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Interventions in Parkinson's disease: Role of executive function

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1. ABSTRACT

The cortico-striatal network plays a major role in executive functions (EF), and is believed to play a role in the pathophysiology of Parkinson's disease (PD). However, the tools to assess EF are limited. This review assesses the impact of all PD interventions, namely, pharmacotherapy, physical exercise and Deep Brain Stimulation (DBS) surgery on EF. The effect of PD pharmacotherapy varies with the drug class, neuropsychological test used and the affected dopamine receptor family. There appears to be a benefit of aerobic exercise on EF, including judgment and attention. The effect of Deep Brain Stimulation on EF might vary with site of brain stimulation, the neuropsychological test performed and the pre-operative cognitive state. The effect of EF on underlying manifestations and as a factor in the pathway to the motor benefit needs to be better assessed with more accurate tests that focus on motor component of EF.

2. INTRODUCTION

The diagnosis of Parkinson's disease (PD) is made using the UK Brain Bank criteria, which takes into account motor symptoms including resting tremor, bradykinesia, rigidity and postural instability (1). Some secondary motor symptoms seen in PD include hypomimia, dysarthria, micrographia, shuffling gait, freezing and festination of gait. It is well understood that PD includes non-motor symptoms such as sleep disorders, cognitive/neuropsychiatric abnormalities, autonomic dysfunction and sensory abnormalities like pain and paresthesias (2). Studies have found that anxiety, Rapid Eye Movement Sleep behavior disorder and loss of olfaction might be present decades before motor symptoms manifest (3, 4). The role of cognitive and other non-motor features of PD and their effect on the motor functionality and quality of life in PD patients is being increasingly recognized and explored.

Traditionally, executive function (EF) has been thought to be mediated by the prefrontal cortex (PFC) (5). Alexander and Crutcher implicated the cortico-striatal network, linking regions of the frontal cortex to striatal structures, via the thalamus and globus pallidus, in playing a vital role in EF (6). As abnormalities in the corticostriatal interactions are believed to play a role in the pathophysiology of PD, the role of EF in the clinical motor manifestations seen in PD patients is worth exploring (7, 8).

PD patients often present with falls which by self-report are frequently secondary to not "paying attention". The prefrontal area of the brain is associated with executive function (attention and decision making), the premotor cortex is involved in the sensory guidance of movement and the supplemental motor area is involved in the planning of complex movement. Studies requiring healthy and PD subjects to focus on a forthcoming motor response have found that in the healthy control subjects attention to action was associated with increased activation, showing increased connectivity of the prefrontal, premotor and supplemental motor areas. This connectivity is altered in patients with PD (9-11).

An important question in assessing EF is whether the neuropsychological tests used to measure EF in patients with motor dysfunction are specific enough to separate "pure" executive dysfunction from motor confounds. For example, the commonly used Trail Making Test (TMT) is dependent on motor processes and is assessed by time to successful completion. In movement disorders, where impairment of motor function is often the most disabling symptom, this might be a major limitation in the accurate assessment of EF. As a result, the final measure of EF is often confounded by the motor function of the patient. Additionally, the performance of a patient on an EF metric in a controlled setting, might not be predictive of the patient's performance on another metric, let alone be predictive of performance in a real life setting (12). Thus, the reported prevalence of executive function in movement disorders might vary with the measure of executive function used. Further, it is important for EF measures to be sensitive enough to differentiate neurodegenerative executive dysfunction from normative age-related changes and to be able to assess EF longitudinally, as the disease progresses.

Data collected in large epidemiological studies involving patients with movement disorders, including PD, often include a single global measure of cognition and extrapolate from these findings to different domains like memory and EF (13, 14). Mamikonyan *et al*. found that mild cognitive impairment, either in single or multiple cognitive domains, occurs in almost one-third of PD patients with intact global cognition as defined by a normal score on the Mini-Mental State Exam (MMSE), a test commonly used in epidemiologic studies (15). Global measures may not be sufficiently sensitive in detecting EF impairments that are prevalent in PD.

