# Cognitive Outcome Following Bilateral Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Comparative Observational Study in the Indian Population

**THESIS**

*Submitted in partial fulfilment of the rules and regulations for the requirement of the degree of DM in Neurology*


**DR. KSHITEEJA JAIN**

DM Neurology Resident

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DEPARTMENT OF NEUROLOGY

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, THIRUVANANTHAPURAM – 695011, India

# DECLARATION

I, Dr Kshiteeja Jain, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram

Date:29.08.20

Dr Kshiteeja Jain

DM Neurology

Resident SCTIMST

# FORWARDED

The candidate, Dr Kshiteeja Jain has completed the project under my guidance.

*Syam Krishnan*

Thiruvananthapuram

Date: 29.08.20

Dr Syam K.

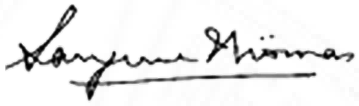
Professor of Neurology

SCTIMST, Trivandrum

(digitally signed)

# FORWARDED

The candidate, Dr Kshiteeja Jain has completed the minimum work required for the project.



Thiruvananthapuram

Date: 29.08.20

Dr. Sanjeev V. Thomas

Professor (Senior Grade) & Head

Department of Neurology

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Dr Kshiteeja Jain
Senior Resident, Neurology
SCTIMST, Trivandrum, Kerala

# SYNOPSIS

The improvement in motor outcomes after bilateral subthalamic nucleus deep brain stimulation (STN DBS) has been well established in patients with Parkinson's disease. However, the cognitive and behavioural changes in these patients have not been accredited with certainty to DBS or its procedure and it remains controversial. We conducted a comparative observational study to assess the effects of bilateral STN DBS on cognition at minimum two years of neurostimulation when compared to a group of patients with PD on medical management alone.

34 patients who underwent DBS were compared to a matched group of 34 medically treated PD patients for neuropsychological scores. The two groups were matched for age, severity of disease, LEDD at baseline and duration of PD. At a mean follow up of around 33 months, compared to medically managed patients, we found a significant decline in verbal fluency scores in the DBS group and a trend for decline was noted in digit span test, both measures of frontal executive function. Though many of the other cognitive scores declined over time in each group, there was no difference between the surgical and medically managed groups, indicating that these are attributable to the natural progression of PD.

Our study demonstrated impairment in the selective cognitive task of verbal fluency and a trend towards impairment in attention, with no other major significant neuropsychological outcomes attributable to STN DBS. We postulate that these effects on fluency and attention are attributable to STN stimulation and modulation of the fronto-striatal circuits. DBS of STN can be considered safe from the cognitive viewpoint in patients with idiopathic Parkinson's disease experiencing motor complications of medical treatment, however, patients should be given adequate information regarding the possible cognitive effects to optimise their quality of life.

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# INTRODUCTION

Parkinson's disease (PD) is a common, potentially disabling progressive neurodegenerative disease (1). It is estimated that more than 10 million people in the world suffer from this disorder and disease prevalence is only expected to rise, as the aging population increases (2). The symptoms of Parkinson's disease encompasses the classic Parkinsonian triad of tremor, bradykinesia, and rigidity associated with dopaminergic denervation, other motor signs associated with nondopaminergic transmission (postural instability and impairment of gait, speech, and posture), and non-motor symptoms (NMS) (3). The non-motor symptoms include autonomic dysfunction, sleep disturbances, behavioural and cognitive changes.

Dopamine replacement therapy still remains the cornerstone for the management of motor symptoms of Parkinson's disease, which dominate the clinical picture in the early and mid-clinical stages of PD in most patients. Dopamine replacement therapy is a purely symptomatic measure and does not modify the progression of the disease. With disease progression, motor complications (motor fluctuations and dyskinesias) arise and compromise the quality of life of patients with PD on medical management.

Deep brain stimulation (DBS) surgery has become a standard of care for selected patients with PD in its moderately advanced disease stages, when they experience motor complications (4–6). Apart from those experiencing motor complications, DBS is also used for patients with PD who have medication refractory and disabling tremor. The established and most widely used targets for DBS in PD are the subthalamic nucleus (STN) or the globus pallidus interna (GPi), though others like the pedunculopontine nucleus and zona incerta have also been tried for specific indications (7,8). Among the two, STN is the preferred target by most centres.

Although the short- and long-term benefits of DBS on motor symptoms are widely recognized, there is debate over the possible cognitive and behavioral effects of this treatment, particularly when STN is targeted (6,8,9). The literature contains few long-term studies and some short-term controlled studies (10–13), on cognitive functions after STN DBS in PD. Neuropsychological investigations conducted from 3 to 6 months after STN DBS showed a worsening of verbal fluency, whereas less consistent effects on other cognitive tasks have been reported in different studies (14).

Ardouin et al., described a deterioration of literal and total lexical fluency 3 to 6 months after chronic STN DBS (15). De Gaspari et al., showed that in the post-surgical period there was a worsening of both letter and category fluency tasks (14). The total number of words and switches decreased, whereas average cluster size was unchanged. Funkiewiez et al., after 3 to 4 years of follow up, reported worsening of both category and total lexical fluency but no evidence of global cognitive dysfunctions (16), whereas other authors reported cognitive and behavioral dysfunction in 24 to 30% of patients (17). At 5 years, neuropsychological evaluation showed significantly worse performances on frontal executive function tasks, probably in parallel with the progression of the disease (18,19).

As PD is a progressive neurodegenerative disease whose course is unaffected by any of the therapies including DBS and the vast majority of patients develop cognitive dysfunction in the long run resulting from spread of neurodegeneration diffusely in the brain, it is often difficult to differentiate the cognitive effects attributable to DBS. The studies conducted in the early post-operative period are also confounded by the lesioning effects of the DBS procedure on the target nuclei and the white matter tracts. Though it is generally agreed upon that STN DBS has definite cognitive effects, there is no consensus on its burden and clinical impact and studies have given divergent results (8,20,21).

We, therefore attempted to explore the cognitive effects of STN stimulation using a prospective comparative observational design, comparing the baseline and follow-up cognitive functions of patients undergoing STN DBS with those of a matched medically managed group.

# REVIEW OF LITERATURE

More than 200 years ago in 1917, James Parkinson in his landmark paper, "An essay on the shaking palsy" described the features of what is now known as Parkinson's disease. Although, fragments of Parkinsonism can be found in earlier descriptions, it was he who succinctly described the motor symptoms of the disease as a constellation of rest tremor, lessened muscular power, abnormal truncal posture, festinant, propulsive gait with intact senses and intellect (22). He noted the progressive nature of the disease, the disability it incurred and called it *paralysis agitans*. Charcot later extended the spectrum, adding bradykinesia and rigidity to the constellation of symptoms, and renamed the condition Parkinson's disease.

Vast advances in the coming years and more so in the previous decades, added substantial information to our knowledge of Parkinson's disease. The non-motor symptoms (NMS), which are often under recognised, account for a large part of the disability of these patients. In 2006, Chaudhari et al., described them to include (23) :

1. Neuropsychiatric non motor symptoms - depression, apathy, impulse control disorders, anxiety, psychosis, hallucinations, mood disorders, apathy, and abulia

2. Cognitive non motor symptoms - executive dysfunction, memory loss, and dementia

3. Dysautonomia - orthostatic hypotension, constipation, urinary incontinence, sexual dysfunction, altered cardiac reflexes, olfactory dysfunction, gastrointestinal dysfunction, and sweating

4. Sleep disorders - insomnia, somnolence, excessive daytime sleepiness, restless legs syndrome, sleep attacks, periodic limb movements of sleep, and rapid eye movement (REM) sleep behaviour disorder

5. Sensory abnormalities - pain, numbness, fatigue, and olfactory impairment

Two distinct types can be recognised by their different clinical features and neuropathological findings. 'Tremor-dominant' PD has a slower progression of symptoms and patients can be disabled by tremor, yet still remain mobile with medications. 'Akinetic-rigid' patients PD patients have a faster progression, more cognitive impairments and develop motor complications with or without tremor (24). A mixed entity is also recognised. Overall, the course was most favorable in tremor-predominant, followed by mixed and akinetic-rigid subgroups (24).

**Pathophysiology**

The classic Parkinsonian triad of tremor, bradykinesia, and rigidity is associated with dopaminergic denervation and other motor signs (postural instability and impairment of gait, speech, and posture) and non-motor symptoms (NMS) are associated with non-dopaminergic dysfunction resulting from neurodegeneration, though some of the NMS like depression, apathy and impulse control disorders have a dopaminergic basis.

The basal ganglia (BG) is a group of nuclei in the brain, comprising the substantia nigra pars compacta (SNc), striatum (Str), subthalamic nucleus (STN), globus pallidus externa (GPe), globus pallidus interna (GPi) and substantia pars reticulata (SNr). Str and STN serve as the input nuclei of the BG receiving dense excitatory projections from the cortex (the cortico-subthalamic excitatory projection is denoted as the hyperdirect pathway to distinguish it from the direct and indirect pathways in the conventional basal ganglia model) , whereas, GPi and SNr are the output nuclei sending inhibitory projections to the thalamus (25). The major input to the basal ganglia is derived from the cortex; virtually the whole of the cortical mantle projects onto the basal ganglia in a highly topographical manner (25). The striatum is the main

portal of entry of the cortical information to the basal ganglia although there are significant cortical projections to the STN. This information is then transmitted to the output nuclei of the basal ganglia, the GPi and the SNr. These send GABAergic inhibitory projections to the thalamus and further glutamatergic innervation to the cortex, resulting in a cortico-basal ganglia-thalamo-cortical loop.

