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Does deep brain stimulation induce apathy in parkinson's disease?

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1. ABSTRACT

Chronic deep brain stimulation (DBS) is an important therapeutic advancement for the treatment of motor symptoms in Parkinson's disease (PD). However, its effects on non-motor symptoms are not well understood. Several studies have reported motivational disturbances and apathy after DBS surgery. Recent studies are beginning to more carefully examine the relationship between DBS and apathy. This review summarizes and evaluates the current state of the literature on apathy after DBS surgery, discusses methodological limitations in the literature, and makes suggestions for future research.

2. INTRODUCTION

Parkinson's disease (PD) is a progressive neurological disorder characterized neuropathologically by loss of neurons in the substantia nigra pars compacta, dopamine depletion in the basal ganglia, degeneration of motor and non-motor circuits, and the presence of Lewy bodies. Patients present with motor symptoms of tremor, bradykinesia (slowness of movement), rigidity, and postural instability. Effective pharmacological treatments exist for PD motor symptoms, such as levodopa and dopamine agonists. However, these treatments only work for a certain window of time, and then decrease in effectiveness. Levodopa can also induce dyskinesias, which are excessive abnormal movements and posturing. In order to overcome the limitations of pharmacological management, surgical treatments such as deep brain stimulation (DBS) are used. The two brain sites targeted in DBS are the globus pallidus internal segment (GPi) and the subthalamic nucleus (STN). It is well established that stimulation of both of these sites reduces motor symptom severity in PD, and that DBS represents an important therapeutic advancement. However, it is not well understood how DBS affects non-motor symptoms. Reports on the non-motor effects of DBS are most commonly studied in bilateral STN cases and have included memory and cognitive decline and psychiatric disturbances such as hallucination, depression, anxiety, and mania (1, 2, 3). In addition to cognitive and mood disturbances, several studies have also reported loss of motivation and apathy after DBS. Apathy can impair patients' functioning through loss of initiative, loss of interest, low energy, and

flat emotions. Postsurgical apathy was first mentioned in the literature as an adverse event and has also been listed in case reports (2, 4). Rather than simply placing apathy in a list of adverse outcomes, research is now beginning to study apathy after DBS more carefully and with a systematic approach. The purpose of the present article is threefold: 1) to review and summarize the literature on apathy after DBS surgery, 2) to discuss methodological limitations in these studies, and 3) to provide suggestions for overcoming limitations in future research.

2.1. Defining Apathy

The term apathy derives its roots from the Greek 'a' 'pathos,' meaning lack of passions. Apathy is defined as a primary lack of motivation that manifests itself in behavioral, cognitive, and emotional symptoms (5). The behavioral symptoms include lack of effort, lack of productivity, and dependence on others to structure one's activities. Cognitive symptoms include loss of interest in new experience and lack of concern about one's personal problems; affective symptoms include flattened affect and lack of response to positive or negative events. The lack of motivation in apathy is primary, and not purely accounted for by intellectual impairment such as dementia, emotional distress, depression, or impaired consciousness (5). Studies have documented that a high prevalence, between 38 and 51% of PD patients, experience symptoms of apathy (6, 7, 8). Data from our laboratory as well as others have also suggested that apathy is a distinct phenomenon from depression and may occur independent of depression in PD patients (8, 9).

2.2. Proposed Mechanisms

Motivation is thought to be mediated by one of the cortico-subcortical circuits, originating in the anterior cingulate. The disruption of this circuit can cause apathy (10). Another aspect of motivation relates to the ability to modify the current motivational state based on reward significance of the environment. This function is thought to depend on the amygdala, hippocampus, prefrontal cortex, and greater limbic lobe; disease affecting these structures may present as apathy (11).

