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ORIGINAL PAPER

‘Woe Betides Anybody Who Tries to Turn me Down.’ A Qualitative Analysis of Neuropsychiatric Symptoms Following Subthalamic Deep Brain Stimulation for Parkinson’s Disease

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Abstract Deep brain stimulation (DBS) of the subthalamic nucleus (STN) for the treatment of Parkinson’s disease (PD) can lead to the development of neuropsychiatric symptoms. These can include harmful changes in mood and behaviour that alienate family members and raise ethical questions about personal responsibility for actions committed under stimulation-dependent mental states. Qualitative interviews were conducted with twenty participants (ten PD patient-caregiver dyads) following subthalamic DBS at a movement disorders centre, in order to explore the meaning and significance of stimulation-related neuropsychiatric symptoms amongst a purposive sample of persons with PD and their spousal caregivers. Interview transcripts underwent inductive thematic analysis. Clinical and experiential aspects of post-DBS neuropsychiatric symptoms were identified. Caregivers were highly burdened by these symptoms and both patients and caregivers felt unprepared for their consequences, despite having received information prior to DBS, desiring greater family and peer engagement prior to neurosurgery. Participants held conflicting opinions as to whether emergent symptoms were attributable to neurostimulation. Many felt that they reflected aspects of the person’s “*real*” or “*younger*” personality. Those participants who perceived a close relationship between stimulation changes and changes in mental state were more likely to view these

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symptoms as inauthentic and uncontrollable. Unexpected and troublesome neuropsychiatric symptoms occurred despite a pre-operative education programme that was delivered to all participants. This suggests that such symptoms are difficult to predict and manage even if best practice guidelines are followed by experienced centres. Further research aimed at predicting these complications may improve the capacity of clinicians to tailor the consent process.

Keywords Neuropsychiatry · Consultation-liaison psychiatry · Parkinson's disease · Deep brain stimulation · Subthalamic nucleus

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for the motor symptoms (tremor, rigidity, bradykinesia) of Parkinson's disease (PD). It involves surgery to position electrodes within this target that emit continuous high frequency stimulation to modulate dysfunctional basal ganglia activity. DBS is typically indicated when motor symptoms become difficult to manage with dopaminergic medication due to the development of motor fluctuations, dyskinesias, or medication-refractory symptoms. Bilateral STN stimulation increases ON time, reduces motor fluctuations and dyskinesias, enhances performance of activities of daily living and improves quality of life [1]. The dose of dopaminergic therapy is often substantially reduced [2]. DBS of the STN (STN-DBS) in PD is set to grow as contemporary evidence suggests that earlier intervention produces superior results than best medical therapy [3].

Approximately 10% of persons treated with STN-DBS develop unintended mood and behavioural changes as a consequence of electrical stimulation that disrupt post-surgical quality of life [4]. These include euphoria, irritability, pathological gambling, hypersexuality and impulsivity, as well as more subtle changes in drive and empathy [4–14]. Henceforth, these putative 'stimulation-dependent' phenomena are referred to as 'neuropsychiatric symptoms', whilst recognising that more generally other symptoms in PD such as anxiety, apathy, psychosis and cognitive dysfunction may also be encompassed by this term. The emergence of these issues may not be recognized by the person with PD or not viewed as problematic. They may alienate the person with PD from their support network, leading to estrangement or relationship separation. Such neuropsychiatric symptoms also raise ethical challenges, including the responsibility of the person for actions committed whilst under the influence of stimulation-dependent mental states [15 16]. Personality change may lead family members to contend that the person is no longer themselves, stimulating debate about the effect of DBS surgery on personal identity [17–19].

The occurrence of neuropsychiatric symptoms in PD is certainly not unique to STN-DBS. Indeed, PD has been referred to as the 'quintessential neuropsychiatric disorder' [20], such is the breadth of psychiatric and cognitive symptoms that may arise in the course of neurodegeneration. Dopamine replacement therapy (in particular dopamine agonist medication) has also been associated with the development of impulse-control disorders [21] and the rate of serious psychiatric side effects is similar amongst persons treated with STN-DBS as compared to matched individuals on best medical therapy [22]. Clinicians are therefore challenged: the risks of psychiatric side effects as a component of STN-DBS should be communicated to patients and their families, but placed into appropriate context – given that persons with PD may benefit greatly from the procedure and the alternatives are not without risk.

The stimulation-dependent nature of psychiatric symptoms has been contested by Gilbert et al. [23], who suggest that they may reflect a worsening of pre-existing psychiatric disorders or aggravation of difficult family relationships in the setting of major surgery, less related to electrical stimulation than to premorbid psychiatric, personality and psychosocial functioning. In particular, these authors propose that debate regarding the neuroethical consequences of DBS relies largely upon speculative assumptions rather than empirical evidence. However, clinical experience indicates that a substantial proportion of psychiatric symptoms arise de novo and in the absence of prior symptomatology, suggesting that there is not a clear 'at-risk' pre-surgical phenotype and that these symptoms may be an unintended consequence of the procedure [24]. Furthermore, the physiological role of the STN in decision-making lends biological plausibility to the view that modulation of this region may produce unintended cognitive and emotional side effects [25]. A direct relationship between the adjustment of electrical stimulation and the onset or remission of psychiatric symptoms has been reported, suggesting that STN-DBS is a proximate cause in many cases [8–11]. Furthermore, the precise site of stimulation within this nucleus is associated with the

onset of psychiatric symptoms, supporting the existence of a biological gradient related to the locus and amplitude of stimulation [26]. Finally, the STN has been employed as a surgical target in DBS for obsessive-compulsive disorder [27], indicating that this subcortical nucleus can be a nexus for psychiatric as well as movement disorders, helping to explain why psychiatric symptoms may arise as a consequence of STN-DBS for PD.

Complex changes in behaviour following STN-DBS are challenging to comprehensively assess with standard quantitative methods. Firstly, instruments that assess mood and personality only measure an operationalised subset of these phenomena; richer concepts such as 'identity' and 'autonomy' are not captured in these scales. Secondly, affected individuals may show deficits in their awareness of these difficulties, which are only revealed after consulting with an informant. Qualitative investigations employ open-ended questions that allow participants to disclose more than pre-determined scales. Moreover, the inclusion of spousal informants provides a second perspective that may corroborate or contrast with the experience of the person with PD. Qualitative methods also capture the participant's 'own voice', meaning that issues relevant to the person with PD are uncovered, assisting with the delivery of patient-centred care. Qualitative studies with people with PD [28 29] and a spouse [30] have increased our understanding of living with a DBS device. However, there has been little research regarding the impact of subthalamic stimulation-induced neuropsychiatric symptoms on persons with PD and their families [23].

