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# Stimulation-induced side effects after deep brain stimulation – a systematic review

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**Review Article**

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## Abstract

*Objective:* Deep brain stimulation (DBS) was approved by Food and Drug Administration for Parkinson's disease, essential tremor, primary generalised or segmental dystonia and obsessive-compulsive disorder (OCD) treatment. The exact mechanism of DBS remains unclear which causes side effects. The aim of this review was to assess variables causing stimulation-induced chronic psychiatric/personality-changing side effects. *Methods:* The analysis of scientific database (PubMed, Cochrane Library, EMBASE) was conducted. The included articles had to be research study or case report and DBS to be conducted in therapeutic purposes. The researches with mental disorders in patients' medical histories were excluded. *Results:* Seventeen articles were used in the review. In the group of movement disorders the characteristic of side effects was strongly related to the placement of the electrode implantation. Tiredness/fatigue was correlated with DBS in thalamus. Implantations in subthalamic nucleus were mostly followed by affective side effects such as depression or suicide. The higher voltage of electrode was connected with more severe depression after implantation. The analysis of affective disorder contained only three articles – two about OCD and one about depression. Forgetfulness and word-finding problems as activities connected with cognition may be an inevitable side effect if obsessive thoughts are to be inhibited. *Conclusion:* DBS of subthalamic nucleus should be seen as the most hazardous place of implantation. As a result there is a strong need of 'gold standards' based on the connectivity research and closer cooperation of scientists and clinicians.

## Summations

- Deep brain stimulation as a therapeutic method is gaining popularity resulting in higher numbers of conducted surgeries and assessed placements of electrode implantation.
- The characteristic of long-term side effects after deep brain stimulation is still mostly unpredictable.

## Considerations

- The review concentrates only on side effects of deep brain stimulation which could lead to blurred vision of this method as lacking positive outcomes.
- Some of the presented side effects, for example, tiredness/fatigue, are hard to categorise between neurological and psychiatric side effects.
- Criteria of exclusion proposed in the review lead to a limited number of articles analysed in order to obtain possibly the most homogenous results.

## Introduction

Deep brain stimulation (DBS) is a neurosurgical method of modulating brain activity by implantation of electrodes to the brain. The very beginning of this technique should be sought in 1870 when the first experiment with dogs' motor cortex took place. The electrical stimulation of this region led to movements of the limbs (Kringelbach *et al*., 2007). However, the broad use of DBS in humans only started over 100 years later. In 1997 the Food and Drug Administration approved the first indications for thalamic DBS for essential tremor and Parkinson disease–related (PD-related) tremor. To this day, approved anatomical targets for DBS are also extended to the subthalamic nucleus/globus pallidus internus, for treating PD, primary generalised or segmental dystonia and obsessive-compulsive disorder (OCD; Miocinovic *et al*., 2013). Through the years several efforts were made to examine the potential of DBS in the treatment of other diseases, such as Gilles De La Tourette (GTS) syndrome or drug-resistant depression.

Nevertheless, there are also many drawbacks of DBS to be carefully considered. The mechanism of technique and its neural effects are yet not fully understood, meaning that much of the clinical research involving DBS has been done under hypotheses with a considerable degree of

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uncertainty (Miocinovic *et al*., 2013). Furthermore, the side effects which can occur after surgical procedure are yet very unpredictable (Cyron, 2016). Reported long-term psychiatric complications associated with DBS, such as personality and mood changes, may possibly be explained by the lack of use of advanced neuroimaging and brain mapping techniques, during pre-surgical planning. Such would involve the study of the whole-brain connectivity fingerprints leaving the candidate an anatomical target for stimulation. Therefore, this review aims to summarise the key findings and limitations found in clinical DBS research.

Possible complications caused by electrode implantation can be divided into four groups: perioperative, postoperative, technical and stimulation-induced side effects (Beric *et al*., 2001).

Perioperative and postoperative side effects are almost inevitable in neurosurgical interventions.

