

A clinical review of deep brain stimulation and its effects on limbic basal ganglia circuitry

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1. ABSTRACT

This paper aims to provide an overview of factors that may contribute to cognitive and mood alterations following DBS (and lesion therapy). A PubMed search based on studies in the English-language was undertaken, and included all publications on the topics of mood and surgery for movement disorders. Information was collected on preoperative and postoperative characteristics of each study, and study methodology was examined. One-hundred and forty published articles were selected and reviewed for mood and behavioral changes following neurosurgery for movement disorders.

A variety of mood and cognitive changes were associated with DBS (and lesion therapy). These alterations of behavior and cognition were seen in all targets but not frequently reported with thalamic DBS. However methodological limitations, small sample sizes, lack of control groups, and the heterogeneity of data reported underscore why interpretation and comparison of limbic effects of DBS remains challenging. The collection and reporting of more standardized minimal data sets will allow for future comparisons, and improve the power required to answer many of the questions raised in this review.

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2. INTRODUCTION

What do we know about deep brain stimulation (DBS) and its effects on limbic basal ganglia brain circuitry? Currently our understanding is largely based on a plethora of studies published in the medical literature. We aim in this paper to provide an overview of factors that may potentially contributing to cognitive and mood alterations following DBS.

We have additionally supplemented this exhaustive review with articles on lesion therapy including subthalamotomy, pallidotomy, leukotomy and temporal lobectomy. Since many lesion therapies have resulted in similar clinical outcomes the information may be complementary for understanding DBS.

Our hope in summarizing this colossal data set was to help to drive the movement toward more standardized data collection and reporting. This review reveals the difficulty in comparing studies that suffer from a lack of standardization of collection of data and of reporting of results.

3. METHODS

A PubMed search was undertaken including all publications on the topics of mood and surgical approaches to movement disorders. Information was collected on pre-operative as well as post-operative characteristics of the studies and on methodology. Key words utilized included “Limbic effects, Mood Changes, Cognitive Function, Depression, Mania, Anxiety, Hypomania, Neuropsychological state, Psychosis, Clinical Outcome, Safety, Aggression, Hallucinations, Confusion, Psychiatric Complications, Suicide, Behavioural Effects, Follow-up Studies, Quality of Life”.

These words were used in association with the term: “Deep Brain Stimulation (of one or more of the following targets: STN, GPi, Thalamus, Anterior Internal Capsule, Nucleus Accumbens), Subthalamotomy, Pallidotomy, Leukotomy Temporal Lobectomy”). Further studies were identified though a manual search of previous review articles, (153, 155-159). The search was based exclusively on publications in the English-language.

All studies were subsequently classified based on findings related to mood and cognition and specific factors were extracted to examine mood and cognitive changes. These factors included surgical target, unilateral or bilateral procedure, number of patients, gender, disease, disease duration, average age, postoperative medication reduction, postoperative imaging, past psychiatric history, timing of limbic effects, type of observed mood and cognitive changes, management of limbic effects, preoperative screening methods, and deep brain stimulator programming (amplitude, pulse width, frequency).

One-hundred and forty published articles were selected and reviewed for mood and behaviour changes following surgery for movement disorders.

The following selection criteria were applied: 1) Articles mentioning in the title specifically cognitive, mood and behaviour within the context of DBS. 2) Follow-up studies for a) verification if limbic effects were reported and b) for analysis of the mood and cognitive effects. 3) Studies reporting on clinical outcome following DBS, with mood and cognitive status assessments made as a mandatory part of the clinical evaluation in the pre- and postoperative setting.

Eighty-three studies reported on STN DBS, sixteen on GPi DBS, five on anterior limb of the internal capsule and nucleus accumbens DBS, five on thalamic DBS, two studies on subthalamotomy, twenty-five on pallidotomy and nine on leukotomy and temporal lobectomy. The few articles reporting on multiple targets were classified in function of the selected target. (The studies on lesion therapy are presented separately in the Appendix section).

For each target and procedure, the analysed findings were organized in the “Results” section and in tables and were divided into the following topics: “General Characteristics, Alterations in Mood and Behaviour, Timing of Limbic Effects, Cognitive Assessment by Verbal Fluency Test, Past Psychiatric History, Postoperative Medication Reduction, Post-operative Imaging, Management of Limbic Alterations, Pre- and Post-operative “on and off” Assessment and Pre-surgical Screening”. For the “on and off” conditions of DBS, we classified all studies according to preoperative and postoperative assessment, detailing which outcome was evaluated: the UPDRS, cognitive, neuropsychological or other clinical variables. Percentages were not always available to display a reference to the total number of studies (related to a particular target). Our summary data is shown therefore in relation to the number of studies which examined a variable(s) of interest (for a specific target). This method was necessary because of the lack of systematic reporting that was encountered during the review.

The changes in mood and cognition were classified, into acute and long-term manifestations. A few selected studies, that discussed topics more exhaustively, were presented in more detail in the section “Neuropsychiatric Complications: Acute and Long Term Effects of Neurosurgery”.

4. RESULTS

There were a variety of mood and cognitive changes that were associated with both DBS and lesion therapy. These alterations of behaviour and cognition were seen in all targets (STN, GPi, anterior limb of the internal capsule, nucleus accumbens), but not frequently reported with thalamic DBS. While pallidotomy seemed associated with multiple neuropsychiatric complications, no changes of mood and behaviour were reported with subthalamotomy. This may have been due to insufficient data and a small sample size. The most consistent findings across studies included depression, confusion

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and mania. The perception that STN DBS more likely induced mood and behavioural changes was at least partly biased by the large number of available STN DBS studies in comparison to other DBS targets. Furthermore GPI DBS studies had considerably smaller sample sizes and shorter follow up durations. This review supported the notion that acute neuropsychiatric changes, as seen in the intraoperative and immediate postoperative period, were associated with DBS in many cases, with misplaced contacts as one potential cause. Alterations that occurred with longer-term follow up seemed associated with disease progression and medication changes. It has been previously suggested that neuropsychiatric symptoms related to DBS may be transient and treatable (155). Our review demonstrated a lack of systematic reporting in the management of these side effects.

The current literature was inconclusive in predicting mood and behavioural side effects. This was mainly due to the heterogeneity of pre-operative screening methods and selection criteria. There was a lack of detailed reporting on precise lead locations in relation to clinical outcome. Postoperative imaging was undertaken in most studies mainly to exclude complications and to formally assess lead location. We will present the main findings of our systematic review, but we concede that it is both difficult and also challenging to develop themes from what is currently reported. We report the data in a systematic way and provide tables so that readers interested in a particular topic can easily reference the material.

4.1. STN DBS (Table 1 and Table 2)

4.1.1. General characteristics

Eighty-three studies reported on findings relative to STN DBS (1-46, 82, 91-100, 103, 108, 110-130, 137-139).

The sample size of the studies varied, from case reports, as in eleven percent or 9/83 of studies (3, 12, 14, 20, 24, 27, 92, 96, 126) to case series as large as 96 subjects (15).

Indication for STN DBS across studies was idiopathic Parkinson's disease ($n = 83$) and the disease duration was 14.28 years ($SD = 3.56$), with an average age of patients operated being 57.7 years ($SD = 6.29$).

Surgical procedures were mostly bilateral, for ninety six percent or 80/83 of studies (1-18, 21-29, 31-39, 40-46, 82, 91-100, 103, 108, 110, 111-119, 121-129, 137-139) with three presenting unilateral data (20, 30, 124).

4.1.2. Presurgical screening

Pre-surgical screening methods varied among studies.

In sixty-three percent or 52/83 of studies, the "Unified Parkinson's Disease Rating Scale", UPDRS, was applied (1, 7, 8, 9, 10, 13, 16, 19, 21, 22, 23, 26, 30, 31, 34, 35, 36, 37, 38, 39, 40, 43, 44, 45, 92, 93, 94, 95, 96, 98,

100, 103, 108, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 121, 123, 124, 125, 129, 130, 137, 138).

In only twenty-four percent or 20/83 of studies, the "Mini Mental State Examination", MMSE, was used (4, 6, 8, 9, 25, 27, 31, 32, 43, 91, 94, 96, 100, 108, 122, 124, 126, 128, 130, 138) and in nineteen percent or 16/83 of studies, the Mattis Dementia rating Scale (MDRS) was administered (1, 6, 7, 9, 15, 26, 27, 33, 41, 45, 91, 99, 110, 116, 126, 129). Finally other pre-operative evaluation tests were used in seventy-five percent or 62/83 of studies (1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 40, 42, 43, 45, 46, 91, 92, 93, 94, 95, 96, 97, 99, 103, 110, 111, 112, 113, 114, 116, 117, 118, 121, 122, 124, 127, 128, 129, 130, 138).

4.1.3. Past psychiatric history

The past psychiatric history was classified as present or absent prior to surgical therapy. We also considered the presence or absence of limbic effects following surgery.