The goal of the present investigation was to explore the meaning and significance of stimulation-related neuropsychiatric symptoms amongst a sample of persons with PD and their spousal caregivers. Here, participants and their spouses were purposively selected from a pool of consecutive surgical candidates based on the postoperative development of neuropsychiatric symptoms attributable to STN-DBS. Interviews were conducted 6–12 months postoperatively, after neuropsychiatric symptoms had been remediated following DBS manipulation. Findings from this study will enhance the capacity of clinicians to educate surgical candidates and respond to the emergence of neuropsychiatric symptoms in a manner that addresses the needs of the person with PD and their family. This will be of increasing importance as subthalamic DBS becomes a more widely utilised intervention [3].

Terminology

In the investigation that follows, a number of ethical and philosophical concepts are identified. To aid the clarity of subsequent discussion we first define what we take these terms to mean and how we take them to be interrelated. We recognise that these concepts have a rich history of debate in the bioethics literature and it is beyond the scope of this study to engage in this analysis.

In order for an agent to be morally responsible for an act (or omission), the consequences of acting (or not acting) must be foreseeable, and the agent must possess autonomous control over her cognitive and volitional capacities. Acting deliberatively or purposely may enhance moral responsibility and blameworthiness. Autonomy is the exercise of a set of mental competences to make a judgement about one's best action in a given situation. Autonomous agents reason consistently, reaching similar conclusions under similar environmental contingencies (i.e. they are sufficiently rational). Furthermore, an autonomous agent reasons and acts on the basis of authentic desires, i.e. the attitudes of the agent that move her to act are identified as her own, being consistent with the agent's evaluation of her values [31]. According to this view, to act authentically and therefore responsibly is to do so in accordance with one's "true self". Selfhood is closely aligned with the concept of personal identity, a construct that is constitutive of responsibility. Broadly, there are two contrasting perspectives on personal identity and what constitutes someone's "true self": a view of selfhood as a form of reflective, self-generated autobiographical narrative (referred to as existentialist) [32], contrasted with an essentialist model that proposes the existence of a deeply immutable inner "core" of being [33]. In what follows we do not take a position on which conception of identity is correct. Identity and selfhood are distinct from personality, which refers to those temperamental or characterological traits that influence a distinctive array of behaviour within an individual.

Methods

Qualitative data was gathered from 20 semi-structured interviews conducted with persons with PD (10) and their spousal caregivers (10) following subthalamic DBS. This study was part of a larger investigation of neuropsychological and neuroanatomical aspects of

psychiatric symptoms [26 34 35] after DBS. Ethical approval was granted by the Human Research Ethics Committees of the Royal Brisbane and Women's Hospital, the University of Queensland, UnitingCare Health and the QIMR Berghofer Medical Research Institute. All participants received written information about the study and signed a consent form.

Participants

A larger cohort of persons with PD (from which these participants were drawn) comprised surgical candidates consecutively recruited at the Asia-Pacific Centre for Neuromodulation between 2013 and 2017, during the assessment of eligibility for STN-DBS. The diagnosis of PD was confirmed by a movement disorders neurologist according to the United Kingdom Queens Square Brain Bank criteria [36]. All persons with PD completed a psychiatric and cognitive evaluation prior to surgery. Individuals without a spousal caregiver, proficiency in English, and those with cognitive impairment, as defined by a Mini Mental State Examination Score (MMSE) of 25 or less, or a clinical diagnosis of PD dementia [37] were excluded from the study. Prior to consenting for surgery, persons with PD and their spousal caregivers completed a 60-min education session run by a psychiatrist (PM) and nurse specialist, including the potential neuropsychiatric side effects of subthalamic stimulation.

DBS electrodes were implanted in a single-stage procedure using a stereotactic apparatus, after the STN was identified via neuroimaging. Intraoperative microelectrode recordings (MER) were employed to establish localisation within the STN and intraoperative test stimulation was performed. Further imaging confirmed satisfactory postoperative lead placement. Postoperatively, stimulation parameters were adjusted non-invasively through an implanted pulse generator sited in the pectoral region. Stimulation titration began as an inpatient, with the amplitude of stimulation gradually increased as dopaminergic medication was slowly withdrawn. Persons with PD returned to the clinic frequently during the first 6 postoperative months for routine neurological and psychiatric assessment, with further DBS manipulation undertaken according to motor symptoms.

Identification of persons with PD who developed psychiatric symptoms (that the investigators had grounds for believing were) attributable to subthalamic DBS used the same process as that reported in prior work [26 34].[1] These persons were identified during a postoperative schedule of repeated neuropsychiatric assessments. A semi-structured diagnostic interview and mental state examination were conducted by the psychiatrist (PM) who had assessed all participants at baseline, with attention to mood elevation, disinhibition, compulsivity and loss of empathy. The contribution of neurostimulation to the presentation was confirmed if symptoms responded promptly to a reduction in the amplitude or change in the locus of stimulation, as assessed by serial mental state examinations and feedback from close family members. These individuals were invited to take part in a qualitative interview, which was also undertaken separately with their spousal caregiver. The present sample of 10 patient-caregiver dyads was drawn from a total cohort of 91 recruited to the overarching investigation. Persons with PD and their caregivers were only approached for interview after their psychiatric symptoms had definitively resolved, at an interval of 6–12 months post-DBS. No individuals declined participation.

Interviews

Interviews used a semi-structured template exploring common psychiatric symptoms attributable to subthalamic DBS and its impact on autonomy, identity and responsibility (Supplementary Material). Participants were encouraged to introduce topics that were not prompted by the interviewer. Persons with PD and their spousal caregivers completed separate interviews to enable open disclosure and the expression of discrepant perspectives. Interviews were conducted face to face by PM with an approximate duration of 60 min. PM maintained field notes and a reflective diary. Audio-recordings of each interview were transcribed verbatim and checked for accuracy, with removal of all potentially identifiable information. All participants were informed verbally and in writing that the content of the interviews would not form part of their medical record.