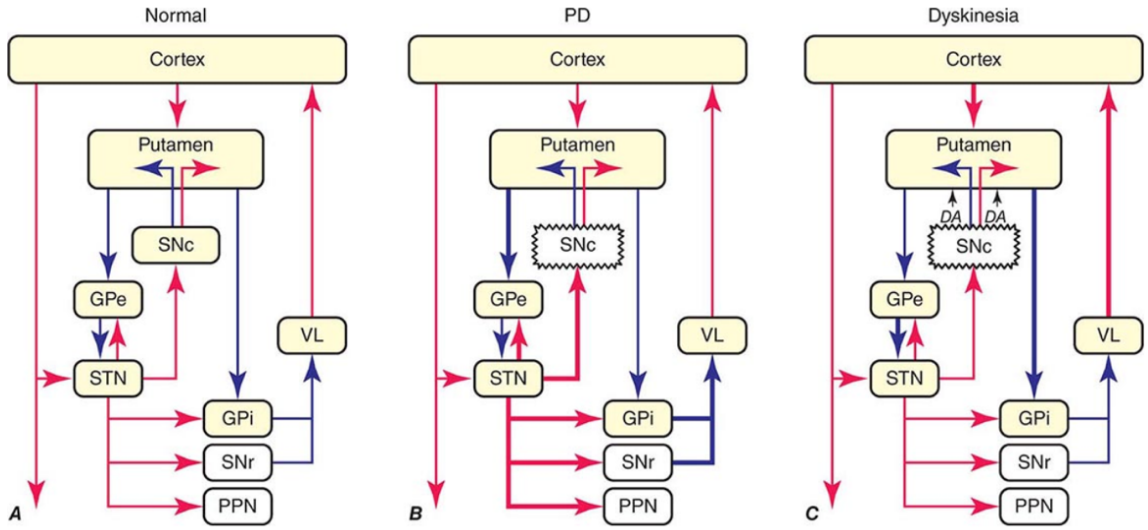


**Figure 1: Classic model of the organization of the basal ganglia in the normal (*A*), Parkinson's disease (PD) (*B*), and levodopa-induced dyskinesia (*C*) state. Inhibitory connections are shown as *blue arrows* and excitatory connections as *red arrows.* (*Derived from JA Obeso et al.,: Trends Neurosci 23:S8, 2000.)***

The transmission of cortical information through the basal ganglia occurs through 2 routes, the 'direct' and 'indirect' pathways (26). In the direct pathway, corticostriatal information is transmitted directly from the striatum to the output nuclei. In the indirect pathway, corticostriatal information is transmitted indirectly to the output nuclei via the complex network interconnecting the GPe and STN. Motor programs from the cortex are differentially

modulated at the striatum by dopaminergic neurons projecting from the SNc. Striatal neurons of the direct and indirect pathway are modulated by D1 and D2 dopamine receptors, respectively. Activation of the direct pathway results in inhibition of GPi and subsequent disinhibition of the thalamus. The indirect pathway has an opposite effect and its activation results in excitation of GPi and subsequent inhibition of the thalamo-cortical output. (Figure 1). The activity in the direct pathway is facilitated by the nigrostriatal dopaminergic system via D1 receptors, while the effect on the indirect pathway is inhibitory, through the D2 receptors. The activity in the two pathways ensure that the appropriate motor programs are selected and facilitated while the unwanted and antagonistic programs are inhibited.

The motor symptoms of Parkinson's disease (PD) are due to the degeneration of dopaminergic neurons in the SNc. According to the classical rate model of PD (26), dopamine depletion results in an imbalance between the direct and indirect striatal pathways. PD dopamine depletion is accompanied by a decreased activation of the direct pathway and an increased activation of the indirect pathway. The increased activation of the indirect pathway leads to a decrease in GPe firing rate and subsequently, an increase in the STN and GPi firing rates. The firing rate of GPi is further amplified by the decreased activation of the direct pathway. Therefore, a hyperactive GPi during PD provides an increased level of inhibition to the thalamus, which results in bradykinesia/akinesia. This is also known as the firing rate model.

Two other models have been described in the pathophysiology of PD. The firing pattern model and the dynamic activity model. Abnormal firing patterns, such as bursts and oscillations, were recorded in the GPe, GPi and STN of parkinsonian patients. Oscillatory local field potentials (LFPs), especially those in the beta frequency band, were also observed in parkinsonian patients using DBS electrodes. Local field potentials (LFPs), at least those at frequencies mainly represent the temporal–spatial summation of post synaptic potentials from the local

neuronal population surrounding an electrode. Beta oscillations therefore are the product of synchronisation across neurons. Dopamine depletion promotes oscillatory activity in the basal ganglia by enhancing connections between the GPe and STN. Oscillatory and/or synchronized firings of the basal ganglia disable individual neurons to process and relay motor-related information, resulting in the failure of appropriate movements. This is the firing pattern model (27).

In the normal state, signals through direct and indirect pathways cause dynamic activity changes in the GPi and release only a selected motor program at a selected time with a clear distinction between the selected and other unselected competing motor program (28). In Parkinson's disease, dopamine depletion reduces movement-related GPi inhibition through the *direct* pathway and facilitates movement- related GPi excitation through the *hyperdirect* and *indirect* pathways. These changes shorten and narrow movement-related GPi inhibition, which leads to the reduction of disinhibition in the thalamus and cortex, resulting in bradykinesia/ akinesia. This is known as the dynamic activity model (28).

**Deep Brain Stimulation and its mechanism of action**

The initial years of medical treatment of PD can often produce excellent results. Dopamine replacement therapy still remains the cornerstone for the management of motor symptoms of Parkinson's disease, which dominate the clinical picture in the early and mid- clinical stages of PD in most patients. Dopamine replacement therapy is a purely symptomatic measure and does not modify the progression of the disease. With disease progression, motor complications (motor fluctuations and dyskinesias) arise and compromise the quality of life of patients with PD on medical management.

Dyskinesia results from a complex interaction of progressive neurodegeneration along with artificial and 'pulsatile' dopaminergic stimulation resulting from dopaminergic therapy. According to severity, dyskinesias are measured on a scale of 0-4 (29). Mild dyskinesia is a near-constant, smooth movement perhaps best described as wiggling and may be intentionally hidden by patients. In the moderate stage, there is a writhing movement and patients often walk with their arms drawn behind them. Severe dyskinesia is choreo-ballistic and disabling. Patients can throw themselves out of a chair, injure bystanders and find the constant movement very tiring (30). The beneficial effect of a given dosage of PD medication tends to last for a shorter period as the disease progresses. This is initially overcome by decreasing the dosage interval. Patients will therefore oscillate in their symptoms from bradykinetic-rigid to moving well to peak-dose dyskinesia, then back to moving well and eventually becoming bradykinetic-rigid. This cycle is repeated with each dose. This pattern is called motor fluctuations which are usually seen after more than five years of dopaminergic therapy (30). In a proportion of patients, the medically refractory symptoms or these complications of treatment can be ameliorated by neurostimulation. Many randomized controlled trials with short and medium term (up to 3-5 years) follow up and several medium and long term (more than a decade) protocol based observational follow up studies have supported the use of deep brain stimulation (DBS) in patients with PD (3–5).

Deep brain stimulation (DBS), a procedure that applies high-frequency electrical stimulation through chronically implanted electrodes into a specific target in the subcortical structures started gaining popularity and acceptance in the 1990s. The ventral intermediate (VIM) nucleus of the thalamus was the first electrically stimulated region for the treatment of PD (31), but it is now targeted in uncommon and much selected circumstances, as tremor is seemingly the sole clinical feature improving significantly with the procedure (32). One of the two different brain regions is currently targeted for DBS in PD: the subthalamic nucleus (STN) or the globus

pallidus interna (GPi) (8). Among the two, STN is the preferred target by most centres. The choice of brain target for DBS should be carried out according to each patient's characteristics, features of PD and the expertise and experience of the centre. Even though DBS has proven benefits in carefully selected patients, its mechanism of action has remained elusive and various hypotheses have been elucidated.

*1. Inhibition hypothesis* : DBS is believed to reduce activity of local neuronal elements and reduce abnormally increased firings or abnormal firing patterns in the STN and GPi and ameliorate parkinsonian motor symptoms (28). The "inhibition hypothesis" goes well with the "firing rate model" and "firing pattern model" of movement disorders. The likely mechanisms which can account for the inhibitory responses during DBS include depolarization block, inactivation of voltage-gated currents (33), and activation of inhibitory afferents (34–36). Chiken et al., confirmed that inhibitory responses induced by GPi- DBS were mediated by GABA receptors (34). The GPi receives inhibitory GABAergic inputs from the striatum and GPe as well as excitatory glutamatergic inputs from the STN. STN DBS generates both excitatory and inhibitory postsynaptic potentials in STN neurons through activation of both glutamatergic and GABAergic afferents (37). Thus, DBS activates these afferent axons in the stimulated nucleus, and the sum effects of this stimulation vary depending on the constitution of the inhibitory and excitatory axon terminals.

*2. Excitation hypothesis :* A study suggested that subthreshold DBS suppresses intrinsic firings in the neuronal cell bodies, while suprathreshold DBS generates spikes at the stimulus frequency in the axons without corresponding firings in the cell bodies (38). Low intensity STN DBS induced GABAergic inhibition in the SNr through antidromic activation of GPe neurons projecting to both the STN and SNr, while STN DBS with higher intensity induced glutamatergic excitation in the SNr through the STN-SNr projections (39). The "excitation

hypothesis" fits well with the "firing pattern model", but not with the "firing rate model". Excitation and/or excitation-inhibition reach the target nucleus along efferent pathways, or along afferent pathways via antidromic activation (39). These activities may change the firing rates and patterns, and normalize or suppress abnormal firings of target nucleus. However, the exact mechanism remains unclear.

