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# Neuropsychology for Movement Disorders Neurosurgery

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**ABSTRACT:** The neuropsychologist plays a crucial role in three phases of the neurosurgical treatment of movement disorder patients, namely screening, outcome evaluation and research. In screening patients, the differential diagnosis of dementia, impact of depression or other psychiatric conditions, and the influence of disease and medication-induced symptoms on cognitive performance must be determined. Postoperatively, systematic evaluations elucidate the cognitive costs or benefits of the procedure. The neuropsychologist is then able to provide feedback and counselling to the professional staff, patient and family to inform management strategies. Neuropsychologists also study alteration of cognitive processing due to lesions or stimulation, which, in tandem with functional imaging, shed light on plasticity in cortical and subcortical processing.

**RÉSUMÉ:** La neuropsychologie dans la neurochirurgie des désordres du mouvement. Le neuropsychologue joue un rôle crucial dans trois phases du traitement neurochirurgical des patients présentant des désordres du mouvement, soit dans le dépistage, l'évaluation des résultats et la recherche. Lors du dépistage des patients, on doit préciser le diagnostic différentiel de la démence, l'impact de la dépression ou d'autres troubles psychiatriques, et l'influence de la maladie et des symptômes médicamenteux sur la performance cognitive. En période postopératoire, les évaluations systématiques permettent d'évaluer les coûts et les bénéfices cognitifs de l'intervention. Le neuropsychologue est alors en mesure de fournir des informations et des conseils au personnel professionnel, au patient et à sa famille pour développer des stratégies de prise en charge appropriées. Les neuropsychologues étudient également les perturbations du processus cognitif dues à des lésions ou à la stimulation qui, de concert avec l'imagerie fonctionnelle, renseignent sur la plasticité des processus corticaux et sous-corticaux.

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To many neurologists, the basal ganglia continue to be primarily associated with motor control. The presence of basal ganglia dysfunction is only unequivocally recognized when certain motor signs and symptoms are manifested. However, there is evidence that in conditions such as Huntington's disease, the presence of cognitive impairment precedes the appearance of motor symptoms.<sup>1</sup>

According to traditional models of neuropathology in Parkinson's disease (PD),<sup>2,3</sup> dopamine (DA) replacement therapy should reverse the effects of the degeneration of the nigrostriatal projections. Indeed, many motor symptoms are corrected in this way for many years.<sup>4</sup> However, it appears that this can only re-establish a tonic DA level in the basal ganglia. It is now postulated that there is a phasic action of striatal DA linked to reinforcement-based learning.<sup>5</sup> This may explain why cognitive dysfunction has often remained unchanged by pharmacotherapy (in some cases worsened, and selected measures mildly improved<sup>6-12</sup>). Furthermore, many patients lose the benefit of l-dopa therapy as the disease progresses. They often develop disabling dyskinesias and/or prolonged bouts of freezing, necessitating neurosurgical intervention to obtain relief. Since all PD patients eventually fall prey to cognitive and sometimes

psychiatric impairment, the prospect of making additional lesions in basal ganglia circuits or disrupting function with deep brain stimulation (DBS) can be expected to exacerbate or hasten such complications.

The rationale for the current neurosurgical treatment for PD (as well as other movement disorders, notably dystonia and essential tremor), is based on the results of animal studies and clinical manifestations of fortuitous strokes, as well as neurophysiological observations made during neurosurgery. These studies have indicated that the reduction of excessive neuronal activity in the internal segment of globus pallidus (GPi) and subthalamic nucleus (STN) results in a dramatic improvement in motor control in PD patients.<sup>3,13,14</sup>

In keeping with the older neurosurgical reports in which

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larger lesions were made, usually localized more anteriorly and dorsally within the pallidum than currently, some personality changes and lateralized cognitive effects were noted.<sup>15,16</sup>

The study of animals with precisely localized experimental lesions in nonmotor components of the basal ganglia revealed behavioural impairments that were in many ways comparable to those seen after frontal lobe lesions.<sup>17,18</sup> Profound behavioural disorders such as abulia or 'psychic akinesia' have been documented in human cases of subcortical stroke (especially bilateral insults).<sup>19,20</sup> Early clinical neurosurgical reports of the outcome of stereotaxic lesions within the basal ganglia or thalamic targets only occasionally documented cognitive and behavioural disturbances (e.g. obsessive-compulsive, language, memory).<sup>21-24</sup> Until recently, such discrepancies between the lab and the operating theatre were attributed to species differences or to the widely disparate means of assessment. Some authors<sup>25</sup> decried the often casual examination of patients, with regard to motor status and especially cognitive status reported in the early outcome studies of pallidotomy.

James Parkinson<sup>26</sup> set the stage for benign expectations and the purely motor function of the basal ganglia when he stated that "...the senses and the intellect remain uninjured..." in PD. Neuropsychologists have now established the expected cognitive profile in PD, that has been described as a pale copy of the type of impairment seen after frontal lobe dysfunction.<sup>27-37</sup> These findings not only finally echo the prior animal studies, but also are congruent with the known anatomical connections of the basal ganglia, emphasizing the strong efferent influences on the frontal lobes, largely via thalamic nuclei ventralis anterior and medialis dorsalis.<sup>34,38</sup>

Specifically, neuropsychological studies of PD patients have defined the presence of a dysexecutive syndrome (i.e. self-monitoring, attention shifting and focus, problem-solving, insight, judgement, strategic thinking, forward planning, working memory) due to dysfunction of the striato-thalamo-cortical circuits that alter the normal function of the dorsolateral prefrontal cortex in particular.<sup>27</sup> Parkinson's disease patients have particular difficulty with attentional switching (extradimensional is shifting attention from the task at hand to another feature of the environment), encoding supraspan information (strategies to log in more information than can be appreciated with immediate attention or more than  $7 \pm 2$  bits of information), organization of sequential information (organizing items in temporal and/or logical order), strategic planning (goal-directed, means-end logical planning, expectation of consequences), visual-spatial problem-solving (nonverbal processing of visual information and especially problems of spatial re-organization), procedural learning (how to execute skills such as visuo-motor abilities, sports, mechanical expertise), implicit and probabilistic learning (learning without awareness based on selective rewards), and working memory (also known as working with memory or operating on temporarily held information).<sup>10,31,34,37,39-46</sup>

## SCREENING

The preoperative neuropsychological assessment is designed not only to rule out patients who might be at risk for dementia, but also to provide a cognitive baseline against which to compare postoperative function. On the optimistic side, it is hoped that the

alleviation of some of the refractory symptoms might improve overall attentional capacity and to lower stress in general. The possibility of improved sleep and self-care capacity would also facilitate the deployment of full remaining cognitive ability. When trying to predict postoperative adverse effects, cognitive weaknesses and general lack of cognitive reserve may predispose such patients to intellectual decline.<sup>47</sup>

In the neuropsychological assessment process it is assumed that patients have been thoroughly assessed medically, ideally having been seen by both a neurologist and neuropsychiatrist. This process normally results in the elimination of clear cases of neurological, medical or psychiatric contraindications.<sup>4,48-50</sup> The typical patient, for example will have a diagnosis of idiopathic PD and will continue to obtain at least some benefit from l-dopa.<sup>51,52</sup> Usually, the presence of refractory fluctuations in symptoms and/or medication-induced dyskinesias (including dystonia) will motivate the referral for determining candidacy for surgery. Other patients referred for assessment include selected individuals with primary dystonia (generalized and segmental), secondary dystonia and, rarely, Huntington's disease. Patients with parkinson-plus syndromes (e.g. multiple system atrophy, cortico-basalganglionic degeneration) or PD patients who do not respond to l-dopa challenge are not expected to benefit from neurosurgical intervention.<sup>50,53</sup>

On this background, neuropsychological assessment determines the cognitive profile of each surgical candidate to aid in differential diagnosis of possible co-morbidity with dementia and to determine capacity for consent to treatment in order to formulate a prognosis. The meaning and significance of the findings of the assessment must be communicated to the patient and caregivers in a clear and thorough manner in order to help them weigh their options and to have realistic expectations. It should be noted that a recent study has indicated that capacity to consent to medical treatment can be significantly affected by the extent of frontal executive dysfunction in patients with PD.<sup>54</sup> One of the difficulties in undertaking such assessments is that the differential diagnosis of early-stage concurrent dementia as well as mood disorders may be nuanced and subtle (i.e. not clinically obvious or revealed by bedside screening methods), requiring specifically-tailored tests and analyses of prefronto-subcortical dysfunction.<sup>29,42-44,55-59</sup> In addition, instead of presenting in a psychologically homogeneous manner, PD patients often display varying degrees of preoperative cognitive and behavioural impairment that may reflect clinical subtypes.

