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Cognitive and Behavioural Changes After Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease

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1. Introduction

In patients with Parkinson's disease, cognitive impairment is common, may be detectable in early disease stages, even in young patients, and may progress to overt dementia. In addition, a variety of psychiatric and behavioural symptoms may occur in Parkinsonian patients, including depression, apathy, anxiety, visual hallucinations, sleep disorders, impulse control disorders, punding and the dopamine dysregulation syndrome. The cognitive and behavioural symptoms observed in these patients may be part of the non-motor symptoms of Parkinson's disease, which can appear in various phases of the disease course.

Various mechanisms might be involved in the pathogenesis of cognitive and behavioral symptoms in Parkinson's disease. Cognitive and behavioural symptoms observed in Parkinsonian patients might be related to disruption of various circuits involving dopaminergic, noradrenergic, cholinergic, and serotonergic systems (Candy et al., 1983; Mayeux et al., 1984; Cash et al., 1987; Mattay et al., 2002). Moreover, in patients with Parkinson's disease and dementia, neuropathological examination (Xuereb et al., 1990; Hughes et al., 1993) may show in several cortical areas the presence of Lewy Bodies (the histopathological hallmark of Parkinson's disease) or neurodegenerative lesions typical of Alzheimer's disease (amyloid plaques and neurofibrillary tangles). Furthermore, in patients with Parkinson's disease pharmacological treatment with anti-Parkinsonian dopaminergic drugs may have beneficial or detrimental effects on distinct cognitive functions (Malapani et al., 1994; Kulisevsky et al., 1996; Mattay et al., 2002) and may also play a role in the development of some behavioural disorders.

Among the cognitive deficits which may be detected in patients with Parkinson's disease, deficits of executive functions (planning, problem solving, set-shifting), mediated by disruption of neural circuits involving the frontal lobes and the basal ganglia, are the most common in both early disease phases and in patients with advanced Parkinson's disease (Morris et al., 1988; Cooper et al., 1991; Robbins et al., 1994; Taylor et al., 1986; Cools et al., 2001; Green et al., 2002).

In addition, memory deficits (Taylor et al., 1986; Harrington et al., 1990; Cooper et al., 1991; Robbins et al., 1994; Dubois and Pillon, 1997), deficits of visuo-spatial cognitive functions

(Boller et al., 1984; Hovestadt et al., 1987; Ransmayr et al., 1987), impairment on language tasks of verbal fluency (Matison et al., 1982; Cooper et al., 1991) and tasks of oral naming (Peran et al., 2003) may occur in individual Parkinsonian patients since early phases and become more frequent in advanced Parkinson's disease (Green et al., 2002).

As to memory deficits, different studies reported in Parkinsonian patients an impairment of episodic memory (Taylor et al., 1986), verbal short-term memory (Cooper et al., 1991), spatial short-term memory (Robbins et al., 1994), and procedural memory (Harrington et al., 1990). In patients with Parkinson's disease and dementia, the pattern of neuropsychological impairment may differ in distinct patient subgroups.

A subgroup of Parkinsonian patients, in which neurodegenerative lesions in the cerebral cortex seem to be less remarkable (Xuereb et al., 1990), may show a pattern of subcortical dementia, mainly characterized by remarkable deficits of executive functions (Litvan et al., 1991), associated with mild to moderate deficits of episodic long-term memory (Helkala et al., 1988) and, in some patients, deficits of visuo-spatial cognitive functions (Mohr et al., 1995), with relative sparing of linguistic and praxic functions (Dubois and Pillon, 1997). In another subgroup of patients with Parkinson's disease and dementia, in which neurodegenerative lesions in the cerebral cortex are more remarkable, in addition to the previously described neuropsychological pattern of subcortical dementia, it is possible to observe a an impairment of other cognitive functions mediated by various cortical areas, namely an impairment of linguistic and praxic functions and severe deficits of episodic long-term memory (Mohr et al., 1990; Mohr et al., 1995; Marsh, 2000).

As to psychiatric and behavioural symptoms which may be observed in patients with Parkinson's disease, depression, apathy, anxiety and visual hallucinations are the most common manifestations. Depressive syndromes (major depression and dysthymic disorder) may occur in up to 45% of Parkinsonian patients (Burn, 2002). Both psychosocial and neurobiological factors might be involved in the pathogenesis of depressive syndromes in Parkinson's disease. The role of psychosocial factors (such as a psychological reaction to motor disability) is suggested by studies reporting a significant correlation between severity of depressive symptoms and severity of motor symptoms (Gotham et al., 1986), while other investigations support the role of neurobiological factors such as a disruption of dopaminergic (Torack e Morris, 1988; Mayberg e Solomon, 1995), noradrenergic (Cubo et al., 2000; Menza et al., 2009) and serotonergic (Paulus e Jellinger, 1991) systems, which may occur in early phases of Parkinson's disease (Braak et al., 2004) and might result in the appearance of depressive symptoms. In some Parkinsonian patients, depressive symptoms may occur some years before the appearance of Parkinsonian motor symptoms, in agreement with the hypothesis of a critical role of neurobiological factors (Aarsland et al., 2009).

Apathy, which is characterised by a reduction in interest, motivation and initiative in daily living activities, is common in patients with Parkinson's disease and was detected in 17% to 70% of Parkinsonian patients in different studies (Leentjens et al., 2008; Pedersen et al., 2009). Although the pathogenic mechanisms involved in apathy in Parkinson's disease need to be further clarified, a dysfunction of the "limbic" circuit (Alexander et al., 1986) of the basal ganglia (which involve the ventral striatum, the anterior part of the cingulate gyrus and the mesial orbitofrontal cortex) might play a critical role.

Psychotic symptoms such as delusions and hallucinations are common in patients with Parkinson's disease and may occur in up to 26% of patients (Sanchez-Ramoz et al., 1996). In patients with Parkinson's disease, hallucinations and delusions may result from multiple pathogenic factors. Although these psychotic symptoms may be induced by the administration of dopaminergic anti-Parkinsonian drugs (Factor et al., 1995; Valldeoriola et al., 1997), they may occur also in Parkinsonian patients who do not receive any pharmacological treatment (Factor et al., 1995). The prevalence of hallucinations and delusions does increase with disease progression. Moreover, cognitive impairment is usually more marked in Parkinsonian patients with hallucinations as compared with Parkinsonian patients without hallucinations (Katzen et al., 2010). Visual hallucinations are the most frequent, are characterised by visions of people or animals, and are usually perceived as unpleasant**.**

Anxiety is also common in patients with Parkinson's disease, although epidemiological studies focussed on the prevalence of anxiety in these patients are still needed. In a recent study carried out in patients with Parkinson's disease in early stages, the prevalence of anxiety was about 27% (Bugalho et al., 2012).