*3. Disruption hypothesis:* In 2016, Chiken et al., showed that DBS activates axon terminals in the stimulated nucleus, induces extensive release of neurotransmitters like GABA and glutamate, and dissociates inputs and outputs within the stimulated nucleus (28). Thus, they proposed an alternate hypothesis that DBS leads to disruption of the abnormal information flow (thereby creating a functional "information lesion") through the cortico-basal ganglia loop in the pathological conditions. Triphasic response composed of early excitation, inhibition and late excitation within the GPi is elicited by cortical stimulation, which are mediated by the hyperdirect, direct, and indirect pathways, respectively. Maurice et al., examined the consequences of STN DBS on cortically evoked responses in SNr neurons of normal rats. Cortically evoked early and late excitation was abolished or largely reduced during STN DBS, whereas cortically evoked inhibition was preserved, suggesting that information flow through the hyperdirect and indirect pathways was blocked by STN DBS without interrupting the direct pathway (40). The "disruption hypothesis" fits well with all the three proposed models or pathophysiology of PD.

The success of DBS largely depends on the careful and meticulous selection of candidates for surgery. It is largely known that only those motor symptoms that respond to levodopa (when the patient is in the best optimized on state) will respond to DBS (41). Exceptions to this are troublesome medical refractory tremor, dyskinesias and on-off fluctuations which also respond to DBS. Non-motor symptoms generally do not respond / respond only to a lesser degree.

Patients with florid non-motor dysfunction, particularly dementia and active psychiatric dysfunction including poorly controlled depression and severe psychosis and any red flag signs for idiopathic PD, are essentially excluded.

DBS is an effective and better alternative to lesion surgery, owing to its reversibility and adjustability. The ability to program and titrate DBS remains one among its biggest assets and hence has largely replaced conventional stereotactic surgeries like thalamotomy or pallidotomy. Although the short- and long-term benefits of DBS on motor symptoms are widely known, there is debate over the possible cognitive and behavioral effects of this treatment.

**DBS in PD and cognition**

Cognitive changes following DBS for PD has been researched and reviewed across multiple studies over the last decade, however the results have been heterogenous. In studies that have compared outcomes in both patients that had undergone STN DBS and patients being treated with drug therapy alone, DBS patients either experienced declines in performance over time or were significantly impaired when directly compared to controls (42). The cognitive domains affected mainly included verbal fluency, executive function, general cognition, visuospatial reasoning and memory, processing speed, and verbal memory (9–14,43–46).

The one cognitive adverse event which is most consistently reported following DBS is a decrease in verbal fluency. Verbal fluency is a complex composite task, with various cognitive subcomponents (e.g. conception and application of a retrieval strategy, shifting between subcategories, vocabulary access, semantic processing) which may overall be classified as either executive or semantic in nature (14). Neuropsychological and neuroimaging studies, in healthy and clinical subjects, support the involvement of a fronto-temporal system including

areas known to be the substrate of executive and semantic processes including (left or bilateral) inferior frontal gyrus, anterior cingulate cortex and superior temporal regions.

Smeding and colleagues reported in a large controlled study of neuropsychological outcome that patients who underwent DBS declined in selective attention, verbal fluency, color naming, and verbal memory following surgery compared with a PD control group tested over the same duration of time (47). The authors stated the outcomes could be linked to executive dysfunction stemming from PD.

Neuropsychological investigations conducted from 3 to 6 months after STN DBS showed a worsening of verbal fluency, whereas less consistent effects on other cognitive tasks have been reported in different studies. De Gaspari et al., showed that in the post-surgical period there was a worsening of both letter and category fluency tasks (14). The total number of words and switches decreased, whereas average cluster size was unchanged. They attributed this to possible lesioning effect along the surgical trajectory and maybe due to high frequency stimulation itself.

Within the 6 month outcome, York et al., demonstrated that patients who underwent STN DBS experienced declines in verbal delayed recall and verbal fluency when compared to PD controls (11). 26% of DBS patients revealed a reliable decline in verbal fluency compared with only 4% of PD controls ($p<0.01$), and 37% of patients who underwent DBS showed a decline on Stroop Color–Word test (SCWT) as opposed to 4% of PD controls after 6 months ($p<0.003$). They attributed this to frontostriatal dysfunction rather than due to disease progression alone.

At two year follow up, Tramontana et al., noted that DBS patients had deficits in phonemic fluency and on several subtests of the Wisconsin Card Sorting Test (WCST), compared to controls. However, these differences were minor when the authors excluded patients who

suffered from an adverse event in the DBS cohort (46). In another two-year follow-up analysis, STN DBS patients exhibited impairments on tasks involving non-verbal recall, processing speed, and verbal fluency (both phonemic and semantic). The authors used RCI to draw inferences only based on the effects of DBS on cognition and to demarcate these effects from PD progression. After computing RCIs, the percentages of patients in both the STN DBS ($n$ = 19) and PD control group ($n$ = 18) that deteriorated on processing speed, phonemic verbal fluency, semantic verbal fluency, non-verbal recall and executive function were 53 vs. 28%, 26 vs. 11%, 29 vs. 29%, 47 vs. 25% and 43 vs. 18%, respectively (44).

In some of the studies, the DBS group performed better or remained stable in comparison to the control group. In their three year long-term controlled study, Zangaglia et al., observed trends for improvement on Verbal Span, Digit Span, Corsi's Block Tapping Test, and Logical Memory Test (measures of memory); whereas, controls had a considerable decrease in WCST and MMSE at 3 years. The authors stated that it could have been due to a learning effect that masked deterioration since alternate versions were not used (9).

In studies which did not study the effect of DBS against a control group, the findings of cognitive impairments compared to baseline, were found to be similar as those studies which were controlled. The outcomes of verbal fluency were variable. There was a trend for decline in verbal fluency up to 5 years post DBS surgery (48,49). Some authors have described an improvement of verbal fluency in the long-term compared to an initial significant reduction in scores, although not to baseline levels; supporting the possibility of a micro-lesion effect in the early post-operative period. (50,51).

In the study by Yamanaka et al., patients had a significant reduction in both semantic and phonemic verbal fluency at one month, however at 12-month follow-up, they found that phonemic completely recovered and semantic fluency had improved (51). Most studies showed

impairment of verbal fluency at one year or more, suggesting disease progression rather than lesion effects. Studies that followed patients post-operatively 5 years or more, found that patients had a significant decrease at 5 years on total and Perseverative Errors on the WCST (executive function), verbal fluency, Raven's color matrices (reasoning), and delayed recall of the RAVLT (memory) (52,53).

Kishore et al., ($n$ = 47), reported no significant cognitive declines at 5 years, however, when analysing individual scores, there were 10 patients who declined in verbal fluency compared to one at baseline (48). This new-onset reduction in verbal fluency, majority of which were mild and clinically insignificant, were detected at the first follow-up assessment itself and with no further worsening. This was believed to be due to the micro-lesioning effect of electrode passage (48).

In an 11-year long-term follow-up study by Rizzone et al., patients had a significant worsening in contrast to baseline on short- term memory (Corsi's Block Test Forward), episodic memory (Immediate and Delayed Recall on the RAVLT), executive function (WCST) and attention (Attentive Matrices) (54). More than 70% of the patients performed in the normal range in most of the neuropsychological tests, despite the development of dementia in 22.7%. The authors attributed these findings to be expected in advanced PD patients. A few studies have reported improvement in cognition parameters of executive dysfunction and memory, however the clinical relevance or significance of these findings could not be established.

In GPi-DBS, most studies did not identify a reduction in verbal fluency, suggesting the possibility that the STN and related circuits may have a more substantial role in verbal fluency processing (55).

The debate between which of the two is better, STN DBS or GPI-DBS, for motor benefits and long term cognitive and psychiatric outcomes of patients with PD has been a long one. Many investigators have sought to resolve this. In a consecutive series of 62 patients, assessed after 3 to 6 months of chronic bilateral stimulation of the subthalamic nucleus (n = 49) or internal globus pallidus (n=13), Ardouin et al., found that on stimulation, performance improved for Trail Making Test A and B, but there was a deterioration in phonemic and total lexical fluency. They concluded that stimulation of either the STN or GPi did not change the overall cognitive performance in PD (15).

In the prospective, randomised, blinded COMPARE trial (21), Okun et al., sought to compare the cognitive and mood effects of unilateral subthalamic nucleus (STN) versus unilateral globus pallidus interna (GPi) deep brain stimulation (DBS) in 52 patients with PD. To evaluate regional settings, the investigators stimulated under four different paradigms: ventral, dorsal, optimal, and off .There were no significant differences in in the co-primary outcome measures of mood and cognition between STN and GPi in the optimal DBS state. However, adverse mood effects were noted when stimulating ventrally to the optimal site in both targets. Furthermore, a worsening for letter verbal fluency was noted in the 3 non-optimal post-DBS states in the STN target only. They concluded that the persistence of deterioration in verbal fluency even in the off DBS state at 7 months was suggestive of a surgical rather than a stimulation-induced effect at the STN target.

In another prospective, randomised, controlled study, Rothlind et al., studied neuropsychological performance in patients with PD at baseline and after 6 months comparing best medical therapy (BMT, n=116) and bilateral DBS (n=164) at either the STN (n=84) or GPi (n=80) (56). Two between group differences were observed at 6 months between GPi and STN. The GPi group had a greater decline in performance on the HVLT; whereas the STN

group worsened to a greater extent in Stroop Word Reading. As these differences were marginal, the two DBS groups were combined and contrasted with the BMT cohort. This resulted in the DBS group demonstrating greater declines in multiple measures of processing speed and working memory. After utilising RCIs, the two DBS groups showed considerable difference in impairment on Digit Symbol Coding test, a measure of processing speed (11.1% STN group; 1.3% GPi-DBS group). Thus, they concluded that in those with PD, the likelihood of significant decline in neuropsychological functioning increases with DBS, but there were no clinically relevant differences between those having undergone STN DBS versus GPi-DBS.