## SUBTYPES OF PARKINSON'S DISEASE AND DIFFERENTIAL DIAGNOSIS OF DEMENTIA IN PARKINSON'S DISEASE

### Subtypes of Parkinson's disease

Recently, there has been progress in defining subtypes of PD based on criteria such as age of onset, motor signs and symptoms, response to l-dopa therapy, receptor binding as imaged with positron emission tomography (PET), neuropsychological profile, and natural history.<sup>60-63</sup> It is possible that these subtypes may represent different phenotypes, eventually leading to the identification of genetically-determined factors (i.e. parkin gene, ubiquitin,  $\alpha$ -synuclein<sup>64</sup>). The choice of optimal therapeutic approach may, in the future, depend on such a complete characterization of patients.

### Differential diagnosis of dementia in PD

Despite current medical expertise, it is still the case that the initial diagnosis of idiopathic PD is only confirmed in 75% of cases seen at autopsy.<sup>65</sup> It has also been established that patients with certain of the non-PD degenerative diseases (with parkinsonism) are at greater risk for dementia, a condition which predisposes patients to a greater risk of further (i.e. beyond expected impact) postoperative cognitive complications.<sup>57,66-69</sup> With regard to the incidence of dementia in PD, figures range from 9.5% in the pure idiopathic form to 54% in cases of less certain diagnoses.<sup>70,71</sup> Typical incidence levels are reported to be around 30%,<sup>4</sup> but the risk of eventually developing a dementia is 6 to 6.6 times as likely as in the non-PD population.<sup>71,72</sup> The accuracy of identifying patients at such risk before proceeding to surgery is important and cannot always be accomplished by a short office or bedside screening procedure. An initial bedside screening of patients can be done with the Mini-Mental-Status-Examination,<sup>73</sup> the Mini-Mental Parkinson's<sup>74</sup> or the Mattis Dementia Rating Scale,<sup>75</sup> but this is not sufficient for the differential diagnosis of concurrent dementia.<sup>47,59</sup>

Problems of differential diagnosis arise in cases of PD with dementia. This refers to dementing conditions such as Alzheimer's disease and other non-Alzheimer cortical dementias (eg. vascular such as multi-infarct, ischemic and leukoariosis) or other degenerative diseases, such as Pick's, dementias lacking distinctive histology, progressive supranuclear palsy, corticobasal ganglionic degeneration, Lewy body disease, or frontal and fronto-temporal dementias.<sup>76-79</sup> Careful neurological, radiological<sup>80,81</sup> and, more recently, MR spectroscopic<sup>82</sup> examinations and history could lead to a timely differential diagnosis.

In a study of 100 consecutive autopsy cases, Hughes and colleagues<sup>83</sup> had concluded that co-morbidity with Dementia with Lewy Bodies (DLB) in PD patients diagnosed as demented, is limited to about 3%. However, a recent postmortem examination of 13 patients who had developed dementia and loss of clinical response to l-dopa therapy found that 12 had DLB.<sup>84</sup> In the Hughes study, co-morbidity with Alzheimer's disease pathological stigmata was of the order of 9%, while for vascular disease (multi-infarct dementia) it was at 2%. The overall conclusion of Hughes and his colleagues was that there was a total of 14% incidence of dementia in PD, which is close to the natural incidence of dementia in the elderly and does not suggest a particular vulnerability of PD patients to become demented. However, in a series of 12 patients with atypical PD, two patients had cortical Lewy body disease, two had Alzheimer changes and two had vascular damage to the striatum. This is equivalent to a 50% incidence of concomitant ancillary disease.<sup>83</sup> The combined effects of age and severity of disease increase the probability of incident dementia in PD.<sup>85</sup> In that study of 150 patients, 28.9 % developed dementia within three to four years of study onset. Given the aforementioned uncertainty about the clinical diagnosis of PD,<sup>65,86</sup> it is clear that there is a high probability that patients referred for surgery are at-risk for a problematic outcome unless careful medical and neuropsychological screening is done systematically. The input from a neuropsychological assessment is often essential in order to determine the presence, degree and nature of cognitive and behavioural impairment in such cases.<sup>78,87,88</sup>

The suitability of a patient for surgery must be established

despite fluctuations of motor or attentional capacity, medication effects, or dyskinesias, which often complicate the clinical presentation.<sup>47,59</sup> The first signs of dementia may not fulfill DSM-IV criteria for a definitive diagnosis.<sup>89</sup> In addition, PD complicated with Alzheimer's disease may present like DLB. Since there is known to be decreased striatal DA in Pick's disease, some parkinsonian symptoms may be present in that condition as well.<sup>78,90</sup> Psychiatric manifestations are often present in DLB (hallucinations, delusions, confusional episodes)<sup>91</sup> but are also seen as drug reactions in PD.<sup>92,93</sup> Other factors, such as age, education, stress tolerance, and stamina, may have an impact on psychological status and its assessment,<sup>6,28</sup> as well as on the outcome of surgery.<sup>69,94</sup>

### Psychiatric manifestations in PD: depression, anxiety and psychotic disorders

In a cohort of 520 PD patients, psychiatric manifestations were catalogued by Vasquez and colleagues.<sup>93</sup> Depression was associated with advancing disease (Hoehn and Yahr stage III) and overt previous psychiatric disturbance. The presence of psychotic disorders was more frequently manifested with early onset of PD and higher doses of l-dopa, while anxiety was associated with motor fluctuations. Shergill and colleagues<sup>95</sup> retrospectively analyzed 100 patients, finding that incidence of psychosis was increased as cognition declined and illness duration increased. Psychiatric symptoms in PD have been reported by many others.<sup>96-99</sup>

The incidence of depression in PD varies between 40-60%.<sup>100-102</sup> Severity of depression may range from apathy to transient dysphoria (due to disabling symptoms and motor limitations) to severe psychotic states.<sup>103-105</sup> Parenthetically, over 22% of PD patients with dementia also fulfill the criteria for severe depression.<sup>70</sup> Furthermore, depression is often also associated with dementing conditions, especially frontal dementia, fronto-temporal dementia and DLB.<sup>87,91</sup> It has long been recognized that a depressive state can mimic dementia (so-called pseudo-dementia) and this confound must be considered in any evaluation of these patients.<sup>106</sup> In the absence of dementia, patients often suffer from labile effect, which if unrecognized and not managed, can result in an overly pessimistic estimation of cognitive capacity.<sup>28,107-111</sup> Typically, however, some degree of lability of mood and milder forms of dysthymia-despondancy are expected. There may be a subset of patients, with depression predating the onset of PD possibly with a genetic predisposition.<sup>112-114</sup> An organic basis for depression has been suggested based on functional imaging and indices of altered 5-HT metabolism.<sup>115,116</sup> Obsessive-compulsive symptoms, such as excessive concern about details and cleanliness, can also be manifested in patients with basal ganglia dysfunction.<sup>117</sup> Furthermore, evidence of rigidity, introversion, orderliness and excessive seriousness and industriousness in personality has been observed pre-morbidly as well as in patients already diagnosed with PD.<sup>114,118-120</sup> Such tendencies can be amplified postsurgically in some patients.<sup>57,67,69,121</sup>

In conclusion, neuropsychological assessment is essential in establishing the presence of concomitant dementia, especially in the early stages. This raises the question concerning the suitability of such patients (i.e. with dual diagnoses) for surgery, especially if they are severely disabled by PD symptoms. The

ethics of such a dilemma cannot be debated here but both the treatment team and the patient and family/caregivers must be made aware of concerns with regard to cognitive risk factors. Since most centres have not operated knowingly on “at risk” patients, it is not known how to establish formal psychometric thresholds for inclusion or exclusion. It is recommended that criteria, adapted from traditional dementia diagnoses, be applied (i.e. performance more than 1.5 SD below premorbid expectation in general intellectual function). Since memory and some aspects of attentional control and executive functions are considered to be already weakened in PD, one could suggest that a further decline (i.e. more than 2 SD below premorbid estimates) be applied for those functions. Those patients whose performance is below the above thresholds should be considered as being at significant risk for surgery. The same logic would apply to remote or “stabilized” psychiatric risk factors, although psychometric indices from personality inventories would have to be interpreted differently. It would appear that those centres reporting the least cognitive postoperative complications (i.e. number and severity), operated only on those patients who were highly responsive to l-dopa challenge, had ample cognitive reserve, were under 60 years of age, and who were historically free of psychiatric illness.

#### NEUROPSYCHOLOGICAL OUTCOME OF POSTEROVENTRAL PALLIDOTOMY (PVP), AND GLOBUS PALLIDAL DEEP BRAIN STIMULATION (GPi-DBS)

Several studies indicated that only l-dopa responsive patients benefit from neurosurgical interventions.<sup>4,48,122,123</sup> Clearly, the aim of the neurosurgeon is to improve motor symptoms without encroaching on adjacent, relatively intact circuits involved in cognition, self-monitoring and emotion.