In a meta-analysis of neuropsychiatric side effects of DBS in PD patients, Appleby *et al*. looked at human studies from 1996 to 2006 and finally reviewed 546 articles (16). Their analysis concluded that there is a relatively high incidence of psychiatric adverse effects including delirium, depression, anxiety and suicidality. DBS-associated cognitive changes were not reported. To determine the effect of physical exercise on cognition in older adults with dementia or other cognitive impairment, Heyn *et al*. reviewed published and non-published manuscripts between 1970 and 2003 (17). Their meta-analysis included 2,020 cognitively impaired subjects, greater than 65 years of age, involved in 30 trials. They concluded that physical exercise was beneficial for cognitively impaired older adults in the domains of physical health, cognitive health and behavioral outcomes. However, there were no available data on PD patients in these studies. Moreover, a potential explanation for such an association was not offered.

Executive dysfunction is associated with functional impairment in older adults and could be predictive of dementia (18). The role of EF in pathophysiology and management of disorders like PD that are defined by a progression of disruption in motor control have yet to be fully appreciated in the literature. A likely reason is the above mentioned issue with metrics of executive function. One way of better understanding this association is to explore the literature regarding effects of various PD interventions on EF. Although there are no known modalities to arrest or slow the progression of disease, interventions can often provide substantial improvement with symptoms and improve quality of life (19). Interventions in PD can largely be grouped into the following: 1) pharmacological therapy, 2) physiotherapy/physical therapy and aerobic exercise, and, 3) surgery, the most common of which is Deep Brain Stimulation (DBS). In our review, we present data published that speaks to the effect of these interventions on EF, thereby commenting on the relevance of EF in PD and its management. We also present the metrics used by various studies to assess EF.

3. INTERVENTIONS AND THEIR EFFECT ON EXECUTIVE FUNCTION: EVIDENCE THUS FAR

3.1. Pharmacological therapy and executive function

Pharmacological therapy is the cornerstone of treatment for PD patients (Table 1). Pharmacologic treatment of PD can be divided into symptom focused and neuroprotective (disease modifying) therapy. At this time, there is no proven neuroprotective, disease-modifying therapy for PD. Symptomatic drugs used for PD include Levodopa/Carbidopa, dopamine agonists, MAO-B inhibitors and COM-T inhibitors (20) aimed largely at treating motor symptoms such as tremor, postural instability and bradykinesia.

3.1.1. Levodopa

PD is pathologically defined as a loss of dopaminergic neurons leading to a deficiency in dopamine. The synthesis of dopamine in the brain involves the conversion of L-tyrosine to L-dopa and then to dopamine (21). To replenish dopamine levels, Levodopa or L-dopa (L-3,4-dihydroxyphenylalanine) is considered the most effective drug in PD. Carbidopa is often given to patients along with Levodopa. Carbidopa allows for greater bioavailability of levodopa in the central nervous system (CNS) by inhibiting the decarboxylation of levodopa to dopamine in the systemic circulation (22).

Although levodopa is one of the most commonly used pharmacological agents for the motor symptoms of PD, it has unintended cognitive and emotional effects, as well. The use of levodopa has been associated with motor effects, such as dyskinesias (uncontrollable movement of one or more parts of the body) and cognitive effects, such as forgetfulness, difficulty with