Data Analysis

Deidentified transcripts were imported into NVivo qualitative analysis software (Mac version 11.4.2, QSR International Pty Ltd., Doncaster, Australia) and analysed

[1] We acknowledge the bioethical debate regarding the attribution of these symptoms, e.g. Gilbert et al. [23]

thematically [38]. Each transcript was read several times before extracts were coded to reflect the experience or perspective of the participants. Coding was an iterative and inductive process, with codes generated, refined and merged, and transcripts re-coded as the data corpus increased. Each transcript was re-coded until saturation, where no further excerpts could be identified. Both PM and KR carried out this initial coding step separately in order to generate diverse perspectives on the data. Discrepancies were discussed between PM and KR until a consensus was reached. Preliminary analyses of the transcripts were conducted in parallel to the interviews, to facilitate reflection during data collection. Subsequently, stable frameworks of codes were identified that cohered as themes, each describing a defined aspect of participants' experience of psychiatric symptoms after subthalamic DBS.

When coding, experience, preconceptions and bias were acknowledged. PM was a psychiatrist with involvement in over 400 cases of DBS for movement disorders. His position was that neurostimulation was causally responsible for the observed behavioural changes amongst these persons with PD, rather than a psychological adjustment to the relief of disability or changing roles in the patient-caregiver dyad. KR was a provisional psychologist with no prior clinical experience or knowledge of the participants. In order to maximise the transparency of subsequent findings the consolidated criteria for reporting qualitative research (COREQ) were employed [39].

Results

Participant Characteristics

The data corpus consisted of 20 qualitative interviews, comprising 10 persons with PD (9 male, 1 female, mean age 59.4, range 36–71) and 10 corresponding spousal caregivers (9 female, 1 male, mean age 57.9, range 35–70). The demographic and clinical characteristics of the persons with PD selected for interview are summarised in Table 1. Persons with PD were predominantly male, but with a broad range of age and variable degree of premorbid psychiatric history. Three had no prior psychiatric history, four had mild-moderate depressive or anxiety disorders and three had more severe behavioural addictions or psychotic symptoms related to dopaminergic therapies. Neuroimaging confirmed that the DBS electrodes were accurately targeted to the STN in all patients (Fig. 1), with favourable motor outcomes from their procedure, manifested by a reduction in objective motor symptom scores and a reduction in the requirement for

Table 1 Demographic and clinical characteristics of the sample

Participant	Age	Gender	Prior Psychiatric History	DBS-Related Symptoms
1	67	Male	Nil	Irritability, hypersexuality, pathological gambling, compulsive spending
2	61	Male	Depression (treated in primary care)	Irritability, compulsive spending, alcohol dependence, aggression, suicide attempt
3	62	Male	Compulsive 'hobbyism' related to PD medication	Impulsivity, dangerous driving, unwise business decisions, hypersexuality
4	46	Male	Nil	Irritability, hypersexuality, compulsive spending
5	67	Male	Psychotic episode related to PD medication	Hypersexuality, verbal disinhibition, leading to family discord
6	64	Male	Depression (treated in primary care)	Manic episode with irritability, aggression, pathological gambling, dangerous driving, leading to involuntary hospitalisation
7	36	Male	Nil	Hypersexuality, verbal disinhibition leading to family discord
8	71	Male	Non-motor fluctuations in anxiety	Irritability, compulsive spending
9	61	Female	Anxiety (treated in secondary care)	Irritability, compulsive spending
10	54	Male	Hypersexuality, compulsive spending, gambling related to PD medication	Irritability, aggression

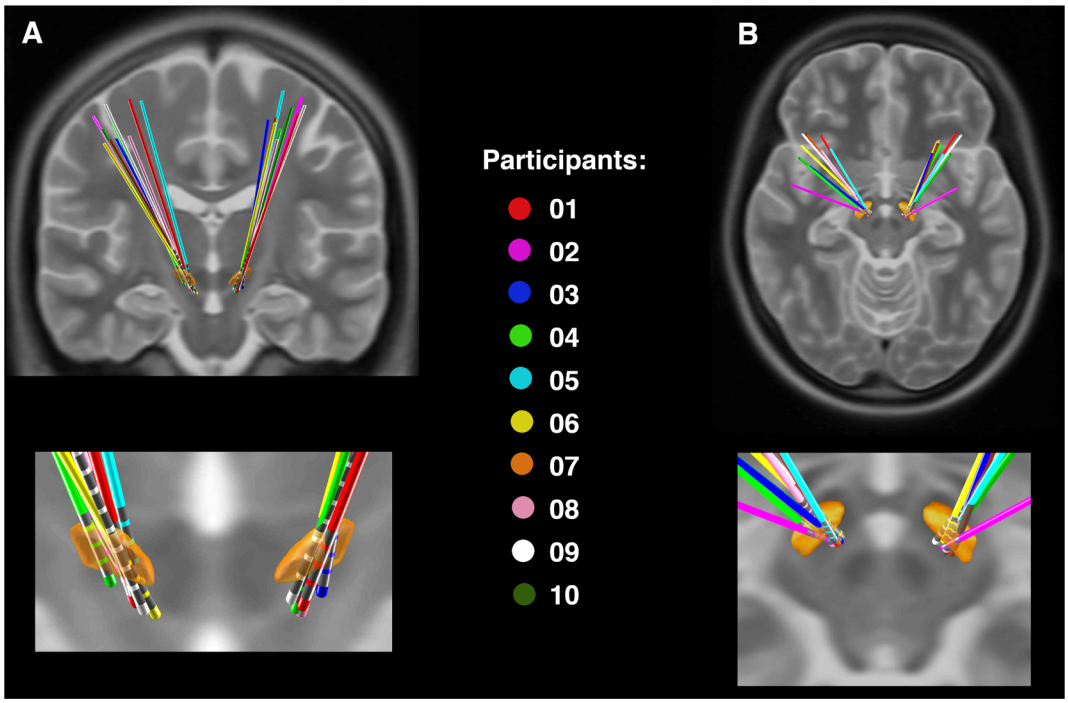

Fig. 1 Localisation of subthalamic deep brain stimulating electrodes. Using the Lead-DBS toolbox [58], preoperative T1 and T2-weighted images were co-registered with the postoperative CT scan and spatially normalised into ICBM_2009b nonlinear asymmetric space. Medtronic 3389 and Boston Vercise electrodes were manually identified, their spatial position was corrected for brainshift, and their trajectory was evaluated with reference to a recent parcellation of the STN [59]. The full pipeline has been described in prior work [26]. A: coronal view of DBS electrodes, B: axial view of DBS electrodes. All electrodes were accurately targeted to the STN

dopaminergic therapies. Quantitative data pertaining to these outcomes has been reported [26 34].