Early reports of the outcome of PVP were optimistic that the goal of motor improvement without iatrogenic sequelae had been achieved.<sup>37,59,124,125</sup> However, subsequent studies with larger groups and more extensive testing indicated hemisphere-specific cognitive impairment and executive dysfunction.<sup>67,126,127</sup> The latest analyses of the neuropsychological impact of PVP indicated only very mild toxicity, revealed especially in verbal fluency tasks.<sup>128,129</sup> It must be recalled, as emphasized by Scott,<sup>124</sup> that failure to find deficits does not rule out their presence, since bedside or insensitive neuropsychological assessment may fail to uncover impairment.

In general, the vast majority of patients are pleased with the clinical neurological outcome of surgery and they, as well as their families, witness the disappearance of drug-induced movement disorders, and increased independence in activities of daily life. What is remarkable and surprising is the fact that ipsilateral benefits are also seen.<sup>130</sup> Few patients are able to have their medication dosage significantly lowered but they perform better overall with improvement quantified with the Unified Parkinson's disease Rating Scale.<sup>53,131</sup>

The dramatic reduction in l-dopa-induced dyskinesias and recovery of functional motor control often is accompanied by a euphoric postoperative reaction during which even problematic cognitive or behavioural impairments are overshadowed. Patients with unilateral PVP insist that they feel fine, both emotionally and behaviourally, but spouses and caregivers paint

a different picture. Minor cognitive and behavioural changes are also masked in general since many patients have evolved into lifestyles, such as retirement, which do not provide opportunities for challenge by novel intellectual or psychosocial situations. Families continue to be protective and also overfunction to compensate for the patients' limitations. During this euphoric phase, the ability of patients to re-engage in a wide range of activities induces some to launch themselves headlong into physical and mental challenges that they previously enjoyed. Patients may develop a maladaptive adjustment disorder due to failure of expected re-insertion into previous activities.<sup>57,132</sup> This failure of patients to cope with their rapid clinical improvement may lead to significant psychic distress and interpersonal problems as has been long-recognized in patients surgically “cured” of epilepsy.<sup>133</sup>

Cases of poor judgement, disinhibition, reckless behaviour, and socially inappropriate behaviour were observed to such an extent that a systematic assessment of personality change was undertaken.<sup>67</sup> It quickly became clear that many of the roughly 25% of patients with such problems had little or no insight into their altered behaviour. When noted by the patients, odd or altered behaviours tended to be rationalized and the consequent disruption minimized. The group of patients assessed developed behavioural or personality changes ranging from apathy and abulia to disinhibition and mania.<sup>67</sup> Mercifully for the caregivers and medical support staff, the problems often spontaneously resolve within a few months, sometimes responding quite well to a combination of medical therapy and behavioural management interventions. It is critical to educate the family and caregivers about the organic basis for the behaviour and how best to structure environment and interaction. Patients are also given feedback about their actions and encouraged to trust the advice and guidance of caregivers. Rarely, behavioural alterations persist beyond 12 months, requiring ongoing monitoring and treatment. The relative risk of persisting problems appears to be quite low (about 5% in our centre after lesions and less after DBS). In other centres, the quality of postoperative monitoring is difficult to establish and patients living in other countries may be lost to follow-up completely. There are, therefore, no good long-term data addressing these issues.

In trying to identify factors which might predispose patients to such reactions, instances of prior psychiatric history were revealed.<sup>121</sup> During screening, these may have been considered too remote to be pertinent, may have been considered well-controlled and, rarely, may have been hidden or minimized by patients and families in order to be accepted for surgery. It is now advised that decompensation may be expected and the treatment team should be ready to deal with such events. For example, if depression was previously a significant factor, then the resumption of treatment with standard antidepressants may prove quite effective in postoperative management.

Although impulsivity and lack of self-monitoring, as well as disinhibition are accompanied by the most troublesome social complications, other patients experience a behavioural shutdown, becoming apathetic, socially withdrawn and anhedonic.<sup>67,69</sup> Only in one other study have similar effects been noted,<sup>134</sup> although anecdotal reports are often discussed whenever movement disorder neurosurgeons congregate.<sup>15,121,132</sup> Careful postoperative management of these behaviourally

disturbed patients requires a multifactorial approach and can involve psychiatry, psychology, social work, home care and family counselling. In some cases, disordered behaviour/mood may resolve over several months but the most severely affected patients remain, to all intents and purposes, permanently changed.

From a cognitive point of view, the expected general improvement in attentional capacity is somewhat borne out. Patients are better able to attend to tasks and are no longer distracted by their drug-induced movement disorder.

Trépanier et al<sup>67</sup> adopted a hypothesis-testing approach, targeting cognitive functions known to be at risk in PD and found deficits in the expected cognitive domains after PVP. Those observations suggested that circuits still participating in processing information in cognitive operations had been damaged, a conclusion also reached by others.<sup>127,135-137</sup> Thus, both hemisphere-specific effects<sup>126</sup> as well as executive functions were affected. Specific deficits after left PVP included deterioration in verbal serial list learning, decreased controlled oral word fluency (semantic and phonemic; i.e. ability to generate lists of words according to category or target letter), and impaired working memory.<sup>66,67,123,127,138-140</sup> The deleterious effects of right PVP proved to be more difficult to demonstrate. Trépanier et al<sup>67</sup> found only transient (i.e. cleared within 12 months) impairment of visual constructional abilities. Recent reports have confirmed the vulnerability of visuoconstructive functions as well.<sup>127,141</sup> Having followed some of these patients now for several years, we can report that there is little recovery of those deteriorated functions, but there is no significant further decline.

Direct tests of procedural and problem-solving functions revealed little change, contrary to expectation.<sup>127,136,137</sup> On reflection, it was surmised that, during the slow cognitive adaptation to disease progression, these most vulnerable functions had probably already been taken over (albeit inefficiently) by alternate circuits, in keeping with the opinion of Marsden and Obeso.<sup>142</sup> There is recent PET evidence that PD patients activate their hippocampal formation when solving a problem as a compensation for their inability to activate the striatum.<sup>143</sup> In the case at hand, PVP may have little impact on certain neuropsychological tasks, since a change of locus of control to cortical levels has already taken place. Thus, further damage to the basal ganglia may be expected to have little or no impact. Other groups have also generally found subtle cognitive effects of these surgeries.<sup>126,129,144,145</sup>

As is often the case with regard to basal ganglia strokes, bilateral lesions are more likely to result in severe behavioural change than unilateral lesions.<sup>20,34,46</sup> In cases of simultaneous, or staged bilateral pallidal lesions, all too often outcome is characterized by catastrophic declines cognitively and also in behavioural control, with a full-blown frontal syndrome being induced.<sup>66,67,69,146</sup> In two of three cases of bilateral PVP in our own series and several cases in another report, a catastrophic behavioural syndrome of the frontal type ensued.<sup>66,67</sup> Thus, some patients developed environmental dependency and imitative and utilization behaviours as described by Lhermitte.<sup>147-149</sup> In one such case requiring prolonged hospitalization, the patient was adamant that he was not depressed or upset by his actions (despite having created public embarrassment to his family).

This lack of insight and judgement was quite characteristic of many cases, even those with unilateral PVP. However, it must be emphasized that this outcome is not obligatory. In one of our cases and in other series, no major behavioural disruption was noted,<sup>66,67,69,135</sup> possibly because of location or size of lesion. Recently, Aziz's team<sup>150</sup> reported a series of 115 consecutive cases of unilateral PVP and bilateral PVP with no mention of adverse cognitive or psychiatric events, although it is not clear to what extent patients were assessed for those conditions. In two recent studies of neuropsychological outcome after bilateral PVP, impairments were seen in attentional set-shifting<sup>136</sup> and in recursive spatial problem-solving.<sup>137</sup>

In conclusion, optimally-placed PVP lesions can benefit PD patients without necessarily causing cognitive impairment. However, since slightly more rostral lesions yield the greatest reduction in drug-induced dyskinesias<sup>151</sup> and it is also those lesions that are associated with cognitive impairment,<sup>152</sup> a benign outcome cannot be guaranteed, especially with bilateral lesions.

Globus pallidal deep brain stimulation may be less cognitively toxic than PVP,<sup>153</sup> possibly because of differential effects on neurons and fibres of passage and the titration of stimulation parameters. This permits bilateral interventions.<sup>69,154,155</sup> As was the case for lesions, location of stimulation within the pallidum (may include the external division of the GP) produces differential effects on parkinsonian symptoms in the on and off drug states.<sup>156</sup> A comparison of the effects of stimulation at different sites within the pallidum on cognitive function has not been done.