In studies that directly compared the two targets, STN had a greater frequency of cognitive declines. The substantial difference in cognitive outcomes between STN- and GPi-DBS could have been due to several factors. The STN and GPi are both basal ganglia nuclei with separate anatomical sensorimotor, associative and limbic areas; but the STN is sufficiently smaller compared to the GPi, the sensorimotor region comprises about one-third of the STN, compared to 53% of the GPi (i.e. unspecific current spread is easier to evoke in STN DBS, potentially influencing cognitive circuits) and more studies have primarily focused on STN DBS compared to GPi- DBS (42). All these could explain STN being associated with more frequent cognitive declines across studies.

Few studies have also sought to investigate the influence of volume of tissue activation (VTA), white matter lesions (WML), electrode trajectory, active contacts, brain perfusion, and microelectrode (MER) tracks on neuropsychological outcomes. Mikos et al., investigated the relationship of the volume and area of activated tissue within the STN with verbal fluency in 17 patients of PD (57). The stimulation patterns examined were no stimulation, ventral stimulation, dorsal stimulation and optimal stimulation. No differences were noted in the verbal fluency scores among the three electrode contacts, but other interactions were reported.

Optimal stimulation correlated positively with VTA inside the STN and letter fluency change scores, implying that more VTA within the STN was associated with better fluency scores compared to off stimulation. There was a negative association with VTA and STN with ventral stimulation, indicating that a larger volume of VTA inside the STN was associated with worse letter fluency performance relative to off stimulation. These relationships were not observed with category fluency, as in the opinion of the authors, category fluency relies more on the temporal lobe. The study demonstrates that a reduction in verbal fluency may not only be due to the surgical impact, but also influenced by stimulation.

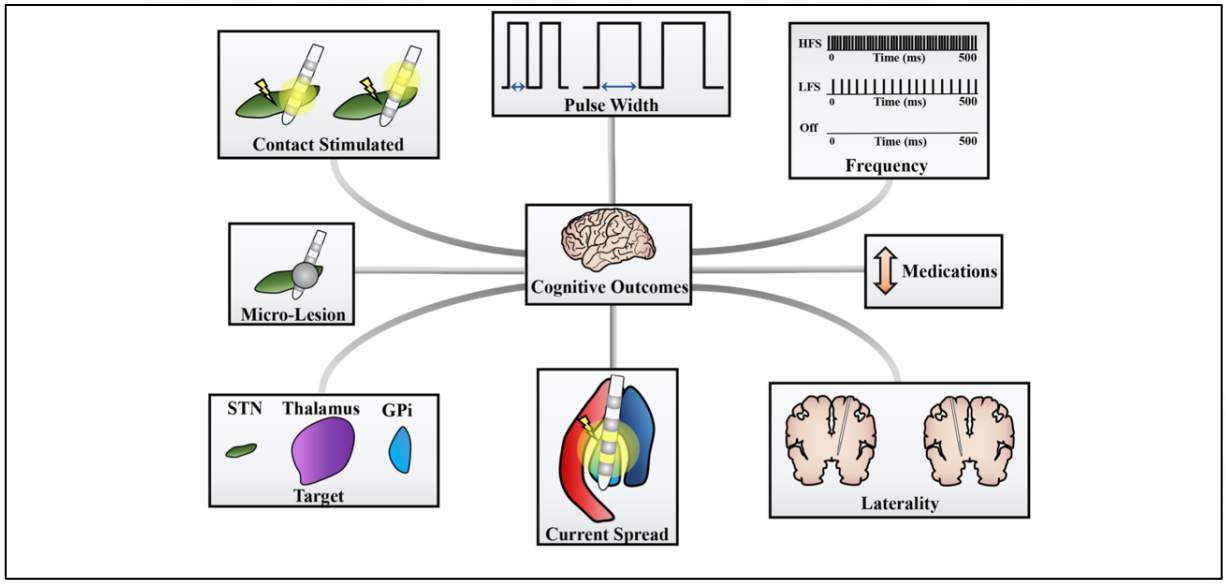


**Figure 2: Potential sources of cognitive changes post-DBS (*Adapted from Eisinger et al.,*].**

These heterogenous results reveal the complexity of PD post DBS. Such variations in outcomes within and across studies may relate to age, disease duration, level of education, dopaminergic medication, baseline assessment, neuropsychological instruments, electrode localization, DBS tract and stimulation settings and time of follow-up (Figure 2).

There are very few studies from India that have looked at long term effect of DBS on cognition and none that have used a control group of patients on optimal medical therapy to compare the cognitive effects attributable to DBS, to the best of our knowledge.

# HYPOTHESIS AND OBJECTIVES

Mechanical lesioning of the STN and the frontal sub cortical white matter tracts by the electrode insertion procedure and modulation of the associative circuits passing through the STN by chronic electrical stimulation result in cognitive deficits in patients who have undergone bilateral STN DBS for PD.

## OBJECTIVES:

1. To assess the cognitive functions in patients with Parkinson's disease who have undergone bilateral STN DBS and minimum 2 years of neurostimulation

2. To compare cognitive outcomes of patients who underwent DBS, pre and post-surgery, at average 24-36 months of follow up

3. To compare the cognitive functions of patients who have undergone bilateral STN DBS with those of patients who have been on medical treatment alone and matched with the STN DBS group for age and duration of PD.

# MATERIALS AND METHODS

We conducted a prospective observational comparison study to assess cognitive effects of chronic bilateral STN DBS in patients with Parkinson's disease (PD) compared to a matched group of PD patients who were medically treated. We studied 34 PD patients having undergone bilateral STN DBS and 34 patients with PD who were on medical therapy alone. Consecutive patients on follow up in the Movement Disorders Clinic, who satisfied the eligibility criteria were included. Recruitment of patients was done by the PI under the guidance of movement disorder specialists (Co- Principal Investigators 1, 2 and Co Investigator 3), from the movement disorders clinic of the Institute.

**Eligibility criteria**:

a) **DBS group**:

Inclusion Criteria: (1) Consecutive patients with PD (In whom the diagnosis has been made by a movement disorder specialist using the standard diagnostic criteria- United Kingdom Parkinson's Disease Society Brain Bank Criteria) who have undergone bilateral STN DBS implantation at least 2 years ago and continuing with stimulation and on regular clinical follow up as per protocol. The patients were recruited from the Movement Disorder clinic of SCTIMST. (2) Age more than 40 years.

Exclusion Criteria: (1) Those with severe physical disability from PD or any co-morbidity, making them unable to complete the neuropsychology assessment. (2) Those with advanced and non-testable dementia as judged by the Co-Principal Investigators (3) Those with less than 10 years of formal education (4) Active psychosis or depression (5) Inability to give informed consent (6) Those who have undergone lesioning surgeries before DBS, or DBS of other

targets. (6) Coexisting neurological conditions (like documented strokes in strategic locations or significant microvascular changes in imaging) which are likely to affect cognitive functions, independent of PD.

Pre-operative evaluation: All patients underwent the standard protocol-based pre-operative evaluation including detailed clinical history and examination, psychiatric evaluation, assessment of motor and non-motor functions in drug-on and drug-off states using standard rating scales including the Unified Parkinson's Disease Rating Scale , and a comprehensive neuropsychological evaluation recommended for assessing cognitive functions in PD (Details are provided below) (58).

Surgical procedure: All patients underwent bilateral stereotactic implantation of quadripolar DBS electrode placement in one session (Medtronic, MN, USA). STN was located by MRI (1.5 T MR Scanner, Signa, General Electric, MW, USA), 5-channel microelectrode recordings (Lead point 4, Medtronic, MN) with Star Drive microelectrode array and macro stimulation in selected tracks. Postoperative MRI was done in all to look for surgical complications. Following surgery, stimulation parameters were adjusted by the treating neurologists on an individual basis so that maximum clinical benefit on motor symptoms was achieved.

b) **Non DBS (Medically treated) group**:

Inclusion criteria: Biologically unrelated controls with PD, matched for age, severity of motor deficits and duration of disease were recruited from the PD cohort on Medical follow up in the Movement Disorder Clinic (These patients have not undergone surgery either because of high

surgical risks due to co morbidities, unwillingness in spite of counselling or non-feasibility of surgery for socioeconomic reasons).

Exclusion criteria: Same as that for DBS group.

**Data Collection:**

Eligibility for participation was assessed during the standard clinical interview and examination done routine clinic visits and eligible subjects were requested to participate. Subjects who gave informed, written consent were recruited on the same day and all the assessments were completed on the same day. The severity of Parkinsonism was documented using the Unified Parkinson's Disease Rating Scale (UPDRS) (59) and staging of severity was done using the Hoehn and Yahr Stage. The participants of non DBS group were also clinically evaluated to rule out any coexistent psychiatric disorder / other relevant ailments. The neuropsychological evaluation was conducted in the medication 'ON' phase (ON stimulation and ON medication for those with DBS) for all subjects. A battery of neuropsychological tests (recommended for neuropsychological evaluation of PD as per the Movement Disorder Society Guidelines) (58), were administered to the patient to assess global cognitive function (MMSE (60), MoCA-M (61,62) , ACE (63–65)) as well as the following five domains: attention and working memory (Trail Making Test A and B (66), digit span test (67–69)); executive function (verbal fluency (63) and Wisconsin Card Sorting Test (70,71)); memory (logical memory and visual recall – subtests of Wechsler Memory Scale (72)); language (subscale of ACE and Frenchay's Aphasia screening test (73)) and visuospatial functions (position discrimination and cube analysis- VOSP battery (74)).