Moreover, the basal ganglia may be viewed as components of a family of functionally segregated, cortico-subcortical reciprocal pathways with motor, oculomotor, associative, and limbic circuits that take origin from regions of the cerebral cortex (12, 13, 14, 15). Although STN DBS is meant to target the motor circuit, some researchers have hypothesized that apathy symptoms after DBS, like other non-motor symptoms, may be caused by stimulation of nonmotor circuits (16, 17). This may occur as a result of the lesion produced by placement of the deep brain stimulator and/or by stimulation itself. Electrodes thought to be placed within the boundaries of the motor circuit may affect parts of the anterior cingulate circuit and limbic circuits underlying motivation. Current spread may influence non-motor circuits depending on the parameters of stimulation (16, 17). Functional MRI studies have also suggested that STN stimulation is associated with downstream metabolic changes in the cerebral cortex, including frontal cortex (18, 19), and this could affect areas associated with motivation. Thus, electrode placement and current spread may be affecting motivation and producing apathy in PD patients who have undergone DBS surgery.

Another theory for apathy changes following STN DBS relates to the reduction in dopaminergic medication requirements that typically occur after the surgery (20). Dopaminergic activity may influence motivational state because of its role in reward, novelty seeking and response to unexpected events (11). Furthermore, dopaminergic drugs may improve parkinsonian apathy (21). Thus, some have speculated that increased apathy after STN DBS surgery occurs as a result of decreasing the dopaminergic medication dosage after surgery (22, 23).

2.3. Relationship between Apathy and Cognition

Several studies have found relationships between apathy and cognitive performance in nonsurgical PD patients. For instance, Dujardin *et al.* (24) noted that apathy level in a large sample of nonsurgical PD patients was mainly related to global cognitive impairment rather than severity of motor symptoms, while Isella *et al.* (7) observed a significant negative association between apathy scores and tests of executive functioning. When examining whether apathy levels change after surgery, it is therefore important to investigate whether related cognitive changes occur—particularly in the domain of executive functioning. The most common cognitive test result to decline significantly after surgery has been verbal fluency (25), so it is relevant to examine whether increases in apathy correlate with this change. A significant correlation could indicate common neuroanatomical or functional mechanisms.

3. SUMMARY OF THE LITERATURE

Many questions remain about the apathy experienced after DBS surgery. For example: What percentage of patients experience apathy after surgery? For how long and how severely are these changes experienced? How do the placement of the lead and the stimulation parameters contribute? What is different about those patients who do versus those who do not have apathy? Perhaps combining all of these questions, we could ask: "What combination of surgery and stimulation factors together with what particular patient characteristics best predicts the patients that will experience significant apathy post-DBS surgery?" Although the current literature cannot yet fully answer this question, progress has been made on several fronts. We would now like to review and examine the studies available in the literature.

We used Medline as a database search engine (dates of search: 7/20/07, 7/21/07; terms: deep brain stimulation, PD, apathy). We found seven studies that examined apathy after DBS that quantified apathy (e.g. used a rating scale). See Table 1. We excluded studies that simply listed apathy as one of a list of adverse events. All seven studies examined apathy after bilateral STN placement. Most studies, but not all, used the Apathy Evaluation Scale-revised version (AES), a scale that was

originally developed by Marin and modified by Starkstein and colleagues (5, 6). It consists of 14 items on a Likert scale that range from 0 (not at all) to 3 (a lot) and total scores range from 0-42. The AES is currently the "gold standard" and most commonly used apathy scale in PD research. In most studies, evaluations occurred prior to DBS surgery and at various follow-up points after surgery. Depending on the study, the follow-up intervals ranged from 3 months to 3 years.