- Technical complications (hardware-related problems) such as electrode or extension wire failure may occur.
- The most unpredictable and yet not well understood are the stimulation-induced side effects. This group will be on focus in this review because of quite a little number of research works done and as a result – rather undiscovered characteristic. It is difficult to control the development of neurological and psychiatric disorders during chronic treatment. Fortunately, many of the complications could be easily prevented if they occur during or shortly after the surgery. These transient problems can be successfully overcome with programming adjustments (Videnovic & Metman, 2008). The diagnosis consists of turning off the device in order to check for changes in symptomatology. Due to the sudden start in the postsurgery follow-up, the aetiology and the triggers of short-time stimulation-induced side effects are relatively clear. Proposed models focus on the level of stimulation intensity (Okun *et al*., 2007). Voltage levels above functional threshold applied right after the implantation may result in spreading the signal into distant brain structures and inhibition of surrounding neural structures (off the target). However, the voltage level must be sufficient to make a change in patients' disorder. Too low stimulation could lead to little/no response. In a case of mania following DBS in obsessive-compulsive disorder (OCD) after implantation into the anterior limb of the internal capsule/nucleus accumbens (ALIC-NA), the intensity of symptoms decreased after programming adjustments (Haq *et al*., 2010). The authors citing the prevalence of transient hypomania with ALIC/NA DBS (50%–67%) (Greenberg *et al*., 2006) as contrasted with subthalamic nucleus (STN) DBS (4%–8%) (Temel *et al*., 2006) state that such a significant difference could be caused by the connectivity profile of these two targets. The ALIC/NA is more richly connected to limbic and frontal regions than the STN (Nakano, 2000). In the case of transient hypomania in STN DBS for PD, the importance of this connection is consistent with evidence from fibre tracking (Coenen *et al*., 2009). After bilateral stimulation, the acute hypomanic episode occurred. The analysis of data revealed that the left electrode is targeting the putative limbic STN tributaries to the medial forebrain bundle (MFB). After adjusting the settings to this specific context the symptoms disappeared.

The problem with chronic side effects is, unfortunately, more complex and difficult to examine. The threshold between them and short-term side effects is not specified by any guidelines; that is why the boundaries are defined by every research group on their own. The lack of easily reversible causes is also a characteristic of chronic side effects. Because of these two aspects of the characteristic of stimulation-induced chronic side effects this group was chosen to be a main part of the review.

**Table 1.** Databases used

| | PubMed | EMBASE | Cochrane Library |
|---|---|---|---|
| Type of study | Case reports, clinical study, clinical trial | Controlled clinical trial, randomised clinical trial | All |

**Table 2.** Search strategy (articles published till the end of 2018)

| Search strategy | PubMed | EMBASE | Cochrane Library |
|---|---|---|---|
| Deep brain stimulation + side effect | 81 | 168 | 170 |
| Deep brain stimulation + adverse effect | 113 | 125 | 107 |
| Deep brain stimulation + complication | 100 | 188 | 191 |
| Deep brain stimulation + side effect + chronic | 18 | 29 | 25 |
| Deep brain stimulation + adverse effect + chronic | 20 | 22 | 16 |
| Deep brain stimulation + complication + chronic | 7 | 29 | 24 |

## Material and methods

The review was based on the literature search according to several criteria:

### *Criteria of inclusion*

- Research study or case report
- DBS conducted for the therapeutic purposes
- At least one full electrode's settings (voltage, frequency, pulse) in the study
- Chronic character of stimulation-induced side effects with voltage independency – device adjustment was not a variable to be a reason for them
- Psychiatric/personality-changing character of side effects
- The precise period of follow-up (at least 1 month)

### *Criteria of exclusion*

- Trial studies conducted in order to evaluate the effects of DBS on cognitive functions
- Mental disorders in patients' medical histories

The literature search was conducted in January 2019. To find the relevant studies, following databases were used: PubMed, EMBASE and Cochrane Library. Only the articles in English were analysed. All of them must have been published till the end of 2018. In case of search settings of the database including the type of the study – case reports and clinical studies/trials were chosen (Table 1).