Impulse control disorders (Ambermoon et al., 2011), punding and the dopamine dysregulation syndrome (Lim et al., 2009) have been increasingly recognized in recent years in patients with Parkinson's disease.

It has been reported that up to 13.6% of Parkinsonian patients (Weintraub et al, 2010) may develop behavioural changes due to a reduced impulse control (pathological gambling, hypersexuality, compulsive eating and buying/shopping). Such impulse control disorders may have dramatic implications for the personal life of the patient and for the patient's family.

In Parkinsonian patients, dopamine replacement therapy might play a role in the pathophysiology of impulse control disorders, by inducing an overstimulation of the mesolimbic dopaminergic system, which is critically involved in response to reward and motivation (Demetriades et al, 2011).

It has been suggested that in patients with Parkinson's disease the risk to develop impulse control disorders (Demetriades et al, 2011) may be increased by several demographic and clinical variables (younger age of onset of Parkinson's disease, treatment with dopamine agonists, male gender, pre-existing psychiatric disorders).

In Parkinsonian patients, the dopamine dysregulation syndrome is characterized by an overuse of dopaminergic anti-Parkinsonian drugs, resulting in the compulsive assumption of higher daily doses than those required to treat motor symptoms (Giovannoni et al., 2000).

Punding is a behavioural disorder in which the patient is frequently engaged in repetitive, stereotyped, non-goal-oriented activities. In patients with Parkinson's disease, punding may be triggered by dopaminergic anti-Parkinsonian drugs.

Deep brain stimulation of the subthalamic nucleus is an established neurosurgical procedure in the treatment of Parkinson's disease, which may remarkably improve the motor symptoms and quality of life in Parkinsonian patients (Hamani et al., 2005).

Deep brain stimulation of the subthalamic nucleus is more effective than best medical therapy in improving Parkinsonian motor symptoms and dyskinesias (Hamani et al., 2005) and allows to obtain a long-lasting decrease of the daily doses of anti-Parkinsonian medications. However, a worsening of axial motor symptoms (postural instability, freezing of gait, difficulties in articulation of speech) may be frequently observed at long-term follow-up, as reported in a 8-year follow-up study carried out in 20 Parkinsonian patients who underwent bilateral deep brain stimulation of the subthalamic nucleus (Fasano et al., 2010).

While the beneficial effects of bilateral deep brain stimulation of the subthalamic nucleus on motor symptoms in patients with advanced PD have been clearly analyzed by several studies, the effects of deep brain stimulation of the subthalamic nucleus on cognition and behaviour may at least partially differ among different studies and need to be further investigated.

2. Cognitive performance in Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus

Several investigations have assessed cognitive functioning in patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus, with variable duration of postoperative follow-up in different studies. In these investigations, statistical comparisons were made between preoperative (baseline) performance of Parkinsonian patients on neuropsychological tasks and postoperative performance on the same tasks.

Across all neuropsychological studies assessing cognitive functioning in patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus, a consistently reported finding is a postoperative decline on tasks of phonological and semantic verbal fluency (Ardouin et al. 1999; Pillon et al. 2000, Daniele et al. 2003; Funkiewiez et al. 2004; Parsons et al., 2006), which was detected already few months after surgery in some studies and gradually increased over time in studies with long-term follow-up (Contarino et al., 2007; Fasano et al., 2010).

On the other hand, different studies reported less consistent findings on other cognitive tasks, including tasks of episodic memory and working memory and tasks assessing frontal cognitive functions (Parson et al., 2006).

2.1 Performance of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus on tasks of verbal fluency

In patients affected by Parkinson's disease who underwent deep brain stimulation of the subthalamic nucleus, a postoperative decline on tasks of phonological and semantic verbal fluency has been consistently reported by all neuropsychological investigations. Such decline on performance on verbal fluency tasks has been usually detected few months after the surgical intervention and has been observed in patients with 1-year (Pillon et al., 2000; Daniele et al., 2003), 3-year (Funkiewiz et al., 2004), 5-year (Contarino et al., 2007; Fasano et al., 2010), and 8-year follow-up (Fasano et al., 2010). A recent study aimed at assessing long-term motor and cognitive outcome 8 years after implants for deep brain stimulation of the subthalamic nucleus in 20 patients with Parkinson's disease (Fasano et al., 2010) detected a

decline on phonological verbal fluency task, which was slightly more pronounced 8 years than 5 years after surgery.

In this study, 8 years after surgery performance on a phonological verbal fluency task could be assessed in 16 Parkinsonian patients. Interestingly, the analysis of raw scores (adjusted for age and educational level) obtained by individual Parkinsonian patients on the letter verbal fluency task at 8-year follow-up showed that only 2 out of 16 patients (12.5%) performed below the normal range and 1 patient (6.2%) scored around the cut-off score, while 13 out 16 patients (81.2%) performed in the normal range (Fasano et al., 2010). These latter findings suggest that in selected cohorts of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus the statistically significant decline on verbal fluency tasks observed as a group effect is associated with large interindividual variability (Contarino et al., 2007) and in some individual Parkinsonian patients might be not remarkable.

It should be pointed out that a poor performance on tasks of verbal fluency is frequently observed also in patients with Parkinson's disease patients treated by pallidotomy, especially after left-sided pallidotomy (Troster et al., 2003) and even in patients with Parkinson's disease who are not treated by neurosurgical procedures (Matison et al., 1982).

Recently, some investigations have attempted to compare performance on verbal fluency tasks in two different groups of patients with Parkinson's disease, namely patients treated by deep brain stimulation of the subthalamic nucleus versus Parkinsonian patients treated only by anti-Parkinsonian drugs (Zangaglia et al., 2009; Castelli et al., 2010; Williams et al., 2011). Such comparative studies consistently found that performance on verbal fluency tasks was significantly better in Parkinsonian patients treated only by anti-Parkinsonian drugs, as compared to patients who underwent deep brain stimulation of the subthalamic nucleus and were followed-up for 6 months (Witt et al., 2008), 1 year (Castelli et al., 2010), 2 years (Williams et al. 2011) and 3 years (Zangaglia et al., 2009).

In a randomized multicentre study (Witt et al., 2008), 123 patients with advanced Parkinson's disease and motor fluctuations were randomly assigned to have deep brain stimulation of the subthalamic nucleus or the best medical treatment for Parkinson's disease (according to the German Society of Neurology guidelines) and underwent neuropsychological and psychiatric examinations to detect possible changes 6 months after surgery, as compared to baseline. Sixty patients were randomly assigned to receive deep brain stimulation of the subthalamic nucleus and 63 patients to have best medical treatment.