Table 1. Summary of the studies reviewed

Reference number	Study Length	Study design	Patient Sample	Interventions	Cognitive Metrics used	Conclusion
(24)	3 months	Pre-post drug trial	Patients with PD, PDD or DLB	Levodopa trial	MMSE, UPDRS, VAS, RDS, SRT, CRT, NPI, DVIG RT, NWM RT, DPIC RT	Increased attention Faster reaction times No adverse effects on cognition
(25)	N/A	Pre-post drug withdrawal	PD patients	Withdrawing levodopa in PD patients currently taking it	MMSE, UPDRS, CANTAB, BDI, Task switching, decision making	Levodopa remediates inflexibility, increases impulsivity
(26)	N/A	Randomized double blinded crossover study	PD patients	Immediate release vs Controlled release levodopa	WCST, Steinberg test,Stroop test, Tower of Hanoi, MMSE, BDI, VAS-M	Slower rise in levodopa leads to better performance in working memory tasks.
(30)	N/A	Randomized trial	PD patients with early/mild disease	Pramipexole vs levodopa vs off medication	UPDRS, mWCST, Stroop test, TMT, Spinler matrices, FAS, CVLT, LDFR, DST	Pramipexole may worsen cognitive functions
(31)	N/A	Randomized crossover study	PD patients with early/mild disease	Neuropsych analysis done as: rotigotine/ cabergoline vs levodopa vs off medication`	UPDRS, FAS, TMT, Stroop test, RAVLT, DST, Tower of London, Raven Matrices Test	Combined stimulation of dopamine receptors preserves cognitive function
(34)	8 weeks	Randomized double blind study	PD patients	Selegiline vs placebo	WAIS, WMS, DST, TMT-B, Stroop test, BDI, HAMD	No specific cognitive effects observed
(35)	8 weeks	Randomized double blind study	Levodopa-naïve Early PD patients	Selegiline vs placebo	UPDRS, WCST, Advanced progressive matrices test	Improved mood No change in cognitive variables
(36)	N/A	Observational trial	PD patients on PD medications	Addition of Tolcapone	UPDRS, EuroQol, NMSS, NMSQuest, VAS	Tolcapone addition may improve non-motor symptoms
(37)	3 weeks	Double blind crossover trial	Normal human subjects	Tolcapone vs placebo	Verbal fluency, Verbal episodic memory, CANTAB test, TMT, WCST, fMRI, Letter Number Span	Tolcapone improves cognition and cortical processing in normal human subjects.
(40)	12 weeks	Pre-post single group pilot study	Individuals with chronic stroke	12 weeks of aerobic and strengthening exercise	Fugl-Meyer score, digit span backwards test, Flanker's test, DB test, WAIS, SIS	Exercise improved selected measures of executive function in people with stroke.
(41)	N/A	Pre-post study	Normal human subjects	30 minutes of stair-climbing	Stroop test	Increase in cardiovascular activity can lead to increased processing speed and lower error rate.
(45)	N/A	Cross-sectional analysis of longitudinal study	Older adults with mild aMCI	Exercise (measured by gait speed and TUG task)	Stroop test, TMT-B test, WMS-R	Physical performance speed is associated with executive function.
(47)	N/A	Observational study	PD patients	Depression (assessed by BDI)	MMSE, FAB, BDI, UPDRS	Depression exacerbates executive dysfunction
(48)	N/A	Pre-post 2 arm test	Elderly patients with diagnosed Major depressive disorder	Exercise	DST, Stroop test, HAMD	Exercise improves some components of cognitive function in depressed elderly

(Contd..)

Table 1. *(Continued)*

Reference number	Study Length	Study design	Patient Sample	Interventions	Cognitive Metrics used	Conclusion
(56)	N/A	Observational trial	People with advanced PD who underwent B/L STN-DBS	B/L STN-DBS surgery	UPDRS, Computerized neuropsychological test battery, HAMD, FAB	B/L STN DBS improves some functions of gait and cognition
(57)	3 years	Prospective naturalistic controlled study	PD patients with B/L STN DBS vs no DBS	B/L STN DBS	MMSE, UPDRS, DST, FAS, WCST, Ravens matrices, CBTT, LMT	Immediate worsening of executive function. Long term worsening of verbal fluency.

falling and maintaining sleep, nightmares, drowsiness and hallucinations (23). A number of studies have been undertaken to further assess the impact of levodopa on cognition. We will continue to focus on those that have assessed components of EF.

In 2006, Molloy *et al*. carried out a study to assess the effect of levodopa on global cognition, alertness, verbal recall, reaction times and accuracy (24). Neuropsychiatric tests were conducted at baseline, immediately after a trial of levodopa and 3 months after treatment. The study reported improved motor function and subjective alertness in patients. Further, no deterioration in reaction times and accuracy was reported. Therefore, patients on levodopa showed improvement in both motor speed and cognitive speed without any difference in accuracy. These neuropsychiatric scores showed continued improvement 3 months post-treatment, even among those PD patients with dementia.