Fifty-two percent of studies documented at least some elements of a past psychiatric history.

The majority of articles, forty percent or 33/83 of studies, reported no significant elements of the past psychiatric history (4, 5, 10, 12, 24, 25, 26, 27, 29, 31, 32, 35, 36, 37, 41, 42, 43, 45, 91, 92, 93, 95, 98, 100, 108, 110, 111, 112, 116, 117, 121, 127, 130). Fewer studies, twelve-percent or 10/83 (1, 3, 18, 19, 20, 22, 23, 97, 98, 121) noted the presence of a potentially significant past psychiatric history.

All ten studies documenting a potentially significant past psychiatric history reported the manifestations of at least some limbic symptoms following intervention (1, 3, 18, 19, 20, 22, 23, 97, 98, 121). However in twenty-seven percent or 22/83 of studies (4, 12, 24, 26, 27, 29, 31, 32, 35, 36, 37, 41, 42, 43, 45, 91, 92, 98, 100, 117, 121, 139), there was a failure to comment on the past psychiatric history and mood and behaviour alterations were thought by the authors to be secondary to DBS.

4.1.4. Cognitive assessment by verbal fluency test

The cognitive domain in STN DBS patients, assessed by the verbal fluency test, revealed a post-operative worsening in nineteen-percent of studies (8, 9, 11, 12, 39, 41, 42, 43, 46, 82, 91, 94, 95, 97, 108, 110).

4.1.5. Preoperative "on and off" assessment

The pre-operative and post-operative assessments were applied across studies for various purposes (clinical, neuropsychological, cognitive, motor, UPDRS) and were performed in a multitude of "on-off" DBS/medication states.

In thirty-nine percent or 32/83 of studies, the UPDRS was applied in "on-off" medication settings (2, 6, 16, 22, 23, 28, 30, 33, 34, 35, 36, 37, 39, 94, 95, 96, 98, 100, 103, 111, 112, 113, 114, 115, 117, 118, 119, 120, 121, 123, 124, 138).

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Table 1. Limbic Manifestations following STN DBS

Sample size	Disease	Target	Postoperative On-Off Status	Screening MDRS MMSE UPDRS Other	Limbic Effects	References
20	Parkinson's Disease	Bilateral STN	UPDRS: Off M/On-Off S	No Yes No Yes	1. Hypomania 2. Mania	4
18	Parkinson's Disease	Bilateral STN	UPDRS Assessment: Off M/On S Off M/Off S On M/Off S On M/On S	Yes No Yes Yes	Depression	23
48	Parkinson's Disease	Bilateral STN	Motor Assessment: Off M/Off S Off M/On S On M/Off S On M/On S	Yes No Yes No	1. Transient confusion 2. Psychosis 3. Hypomania 4. Depression	26
3	Parkinson's Disease	Bilateral STN	Motor assessment: On-Off M/On S	No No No Yes	Mania	29
26	Parkinson's Disease	Bilateral STN	Clinical Assessment: Off M/On S Off M/On S On M/Off S On M/On S	No No Yes Yes	1. Confusion 2. Depression 3. Hallucination	35
77	Parkinson's Disease	Bilateral STN	Clinical Assessment: Off M/On S	Yes No No No	1. Aggressive impulsive episodes 2. Suicide 3. Apathy 4. Depression 5. Psychosis 6. Hypomania	41
37	Parkinson's Disease	Bilateral STN	Motor Assessment: Off M/Off S Off M/On S On M/Off S On M/On S	Yes No Yes Yes	1. Disinhibition 2. Depression 3. Progressive cognitive deterioration 4. Apathy 5. Hallucinations 6. Psychosis 7. Aggressive behaviour 8. Suicide attempt	45
65 (Initially included 72 patients: Seven patients lost to follow up)	Parkinson's Disease	Bilateral STN	UPDRS Assessment: On-Off M/On-Off S	No No Yes Yes	1. Worsening of depressive symptoms 2. Anxiety 3. Worsening of Obsessive-Compulsive symptoms 4. Psychosis 5. Apathy 6. Cognitive decline	95
24	Parkinson's Disease	Bilateral STN	Clinical Assessment: On-Off M/On-Off S	No No No Yes	1. Worsening of depression 2. Transiently suicidal ideation 3. Delirium	97
23 STN: 12 GPi: 11	Parkinson's Disease	Bilateral STN Bilateral GPi	Clinical Assessment: On M/On S	No Yes Yes No	1. Mild delirium 2. Transient anxiety 3. Hallucinations	100
22	Parkinson's Disease	Bilateral STN	UPDRS Assessment: Off M/Off S Off M/On S On M/Off S On M/On S	No No Yes No	Intraoperative: 1. Transient psychotic reaction (with hallucinations and delusions). Postoperative: 1. Increased sexuality 2. Depression	125
49	Parkinson's Disease	Bilateral STN	Neuropsychological Assessment: On-Off M/On S	Yes No Yes Yes	3 months postoperative: 1. Delirium 2. Impulsive aggressive behaviour 3. Hypomania 4. Dementia 5. Apathy 6. Hypomania 3 months-5 years postoperative: 1. Depression 2. Suicide attempts 3. Hallucinations 4. Psychosis 5. Apathy 6. Hallucinations 7. Dementia 8. Apathy	129
2	Parkinson's Disease	Case 1 and 2:	Clinical Assessment:	No No Yes No	Mania	98

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		Bilateral STN Case2: Previous left sided pallidotomy	On M/Off S			
2	Patient 1: Severe rigid-akinetic PD Patient 2: Severe PD	Bilateral STN	Clinical Assessment: On S	No No Yes Yes	Mania	121
1	Parkinson's Disease	Bilateral STN	Neuropsychological Assessment: On-Off S	No No No Yes	1. Apathy 2. Dysphoria 3. Profound anhedonia, 4. Blunted affect.	3
1	Parkinson's Disease	Bilateral STN	NM	No No No Yes	1. Hypomania 2. Mania 3. Psychosis	12
1	Parkinson's Disease	Unilateral, left STN	Cognitive Assessment: On/Off S	No No No Yes	1. Fear 2. Panic 3. Anxiety	20
1	Parkinson's Disease	Bilateral STN	Motor Assessment: On M/On-Off S	No No No Yes	1. Depression 2. Hypo-mania	24
1	Parkinson's Disease	Bilateral STN	Clinical Assessment: On S	Yes Yes No No	Aggression	27
1	Parkinson's Disease	Bilateral STN	UPDRS Assessment: On-Off M	No No Yes Yes	Mania	92
1	Parkinson's Disease	Bilateral STN	Clinical Assessment: Off M/On S	No Yes No No	Visual hallucinations Off S: Hallucinations disappeared. On S: Hallucinations appeared.	126

S = Stimulation, M = Medication, UPDRS = Unified Parkinson's Disease Rating Scale, On-Off = On and Off

Neuropsychological assessment was carried out in eighteen percent or 15/83 of studies (3, 5, 10, 11, 12, 15, 21, 32, 43, 93, 99, 108, 110, 116, 129).

Eight percent or 7/83 of studies, reported on the “clinical” evaluation of the subjects (17, 27, 40, 41, 97, 125, 137).

Motor function was evaluated in fourteen percent or 12/83 of studies (1, 7, 9, 13, 24, 25, 26, 29, 38, 44, 45, 46).

In nine percent or 8/83 of studies, the details of the subjects assessment were not specified (4, 19, 92, 122, 126, 127, 128, 137).

4.1.6. Postoperative imaging

Post-operative imaging was documented in a relative small number of STN DBS studies.

Only forty-seven percent or 39/83 of studies (1, 3, 9, 11, 13, 14, 16, 17, 18, 19, 20, 21, 23, 25, 27, 29, 32, 35, 36, 38, 40, 41, 44, 46, 92, 93, 94, 95, 108, 110, 111, 112, 114, 118, 121, 124, 126, 128, 138, 139) documented the performance of post-operative imaging, and this was obtained in most cases to exclude complications and/or to verify lead location. Almost all studies failed to describe in detail their applied methodology.

4.1.7. Postoperative “on and off” assessment

The postoperative assessment was performed in thirty-six percent or 30/83 of studies using the UPDRS (2, 4, 6, 16, 22, 23, 28, 30, 33, 35, 36, 37, 39, 92, 94, 95, 96, 98, 103, 111, 113, 114, 117, 118, 119, 120, 123, 125, 127, 138).

A neuropsychological assessment was documented in seventeen percent or 14/83 of studies (3, 5, 7, 10, 11, 15, 32, 41, 99, 108, 110, 116, 122, 129).

Fourteen percent or 12/83 of studies mentioned a “clinical” assessment (12, 17, 27, 34, 40, 96, 97, 98, 100, 121, 126, 137).

Motor functioning was examined in thirteen percent or 11/83 of studies (1, 9, 13, 24, 25, 26, 29, 38, 44, 45, 46).

