

## **The use of DBS stimulation in mental disorders – opportunities and risks**

Anna Z. Antosik-Wójcińska, Łukasz Świącicki

Second Department of Psychiatry, Affective Disorder Unit,  
Institute of Psychiatry and Neurology in Warsaw

### **Summary**

Enlarging the knowledge on the biological background of mental disorder is the cause of the growth of interest in cooperation between psychiatrists and neurosurgeons. The experience gained over the last 20 years in research on the use of neuromodulation techniques in neurological disorders suggest that deep brain stimulation (DBS), in addition to improving the neurological condition can lead to positive changes in mood and drive. The use of functional brain research and neuroimaging allowed us to isolate key areas for the emergence of depressive symptoms and obsessive-compulsive disorder. The results of recent studies on the use of DBS in psychiatric disorders indicate, however, both the high efficiency of this method and possible complications and risks associated with it. The paper briefly presents the opportunities of using this method in drug-resistant patients, not responding to other, less invasive forms of treatment, as well as the potential risks and difficulties. However, further research in this area are still required to determine the actual effectiveness of the method, the optimal stereotactic targets, neurostimulation parameters, the risk of side effects and ways to avoid them.

**Key words:** deep brain stimulation, DBS, depression, obsessive-compulsive disorder

### **Introduction**

With advances in medical science increases our knowledge on the background of mental disorders and the mechanisms responsible for the occurrence of individual symptoms, but still our ability to help in the case of drug-resistant disorders, not responding to standard methods of treatment is very limited. The result of our helplessness was directing to neuromodulation techniques that brought rays of hope in areas that previously seemed to be inaccessible. The technique of deep brain stimulation

(DBS) is one of the most promising in case of severe disorders significantly impairing functioning of the patient.

Although the exact mechanism of action of deep brain stimulation is unknown, on the basis of the current research results, it is believed that the stimulator implanted in the chest skin, through the subcutaneous electrode with the tip placed in the brain, sends impulses of a certain frequency, disables the functions of structures, that are hyperactive in various diseases, modifies the function of the loop, and aligns neuronal metabolism in the stimulated area and the neighbouring areas. These interactions take place both at the level of a single neuron (depolarization block resulting from the inactivation of voltage-dependent sodium channel, synaptic inhibition and synaptic depression), and at the level of neuronal loop and neurochemical changes.

The increasing use of DBS in neurological diseases such as Parkinson's disease (PD), dystonia, essential tremor, tremor in multiple sclerosis, or drug-resistant epilepsy resulted in subsequent publications documenting the improvement in the neurological state accompanied by improvement of mental state of patients.

After the first observations made by Kosel, Pool and Fontaine [1], more publications, mainly regarding antidepressant activity, reduction of fear and anxiety and recovery from anhedonia, appeared regularly. It was observed that the implantation of electrodes in areas generally not responsible for the affection brought a reduction in the severity of obsessive – compulsive disorder [2] which, combined with a better knowledge of the functioning of cortical-striato-thalamo-cortical loop, led to the use of this methods for the treatment of depression and obsessive-compulsive disorders. Neuromodulation in the surgical treatment of mental disorders relates mainly to the anterior limb of the internal capsule, area 25 according to Brodmann (BA25) and the nucleus accumbens. Basal ganglia with numerous functional interactions between them are of particular importance. The key areas in the treatment of depression are: cingulate gyrus, especially Brodmann area 25, inferior thalamic peduncle, caudate nucleus, nucleus accumbens, and to a lesser extent also subthalamic nucleus, internal globus pallidus and internal capsule. [1–4].

Functional studies of the brain in people with obsessive-compulsive disorder showed hypermetabolism in orbitofrontal cortex, [1, 2, 4], and in patients with depression hypermetabolism in Brodmann area 25 with a decrease of activity in other cortical areas of the frontal lobes. The use of deep brain stimulation is intended to disable areas showing excessive activity and to realign function areas where activity was pathologically reduced.

A study by Mayberg et al. conducted in a group of six patients with severe treatment-resistant depression, treated with DBS stimulation is considered to be a breakthrough in the deliberate use of DBS stimulation to treat depression; the results of the study were presented in March 2005 [1, 2, 4]. Patients observed improvement in symptoms, they reported a feeling of “sudden tranquillity” and “resolution of a vacuum” and the

study of blood flow showed a decrease in activity of BA25, the effect was observed in the third as well as in the sixth month of the treatment [1, 2, 4]. According to Greicius et al., hyperactivity of BA25 is correlated with the duration of the current episode of depression [1].