Cools *et al*. sought to assess the effect of dopaminergic withdrawal in PD patients on medication (25). After stopping levodopa, task switching costs, decision making and impulsivity were assessed. The study reported that patients 'off'levodopa showed an increase in task switching costs, which improved after the patients were given levodopa again. On the other hand, these patients showed increased impulsivity as seen by odd betting behaviors when they were 'on' medication as compared to when they were 'off' medication. Results of this study suggest that levodopa may improve cognitive flexibility but also leads to increased impulsivity.

The effect of levodopa on cognition further varies according to the pharmacokinetics properties of dopamine, with a slower rise leading to better cognitive function. The pharmacokinetic properties of dopaminergic drugs in PD patients often leads to reported fluctuations in the motor benefit they experience from these medications. In a randomized, double blind, crossover trial, Pascual-Sedno *et al*. assessed the differential effect of rate of levodopa uptake on motor and executive functions. Executive function was defined on the basis of performance on four tasks of executive function: Wisconsin Card Sorting Test-WCST, Sternberg test, Stroop and Tower of Hanoi, 1 hour before and over 6 hours after immediate and controlled release Levodopa dose. They reported a difference in performance on executive function tasks according to the nature of the task performed and the rate of levodopa uptake/bioavailability. PD patients on controlled release levodopa, representing a slower rise in levels, performed better on these tests especially those measuring flexibility in working memory (26).

3.1.2. Dopamine agonists

Dopamine agonists include drugs like pramipexole and ropinirole (non-ergot derivates), rotigotine and cabergoline (ergot derivates) and the now sparingly used, apomorphine. By their agonistic action on the D-2 dopamine receptor (apomorphine acts on D-1 receptor as well, ropinirole and cabergoline have an affinity for D-3 and D-1 receptors too) (27), these mimic the role of dopamine in the brain. Dopamine agonists are less effective than levodopa in managing the motor symptoms of Parkinsonism (19). Nonetheless, dopamine agonists, alone or in association with levodopa, are established as effective drugs for the symptomatic treatment of PD. Yamamoto & Schapira reported a decrease in innervation of nigrostriatal neurons with dopamine agonist use (28). Because of the disabling side effect of motor dyskinesia observed in patients with levodopa, dopamine agonists are sometimes preferred in patients who are highly sensitive to levodopa medication.

The side effect profile of dopamine agonists resembles that seen with levodopa including hallucinations, drowsiness and sleep issues. In 2009, a Cochrane review conducted by Antonini and Cilia reported an increased incidence of impulse control disorders with dopamine agonist use, including hoarding, pathological gambling and hypersexuality (29).

In 2013, Brusa *et al*. designed a randomized cross-over study involving non-demented PD patients to compare the effect of dopamine agonists with the pharmacological gold standard levodopa on cognitive functions independent of motor functioning. A previous study done by them in 2003 had shown that pramipexole lead to a depreciation in attention, verbal memory and verbal fluency, as compared to levodopa (30). In the

2003 study, executive function was measured using TMT, Stroop Color Word Naming test, Spinler Matrices and Modified Wisconsin Card Sorting test. They concluded that pramipexole treatment may not show the improvement produced by levodopa on executive function (as evaluated by Stroop test) and further may lead to worsening of attention (as evaluated by TMT and Spinler Matrices). However, the study in 2013, which used rotigotine and cabergoline as the dopamine agonist arm of the study showed that neither the dopamine agonists used, nor levodopa affected performance on cognitive testing. The measures of executive function used included TMT (A, B and B-A), Stroop color word naming test and tower of London test with the UPDRS section III administered at every neuropsychological assessment to verify that the motor function was similar. Brusa *et al*. concluded that drugs with affinity to both D1 and D2 receptors (levodopa, rotigotine and cabergoline) do not adversely affect cognitive function, while drugs with pure D2 receptor affinity do (31).

Hence the effect of dopamine agonists on EF might vary with the dopamine receptor families involved. Other studies in literature have had mixed results, indicating that the above mentioned hypothesis might be worth further exploration.

3.1.3. MAO-B inhibitors

Monoamine oxygenase inhibitors or MAO-B inhibitors were among the first drugs tried for treatment of PD. Although both selegiline and rasagiline have been used alone and in combination with other PD medications for motor Parkinsonism, they are largely preferred as anti-depressant agents in patients with PD. With their additional beneficial effect on motor symptoms these are particularly suited to PD patients with depressive symptoms.