Studies can be divided into those that examined apathy at less than one year, and those that examined apathy at greater than one year after DBS surgery. Three of the seven studies had follow-up periods of less than one year. These were: Funkiewiez *et al.* (23), Drapier *et al.* (26), and Czernecki *et al.* (27). Funkiewiez et al. and Drapier et al. both examined the long term effects of DBS, assessing patients prior to surgery and comparing those rates to apathy after surgery. Czernecki et al. did not assess patients prior to surgery, but focused on the acute effects of STN stimulation in patients with stimulation turned ON or OFF (27). Funkiewiez *et al.* (23) administered the AES and the Beck Depression Inventory-I (BDI-I) to 22 nondemented PD patients prior to surgery, and 3 months after bilateral STN DBS. Results indicated that AES scores were significantly higher after surgery (mean score pre-DBS = 7 and post-DBS = 8, $p < .05$). Depression scores, on the other hand, were significantly lower after surgery (mean score pre-DBS = 11 and post-DBS = 7, $p < .01$). Notably, neither the pre-DBS nor the post-DBS apathy values were at or above 14, which has been determined as the cut-off point for clinically significant apathy (6). The authors report that one of their patients scored higher than 14 pre-DBS and five scored higher than 14 after DBS (23). They did not examine whether additional patient characteristics of the apathetic group differed from the rest of their sample, nor did they note whether the same individual patient that was elevated pre-DBS remained so at the post-DBS evaluation. Doing so would have helped to determine whether patients with high apathy before surgery remain that way, as well as what characteristics might be different about those that develop apathy de novo after surgery. The authors did not investigate the associations between apathy and levodopa dose reduction or between apathy and cognitive performance.

Drapier *et al.* (26) assessed 15 nondemented patients prior to DBS surgery, at 3 months, and at 6 months after surgery. They administered the AES and the original Marin scale, Montgomery and Asberg Depression Rating Scale (MADRS), and the Association for Methodology and Documentation in Psychiatry anxiety scale (AMDP-AT). The authors included a carefully matched control group of 15 PD patients with baseline levels of apathy that did not differ from baseline levels of apathy in the surgery group. This was an elegant study component because it allowed the authors to provide a carefully matched control group of wait list surgery candidates and assess them for fluctuations in apathy levels over the course of PD. Their controls were studied at baseline and nine months later, and the results indicated that mean apathy scores were not significantly different from baseline to nine months. However, mean apathy scores in the surgical group were significantly higher both 3 months and 6 months after DBS surgery compared to before surgery. Depression and anxiety were not significantly different for either the surgery or the control group. Unlike the Funkiewiez *et al*, (23) study, Drapier *et al*, (26) found that mean apathy scores were at the clinically significant level after surgery. In the surgery group, on average, they were greater than 14 at both the 3 month and 6 month follow-ups and just below 14 prior to surgery (pre-DBS AES scores = 13.0. ± 6.5.; 3 months = 16.5. ± 7.5.; 6 months = 18.8. ± 9.7.). They found that 40% of their sample scored ≥ 14 preoperatively, 53% at 3 months postoperatively, and 60% at 6 months postoperatively. There was not a significant difference between the percentage of patients that scored ≥ 14 at 3 and 6 months. The authors conclude that this indicates "some patients became apathetic and others worsened their apathetic syndrome" (26). No relationship was found between levodopa dosage reduction and apathy levels. Although the authors found worsening on several neuropsychological tests after surgery, there were no significant correlations between the change in apathy scores or the change in neuropsychological test scores (including verbal fluency) from pre to post surgery. The authors also examined the placement of electrodes within the STN and concluded that the leads of the patients in the apathetic group were more ventrally and internally placed within the STN than those of the non-apathetic group. However, there were no statistical values reported on the differences in placement parameters.

Thus, both of the previous studies found that chronic deep brain stimulation in bilateral STN led to a significant increase in apathy levels, with one study reporting mean ratings below the clinical cut-off levels (23) and one study reporting ratings above the clinical cut-off levels (26). Czernecki *et al.* (27) took a different approach and examined acute changes in apathy ON and OFF stimulation. Ten months after surgery, 18 nondemented patients had their medications withheld overnight and then completed the AES when the stimulator was turned ON and at least 1 hour after the stimulator had been turned OFF. Results indicated that mean apathy scores decreased (improved) ON stimulation versus OFF stimulation (mean AES ON score = 11.2. ± .9 and mean AES OFF score = 13.4. ± 1.2.). Thus, apathy was reduced acutely with stimulation. They found this improvement to be comparable to the decrease in apathy scores in a comparison group of nonsurgical PD patients tested on compared to off their dopaminergic medications. The authors conclude that apathy is not an inevitable result of neurosurgery and may improve with stimulation (27).