After 6 months, the group of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus showed a significantly greater decline on tasks of phonological and semantic verbal fluency, as compared to the group of patients treated with the best medical treatment. These findings suggest that the impairment on verbal fluency tasks observed in patients who underwent subthalamic implants is not simply due to disease progression, but might be rather due to the neurosurgical intervention.

In a prospective 3-year follow-up study (Zangaglia et al., 2009), 32 Parkinsonian patients underwent deep brain stimulation of the subthalamic nucleus, while 33 Parkinsonian patients, even though eligible for this surgical procedure, declined surgery and were treated only by anti-Parkinsonian drugs. In this latter study, as compared to the group of patients

treated with the best medical treatment, the group of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus showed at 1-month and 3-year follow-up a significantly greater decline on a task of phonological verbal fluency.

In conclusion, the postoperative decline on verbal fluency tasks in patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus does not seem to have clinically meaningful effects on daily living activities, even in patients with long-term follow-up (Contarino et al., 2007).

Various hypotheses have been proposed to account for the postoperative decline on tasks of verbal fluency observed in patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus. On one hand, it has been suggested that the postoperative decline on such fluency tasks might be due to the neurosurgical procedure, namely to surgical microlesions affecting cortical-basal ganglionic circuits involved in word retrieval processes (Troster et al., 2003). This hypothesis is supported by the observation that the decline on verbal fluency tasks in Parkinsonian patients has been usually detected in very early phases after the subthalamic implant. An alternative hypothesis suggests that is the stimulation of the subthalamic nucleus which might lead to a decreased activity of various cortical areas in the left cerebral hemisphere (inferior frontal, insular and temporal areas), giving rise to a decreased performance on verbal fluency tasks (Schroeder et al. 2003).

2.2 Performance of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus on tasks of episodic memory and abstract reasoning

As suggested by a meta-analysis on neuropsychological studies in patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus (Parsons et al., 2006), a statistically significant but small decline of postoperative performance on tasks of episodic verbal memory has been reported in some investigations (Alegret et al., 2001; Daniele et al., 2003; Dujardin et al., 2001; Jahanshahi et al., 2000; Pillon et al., 2000; Saint-Cyr et al., 2000; Trepanier et al., 2000), but not in others. Such postoperative decline on episodic verbal memory tasks was detectable already 3 months after surgery in some studies (Alegret et al., 2001; Daniele et al., 2003), while in one cohort became not statistically significant at 1-year follow-up (Daniele et al., 2003).

In a recent study which attempted to compare performance on various neuropsychological tasks in two different groups of patients with Parkinson's disease followed-up for 12 months, namely 105 patients treated by deep brain stimulation of the subthalamic nucleus versus 40 Parkinsonian patients treated only by anti-Parkinsonian drugs (Smedding et al., 2011), performance at 6 and 12 months of postoperative follow-up on tasks of episodic verbal memory (immediate and delayed recall of the Rey's Auditory Verbal Learning Test) was significantly poorer in Parkinsonian patients who underwent subthalamic implants, as compared to patients treated only by anti-Parkinsonian drugs.

As to studies with long-term follow-up, a statistically significant but slight decline on episodic verbal memory tasks (immediate and delayed recall of the Rey's Auditory Verbal Learning Test) as compared to preoperative baseline was detected 8 years after subthalamic implants (Fasano et al., 2010).

However, in the cohort of 16 Parkinsonian patients followed up in such long-term study (Fasano et al., 2010), the analysis of individual raw scores (adjusted for age and educational level) showed that at 8-year follow-up on the immediate recall subtest of the Rey's Auditory Verbal Learning Test only 3 out of 16 Parkinsonian patients (18.7%) performed below the normal range and 1 out of 16 patients (6.2%) scored around the cut-off score discriminating between normal and pathological performance, while 12 out of 16 patients (75%) performed in the normal range.

In the same cohort, on the delayed recall subtest of the Rey's Auditory Verbal Learning Test, only 3 out of 16 Parkinsonian patients (18.7%) at 8-year follow-up performed below the normal range, while 13 out of 16 Parkinsonian patients (81.2%) performed in the normal range (Fasano et al., 2010).

These latter individual data suggest that in selected cohorts of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus the statistically significant decline on episodic verbal memory tasks observed as a group effect is associated with a large interindividual variability and might be not remarkable in some individual Parkinsonian patients.

A statistically significant but slight decline on a task of abstract reasoning (Raven's Progressive Matrices '47) was reported in neuropsychological studies in the same cohort of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus, which were assessed 5 years (Contarino et al., 2007) and 8 years after surgery (Fasano et al., 2010).

However, at 5-year follow-up the analysis of individual raw scores (adjusted for age and educational level) obtained by 11 individual Parkinsonian patients showed that on such task of abstract reasoning (Raven's Progressive Matrices '47) only 2 out of 11 Parkinsonian patients performed slightly below the normal range, while the remaining 9 patients performed in the normal range (Contarino et al., 2007).

Similarly, at 8-year follow-up the analysis of the raw scores (adjusted for age and educational level) obtained by 16 individual Parkinsonian patients on Raven's Progressive Matrices '47 showed that only 1 out of 16 patients scored around the cut-off score, while the remaining 15 patients performed in the normal range (Fasano et al., 2010).

These individual data suggest that in selected cohorts of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus the statistically significant decline on tasks of abstract reasoning observed as a group effect at long-term follow-up might be not remarkable in individual Parkinsonian patients.

2.3 Performance of Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus on tasks assessing cognitive functions mediated by the frontal lobes

In patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus, different effects have been described on neuropsychological tasks assessing distinct cognitive functions mediated by the frontal lobes.

On one hand, various studies reported after subthalamic implants an impaired performance on frontal tasks assessing response inhibition, such as the interference subtest of the Stroop

test (Jahanshahi et al., 2000; Schroeder et al., 2002; Witt et al., 2004), in ON-stimulation condition as compared to the OFF-stimulation condition.

A positron emission tomography study showed that such impaired performance on the interference subtest of the Stroop test in the on-stimulation condition was associated with decreased activation in both the right anterior cingulate cortex and the right ventral striatum (Schroeder et al., 2002).

In a previously mentioned randomized multicentre study (Witt et al. , 2008) carried out in 123 Parkinsonian patients who were randomly assigned to receive deep brain stimulation of the subthalamic nucleus (n =60) or to have best medical treatment (n=63), as compared to the best medical treatment group the group of patients treated by deep brain stimulation showed 6 months after surgery a significantly greater decline on several variables of the Stroop test. This finding might be accounted for by a dysfunction of neural circuits involving the basal ganglia and the frontal lobes, which might play a critical role in response selection (Witt et al., 2008) and response inhibition.