Fewer studies, ten percent or 8/83, specified the “on-off” conditions for the cognitive state assessment (1, 8, 14, 18, 19, 20, 91, 130).

Four percent or 3/83 of studies, did not mention details of the patient’s assessment (12, 92, 124).

4.1.8. Postoperative medication reduction

Analysis of postoperative medication reduction yielded following results:

The majority of studies, seventy-percent or 58/83 (1, 4, 6, 7, 8, 9, 10, 12, 16, 21, 22, 23, 24, 25, 26, 29, 30, 31, 33, 34, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 82, 91, 92, 93, 94, 95, 97, 98, 100, 103, 108, 110, 111, 112, 114, 117, 119, 120, 121, 122, 123, 124, 125, 126, 129, 137, 138), documented medication reduction in the post-operative period. In four studies no medication reduction occurred in the postoperative phase (11, 27, 28, 96). The remaining twenty-three percent of studies, did not remark on the post-surgical pharmacological management. When post-surgical medication reduction was documented, sixty-seven percent or 38/57 of studies (1, 4, 7, 9, 12, 16, 21, 22, 23, 24, 26, 29, 31, 36, 37, 38, 39, 41, 42, 43, 45, 82, 91, 92, 93, 95, 97, 98,

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Table 2. STN DBS surgical parameters

Amplitude	Pulse Width	Frequency	Postoperative Imaging	References
At 3 months: Mean V: Right: 1.8. +/- 0.6. V// Left: 1.9. +/-0.9. V At long-term: Mean V: Right: 2.6.+/-0.8. V// Left: 2.6. +/- 0.9 V	At 3 months: Right: 333.2,+/-126.8. msec// Left: 188.7.+/-139.7. msec At long-term: Right: 169.3,+/-62.9. msec// Left: 177.7.+/-90.6. msec	At 3 month: Right: 134.5.+/-14.0. Hz// Left: 141.6.+/-23.0. Hz At long-term: Right: 169.3.+/-62.9. Hz// Left: 177.7.+/-90.6. Hz	NM	4
2.9. +/- 0.4. V	68 +/- 13 msec	140 +/- 16 Hz	Yes	23
At 6 months: 2.9. +/- 0.6. V At 12 months: 3.1. +/- 0.6. V At 24 months: 2.9. +/- 0.6. V	At 6 months: 134 +/- 12 msec At 12 months: 136 +/-14 msec At 24 months: 137 +/- 10 msec	At 6 months: 62 +/- 9 Hz At 12 months: 62 +/- 9 Hz At 24 months: 66 +/- 12 Hz	NM	26
2-3.2. V	60msec	130 Hz	Yes	29
At 12 months: 3.1. V +/- 0.4.	At 12 months: 60 msec	At 12 months: 130-200 Hz	Yes	35
In patient with depression: Right: 2.4. V Left: 2.6. V In patient with positive PPH: Right: 3.6. V Left: 3.2. V	In patient with depression: Right: 60 msec Left: 60 Hz In patient with positive PPH: Right: 90 msec Left: 90 msec	In patient with depression: Right: 130 Hz Left: 130 Hz In patient with positive PPH: Right: 185 Hz Left: 185 Hz	Yes	41
At 6 months: Right: 2.6. V Left: 2.7. V At 24 months: Right: 2.7. V Left: 2.9. V At 60 months: Right: 2.8. V Left: 2.9. V	At 6 months: Right: 61 msec Left: 65 msec At 24 months: Right: 63 msec Left: 63 msec At 60 months: Right: 64 msec Left: 62 msec	At 6 months: Right: 148 Hz Left: 157 Hz At 24 months: Right: 151 Hz Left: 153 Hz At 60 months: Right: 150 Hz Left: 148 Hz	NM	45
Right: 3.3. V Left: 3.3. V	Right: 67.5. msec Left: 68.5. msec	NM	Yes	95
NM	NM	NM	NM	97
NM	NM	130-180Hz	NM	100
At six months: 1.8.5 +/-0.2.9 V At last FU: 2.9.2 +/-0.3.5 V	NM	NM	NM	125
At 1 year: 2.8.+/-0.6.V At 5 years: 3.1.+/- 0.4.V	At 1 year: 61+/-6 msec At 5 years: 64+/-12 msec	At 1 year: 143+/-19Hz At 5 years: 145 +/- 19 Hz	NM	129
Case 1: Right: 2.0.V Left: 1.8.V Case2: Right: 1.7.V Left: 1.3.V	Case 1 and 2: 90 msec	NM	NM	98
NM	NM	NM	Yes	121
Left: 3.3.V Right: 2.5. V	Left: 60 msec Right: 60 msec	Left: 145 Hz Right: 130 Hz	Yes	3
Right:2.6. – 3.5. V Left: 2.2. –3.7. V	60 msec	130 Hz	NM	12
1.5. V	90 msec	130 Hz	Yes	20
2.4. V	60 msec	130 Hz	NM	24
2V	60 msec	140 Hz	Yes	27
2.2. V – 2.5. V	60 msec	130 Hz	Yes	92
3.5. V	60 msec	130 Hz	Yes	126

V = Volt, Hz = Hertz, msec = milliseconds, FU = Follow up, NM = Not mentioned, PPH = Past Psychiatric History

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Table 3. Limbic manifestations following GPI DBS

Sample size	Disease	Target	Postoperative On-Off Status	Screening MDRS MMSE UPDRS Other	Limbic Effects	References
16	Dystonia	Bilateral GPi	Neuropsychological Assessment: On-Off M/On S	No No No Yes	Suicide	50
11	Parkinson's disease	Bilateral GPi	Clinical Assessment: Off M/Off S Off M/On S On M/Off S On M/On S	No No Yes No	Manic psychosis	52
15	Dystonia	Bilateral GPi	NM	Yes No No Yes	NM	54
1	Parkinson's disease	Bilateral GPi	Neuropsychological Assessment: On M/On S	No No Yes Yes	(Hypo-) Mania	48

“-“ = and, “?” = “and”, S = Stimulation, M = Medication, NM = Not mentioned

Table 4. GPI DBS surgical parameters

Amplitude	Pulse Width	Frequency	Postoperative Imaging	References
Patient 1: 1.7. V Patient 2: 3.7. V	Patient 1: 60 msecs Patient 2: 90 msecs	Patient 1: 180 Hz Patient 2: 185 Hz	Yes	50
3.4. +/- 0.6. V	163.6. +/- 85.2. msecs	175.2. +/- 19.8. Hz	NM	52
3.1.V	106.0. msec	142.3. Hz	Yes	54
NM	NM	NM	Yes	48

V = Volt, msecs = milliseconds, Hz = Hertz, NM = Not mentioned

100, 110, 112, 117, 119, 120, 121, 122, 129, 137), annotated mood and behavioural alterations following DBS.

4.1.9. Timing of limbic effects

Limbic symptoms seemed to occur most frequently in the postoperative period, in eighty-eight percent of studies. In our analysis we subdivided the postoperative period into days, weeks, months and years as this resulted in further clarity on this issue. In eight percent or 5/59 of studies, limbic manifestations were reported after weeks of surgery (5, 9, 22, 97, 117) and in fourteen-percent or 8/59 of studies, they occurred years after DBS (1, 4, 18, 19, 39, 43, 95, 96). Fewer studies, 5 percent or 3/59, described limbic alterations within the first few days following surgery (13, 29, 121). In twelve percent or 7/59 of studies (2, 3, 26, 27, 35, 115, 125), limbic effects were reported in the intra-operative and immediate post-operative period. Tabulation revealed that the postoperative period was the time of occurrence of alterations in mood and behaviour, in fifty-four percent or 32/59 of studies, but there were no further specifics in these studies defining the period (7, 15, 21, 23, 26, 28, 31, 32, 35, 36, 37, 38, 41, 42, 45, 82, 91, 94, 98, 99, 100, 111, 112, 114, 119, 120, 122, 126, 129, 130, 137, 138).

4.1.10. Alterations in mood and behaviour

Seventy-one percent or 59/83 of studies reported on limbic manifestation following STN DBS (1-5, 7, 9, 12-15, 18-23, 26-29, 31, 32, 35-39, 41-43, 45, 82, 91, 92, 93, 95-100, 103, 108, 111-115, 117, 119-122, 125, 126, 129, 137, 139). The limbic effects were variable across all studies. Mood disorders were reported in thirty-seven percent or 22/59 of studies (3, 9, 22, 23, 24, 26, 30, 35, 38, 39, 41, 43, 45, 93, 95, 96, 97, 119, 120, 122, 125, 129) psychotic symptoms in twenty-seven percent or 16/59 of studies (18, 23, 26, 28, 32, 35, 41, 45, 95, 96, 97, 100, 119, 125, 126, 129) and in fifty-four percent or 32/59 of studies confusion, hypomania and mania were reported (4, 12, 14, 15, 19, 24, 26, 29, 31, 32, 34, 36, 37, 41, 42, 43, 82, 91, 92, 93, 96, 98, 112, 114, 117, 119,

120, 121, 125, 129, 137). Suicide (attempted and ideation) was remarked on in twelve percent or 7/59 of studies (18, 22, 41, 95, 97, 119, 129). Anxiety and aggression were seen in twenty percent or 12/59 of studies following DBS (2, 7, 10, 27, 41, 45, 95, 96, 100, 111, 117, 129). Laughter and pseudobulbar crying were each reported one time (13, 20). Improvement of previous psychiatric symptoms was indicated in eight percent or 5/59 of studies (5, 95, 108, 113, 119).