#### NEUROPSYCHOLOGICAL OUTCOME OF SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION (STN-DBS)

Bilateral STN-DBS is currently considered to be the treatment of choice for PD since this fundamentally ameliorates symptoms and permits drastic reductions in medication.<sup>51,130,157</sup> It is thought that DBS blocks the action of the STN, thus reducing its widespread excitatory influence (glutamatergic) throughout the striatal circuitry (and perhaps also directly into the thalamus). However, recent studies have suggested that excitatory effects may also be produced.<sup>158-160</sup>

Since at best, STN-DBS results in motor improvement only as good as the best l-dopa response,<sup>157</sup> one might suspect that there would be little improvement in cognition other than the indirect effect of alleviating motor control problems and so liberating attentional resources to be allocated back to cognitive or behavioural processing.<sup>161</sup> In younger patients, cognitive costs are essentially negligible.<sup>154</sup> There is evidence for a statistically mild improvement in some executive functions, but this may be without clinical importance.<sup>162</sup> It is intriguing that cessation of stimulation does not lead to a loss of this so-called improvement,<sup>163</sup> suggesting that other circuits, outside of the sphere of influence of the basal ganglia may permanently take over functions.<sup>143,164,165</sup> Alternately, a nonspecific improvement in the allocation of attentional resources may be responsible, and this could take some time to decompensate after the stimulation is interrupted. In contrast, in older patients, not only is clinical motor benefit less dramatic, but significant cognitive impairment may ensue.<sup>57</sup> When present, the full gamut of cognitive impairment is seen,

those functions dependent on executive mechanisms being at greatest risk. Idiosyncratic behavioural and personality problems may also develop and, if so, sometimes require psychiatric management. Acutely, immediately after surgery, it is common to observe transient states of confusion (especially in the elderly), or hypomania (especially in the younger) lasting days to months in all patients.

Subthalamic nucleus deep brain stimulation has also been reported to induce instantaneous or insidious alterations of mood experienced as euphoria/hilarity or depression/apathy (abulia).<sup>66,69,166-168</sup> The STN is a relatively small target and DBS electrodes may inadvertently be placed suboptimally. This may be responsible for the reported cases of depression, euphoria or anger, although these events appear to be relatively rare. Careful adjustment of stimulation parameters and the choice of electrode contacts for activation may minimize some of these problems but more studies will definitely be needed. There has been no satisfactory explanation in anatomical or physiological terms for these effects. Because of this potential danger, further exploration of GPi-DBS is expected.<sup>135,169,170</sup>

It has become clear that outcome of DBS is, therefore, predicted by age at surgery, extent of response to l-dopa challenge, and rigorous neuropsychological screening.<sup>69,154</sup> The cognitive impact of DBS within the basal ganglia has been interpreted as evidence both for the facilitation of cortically-based functions and the interruption of striatally-based processing.

In conclusion, for ideally-selected patients, neurosurgical intervention appears to be relatively benign from a cognitive and psychological perspective. However, there continue to be individual cases of cognitive and behavioural compromise in all centres. In addition, it is difficult to assess extent of clinical impact of minor cognitive changes (i.e. in the range of 1 SD) as measured psychometrically. It can be argued that retired patients with adequate caregiver support can continue to manage quite well cognitively since this is not significantly challenged. It is certainly also the case that the dramatic improvement in motor symptoms has a major positive impact on their quality of life. Long-term reduction of cognitive reserve, in interaction with normal aging and disease progression, may prove extremely difficult to assess. Given the above, can the expense of extensive neuropsychological evaluations be justified in this age of managed health care and fiscal conservatism? To the extent that patients with concomitant dementia can be eliminated from surgery, then the projected extra cost of their future care (i.e. possible institutionalization, home care, psychiatric treatment) would be kept to that expected for standard PD. For those operated patients who experience minor but perceptible complications, it would be hoped that the preparedness of the treatment team and family/caregivers would optimize care and avert catastrophic consequences.

Clearly, neuropsychological expertise is best focussed on the so-called "grey zone" cases who pass regular medical screening procedures but in whom concerns are raised. Only by continued research and systematic follow-up will indices predicting post-operative complications be established. That being said, all of the above considerations only hold for cases operated by expert neurosurgeons who can virtually guarantee precise electrode placement.

## RESEARCH

Major questions remain with regard to the way in which PVP or DBS alter information processing in the basal ganglia circuitry. A corollary question pertains to the cortical and cerebellar compensations induced by these interventions. It is highly likely, therefore, that these surgical procedures disconnect dysfunctional basal ganglia circuits in whole or in part and that there is a shift of locus of control and mode of information processing outside of the basal ganglia.

Neuropsychological studies have attempted to differentiate frontal from basal ganglia dysfunction in PD,<sup>32,44,81,163,171</sup> a difficult analysis considering the multiplexed nature of information processing.<sup>46,172,173</sup> The defocusing of information processing in the basal ganglia caused by loss of DA has been proposed to be at the origin of cognitive dysfunction in PD.<sup>172,174</sup> Schultz and his colleagues<sup>5</sup> have also emphasized the critical role of DA in reinforcement-based learning, a recognized weakness in PD patients.<sup>29,175</sup>

Functional neuroimaging has revealed altered regional cerebral blood flow due to either PVP or DBS,<sup>164,165,176,177</sup> both in passive and motor activation conditions. Although it has been possible to show the alteration of circuit activation with thalamic DBS,<sup>178</sup> a similar demonstration with STN-DBS has so far proven to be elusive (Saint-Cyr et al, unpublished observations). However, it has been possible to demonstrate altered processing in cortical circuits during lexical retrieval in the presence of STN DBS (McAndrews et al, in preparation). Positron emission tomography studies of regional cerebral blood flow have typically shown frontal and subcortical hypoperfusion at rest in PD.<sup>179</sup> When PD patients perform motor activation tasks, such as finger sequence movements or random joystick movements, there is an underactivation of the supplementary motor area but overactivation of premotor and parietal cortical areas.<sup>164,177,180</sup> In those same studies, after PVP or clinically effective GPi or STN DBS, these blood flow anomalies tend to return towards normal patterns seen in control subjects. Recently, Sestini and colleagues<sup>181</sup> showed increases not only in and around the supplementary motor area (BA6, 8), but also in the dorsolateral prefrontal cortex (BA9/10, 46), and anterior cingulate (BA 32).

Other studies have compared DBS in the GPi vs STN<sup>69,154</sup> with a suggestion that the former may be less toxic. Mild improvement in some aspects of executive processing has been demonstrated after STN DBS.<sup>162</sup> If DBS is directly responsible for altered cognitive processing, as it appears to be for the amelioration of motor symptoms, the cessation of stimulation should rapidly reverse any induced cognitive effects. When this hypothesis was directly tested, the mild improvements or impairments found (i.e. preoperative performance compared to postprogramming) remained unchanged with stimulation on or off.<sup>163</sup> This puzzling finding suggests that one effect of the stimulation may be to disconnect basal ganglia outflow from its thalamo-cortical targets.

In another study, Schubert et al<sup>182</sup> concluded that GPi-DBS was as equally effective in overcoming bradykinesia as l-dopa treatment (for simple reaction time) but without the speed accuracy trade-off induced by the latter (in a multiple choice reaction time task). This suggests that GPi-DBS can mimic but not duplicate the drug action. In a PET imaging study of the effect of STN-DBS, Schroeder et al<sup>183</sup> found a correlation

between increased response time on the Stroop task (i.e. increased time to name colours spelled in incongruent coloured ink) and decreased activation of the right anterior cingulate and ventral striatum while there was increased activation of the left angular gyrus. This was interpreted as a reflection of response conflict and verbal suppression of prepotent responses. In other words, under conditions of stimulation, top-down cortically based processing is brought into play to compensate for decreased striatal function.

These observations suggest that shifts in neural circuit activation during cognitive challenge may reflect abandonment of blocked circuits and the recruitment of alternate systems that may perform roughly equivalent processing. However, lest we attribute all behavioural changes to the effects of brain stimulation, Pollo et al<sup>184</sup> have recently reported a placebo effect of stimulation on movement speed. This is reminiscent of the surprising demonstration of a placebo effect in l-dopa-induced reduction of raclopride binding.<sup>185</sup> Therefore, altered behavioural strategies and expectations may also lead to altered modes of neural processing.

Correlative studies analyzing PVlesion location to cognitive outcome have been published<sup>152</sup> but a similar analysis awaits to be done with respect to site of stimulation in and adjacent to the STN. Several recent studies have shown that MRI can accurately document electrode location<sup>186-188</sup> thus setting the stage for such analyses.

## CONCLUSIONS

Neuropsychology plays a very critical role in patient selection (screening) and in monitoring psychological outcome of neurosurgical interventions for the treatment of selected movement disorders such as PD.