The search strategy was based on the priority of the type of the manipulation (DBS) and the presence of side effects. The characteristic of complications – chronicity and stimulation-induction – was the additional variable (Table 2).

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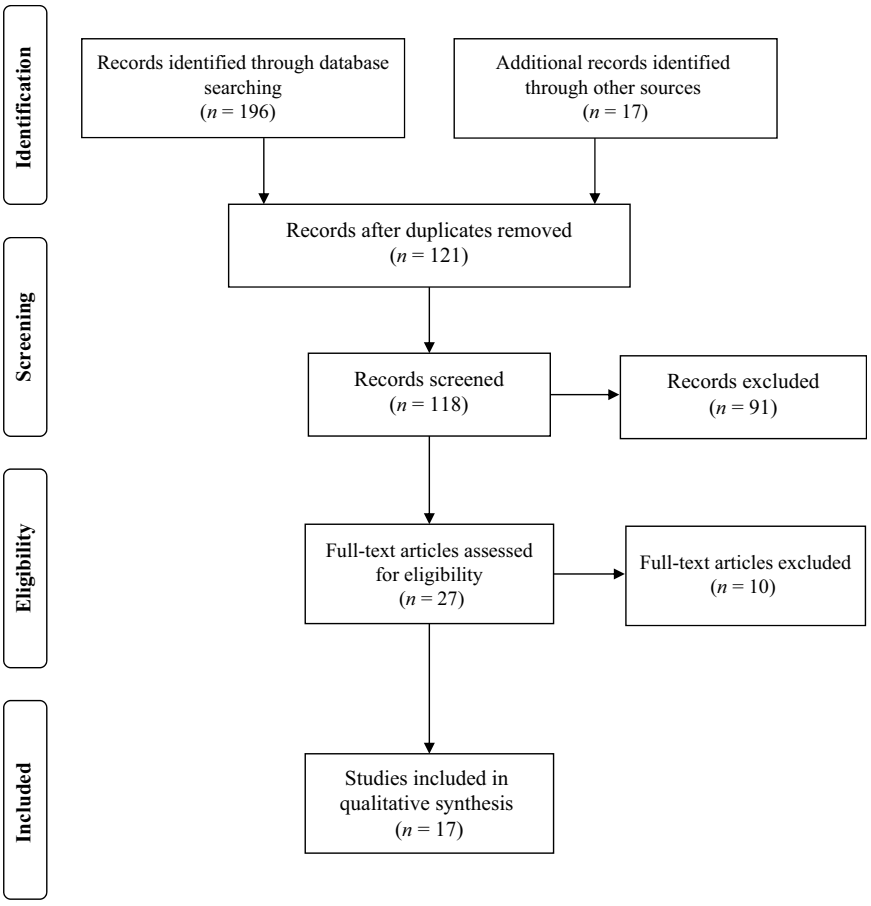



**Fig. 1.** Study selection based on the PRISMA (Moher *et al.*, 2009).

All articles in search strategies 'Deep Brain Stimulation' AND 'Adverse Effect/Side Effect/Complication' AND 'Chronic' were read. Their analysis was focused on the personality-changing/psychiatric characteristic of side effects.

References from the articles were also used in order to include relevant studies not found in databases stated earlier.

After the analysis of inclusion and exclusion criteria 17 studies were used in the review (Fig. 1).

## Results

See Tables 3 and 4.

## Discussion

Up to date, the Food and Drug Administration approved the indications for thalamic DBS for essential tremor, Parkinson disease-related (PD-related) tremor and the subthalamic nucleus/globus pallidus internus DBS for PD, primary generalised or segmental dystonia and obsessive-compulsive disorder (OCD; Miocinovic *et al.*, 2013). DBS could be used when other methods of treatment (e.g. pharmacotherapy) are not effective.