The study conducted by Kosel et al. in 2007 (after [2]) showed that the stimulation of the internal globus pallidus may produce an antidepressant effect; the authors explain that any interference in the subcortical area can modify function of the structures responsible for emotions.

Kosel's observations have been confirmed by Stathis et al., [2] who indicated that the connection between the basal ganglia and the limbic system is the potential site of action of DBS in the treatment of depression. It should be noted that all the DBS stimulation locations are anatomically and functionally connected, thus placing electrodes probably influences the same limbic loop whose function is impaired in depression and obsessive-compulsive disorder.

#### Improvement of the mental state associated with the use of DBS

The results of the study of Bewernick et al. [5] including 11 patients with treatment-resistant depression undergoing deep brain stimulation of the nucleus accumbens were very encouraging. Five of the eleven patients responded to treatment and the improvement maintained for a period of four years. The criterion of response was the reduction of the number of points in the HAMD (Hamilton Rating Scale for Depression) by at least 50 %. The criteria of drug resistance was very strict: at least 21 points in a 28-item HAMD, less than 45 points on the General Assessment of Functioning (GAF), at least four episodes of MDD in medical history and current episode of chronic, lasting for at least two years, lack of response during the treatment with an antidepressant from at least three different groups, lack of improvement during the combination treatment with at least two antidepressants, ineffective electroconvulsive therapy ( $\geq 6$  bitemporal ECT), lack of efficacy of psychotherapy ( $\geq 20$  sessions), no other psychiatric diagnoses besides depression, staying for at least six weeks prior to the study on a stable dose of medication or without medication. Taking into consideration such criteria for inclusion in the study obtaining a good response to treatment in 45% of patients appears to be unreachable using standard methods of treatment. What is important, improvement occurred already after one month of stimulation, and a mental state stabilized within the first 6–8 months and remained at almost the same level during the entire study period. The results of the study conducted by Bewernick et al. are consistent with earlier research conducted by Kennedy [6] et al. (2011, a group of 14 patients, the study showed a good response to treatment in 45% of patients, in assessed after 3 years in 60%, in assessment after 6 years in 55%) and Malone [7] (2010, a group of 17 patients; after 12 months good response to treatment was found in 53 % of patients; in the last follow-up evaluation taking place after 14–67 months a positive response

to treatment was found in 71 % of patients). What is important, inclusion criteria for the studies by Kennedy and Malone were similarly restrictive, with the difference that in the study described by Kennedy patients with current depressive episode lasted at least a year were qualified to the study, while in the study of Bewernick and Malone [5, 7] required two years of current depression. The use of similar criteria at baseline and similar methodology enables a comparison of the results of these three works. The results can be considered as encouraging. Recently, Lozano et al. [8] published the results of a pilot study conducted in a group of 21 patients with treatment-resistant depression undergoing deep brain stimulation with the electrode placement in the cingulate gyrus. As early as one month after the start of stimulation good response to treatment was observed in 57% of patients (good response defined as a reduction in the number of points on the HAMD-17 by at least 50%). Improvement of the mental state maintained for six months of observation, the proportion of response after 6 months was 48 % and after 12 months – 29%.

If we consider the risk of relapse of depression in patients with history of major depressive episodes, no mental deterioration over a period of several months to several years after the start of stimulation supports the effectiveness of DBS in the prophylactic treatment of severe, drug-resistant depression. It should be noted that there are no clearly formulated rules for eligibility for DBS implantation due to mood disorders and the criteria for inclusion in the study reported in some publications may raise some doubts. It should be also considered whether BDI (Beck Depression Inventory) and HAMD-17 scales, used by most of researchers to assess the severity of depressive symptoms, are the most appropriate tools. It seems to be more appropriate to assess this group of patients using MADRS (Montgomery–Åsberg Depression Rating Scale).

Currently, the main targets of stereotactic treatment of depression are: ventral striatum/nucleus accumbens, Brodmann area 25, inferior thalamic peduncle, the dorsal cingulate gyrus and lateral habenula [9].

When it comes to diseases other than mood disorders, DBS is mostly used in the sever obsessive-compulsive disorder (OCD) that is resistant to standard treatment. In the past, ablative procedures performed in the area of the ventral anterior limb of the internal capsule were considered to be the most effective method of treatment of obsessive-compulsive disorder. On this basis it was considered to use bilateral stimulation of the anterior limb of internal capsules. The authors report that improvement of 35 % in the Y-BOCS scale was observed in a half of the patients [2, 3]; a part of the patients showed the reduction of the symptoms at the level of 81–83%. Although small group of patients were observed, the reproducibility of the results and the degree of improvement led to the registration of DBS as a therapeutic method in OCD. In the European Union this method is registered and applied in patients with this diagnosis since 2009.