The patients in non DBS group were matched for age, severity and duration of disease with the DBS group; such participants were selected from the PD patients' pool attending the Movement Disorder Clinic at SCTIMST. The same set of neuropsychological tests were administered to this group as well. This battery of tests was composed of the minimum number of tests required for cognitive assessment and diagnosis of cognitive impairment in patients with Parkinson's disease as per the recommendations of the International Parkinson's Disease and Movement Disorder Society guidelines (58). The administration of these neuropsychological tests were done by the Co-Investigator 2, who is a qualified Neuropsychologist and required 1-1.5 hours on average for the assessment.

The battery of tests was repeated 24-36 months after the surgical procedure in the DBS cohort. The tests were repeated in the medically managed group, at a similar interval too.

**Data Analysis:**

Statistical analyses of all data sets was performed by using the Medical Statistics Software SPSS, Windows, Version 21.0 (IBM, Armonk, New York) with the help of a medical statistics expert. Parametric and non-parametric data within each group was compared using paired Student's t test and Wilcoxon signed rank test, respectively. Comparison between continuous variables between the two groups was done by unpaired Student's t test. The comparison between the different neuropsychological variables for DBS and non DBS group was done using Mann Whitney U test. A level of significance of p value $<0.05$ was chosen.

The study protocol was reviewed and approved by the Department of Neurology, SCTIMST, the Technical Advisory Committee (TAC) for Clinical Studies, SCTIMST and the Institutional Ethics Committee (IEC).

# RESULTS

We studied a total of 34 patients with Parkinson's disease who had undergone DBS surgery and had at least 2 years of neurostimulation (DBS group), and 34 patients who were on medical management alone (non DBS group) as part of this study. All the DBS patients had their baseline clinical and neuropsychological data collected as part of the standard surgical protocol being followed for patients undergoing DBS in the Institute.

The control patients were chosen from another ongoing ICMR-funded research project longitudinally evaluating the cognitive functions in PD and all had the same battery of neuropsychological tests applied at baseline. The clinical and neuropsychological assessments for follow-up data collection were conducted between October 2018 and April 2020. Informed consent was obtained from all the patients.

**Demographics**

The DBS group comprised of 25 males and 9 females, with a mean age of 55.53 (±7.36) years. The non DBS group comprised of 24 males and 10 females and had a mean age of 58.21 (±6.06) years. The mean age and sex ratios between the two groups were not found to be statistically significant.

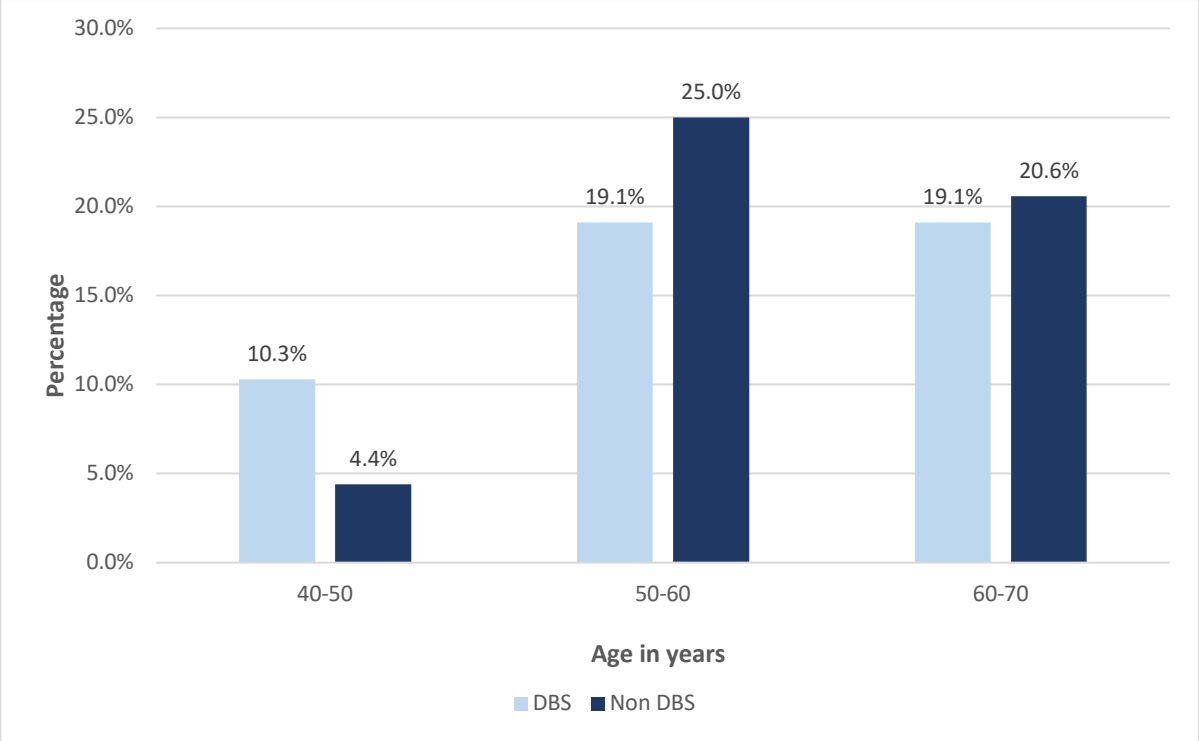


**Figure 3: Age distribution of the two study groups**

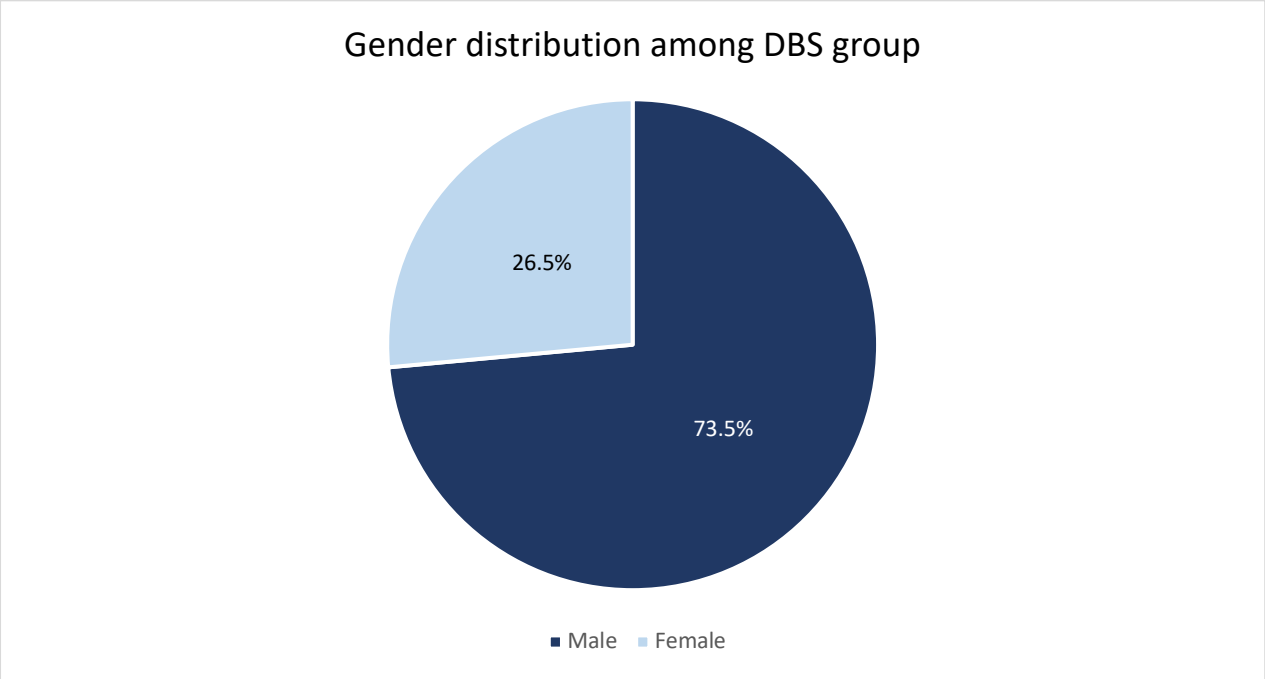


**Figure 4: Gender distribution among DBS group (n = 34)**

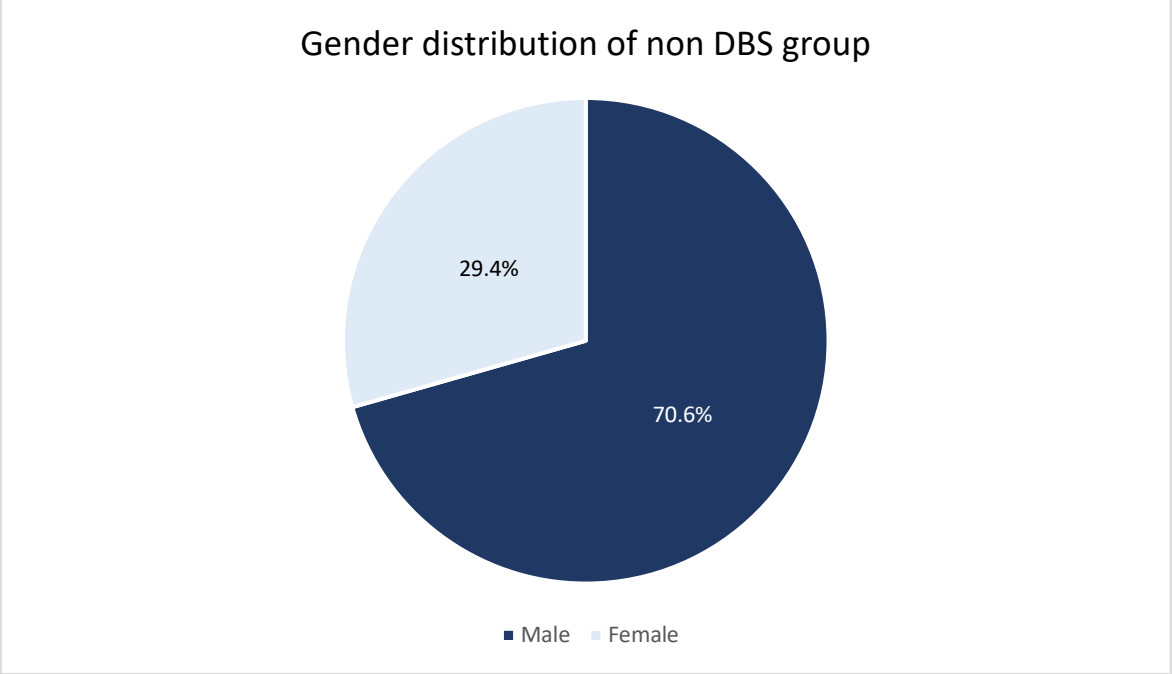


**Figure 5: Gender distribution among the non DBS group (n=34)**

The various demographic and clinical data are summarised in Table 1

| **Parameter** | **DBS** | **Non DBS** | **p value** |
|---|---|---|---|
| Age, Mean (SD) | 55.53 (±7.36) | 58.21 (±6.06) | 0.106 ** |
| Female Sex, n (%) | 9 (26.5%) | 10 (29.4%) | 0.787 * |
| Age of onset, Mean (SD) | 44.24 (±7.44) | 46.03 (±6.41) | 0.291 ** |
| Duration of Disease in years, Mean (SD) | 11.24 (±2.39) | 11.94 (±1.98) | 0.189 ** |