4.1.11. Management of limbic alterations

In fifteen percent or 9/59 of studies limbic effects were managed through a change in DBS programming (3, 13, 22, 24, 27, 92, 98, 117, 121, 139), and in thirty-one percent or 18/59 of studies through a pharmacological approach. The medication change was poorly documented in all studies (14, 18, 20, 22, 23, 26, 29, 32, 35, 36, 41, 96, 97, 100, 112, 121, 122, 126). Spontaneous resolution of symptoms was present in seven-percent or 4/59 of studies (26, 31, 35, 100), while irreversible alterations were reported in only two studies (26, 36).

4.2. GPi DBS (Table 3 and Table 4)

4.2.1. General characteristics

Sixteen studies on GPi DBS were located and reviewed (11, 47, 48, 49, 50, 51, 52, 53, 54, 76, 101, 104, 109, 131, 132, 133).

The sample sizes for studies varied from case reports (48, 49, 132) to 20 total subjects (109).

The indication for GPi DBS was Parkinson's disease in fifty percent or 8/16 of studies (11, 47, 51, 52, 53, 76, 104, 109) with a disease duration of 12.8 years (SD = 2.20) across studies, and an average age of subjects of 53.1 years (SD = 7.40). Dystonia was the indication in twenty-five percent or 4/16 of studies (50, 54, 131, 133) with an average disease duration of 15 years (SD = 4.2) and an average age of subjects of 41.3 years (SD = 8.05). GPi DBS was also applied in Tourette's syndrome (with associated OCD) in one study

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(132) in a sixteen year old subject with a disease duration of twelve years.

GPI DBS was bilateral in sixty-eight percent or 11/16 of studies (11, 48, 49, 50, 52, 53, 54, 101, 131, 132, 133), and unilateral in twenty-five percent or 4/16 of studies (47, 76, 104, 109). One study had both unilateral and bilateral cases (51).

4.2.2. Preoperative screening

A significant heterogeneity was seen with regard to the applied screening methods.

The MDRS was applied in twenty five percent or 4/16 of studies (49, 53, 54, 104). In further twenty five percent or 4/16 of studies the UPDRS (48, 52, 104, 109), was used for screening. The MMSE was applied in nineteen percent or 3/16 of studies (49, 51, 109). Other screening tools, in varying combination were utilized in eighty-one percent or 13/16 of studies (48, 11, 50, 51, 53, 54, 76, 101, 104, 109, 131, 132, 133).

4.2.3. Past psychiatric history

Past psychiatric history was rarely mentioned in GPI studies with seventy-five percent or 12/16 of studies (11, 49, 51, 52, 53, 54, 76, 101, 104, 109, 131, 133) failing to mention this factor. In thirteen percent or 2/16 of studies (50, 132), it was annotated as positive and in another thirteen percent (47, 48) it was remarked as being absent.

4.2.4. Cognitive assessment by verbal fluency test

The verbal fluency test worsened in the post-operative period in seventy-eight percent or 7/9 of studies (47, 11, 49, 53, 101, 104, 133), was unchanged in two (54, 109), and not mentioned in the remaining studies (48, 50, 51, 52, 76, 131, 132).

4.2.5. Preoperative “on and off” assessment

The pre-operative assessment of subjects occurred in a variety of “on-off” medication conditions.

Neuropsychological evaluation was pursued in four studies (11, 47, 49, 109).

UPDRS/motor score was applied for assessment in seven studies (51, 52, 53, 76, 124, 131, 133).

Five studies did not report on the assessment settings (48, 50, 54, 104, 132).

4.2.6. Postoperative imaging

Post-operative imaging was sought in fifty-six percent or 9/16 of studies (11, 48, 49, 50, 51, 53, 54, 131, 133), while in the remaining forty-four percent of studies it was not mentioned (47, 52, 76, 101, 104, 109, 132).

4.2.7. Postoperative “on and off” assessment

For the postoperative assessment, in fifty-six percent or 9/16 of studies the “on-off” DBS/medication state was applied within the context of a neuropsychological evaluation (11, 48, 47, 49, 50, 54, 101, 104, 109). For fifty-percent or 8/16 of studies the

UPDRS/motor score was applied (51, 52, 53, 76, 124, 131, 132, 133).

4.2.8. Postoperative medication reduction

Medication reduction in the postoperative period was reported on in twenty five percent or 4/16 of studies (48, 49, 54, 131), while in only six percent there was clear documentation of lack of medication reduction following DBS (51). Two studies reported an increase in medication in the post-surgical period (52, 133). And in fifty-six percent or 9/16 of studies (11, 47, 50, 53, 76, 101, 104, 109, 132), there was no comment on the details of pharmacological management.

4.2.9. Timing of limbic effects

The time period for occurrence of limbic and behavioural manifestations was variable (48, 50, 52, 101). One study mentioned days to weeks following DBS (48). Another cited weeks (50) and one mentioned loosely “months” after DBS (101). In two studies effects were reported years following the intervention (50, 52).

4.2.10. Alterations in mood and behaviour

Alterations in mood and behaviour following GPI DBS were reported in thirty-one percent or 5/16 of studies (48, 52, 50, 54, 76). Mania and hypomania were observed in forty percent or 2/5 of studies (48, 52), and suicide was reported only once (50). Mild improvement of depression was commented on in forty percent or 2/5 of studies (54, 76).

4.2.11. Management of limbic effects

Only two studies reported on the management of mood and behaviour following DBS. Pharmacological treatment was mentioned once (48) and switching to STN DBS was mentioned in one study (52).

4.3. DBS of anterior internal capsule and nucleus accumbens (Table 5 and Table 6)

4.3.1. General characteristics

Five studies were reviewed (57, 58, 59, 60, 160). Studies were largely case reports (57, 59, 60) with one study reporting on six subjects (160). Obsessive compulsive disorder was the main indication for surgery in three studies (59, 60, 160). Severe anxiety disorder and obsessive compulsive disorder was addressed in one study (58) and Tourette’s syndrome was the indication for surgery in one study (57). Bilateral anterior limb of the internal capsule DBS was performed twice (57, 160). Unilateral nucleus accumbens DBS (58) and bilateral anterior internal capsule and region of the nucleus accumbens DBS were utilized once each (59, 60).

4.3.2. Preoperative screening

All four studies applied variable pre-and postoperative screening methods, other than the MDRS, MMSE and UPDRS.

4.3.3. Preoperative “on and off” assessment

The preoperative “on-off” medication assessment was not mentioned in three studies (57, 58, 160). One study clearly assessed “on” medication state (59).

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Table 5. Limbic manifestations following anterior internal capsule, nucleus accumbens DBS

Sample size	Disease	Target	Postoperative On-Off Status	Limbic Effects	References
4	1. Severe anxiety disorder 2. OCD	Unilateral NA: Right	Clinical Assessment: On S	Improvement of anxiety and OCD symptoms	58
1	OCD	Bilateral NA and AIC	Clinical Assessment: Off S	1. Fear 2. Panic 3. Elevated mood	59
1	OCD	Bilateral AIC and NA	Clinical Assessment: On S	Half-smile	60
1	Tourette syndrome	Bilateral AIC	Clinical Assessment: On S	1. Apathy 2. Depression 3. Hypomania	57

OCD = Obsessive Compulsive disorder, AIC = Anterior internal capsule, NA = Nucleus Accumbens, S = Stimulation

Table 6. Anterior internal capsule, nucleus accumbens dbs surgical parameters

Amplitude	Pulse Width	Frequency	Postoperative Imaging	References
2-6.5.V	90 msec	130 Hz	NM	58
6V	210 msec	135 Hz	Yes	59
2V	210 msec	185 Hz	Yes	60
5 V	160 msec	130 Hz	Yes	57

V = Volt, msec = milliseconds, Hz = Hertz

4.3.4. Post-operative imaging

Postoperative imaging was undertaken in four studies (57, 59, 60, 160) and not mentioned in one (58).

4.3.5. Post-operative “on and off” assessment

In the postoperative period subjects were assessed in the “on” stimulation condition in four studies (57 - 60) and in the “on and off” stimulation state in one study (160).

4.3.6. Postoperative medication reduction

The postoperative pharmacological management was not specifically reported in any study (57 – 60, 160).

4.3.7. Timing of limbic effects

Alterations in mood and behaviour were observed in the intra-operative period in two studies (59, 60) and in the postoperative period in two further studies (57, 160). Timing was not mentioned in one study (58).