Deep brain stimulation is also used to treat severe cases of Tourette syndrome [2]. The stereotactic targets in this case are: thalamus, globus pallidus, anterior limb of the internal capsule and nucleus accumbens. The latter location is also taken into account in the treatment of alcohol dependence. Previously conducted research on the stimulation of nucleus accumbens in patients with alcohol dependence syndrome indicated that chronic stimulation of DBS reduced alcohol craving, which was explained by the effects on the reward system, however, a small number of people was studied [3].

Currently, the studies on the possible use of DBS stimulation in indications such as heroin addiction, pathological aggression, anxiety disorders with panic disorder and generalized anxiety, eating disorders (anorexia and bulimia), morbid obesity, dementia in Alzheimer's disease, are conducted [3]. Conclusions from previous studies are equivocal, therefore further work on the neurobiological bases of these disorders, which would determine where in reciprocally incorporated loops should we interfere to get the desired permanent effect, is needed.

#### Risks associated with the use of DBS

Despite many reports indicating improvement of mood, drive, the ability to feel pleasure, reduction of fear and anxiety, reduction of the severity of obsessions and compulsions etc. after DBS stimulation, there are also some critical publications. The authors pay particular attention to the fact that stimulation may, in some cases, induce or exacerbate symptoms of depression or, on the contrary – induce a manic episode, result in the onset of psychotic symptoms or cause the disturbance of consciousness.

Bejjani et al. [10] described the case of a patient who within a few minutes after the start of stimulation demonstrated symptoms of severe depression lasting until the stimulator was off. These symptoms disappeared almost immediately after cessation of stimulation.

Similar cases of rapid deterioration of mood after the start of stimulation are rare, opposite cases – elevated mood, increased activity and improvement of self-esteem – are observed more often. In the literature, there are case reports of patients with symptoms of hypomania [11, 12], mania [13, 14] or even mania with psychotic symptoms [15, 16] after the use of deep brain stimulation.

Troster [17], Schneider [18] and Krack [19] published a study documenting the incidence of sustained long-term hypomania in patients undergoing stimulation due to PD. Kulisevsky et al. [14] described the cases of three patients (in a group of 15 patients who underwent DBS) who demonstrated the manic symptoms within 48 hours after the start of stimulation, which resolved gradually over two weeks after changing the settings of the stimulation.

In a study by Funkiewiez et al. [15] involving 77 patients with PD undergoing stimulation of subthalamic nucleus, the authors describe the symptoms of hypomania in 5 patients (6.5%), while in four of them, these symptoms have passed spontane-

ously within a few weeks, in one subject elevated mood lasted for a period of three years of the study.

The most threatening and most serious complications of deep brain stimulation are without any doubts depressive symptoms with suicidal thoughts and intentions. Results of a study conducted by Soulas et al., which included 200 patients undergoing stimulation of subthalamic nucleus in Parkinson's disease, caused a lot of anxiety [20]. Two suicides and four failed suicide attempts (3% of patients) were found in this group. Similar results were presented by Appelby et al. [21], who conducted a meta-analysis of 808 articles on the application and effectiveness of DBS in different diseases. Based on the analysis involving 10,339 patients, they determined the risk of suicide in the population of patients treated by DBS as 0.16–0.32 %. The greatest risk of attempted suicide was associated with stimulation of the thalamus (VIM DBS, 5.4%), slightly lower with stimulation of the internal globus pallidus (GPi-DBS). Stimulation of the subthalamic nucleus was associated with an increased risk of suicidal thoughts in 5 out of 7 analyzed studies.

Although the overall suicide rate in patients undergoing stimulation in comparison with the general population (0.16–0.32 %) was not high, when we consider that in patients with Parkinson's disease suicides occur 10 times less frequently than in the general population [21] these results, however, seem to be alarming and point to the need for long-term observation because of the increased risk of suicidal thoughts and intentions in patients after implantation [22].

Patients eligible for deep brain stimulation for neurological diseases should be carefully evaluated for the presence of mental disorders, both before and after the surgery, including gathering detailed information concerning previous episodes of depression, mania or psychotic symptoms, because they increase the risk of a recurrence of these symptoms after switching the stimulator [22, 23].

