The cognitive safety of deep brain stimulation in refractory psychiatric disorders

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Over the last decade, deep brain stimulation (DBS) has revolutionized the treatment of movement disorders and is now being used experimentally to treat refractory psychiatric disorders as well. DBS is a neurosurgical treatment involving the implantation of electrodes, which send electricity to specific targets deep in the brain. DBS in psychiatric disorders such as Tourette syndrome (TS), obsessive-compulsive disorder (OCD), major depression (MD) is based on focal neuromodulation of cortico-basal ganglia-thalamocortical loops involved in the control of behaviour and emotions paralleling the effect of modulating the motor circuit to treat movement disorders such as Parkinson's Disease (PD). DBS has crucial advantages over ablative procedures, performed mainly in the past, since it is reversible and adjustable [1]. However, it is not without risks and its cognitive safety is questionable. This study reviews the cognitive outcome of DBS in refractory TS, OCD and MD.

We searched PubMed and Medline for articles in English published up to December 2011 using combinations of the following terms: neuropsychological, cognitive, executive function, memory, attention, deep brain stimulation, neurosurgery, stereotaxy, TS, tics, OCD, MD, anxiety and mood. The retrieved abstracts were reviewed and the reference sections of the selected articles were screened for relevant studies.

Overall, the studies on DBS in TS, OCD and MD are based on small sample sizes and case reports, including follow-up data or (multicentre) combinations of original samples. Except for MD, relatively few studies reported on cognitive outcome. See Table 1 for the relevant studies. Owing to space considerations, case reports were excluded for review.

1. DBS in TS

TS is a neurodevelopmental disorder consisting of multiple motor and one or more vocal tics with onset in childhood. Comorbid symptoms include Attention Deficit Hyperactivity Disorder, OCD and obsessive-compulsive behaviour, self-injurious behaviour, depression and anxiety. These associated comorbidities are present in about 90% of clinically referred TS patients and have a significant impact on quality of life [12]. In a small number of patients, available treatment options such as pharmacological and cognitive behavioural therapy (CBT) are ineffective or cause intolerable side effects. When adults with severe tics are considered refractory to standard treatment, DBS may be an option. Since 1999, 25 studies including a total of 69 patients and 10 different targets have been published. In the majority of patients DBS resulted in significant tic reduction (50–99%) and in some cases there was also a positive effect on comorbidities [12]. Fatigue or reduced energy was the most reported DBS-related adverse effect [2,12]. Neuropsychologically (see Table 1), no changes have been found between baseline and as-

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Table 1
DBS and cognitive outcome in patients with refractory psychiatric disorders

Syndrome	Target	Design	Cognitive outcome	Reference
TS	Thalamus	double-blind/open-label, $n = 6$, 12 months FU	decrease in selective attention	[2]
TS	Thalamus	open-label, $n = 15$, 24 months FU	no decline but improvement in mental speed/cognitive flexibility	[3]
TS	Thalamus/GPi	controlled double-blind randomized crossover $n = 3$, up to 10 months	no changes in all (4) conditions	[4]
OCD	VC/VS	randomized staggered onset, double-blind, $n = 6$, 6 and 12 months FU	no changes at 6 and 12 months	[5]
OCD	VC/VS	open-label, $n = 10$, FU cognition at 10 months	no individual changes but improvement of group in recall of prose passages	[6]
OCD	ALIC	double-blind/open-label, $n = 4$, 6 months FU	no changes at a group level	[7]
MD	SCG	open-label, $n = 8$ FU cognition at 6 months	no change in test scores	[8]
MD	NAC	open-label, $n = 10$ 12 months FU	improvement at a group level in attention, learning and memory, executive function, visual perception	[9]
MD	VC/VS	open-label, $n = 10$ FU cognition at 6 months	improvement at a group level in verbal memory (logical memory delay)	[10]
MD	SCG	open-label, $n = 6$ FU cognition at 12 months	no change based on reliable change indices	[11]

TS = Tourette syndrome; FU = follow-up; GPi = globus pallidus internus; OCD = obsessive compulsive disorder; VC/VS = ventral capsule/ventral striatum; ALIC = anterior limb of the internal capsule; MD = major depression; SCG = subcallosal cingulate gyrus; NAC = nucleus accumbens.

session up to two years after surgery, except for an improvement in mental speed/cognitive flexibility [3] and a decline in selective attention and response inhibition [2]. However, reliable change indices showed a decline in only one of the six patients [2].

2. DBS in OCD

OCD is a heterogeneous, chronic, and disabling anxiety disorder, characterized by disturbing intrusive thoughts (obsessions) and repetitive ritualized behaviours (compulsions) aimed at reducing anxiety and discomfort. OCD significantly interferes with an individual's daily routine and has considerable repercussions on family and social life and occupational functioning. It is estimated that about 10% of patients remains severely affected despite optimal pharmacological therapy and CBT. In total about 100 refractory OCD patients have been reported with DBS in five different targets. Overall, the reported success rates were > 50%. Chronic mood improvement appeared to be a favourable side effect of DBS, whereas transient hypomania was the most reported adverse effect [13]. DBS has not been associated with evident cognitive decline or improvement (see Table 1) but subjective data with complaints of forgetfulness and word finding have been reported following bilateral stimulation of the nucleus accumbens (NAC) [14].

3. DBS in MD

MD is a complex, multisystem illness characterized by persistently depressed mood or decreased interest in usual activities accompanied by difficulty concentrating, insomnia or hypersomnia, psychomotor retardation or agitation, weight gain or loss, increased or decreased appetite, or feelings of worthlessness or guilt. Even though many patients with depression will respond well to pharmacological treatment, psychotherapy and electroconvulsive therapy, a significant proportion of patients is refractory to treatment. So far, studies with DBS in five different targets have been published, especially in the subcallosal cingulate gyrus (SCG). About 50% of patients responded with a substantial reduction (40–50%) in depressive symptoms during acute and long-term bilateral stimulation but some cases with increased levels of depression, hypomania and suicide (attempts) have also been reported [15]. In general, patients suffering from depression frequently show cognitive disturbances, which emphasizes the importance of treatments with cognitive safety. So far, studies of DBS in MD did not reveal any evidence for DBS-associated cognitive decline (see Table 1). Indeed, significant cognitive improvement occurred independently of a reduction of depressive symptoms and changes in stimulation parameters. Especially the NAC might have an independent augmenting effect on cognition [9], but cognitive improvement was also found in patients with

SCG-DBS [11]. However, this improvement was not significant in terms of reliable change indices.

In conclusion, the results of DBS in TS, OCD and MD show different but substantial degrees of success and side effects were mostly transient, relatively well tolerated or inverted by changing stimulus parameters [1]. Relatively few studies, especially in case of TS and OCD, reported on cognitive outcome and all sample sizes were relatively small with variation in neuropsychological tests used. Overall, DBS has not been associated with clinically significant cognitive decline, providing support for its cognitive safety. Moreover, improved cognitive performance, independent of the antidepressant effect, was found in patients with DBS for MD, especially when stimulating the NAc.

Given the small number of studies and their limited power, the cognitive consequences of DBS in refractory psychiatric disorders need to be further studied. Like in DBS for PD [1], reduced impulse control underlies the serious adverse events, which may have implications for cognition.

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