The role of neuropsychology is to provide the psychometric basis for the differential diagnosis of concomitant dementia or other neuropathological process with a significant impact on the individual patient's cognitive reserve. It is thought that this impact is proportional to the risk of postoperative cognitive compromise. The exact threshold used to establish the clinical significance of such risk has not been determined but should be a goal for the future. Secondly, the neuropsychologist evaluates the psychosocial factors contributing to current cognitive and psychological function and estimates the patient's capacity to tolerate the stress of the surgery. These factors are also pertinent to the amount and quality of postoperative support available to the patients. Thirdly, there is an important role to be played in the education of patients and their caregivers concerning expected outcome, as well as providing follow-up assessments and support.

Although the current models of basal ganglia function do provide guidance for the neurosurgeon and have some predictive power, they are almost certainly wrong.<sup>189,190</sup> These surgical procedures, therefore, offer the opportunity to experimentally manipulate basal ganglia circuit function and to study the manner in which cognitive processing is affected as well as the reorganization of the compensatory cortical and cerebellar circuits.

Since there is growing evidence that alternate neural circuits are recruited to compensate for disabled fronto-striatal circuits,

this neural plasticity must be studied and understood. From a rehabilitation perspective, patients may profit from different forms of management for daily function than previously due to the induced shifts in neural processing. These shifts can be investigated neuropsychologically at both the behavioural and neural imaging levels. Finally, the lessons learned from these surgeries may well be applicable to future forms of treatment.

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## REFERENCES

1. Paulsen JS, Zhao H, Stout JC, et al. Clinical markers of early disease in persons near onset of Huntington's disease. *Neurology* 2001; 57(4): 658-662.
2. Albin RL, Aldridge JW, Young AB, Gilman S. Feline subthalamic nucleus neurons contain glutamate-like but not GABA-like or glycine-like immunoreactivity. *Brain Res* 1989; 491(1): 185-188.
3. Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. *Curr Opin Neurobiol* 1996; 6(6): 751-758.
4. Lang AE, Lozano AM. Parkinson's disease - first of two parts. *N Eng J Med* 1998a; 339(15): 1044-1053.
5. Schultz W, Tremblay L, Hollerman JR. Reward prediction in primate basal ganglia and frontal cortex. *Neuropharmacology* 1998; 37: 421-429.
6. Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain* 1988; 111(2): 299-321.
7. Pullman SL, Watts RL, Juncos JL, et al. Dopaminergic effects on simple and choice reaction time performance in Parkinson's disease. *Neurology* 1988; 38(2): 249-254.
8. Lange KW, Robbins TW, Marsden CD, et al. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology* 1992; 107(2-3): 394-404.
9. Malapani C, Pillon B, Dubois B, Agid Y. Impaired simultaneous cognitive task performance in Parkinson's disease: a dopamine-related dysfunction. *Neurology* 1994; 44(2): 319-326.
10. Owen A, Sahakian B, Hodges J, et al. Dopamine-dependent frontostriatal planning deficits in early Parkinson's disease. *Neuropsychology* 1995; 9(1): 126-140.
11. Kulisevsky J, Avila A, Barbanj M, et al. Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels. *Brain* 1996; 119(6): 2121-2132.
12. Malapani C, Rakitin B, Levy R, et al. Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction. *J Cog Neuroscience* 1998; 10(3): 316-331.
13. Starr PA, Vitek JL, Bakay RAE. Deep brain stimulation for movement disorders. *Neurosurg Clin N Am* 1998a; 9: 381-402.
14. Lozano AM, (Ed). *Movement Disorder Surgery*. Basel: Karger, 2000.
15. Louw DF, Burchiel KJ. Ablative therapy for movement disorders. Complications in the treatment of movement disorders. *Neurosurg Clin N Am* 1998; 9: 367-373.
16. Wilkinson SB, Tröster AI. Surgical interventions in neurodegenerative disease: impact on memory and cognition. In: Tröster AI, (Ed). *Memory in Neurodegenerative Disease: Biological, Cognitive, and Clinical Perspectives*. Cambridge, UK: Cambridge University Press, 1998: 362-376.
17. Divac I. Neostriatum and functions of the prefrontal cortex. *Acta Neurobiol Exp (Warsaw)* 1972; 32: 461-477.
18. Rosvold E. The frontal lobe system: cortical-subcortical relationships. *Acta Neurobiol Exp (Warsaw)* 1972; 32: 439-460.

19. Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain* 1994; 117: 859-876.
20. Dubois B, Defontaine B, Deweer B, Malapani C, Pillon B. Cognitive and behavioral changes in patients with focal lesions of the basal ganglia. *Adv Neurol* 1995; 65: 29-42.
21. McFie J. Psychological effects of stereotaxic operations for the relief of parkinsonian symptoms. *J Mental Science* 1960; 166: 1512-1517.
22. Ricklan M, Diller L, Weiner H, et al. Psychological studies on effects of chemosurgery of the basal ganglia in parkinsonism. I. Intellectual functioning. *AMA Arch Gen Psychiatry* 1960a; 2: 32/22-42/32.
23. Ricklan M, Diller L, Weiner, H. Psychological studies on effects of chemosurgery of the basal ganglia in parkinsonism. II. Aspects of personality. *AMA Arch Gen Psychiatry*, 1960b; 2: 71/267-79/275.
24. Kocher U, Siegfried J, Perret E. Verbal and nonverbal learning ability of Parkinson patients before and after unilateral ventrolateral thalamotomy. *App Neurophysiol* 1982; 45: 311-316.
25. Guridi J, Lozano AM. A brief history of pallidotomy. *Neurosurgery* 1998; 41: 1169-1183.
26. Parkinson J. *An Essay on the Shaking Palsy*. London: Sherwood, Neely and Jones, 1817.
27. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. *Brain* 1986; 109(5): 845-883.
28. Taylor AE, Saint-Cyr JA, Lang AE. Parkinson's disease. Cognitive changes in relation to treatment response. *Brain* 1987; 110(1): 35-51.
29. Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. *Brain* 1988; 111(4): 941-959.
30. Taylor AE, Saint-Cyr JA, Lang AE. Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". *Brain Cog* 1990; 13: 211-232.
31. Dubois B, Boller F, Pillon B, Agid Y. Cognitive deficits in Parkinson's disease. In: Corkin S, Boller F, Grafman J, (Eds). *Handbook of Neuropsychology* Vol 5. Amsterdam: Elsevier, 1991: 195-240.
32. Owen AM, James M, Leigh PN, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* 1992; 115: 1727-1751.
33. Elsinger PJ, Grattan LM. Frontal lobe and frontal-striatal substrates for different forms of human cognitive flexibility. *Neuropsychologia* 1993; 31: 17-28.
34. Saint-Cyr JA, Taylor AE, Nicholson K. Behavior and the basal ganglia. *Adv Neurol* 1995; 65: 1-28.
35. Owen AM, Doyon J, Dagher A, et al. Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. *Brain* 1998; 121: 949-965.
36. Rogers RD, Sahakian BJ, Hodges JR, et al. Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain* 1998; 121: 815-842.
37. Troster AI, Woods SP. Neuropsychological Aspects of Parkinson's Disease and Parkinsonian Syndromes. In: Pahwa R, Lyons KE, Koller WC, (Eds). *Handbook of Parkinson's Disease*. (3rd ed.) New York: Marcel Dekker, 2003, in press.
38. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamo-cortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. In: *Progress in Brain Research*, Vol. 85. Amsterdam: Elsevier, 1990: 19-146.
39. Brown RG, Marsden CD. Cognitive function in Parkinson's disease: from description to theory. *Trends Neurosci* 1990; 13(1): 21-29.
40. Saint-Cyr JA, Taylor AE, Trépanier LL, Lang AE. The caudate nucleus: head ganglion of the habit system. In: Vallar G, Cappa SF, Wallesch CW, (Eds). *Neuropsychological disorders associated with subcortical lesions*. Oxford: Oxford Science Publications, 1992: 204-226.
41. Saint-Cyr JA, Taylor AE. The mobilization of procedural learning. The "key signature" of the basal ganglia. In: Butters N, Squire LR, (Eds). *Neuropsychology of Memory* (2nd ed). New York: The Guilford Press, 1992: 188-202.
42. Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. *J Neurol* 1997; 244: 2-8.
43. Knoke D, Taylor A, Saint-Cyr J. The differential effects of cueing on recall in Parkinson's disease and normal subjects. *Brain Cogn* 1998; 38: 261-274.
44. West R, Ergis AM, Winocur G, Saint-Cyr J. The contribution of impaired working memory monitoring to performance of the self-ordered pointing task in normal aging and Parkinson's disease. *Neuropsychology* 1998; 12: 546-554.
45. Owen AM, Doyon J. The cognitive neuropsychology of Parkinson's disease: a functional neuroimaging perspective. In: Stern GM, (Ed). *Parkinson's Disease: Advances in Neurology* (Vol. 80). Philadelphia: Lippincott, Williams & Wilkins; 1999: 49-56.
46. Saint-Cyr JA. Frontal-striatal circuit functions: context, sequence and consequence. *J Int Neuropsych Soc*. In press.
47. Saint-Cyr JA, Trépanier LL. Neuropsychologic assessment of patients for movement disorder surgery. *Mov Disord* 2000; 15(5): 771-783.
48. Lang AE, Lozano AM. Parkinson's disease - second of two parts. *N Eng J Med* 1998b; 339(16): 1130-1143.
49. Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999; 14(4): 572-584.
50. Lang AE, Widner H. Deep brain stimulation for Parkinson's disease: patient selection and evaluation. *Mov Disord* 2002; 17(Suppl 13): S94-S101.
51. Krack P, Pollak P, Limousin P, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain* 1998; 121(3): 451-457.
52. Benabid AL, Krack PP, Benazzouz A, et al. Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: methodologic aspects and clinical criteria. *Neurology* 2000; 55(12 Suppl 6): S40-S44.
53. Lang AE, Lozano AM, Montgomery E, et al. Posteroventral medial pallidotomy in advanced Parkinson's disease. *New Eng J Med* 1997; 337(15): 1036-1042.
54. Dymek M, Marson D, Atchison P. Executive dysfunction and capacity to consent to treatment in Parkinson's disease. *Arch Clin Neuropsych* 1999; 14: 48.
55. Jahanshahi M, Brown RG, Rothwell JC, et al. Subthalamic nucleus (STN) and globus pallidus (GPi) stimulation in Parkinson's disease: II. Effects on executive function and working memory. *Mov Disord* 1997; 12 (Suppl 1): 130.
56. Stebbins GT, Gabrieli JD, Masciara F, Goetz CG. Cognitive processing speed affects both working memory and strategic memory in PD and normal aging. *Mov Disord* 1997; 12: 128.
57. Saint-Cyr JA, Trépanier LL, Kumar R, et al. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain* 2000; 123: 101-118.
58. Peavy GM, Salmon D, Bear PI, et al. Detection of mild cognitive deficits in Parkinson's disease patients with the WAIS-R NI. *J Int Neuropsychol Soc* 2001; 7(5): 535-543.
59. Tröster AI, Fields JA. The role of neuropsychological evaluation in the neurosurgical treatment of movement disorders. In: Tarsy D, Vitek JL, Lozano AM, (Eds). *Surgical Treatment of Parkinson's Disease and Other Movement Disorders*. Totowa, NJ: Humana Press. 2003;213:240.
60. Huber S, Christy J, Paulson G. Cognitive heterogeneity associated with clinical subtypes of Parkinson's disease. *Neuropsychiatry Neuropsychol Behav Neurol* 1991; 4: 147-157.
61. Filoteo JV, Rilling LM, Cole B, et al. Variable memory profiles in Parkinson's disease. *J Clin Exp Neuropsychol* 1997; 19: 878-888.
62. Graham J, Sagar H. A data-driven approach to the study of heterogeneity in idiopathic Parkinson's disease: identification of three distinct subtypes. *Mov Disord* 1999; 14: 10-20.
63. Stocchi F, Brusa L. Cognition and emotion in different stages and subtypes of Parkinson's disease. *J Neurol* 2000; 247(Suppl 2): II114-II121.