As explained by Okun et al. [24] patients with depression with suicidal thoughts in medical history are in a group of increased risk of worsening of depression after starting deep brain stimulation. The researchers pointed out that in a group of 110 patients with Parkinson's disease evaluated after the start of stimulation using the UPDRS (Unified Parkinson's Disease Rating Scale) and the Beck Depression Inventory [24], patients without a history of mood disorders achieved greater motor improvement and had lower scores on depression rating scale (about 11.6%) than those who have suffered from depression in the past. A similar relationship is between the presence of elevated mood (hypomania, mania) and symptoms of psychotic disorders, and the risk of relapse after switching the stimulator.

These reports are the cause of differences in opinions about DBS use in the acute stage of depression. This issue raises serious ethical concerns, as the consent for surgery could mean the potential exposure to complications associated with not fully proven, invasive method, and depriving patients of the benefits of other methods with proven

efficacy. Currently in the recommendations for implantation of DBS in patients with PD established by the Section of Extrapyrarnidal Diseases of Polish Neurological Society include the following phrase: “the disease must cause significant distress or severe impairment of psychosocial functioning and the prognosis without surgery must be negative”. However, the use of this phrase in case of patients with severe depression leaves some uncertainty in interpretation. There is always the question whether the possibilities to assist with the use of standard methods of treatment were exhausted and the prognosis is really unfortunate. The other concern is the risks and suffering associated with trying further drug combinations and delaying the moment of using neuromodulation. Defining of drug resistance also seems to be insufficient, since there is still no clear and widely accepted definition of drug resistance.

In addition to the risk of mental side effects there is also the risk of physical complications associated with neurosurgery (including infection, intracerebral haemorrhage, complications related to anaesthesia ) and a number of side effects associated with stimulation itself such as sensations of fatigue, feeling hot or cold, profuse sweating, shivering [1].

It should be noted that guidelines in the case of post-implantation somatic side-effects, mood disorders or psychotic decompensation are yet not developed. According to most authors in case of any event of mental disorders after starting the stimulation, the stimulator should be turned off and after symptoms resolve it should be re-started in order to verify the causal link between the same electrical stimulation of DBS and the manifestation of the side effects [1]. Some researchers indicate that in the case of obvious neurological improvement it should be considered whether continuation of stimulation and symptomatic treatment (e.g. antidepressant, antipsychotic, anxiolytic) would be appropriate. Due to the small percentage of this type of complications in neurological patients and a very small number of patients treated with DBS for mental disorders it is difficult to make a clear assessment of the risks associated with this method.

Further observational studies conducted on a larger group of patients will provide data on the optimal stereotactic target, neurostimulation parameters, the individual risk of side effects and methods of avoiding them.

It should also be noted that in the group of patients undergoing prequalification procedure for implantation of DBS the incidence of depression, anxiety and psychotic symptoms was higher than in the general population of patients with PD (depressive symptoms were observed in 60% of patients, psychotic symptoms in 35% and anxiety in 40%) [22]. This confirms the thesis that the risk of mental disorders increases with the severity of the disease and patients with the most severe symptoms of PD are also the group most predisposed to psychiatric symptoms and shows how important it is to conduct a thorough psychiatric and neuropsychological examination both to qualify for the surgery, as well as in the period following it [25].

## Recapitulation

In this brief review, we have tried to demonstrate both the unique mechanism of action of DBS resulting in the improvement of mental health in the group of the patients with neurological disorders as well as in the group of patients treated because of mental disorders which are persistent, not responding to a standard therapy. Despite a number of encouraging reports indicating the improvement of mood, activity, ability to feel pleasure, reduction of fear and anxiety, there are also critical publications. To determine the actual effectiveness of the method, the optimal stereotactic targets, neurostimulation parameters, the risk of side effects and ways to avoid them – further research are needed. A major difficulty is to carry out double-blind studies. Because symptoms occur with the delay, the data should be collected in the course of at least several months of observation, what is associated with ethical concerns. The implantation of the DBS is associated with surgical intervention within the central nervous system, and some complications such as local infections and massive fatal intracerebral haemorrhage or neurostimulating system components displacement may occur. Despite the encouraging results of preliminary studies, in the treatment of mood disorders DBS remains an experimental method limited to centres with neurosurgical facilities and developed diagnostic neuroimaging and to strictly selected group of patients not responding to other, less invasive forms of treatment.

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Address: Anna Z. Antosik-Wójcińska  
Institute of Psychiatry and Neurology in Warsaw  
02-957 Warszawa, Sobieskiego Street 9