### *Movement disorders*

Parkinson's disease, essential tremor and GTS DBS were analysed. According to Table 3 there are clear indications that chronic side effects in movement disorders DBS are strongly related to the placement of the electrode implantation (Burkhard *et al.*, 2004; Deuschl *et al.*, 2006; Soulas *et al.*, 2008; Børretzen *et al.*, 2014). Thalamus should be perceived as more predictable than STN – in the group of GTS patients the possible complications were very specific and sensitive to this placement (Ackermans *et al.*, 2006, 2011). In every analysed case there was some information about tiredness/fatigue after the surgery (in Table 3 the value is 33.33% because of the patients with prior mental disorders). This observation suggests the local character of stimulation without the effect on the limbic system. The attention-related processes (mediated by centromedian nucleus) inhibition by DBS could be perceived as an inevitable complication of the therapy. Nevertheless, the lack of affective changes is surprising because of the richly developed connections of this region with amygdala and hippocampus (Eckert *et al.*, 2012). Based on this evidence, the theory could be created that adverse effects seen in PD therapy are caused by other structures.

Side effects caused by STN targeting, despite the motor nature of the region, are mostly affective (Molinuevo *et al.*, 2000; Thobois *et al.*, 2002; Krack *et al.*, 2003; Burkhard *et al.*, 2004; Rodriguez-Oroz *et al.*, 2005; Deuschl *et al.*, 2006; Doshi & Bhargava, 2008; Soulas *et al.*, 2008; Børretzen *et al.*, 2014). These complications are likely to be considered as the results of complex brain connectivity. The stimulation of STN leads to the inhibition of fusiform gyrus which debilitates the identification of facial expressions of negative emotions (Geday *et al.*, 2006). The rich connectivity with centromedian nucleus could induce side effects comparable with those observed during GTS therapy (Brunenberg *et al.*, 2012). Except associative areas, STN DBS is primarily affecting limbic regions. Ventral pallidum is involved in addictive and hedonic activities which could affect the hypersexuality (Berridge & Kringelbach, 2015; Blum *et al.*, 2015).

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**Table 3.** Movement disorders