4.3.8. Alterations in mood and behaviour

Mild apathy, depression and hypomania were each reported one time (57). Fear and panic with stimulation through the deepest contact, while euphoria and slightly hypomania with stimulation through more dorsal contacts was documented in a single study (59). A predominately contralateral smile to the stimulating electrode reported in two studies (60, 160) was quantitated in one study (60). One study reported on the nearly total abatement from anxiety and OCD symptoms following surgery (58), and two studies documented improvement in the overall clinical presentation (57, 59).

4.3.9. Management of limbic manifestations

Three studies reported that the limbic effects could be managed through turning off the DBS (59, 60, 160).

4.4. DBS of thalamus

4.4.1. General characteristics

Five studies were reviewed (55, 56, 76, 102, 105). The sample sizes varied from six subjects (55) to

thirty-eight subjects (105). Thalamic DBS was undertaken in four studies (55, 56, 76, 102, 105). Unilateral DBS was reported in three studies (55, 56, 105), bilateral DBS in one (102).

The indication for surgery was advanced Parkinson’s disease (55, 56, 76, 102) with an 8.6 year (SD = 1.9) average disease duration and an average age of subjects of 55.8 years (SD = 21.9). Essential tremor studies (102, 105) had a disease duration of 12.5 years (SD = 2.12) and an average age of 68.5 years (SD = 9.19).

4.4.2. Preoperative screening

For screening the MDRS was mentioned twice (55, 102), the UPDRS assessments twice (56, 102) and the MMSE once (102).

4.4.3. Preoperative “on and off” assessment

Neuropsychological preoperative assessment was pursued in three studies (55, 56, 105) and UPDRS in one (76).

4.4.4. Postoperative imaging

The postoperative pharmacological treatment was not documented in all five studies. Postoperative imaging was documented in only one study (55).

4.4.5. Postoperative “on and off” assessment

In the postoperative setting, a neuropsychological assessment was pursued in three studies (55, 102, 105). Motor and UPDRS were used in two (56, 76).

4.4.6. Postoperative medication reduction

The postoperative pharmacological treatment was not documented in all five studies.

4.4.7. Alterations in mood and behaviour

No limbic manifestations were reported. One study observed an improvement in mood and anxiety symptoms following surgery (55), while a second study annotated that no significant postoperative changes with regard to the mood state were observed (76).

5. NEUROPSYCHIATRIC COMPLICATIONS: ACUTE AND LONG TERM EFFECTS ON MOOD AND COGNITION OF DBS

5.1. STN DBS and limbic manifestations

5.1.1. Acute changes with STN DBS

5.1.1.1. STN DBS inducing depression

Stefurak *et al.* described (3) a single patient experiencing mood changes induced within thirty seconds of commencing stimulation through the right lower contacts (the 0 and 1 cathodal contacts). The mood alterations manifested were apathy, dysphoria, profound anhedonia and blunted affect. When stimulation was terminated the mood returned to baseline. The patient was diagnosed with depression at age twelve and had a lifetime bout with symptoms over the next twenty-two years. She was treated with medication and electroconvulsive therapy and reported to be free of psychiatric symptoms at the time of assessment for DBS. Reconstruction and stereotactic transformation of the T1 MRI showed the left electrode within the inferior STN, whereas the right electrode was marginally superior and lateral to the STN within the fields of Forel and zona incerta.

Blood-oxygen-level-dependent (Bold) signal changes were observed within the motor areas with left DBS whereby right DBS evidenced changes in the superior prefrontal cortex, anterior thalamus, caudate and brainstem and had marked and widespread decreases in medial prefrontal cortex. The mood alterations disappeared spontaneously within four weeks without change in stimulation parameters.

A direct relationship between stimulation and alteration in mood was also described by Bejjani *et al.* (24). Profound sadness, guilt, sense of uselessness and hopelessness were observed within five seconds after stimulation through the left inferior contact (cathodal 0). The symptoms disappeared after approximately 90 seconds after turning off the device. The contacts were identified on MRI T1-weighted images, and by the use of the Schaltenbrand and Wahren atlas. The left contact 0 was located central to the substantia nigra, with contacts 1 and 2 located in the STN. Stimulation through the two dorsal contacts ameliorated the motor symptoms. PET (Positron-Emission-tomography) studies in “on-off” stimulation setting with the patient blinded to the stimulation conditions resulted in an induction of symptoms when using the left inferior contact, correlated to an increased blood flow in the right parietal lobe, orbitofrontal cortex, left GPi, left amygdala and anterior thalamus. These changes were associated with a clinically depressed mood.

5.1.1.2. STN DBS inducing mania

Kulisevsky *et al.* reported (29) manic symptoms one day following bilateral STN DBS, in three of fifteen treated subjects. The psychiatric history was annotated as absent in all three subjects. The T1 weighted MRI evidenced electrode placement in the midbrain, caudal to the STN (contact 0). The precise position of the tip of the electrode could not be exactly determined due to electrode induced artifact. Limbic-related regions, such as the

(orbito-) frontal cortex and thalamus, were spared by the electrode trajectory. The manic state in all three subjects could be reproduced by stimulation through the lower or more ventral contacts. Complete disappearance of the manic state was achieved after modifying the stimulation to “higher” or more dorsal contacts. In a recent study (139), using a three-dimensional histological atlas of the human basal ganglia, contact 1, inducing hypomanic behaviour, was thought to be localized to the anteromedial STN. The dorsal contacts did not induce any mood and behaviour changes. Ulna *et al.* recorded (92) manic behaviour within minutes of modifying stimulation parameters in a patient. Initially an euthymic state was documented with bilateral stimulation with contacts 1 and 5. Subsequently, bilateral stimulation with contacts 0 and 4 induced mania, and it was further seen with unilateral stimulation through contacts 1 and 4. Unilateral stimulation with contacts 0 and 5 revealed similar clinical findings. The manic state was managed by a change of stimulation contacts from ventral contacts 0 and 4 to the immediately dorsal contacts 1 and 5. The deepest contacts inducing mania were shown to be located within the substantia nigra. A complex episode, with regard to management of the manic behaviour, was reported by Herzog and colleagues (12). Mania developed in a sixty-five year old woman, one week after initiating stimulation. The attempts to manage the mania by reducing her medication and stimulation parameters induced a worsening of her motor state and a deterioration of her mood with anhedonic feelings. Reduction or arrest in stimulation failed to improve her manic behaviour. Clozapine was initiated and the psychotic symptoms disappeared, however a bipolar picture persisted. Carbamazepine was added, and the affective disorder remitted within three months of treatment initiation. She was subsequently kept on clozapine and her mood was reported to be stable. The study did not mention the precise contact localization. Finally Romito *et al.* reported (121), two patients who experienced manic behaviour induced by bilateral STN DBS. One patient presented with a previous psychiatric history of depressive illness and a family history for psychiatric illness. In a second subject the psychiatric history was recorded as absent. In the first patient, two days following implantation and one day prior to initiation of STN stimulation, mania was annotated and subsided after three months without the need of treatment. In the second patient, mania was observed three days after implant and shortly following the first STN stimulation. A change in stimulation settings in this subject had no immediate effect. Symptoms abated spontaneously following eight months of follow-up. Postoperative imaging showed in the first patient contact 1 of the right lead in the right STN and contact 0 of the left lead in the left STN. For the second patient postoperative contact definition revealed contact 0 of the right lead in the right STN and contact 1 of the left lead in the left STN.

5.1.1.3. STN DBS inducing psychosis

Hallucinations lasting for two days with spontaneous resolution were observed in the postoperative setting by Ostergaard *et al.* (35). None of the patients had significant dementia, depression, or any significant medical disease prior to STN DBS. A postoperative MRI was undertaken to verify lead positioning and to exclude

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complications, but a more detailed description of the contact localization was not provided. An intraoperative transient psychotic reaction with hallucinations and delusions, which resolved spontaneously, was noted, in one patient, by Romito *et al.* (125).

Visual hallucinations occurring in the “on” stimulation setting and disappearing when the stimulators were turned “off”, was recorded by Diederich *et al.* (126). The patient in Diederich’s study was managed with antipsychotic medication and the stimulators were left “on”, because the “off” stimulating setting resulted in tremor that was untenable for the patient.

5.1.2. Long term changes with STN DBS

5.1.2.1. STN DBS and depression

In a cohort study (23), with a 12 month follow up, severe melancholic depression with psychosis requiring hospitalisation was reported. In twenty-eight percent of the eighteen patients treated by bilateral STN DBS for Parkinson’s disease, mild depression was diagnosed. Two patients had a history of depression, but not at the time of initial surgery. In another longitudinal study with a follow up of 15 months (95), ten percent of patients, treated with STN DBS for Parkinson’s disease, reported increased scores on items relative to suicidal ideation. Twelve percent of the subjects experienced higher levels of anxiety. In seven percent of patients, worsening of obsessive-compulsive and paranoid traits occurred. Clinically relevant apathy was noted in eight percent of subjects.