On the other hand, in patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus an improved postoperative performance has been reported in early phases of follow-up (6 six months after surgery) up to 26 months on neuropsychological frontal tasks assessing cognitive flexibility, such as the Modified Wisconsin Card Sorting Test (Jahanshahi et al., 2000; Daniele et al., 2003) and tasks of random number generation (Witt et al., 2004).

In a neuropsychological study carried out in 20 Parkinsonian patients who underwent bilateral deep brain stimulation of the subthalamic nucleus (Daniele et al., 2003), patients were tested 3 months after surgery with stimulators switched off, while 6 and 12 months after surgery they were tested with stimulators switched on. In this study, an improved performance on a task of cognitive flexibility (Modified Wisconsin Card Sorting Test) was detected 6 and 12 months after surgery, when stimulators were switched on. It was hypothesised that such improved performance on the Modified Wisconsin Card Sorting Test could arise either from a genuine improvement of a specific frontal executive function such as cognitive flexibility (i.e. set-shifting ability) due to subthalamic implants or, alternatively, from a practice effect resulting from the repeated administration of the same cognitive task over time (Daniele et al., 2003).

In a study carried out in 23 Parkinsonian patients who underwent bilateral deep brain stimulation of the subthalamic nucleus and were tested 6 to 12 months after surgery with stimulators switched on or off in random order (Witt et al., 2004), in the ON-stimulation condition there was a poorer performance on a task of response inhibition (interference subtest of the Stroop test) and an improved performance on a task of cognitive flexibility (random number generation), as compared to the OFF-stimulation condition.

These findings are at least partially consistent with the results of a preliminary study carried out in 7 Parkinsonian patients treated by bilateral deep brain stimulation of the subthalamic nucleus (Jahanshahi et al., 2000), who were tested at variable intervals after surgery (4 to 26 months after surgery, with a mean of 11.7 months) with stimulators switched ON or OFF in random order. In this latter study, in the ON-stimulation condition there was a better performance on tasks of cognitive flexibility (random number generation, Modified Wisconsin Card Sorting Test), as compared to the OFF-stimulation condition.

On the whole, these studies suggest that stimulation of the subthalamic nucleus might have different effects on distinct neural circuits involving the basal ganglia and the frontal lobes, resulting in a potential improvement of performance on neuropsychological tasks assessing cognitive flexibility (set-shifting ability) and a potential impairment of performance on neuropsychological tasks assessing response inhibition.

As to studies with long-term follow-up, a statistically significant but slight decline on a task of cognitive flexibility (number of correct criteria discovered on the Modified Wisconsin Card Sorting Test) was detected 8 years after subthalamic implants, as compared to preoperative baseline (Fasano et al., 2010). In this study, as to the number of correct criteria on the Modified Wisconsin Card Sorting Test, the analysis of individual raw scores of a cohort of 15 Parkinsonian patients showed that at 8-year postoperative follow-up 6 out of 15 patients (40%) performed below the normal range, while the remaining 9 patients (60%) performed in the normal range (Fasano et al., 2010).

Eight years after surgery, Parkinsonian patients with a worsening of postoperative performance (increased number of total errors as compared to baseline) on the Modified Wisconsin Card Sorting Test showed significantly higher scores on items assessing postural stability (namely, a poorer postural stability), as compared to patients in which postoperative performance on the Modified Wisconsin Card Sorting Test (number of total errors as compared to baseline) was improved or unchanged (Fasano et al., 2010).

As to decision-making processes, in which the subthalamic nucleus and prefrontal cortical areas might play a critical role, some studies reported after deep brain stimulation of the subthalamic nucleus (Frank et al., 2007) a reduced ability of Parkinsonian patients to slow down their decisions in high-conflict conditions (namely, an increased impulsivity), while other studies detected an improved performance on tasks of reward-based decision learning (VanWouve et al, 2011).

2.4 Long-term cognitive follow-up in patients treated by deep brain stimulation of the subthalamic nucleus

To summarise the results of the previously mentioned study which assessed motor and cognitive outcome in Parkinsonian patients 8 years after subthalamic implants (Fasano et al., 2010), this investigation reported a statistically significant decline on a phonological verbal fluency task and a statistically significant but slight decline on tasks of abstract reasoning (Raven's Progressive Matrices '47), episodic verbal memory (immediate and delayed recall of the Rey's Auditory Verbal Learning Test), executive functioning (number of correct criteria on the Modified Wisconsin Card Sorting Test).

2.5 Prevalence of dementia in patients treated by deep brain stimulation of the subthalamic nucleus

In studies implementing strict selection criteria in recruiting Parkinsonian patients for deep brain stimulation of the subthalamic nucleus, the prevalence of dementia was relatively low, even at long-term follow-up (Krack et al., 2003; Fasano et al., 2010).

In a 5-year follow-up study, the prevalence of dementia was 6%, as 3 out of 49 patients developed dementia 5 years after surgery (Krack et al., 2003).

In the cohort of Parkinsonian patients with 8-year follow-up mentioned above (Fasano et al., 2010), there was a 5% prevalence of dementia. In this latter study, 5 years after surgery only one out of 20 patients developed dementia, which had progressed at 8 years (Fasano et al., 2010). Such prevalence rates are lower than those reported in other studies investigating less strictly selected Parkinsonian patients, such as one study reporting in Parkinsonian patients a 38% prevalence of dementia after 10 years of follow-up (Hughes et al., 2000).

However, in one 3-year follow-up study carried out in 57 Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus (Aybek at al., 2007), dementia appeared in 5 out of 57 patients (8.7%) 6 months post surgery and in 24.5% of the patients 3 years post surgery, while the rest of the cohort remained cognitively stable over the whole follow-up. These Authors pointed out that in their cohort the prevalence of dementia over 3 years after deep brain stimulation of the subthalamic nucleus is similar to the prevalence reported in medically treated patients (Aybek at al., 2007). Moreover, in this cohort of patients treated by deep brain stimulation of the subthalamic nucleus some demographic and clinical variables (older age, presence of hallucinations, poorer performance on executive tasks) were preoperative risk factors of developing dementia (Aybek at al., 2007).

The observation of a relatively high prevalence (8.7%) of dementia 6 months post surgery may suggest the hypothesis that less strict selection criteria were employed in this study (Aybek at al., 2007), as compared with other studies with long-term follow-up reporting a lower incidence of dementia (Krack et al., 2003; Fasano et al., 2010).