The four remaining studies on postsurgical apathy had follow-up periods longer than one year (28, 22, 29, 30). One of these studies used the AES, one used the Frontal Lobe Personality Scale (FLOPS) apathy subscale, and the other two used a single item from the Unified Parkinson's Disease Rating Scale (UPDRS item 4 on "Motivation/initiative"). Using the FLOPS (both patient and caregiver versions) and the Geriatric Depression Scale (GDS), Saint-Cyr *et al.* (28) assessed 11 nondemented

Table 1. Apathy outcome following chronic deep brain stimulation reported by study, surgical treatment, sample size (n), evaluation period, apathy measures, and outcome

Study	N	Control Group	Apathy Scale	Pre-DBS	Post 1	Post 2	Mean % reduction of L-dopa equivalent dosage after surgery	Outcome
23	22	None	AES	Testing period not specified	3 mo.	N/A	77.5.%	Apathy mean score significantly increased at 3 mo post-DBS vs. pre-DBS; Individual patient data showed 1 patient ≥ 14 pre-DBS and 5 patients ≥ 14 post-DBS;
26	15	15 demographically matched assessed, then re-assessed after 9 mo.	AES & Marin	3 mo.	3 mo.	6 mo.	18.8.% from pre to 3 months, 22.2.% from pre- to 6 months	Apathy mean score significantly increased at both time points post-DBS vs. pre-DBS; No difference in apathy for controls
27	18	23 demographically matched assessed "on" and "off" L-dopa	AES measured acutely with STN stimulator turned "on" then "off" (Off L-dopa for both conditions)	N/A	10 mo.	N/A	84%	Apathy mean score significantly decreased (improved) when STN stimulation was on vs off; Controls apathy score significantly decreased when L-dopa was given versus withdrawn
28	11	None	Frontal Lobe Personality Scale (FLOPS) Apathy subscale	Testing period not specified	3-6 mo.	9-12 mo.	47-54%	FLOPS Apathy subscale significantly increased at 9-12 mo. vs. baseline for caregiver rated version; No significant difference in patient version
22	77	None	UPDRS item 4	Testing period not specified	1 year	3 years	67%	Apathy mean score on UPDRS item 4 significantly increased at 3 years post-DBS vs. pre-DBS, trend increase at 1 year post-DBS vs. pre-DBS
29	72	None	UPDRS item 4	2-wks	12-20 mo.	N/A	55.8.%	No significant difference was detected in apathy on the UPDRS item 4 post-DBS vs. pre-DBS;
30	19	None	AES	2 wks	13-23 mo.	N/A	52.1.%	No significant difference detected in mean apathy scores post-DBS vs. pre-DBS; Individual patient data showed: 1 SD (4 point) increase-31% (6/19), decrease-16% (3/19), no 4 change-53% (10/19)

Note: Abbreviations used: AES = Apathy Evaluation Scale, UPDRS = Unified Parkinson's Disease Rating Scale, SD = standard deviation

bilateral STN patients prior to surgery, as well as between 3-6 months and between 9-12 months after surgery. Results indicated significantly higher FLOPS apathy subscale scores when caregivers rated the patients at 9-12 months, but no significant difference when patients rated themselves. Additionally, there were no differences in depression scores before or after surgery. The authors did not examine the relationships between apathy and levodopa dosage reduction or between apathy and cognitive performance.