64. Gwinn-Hardy K. Genetics of parkinsonism. *Mov Disord* 2002; 17(4): 645-656.
65. Rajput AH. Frequency and cause of Parkinson's Disease. *Can J Neurol Sci* 1992a; 19: 103-107.
66. Scott R, Gregory R, Hines N, et al. Neuropsychological, neurological and functional outcome following pallidotomy for Parkinson's disease. A consecutive series of eight simultaneous bilateral and twelve unilateral procedures. *Brain* 1998; 121(4): 659-675.
67. Trépanier LL, Saint-Cyr JA, Lozano AM, Lang AE. Neuropsychological consequences of posteroventral pallidotomy for the treatment of Parkinson's disease. *Neurology* 1998; 51(1): 207-215.
68. Lang A, Duff J, Saint-Cyr J, et al. Posteroventral medial pallidotomy in Parkinson's disease. *J Neurol* 1999; 246 (Suppl 2): II28-II41.
69. Trépanier L, Kumar R, Lozano A, et al. Neuropsychological outcome of neurosurgical therapies in Parkinson's disease: a comparison of GPi pallidotomy and deep brain stimulation of GPi or STN. *Brain Cog* 2000; 42(3): 324-347.
70. Aarsland D, Tandberg E, Larsen JP, et al. Frequency of dementia in Parkinson disease. *Arch Neurol* 1996; 53: 538-542.
71. Aarsland D, Ballard C, McKeith I, Perry RH, Larsen JP. Comparison of extrapyramidal signs in dementia with Lewy bodies and Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2001; 13(3): 374-379.
72. Mayeux R, Chen J, Mirabello E, et al. An estimate of the incidence of dementia in idiopathic Parkinson's disease. *Neurology* 1990; 40: 1513-1517.
73. Jefferson AL, Cosentino SA, Ball SK, et al. Errors produced on the mini-mental state examination and neuropsychological test performance in Alzheimer's disease, ischemic vascular dementia, and Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2002; 14(3): 311-320.
74. Mahieux F, Michelet D, Manificier M-J, et al. Mini-Mental Parkinson: first validation study of a new bedside test constructed for Parkinson's disease. *Behav Neurol* 1995; 8: 15-22.
75. Mattis S. *Dementia Rating Scale: Professional manual*. Odessa, Florida: Psychological Assessment Resources, 1988.
76. Chui HC, Perlmuter LS. Pathological correlates of dementia in Parkinson's disease. In: Huber SJ, Cummings JL, (Eds). *Parkinson's Disease: Neurobehavioral Aspects*. New York: Oxford University Press, 1992: 164-177.
77. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; 47: 1113-1124.
78. Pasquier F, Delacourte A. Non-Alzheimer degenerative dementias. *Curr Opin Neurol* 1998; 11: 417-427.
79. McKeith IG, Burn D. Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia. *Neurol Clin* 2000; 18: 865-902.
80. Tedeschi G, Litvan I, Bonavita S, et al. Proton magnetic resonance spectroscopic imaging in progressive supranuclear palsy, Parkinson's disease and corticobasal ganglionic degeneration. *Brain* 1997; 120: 1541-1552.
81. Antonini A, Kazumata K, Feigin A, et al. Differential diagnosis of parkinsonism with [<sup>18</sup>F] fluorodeoxyglucose and PET. *Mov Disord* 1998; 13: 268-274.
82. Summerfield C, Gomez-Anson B, Tolosa E, et al. Dementia in Parkinson disease: a proton magnetic resonance spectroscopy study. *Arch Neurol* 2002; 59(9): 1415-1420.
83. Hughes AJ, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. *Arch Neurol* 1993; 50: 140-148.
84. Apaydin H, Ahlskog JE, Parisi JE, et al. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. *Arch Neurol* 2002; 59(1): 102-112.
85. Levy G, Schupf N, Tang MX, et al. Combined effect of age and severity on the risk of dementia in Parkinson's disease. *Ann Neurol* 2002; 51(6): 722-729.
86. Rajput AH. Prevalence of dementia in Parkinson's disease. In: Huber SJ, Cummings JL, (Eds). *Parkinson's Disease: Neurobehavioral Aspects*. New York: Oxford University Press, 1992b: 119-131.
87. Absher JR, Cummings JL. Noncognitive behavioral alterations in dementia syndromes. In: Spinnler H, Boller F, (Eds). *Handbook of Neuropsychology*. New York: Elsevier, 1993: 315-338.
88. Dalla Barba G, Boller F. Non-Alzheimer degenerative dementias. *Curr Opin Neurol* 1994; 7(4): 305-309.
89. Jacobs DM, Marder K, Côté LJ, et al. Neuropsychological characteristics of preclinical dementia in Parkinson's disease. *Neurology* 1995; 45: 1691-1696.
90. Lieberman AP, Trojanowski JQ, Lee VM, et al. Cognitive, neuroimaging, and pathological studies in a patient with Pick's disease. *Ann Neurol* 1998; 43: 259-265.
91. Papka M, Rubio A, Schiffer RB. A review of Lewy body disease, an emerging concept of cortical dementia. *J Neuropsychiatry Clin Neurosci* 1998; 10: 267-279.
92. Saint-Cyr JA, Taylor AE, Lang AE. Neuropsychological and psychiatric side effects in the treatment of Parkinson's disease. *Neurology* 1993; 43: S47-S52.
93. Vazquez A, Sempere AP, Duarte J, et al. Psychiatric manifestations and their predictive risk factors in Parkinson disease (Survey of a cohort of 520 patients). *Mov Disord* 1997; 12: 128.
94. Vingerhoets G, van der Linden C, Lannoo E, et al. Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999; 66: 297-304.
95. Shergill SS, Walker Z, Le Katona C. A preliminary investigation of laterality in Parkinson's disease and susceptibility to psychosis. *J Neurol Neurosurg Psychiatry* 1998; 65: 610-611.
96. Brown RG, MacCarthy B. Psychiatric morbidity in patients with Parkinson's disease. *Psychol Med* 1990; 20(1): 77-87.
97. Menza MA, Robertson-Hoffman DE, Bonapace AS. Parkinson's disease and anxiety: comorbidity with depression. *Biol Psychiatry* 1993; 34: 465-470.
98. Meara J, Hobson P. Depression, anxiety and hallucinations in Parkinson's disease. *Elder Care* 1998; 10: S4-S5.
99. Wolters EC. Dopaminomimetic psychosis in Parkinson's disease patients. *Neurology* 1999; 52 (Suppl 3): S10-S13.
100. Cummings J. Depression and Parkinson's disease: a review. *Am J Psychiatry* 1992; 149: 443-454.
101. Poewe W, Luginger E. Depression in Parkinson's disease: impediments to recognition and treatment options. *Neurology* 1999; 52 (Suppl 3): S2-S6.
102. Edwards E, Kitt C, Oliver E, et al. Depression and Parkinson's disease: a new look at an old problem. *Depress Anxiety* 2002; 16(1): 39-48.
103. Starkstein SE, Mayberg HS, Leiguarda R, et al. A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1992; 55: 377-382.
104. Cole SA, Woodard JL, Juncos JL, et al. Depression and disability in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1996; 8: 20-25.
105. Shulman LM. Apathy in patients with Parkinson's disease. *Int Rev Psychiatry* 2000; 12: 298-306.
106. Fields JA, Norman S, Straits-Tröster KA, Tröster AI. The impact of depression on memory in neurodegenerative disease. In: Tröster AI, (Ed). *Memory in Neurodegenerative Disease: Biological, Cognitive, and Clinical Perspectives*. New York: Cambridge University Press, 1998: 314-337.
107. Taylor AE, Saint-Cyr JA. Depression in Parkinson's disease: reconciling physiological and psychological perspectives. *J Neuropsychiatry Clin Neurosci* 1990; 2(1): 92-98.
108. Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG. Cognitive impairments and depression in Parkinson's disease: a follow up study. *J Neurol Neurosurg Psychiatry* 1990; 53: 597-602.
109. Tröster AI, Stalp LD, Paolo AM, et al. Neuropsychological impairment in Parkinson's disease with and without depression. *Arch Neurol* 1995; 52: 1164-1169.
110. Kuzis G, Sabe L, Tiberti C, et al. Cognitive functions in major