2.6 Conclusive remarks on the effects deep brain stimulation of the subthalamic nucleus on cognition

Most neuropsychological studies in Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus share a methodological limitation, namely the lack of a control group of medically-treated Parkinsonian patients, which should be matched at baseline to patients who undergo deep brain stimulation of the subthalamic nucleus as to various clinical and demographic variables (age, educational level, overall cognitive status, severity of motor impairment).

Comparisons between Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus and medically treated Parkinsonian patients may allow to take into account cognitive decline due to aging and disease progression, particularly in patients with long-term follow-up.

However, in most studies which recruited a control group of medically-treated Parkinsonian patients the follow-up was relatively short, with follow-up periods of 6 months (Witt et al., 2008), 1 year (Castelli et al., 2010), 2 years (Williams et al., 2011) and 3 years (Zangaglia et al., 2009). Studies recruiting a control group of medically-treated Parkinsonian patients with a longer follow-up period are currently needed.

Only some neuropsychological investigations have attempted to discriminate between the effects on cognitive performance of the surgical intervention and the effects on cognitive performance of deep brain stimulation of the subthalamic nucleus itself (Jahanshahi et al., 2000; Pillon et al., 2000; Daniele et al., 2003), by comparing cognitive performance on

neuropsychological tasks in different stimulation condition, namely with stimulators turned "ON" versus with stimulators turned "OFF".

In one study (Jahanshahi et al., 2000), performance on neuropsychological tasks of executive functions was investigated in 7 patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus and 6 patients treated by deep brain stimulation of the internal globus pallidus. Patients were assessed three times: with stimulators OFF, with stimulators ON, with stimulators OFF gain. With stimulators ON, in both groups of patients (Jahanshahi et al., 2000) there was a decline in a conditional associative learning task and an improved performance on several tasks assessing executive functions (Trail Making test part A and B, missing digit test, paced visual serial addition test, colour naming subtest of the Stroop Test). Moreover, with stimulators ON, only the subthalamic group showed a significant improvement on some additional tasks assessing executive functions (random number generation, Modified Wisconsin Card Sorting Test).

In another study (Pillon et al., 2000), cognitive performance of Parkinsonian patients treated by deep brain stimulation of either the subthalamic nucleus or the internal globus pallidus was assessed postoperatively at 3 months and 12 months, in different stimulation conditions. In this study, the group of patients treated by subthalamic implants showed in ON-stimulation condition an improved cognitive performance on neuropsychological tasks of psychomotor speed and spatial working memory (Pillon et al., 2000).

In patients with Parkinson's disease, the investigation of the effects on cognition of deep brain stimulation of the subthalamic nucleus as compared to the internal globus pallidus is of remarkable importance, in order to establish the potential beneficial and detrimental effects of both procedures.

In patients with Parkinson's disease who were treated by unilateral (Vingerhoets et al., 1999) or bilateral (Field et al., 1999) deep brain stimulation of the internal globus pallidus, preliminary short-term studies with a 3-month follow-up did not detect significant postoperative changes in cognitive performance.

By contrast, some investigations detected a mild decline on tasks of semantic verbal fluency (Volkmann et al., 2004) or executive dysfunction (Dujardin et al., 2000) in patients treated by bilateral deep brain stimulation of the internal globus pallidus and a mild decline on visuoconstructional tasks and on tasks of semantic verbal fluency in patients who underwent unilateral deep brain stimulation of the internal globus pallidus (Tröster et al., 1997).

A prospective randomized trial assessed cognition and mood in 23 patients treated by unilateral deep brain stimulation of the internal globus pallidus, as compared to 22 patients treated by unilateral deep brain stimulation of the subthalamic nucleus (Okun et al., 2009).

In this study, a significantly greater decline on a task of phonological verbal fluency was detected 7 months after surgery in the group who underwent subthalamic implants, as compared to the group treated by deep brain stimulation of the internal globus pallidus.

Moreover, in a multicenter long-term study carried out in 35 Parkinsonian patients treated by bilateral deep brain stimulation of the subthalamic nucleus and in 16 patients treated by bilateral deep brain stimulation of the internal globus pallidus (Moro et al., 2010), 5 to 6

years after surgery the occurrence of cognitive decline was higher in the group with subthalamic implants (23% of patients), as compared to the group with implants in the internal globus pallidus (12% of the patients).

In conclusion, although cognitive morbidity after deep brain stimulation of the subthalamic nucleus is relatively low, deep brain stimulation of the internal globus pallidus seems to have even a lower cognitive morbidity and might be a safer option in Parkinsonian patients who are more at risk for cognitive impairment.

3. Effects of deep brain stimulation of the subthalamic nucleus on behavioural symptoms

In Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus, both transient behavioural symptoms (apathy, manic symptoms, hypersexuality) and persistent behavioural symptoms (apathy, impulse control disorders, punding, depression with increased suicidal tendencies in some patients) have been described. On the other hand, some studies reported in Parkinsonian patients treated by subthalamic implants a postoperative improvement of behavioural symptoms (depression, anxiety, hallucinations, impulse control disorders).

3.1 Effects of deep brain stimulation of the subthalamic nucleus on mood

3.1.1 Depressive symptoms: Clinical presentation, evolution, and pathophysiology

After implants for deep brain stimulation of the subthalamic nucleus, some studies detected a postoperative improvement of depression (Daniele et al., 2003; Houeto et al., 2006; Kalteis et al., 2006) or no change in depressive symptoms (Drapier et al., 2006; York et al., 2008), while other studies reported the appearance or the worsening of depressive symptoms (Takeshita et al. 2005, Castelli et al., 2006; Temel et al. 2006).

In patients with Parkinson's disease treated by deep brain stimulation of the subthalamic nucleus, the proportion of subjects in which depressive symptoms appear or worsen after surgery as a persistent behavioural change varies between 2% up to 33%, according to different studies (Takeshita et al., 2005, Temel et al., 2006). Such appearance or worsening of depressive symptoms may be detected also in Parkinsonian patients who show a satisfactory postoperative improvement of motor symptoms.

A previously mentioned long-term follow-up study in 20 consecutive Parkinsonian patients who received by deep brain stimulation of the subthalamic nucleus (Fasano et al., 2010) did not detect any significant postoperative change on scales assessing depression 8 years after surgery, as compared with preoperative baseline.

In a previously mentioned prospective randomized study aimed at comparing mood in 22 patients treated by unilateral deep brain stimulation of the subthalamic nucleus and 23 patients treated by unilateral deep brain stimulation of the internal globus pallidus, 7 months after surgery changes in mood did not significantly differ between the two groups of patients (Okun et al., 2009).