Clinical Vignettes

Brief clinical vignettes are summarised below to provide a narrative context for each patient.

Person with PD 01

A 64-year old male with an 11-year history of tremor-dominant PD. A retired senior government administrator with no personal or family history of psychiatric illness and no impulse control disorders despite long-term treatment with a dopamine agonist. One month after STN-DBS, he developed a coarsening of personality manifest with crude language, irritability and sexualised behaviour. He threatened to set up a rival DBS program, became preoccupied with sports betting and purchased a sports car on an internet auction. His symptoms remitted at 3-months postoperatively when his stimulation was moved to a more dorsal contact on both electrodes and a bipolar configuration (anode and cathode both localised to the electrode resulting in a more focussed stimulation field) was employed.

Person with PD 02

A 61-year old male with a 5-year history of tremor-dominant PD. A retired sales executive with a history of depression emerging as an early symptom of PD, responsive to antidepressant medication. He developed an early postoperative hypomania characterised by euphoria and psychomotor agitation, which settled after 1 month. However, subsequent to an increase in stimulation 5-months postoperatively, he abruptly became irritable, began drinking heavily, purchased $2000 of camping equipment, assaulted his wife and attempted suicide by jumping from a hotel window. His symptoms remitted with a switch to bipolar stimulation on both electrodes.

Person with PD 03

A 62-year old male with a 23-year history of akinetic-rigid PD. On long-term sickness benefits due to his PD,

he had developed dopamine dysregulation on a duodopa infusion and was manipulating his dose so as to engage in compulsive woodworking. This behavioural addiction resolved after STN-DBS, but 3–7 months later, his wife complained of impulsive behaviour: he was attempting to open a nightclub and was apprehended by the police driving his mobility scooter on a busy highway. His wife also described a new habit of fetishistic masturbation. His symptoms remitted with a reduction in stimulation amplitude.

Person with PD 04

A 46-year old male with a 4-year history of tremor-dominant PD. Serving in the armed forces, he had no prior psychiatric history. Three months after STN-DBS, he developed an elevated mood with irritability, verbal disinhibition, compulsive spending and hypersexuality. He purchased expensive wine, paintings and solicited sex on the internet. His symptoms remitted with a switch to bipolar configuration, move to more dorsal electrodes and reduction in stimulation amplitude.

Person with PD 05

A 67-year old male with a 13-year history of tremor-dominant PD. A former naval serviceman, he had developed a delusion of infidelity during treatment with a dopamine agonist. This had resolved following cessation of the drug, but was associated with a subsequent depressive episode, remitted at the time of DBS. He displayed euphoria and verbal disinhibition in the first week after STN-DBS, which settled spontaneously. However, subsequent to increases in stimulation amplitude during the following 6 months, he displayed abrupt changes in affect characterised by elation, irritability and hypersexuality, demanding sex from his spouse. These symptoms responded to moving the stimulation to more dorsal electrode contacts and a reduction in stimulation amplitude.

Person with PD 06

A 64-year old male with a 5-year history of tremor-dominant PD. A factory worker, he had a history of recurrent depressive disorder treated in primary care. Immediately after STN-DBS, he reported a non-motor effect of stimulation with resolution of his depressive symptoms, a phenomenon that was also positively received by his family. However, 9-months later a second contact was activated on the right electrode to manage residual motor symptoms, which led to the rapid development of a manic syndrome. This was associated with irritability, threats to his family, gambling and dangerous driving, eventuating in arrest and involuntary hospitalisation. His device was turned off and he was treated with mood stabilising medication and antipsychotics, with subsequent resumption of DBS under the initial postoperative settings. This case has previously been reported [35].

Person with PD 07

A 36-year old male with a 5-year history of tremor-dominant PD. A manual labourer, he had no prior psychiatric history and no background of impulse-control disorders despite treatment with a dopamine agonist. One month after STN-DBS, his wife described the emergence of a 'forceful' personality (previously he had been reserved) associated with a preoccupation with sex and agitation discernible on mental state examination. His symptoms remitted with a bipolar configuration and a move to more dorsal electrode contacts, but re-emerged at 3-months subsequent to further stimulation increases and remitted again with a reduction in stimulation amplitude.

Person with PD 08

A 71-year old male with a 5-year history of tremor-dominant PD. A retired scientist, he experienced non-motor fluctuations with cyclical anxiety symptoms in the inter-dose interval between doses of his levodopa. Two months after DBS, he developed an elevated mood in the irritable range after a stimulation increase. He presented with an uncharacteristically entitled affect and accused his treating clinicians of being incompetent. Upon admission, he attempted to buy artwork on the walls of the hospital and tried to give cash to the nursing staff. His family reported that he had bought artwork for them against their wishes. His symptoms remitted with a reduction in stimulation amplitude.

Person with PD 09

A 61-year old female with a 5-year history of tremor-dominant PD. A retired teacher, she had a history of generalised anxiety in the setting of her movement

disorder and had been treated by a psychiatrist for these symptoms. In the first week after DBS, she became uncharacteristically irritable with outbursts of inappropriate anger directed towards her husband. She had poor insight into her changed behaviour and these outbursts persisted despite intensive DBS reprogramming. Her husband also reported compulsive spending. Eventually her right STN electrode was repositioned surgically (to a more dorsolateral region of the nucleus) and her symptoms remitted.

Person with PD 10

A 54-year old male with a 5-year history of akinetic-rigid PD. A retired postal officer, he had a history of impulse control disorders during treatment with dopamine agonist medication. These included pathological gambling, compulsive spending and hypersexuality comprising the compulsive use of internet pornography. His behavioural addictions remitted after STN-DBS corresponding with a reduction in his dopaminergic medication. However, 2-months after surgery, he became irritable and his wife reported dangerous driving and threats of aggression. On mental state exam, he was agitated with pressure of speech and verbal disinhibition. His symptoms remitted with the use of a bipolar configuration and dorsal electrode contacts.