| Primary disorder | Target (side) | Study/type of used stimulation | Primary electrodes' settings | Detailed localisation of DBS | Final electrodes' settings | F/U | SE | % SE |
|---|---|---|---|---|---|---|---|---|
| Parkinson's disease (PD) | Subthalamic nucleus (bilaterally) | Wojtecki *et al.* (2007)<br>Monopolar | – | – | 1 c., 3.8V, 90 µs, 130 Hz<br>1 c., 2.5V, 60 µs, 130 Hz | 3 y | Short stereotypical un- controllable episodes of crying without feeling sad | *N* = 1 |
| | | Doshi and Bhargava (2008)<br>Monopolar | – | – | 2/3 c., 1.9 V, 60 µs, 130 Hz<br>2 c., 3.4/3.3 V, 60 µs, 130/185 Hz | 1 mo.<br>5 y | Hyper-sexuality | *N* = 2 |
| | | Burkhard *et al.* (2004) | – | Electrode at target at MRI scan/autopsy | 1 c, 3.7/3.5 V, 90 µs, 185 Hz | 4 y | Committed suicide | *N* = 1 |
| | | Soulas *et al.* (2008) | – | – | 2/6c., 2.8/2.1 V, 90 µs, 160 Hz<br>3/6c., 2.8/3.4 V, 90 µs, 130 Hz<br>3/6c., 1.8/2.0 V, 90 µs, 130 Hz | 5 mo.<br>14 mo.<br>6 mo. | Committed suicide<br>Attempted suicide | 0.5% *N* = 200<br>1% *N* = 200 |
| | | Molinuevo *et al.* (2000)<br>Monopolar | – | 2 mm posterior, 5 mm ventral to the midcommissural point, 2 mm to the intercommissural line | 3.1 ± 0.7V, 60 µs, 130 Hz | 6 mo. | Depression | 6.67% *N* = 15 |
| | | Deuschl *et al.* (2006) | 60 µs, 130 Hz | 0–3 mm behind the midcommissural point, 4–6 mm below the intercommissural line, and 11–13 mm lateral to the midplane of the third ventricle | 2.9 ± 0.6 V, 63 ± 7.7 µs, 139 ± 18 Hz | 5 mo. | Committed suicide | 1.29% *N* = 78 |
| | | Thobois *et al.* (2002)<br>Monopolar/bipolar (*N* = 1) | 1/2 c., 2.9 ± 0.6 V, 68 ± 13 µs, 140 ± 16 Hz | 3 mm posterior to the midpoint of the bicommissural line, 4 mm inferior to the anterior commissure-posterior commissure (AC-PC) line, 12.5 mm lateral to midline | – | 6 mo. | Depression with psychosis | 5.56% *N* = 15 |
| | | Vesper *et al.* (2002) | 2.5 V, 108 µs, 134 Hz | Postsurgical evaluation revealed optimal placement in case of 46.43% interventions | 3.1 V, 98 µs, 133 Hz | 12 mo. | Confusion | 5% *N* = 38 |
| | | Krack *et al.* (2003)<br>Monopolar | – | – | 3.1 ± 0.4 V, 64 ± 12 µs, 145 ± 19 Hz | 5 y | Hallucinations apathy | 6.12% 10.20% *N* = 49 |
| | | Rodriguez-Oroz *et al.* (2005)<br>Monopolar (80%) | 2.7 ± 0.6 V, 76 ± 34 µs, 148 ± 22 Hz | – | 3.1 ± 0.5 V, 72 ± 20 µs, 151 ± 23 Hz | 3–4 y | Depression | 6.12% *N* = 49 |
| | Globus pallidus internus (Bilaterally) | Rodriguez-Oroz *et al.* (2005)<br>Monopolar (70%) | 3.1 ± 0.8 V, 105 ± 44 µs, 169 ± 22 Hz | – | 3.2 ± 0.4 V, 115 ± 54 µs, 163 ± 25 Hz | 3–4 y | – | 0% *N* = 20 |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Essential tremor (ET) | Subthalamic nucleus (unilaterally/bilaterally) | Børretzen *et al.* (2014) | 2.3 V, 90 µs, 148 Hz | 30% of the AC-PC distance anterior to PC, 50% of the AC-PC distance lateral of the midline, 0–2 mm superior to the AC-PC line | – | 7 mo. | Committed suicide | 2%<br>*N* = 46 |
| Gilles de la Tourette syndrome (GTS) | Thalamus: crosspoint of centromedian nucleus, substantia periventricularis, nucleus ventro-oralis internus (bilaterally) | Ackermans *et al.* (2006) Monopolar | 60 µs, 100 Hz | 5 mm lateral to the AC–PC line, 4 mm posterior to the midcommissural point, at the AC–PC plane | 3.78 V, 108 µs, 102 Hz | 1 y | Fatigue | 33.33%<br>*N* = 6 |
| | | Ackermans *et al.* (2011) Monopolar (50%) | – | | 6.4 V, 120 µs, 130 Hz | 1 y | Fatigue<br>Libido decrease | *N* = 1 |
| | Thalamus + Globus pallidus internus (bilaterally) | | | As mentioned before + 21.5 mm lateral to the AC–PC line, 4 mm anterior to the midcommissural point, 3 mm inferior to the AC–PC plane | 3.1 V, 210 µs, 170 Hz | | Fatigue | *N* = 1 |

C, canal; F/U, follow-up; SE, side effects; y, year; mo., month.

**Table 4.** Affective disorders

| Primary disorder | Target (side) | Study/type of used stimulation | Primary electrodes' settings | Detailed localisation of DBS | Final electrodes' settings | F/U | SE | % SE |
|---|---|---|---|---|---|---|---|---|
| Obsessive-compulsive disorder (OCD) | Nucleus accumbens (bilaterally) | Mantione *et al.* (2014) | 2/3c., 5.0 V, 90 µs, 185 Hz | 3 mm in front of the anterior border of the anterior commissure (AC), 7 mm lateral, 4 mm below the line connecting the AC and posterior commissure (PC) | – | 6 mo. | Change in musical preferences | *N* = 1 |
| | | Mantione *et al.* (2015)<br>Denys *et al.* (2010)<br>Monopolar | 2/3c., 3.5–5.0 V, 90 µs, 130 Hz | | 2/3c., 3.5–5.0 V, 90 µs, 130 Hz | 8 mo. | Forgetfulness<br>Word-finding problems<br>Increased libido | 31.25%<br>18.75%<br>43.75%<br>*N* = 16 |
| Depression | Subcallosal cingulate gyrus (unilaterally/bilaterally) | Kennedy *et al.* (2011) Monopolar | – | – | 4.3 V, 70.6 µs, 124.7 Hz | 3 y<br>6 y | Probable suicide | 10%<br>*N* = 20 |