In those Parkinsonian patients who show a postoperative improvement of depressive symptoms, such improvement has been interpreted as resulting either from a psychological

response to the amelioration of Parkinsonian motor symptoms (Jahanshahi et al., 2000) or to the effects of deep brain stimulation of the subthalamic nucleus on neural systems which play a role in mood (Romito et al., 2002).

It has been hypothesized that in Parkinsonian patients treated with subthalamic implants postoperative depression might result either from the reduction of daily doses of dopaminergic drugs (Giovannoni et al, 2000) or from an indirect inhibition of the activity of serotonergic neurons in the dorsal raphe nuclei induced by deep brain stimulation of the subthalamic nucleus (Temel et al., 2007), possibly through various structures (ventral pallidum, substantia nigra pars reticulata, medial prefrontal cortex) which directly project to dorsal raphe nuclei (Tan et al., 2001).

3.1.2 Depressive symptoms: Treatment and prognosis

After deep brain stimulation of the subthalamic nucleus, suicidal tendencies have been reported in some Parkinsonian patients (Soulas et al., 2008; Voon et al., 2008).

In a retrospective survey carried out in 5311 Parkinsonian patients treated with subthalamic implants (Voon et al., 2008) the rate of completed suicide was 0.45%, while the rate of attempted suicide was 0.90%. In this study, an increased risk of attempted suicide was associated with a number of factors (postoperative depression, previous history of impulse control disorders or compulsive medication use, being single) and the highest rate of suicides was detected in the first postoperative year.

In another retrospective survey carried out in a smaller sample (n = 200) of Parkinsonian patients who underwent subthalamic implants (Soulas et al., 2008), despite a remarkable motor improvement, there was a higher than expected frequency of suicide (1% of completed suicide, 2% of attempted suicide) and suicidal behaviour was associated with postoperative depression and altered impulse control.

These latter studies (Soulas et al., 2008; Voon et al., 2008) show that there might be an increased risk of suicidal behaviour in Parkinsonian patients treated with subthalamic implants, suggesting that the main risk factor for attempted and completed suicide is postsurgical depression, which on postoperative follow-up should be adequately diagnosed and treated with anti-depressant drugs.

3.1.3 Manic symptoms: Clinical presentation, evolution, and pathophysiology

A systematic review of a large sample (n = 1398) of Parkinsonian patients who underwent bilateral brain stimulation of the subthalamic nucleus showed that the occurrence of manic symptoms was reported in about 4% of PD patients (Temel et al., 2006), more frequently early after surgery (Romito et al., 2002; Schupbach et al., 2005; Visser-Vandewalle et al., 2005; Contarino et al., 2007).

Manic symptoms in patients treated by subthalamic implants mostly last few hours or few days and are usually observed after stimulation of contacts in the ventral part of the substantia nigra, probably in the substantia nigra pars reticulata (Ulla et al., 2006; Ulla et al., 2011).

In some patients, however, manic symptoms might be induced by stimulation of contacts within the subthalamic nucleus (Ulla et al., 2011; Mallet et al., 2007), especially by

stimulation of a ventral contact of the electrode within the subthalamic nucleus. In these cases, manic symptoms may disappear by switching off this ventral contact (Mallet et al. 2007). It has been also suggested that stimulation of axons projecting from medial (limbic) subthalamic nucleus to the medial forebrain bundle might give rise to transient reversible hypomania (Coenen et al., 2009).

In Parkinsonian patients who show stimulation-induced manic symptoms after subthalamic implants (Ulla et al., 2011), positron emission tomography showed during the manic state an increase of regional cerebral blood flow in various structures (anterior cingulate cortex, the medial prefrontal cortex, primary motor cortex, globus pallidus), mainly in the right cerebral hemisphere.

These findings support the hypothesis that a dysfunction of limbic structures (particularly, the anterior cingulate cortex and the medial prefrontal cortex) in the right cerebral hemisphere, induced by stimulation of the substantia nigra or the subthalamic nucleus, might play a critical role in the pathophysiology of manic states induced by subthalamic implants in Parkinsonian patients.

3.1.4 Manic symptoms: Treatment and prognosis

In Parkinsonian patients, manic symptoms may disappear after switching to other targets to be stimulated (Raucher-Chene et al., 2008) or readjusting the parameters of stimulation (Mandat et al., 2006).

3.2 Effects of deep brain stimulation of the subthalamic nucleus on apathy

3.2.1 Apathy: Clinical presentation, evolution, and pathophysiology

Apathy, which may be defined as loss of motivation (Marin, 1991), is a common behavioural symptom in patients with Parkinson's disease.

Most studies assessing apathy before and after surgery in Parkinsonian patients treated by subthalamic implants found a postoperative worsening of apathy (Funkiewiez et al., 2004; Schupbach et al., 2005; Drapier et al., 2006; Contarino et al., 2007; Le Jeune et al., 2009; Porat et al., 2009; Thobois et al., 2010), while two studies found no postoperative change in apathy (Castelli et al., 2006; Castelli et al., 2007). By contrast, in Parkinsonian patients who underwent bilateral deep brain stimulation of the subthalamic nucleus a transient improvement of apathy was detected after acute subthalamic stimulation, namely in ON stimulation as compared to OFF stimulation condition (Czernecki et al., 2005). To our knowledge, no study reported in Parkinsonian patients a significant improvement of chronic apathy following subthalamic implants.

It has been reported that after subthalamic implants a postoperative worsening of apathy may occur in the absence of significant postoperative changes of depression or anxiety (Drapier et al., 2006).

In a recent study (Kirsh-Darrow et al., 2011), apathy was assessed in Parkinsonian patients who underwent either unilateral deep brain stimulation of the internal globus pallidus (n = 15) or unilateral deep brain stimulation of the subthalamic nucleus (n = 33) and in a control group of medically treated Parkinsonian patients (n = 48). The results of this study show

that apathy progressively increased up to 6 months after both subthalamic and pallidal unilateral implants, while it was unchanged in the non-surgical group of Parkinsonian patients (Kirsh-Darrow et al., 2011). In this study, the degree of apathy in patients who underwent deep brain stimulation was not related to postsurgical changes in levodopa equivalent daily doses (Kirsh-Darrow et al., 2011).

In a prospective study focused on the occurrence of apathy and associated symptoms in 63 patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus (Thobois et al., 2010), apathy appeared in 34 patients after a mean of 4.7 months and was reversible in 17 patients by the 12-month follow-up.

In this study, [11C]-raclopride positron emission tomography showed that binding values were greater in apathetic Parkinsonian patients in various structures (orbitofrontal, dorsolateral prefrontal, posterior cingulate and temporal cortices, left striatum and right amygdala) bilaterally, suggesting a greater dopamine D2/D3 receptor density or reduced synaptic dopamine level in such structures.