MAO-B inhibitors work by inhibiting the enzyme monoamine oxygenase which is responsible for the breakdown of monoamines such as dopamine, serotonin and noradrenalineexplaining its beneficial effect on both motor and depressive symptoms in PD patients (32). MAO-B inhibitors prolong and enhance the effect of levodopa by inhibiting its breakdown. Side effects frequently seen with selegiline use include nausea, orthostatic hypotension and insomnia. However, the most important side effect is seen in PD patients who combine its usage with SSRIs like fluoxetine, which causes a combined, enhanced effect called serotonergic syndrome which is a life threatening syndrome characterized by acute mental changes, tremors, myoclonus, restlessness and diaphoresis (14, 33). As it has a strong anti-depressant action, secondary to prolonged action of serotonin, noradrenaline and dopamine in the brain, there have been few studies in the past to assess if there is an independent effect on cognition/EF.

In 1991, Hietanen conducted a randomized, double blind study which looked at the effect of selegiline on attention, cognitive flexibility, memory, reasoning and visuospatial abilities apart from motor function and depression. Executive function was defined using TMT-B (both errors and processing time were coded), stroop color test and continuation of a simple alternating figure. Tapping speed, dexterity and writing speed were assessed for motor evaluation. Reaction and movement times were measured by a computer controlled method. The study reported no significant improvement in metrics of cognition including EF. There was a slight improvement in learning which was hypothesized to be secondary to arousal (34). Similarly, in a study conducted in 1995, Dalrymple-Afford *et al*. concluded that selegiline improved mentation and activities of daily living measured using the UPDRS (perhaps as a result of improved mentation) but showed no clear beneficial effect on executive function measured using the Wisconsin Card Sorting Task and the advanced progressive matrices test (35).

With the FDA approval of rasagiline for PD treatment, there have been a number of studies (TEMPO and PRESTO trails) assessing cognitive effects of rasagiline. While rasagiline does improve mentation and behavior it has not shown any significant independent effect on cognitive variables (33). These results are in accordance with the widely accepted lack of beneficial independent effect of MAO-B inhibitors on cognitive variables, as seen previously with selegiline.

Thus, the only beneficial effect of MAO-B inhibitors on EF seems to be secondary to its effect on arousal. There has not been any independent effect shown in studies.

3.1.4. COM-T inhibitors

COM-T inhibitors or Catechol-O-methyltransferase inhibitors, such as tolcapone and entcapone, are used as adjuvants with Levodopa/Carbidopa in the treatment of PD. The side effects of COM-T inhibitors include diarrhea, dizziness, hallucinations, confusion and in rare cases, severe liver damage (14).

Since COM-T inhibitors are almost always given in conjunction with levodopa, its independent effect on EF is seldom a topic of interest in PD patients. Muller *et al*. conducted an observational trial in which PD patients already on levodopa treatment, who additionally took tolcapone, had improved non motor symptoms, using a previously validated non-motor symptom assessment scale for PD (36). In a study by Apud *et al*. in 2007, 47 non-PD affected subjects underwent testing for EF (CANTAB test, TMT, Wisconsin Card Sorting test and Letter Number Span) and 34 of those subjects underwent testing for prefrontal information processing via functional

magnetic resonance imaging). They concluded that tolcapone improved working memory, EF and pre-frontal cortex function (37). Therefore, from these studies, it does seem that EF is an important beneficiary of the effect of COM-T inhibitors.