Funkiewiez *et al.* (22) and Castelli *et al.* (29) both assessed apathy with item 4 on the UPDRS. This item is rated on a 0-4 basis where 0 = normal, 1= less assertive than usual, more passive, 2= loss of initiative or disinterest in elective (non-routine) activities, 3 = loss of initiative or disinterest in day-to-day (routine) activities, and 4 = withdrawn, complete loss of motivation. Funkiewiez *et al.* administered UPDRS item 4 and the BDI to 77 bilateral STN patients prior to surgery and at 1 year and 3 years after surgery. Results indicated that apathy, based on item 4, significantly increased from pre-surgery to 3 years and increased at a trend level from pre-surgery to 1 year. There was no difference in depression scores. The authors suggested that the increase in apathy might be due to the reduction in dopaminergic treatment (Table 1); however, they did not formally examine the association between dopaminergic reduction and apathy scores. The authors also administered a battery of neuropsychological tests and found that verbal fluency declined significantly after surgery. Postoperative apathy scores correlated significantly with category fluency, but not with other tests of executive function. The authors suggested that verbal fluency might have declined as a result of the deficits in self-activation associated with apathy (22).

Castelli *et al.* (29) administered the UPDRS item 4, the BDI, and the State Trait Anxiety Inventory (STAI) prior to surgery and 12-20 (average of 15 months) months after surgery. In contrast to the previous study, Castelli *et al.* did not detect a significant difference in apathy as assessed by item 4. The authors found that depression score modestly, but significantly improved and no difference was detected across time in anxiety score. They found a significant decrease in verbal fluency performance after surgery, and apathy levels did not correlate with verbal fluency changes. No correlations were found between dopaminergic medication reduction and mood changes (29).

In a second study by Castelli and colleagues (30), the authors examined apathy with the AES. They tested 19 bilateral STN patients prior to surgery and at an average of 17 months post surgery (range 13-23 months). They did not detect a significant difference between apathy scores pre and post-DBS (mean apathy AES scores pre = 11.6. ± 4.1., post = 12.6. ± 5.3). The authors evaluated individual patients by looking at changes greater than or equal to 1 standard deviation (e.g. in this case 4.1. points). They found that 31% (6/19) of PD patients had an increase in apathy over the follow-up period, 16% (3/19) had a decrease, and 53% (10/19) did not have a 4 point or greater change. They did not find a relationship between apathy and reduced levodopa dosage, or between apathy and verbal fluency performance. Similar to their previous study, they also found that depression scores modestly but significantly improved (30).

4. CONCLUSIONS

Examining all seven studies together, there were four reports of increases in mean apathy score from pre-surgery to post-surgery (22, 23, 26, 28), two reports that did not show a change from pre-surgery to post-surgery (29, 30), and one report of reduction in acute apathy when stimulators were switched from off to on (27). None of the examinations of chronic DBS found a significant improvement (reduction) in mean apathy scores across time. Although Castelli *et al.* (30) found that 16% (3/19) of patients had a reduction of 4 points or more in their apathy score, apathy scores for the majority of patients did not change (53%) or increased (31%). Therefore, it can be concluded that apathy is not improved by DBS surgery.

The study by Drapier and colleagues (26) is the most well controlled study due to their inclusion of a carefully matched control group. The authors compared a sample of wait list DBS candidates whose baseline apathy scores were not significantly different from the baseline scores of the pre-surgical DBS group. Then, they assessed the control group 9 months later and the DBS group 3 and 6 months post surgery. This was an important contribution to the literature because it allowed the comparison of postsurgical apathy to possible changes in apathy over time in a matched control group. Results from this study indicated that while control patients' apathy scores did not change, DBS patients' apathy scores increased from pre-surgery to 3 months and 6 months post-surgery.

5. PERSPECTIVES: METHODOLOGICAL LIMITATIONS & SUGGESTIONS FOR FUTURE STUDIES

A primary hypothesis for apathy changes after STN DBS is that motivational circuits are being affected by electrode placement or current spread. Yet only one study evaluated the relationship between electrode placement and apathy (26). Drapier *et al.* (26) reported that apathetic patients had placement more internally and ventrally in the STN than nonapathetic patients. Animal studies indicate that the limbic region of the STN is located more ventrally and internally than the motor region (13), and it is possible that stimulation affected limbic circuits in the apathetic patients. This needs to be investigated further, especially because the authors did not report their statistical analyses regarding these findings.