Schuepbach *et al.* commented in “Stimulation of the Subthalamic Nucleus in Parkinson’s Disease: A Five Year Follow-up” (45) the occurrence of transient and permanent adverse effects in patients treated with bilateral STN DBS. The side effects ranged from depression, apathy and disinhibition to suicide attempts.

Worsening of depression and transient suicidal ideations, were observed by Berney *et al.* (97). Thirty-eight percent had potentially significant past psychiatric histories. The depressive symptoms due to DBS were managed in this study with anti-depressants.

5.1.2.2. STN DBS inducing mania

Visser-Vandewalle *et al.* (4) observed manic behaviour in twenty percent of her cohort. In three subjects, the manic state was observed just following discharge from the hospital. Two of the patients manifested hyperactivity and verbal aggressiveness as their main symptoms. Dopaminergic medication was reduced by 61.3 percent at three month follow up and by 47.2 percent at long term follow up. Visser-Vandewalle and colleagues argued that depression following STN DBS could be, as one possible cause, the consequence of postoperative decrease in levo-dopa resulting in a reduction of the psychotropic effect of levo-dopa.

Herzog *et al.* (26) reported the occurrence of variable behavioural and limbic manifestations in nineteen percent of the forty-eight patients. The MDRS was reported in the pre-operative setting as normal (mean score of 136) Medication was progressively reduced by 67.8.% at two

year follow-up. In 10.5 percent of the patients medication was stopped entirely. Psychotic syndrome was observed in two patients, and hypo-mania in two. Five patients were diagnosed with depression. All of these manifestations of mood and behaviour effects related to DBS resolved quickly and without specific therapy. Only one patient suffering from manic symptoms required anti-psychotic treatment. These symptoms appeared in the “on” stimulation setting in parallel with the disappearance of the “off”-period parkinsonian symptoms. This patient required a long-term psychiatric inpatient and outpatient treatment.

5.1.2.3. STN DBS inducing psychosis

Funkiewiez *et al.* (41), reported the occurrence of permanent psychosis in one subject of their seventy-seven treated patients. The patient, a fifty-nine year old with akinetic, rigid PD, experienced mania and hypersexuality while on bromocriptine (75 mg) that occurred soon after his disease onset. Preoperatively he suffered from mild depression. At twelve months following DBS, his dopamine treatment was stopped. Six weeks later he became seriously depressed with suicidal ideations. He was started on venlafaxine and low dose levo-dopa. Stimulation parameters were not changed. His suicidal ideations disappeared, however his depressive mood remained. Venlafaxine was stopped and bromocriptine resumed. With a small dose of dopaminergic treatment his mood returned to baseline.

Visual hallucinations with multiple psychotic symptoms, not responding to modification of stimulation parameters and not responsive to turning off the stimulators, was reported in a single patient by Valdeoriola *et al.* (96). The preoperative MMSE was reported to be 28/30 with no clinically evident signs of cognitive impairment. The neuropsychological assessment was normal, except for the presence of a mild slowness of cognitive processing, and free recall impairment. Fluctuating confusion, visual hallucinations and paranoid ideations were observed only 1 ½ years following surgery. The follow-up MMSE score was reported at 22/30. The patient exhibited further violent behaviour towards relatives and was started on clozapine to reduce his aggression. The mental status remained unchanged with the stimulation turned off for one week, but worsening of parkinsonism required consequently the re-initiation of the stimulation. Galantamine mildly improved the psychiatric symptoms. The patient died three-and-half years later from pneumonia. The pathological examination revealed moderate inflammatory infiltrates of T-lymphocytes and a mild astrocytic gliosis surrounding the leads. Post-mortem examination revealed alterations consistent with diffuse Lewy body disease. The authors concluded that the clinical manifestations and the course of the disease were typical for Parkinson’s disease-dementia suggesting that alterations in mood and behaviour following STN DBS were likely not directly related to STN DBS, but may have been exacerbated by it.

Hallucinations resolving with levo-dopa reduction, in a subject treated with STN DBS have also been precisely reported (100).

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5.2. GPi DBS and limbic manifestations

5.2.1. Acute changes with GPi DBS

5.2.1.1. GPi DBS on mood

Miyawaki *et al.* (48), reported the complex management of a patient experiencing mania with right, left, and bilateral GPi DBS. The forty year old patient, presented with no personal or family history of affective or psychiatric illness. The postoperative T1 MRI revealed the leads *in situ*. Initially a hypomanic state, after right implantation, but prior to activation was documented. Bilateral stimulation was commenced at postoperative day twelve. Three days later, a further manic episode was described. The patient exhibited a decreased need for sleep, and rapid, slurred speech. One week later, stimulation on both sides was terminated. At the twenty-seventh day post-surgery, right re-activation occurred and was associated with an additional manic episode. The patient exhibited a reduced need for sleep, and the perception of increased energy. Two days later the left device was activated with modified settings, (reduced frequency and increased voltage), with the right device turned off. Over the ensuing days a further manic episode was diagnosed, requiring hospital admission for three more days. The patient was discharged with both stimulators turned on, and subsequently another manic episode occurred. Seventy-nine days following the intervention the levodopa dosage was modified to 1250 mg/day without report of any major mood fluctuations. A PET study in the on-off stimulation setting, but without clinical evidence of mania, showed a reduced flow in the left hippocampus and parahippocampus in all three DBS conditions under which mania was previously manifested.

5.2.2. Long term changes with GPi DBS

5.2.2.1. GPi DBS on Mood

Volkman *et al.*, (52), commented on an episode of manic psychosis in a patient seen three years after GPi DBS. The DBS target was changed from GPi to STN with a complete termination of dopaminergic drugs and the psychiatric symptoms resolved.

Two studies reported an amelioration of the neuro-psychiatric condition of patients following intervention (53, 54).

Haelbig *et al.*, (54), observed in fifteen subjects treated with bilateral GPi DBS for dystonia a mild improvement in depression at the 3 months and 12 months following surgery. Straits-Troester *et al.* (76), observed in nine patients, treated with unilateral GPi DBS, decreased anxiety in the postoperative period, with improved psychosocial functioning and decreased depression.

5.3. Anterior limb of internal capsule and nucleus accumbens DBS and limbic manifestations

5.3.1. Acute changes with anterior limb of internal capsule and nucleus accumbens DBS

Flaherty *et al.* (57), observed in a patient treated with bilateral DBS for Tourette syndrome, mild apathy and depression with high-voltage stimulation of ventral contacts (in the vicinity of the nucleus accumbens) and hypomania with high-voltage stimulation at dorsal contacts. In another report Shapira *et al.* observed (59), a patient treated for

OCD with bilateral DBS of the nucleus accumbens and anterior limb of the internal capsule, who exhibited mood and affective changes. The psychiatric history of the patient was significant for recurrent major depressive disorders and melancholic features (DSM-4) and the patient was treated with antidepressants. Fear and panic were induced with contact 0, while elevated mood, with an euphoric, slight haze was annotated with contact 3. By switching off the stimulator the symptoms disappeared.

6. DISCUSSION AND CONCLUSION

There are many potential changes in limbic and cognitive functions following DBS. The lack of standardization of reporting clouds our ability to interpret results. Many of the studies reviewed lacked coherent data on important and potentially necessary factors that should be examined when attempting to interpret behavioural changes.

We noted significant variability in many factors including the target, number of patients, disease duration, average age, postoperative medication reduction, past psychiatric history, timing of limbic effects, type of observed mood changes, preoperative screening methods as well as the condition of the DBS device.

Despite the largely contrasting results of many studies, certain patterns could be appreciated. These patterns became more evident when classifying the alterations of mood and behaviour into acute versus long-term effects. Acute changes were predominantly reported as the direct consequence of stimulation parameters and lead location (3, 24, 29, 92, 139). This notion was supported by the evidence that many of the observed neuropsychiatric side effects were reversible with changing of the location of the stimulating contacts (3, 24, 29, 57, 59, 60, 92, 139). STN DBS was most frequently associated with limbic symptoms (3, 24, 29, 92, 139), which, may have been due to several factors including the size of the STN (approximately 150 mm³) (146), the surrounding structures, and also bias (the majority of available studies reported on STN rather than other targets). Additionally, more imaging data may have revealed that DBS contacts may have been sub-optimally placed within the STN (139) or surrounding structures (3, 24, 29). A recent study (139), proposing a model considering the STN as a nexus for the integration of motor, limbic and associative information used an interactive three-dimensional atlas of the human basal ganglia for DBS contact visualization. This type of detailed approach may be able to aid in encoding the effects of DBS. The pooled data from many cases would have the potential to reveal a location in the anteromedial limbic STN, or other neuroanatomical locus that could translate to the observed specific mood or cognitive changes. More research is needed in this area. Current spread into other non-motor areas may also result in limbic manifestations as was shown by Okun *et al.* (154). Neuropsychiatric complications have similarly been observed with lesion therapy (61, 74, 77), lobectomy (85, 90) and leukotomy (88), and this may lend support to the notion that disruption in multiple basal ganglia loops may result in limbic and cognitive changes despite the type of therapy.