3.2. Aerobic exercise, physical therapy, physiotherapy and executive function

The benefits of exercise on mobility, daily function and health are well established. In recent years, the benefits of exercise on cognitive performance in the healthy individual have been increasingly explored. Physical activity during childhood and adolescence has been found to be a lifestyle factor influencing physical and mental health into adulthood and later in life (38). Studies have shown that adults engaging in fitness training vs. controls have higher levels of executive function. Older adults involved in aerobic exercise have better attention and memory updating (38). Increased physical activity has shown to be beneficial in preserving cognitive function and delay dementia in older adults. Moreover, there appears to be a dose-response relationship between physical activity and cognitive function in older adults, with even modest levels of physical activity leading to significant benefits to cognitive aging (39). These benefits of exercise may be secondary to the increased volumes observed on brain MRI of the pre-frontal and temporal grey matter as well as anterior white matter (40). While cardiovascular pathways have been recognized as an important mechanism of this benefit, recent randomized controlled trials have shown an impact on executive control associated with multiple activity pathways. Neurotrophins, including brain derived neurotrophic factor (BDNF), insulin like growth factor-1 (IGF-1) and estrogen, may also serve as mediators in the pathway of the beneficial effect seen with both aerobic and anerobic exercise (39).

The literature linking physical exercise to cognitive benefits in healthy older adults has been hypothesized to benefit cognition in older adults suffering from neurological disorders such as dementia, chronic stroke, traumatic brain injury and multiple sclerosis. Heyn *et al*. conducted a meta-analysis of randomized trials spanning 30 years on the effect of exercise in cognitively impaired older adults (17). The meta-analysis reported beneficial effect of exercise on cognition, although the mechanism of such a benefit is not completely understood.

In a pre-post pilot study assessing the benefits of an aerobic exercise regime on older adults with a history of chronic stroke, Kluding *et al*. evaluated the relationship between aerobic exercise capacity and EF. EF was measured using digit span backwards and Flanker test. Aerobic fitness aerobic fitness (VO_2peak, 6-minute walk distance) and function (Fugl-Meyer, 10-meter walk speed) were also evaluated. They found a significant correlation between improved aerobic capacity and improved performance on the Flanker test (r=0.7.4; p=0.0.2) (40). Tam assessed changes in EF (assessed using the color-naming Stroop test) before and within 30 minutes of stair climbing and before and after 'non-exercise' as control. The study reported an improvement in processing speed and a decrease in error, perhaps pointing towards a possible direction for further research for a mechanism (41).

A prospective investigation in the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS) concluded that higher levels of physical activity were associated with a lower risk of PD in men (42). The investigation however, could not comment on potential underlying mechanisms of benefit. While there is limited information on the effect of exercise on dopamine levels in humans, Petzinger *et al*. demonstrated an increase in total dopamine levels in rodents with exercise, although they concluded that such a benefit might be dependent on the presence or absence of a nigrostriatal lesion (43). Similarly, from their experiments on the effect of habitual physical activity on dopamine transmission in animal models, Foley *et al*. concluded that habitual physical activity may contribute to an increase in dopamine synthesis and a reduction in D2 receptor inhibition in the substantia nigra (44).

In the absence of ability of the PD patient to independently engage in moderate aerobic exercise, physical therapy is often advised by neurologists. In a cross-sectional analysis, Mc Gough *et al*., in their study on sedentary older adults with mild cognitive impairment, sought to assess the association between the results of 2 commonly used tests used by physical therapists (gait speed and Timed "Up and Go" test or 'TUG') on EF (evaluated by TMT-B and Stroop Color word test). They found an association between TMT-B (p=0.0.03) and Stroop Color word test (p=0.0.1) and gait speed, indicating that a slower gait speed as associated with a lower EF. Further longer time on TUG was also found to be associated with a lower score on TMT-B (p<0.0.01) and Stroop Color. (45) These results suggest that physical therapy could improve EF in older cognitively impaired adults.

An important factor to consider in the effects of aerobic exercise and physical therapy on improving EF and cognitive function is underlying depression. Depression has been described as one of the most important non-motor manifestations in PD. It impairs motility and affects activities of daily living. In fact, the National Parkinson's Foundation has implicated depression to be twice as devastating as motor impairments for the health of a PD patient (46). Depression in older adults often presents as cognitive slowing and is known as 'pseudo-dementia'. In a study by Kummer *et al*., 82 PD patients were assessed for PD severity (UPDRS, Schwab-England Scale, and Hoehn-Yahr Scale), depression (Beck Depression

Inventory or 'BDI') and executive function (Frontal Assessment Battery or 'FAB' and MMSE). Scores on the FAB, but not the MMSE, worsened with increased scores on BDI, in PD patients with a lower educational level. It was concluded that depression may worsen EF, especially in subjects with lower educational level (47).