C, canal; F/U, follow-up; SE, side effects; y, year; mo., month.

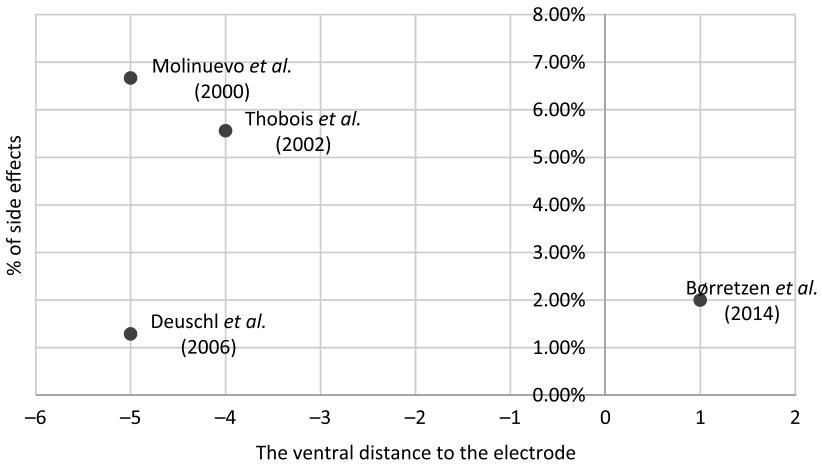



**Fig. 2.** The relationship between the ventral distance to the electrode and % of side effects. The zero point stands for midcommisural line.

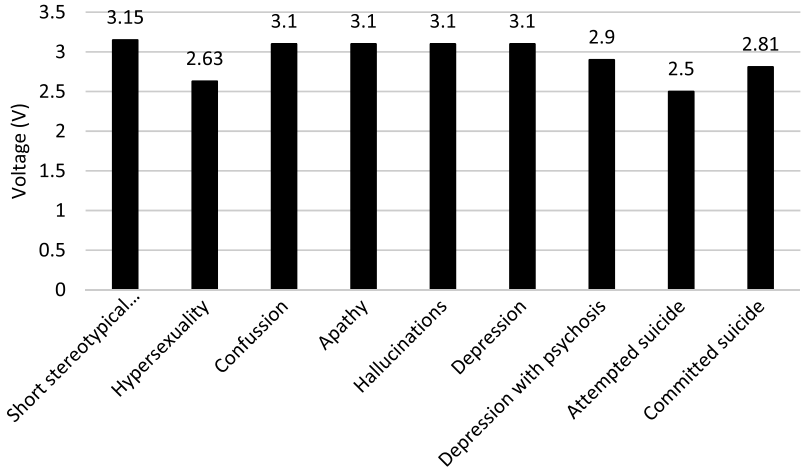



**Fig. 3.** The relationship between type of side effect and mean voltage used in the studies.

Nucleus accumbens is used as a target at the experimental treatment of depression (Bewernick *et al.*, 2010). Orbitofrontal cortex and anterior cingulate cortex are thought to be in charge of emotion and motivation control – the link to depressive side effects (Bush et al., 2000; Drevets, 2007). These structures were also seen to be highly activated after stimulation (Knight *et al.*, 2015). Such an effect could be observed in patients with more ventral STN DBS. However, the postmortem analysis of a patient who committed suicide revealed an accurate localisation of electrode (Burkhard *et al.*, 2004). In addition, the ventral distance of the electrode is not conclusive (Fig. 2). During postsurgical evaluation only in 46.43% cases the optimal placement was obtained (confusion – 5%) (Vesper *et al.*, 2002).