- depression and Parkinson disease. *Arch Neurol* 1997; 54: 982-986.
111. Norman S, Tröster AL, Fields JA, Brooks R. Effects of depression and Parkinson's disease on cognitive functioning. *J Neuropsychol Clin Neurosci* 2002; 14: 31-36.
  112. Starkstein S, Leiguardia R, Gershan O, et al. Neurosurgical disturbance in hemiparkinson's disease. *Neurology* 1987; 37: 1762-1764.
  113. Fahim S, van Duijn CM, Baker FM, et al. A study of familial aggregation of depression, dementia and Parkinson's disease. *Eur J Epidemiol* 1998;14: 233-238.
  114. Heberlein I, Ludin HP, Scholz J, Vieregge P. Personality, depression, and premorbid lifestyle in twin pairs discordant for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1998;64: 262-266.
  115. Sano M, Stern Y, Côté L, et al. Depression in Parkinson's disease: a biochemical model. *J Neuropsychiatry Clin Neurosci* 1990; 2: 88-92.
  116. Mayberg HS, Solomon DH. Depression in Parkinson's disease: a biochemical and organic viewpoint. *Adv Neurol* 1995; 65: 49-60.
  117. Stojanovic M, Filipovic SR, Kacar A, et al. Obsessive-compulsive symptoms in Parkinson's disease. *Mov Disord* 1997; 12: 128.
  118. Glosser G, Clark C, Freundlich B, et al. A controlled investigation of current and premorbid personality: characteristics of Parkinson's disease patients. *Mov Disord* 1995; 10: 201-206.
  119. Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. *J Neuropsychiatry Clin Neurosci* 1994; 6(4): 358-370.
  120. Côté L. Depression: Impact and management by the patient and family. *Neurology* 1999; 52(Suppl 3): S7-S9.
  121. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. *J Neurol Neurosurg Psychiatry* 2002; 72(6): 701-707.
  122. Kazumata K, Antonini A, Dhawan V, et al. Preoperative indicators of clinical outcome following stereotaxic pallidotomy. *Neurology* 1997; 49: 1083-1090.
  123. Samuel M, Caputo E, Brooks DJ, et al. A study of medial pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications. *Brain* 1998; 121: 59-75.
  124. Scott RB. Cognitive function and pallidotomy. *J Neurol Neurosurg Psychiatry* 1998; 65(2): 148.
  125. York MK, Levin HS, Grossman RG, et al. Neuropsychological outcome following unilateral pallidotomy. *Brain* 1999; 122: 2209-2220.
  126. Green J, Barnhart H. The impact of lesion laterality on neuropsychological change following posterior pallidotomy: a review of current findings. *Brain Cog* 2000; 42(3): 379-398.
  127. Stebbins GT, Gabrieli JDE, Shannon KM, et al. Impaired frontostriatal cognitive functioning following posteroventral pallidotomy in advanced Parkinson's disease. *Brain Cog* 2000; 42(3): 348-363.
  128. De Bie RM, De Haan RJ, Schuurman PR, et al. Morbidity and mortality following pallidotomy in Parkinson's disease: a systematic review. *Neurology* 2002; 58: 1008-1012.
  129. Green J, McDonald WM, Vitek JL, et al. Neuropsychological and psychiatric sequelae of pallidotomy for PD: clinical trial findings. *Neurology* 2002;58(6):858-865.
  130. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of the effects of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998a; 51(3): 850-855.
  131. Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPI pallidotomy on motor function in Parkinson's disease. *Lancet* 1995; 346: 1383-1387.
  132. Perozzo P, Rizzone M, Bergamasco B, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: comparison of pre- and postoperative neuropsychological evaluation. *J Neurol Sci* 2001; 192(1-2): 9-15.
  133. Wilson S, Bladin P, Saling M. The "burden of normality": concepts of adjustment after surgery for seizures. *J Neurol Neurosurg Psychiatry* 2001; 70(5): 649-656.
  134. Shannon KM, Penn RD, Kroin JS, et al. Stereotaxic pallidotomy for the treatment of Parkinson's disease. Efficacy and adverse effects at 6 months in 26 patients. *Neurology* 1998; 50: 434-438.
  135. Ghika J, Ghika-Schmid F, Fankhauser H, et al. Bilateral contemporaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects. Report of four cases and review of the literature. *J Neurosurg* 1999; 91(2): 313-321.
  136. Scott RB, Harrison J, Boulton C, et al. Global attentional-executive sequelae following surgical lesions to globus pallidus interna. *Brain* 2002; 125(Pt 3): 562-574.
  137. Turner KR, Reid WG, Homewood J, et al. Neuropsychological sequelae of bilateral posteroventral pallidotomy. *J Neurol Neurosurg Psychiatry* 2002; 73(4): 444-446.
  138. Crowe SF, O'Sullivan JD, Peppard RF, et al. Left posteroventral pallidotomy results in a deficit in verbal memory. *Behav Neurol* 1998; 11: 79-84.
  139. Uitti RJ, Wharen RE, Jr Turk MF, et al. Unilateral pallidotomy for Parkinson's disease: comparison of outcome in younger versus elderly patients. *Neurology* 1997; 49: 1072-1077.
  140. Masterman D, DeSalles A, Baloh RW, et al. Motor, cognitive, and behavioral performance following unilateral posterior pallidotomy for Parkinson's disease. *Arch Neurol* 1998; 55: 1201-1208.
  141. Tröster AI, Fields JA, Wilkinson SB, et al. Unilateral pallidal stimulation for Parkinson's disease: neurobehavioral functioning before and 3 months after electrode implantation. *Neurology* 1997; 49: 1078-1083.
  142. Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* 1994; 117: 877-897.
  143. Dagher A, Owen AM, Boecker H, et al. The role of the striatum and hippocampus in planning: a PET activation study in Parkinson's disease. *Brain* 2001; 124(5): 1020-1032.
  144. De Bie RM, Schuurman PR, Bosch DA, et al. Outcome of unilateral pallidotomy in advanced Parkinson's disease: cohort study of 32 patients. *J Neurol Neurosurg Psychiatry* 2001; 71(3): 375-382.
  145. Woods SP, Fields JA, Tröster AI. Neuropsychological sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a critical review. *Neuropsych Rev* 2002;111-126.
  146. Galvez-Jimenez N, Lozano AM, Duff J, et al. Bilateral pallidotomy pronounced amelioration of incapacitating levodopa-induced dyskinesias but accompanying cognitive decline. *Mov Disord* 1996; 11: 242.
  147. Lhermitte F. 'Utilization behaviour' and its relation to lesions of the frontal lobes. *Brain* 1983; 106(2): 237-255.
  148. Lhermitte F, Pillon B, Serdaru M. Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: a neuropsychological study of 75 patients. *Ann Neurol* 1986; 19(4): 326-334.
  149. Lhermitte F. Human autonomy and the frontal lobes. Part II: Patient behavior in complex and social situations: the "environmental dependency syndrome". *Ann Neurol* 1986; 19(4): 335-343.
  150. Parkin SG, Gregory RP, Scott R, et al. Unilateral and bilateral pallidotomy for idiopathic Parkinson's disease: a case series of 115 patients. *Mov Disord* 2002; 17(4): 682-692.
  151. Gross RE, Lombardi WJ, Lang AE, et al. Variability in lesion location following microelectrode-guided pallidotomy. II. Relationship of lesion location to clinical outcome following microelectrode-guided pallidotomy for Parkinson's disease. *Brain* 1999;122 ( Pt 3): 405-416.
  152. Lombardi WJ, Gross RE, Trépanier LL, et al. Relationship of lesion location to cognitive outcome following microelectrode-guided pallidotomy for Parkinson's disease: support for the existence of cognitive circuits in the human pallidum. *Brain* 2000; 123: 746-758.
  153. Dujardin K, Krystkowiak P, Defebvre L, Blond S, Destee A. A case of severe dysexecutive syndrome consecutive to chronic bilateral pallidal stimulation. *Neuropsychologia* 2000; 38: 1305-1315.
  154. Ardouin C, Pillon B, Peiffer E, et al. Bilateral subthalamic or

- pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. *Ann Neurol* 1999; 46: 217-223.
155. Fields JA, Tröster AI, Wilkinson SB, et al. Cognitive outcome following staged bilateral pallidal stimulation for the treatment of Parkinson's disease. *Clin Neurol Neurosurg* 1999; 101: 182-188.
  156. Bejjani B, Damier P, Arnulf I, et al. Pallidal stimulation for Parkinson's disease. Two targets? *Neurology* 1997; 49(6): 1564-1569.
  157. Krack P, Pollak P, Limousin P, et al. From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. *Brain* 1999; 122(6): 1133-1146.
  158. Ashby P, Strafella A, Dostrovsky JO, Lozano A, Lang AE. Immediate motor effects of stimulation through electrodes implanted in the human globus pallidus. *Stereotact Funct Neurosurg* 1998; 70(1): 1-18.
  159. Bejjani BP, Arnulf I, Houeto JL, et al. Concurrent excitatory and inhibitory effects of high frequency stimulation: an oculomotor study. *J Neurol Neurosurg Psychiatry* 2002; 72(4): 517-522.
  160. Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation. *Neurology* 2000; 55(12 Suppl 6): S13-S16.
  161. Brown RG, Dowsey PL, Brown P, et al. Impact of deep brain stimulation on upper limb akinesia in Parkinson's disease. *Ann Neurol* 1999; 45(4): 473-488.
  162. Jahanshahi M, Ardouin CMA, Brown RG, et al. The impact of deep brain stimulation on executive function in Parkinson's disease. *Brain* 2000; 123(6): 1142-1154.
  163. Pillon B, Ardouin C, Damier P, et al. Neuropsychological changes between "off" and "on" STN and GPi stimulation in Parkinson's disease. *Neurology* 2000; 55(3): 411-418.
  164. Limousin P, Greene J, Pollak P, et al. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol* 1997; 42(3): 283-291.
  165. Carbon M, Eidelberg D. Modulation of regional brain function by deep brain stimulation: studies with positron emission tomography. *Curr Opin Neurol* 2002; 15(4): 451-455.
  166. Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high frequency deep brain stimulation. *N Engl J Med* 1999; 340: 1476-1480.
  167. Stefurak TL, Mikulis D, Mayberg H, et al. Deep brain stimulation associated dysphoria and cortico-limbic changes detected by fMRI. *Mov Disord* 2001; 16(Suppl. 1): S54-S55.
  168. Krack P, Kumar R, Ardouin C, et al. Mirthful laughter induced by subthalamic nucleus stimulation. *Mov Disord* 2001; 16: 867-875.
  169. Bejjani BP, Damier P, Arnulf I, et al. Deep brain stimulation in Parkinson's disease: opposite effects of stimulation in the pallidum. *Mov Disord* 1998; 13(6): 969-970.
  170. Yelnik J, Damier P, Bejjani BP, et al. Functional mapping of the human globus pallidus: contrasting effect of stimulation in the internal and external pallidum in Parkinson's disease. *Neuroscience* 2000; 101(1): 77-87.
  171. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *J Neurosci* 1989; 9: 582-587.
  172. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Progress Neurobiol* 1996; 50: 381-425.
  173. Wise SP, Murray EA, Gerfen CR. The frontal cortex-basal ganglia system in primates. *Crit Rev Neurobiol* 1996; 10(3-4): 317-356.
  174. Filion M, Tremblay L, Matsumura M, Richard H. Focalisation dynamique de la convergence informationnelle dans les noyaux gris centraux. *Rev Neurol (Paris)* 1994; 150(8-9): 627-633.
  175. Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. *Science* 1996; 273: 1399-1402.
  176. Davis KD, Taub E, Houser D, et al. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. *Nat Med* 1997; 3: 671-674.
  177. Ceballos-Baumann A, Boecker H, Bartenstein P, et al. A positron emission tomography study of subthalamic nucleus stimulation in Parkinson's disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. *Arch Neurol* 1999; 56: 997-1003.
  178. Rezaei AR, Lozano AM, Crawley AP, et al. Thalamic stimulation and functional magnetic resonance imaging: localization of cortical and subcortical activation with implanted electrodes. Technical note. *J Neurosurg* 1999; 90(3): 583-590.
  179. Fukuda M, Edwards C, Eidelberg D. Functional brain networks in Parkinson's disease. *Parkinsonism Relat Disord* 2001; 8(2): 91-94.
  180. Samuel M, Ceballos-Baumann AO, Holmes AP, et al. Pallidotomy in Parkinson's disease increases SMA and prefrontal activation during performance of volitional movements: an H<sub>2</sub><sup>15</sup>O PET study. *Brain* 1997; 120: 1301-1313.
  181. Sestini S, Scotto di Luzio A, Ammannati F, et al. Changes in regional cerebral blood flow caused by deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *J Nucl Med* 2002; 43(6): 725-732.
  182. Schubert T, Volkmann J, Muller U, et al. Effects of pallidal deep brain stimulation and levodopa treatment on reaction-time performance in Parkinson's disease. *Exp Brain Res* 2002; 144(1): 8-16.
  183. Schroeder U, Kuehler A, Haslinger B, et al. Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. *Brain* 2002; 125(9): 1995-2004.
  184. Pollo A, Torre E, Lopiano L, et al. Expectation modulates the response to subthalamic nucleus stimulation in parkinsonian patients. *Neuroreport* 2002; 13(11): 1383-1386.
  185. de la Fuente-Fernandez R, Ruth TJ, Sossi V, et al. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 2001; 293(5532): 1164-1166.
  186. Saint-Cyr JA, Hoque T, Pereira LCM, et al. The MRI localization of clinically effective stimulating electrodes in the human subthalamic nucleus. *J Neurosurg* 2002; 97: 1152-1166.
  187. Lanotte MM, Rizzone M, Bergamasco B, et al. Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. *J Neurol Neurosurg Psychiatry* 2002; 72(1): 53-58.
  188. Starr PA, Christine CW, Theodosopoulos PV, et al. Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging-verified lead locations. *J Neurosurg* 2002; 97(2): 370-387.
  189. Parent A, Cicchetti F. The current model of basal ganglia organization under scrutiny. *Mov Disord* 1998; 13(2): 199-202.
  190. Parent A, Levesque M, Parent A. A re-evaluation of the current model of the basal ganglia. *Parkinsonism Relat Disord* 2001; 7(3): 193-198.