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Neuropsychiatric changes that occur with long duration from DBS implantation, are more difficult to evaluate, as they could be the result of the natural progression of Parkinson's disease or other movement disorder related syndromes (141, 147, 148, 149, 150, 151, 152), pharmacological treatment (142, 143, 145, 151), or even long term effects of stimulation (1, 4, 18, 19, 39, 50, 52, 43, 95, 96). Mania was an interesting effect encountered following DBS in several reports. Its occurrence was annotated in the intraoperative and immediate postoperative period and thought by most authors to be referable to ventral lead locations (12, 29, 48, 92, 139). Mania however was also documented after a time delay (4, 26, 52), and there is some suspicion that medication as well as preoperative psychiatric status may influence its occurrence (143).

Other long-term complications seen following DBS such as cognitive impairment, and increased impulsivity may also occur independently of stimulation. Cognitive impairment is well known as an intrinsic aspect of Parkinson's disease (152) and can be worsened by medications such as anticholinergics, amantadine, and dopamine agonists (144) rendering the interpretation of this finding cloudy. Increased impulsivity and other neuropsychiatric complications have been observed as a direct effect of dopaminergic management (145) regardless of DBS status. However, unique to DBS neuropsychiatric symptoms may be that they occur secondary to dopaminergic medication reduction, mainly undertaken in the postoperative period following STN DBS as this may result in a reduction in its psychotropic effect (129). Krack and colleagues observed in a large prospective study (129) three months following surgery, two percent of patients with depressive symptoms. In the period between three months and five years, with progressive medication reduction at the follow up visits (at 1 year, 3 years and 5 years), the percentage of patients with depressive symptoms however increased to seventeen percent. The reduction in dopaminergic dosage along with the natural history of the disease may play a role in the occurrence of mood changes.

How neurosurgical intervention may exacerbate pre-existing illness remains difficult to evaluate given the lack of standardized preoperative screening methods. Structured psychiatric assessments and consensus on which screening methods and cut-offs should be implemented are urgently needed. The lack of control groups in all studies also further complicates interpretation.

In conclusion we can say that DBS may result in many neuropsychiatric complications. Acute changes are likely a direct result of either surgical intervention or DBS stimulation, whereas long-term changes may have many other factors influencing their occurrence including pharmacological management, disease progression, and underlying co-morbidities. Methodological limitations, small sample sizes, lack of control groups, and the heterogeneity of data reported underscore why the interpretation and comparison of limbic effects of DBS remains difficult and somewhat controversial.

It will be important in reporting effects of DBS that authors try to disclose the following factors which may affect outcome: the surgical target(s), unilateral or bilateral procedure, number of patients, gender, disease duration, average age, postoperative medication reduction, postoperative imaging, past psychiatric history, timing of limbic effects, type of observed mood and cognitive changes, management of limbic effects, postoperative screening methods, and deep brain stimulator programming (amplitude, pulse width, frequency). Additionally it will be useful to make direct comparisons between studies by including the following information: pre- and post-operative "on and off" assessment, and pre-surgical screening. Standardization of DBS with collection and reporting of a similar minimal data sets will allow for future comparisons and also potentially yield the power needed to answer many of the questions raised in this review.

7. APPENDIX

7.1. Subthalamotomy (Table 7)

7.1.1. General characteristics

Two studies were included in our review of subthalamotomy (83, 84). Indications for subthalamotomy were limited to advanced Parkinson's disease, with an average disease duration of 11.5 years (SD = 0.70) and an average age of patients of 57.5 years (SD = 0.70). The surgical procedure was reported as unilateral in one (83), and bilateral in another (84). Sample sizes varied, from 13 subjects (83) to 18 subjects (84).

7.1.2. Preoperative screening

Screening tests administered included the MDRS (84), MMSE (84), UPDRS (83, 84).

7.1.3. Past psychiatric history

There was no comment on the past psychiatric history of the patients in either study.

7.1.4. Preoperative "on and off" assessment

For the preoperative assessment the UPDRS was used once (83), and "motor" evaluation once (84).

7.1.5. Postoperative imaging

Both studies performed postoperative imaging to evaluate lesion location.

7.1.6. Postoperative "on and off" assessment

For the postoperative assessment the UPDRS was used once (83), and "motor" evaluation was utilized one time (84).

7.1.7. Postoperative medications reduction

Postoperative medication reduction was documented in both studies.

7.1.8. Alterations in mood and behaviour

Limbic symptoms following intervention were not reported (83), but in the second study it was

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Table 7. Limbic manifestations following subthalamotomy

Sample size	Disease	Target	Postoperative On-Off Status	Screening MDRS MMSE UPDRS Other	Limbic Effects	References
13	Parkinson's disease	Unilateral Subthalamotomy	UPDRS Assessment: On-Off M	No No Yes No	NR	83
Staged surgery: 7 pts Simultaneous surgery: 11 pts	Parkinson's disease	Bilateral Subthalamotomy	Motor Assessment: On-Off M	Yes Yes Yes Yes	NR	84

pts = patients, NR = Not reported, “-“ = “and”, M = Medication, UPDRS = Unified Parkinson's Disease Rating Scale

Table 8. Limbic manifestations following pallidotomy

Sample size	Disease	Target	Postoperative On-Off Status	Screening MDRS MMSE UPDRS Other	Limbic Effects	References
26	Parkinson's disease	Unilateral ventral medial pallidotomy: 21 left/5 right PT	Motor Assessment: On M	No No Yes Yes	1. Impaired level of consciousness with focal seizures, followed by disinhibition, hallucinations. 2. Transient confusion 3. Reduction of motivation	61
20	Parkinson's disease	Unilateral/Bilateral posteroventral pallidotomy	Cognitive Assessment: On M	No No No Yes	1. Intermittent confusion 2. Psychotic depression 3. Increased frequency and intensity of panic attacks	62
13	Parkinson's disease	Bilateral posteroventral pallidotomy	Clinical Assessment: On/Off M	No Yes Yes No	1. Personality change 2. Emotional flattening 3. Confusional state	65
38	Parkinson's disease	Unilateral ventral Pallidotomy: 14 right PT 14 left PT	NM	No Yes No Yes	Depression	70
26	Parkinson's disease	Unilateral PT	H&Y Assessment: On/Off M	No No Yes Yes	Paranoid psychosis	71
44	Parkinson's disease	Unilateral PT: 22 pts Staged bilateral PT: 5 pts Simultaneous bilateral PT: 17 pts	NM	No No No Yes	Depression	74
17	Parkinson's disease	Unilateral Posteroventral Pallidotomy	Clinical Assessment: On/Off M	No Yes Yes No	1. Depression 2. Hypersomnia 3. Dementia and prominent visual hallucinations	77
6	Parkinson's disease	Unilateral/Bilateral PVP	NM	No No Yes Yes	1. Apathy 2. Loss of motivation 3. Loss of initiation	82
2	Parkinson's disease	Unilateral Pallidotomy	Neuropsychological Assessment: Off M	No No No Yes	Mania (transient)	79
1	Parkinson's disease	Right Pallidotomy	Clinical Assessment: Off M	No No No Yes	Hypersexuality and paraphilia	78

PT = Pallidotomy, pts = patient(s), “/” = “and”, PVP = Posteroventral pallidotomy, M = Medication, NM = Not mentioned, H&Y = Hoehn and Yahr stage

commented that an “unexpected improvement in a number of neuropsychological tests” occurred (84).

7.2. Pallidotomy (Table 8)

7.2.1. General characteristics

Twenty-five studies were reviewed (61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 106, 107). The indication for pallidotomy was advanced Parkinson's disease, in eighty-eight percent of studies (61, 62, 63, 65, 66, 67, 68, 69, 70, 71, 73, 74, 76, 77, 78, 79, 80, 81, 82, 82, 106, 107). The average disease duration was 14.8 years (SD = 4.01) and the average age of patients was 60.25 years (SD = 3.61). “Drug induced tardive dyskinesia”, of twenty-nine years duration, was another indication for pallidotomy (72) in a fifty-one year old subject. Study samples varied from case reports (72, 78) to upwards of 44 subjects (74). Posteroventral

pallidotomy was documented as the surgical target in sixty-four percent or 16/25 of studies (62, 63, 64, 65, 66, 67, 68, 72, 73, 75, 77, 80, 81, 82, 106, 107). Unilateral posteroventral pallidotomy was reported in forty-eight percent or 12/25 of studies (62, 63, 64, 67, 68, 72, 73, 80, 81, 82, 106, 107). Bilateral posteroventral procedures were undertaken in twenty-four percent of studies (65, 66, 75, 77, 82, 107). Unilateral ventral-medial pallidotomy was reported in two studies (61, 70) and unilateral posteroventral pallidotomy in one (69). Twenty-four percent or 6/25 of studies did not specify the pallidotomy target (71, 74, 76, 78, 79, 83).