| | | | |
|---|---|---|---|
| Years of education, Mean (SD) | 13.47 (±2.22) | 12.35 (±2.27) | **0.044** ** |
| Follow up duration in months , Mean (SD) | 33.26 (±3.72) | 32.65 (±4.48) | 0.538 ** |
| UPDRS III at baseline (Medication-off) Mean (SD) | 47.76 (±5.28) | 45.29 (±5.48) | 0.063 ** |
| UPDRS III at follow up (Medication-Off) Mean (SD) | 16.47 (±4.36) | 49.09 (±5.19) | **<0.0001** ** |
| UPDRS II at baseline (Medication-Off) Mean (SD) | 26.53 (±3.03) | 25.47 (±2.80) | 0.139 ** |
| UPDRS II at follow up (Medication-Off) Mean (SD) | 11.21 (±3.13) | 26.94 (±3.18) | **<0.0001** ** |
| LEDD at baseline Mean (SD) | 758.97 (±156.17) | 713.82 (±160.17) | 0.244 ** |
| LEDD at follow up Mean (SD) | 482.06 (±110.34) | 771.47 (±185.05) | **<0.0001** ** |

*Analysed using Pearson Chi-Square

** Analysed using Unpaired Student's t test

**Table 1: Demographic data of the two study groups**

We sought to match the two groups for age at baseline assessment and duration of illness to remove any confounding bias of these factors on the neuropsychological tests. Age and gender distribution between the two groups were comparable, with no statistically significant difference between them. The mean age at onset and duration of illness were also similar between the two groups. The mean levodopa equivalent daily dosage (LEDD) at baseline did not differ between the two groups (p=0.244).

The mean educational years was marginally higher (p=0.04) among patients of the DBS group (13.47 ± 2.22 years) when compared to those in the non DBS group (12.35 ± 2.27 years). When absolute values are considered, this may have little clinical significance.

The mean UPDRS II and UPDRS III scores in drug-off state at baseline were similar between the groups (p=0.139; p=0.06). Thus, the patients in the two groups had comparable severity of disease at baseline. At mean follow up of around 32.96 ± 4.097 months, UPDRS II and III scores were significantly lower in the DBS group (11.21 (±3.13); 16.47 ± 4.36) in drug-off state when compared to the non DBS group (26.94 (±3.18); 49.09 ± 5.19) (Figure 6).

The improvement in motor outcome is well established with DBS as it is the very reason why DBS is undertaken in patients with severe motor symptoms, dyskinesias and/or motor fluctuations. As patients' motor activities of daily living, measured by UPDRS II are greatly dependent on their overall motor outcomes, this too is expected post DBS. In line with the improvement in motor scores, the LEDD significantly reduced in the DBS group ($p < 0.0001$).

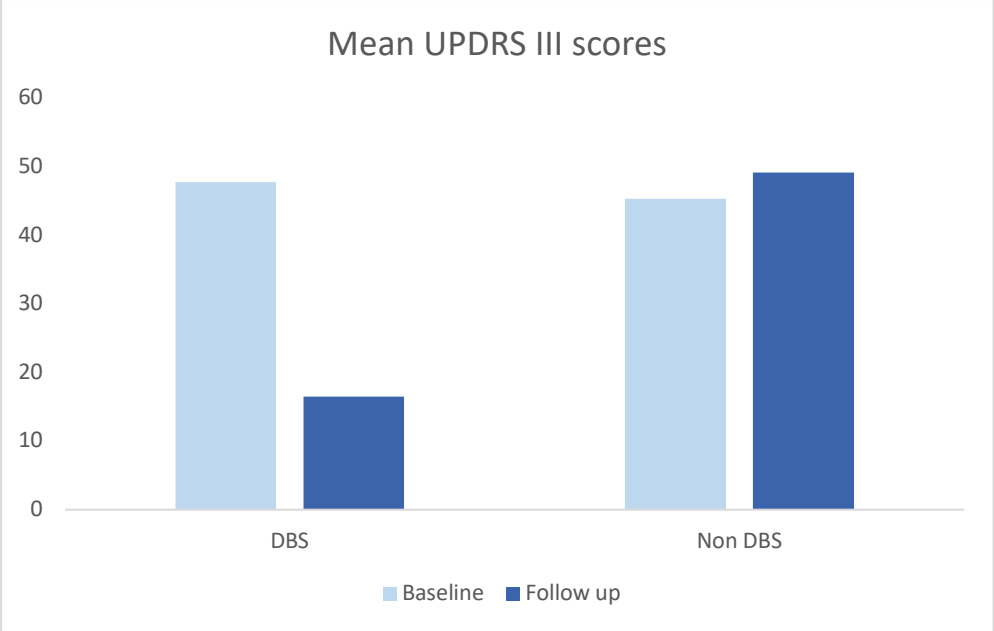


**Figure 6: Mean UPDRS III scores (drug-off) at baseline and follow up between the two groups**

## Neuropsychological variables at baseline between the two groups

| Parameter | DBS | Non DBS | p value |
|---|---|---|---|
| ACE, Mean (SD) | 87.59 (±3.55) | 86.56 (±4.07) | 0.403 * |
| BDI, Mean (SD) | 8.44 (±2.72) | 7.59 (±3.18) | 0.173 * |
| MMSE, Mean (SD) | 27.71 (±1.17) | 27.68 (±1.20) | 0.924 * |
| MOCA, Mean (SD) | 26.12 (±2.27) | 25.53 (±1.94) | 0.328 * |
| Trail A, Mean (SD) | 75.53 (±20.69) | 79.29 (±21.64) | 0.466 ** |

| | | | |
|---|---|---|---|
| Digit Span, Mean (SD) | 11.71 (±2.08) | 12.38 (±2.12) | 0.231 * |
| Verbal fluency, Mean (SD) | 11.65 (±1.25) | 12.06 (±1.13) | 0.198 * |
| WCST errors, Mean (SD) | 3.53 (±2.47) | 3.21 (±2.75) | 0.454 * |
| Language, Mean (SD) | 27.29 (±0.91) | 27.50 (±0.62) | 0.447 * |
| Aphasia, Mean (SD) | 28.32 (±1.30) | 28.65 (±0.98) | 0.359* |
| Visual memory, Mean (SD) | 17.59 (±9.57) | 18.41 (±6.58) | 0.632 * |
| Logical memory, Mean (SD) | 15.09 (±4.76) | 13.68 (±4.48) | 0.147 * |
| Position discrimination, Mean (SD) | 19.15 (±0.89) | 18.91 (±0.75) | 0.151 * |
| Cube Analysis, Mean (SD) | 8.21 (±1.55) | 8.53 (±1.60) | 0.287 * |

***Analysed using Mann Whitney U test**

****Analysed using unpaired student's t test**

**Table 2: Comparison of neuropsychological variables between the two groups at baseline**

At baseline, the measures of cognitive function were comparable between those patients who had undergone DBS and those who were on medical management alone, with no statistically significant differences between them (Table 2).

**Neuropsychological scores at baseline and follow up within each group**

The neuropsychological variables were compared at baseline ($T_0$) and at mean follow up of 32.96 ± 4.097 ($T_1$) months in each group separately.

**1. DBS group**

| **Parameter** | **Baseline ($T_0$)** | **Follow up ($T_1$)** | **p value** |
|---|---|---|---|
| ACE, Mean (SD) | 87.59 (±3.55) | 86.12 (±4.38) | **0.005 *** |
| BDI, Mean (SD) | 8.44 (±2.72) | 8.68 (±4.26) | 0.959 * |
| MMSE, Mean (SD) | 27.71 (±1.17) | 27.32 (±1.93) | 0.133 * |
| MOCA, Mean (SD) | 26.12 (±2.27) | 25.35 (±2.88) | **0.003 *** |
| Trail A test, Mean (SD) | 75.53 (±20.69) | 80.03 (±27.21) | **0.035 **** |
| Digit Span, Mean (SD) | 11.71 (±2.08) | 10.44 (±2.74) | **<0.0001 *** |
| Verbal fluency, Mean (SD) | 11.65 (±1.25) | 10.50 (±1.62) | **<0.0001 *** |
| WCST errors, Mean (SD) | 3.53 (±2.47) | 4.35 (±2.94) | **0.002 *** |
| Language (ACE), Mean (SD) | 27.29 (±0.91) | 27.12 (±1.30) | 0.153 * |
| Aphasia Battery, Mean (SD) | 28.32 (±1.30) | 27.76 (±1.60) | **0.003 *** |

| | | | |
|---|---|---|---|
| Visual memory, Mean (SD) | 17.59 (±9.57) | 16.65 (±10.57) | **0.013 *** |
| Logical memory, Mean (SD) | 15.09 (±4.76) | 12.68 (±6.12) | **<0.0001 *** |
| Position discrimination, Mean (SD) | 19.15 (±0.89) | 18.85 (±1.21) | 0.135 * |
| Cube Analysis, Mean (SD) | 8.21 (±1.55) | 7.97 (±1.82) | 0.117 * |

***Analysed using Wilcoxon signed rank test**

****Analysed using paired student's t test**

**Table 3: Cognitive scores at baseline and follow up in the DBS group**

Global cognition, assessed by mean ACE and MOCA scores were found to be significantly lower at follow up (86.12 ±4.38; 25.35 ±2.88) than at baseline (87.59 ±3.55; 26.12 ±2.27) in the DBS group. MMSE scores were comparable pre and post DBS.

