

New insights in deep brain stimulation for Tourette syndrome

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Valorisation



Tourette Syndrome (TS) is a childhood-onset neurodevelopmental disorder characterized by multiple motor and one or more vocal tics. It is frequently accompanied by comorbid behavioural disorders and they often cause even more impairment than the tics themselves. TS affects between 0.4% - 3.8 % of the general population. Mainly children between 5 and 18 years of age suffer from the disease and the prevalence in this group lies around 1%. Individuals in all countries worldwide can be affected, although to different degrees. Fortunately, TS is often self-limiting around adolescence. About one third of children experiences a significant tic reduction during adolescence and another third becomes completely tic-free. Yet, still one third of children does not experience this remission, and some not only experience tic worsening during adolescence but they develop the most severe forms of TS. In those patients, TS has a devastating influence on their lives and social environments. Since there is no cure for TS, treatment aims to diminish or alleviate tics and comorbid symptoms. Despite behavioural therapy and pharmacological treatment, a small subgroup of patients fails to respond to treatment or experiences intolerable side effects. These patients are often not able to go to school or work, tend to avoid social activities, are not able to develop friendships or an affective relationship, and have a low self-esteem. For those severely affected TS patients, Deep Brain Stimulation (DBS) has emerged as a therapeutic escalation. In refractory cases of well selected TS patients, DBS of different targets within the thalamus and the basal ganglia (BG) seems to be a promising treatment. A key factor in attaining optimal results is target selection, a topic still under debate due to the complex clinical profile presented by TS patients. Nine separate brain areas have been targeted with DBS so far in TS patients.

This thesis contributes to the clinical evidence that DBS, targeting the medial thalamus and the anterior internal globus pallidus (GPi), seems to be a safe and effective treatment in strictly selected TS patients at the short-term. We found an increasing disbalance of therapeutic effects and side effects at long-term follow-up with thalamic DBS, often leading to either switching the stimulator off or new surgery with a different target. DBS of the anterior GPi was found to be effective in reducing tic severity, and possibly also Obsessive-Compulsive behaviour (OCb), without serious side effects, at both the short-term and the long-term. Because of this we think that DBS for future refractory TS patients should target the anterior GPi and not the thalamus. However, we believe that the choice for a single DBS target in TS is unfeasible given the heterogeneity of the disease. As such we need to switch towards tailored targeting instead of trying to find the optimal target for all patients. This tailored targeting should be based on the main symptoms of a patient, e.g. tics or comorbid behavioural disorders. Besides the specific target another clinical issue considers the age limit for DBS in TS. In spite of our experienced difficulties with adolescent DBS for TS, we think that there should be no strict age limit for indicating DBS and decisions should be made on individual circumstances and symptomatology. Waiting for an eventual spontaneous regression around adolescence might cause irreparable damages to the patient's future

life. We think that ongoing ethical discussion is of major importance and should precede future practices and accompany the current practice of indication and treatment.

The development of DBS in TS proceeds slowly since it is not (yet) approved by the Food and Drug Administration (FDA) and the European Commission (EC), because of the lack of evidence due to the difficulty of performing high quality research in a randomized controlled fashion, coupled with the variable effect of surgery, the large number of targets, and the overall small numbers of TS patients with DBS worldwide. The experimental character of the treatment holds up further steps towards approval. Since patients are more cautious in undergoing the treatment and they can only be operated in a research setting, the numbers of included TS patients remain low, making it very difficult to obtain enough high-quality evidence for approval by the regulatory agencies. The various centres use different techniques and targets, making it difficult to obtain and interpret large-scale outcomes. Multicentre randomized controlled trials would theoretically be desirable, but difficult to realize due to practical reasons and would stretch over many years. Moreover, during such trial new insights might be gained, e.g. pointing to different surgical targets or other changes in the procedure, which would be unethical to withhold from later participants. In order to optimally benefit from the clinical experience, we think that all cases of DBS for TS should be entered in a central database covering a range of standardized information, initiated by the Tourette Syndrome Association (TSA). The main goal is to share data, uncover best practices, improve outcomes, and provide critical information to regulatory agencies. Despite the difficulties and uncertainties about DBS in refractory TS patients, we believe that DBS holds a promise for becoming an established treatment. We will participate in continuing the development of DBS for refractory TS patients by further exploring the effects of surgery in our own centre and by contributing to the TSA database.