Coding and Themes

A coding tree was developed from the data corpus, from which a network of primary and secondary themes was identified (Fig. 2). Illustrative excerpts are provided in the text below and as Supplementary Material.

Theme 1: Clinical Aspects of Neuropsychiatric Symptoms

Caregiver Burden

Stimulation-dependent neuropsychiatric symptoms were universally problematic for spousal caregivers. Caregivers spoke of their partner "*no longer being the person I married*" and described a change in the spousal role to that of "*parent*", "*flatmate*", "*nurse*" or even "*sexual object*". Those with younger children struggled to explain behavioural changes to their offspring. Caregivers were troubled by verbal disinhibition and irritability, rating this as more burdensome than motor symptoms.

> *My biggest fear... I can cope with absolutely anything, if he's quadriplegic it's fine, I can deal with that, but I can't deal with – the psychiatric changes, it scares me too much. How he behaved, how he was when he was back there, I can't do that again.* (Spouse 05)

Even after resolution of neuropsychiatric symptoms, caregivers struggled to forgive their partners, particularly if DBS had revealed "*skeletons in the closet*" or there had been lack of insight on the part of the person with PD.

> *We haven't done any counselling at all and I think we need to. As a spouse, you need to be prepared that these things can happen and that husbands or partners can turn feral [wild] and not to - we were told not to take it to heart - whatever is said is said out of - they can't help it. But in saying that, that's*

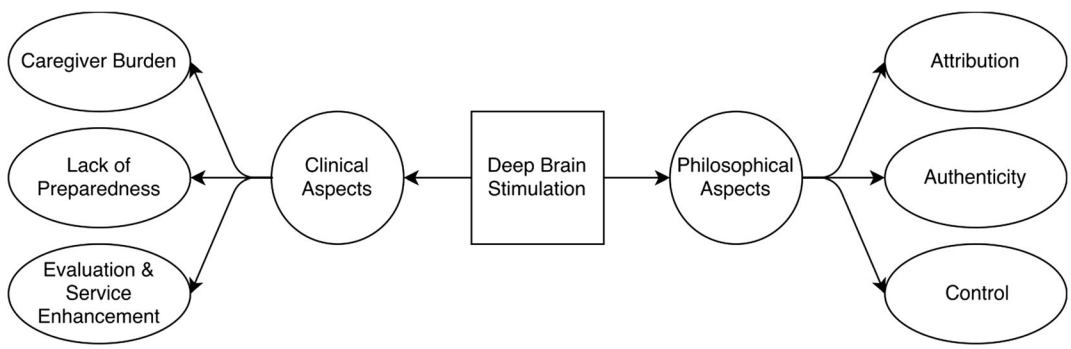

Fig. 2 Primary and Secondary Themes Identified from the Data Corpus

kind of not enough. You still hold - I mean, I do - I still hold on to things that were said and things that were done because it's ultimately affected our relationship. That's something that I have to move on from but it's really difficult. (Spouse 07)

The connection of these symptoms to neurostimulation was problematic for some caregivers, who perceived themselves as helpless actors.

This illness is something different. Everything else in your life you work harder, you tough it out, and whether it's a problem in a relationship or whatever, you work through it. This shit, it's all in someone else's hands. The most helpless feeling you'll ever have. It really is. (Spouse 09)

Lack of Preparedness

Almost all participants, both persons with PD and their caregivers, reported being ill-prepared for the nature and impact of stimulation-dependent neuropsychiatric symptoms. This was despite the inclusion of an education session on the potential emergence of these symptoms for all participants during the preoperative multidisciplinary evaluation. Some participants denied ever receiving information about neuropsychiatric complications, whilst others acknowledged that their desperation to receive treatment for their motor symptoms clouded contemplation of this matter.

I probably sort of looked on the bright side and thought, oh well, I'll be right… Maybe it wasn't their fault that they - they probably did say it but you know when you're sort of a bit desperate I guess you don't sit on that negative sort of thing. (Person with PD 08)

Other participants recalled receiving education but were unable to reference the personal significance of this in the absence of any prior psychiatric history.

It's a bit like childbirth [laughs]. It's kind of like no matter how much preparation you do, it's just something you've got to experience yourself… Truly we didn't think that - we sort of just hoped we'd skate through without having those kind of experiences. (Spouse 01)

Caregivers reported that this perceived lack of preparedness delayed them from seeking treatment for the person with PD.

Had they said to me he may have a change of personality, then I could have said well this has happened, and got on to it sooner. From my point of view, I've had to learn the hard way about the side effects. (Spouse 02)

Evaluation and Service Enhancement

Even after having experienced or witnessed neuropsychiatric complications, persons with PD and their caregivers reported that they would still make the same decision to undergo neurosurgery and would cautiously recommend it to other individuals. This positive perspective was driven by the improvement in motor symptoms and reduction in medication requirements noted by participants. However, participants were forthcoming with suggestions about how the model of care could be improved for future surgical candidates. They expressed a preference for more education to improve their preparedness for emergent neuropsychiatric symptoms, through peer support and engagement with close family members.

Make sure the whole family would be well and truly aware… again these adjustments on the DBS system are not just for an individual, the whole family need to be aware of it and how much adjustment and what's being done. Because from my own personal experience, I found out just how much it can affect you and not in a good way at all and that in turn reflects on the family and they've been through hell and back over this. (Person with PD 02)

Some participants expressed a preference for the science of DBS to be developed to allow more accurate predictions of motor and neuropsychiatric outcome.

I have a sense that while there's a lot of experience around, there's not a lot of firm, really solid knowledge about what happens once we start tweaking [adjusting the DBS]. It's very - there's a real trial and error aspect to it, which I probably thought would be less the case - that it would be more known, more rigorous if I can put it that way.

I understand that it's a fairly new technology, so we're part of that developing of that rigour. (Spouse 01)

Theme 2: Philosophical Aspects of Neuropsychiatric Symptoms

Attribution and Responsibility

The language of participants revealed complex beliefs about the role of neurostimulation in precipitating observed behavioural changes. Many participants made statements that ascribed problematic behaviour to subthalamic stimulation, whilst maintaining a belief in personal responsibility for action.