At follow up, patients took significantly longer time to complete the Trail A test (80.03 ±27.21) than at baseline (75.53 ±20.69). The mean digit span, a test of working memory and attention, was found to be lower on follow up (10.44 ±2.74) when compared to baseline (11.71±2.08) values. A higher number of WCST errors (measure of set shifting) were reported on follow up (p=0.002) (Table 3, Figure 7).

Mean verbal fluency (10.50 ±1.62) and Frenchay's Aphasia test scores (27.76 ±1.60) were found to be significantly lower on follow up in the DBS group when they were compared to values at baseline. The other tests of language, as a subscale of ACE were found to be

comparable pre and post DBS. Both verbal ($p < 0.0001$) and visual memory ($p = 0.013$) were found to be significantly worse on follow up, which may be expected due to disease progression itself. Measures of visuospatial function did not differ during the duration of assessment. The anxiety and depression scores were not found to differ significantly, either.

None of the patients had dementia at baseline or follow-up.

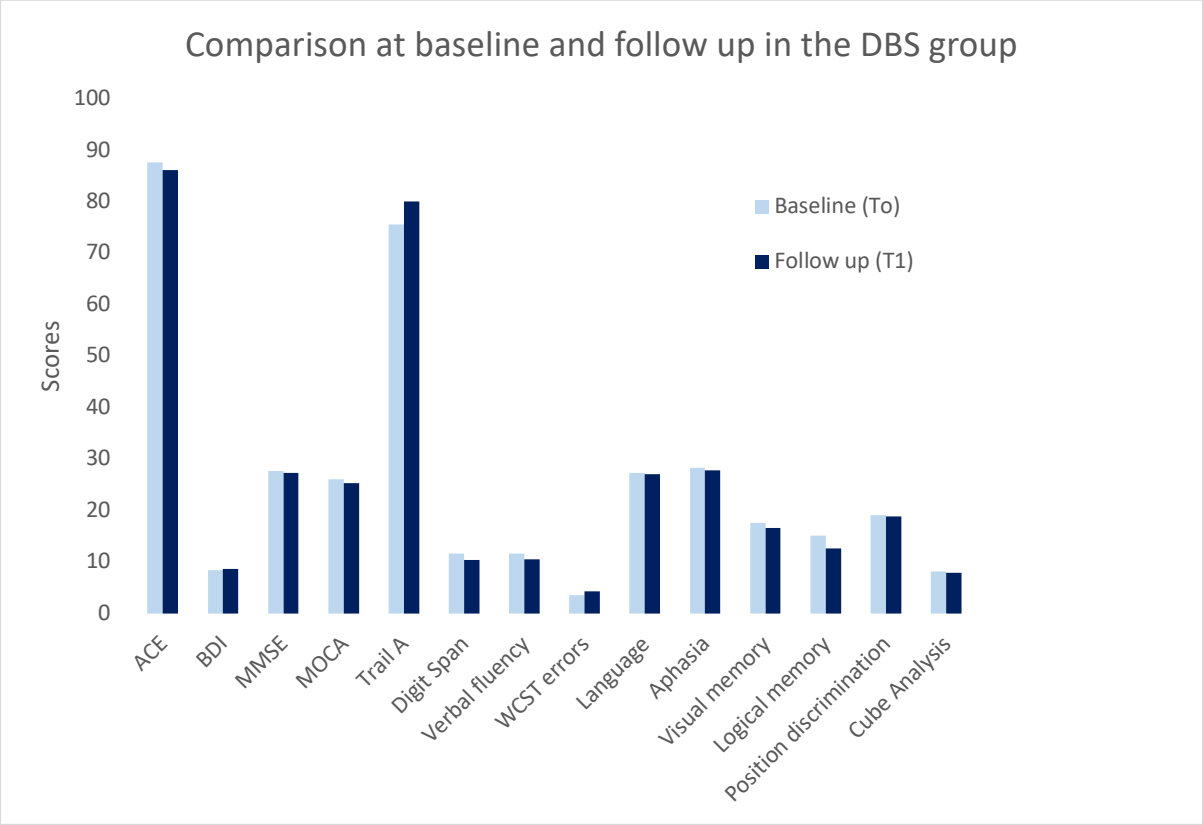


**Figure 7: Comparison of neuropsychological scores at baseline and follow up in the DBS group**

**2. Non DBS group**

| **Parameter** | **Baseline ($T_o$)** | **Follow up ($T_1$)** | **p value** |
|---|---|---|---|
| ACE, Mean (SD) | 86.56 (±4.07) | 85.03 (±5.54) | **0.002 *** |
| BDI, Mean (SD) | 7.59 (±3.18) | 7.47 (±3.55) | 0.888 * |
| MMSE, Mean (SD) | 27.68 (±1.20) | 27.06 (±1.94) | **0.007 *** |
| MOCA, Mean (SD) | 25.53 (±1.94) | 24.68 (±2.58) | **<0.0001 *** |
| Trail A, Mean (SD) | 79.29 (±21.64) | 81.85 (±24.12) | 0.173 ** |
| Digit Span, Mean (SD) | 12.38 (±2.12) | 11.71 (±2.60) | **0.005 *** |
| Verbal fluency, Mean (SD) | 12.06 (±1.13) | 11.47 (±1.71) | **0.002 *** |
| WCST errors, Mean (SD) | 3.21 (±2.75) | 3.79 (±3.59) | 0.075 * |
| Language (ACE), Mean (SD) | 27.50 (±0.62) | 27.21 (±0.77) | 0.048 * |
| Aphasia Battery, Mean (SD) | 28.65 (±0.98) | 28.32 (±0.91) | 0.058 * |
| Visual memory, Mean (SD) | 18.41 (±6.58) | 17.38 (±7.86) | 0.061 * |
| Logical memory, Mean (SD) | 13.68 (±4.48) | 11.41 (±5.20) | **<0.0001 *** |

| | | | |
|---|---|---|---|
| Position discrimination, Mean (SD) | 18.91 (±0.75) | 18.74 (±0.99) | 0.335 * |
| Cube Analysis, Mean (SD) | 8.53 (±1.60) | 8.09 (±2.19) | **0.025 *** |

***Analysed using Wilcoxon signed rank test**

****Analysed using paired student's t test**

**Table 4: Cognitive scores at baseline and follow up in the non DBS group**

In the non DBS group, mean ACE, MMSE and MOCA scores were found to be significantly lower on follow up (85.03±5.54; 27.06±1.94; 24.68±2.58) than at baseline (86.56±4.07; 27.68±1.20; 25.53±1.94). At follow up, the time taken to complete Trail A test and errors on WCST were found to be comparable. The mean digit span, was found to be significantly lower on follow up (11.71±2.60) when compared to baseline (12.38 ± 2.12) (Table 4).

Patients who were on medical management alone had worse mean verbal fluency (11.47 ±1.71) scores on follow up when these values were compared to baseline (12.06±1.13). The other tests of language domain did not reach statistical significance over the period of follow up. In these patients, logical memory declined on follow up ($p<0.0001$), whereas visual memory did not. Measures of visuospatial function showed varied results with test of position discrimination scores being comparable ($p=0.335$) and the test of cube analysis scores being significantly low on follow up ($p=0.025$) (Figure 8).

Similar to DBS group, none of the patients in the medical management group were demented at baseline and none developed dementia during follow-up.

