤1 Hz acts like long term depression (LTD), which has been characterized as a 'virtual' lesion (Ridding & Rothwell, 2007; Pascual-Leone, Bartes-Faz & Keenan, 1999). TMS of the left temporal parietal cortex decreased auditory hallucinations in some, though not all studies (Jandl, 2010). However, TMS effects are self limited in terms of duration, and the TMS application is restricted to superficial cortical regions. Meta-analyses revealed at best a moderate effect-size of TMS in the treatment of auditory hallucinations, and in the largest randomized controlled trial no superiority of TMS compared to placebo has been found (Aleman, Sommer & Kahn, 2007; Slotema et al., 2010; Slotema et al., 2011). In conclusion, the expertise in TMS is of limited value regarding the target selection for DBS, especially as the latter is delivered exclusively to subcortical brain regions.

According to recent data the electro-convulsive therapy (ECT) has been demonstrated to be of the most successful non-pharmacological treatments in schizophrenia (Payne & Prudic, 2009). Yet, only few conclusions can be drawn from ECT, as it apparently acts on a plethora of biological mechanisms. Gene expression is thought to be modified by ECT, fostering neuroprotection, neuroplasticity, and neurotransmission (Kato, 2009). The broad range of beneficial effects of ECT may facilitate its application in various psychiatric disorders, but limits the commensurability with other techniques and for example Catatonia has very good indication of ECT in schizophrenia. Here ECT is thought to reinforce GABAergic modulation

of dopaminergic transmission in thalamo-cortical circuits (Daniels, 2009; Sanacora et al., 2003). The putatively causative dysregulation of GABA emerges primarily from cortical regions (Northoff, 2002), which are inaccessible for DBS.

3. SECOND APPROACH: MODULATION OF DOPAMINERGIC NEUROTRANSMISSION

Building on the pathophysiologcal assumptions of Kapur, Mikell and colleagues suggested two subcortical regions (Mikell et al., 2009; Kapur, 2003) as putative target structures for DBS. Kapur et al. (2005) had hypothesized that dopaminergic neurotransmission, which acts as a relevance detector in healthy subjects, e. g., in the reward system, misattributes salience to random stimuli in schizophrenia due to spontaneous and context-independent activity (Kapur, Mizrahi & Li, 2005). This dysfunction of the phasic dopamine release may lead to pathological salience and consecutively to positive symptoms. Based on this hypothesis and considering findings of dopaminergic hyperactivity of the anterior hippocampus (AHC) in psychosis, Mikell and colleagues identified the AHC and its efferences to the nucleus accumbens (NAcc) as putative target structures for DBS (Mikell et al., 2009). The authors considered functional lesioning of the AHC being safe and efficient in reducing dopaminergic hyperactivity in this brain region. Regarding the NAcc, Mikell et al. suggested that DBS would balance the dopaminergic transmission by fostering tonic and inhibiting phasic dopamine release in parallel. Alternatively, the authors pointed out that stimulation may target the ventral pallidum (VP) resulting in promoting both, tonic and phasic dopamine, and the ventral tegmental area (VTA) resulting in direct modulation of dopamine release. DBS of the VTA, however, has been deferred due to technical objectives.

Goto and colleagues suggested that phasic dopaminergic transmission in the NAcc contributes to enforcement learning and reward processing by facilitating afferent projections from the limbic system via modulation of the D1 receptor (Goto, Otani & Grace, 2007). Striatal D2 receptors, in turn, appears being under the control of tonic dopamine in the resting state. Modulation of tonic dopamine, which may be crucial in context dependent modification of behavior, is thought to balance afferent input from the prefrontal cortex (PFC). Considering the mechanism of action of antipsychotic drugs it appears evident, that suppression of dopaminergic hyperactivity in the striatum leads to alleviation of psychotic symptoms (Kapur & Mamo, 2003). However, it has been suggested that the benefits of dopamine suppression depend on the stage of illness (Juckel et al., 2006a; Rosenfeld, Lieberman & Jarskog, 2010). In post-acute stages, when positive symptoms have already remitted, inhibition of dopaminergic transmission may lead to a reinforcement of negative symptoms and deficits in social cognition. Furthermore, Kapur (Kapur, 2003; Kaour & Mamo, 2003) pointed out that aberrant salience presumably represents not the main cause of positive symptoms, but accounts for their prominence in the individual's experience. The main effect of antipsychotic medication acting on dopamine may thus be a rather psychological one: as psychotic experiences lose their pathological salience the individual is able to cope with it. This adds doubt to the approach by Mikell and colleagues because negative and cognitive symptoms take on greater significance in the prognosis of schizophrenia (Harvey et al., 2006).