7.2.2. Presurgical screening

For screening the UPDRS was used in forty-four percent or 11/25 of studies (61, 63, 65, 67, 68, 69, 71, 77, 82, 106, 107). The MMSE was applied in twenty-eight

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percent (64, 65, 66, 70, 77, 81, 106). The MDRS was mentioned in one study (80).

7.2.3. Past psychiatric history

The past psychiatric history was not mentioned in seventy-two percent or 18/25 of studies (63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 76, 77, 80, 81, 82, 83). In seventy-one percent or 5/7 of studies the history was documented as not present (61, 78, 79, 106, 107) and in twenty-nine percent or 2/7 of studies it was annotated as positive (62, 72).

7.2.4. Cognitive assessment by verbal fluency test

Cognitive functioning, evaluated by the verbal fluency test, worsened in fifty percent or 6/12 of studies (66, 68, 74, 80, 106, 107). It was reported unchanged in forty-seven percent of studies (64, 70, 75, 81, 83), and not mentioned in the remaining fifty-two percent of studies (61, 62, 63, 65, 67, 69, 71, 72, 76, 77, 78, 79, 82).

7.2.5. Preoperative “on and off” assessment

The pre-operative and postoperative assessment varied across the studies. Neuropsychological assessment was documented in forty percent or 10/25 of studies (64, 68, 75, 69, 70, 79, 82, 83, 106, 107). Clinical evaluation was noted in 20 percent of studies (65, 66, 74, 77, 78). UPDRS was used for evaluation in twenty percent (67, 71, 72, 76, 106). Cognitive assessment was reported in twelve percent (62, 80, 81). Two studies evaluated the “motor” functioning (61, 73), with two further studies not specifying an applied pre-operative assessment (83).

7.2.6. Postoperative imaging

Sixty percent or 15/25 of studies reported on postoperative imaging (61, 64, 65, 66, 71, 72, 73, 75, 78, 79, 80, 81, 82, 106, 107).

7.2.7. Postoperative assessment

In the postoperative period a neuropsychological evaluation was reported in thirty six percent or 9/25 of studies (64, 68, 75, 69, 70, 79, 83, 106, 107). The UPDRS was used for twenty percent of studies (63, 67, 71, 76, 106). The evaluation was remarked as “clinical” in a further twenty percent of studies (65, 66, 74, 77, 78). Cognitive assessment was annotated in twelve percent (62, 80, 81). “Motor” evaluation was reported in two studies (61, 73) and not mentioned in one (72).

7.2.8. Postoperative medication reduction

Postoperative medication reduction was reported in twenty percent or 5/25 of studies (69, 74, 80, 83, 107), while in thirty-six percent no medication reduction was reported (62, 63, 64, 66, 67, 77, 78, 80, 81). In sixteen percent of studies medication was increased (61, 71, 80, 107).

7.2.9. Timing of limbic effects

The alterations of mood and behaviour were observed in all studies in the postoperative period, but there were no comments on their precise time occurrence.

7.2.10. Alterations in mood and behaviour

Forty-four percent or 11/25 of studies documented alterations in mood and behaviour (61, 62, 65, 67, 70, 71, 74, 77, 78, 79, 82). Depression was observed in forty-five percent or 5/11 of studies (61, 68, 70, 74, 77), while transient confusion was reported in twenty-seven percent (61, 62, 65). Hallucinations were remarked on in two studies (61, 77). One study (62), observed psychotic depression in a single subject, with a history of major depressive disorder and generalized anxiety disorder. In one further study paranoid psychosis was reported (71). No limbic manifestations were mentioned in the remaining fifty-six percent or 14/25 of studies (63, 64, 66, 68, 69, 71, 73, 75, 76, 80, 81, 83, 106, 107).

7.2.11. Management of limbic alterations

Pharmacological treatment of limbic symptoms was reported in two studies (77, 78). ECT treatment was mentioned in one (62). Management was not addressed in the eight remaining studies (61, 65, 67, 70, 71, 74, 79, 82).

7.3. Leukotomy and temporal lobectomy (Table 9)

7.3.1. General characteristics

Nine studies were reviewed (85, 86, 87, 88, 89, 90, 134, 135, 136). The sample sizes varied from case reports (88) to case series with up to 49 subjects (86). The indication for surgery in seventy-eight percent or 7/9 of studies was epilepsy (85, 86, 87, 88, 90, 134, 136). The disease duration in this group was 24 years (SD = 0.81) and average age was 37.4 years (SD = 7.92). Further indications for leukotomy included obsessive compulsive disorder (OCD) in two studies (89, 136), major depressive disorder (89), schizophrenia (135) and personality disorder (135). Temporal lobectomy was performed in four studies (85, 86, 87, 90). Limbic leukotomy (89), amygdalotomy and fornicotomy (134), amygdalotomy (135), temporal lobectomy and small parietal corticectomy (88), cingulated lesioning and orbitomedial lesioning (136) were also reported as interventions. The preoperative psychiatric diagnosis was noted as positive in six studies (85, 86, 89, 134, 135, 136) and not mentioned in two (87, 88).

7.3.2. Alterations in mood and behaviour

Following surgery, mania was observed in one study (85). One study (88) observed in a single patient the loss of emotional attachment to family members, a condition described by the authors as “resembling Capgras syndrome”. One study (89) reported that limbic leukotomy was associated with “substantial benefit”. This same study documented two suicides following surgical intervention, one in a patient with mood disorder, and in a second instance the diagnosis was OCD. Both patients exhibited previous suicidal ideations and had previous suicide attempts. This study reported on five of the total treated 21 patients who suffered from short-term memory disorder. It was transient in three, and persistent in two. In five more patients transient apathy was noted. One study (90), mentioned after left temporal lobectomy an increase in depression and decrease in socialization. Improvement post-intervention was reported in five studies (86, 87, 134, 135, 136).

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Table 9. Limbic manifestations following leukotomy and temporal lobectomy

Sample size	Gender	Average Age	Disease	Disease duration	Postoperative Psychiatric Assessment	References
19	3 m/8 f	LTLE: 38.5 y RTLE: 27.4 y	Epilepsy	NM	LTLE: Increase in depression and decrease in socialization (compared with RTLE).	90
18	6 m/2 f	NM	Epilepsy	12-16 y	Improvement and worsening of psychiatric state (observed across patients)	134
8	14 m/4 f	23.0 y	Schizophrenia: in 4/18 pts Personality disorder: in 6/18 pts Mental subnormality: in 8/18 pts Associated Epilepsy: in 5/18 pts	NM	Improvement and worsening of psychiatric state (observed across patients)	135
1	m	50 y	Epilepsy	24 y	Patient postoperatively lost emotional attachment to family members. A condition resembling Capgras syndrome.	88

m = male, f = female, NM = Not mentioned, y = years, LTLE = Left temporal lobectomy, RTLE = Right temporal lobectomy, pts = patients

7.4. Neuropsychiatric complications: acute and long term complications: effects on mood and cognition of lesion therapy

7.4.1. Pallidotomy and limbic manifestations

7.4.1.1. Acute changes following pallidotomy

In "A Study of Medial Pallidotomy for Parkinson's disease: Clinical Outcome, MRI Location and Complications" by Samuel and colleagues (61), variable side effects were reported following unilateral ventral medial pallidotomy. One patient showed an impaired level of consciousness with focal seizures, followed by disinhibition and hallucinations. The MRI evidenced a small deep hemorrhage at the operative lesion site and a second small superficial mesial frontal haematoma that was associated with infarction of the mesial frontal cortex. A second subject developed transient confusion lasting for 2 days, with the MRI showing a hemorrhage close to lesion site. A third patient was diagnosed with a depressive episode. Two further patients manifested reduction of motivation. Occurrence was transient in the first patient and in the second it took five months to reach resolution.

7.4.2.1. Long term changes following pallidotomy

Valdeoriola and colleagues reported in "Four Year Follow-up Study After Unilateral Pallidotomy in Advanced Parkinson's disease" (77), transient depression following unilateral posteroventral pallidotomy in a single patient. Permanent hypersomnia was recorded in one patient, while in two others dementia and prominent visual hallucinations were seen. A mild to moderate depression with an incidence of 38.2 percent, following unilateral ventral pallidotomy, was reported by Perrine (70). Favre *et al.* (74), noted that unilateral pallidotomy significantly improved dyskinesias, and bilateral pallidotomy improved slowness, rigidity, tremor and dyskinesias. Speech function was worsened in some patients. One third of the forty-four patients were at least slightly more depressed following surgery. Favre and colleagues concluded, that depression could be overlooked easily in the absence of a formal neuropsychological and or psychiatric evaluation, particularly when significant motor improvement is evidenced.

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