Where do you think those urges came from? (Interviewer)

Largely out of my situation of boredom. I think they're an expression of my own freewill. It's just me thinking about it a lot more because my brain is more active. I'm the first to agree with that and I wouldn't want that any other way. So woe betides anybody who tries to turn me down. (Person with PD 01)

Well, I felt it was my freewill, but yeah, as I say, it's freewill, but driven by my brain, the stimulation of my brain, because that wasn't me at all. (Person with PD 02)

One person with PD credited subthalamic DBS with curing his longstanding depression but saw other behavioural changes as reflective of his unique personal history.

The minute I opened my eyes [after the operation] my depression and anxiety had been lifted and I've never felt depressed and never felt anxious since that day… it has changed my character… Maybe buying a few presents for the kids, the grandkids, she might feel that I might overdo it at times. But there's a reason behind that too that she doesn't understand. When I grew up, I grew up with nothing. My parents weren't very well off at all. I sort of felt I missed out, so I'm trying to probably give the grandkids a little bit more. I see a smile on their face, I get more enjoyment out of them getting that doll or that little motorised car or whatever it is, and what they get. So not DBS. (Person with PD 06)

Even when participants held a very biological view of emergent neuropsychiatric issues, this did not necessarily affect their application of moral character to an action.

I've seen with this that people can change pretty quick just from a wire. Same person, same mind, or same brain, just shift a bit of voltage somewhere and a different person … But I don't see why I should condone bad behaviour. Whether you're crook [ill] or not, bad behaviour is bad behaviour. (Spouse 09)

Some participants expressed a sense of bewilderment when attempting to disentangle this question of culpability.

I don't know what's [the person with PD] anymore and what's the DBS. I don't know if he's changed as a person or if a lot of it is the DBS. It's a hard one to answer, because I'm confused in my head of what's real and what's not real anymore. (Spouse 10)

Authenticity

Many participants viewed the emergence of neuropsychiatric symptoms as reflecting some aspects of the person's "*real*" self that PD took away and which DBS allowed to re-emerge.

I was very outspoken too, and - but a lot also was my personality coming back. Because I'd just [previously with PD] let things go, whereas I'd always been very outspoken. I was sort of back to my old self in a lot of ways. (Person with PD 09)

While the changes were seen as being consistent with their "*real*" pre-PD self, the degree of behavioural change was sometimes seen as exaggerated or a return to a much younger self.

To some extent I think that they're probably - at least in [person with PD's] case kind of unique to him. They're not alien to what he used to be. They're exaggerations of how he would once have

behaved anyway… it's just like everything with the knobs turned up or the volume turned up… we're back to the 20-25-year-old personality that's not very nuanced and not all that willing to compromise. (Spouse 01)

Participants who observed large positive changes in mental state subsequent to DBS adjustments were more likely to endorse a return to true selfhood.

Yes, when first readjusted I was like my old self. I couldn't believe how I felt. My wife and I could get on reasonably well… I felt my old self and that was what our children say, that we lost you at some stage, but now you're your old self again. (Person with PD 02)

However, the change to a less passive self caused problems for caregivers, particularly when the person with PD was no longer willing to adhere to established roles within the family system. This appeared to be driven by changes in mood, rather than a simple reduction in disability due to the relief of motor symptoms.

…he didn't want me looking after him and was calling me controlling, whereas normally it was - as I said, we were just a team. I don't call it controlling. I call it helping… it just triggered some… dark side. (Spouse 07)

Control

Participants who viewed neuropsychiatric symptoms as inauthentic, attributed behaviours to the DBS and perceived a loss of control or freewill.

I knew I was saying it but I knew I shouldn't be saying it. See what I mean? It's just - you've just got no control. Yeah, it was no control, no filter. No circuit breaker, no - it was odd. It was…it just gets rid of all your inhibitions. (Person with PD 04)

However, for some participants the surgery appeared to offer an additional and desirable ability to control personality and behaviour.

We call him the Energizer Bunny and when the friends walk in, they'll say to him, are we switched on today, or switched up, because he's just got this energy. Then when you turn him down… in the afternoon he'd have to have a little nap. Well he doesn't like that. He likes to have this Energizer Bunny energy. Since he's had a taste of it, he really likes it. It's almost like an addiction actually… to me, it's almost like control. (Spouse 02)

Participants who saw neuropsychiatric symptoms as authentic were less likely to perceive a loss of control.

But I felt I was getting better each day, and I was very aware of what was happening. Physically there wasn't anything I could do about it, but with my verbal language and that I was starting to sort of think, this is no good, I've just got to stop it [being outspoken], and I was slowly getting better… I thought I was sort of getting control of it. (Person with PD 09)

However, the views of persons with PD and spouses were sometimes discrepant on this matter.

If she'd have seen a video of herself she'd have been surprised. In her mind, she thinks that she was fine, and she still believes that she was fine. But you understand from her point too because of where that wire was, she was high, for want of a better term, and feeling like a million bucks… that she's like superman. Almost like someone on drugs, but didn't believe that anything she was doing was wrong… It didn't get better. It just escalated. Every time they turned the unit, the voltage up she went up a level… You can't believe that a little bit of voltage would shift someone from there to there in that little bit of time. (Spouse 09)

Participants (both spouses and persons with PD) who observed this close relationship between stimulation changes and changes in mental state were more likely to view neuropsychiatric symptoms as inauthentic and uncontrollable.

Then on Monday when it had been increased to three that was when I was sort of - something was happening that wasn't typical of me… I sort of felt irritable. Something was going on there... I was aware that I was like that, but I couldn't seem to do too much about it. Then no, I don't understand what was happening or what was causing that. I

was sort of over cooked, I was too stimulated, and maybe it had been increased too quickly. (Person with PD 08)

Discussion

The emergence of significant neuropsychiatric symptoms (such as mood changes, reckless decision-making and addictive behaviours) following STN-DBS can have a significant impact on the quality of life of both persons with PD and their families. We know little about the way in which these individuals understand the causes and emergence of these behaviours, how they impact upon their lives and relationships, and what information or support they receive. This study provides a qualitative examination of these issues. Our study also enriches our understanding of the philosophical aspects of these phenomena, capturing how such symptoms, when they arise, impact on autonomy and identity.