Negative and cognitive symptoms however may be interlocked with the former, mediating the availability of the latter (Harvey et al., 2006; Ventura et al., 2009). Dysfunction of the ventral striatum has been hypothesized to contribute significantly to negative symptoms resulting in fundamental impairments of hedonia and motivation (Juckel et al., 2006b). The overall level of motivation and hedonia, however, seems to depend on tonic dopamine transmission (Niv et al., 2007). This becomes evident as DBS of the NAcc in depression leads to remission of anhedonia, i. e., recovery of hedonic pleasure (Schlaepfer et al., 2008). But regarding schizophrenia, these results are of limited advantage. Virtually complete suppression of dopamine has indeed been demonstrated to suspend both, motivation and

hedonia (Juckel et al., 2006a; Hamamura & Harada, 2007). The partial dopamine agonist aripiprazole, in turn, has not been found superior in treating negative symptoms of schizophrenia, although a suppression of phasic dopamine and a reinforcement of tonic dopamine by this substance have been suggested (Hamamura & Harada, 2007; Mazza et al., 2009; Leucht et al., 2009).

Following the hypotheses on modulation of the dopaminergic system the lateral habenula is a potential target for DBS. The habenula inhibits the substantia nigra pars compacta (SNc) and the VTA, both playing a crucial role in dopaminergic transmission, as well as the serotonergic medial and dorsal raphe nuclei. Some studies have demonstrated a calcification of the habenula in individuals with schizophrenia and suggested a pivotal role of this brain region in the pathophysiology of the disorder (Sandyk, 1992). Further evidence arises from genetic findings which have shown that alterations of the neuregulin-1 (NRG-1) gene are associated with schizophrenia; moreover NRG-1 is expressed primarily in the habenula (Corfas, Roy & Buxbaum, 2004; Williams et al., 2003; Yang et al., 2003; Steiner et al., 1999). In animal models, lesions of the habenula have been demonstrated to contribute to non-specific impairments of both, memory and attention, comparable to the findings in human schizophrenia patients (Lecourtier & Kelly, 2005; Lecourtier, Neijt & Kelly, 2004). In animals, the conventional antipsychotic drug haloperidol has been shown to improve the cognitive deficits caused by habenula lesions.

Moreover, habenula lesions lead to impaired pre-pulse inhibition (PPI), a marker where impairment has been repeatedly observed in schizophrenia. The dishinibition of dopaminergic and serotonergic pathways resulting from disabling the habenula thus appears to affect learning primarily (Shepard, Holcomb & Gold, 2006). Following these considerations, DBS of the habenula ought to act in an activating, i. e., low-frequency, mode to counteract the diminished inhibitory effect. However, only single symptoms can be modeled in animals. Schizophrenia as a syndrome, i. e., a collection of various symptoms with a largely unknown pathophysiology, remains beyond the scope of such models. Hence, even though DBS might be able to improve some cognitive symptoms of schizophrenia in humans, it remains questionable if the complex syndrome itself would sufficiently benefit. The technical feasibility of modulating the dopaminergic neurotransmission in target regions of DBS, in turn, has been proven: DBS of the STN in individuals with idiopathic Parkinson's disease allows for reducing the L-dopa dosage, and animal studies have demonstrated that DBS of the STN results in a reversible increase of dopamine and its metabolites in the striatum and the NAcc Mikell et al., 2009; Kapur, 2003; Kapur Mizrahi & Li, 2005). Electrophysiological studies have demonstrated consistently that the activation of SNr and the GPi are decreased by STN-DBS (Paul et al., 2000; Meissner et al., 2003; Meissner et al., 2002; Meissner et al., 2001; Winter et al., 2008). Analogous changes have been found in other transmitter systems, e. g., glutamatergic and GABAergic pathways of the basal ganglia network (Benazzouz et al., 1995; Benazzouz et al., 2000a; Benazzouz et al., 2000b; Robledo & Feger, 1990; Bruet et al., 2003). In summary, DBS has been found to impact on neurotransmission.

4. THIRD APPROACH: MODULATION OF NEURAL OSCILLATIONS

According to the current knowledge, neural oscillations are fundamental to information processing (Buzsaki & Draguhn, 2004; Uhlhaas et al., 2009). Oscillations are thought to represent the coordinated communication between brain regions. Observed oscillations cover frequencies of 0.5 Hz (delta) to more than 200 Hz (gamma). Thereby, frequency and scales of cortical integration display an inverse relationship, i. e., higher frequencies represent local interactions whereas lower frequencies mirror large scale integrations (von Stein & Sarntheim, 2000).

Beta and gamma oscillations, however, are thought to contribute to cognitive and sensimotor processes, and are hypothesized to play a pivotal role in the pathophysiology of neuropsychiatric disorders, e. g., idiopathic Parkinson's disease and schizophrenia.