In 2011, Vasques *et al*. showed that moderate physical exercise improves attention and processing speed in the depressed elders as well. In this study, elderly patients with diagnosed major depressive disorder underwent cognitive testing (Digit Span Test and a Stroop Color-Word Test) before, during, immediately after and 15 minutes after an exercise session on the electric treadmill. While there was no change in the Digit Span test between control and exercise, results of the Stroop Color-Word Test improved after physical exercise, indicating a positive effect of exercise on cognition in patients with dementia, especially attention and inhibitory control (48).

Tabak *et al*. further assessed the effect of an 8-week program of aerobic exercise training on a stationary bicycle on EF (assessed by the MoCA, Parkinson's Disease Cognitive Rating Scale and the Color Trails Test 1 and 2) and subjective sense of mood in 2 PD patients (49). Both studies reported an improvement in EF and subjective improvements in mood.

Based on studies included in this analysis, there seems to be some benefit of aerobic exercise on PD symptoms, with indications that exercise might improve EF, including judgment and attention in the presence and absence of depression (40,41,49).

3.3. Deep brain stimulation and executive function

Deep brain stimulation (DBS) is currently used as a treatment modality when the beneficial effect of medications has either been exhausted, or if the side effect profile of medications is disabling for the PD patient. The extent of the beneficial effect of DBS experienced by PD patients is largely similar to the maximum amount medications can provide, and sometimes reportedly better (50). PD patients, therefore, are greatly able to reduce their drug dosage (51).

The mechanism of action of DBS is not completely understood. However, it is agreed that it involves creating a reversible lesion or 'micro infarct' inside the targeted area of the brain (52). Since the procedure is far less invasive, has a better side effect profile and has largely better functional outcomes, DBS is currently preferred to pallidotomy as the surgical procedure of choice in PD patients (53).

For PD patients exhausted on medical therapy, the three regions of the brain usually targeted are the subthalmic nucleus (STN), the Globus Pallidus pars interns (GPi) and the ventralis intermedius nucleus of the thalamus (Vim). While the Vim is preferred as a target for tremors, GPi and STN are preferred if bradykinesia and rigidity are the more disabling symptoms. GPi is known to have a more beneficial effect than STN for dyskinesias (52).

Careful selection of the patient who is appropriate for DBS is critical to outcomes. Potential complications with the surgical procedure include hemorrhage, infection/erosion and hardware (i.e., electrode) complications (54). One of the most important pre-surgical determinants is the neuropsychological evaluation. Specifically, DBS may be temporarily deferred or declined in patients with pre-operative cognitive impairment. Such patients are recognized as poor candidates and may worsen after surgery (52). Neuropsychiatric side effects reported with STN-DBS include mood disorders such as depression, hypomania/euphoria and suicidal intent and cognitive impairment including executive dysfunction, memory worsening and decline in verbal fluency (50).

Therefore, while the effect of DBS surgery on the motor aspect of movement disorders has been the primary area of interest for therapeutic reasons, the effect of DBS on cognition seem to be more important while assessing side effects and quality of life post-surgery. The impact of DBS on cognition is widely accepted. With a better understanding of the underlying processes and mechanisms, it might be possible to stimulate the correct areas of the brain in carefully selected patients to benefit cognition. A small phase I study on the use of DBS as a 'brain pacemaker' for Alzheimer's disease has shown promising results (55). Currently, a trial for the use of DBS targeting the fornix, as a treatment modality for Alzheimer's disease is underway.

The results of studies on DBS for cognitive outcomes have been mixed. In a meta-analysis of 546 articles over 10 years from 1995-2006, Appleby *et al*. found that while 13% reported a decline in cognitive variables, 12% of the studies reported an improvement and 57% reported no change (16). Similarly, Seri-Fainshtat *et al*., in their study on 28 post-DBS PD patients, reported an improvement in gait speed and attention post-DBS but no overall improvement in EF assessed by a previously validated computerized version of the Go-No-Go and the Stroop interference tests (56).