In comparison to the short-time side effects, the relationship between electrodes' settings and the possible complications is less visible. Interestingly, the patients with depression had higher voltage level than those with suicidal actions (Fig. 3). The exception in this remark is a group of patients who committed suicide. This observation could lead to the hypothesis that a patient with suicidal thoughts is more susceptible to the DBS stimulation. The group of patients with attempted suicide had DBS with voltage the lowest of all groups – higher parameters were leading to more desperate suicide actions. The other possible explanation of this phenomenon is that the future suicides had better outcomes; that is why they were more able to be deadly for themselves.

The analysis of adverse effects caused by DBS in the group of patients with movement disorders leads also to some restrictions. In parallel with PD progression, the hallucinations or depression with psychosis could appear as a part of the disorder not caused by implantation (Fénelon *et al.*, 2000; Mayeux *et al.*, 1981). Hypersexuality and cortical disinhibition are also found as a pathological component during anti-Parkinson therapy (Evans *et al.*, 2009; Codling *et al.*, 2015). The higher number of depression or suicidal attempts in comparison to the society is an inevitable aspect of chronic diseases (Cheattle, 2011). Due to these conditions, the probable complications could be hardly distinguished from the pathological progress of disorder.

### *Affective disorders*

Due to eligible features of included articles, only three research studies were analysed – two about OCD and one about depression. The placements of electrodes' implantation differ from those that are used in movement disorders. Forgetfulness and word-finding problems as activities connected with cognition may be a natural outcome if obsessive thoughts are to be inhibited. Such a statement is convergent with fatigue after the treatment of GTS (excessive movement activity) (Ackermans *et al.*, 2006, 2011). These complications could be explained by resting-state functional magnetic resonance imaging (fMRI) which revealed that nucleus accumbens

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DBS affects frontostriatal networks (Figee *et al*., 2013). The excessive connectivity between the nucleus accumbens and the lateral prefrontal cortex and medial prefrontal cortex is decreased after the implantation of electrodes.

The analysis of adverse effects after DBS in depression group is problematic due to the probable progress of the disorder. Cited cases of probable suicides could be caused by electrodes' implantation or the worsening of major depression disorder (MDD). To expand the numbers of presented complications it is valuable to set that in excluded articles (mostly because of not defining the sustainability of side effects) the hospitalisations on account of suicidal ideations or disorder progression were in the majority. This observation leads to the statement that adverse effects caused by DBS could be in fact the cases of patients who are resistant to the treatment. The use of imaging methods in subcallosal cingulate gyrus targeting is also inconclusive (Johansen-Berg *et al*., 2008). The DBS effect could be mediated by strong connections to orbitofrontal cortex, nucleus accumbens, amygdala or hippocampus. Such a diversity makes an analysis of probable adverse effects causes even more challenging.

## Conclusions

The number of available studies related to DBS and side effects caused by this manipulation is still insufficient. The better cooperation between neurosurgeons and psychiatrists/psychologists could improve this situation and lead to more effective paradigms. According to analysed studies, a 'gold standard' of electrodes' settings is highly required. Most of presented by researchers side effects are voltage dependent. During the follow-up, transient episodes of mania/depression/anxiety were eliminated by DBS adjustment. The optimal electrodes' settings should be specified as both effective and secure for the patients. However, this requirement is connected with the problem of connectivity. In cited studies, there were only a few with the exactly specified target of implantation. The use of brain mapping such as MNI is the opportunity to obtain more predictable results. The 'gold standard' in the field of placement is also highly needed.

The postulated technical changes should be introduced together with more specific patients' recruitment. Despite the use of DBS in the most resistant and chronic cases, the thorough evaluation of electrodes' impact on the brain requires the exclusion of the patients with any psychiatric disorders (in the group of movement disorders) or any other than the dominant psychiatric disorder. The proposed modification, no matter how hard to be introduced, may give the opportunity to differ the psychiatric side effects from the pathological progress of the diseases.

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