Supporting Caregivers

From a clinical perspective, emergent neuropsychiatric symptoms (as operationalised and identified by a psychiatrist) were particularly burdensome for caregivers, who reported changes in relational dynamics and enduring difficulties even after a recovered episode. In particular, caregivers often reported feeling helpless and overwhelmed by the changes observed in their partner. This finding is consistent with previous reports demonstrating that burden amongst PD caregivers is highly correlated with comorbid psychiatric symptoms [40 41]. We suggest that the wellbeing of caregivers should be explicitly considered by clinicians who encounter these neuropsychiatric symptoms in their patients. The persistent distress reported by caregivers may require provision of psychological assistance even after neuropsychiatric symptoms have abated in order to facilitate relational readjustment. Future work will evaluate the effectiveness and acceptability of psychological care in this population.

Enhancing Understanding

These personal perspectives also highlight how neuropsychiatric symptoms are unexpected by persons with PD and their families, despite prior education about the potential for behavioural changes. Most participants identified knowledge gaps in the psychiatric domain, with the majority able to recall accurate information regarding surgical complications of DBS and motoric benefits. Some participants disregarded information about psychiatric risks as they were preoccupied with addressing their motor symptoms, or they discounted the likelihood and impact of developing psychiatric symptoms, especially if they had no significant prior experience of psychiatric illness. However, it is important that surgical candidates and their families are explicitly prepared for this possibility, especially given that our participants perceived that ill-preparedness impaired their capacity to respond and cope with neuropsychiatric symptoms, and often delayed their help-seeking responses. Addressing this challenge may include the use of a structured instrument to deliver preoperative education. Further research is needed to develop such a tool, although the findings in this investigation will help identify knowledge gaps or when families are not likely to process information about the risk of behaviour change. Furthermore, clinicians may wish to employ a process of "corrected feedback" [42] whereby the clinician can test the level of comprehension of imparted information. Corrected feedback also views the communication of important and complex clinical information as an ongoing process both prior and subsequent to the relief of motor symptoms. Enhancing understanding may also necessitate greater clinician engagement with PD support groups, which offer fellowship and advice to many persons with PD. Perhaps it is easier for those persons who have some "lived experience" of psychiatric symptoms to conceptualise themselves or their spouses receiving psychiatric care.

Managing Unpredictability

Given the relative unpredictability of postoperative psychiatric symptoms, it remains uncertain how forthcoming clinicians should be regarding the "unknowns" of DBS. Unexpected and harmful neuropsychiatric symptoms may occur after STN-DBS, despite the oversight of a large and experienced movement disorders centre that follows best practice guidelines, including an embedded psychiatrist, preoperative psychiatric evaluation of all surgical candidates and a preoperative education programme delivered to spousal caregivers. It has previously been suggested that neuropsychiatric effects may be an integral, albeit unintended, consequence of STN-DBS for PD [24]. Other

nuclei in the basal ganglia, specifically the internal segment of the globus pallidus (GPi), have been advanced as a "safer" target for DBS [43] but these outcomes have been contested [44 45]. Could the choice of target be adapted to favour the GPi in persons prone to psychiatric complications? However, based on information that can be derived from a standard clinical assessment and mental state examination, it seems unlikely that a psychiatrist can accurately predict an "at risk" patient. Whilst false negatives are clearly a concern in this scenario, a false positive identification of an "at-risk" individual may also harm a patient by implementing a bias towards a surgical treatment option that ultimately has a lesser benefit for their quality of life [44]. Furthermore, it is also difficult to prospectively quantify the magnitude of future harm arising from subthalamic DBS. Although the cases reported in this investigation are clearly at the most severe end of the spectrum, there are a greater number of cases in which no neuropsychiatric symptoms arise or any emergent symptoms are detected quickly and addressed through prompt intervention with minimal or no enduring harm. What is the threshold of potential harm at which alternative targets should be considered? We agree with previous suggestions that the ultimate choice of target should be undertaken by the neurologist and neurosurgeon after a discussion with the surgical candidate and their family, during which the benefits and risks of stimulation at available targets can be considered [24].

Contradictory Narratives of Causation and Control

> "*I regard the mind-body problem as wide open and extremely confusing*"
>
> Saul A. Kripke, Naming and Necessity [46].

Many of us invoke differing narratives to explicate our behaviour, which may comprise neuroscientific, psychological and social understandings [47]. Our participants also employed a diverse explanatory framework, utilising both deterministic and moral paradigms. As a result, their attempts to make sense of their experiences in the context of DBS were frequently contradictory. The attitude of some caregivers was reminiscent of Immanuel Kant's assertion: "*... although we believe that the action is thus determined, we none the less blame the agent*" [48] describing behaviour as "*bad*" or "*childish*" despite endorsing a biological model of causation. This parallels findings in addiction, in which clinicians employ a neurobiological framework but retain a belief in the capacity of the individual to exercise control [49]. It is also conceivable that the connection of neuropsychiatric symptoms with DBS titration, or the biological model espoused by treating clinicians, challenged existing attitudes held by participants, causing them to switch between determined and moral modes of explanation. It has been argued that neuromodulation confronts the "folk dualism" of some persons [50]. Moreover, responsibility is not a unitary construct and can be seen as a syndrome of concepts, including causal relationships between intention, action and outcome, as well as moral judgements that an individual is blameworthy [51]. In addition, a distinction can be made between attributing moral character to an action and attributing moral responsibility for an action to an agent. This attributional ambiguity and complexity in the ways we tend to talk about responsibility may contribute to the distress experienced by many participants.

One further possibility is that these contradictory narratives serve a purpose in providing moral justification for action. In parents of children with attention deficit hyperactive disorder (ADHD), definitions of authenticity shift according to prevailing cultural norms and developmental ideals [52]. In our cohort, participants moved between particular frameworks of attribution and authenticity depending on their utility in explicating positive and negative behaviours. For example, behaviours that were evaluated negatively, such as irritability, disinhibition and relationship disruption, were often construed as arising from the exogenous and malign influence of stimulation. However, phenomena such as increased energy, generosity and extraversion were often seen as an opportunity to return to a more authentic self, facilitated rather than imposed by DBS (see Supplementary Material for further excerpts).