However, in their prospective study on PD patients with DBS surgery, Zangaglia *et al*. reported worse EF (assessed by logical executive function task scores) and verbal fluency (assessed by FAS scores) immediately post-surgery and significant worsening of verbal fluency 3 years after (57).

In their review of cognitive outcomes post-DBS, Borgohain *et al*. recognized the importance of the surgical

target on cognitive outcomes. Their review reported mild worsening in verbal fluency with STN-DBS, while GPi-DBS showed no change in cognition (58).

EF in post-DBS PD patients might vary with site of brain stimulation, the neuropsychological test performed and the pre-operative cognitive status of the patient (52). Practicing caution and in the absence of a full-proof predictor algorithm, a poor preoperative cognitive function is considered a contraindication to DBS surgery.

4. CONCLUSION

EF is known to be associated with flexibility of thought, processing speed, decision-making and inhibition of irrelevant actions in the execution of deliberate motor action (59). The repetition of excessive motor function (resting tremor), slowness of deliberate action (bradykinesia) and freezing of gait characterizes some of the recognizable motor features of PD. Our review on these interventions, their side effects and their impact on cognitive outcomes indicates that all forms of PD interventions namely, pharmacotherapy, exercise/physical therapy and DBS, appear to impact EF. A clear mechanistic pathway between EF and PD is difficult to extract from available literature. However, there are some promising leads moving forwards. Loss of cells in norepinephrine-locus cerulus is essential to the pathophysiology of PD and norepinephrine uptake inhibitors like Atomoxetine have been shown to have some benefit with clinical manifestations in executive dysfunction in PD (60). Currently, a phase II trial is underway further evaluating this effect (61). Although the association between EF and PD is likely complex with multiple factors involved, our review of the available evidence suggests that multiple components of EF are key to the symptoms of PD. Moving forward one major objective may be to place greater emphasis on the assessment of components of EF with a particular focus on the motor component of EF, such as the EXIT-25 test and the Frontal Assessment Battery (FAB) (62). With more accurate testing, a potential role of EF as a prognostic marker for PD severity can also be explored. Whether EF is an important factor in the pathophysiology of manifestations of PD and/or a factor in the pathway to the motor benefit seen with interventions needs to be better understood. As such, a broader understanding of the role of EF in PD could have important ramifications for further understanding and managing PD.

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Abbreviations: aMCI: amnestic Mild Cognitive Impairment, B/L STN: Bilateral Subthalmic Nucleus, BDI: Beck Depression Inventory, CBTT: Corsi Block Tapping Test, CRT: Choice Reaction Time, CVLT: California Verbal Learning Test, DB: Digit Span Backwards test, DBS: Deep Brain Stimulation, DLB: Dementia with Lewy bodies, DPIC RT: Delayed Picture Recognition Reaction Time, DST: Digit Span Test, DVIG RT: Digit Vigilance Reaction Time, FAB: Frontal Assessment Battery, fMRI: functional Magnetic Resonance Imaging, HAMD: Hamilton Depression Rating Scale, ICD: Impulse Control Disorders, LDFR: Long Day Free Recall, LMT: Logical Memory Test, MMSE: Mini Mental State Exam, mWCST: modified Wisconsin Card Sorting Test, NMSQues: Non Motor Screening Questionnaire, NMSS: Non Motor Screening assessment Scale, NPI: Neuro-Psychiatric Index, NWM RT: Numeric Working Memory Reaction Time, PD: Parkinson's disease, PDD: Parkinson's disease with dementia, RAVLT: Ray Auditory Verbal Learning Test, RDS: Reverse Digit Span, SIS: Stroke Impact Scale, SRT: Simple Reaction Time, TMT: Trail Making Test, TMT-B: Trail Making Test Part B, TUG: Timed Up and Go task, UPDRS: Unified Parkinson's Disease Rating Scale, VAS: Visual Analogue Scale, VAS-M: Visual Analogue Scale-Mood, WAIS: Wechsler Adult Intelligence Scale, WCST: Wisconsin Card Sorting Test, WMS-R: Wechsler Memory Scale-Revised

Key Words: Executive Function, Parkinson's Disease, DBS, Neuroepidemiology, Review

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