3.2.2 Apathy: Treatment and prognosis

The effects of a 6-week treatment with the dopamine D2-D3 agonist ropinirole was investigated in 8 Parkinsonian patients who developed apathy after complete withdrawal from dopaminergic medication, following successful subthalamic implants (Czernecki et al., 2008). In 7 out of 8 Parkinsonian patients (in which the stimulation contacts were located within the subthalamic nucleus), ropinirole induced an improvement of apathy, while only one patient (in whom the stimulation contacts were located within the zona incerta) remained apathetic. This study suggests that in Parkinsonian patients treated by subthalamic implants apathy may result from a dopaminergic deficiency in associative limbic areas and can be effectively treated in most patients by dopaminergic agonists administered postoperatively (Czernecki et al., 2008).

3.3 Effects of deep brain stimulation of the subthalamic nucleus on anxiety

3.3.1 Anxiety: Clinical presentation, evolution, and pathophysiology

After subthalamic implants, a number of studies showed in Parkinsonian patients a postoperative improvement of anxiety (Daniele et al., 2003; Houeto et al., 2006; Kalteis et al., 2006; Schupbach et al., 2007) or no change in anxiety symptoms (Drapier et al. , 2006; York et al., 2008), while other studies reported the appearance or the worsening of anxiety (Rodriguez-Oroz et al. 2005; Castelli et al., 2006).

The postoperative improvement of anxiety observed in some studies might result from the beneficial effects of subthalamic implants on the motor symptoms of Parkinson'disease (Daniele et al., 2003).

On the other hand, in Parkinsonian patients treated by subthalamic implants, in which a marked reduction of daily doses of dopaminergic drugs is usually obtained postoperatively, it has been hypothesized that a postoperative worsening of anxiety might result from a delayed dopamine withdrawal syndrome (Thobois et al., 2010).

In Parkinsonian patients, individual differences in both dopaminergic treatment and in the extent of denervation of dopaminergic mesolimbic systems might explain the variable

effects of deep brain stimulation of the subthalamic nucleus on anxiety, mood and motivation/apathy (Thobois et al., 2010).

3.3.2 Anxiety: Treatment and prognosis

So far, the issue of treatment of anxiety symptoms in Parkinsonian patients who undergo subthalamic implants has been poorly investigated.

In a study with a 6-month follow-up period in which patients were randomly assigned to have subthalamic implants (n = 63) or the best medical treatment for Parkinson's disease (n = 60), anxiety was reduced in the subthalamic implant group, as compared with the medically-treated group (Witt et al., 2008). In a long-term follow-up study in 20 Parkinsonian patients who received subthalamic implants, 8 years after surgery no significant change was observed on a scale assessing anxiety, as compared with baseline (Fasano et al., 2010).

3.4 Effects of deep brain stimulation of the subthalamic nucleus on psychotic symptoms

3.4.1 Psychotic symptoms: Clinical presentation, evolution, and pathophysiology

In Parkinsonian patients treated by bilateral subthalamic implants, hallucinations and delusions may appear as transient behavioural symptoms shortly after surgery (Romito et al., 2002).

It is still matter of debate whether Parkinsonian patients with history of hallucination may be good candidates for subthalamic implants.

A retrospective review of 10 Parkinsonian patients who suffered from severe medication-induced hallucinations or delusions and underwent bilateral subthalamic implants (Umemura et al., 2011) showed that such psychotic symptoms disappeared in 8 out of 10 patients after postoperative reduction of dopaminergic medication. By contrast, in 2 out of 10 patients hallucinations and delusions worsened immediately after surgery (despite complete withdrawal of dopaminergic medication), but disappeared after treatment with anti-psychotic drugs for some months (Umemura et al., 2011). On the whole, such retrospective review suggests that deep brain stimulation of the subthalamic nucleus is a good treatment option in Parkinsonian patients with medication-induced hallucinations or delusions, provided that the possible worsening of psychotic symptoms which may be observed in a subgroup of patients is carefully monitored and treated.

In a further study aimed at assessing the effects of subthalamic implants on preexisting hallucinations in 18 patients with advanced Parkinson's disease (Yoshida et al., 2009), six months after the implant there was a significant postoperative improvement of severity of hallucinations, as compared with baseline.

These latter studies (Umemura et al., 2011; Yoshida et al., 2009) suggest that in patients with advanced Parkinson's disease a history of hallucinations is not a contraindication to subthalamic implants.

In conclusion, it might be hypothesized that in most Parkinsonian patients with medication-induced hallucinations a postoperative reduction of dopaminergic anti-Parkinsonian drugs might play a critical role in the postoperative improvement of hallucinations.

3.4.2 Psychotic symptoms: Treatment and prognosis

As mentioned above, treatment with anti-psychotic drugs is indicated in Parkinsonian patients in whom hallucinations and delusions worsen immediately after surgery (Umemura et al., 2011). In a group of Parkinsonian patients followed up for 3 years after deep brain stimulation of the subthalamic nucleus, the use of antipsychotic drugs was stable until 1 year, while there was a subsequent increase in the use of antipsychotic drugs at 3 years (Zibetti et al., 2009).

3.5 Effects of deep brain stimulation of the subthalamic nucleus on impulse control disorders

3.5.1 Impulse control disorders: Clinical presentation, evolution, and pathophysiology

In Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus, impulse control disorders (pathological gambling, hypersexuality, compulsive eating and buying/shopping) may occasionally appear after surgery, while in most cases preexisting impulse control disorders may improve or disappear after subthalamic implants (Broen et al., 2011; Witjas et al., 2005; Bandini et al., 2007; Ardouin et al., 2006; Lim et al., 2009).

As to pathological gambling (Lim et al., 2009) and hypersexuality (Doshi & Bargava, 2008), these disorders may be occasionally be observed in some Parkinsonian patients after subthalamic implants, while Parkinsonian patients may rarely develop compulsive eating after subthalamic implants (Zahodne et al., 2011). A weight gain, which may result from multiple pathogenic factors besides compulsive eating, may be detected in up 48% of Parkinsonian patients after deep brain stimulation of the subthalamic nucleus (Piboolnurak et al., 2007).

In Parkinsonian patients who show a postoperative improvement of preexisting impulse control disorders, such improvement might be due to at least two mechanisms. The most plausible mechanism is a reduction of dopaminergic medication after the subthalamic implants, which leads to decreased stimulation of mesolimbic dopaminergic circuits (Ardouin et al., 2006). Alternatively, it has been proposed that deep brain stimulation of the subthalamic nucleus may induce inhibitory effects on dopaminergic and serotoninergic pathways ascending to limbic circuits involved in reward (Witjas et al., 2005).