The perception of control exercised by participants with PD over neuropsychiatric symptoms after STN-DBS was variable. Some (e.g. person with PD 04) experienced a loss of autonomy manifest with lowered inhibitions and the perception of action contra to his identified values for normative behaviour. Others (e.g. person with PD 09) recognised that her actions had been out of keeping with her pre-surgical temperament but reasoned that she was able to exert voluntary suppression of those behaviours identified as problematic. Still others (e.g. person with PD 02) actively sought out changes in mood engendered by higher levels of

stimulation, reminiscent of other cases previously reported [53]. In this latter excerpt, there is even a suggestion that the DBS is controlling the person with PD.

Interestingly, no participant (person with PD or caregiver) raised concerns about a *change* of identity per se subsequent to STN-DBS. The language used by many participants evoked a notion of an essentialist "core" self, which had been suppressed by PD and released by DBS to a varying degree. However, DBS did not appear to disrupt the integration of these (sometimes radical) changes into the autobiographical narrative of the person with PD, even when viewed from the caregiver's perspective and even when acknowledging the causal role of brain manipulation in precipitating these changes [17 54]. Instead, when concerns were expressed by participants, these were primarily in the domain of autonomy, using phrases such as "on drugs" or "no circuit breaker". Again, this language seems to reflect a perception of a dysfunction in the cognitive machinery of autonomous decision making, leading to the expression of inauthentic behaviours rather than a shift in an underlying authentic selfhood.

It appears that participants (both persons with PD and caregivers) who noted a close relationship between stimulation changes and changes in mental status were more likely to conclude that these symptoms were inauthentic and uncontrollable. One could speculate that a close temporal association emphasises the connection between psychiatric symptoms and brain manipulation, which makes participants more likely to externalise this relationship. It is also possible that neuropsychiatric symptoms arising abruptly subsequent to stimulation manipulation are more likely to be of a negative valence, reflecting a more severe phenotype of neuropsychiatric dysfunction.

Limitations

The biological model of PM was acknowledged and may have affected data gathering and analysis. Furthermore, the dual clinical and investigative role of PM may have limited information disclosed due to concerns regarding confidentiality. We endeavoured to overcome the first issue by developing an investigative team with clinical and non-clinical backgrounds, with a spectrum of prior knowledge about the participants, in order to allow diverse perspectives. Participants provided constructive criticism of the clinical team, suggesting that they were willing to offer opinions and that PM's dual role did not prevent frank disclosure in this domain. Also, over 90% of participants in this investigation were male. This reflects a bias towards male gender in those accessing DBS at this centre (78% of all participants in the recruited cohort). Previous studies of drug addiction have identified gender differences in the attribution of control and responsibility [55]. Further research is needed to determine whether these findings are also applicable to female patients.

The emergence of neuropsychiatric symptoms after STN-DBS for PD is a complex matter, with potential contributions from non-motor progression of neurodegeneration, dopaminergic therapies, as well as neurostimulatory effects [5]. However, in this investigation, our rigorous assessment schedule [26 34], involving a multidisciplinary neurological and psychiatric evaluation, increased the likelihood that observed symptoms were attributable to stimulation rather than other causes. However, we acknowledge that we are unable to definitively answer "the causal question" as posed by Gilbert et al. [23] and discussed by Pugh et al. [56]. In our cohort, neuropsychiatric symptoms arose alongside clinically meaningful reductions in motor disability. Therefore, it remains possible that observed changes in mood, cognition and behaviour were indirect effects resulting from an amelioration of the participant's condition. We suggest that our method of specifying stimulation-dependent neuropsychiatric symptoms increases the likelihood of a causal relationship – i.e. onset with adjustment of stimulation and offset with further adjustment of stimulation and we also point to the wealth of neuroscientific data implicating the STN in the genesis of psychiatric symptoms (reviewed in [25]).

It is also important to acknowledge that STN-DBS has been shown to be of equivalent safety when compared with medical therapy [22], with some surgical centres reporting a postoperative reduction in problematic neuropsychiatric symptoms due to the reduction in dopaminergic medication afforded by neurostimulation [57]. To some degree this is reflected in our sample, with a change in the behavioural phenotype of participants 3, 5 and 10, who all had significant pre-surgical neuropsychiatric difficulties attributable to dopaminergic therapies.

Conclusions

In this investigation, we have shown that stimulation-dependent neuropsychiatric symptoms following STN-

DBS are often harmful and burdensome to persons with PD and their spousal caregivers.[2] Some participants did not fully integrate the information about potential psychiatric harms when it was delivered to them prior to surgery and further research will be important to identify new ways of preparing candidates in a way that is meaningful and memorable. Further work examining the neural basis of these symptoms may also assist clinicians to improve the informed consent process and deliver more reliable predictors of outcome, which at present remains affected by a degree of uncertainty.

There is evidence to support a causal link between stimulation and the emergence of psychiatric symptoms in our participants, which corresponds with existing data in the quantitative domain. However, many persons with PD did not hold an exclusively deterministic view and gave justified reasons for their (or their spouse's) behaviour that did not rely on a biological model. Furthermore, some participants actively sought out changes in their mental state that were linked to stimulation, despite identifying that their behaviour under these conditions was markedly different from baseline. Whereas a "scientific", neurobiological analysis of this phenomenon has many potential benefits, including improved understanding of neural mechanisms, prognostication, effective therapies and a reduction in stigma experienced by sufferers, further work is needed to clarify whether a bias towards deterministic or moral explanations helps or hinders the ability of participants to manage the burden and harms associated with neuropsychiatric symptoms. None of our participants considered that a change in identity had been precipitated by DBS, but some perceived that their autonomy (or that of their spouse) had been overridden by the device. This was most common for symptoms with negative consequences and for those symptoms with a close temporal connection to DBS manipulation. For these participants, inauthentic behaviour was considered to arise from a dysfunction in the competencies of autonomous decision making, rather than from a shift in authentically-held values. We hope that the empirical data that we have provided will contribute to further philosophical debate in this area.

[2] We acknowledge that some participants appeared to welcome or seek out changes in mental state attributable to neurostimulation. However, this was often later associated with harmful sequelae, e.g. person with PD 02 – suicide attempt; person with PD 06 – arrest and involuntary hospitalisation.

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Compliance with Ethical Standards

Conflict of Interest PM has received an honorarium for a speaking engagement with Boston Scientific and financial support for attending a conference from Abbott.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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