Another theory of apathy change after STN DBS has to do with the reduction in levodopa medication after the surgery. Although all of the studies demonstrated reductions in levodopa dosage following surgery (Table 1), only three out of seven examined the relationship between medication reduction and apathy (26, 29, 30). These studies did not find a significant relationship between reductions in levodopa and apathy.

Another approach to investigating possible mechanisms of apathy change after DBS involves exploring whether they co-occur with changes in cognition. Only one of the studies examining the relationship between apathy and the cognitive test most frequently reported to decline after surgery – verbal fluency – found a significant association (22). The other studies examining this relationship did not find a significant association (26, 29, 30).

There are a number of limitations in the literature on postsurgical apathy in PD. First, there are limitations in the number and breadth of studies available. Only 7 studies were found that quantitatively examined apathy changes after bilateral STN surgery and their breadth is severely limited by not including additional target sites (GPi) or type of electrode placements (unilateral vs. bilateral). Second, only one out of seven studies examined of the relationship between electrode placement and apathy (26). As a prevailing theory for apathy after DBS involves electrode placement and possible inadvertent stimulation of apathy circuits, it is extremely important to evaluate the location of the leads in apathetic versus nonapathetic individuals. Further, although studies reported reductions in levodopa dosage after surgery, most studies did not evaluate the association between the levodopa reduction and apathy.

The majority of studies did not include control groups. Control groups are necessary to tease apart changes over the disease course of PD from changes in apathy levels due to surgery. Currently, the degree of fluctuation in apathy level over the disease course of PD is not well understood. It may be especially important to use control groups to take into consideration potential "natural"

fluctuations. Ideally, control groups would consist of demographically matched PD patients that are also surgery candidates. This matching would reduce the variability between surgery and control groups and allow more clear conclusions to be drawn about the effects of surgery.

Finally, careful consideration should be given to the appropriate assessment of apathy. Recent research from our laboratory has indicated that the single item from the UPDRS (UPDRS item 4) does not have an adequate balance of sensitivity and specificity to accurately measure apathy (unpublished data from our laboratory, presented at the 2007 Parkinson's Study Group). Furthermore, it is not clear whether apathy scores can effectively be measured transiently using the AES as Czernecki *et al.* did, because the items are worded to assess longer-term symptoms. According to Starkstein, Ingram, Gaureau & Mizrah (31), apathy can be measured only after a long lapse of time with regard to patients' habits and behaviors.

If methodologically rigorous studies continue to replicate the results of increased apathy postsurgery, there are several important topics to consider. First, it is important to investigate whether the increase is clinically significant. Increases in apathy scores that reach statistical significance do not necessarily translate into day-to-day functional impairment. Future studies will need to examine what level of increase (e.g. 5 points, 6 points, etc) translates into reductions in quality of life for the patient. Further, calculating effect sizes and reliable change indices could be used to quantify the magnitude and clinical significance of the effect above and beyond simple statistical significance values.

It will be important to determine which patients are at increased risk for apathy postsurgery. It may be that certain patient characteristics, for example premorbidly high apathy and depression, or certain cognitive impairments predict risk for increase in apathy. This, in combination with determining how surgical parameters such as placement of the electrode affect apathy, will assist in determining which patients will have increased risk for apathy after DBS.

In conclusion, although progress has been made in understanding apathy symptoms following DBS surgery, there are still many issues to address in future research. Most importantly, additional sites (e.g. Gpi) need to be investigated and matched control groups need to be used. Measures should be taken to examine effect sizes and reliable change indices, the clinical meaning of statistical differences, and the relationship of apathy to electrode placement and levodopa reduction. We are confident that research on apathy after DBS surgery will continue to advance and will improve our understanding and treatment of PD.

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