In schizophrenia, various changes in oscillatory activity may culminate in dysfunctional neural (de-)synchronization, as it has been demonstrated in electroencephalographic (EEG) and magnetoencephalographic (MEG) investigations (Uhlhaas & Singer, 2010). Differences in baseline oscillatory activity have been found between schizophrenia and other neuropsychiatric disorders and healthy individuals, respectively (Boutros, 2008). Moreover, an association of neural oscillations with symptom dimensions has been demonstrated. Deficits in beta/gamma bands may contribute to perceptual impairments, and neural synchronization has been found correlated with positive and negative symptom dimensions of schizophrenia (Spencer et al., 2004; Uhlhaas et al., 2008; Uhlhaas et al., 2006). Changes in alpha synchronization during a memory task have been found to be correlated with task performance (Haenschel et al., 2010).

Neural oscillations are thought to arise from the complex interactions of different neurotransmitter systems. Particularly the GABAergic interneurons of the brain may be crucial in the generation of higher frequency oscillations, i. e., beta and gamma (Uhlhaas & Singer, 2010). Generally speaking, neural oscillations represent metastable states of synchronized neural activity, which are preferentially formed (so called 'attractors') and relatively protected against spontaneous activity (so called 'noise') (Rolls et al., 2008). Increasing noise is thought to destabilize attractor states. Depending on the brain regions affected, increase in noise leads to, e. g., distraction of attention (cognitive symptoms, PFC) or volitional and affective disturbances (negative symptoms, ACC and OFC), respectively (Rolls et al., 2008).

It has been demonstrated in idiopathic Parkinson's disease that DBS leads to the recovery from pathological oscillatory patterns. However, DBS has to be delivered to the pivotal structure in the hierarchy of pathophysiology to restitute the network. Hence, it is a prerequisite of successful DBS to locate the neural sources of aberrant oscillations. The source localization of event-related potentials has been demonstrated being a possible though not trivial procedure (see, e. g., (Teubner et al., 2005). Albeit relating scalp EEG to localized neural activity appears thus feasible, EEG source analysis lags largely behind the precise mapping of pathological oscillations realized by simultaneous measurement of deep-brain EEG (STN) and EMG in idiopathic Parkinson's disease (Timmermann et al., 2003, 2004).

A clear correspondence between the phenomenological and the neurophysiological domains, both presumably converging on the same pathophysiological component, is necessary to guide DBS treatment. In idiopathic Parkinson's disease, for instance, it has been demonstrated that both, the pathological hypersynchronization of basal ganglia (13 – 30 Hz) and the tremor frequency simultaneously decrease by high-frequency DBS (Kuhn et al., 2006; Kuhn et al., 2004). Animal models provided evidence that high-frequency DBS decreases the firing of STN neurons, which leads to neural desynchronization and consecutive recovery from idiopathic Parkinson's disease motor symptoms (Meissner et al., 2005).

In schizophrenia, impaired neural oscillations might be associated with particular cognitive symptoms. Some investigations have found correlations of neural synchronization with memory performance and sensory processing, respectively (Spencer et al., 2004; Uhlhaas et al., 2008; Uhlhaas et al., 2006; Haenschel et al., 2010). Reduced synchronization, for instance, has been demonstrated in the anterior cingulate cortex (ACC) during an auditory discrimination task (Gallinat et al., 2002). However, it appears questionable if the modulation of a particular symptom embedded in a system of various disordered components leads to a recovery from the full range of deficits. Sensory processing and higher order cognitive performance display mutual dependence: perception contributes significantly to proper cognition (bottom-up) and cognition, in turn, modulates perception (top-down) (Javitt, 2009; Adcock et al., 2009). Thus, framing a valid hypothesis regarding schizophrenia by assuming a close relationship between phenomenology and neurophysiology appears critical.

Alternatively, DBS treatment in schizophrenia may aim at improving symptom domains rather than particular symptoms. It has been hypothesized recently that DBS of the ACC might lead to improvement of negative symptoms (Arends & Winterer, 2008). However, such approaches presuppose that the target structure plays a pivotal role in the pathophysiology of the symptom domain. Exclusively on that condition, DBS would be able to rebalance a dysfunctional system presumably driven by a plethora of pathogenic factors. Furthermore, neurophysiological and the conditioned clinical symptoms should possess a stable relation. It has been demonstrated in a quantitative EEG analysis, for instance, that increased amplitudes in the theta range (4 – 8 Hz) correlate with the improvement of symptoms under clozapine, but the correlations became unstable with longer duration of treatment (Gross et al., 2004). However, correlations of theta power with negative symptoms (Scale for the Assessment of Negative Symptoms, (Andreasen, 1984) have been found in antipsychotic-naïve individuals as well (Gschwandtner et al., 2009). Nevertheless, identifying a particular brain structure as a target region of DBS based on the aforementioned correlations would overstrain these findings.