On the other hand, in some Parkinsonian patients, impulse control disorders appear after subthalamic implants, notwithstanding with a postoperative reduction of doses of dopaminergic drugs (Romito et al., 2002; Doshi and Bargava, 2008; Smeding et al., 2007; Sensi et al., 2004; Lim et al., 2009). In these latter patients, it might be hypothesised that deep brain stimulation of the subthalamic nucleus may induce changes in the activity of limbic circuits involving the subthalamic nucleus or involving fibres adjacent to this nucleus, giving rise to a tendency to impulsivity (Demetriades et al, 2011). A neurophysiological study aimed at recording local field potentials in the subthalamic nucleus of Parkinsonian patients patients treated by deep brain stimulation of the subthalamic nucleus (Rodriguez-Oroz et al., 2011) showed an oscillatory theta-alpha activity in the ventral subthalamic nucleus, which was associated with impulse control disorders, suggesting that such limbic ventral subthalamic area might be involved in the development of impulse control disorders in these Parkinsonian patients.

It has been previously mentioned that the subthalamic nucleus and prefrontal cortical areas might play a critical role in decision-making processes and that patients with Parkinson's disease may show after deep brain stimulation of the subthalamic nucleus a reduced ability to slow down their decisions in high-conflict conditions, resulting in increased impulsivity (Frank et al., 2007).

3.5.2 Impulse control disorders: Treatment and prognosis

In a cross-sectional study aimed at comparing Parkinsonian patients treated by subthalamic implants versus Parkinsonian patients treated by anti-Parkinsonian drugs but eligible for deep brain stimulation (Halbig et al. , 2009), impulsivity was assessed by the Barratt Impulsiveness Scale and was higher in patients with subthalamic implants. In this study, the prevalence of impulse control disorders was higher (3 out of 16 subjects, namely 19%) in patients treated by subthalamic implants than in medically treated Parkinsonian patients (3 out of 37 subjects, namely 8%). The Authors suggest that screening for impulsivity and impulse control disorders should be performed prior to deep brain stimulation (Halbig et al. , 2009).

In conclusion, since the effects of brain stimulation of the subthalamic nucleus on impulse control disorders in Parkinsonian patients are variable, the prognosis of such disorders may vary from patient to patient, although in most Parkinsonian patients preexisting impulse control disorders may improve or disappear after subthalamic implants. Further studies are needed in order to clarify the issue of treatment strategies in those patients in whom impulse control disorders do appear or worsen after surgery.

3.6 Long-term behavioural follow-up in patients treated by deep brain stimulation of the subthalamic nucleus

In the previously mentioned study assessing motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants (Fasano et al., 2010), in the overall group of patients there was no significant change 8 years after surgery on behavioural scales assessing depression and anxiety, as compared to preoperative baseline. In the cohort of 20 Parkinsonian patients who completed the 8-year follow-up (Fasano et al., 2010), a number of persistent behavioral adverse events were reported, such as depressive symptoms (in 25% of the patients), apathy (in 20% of the patients), psychotic symptoms (in 20% of the patients), hypersexuality (in 5% of the patients).

3.7 An explicative case of a Parkinsonian patient with manic symptoms after bilateral subthalamic implants

A 52-year-old right-handed man presented a 11-year history of severe rigid–akinetic Parkinson's disease, which became poorly responsive to anti-Parkinsonian medication (Romito et al., 2002). This patient, who had a family history of major depression, at the age of 26 years suffered from a major depressive episode, during his father's terminal illness.

The patient received a implant of quadripolar leads bilaterally in the subthalamic nucleus under stereotactic guidance. Compared to preoperative assessment, he showed a marked improvement of Parkinsonian motor symptoms and activities of daily living, while wearing-off phenomena and on-state dyskinesias (reported before the implantation) disappeared.

Two days after the implant, the patient developed a manic syndrome (Romito et al., 2002), characterized by inflated self-esteem and grandiosity, marked increase in goal-directed activities, need to purchase unneeded items, decreased need for sleep, planning of hazardous business investments, flights of ideas. His appetite decreased and the patient lost 5 to 6 kg. Sexual desire and sexual activity increased and the patient had frequent spontaneous erections, although he was not on dopamine agonists. Despite a lack of interest in religion, he started to spend much time in writing poems on religious themes. Moreover, the patient became irritable, litigious, and over-reactive. A diagnosis of manic episode was made.

When the stimulator was turned off, there was a rapid worsening of Parkinsonian motor symptoms but manic symptoms did not improve (Romito et al., 2002).

In this patient, all antiparkinsonian medication was discontinued 1 month after surgery. Stimulation settings remained unchanged from the second month on. During postoperative follow-up up to 12 months after surgery, he showed no significant change in cognitive performance on neuropsychological tasks, as compared to preoperative performance.

In agreement with his wife, the patient was followed up very carefully, but no pharmacological treatment for manic symptoms was prescribed. Three months after their onset, manic symptoms gradually decreased and then disappeared completely. Twelve months after the subthalamic implant, the patient showed a slight reduction of initiative, in the absence of any significant impairment in daily living activities (Romito et al., 2002).

4. Conclusions

Cognitive and behavioural disturbances in patients with Parkinson's disease seem to be relatively more frequent after deep brain stimulation of the subthalamic nucleus, as compared with deep brain stimulation of the internal globus pallidus. This finding might be at least partially due to the fact that the subthalamic nucleus is a smaller target, with different neural circuits (motor, associative, and limbic circuits) in close proximity to each other. Thus, electrode misplacements or current spreading to non-motor circuits involving the subthalamic nucleus may give rise to cognitive and behavioural disturbances after subthalamic implants.

On the whole, nonetheless, most studies agree about the view that the cognitive and behavioural morbidity of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease can be considered relatively low, even in the long term, provided that appropriate criteria are used to select candidates for neurosurgery,

Further studies are certainly needed to elucidate the pathophysiological mechanisms underlying the postoperative cognitive and behavioural changes which may be observed in Parkinsonian patients treated by deep brain stimulation of the subthalamic nucleus.

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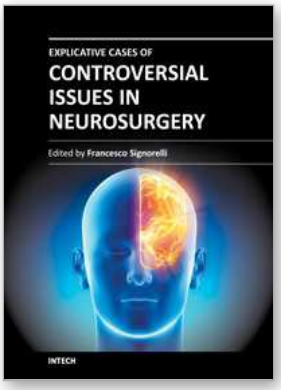

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