In conclusion, the diversity of pathological neuronal activity opposes valid predictions regarding a possible clinical benefit in individuals with schizophrenia. Neural oscillations, however, mirror the activity of a complex network constituted by populations of neurons which dynamically pattern information processing ensembles. Thus, the sources of oscillations cannot be located to specific brain regions. There might admittedly exist pacemaker regions, but non-invasive measurements allow not for deducing the number of generators involved. Moreover, many investigations have demonstrated complex patterns of both, reduced and increased activity. Thus, oscillations in schizophrenia may represent a complex dysfunctional neuronal modulation rather than particular deficits.

5. FOURTH APPROACH: TRANSLATIONAL RESEARCH

Animal models provide some opportunities for DBS research: (1) multiple brain areas can be targeted in parallel, (2) the effects of different stimulation settings can be compared, and (3) both, in-vivo and post-mortem studies can be conducted within feasible time periods. Moreover, behavioral effects of different stimulation settings provide information elucidating the underlying pathophysiology. The translation of the results in human medicine is possible, if the models are valid. Some recent studies proved model validity in OCD (Mundt et al., 2009; Klavier et al., 2009; Klavier, Winter & Joel, 2011; Djodari-Irani et al., 2010; Winter et al., 2008), depression (Hamani & Nobrega, 2010; Hamani et al., 2010), and substance dependency (Vassoler et al., 2008; Rouaud et al., 2010) (for overview see Winter, Harnack & Kupsch, 2010).

A collection of animal models appears valid regarding some pathophysiological aspects of schizophrenia (Feldon & Weiner, 2009). A pilot study has demonstrated that high-frequency DBS of the medial prefrontal cortex (MPFC) and the mediodorsal thalamus, respectively, as well as the low-frequency stimulation of the globus pallidus led to recovery from PPI deficits in rats. In contrast, DBS of the STN has found not to be efficacious. Stimulation of the NAcc, in turn, has led to schizophrenia-like behavior in healthy control rats. However, the aforementioned results warrant replication in other animal models and behavior paradigms, respectively.

6. CONCLUSIONS

Recent results of DBS treatment of psychiatric disorders are auspicious. Although the current state of knowledge is not yet sufficient to validly evaluate effect sizes, the present expertise gives hope that DBS may sufficiently alleviate treatment resistant OCD and tourette syndromes. However, the story of success told by the recent history of DBS treatment fostered

speculations on establishing this new treatment in various other disorders. Particularly schizophrenia, which still represents one of the most critical disorders in terms of prognosis because of long-lasting deficits in a significant number of subjects, has increasingly gained attention. In the present paper, some approaches addressing the feasibility of hypothesized DBS treatment in schizophrenia were discussed.

The knowledge on the role of dopamine in the pathophysiology of schizophrenia makes it plausible to target this neurotransmitter system by DBS. Stimulation treatment, it has been hypothesized, may be employed to decrease dopaminergic hyperactivity. However, results demonstrating that the role of dopamine depends on the stage of illness call into question if individuals would benefit of the constant stimulation provided by DBS.

The modulation of pathological oscillatory neural activity represents another plausible approach. Findings in idiopathic Parkinson's disease demonstrating that dysfunctional neuronal synchronization can be rebalanced by DBS lend further support on this. However, methodological issues exist regarding the source localization of EEG oscillations. Furthermore, the relationship of oscillations and clinical symptoms is yet opaque.

Animal research provides the opportunity to model partial aspects of the disorder and to investigate the respective impact of DBS. However, even if DBS treatment of a particular symptom might be successful in animals, the integration of the modeled symptom in the context of the disorder warrants discussion. Nevertheless, animal research must be employed to validate the efficacy of DBS prior to its application in humans. The translational approach has already proven methodological validity in OCD, alcohol dependency, and depression, respectively. Hence, discussions on DBS in schizophrenia should consider the results of animal research in identifying target regions for DBS.

In summary, DBS in psychiatric disorders is only at the beginning. Especially in considering the precarious history of psychosurgery, putative new applications of DBS must be carefully appraised. DBS treatment of schizophrenia, however, appears premature with regard to the current knowledge. Although some conclusions can be drawn from DBS treatment in idiopathic Parkinson's disease, the significance of the recent findings regarding schizophrenia remains unclear. Moreover, the unquestioned transfer of results from one disorder to another appears dubious. The recent findings on the pathophysiology of schizophrenia should be further validated to put approaches of a respective DBS treatment on a sound basis. At this stage, we can only hope that further evidence will be rapidly collected. However, the crucial expertise can only be obtained empirically. Nevertheless, the application of DBS in schizophrenia should not be considered unless knowledge is sufficient to allow for hypotheses of maximum verisimilitude.

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