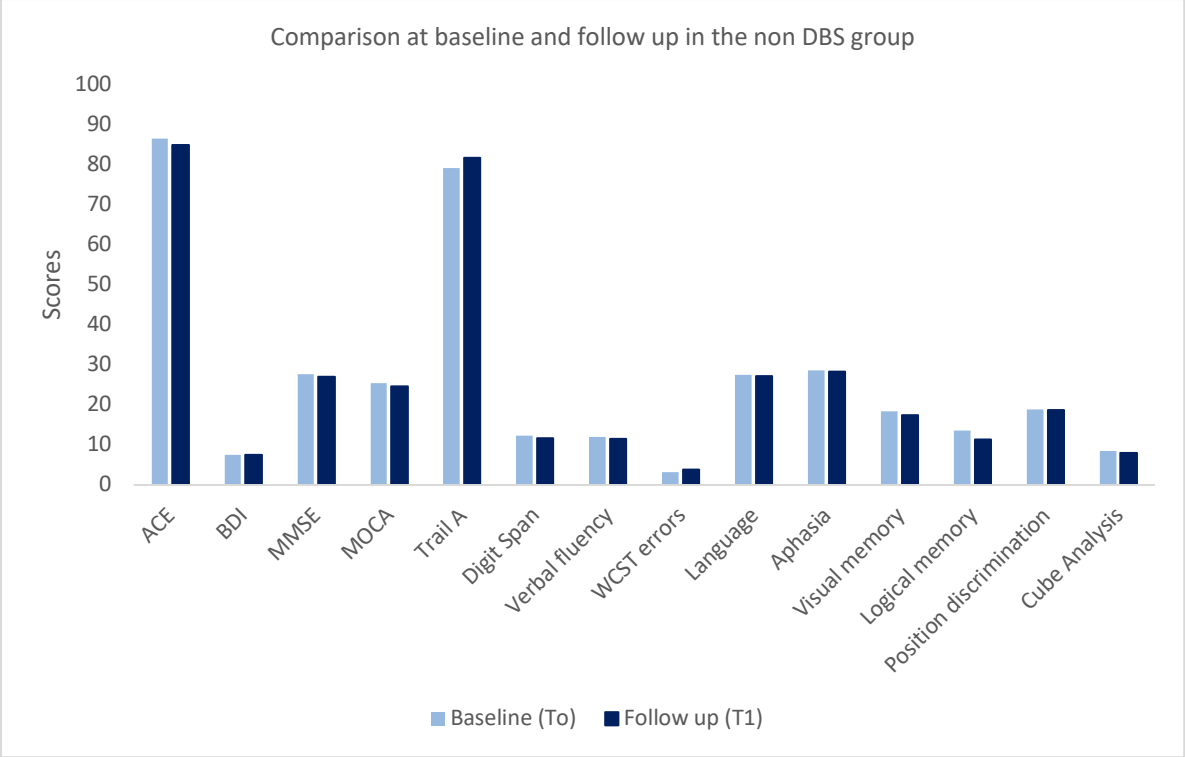


**Figure 8: Comparison of neuropsychological scores at baseline and follow up in the non DBS group**

As evidenced by differences in both the groups, with and without DBS, these results are expected due to natural progression of disease in PD. A better measure would be to calculate the decline from baseline between these groups and test for significance. Also, to further ascertain whether the DBS procedure has a bearing on the cognitive scores, we compared the cognitive scores between the two groups at follow up.

**Comparison of neuropsychological scores between DBS and non DBS group**

**1. Neuropsychological variables at follow up between the two groups**

| **Parameter** | **DBS** | **Non DBS** | **p value** |
|---|---|---|---|
| ACE, Mean (SD) | 86.12 (±4.38) | 85.03 (±5.54) | 0.546 * |
| BDI, Mean (SD) | 8.68 (±4.26) | 7.47 (±3.55) | 0.225 * |
| MMSE, Mean (SD) | 27.32 (±1.93) | 27.06 (±1.94) | 0.588 * |
| MOCA, Mean (SD) | 25.35 (±2.88) | 24.68 (±2.58) | 0.355 * |
| Trail A, Mean (SD) | 80.03 (±27.21) | 81.85 (±24.12) | 0.771 ** |
| Digit Span, Mean (SD) | 10.44 (±2.74) | 11.71 (±2.60) | 0.073 * |
| Verbal fluency, Mean (SD) | 10.50 (±1.62) | 11.47 (±1.71) | **0.020** * |
| WCST errors, Mean (SD) | 4.35 (±2.94) | 3.79 (±3.59) | 0.243 * |
| Language, Mean (SD) | 27.12 (±1.30) | 27.21 (±0.77) | 0.653 * |
| Aphasia, Mean (SD) | 27.76 (±1.60) | 28.32 (±0.91) | 0.126 * |
| Visual memory, Mean (SD) | 16.65 (±10.57) | 17.38 (±7.86) | 0.773 * |

| | | | |
|---|---|---|---|
| Logical memory, Mean (SD) | 12.68 (±6.12) | 11.41 (±5.20) | 0.449 * |
| Position discrimination, Mean (SD) | 18.85 (±1.21) | 18.74 (±0.99) | 0.446 * |
| Cube Analysis, Mean (SD) | 7.97 (±1.82) | 8.09 (±2.19) | 0.478 * |

***Analysed using Mann Whitney U test**

****Analysed using unpaired student's t test**

**Table 5: Comparison of neuropsychological scores between the two groups at follow up**

At mean follow up of 32.96 ± 4.097 months, patients who had undergone DBS (10.50±1.62), showed significantly lower (p=0.02) scores of verbal fluency when compared to those who were on medical management alone (11.47±1.71) (Figure 9). Patients in the non DBS groups performed better on the digit span test. However, this did not reach statistical significance (p=0.07). Rest of the measures of global cognition, executive function, language, memory and visuospatial function did not differ significantly between the two groups. Follow up anxiety and depression scores between the two groups were also comparable, thereby negating any confounding bias on the cognitive scores (Table 5, Figure 10).

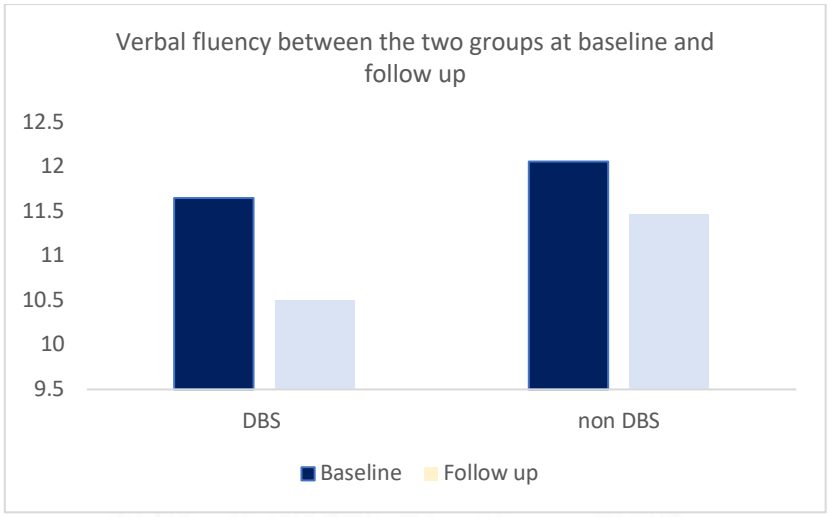


**Figure 9: Comparison of verbal fluency between the two groups at baseline and follow up**

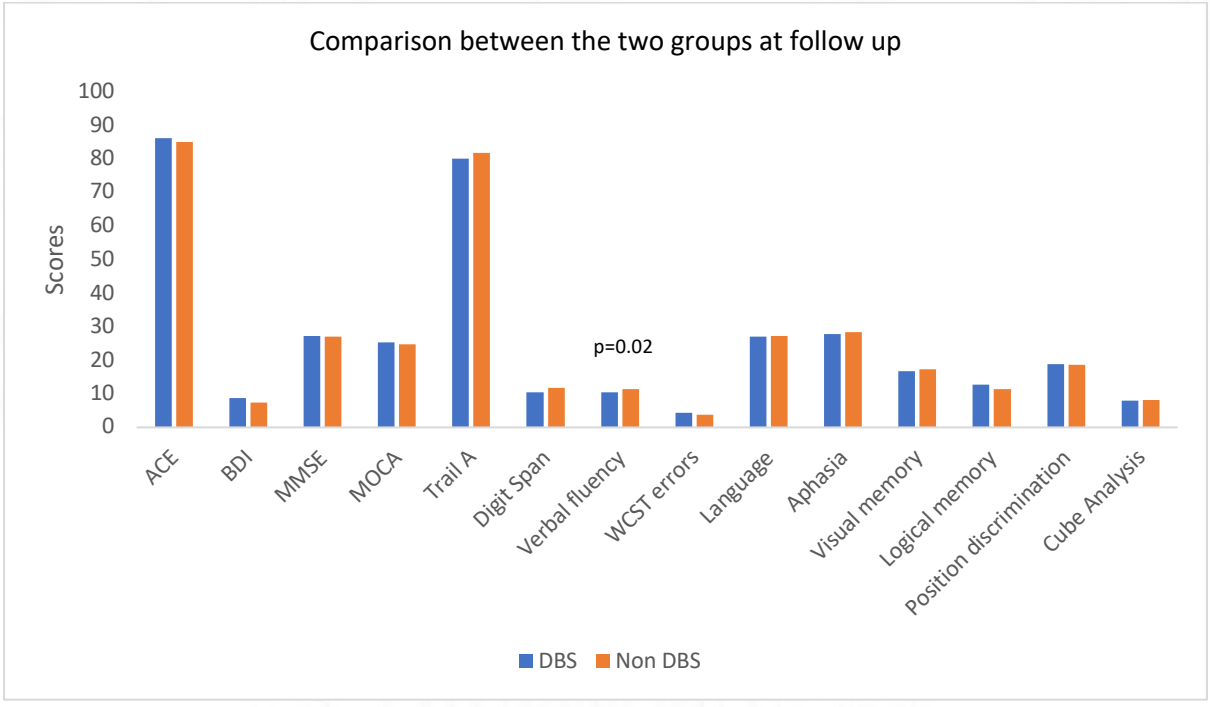


**Figure 10: Comparison of neuropsychological scores between the two groups at follow up**

**2. Comparison of decline between the neuropsychological variables of the two groups**

| **Parameter (Decline)** | **DBS** | **Non DBS** | **p value** |
|---|---|---|---|
| ACE, Mean (SD) | 1.47 (±2.78) | 1.53 (±2.49) | 0.965 * |
| BDI, Mean (SD) | -0.24 (±3.88) | 0.12 (±4.20) | 0.897 * |
| MMSE, Mean (SD) | 0.38 (±1.33) | 0.62 (±1.21) | 0.355 * |
| MOCA, Mean (SD) | 0.76 (±1.30) | 0.85 (±1.13) | 0.849 * |
| Trail A, Mean (SD) | -4.50 (±11.91) | -2.62 (±10.67) | 0.495 ** |
| Digit Span, Mean (SD) | 1.26 (±1.33) | 0.68 (±1.25) | 0.061 * |
| Verbal fluency, Mean (SD) | 1.15 (±1.23) | 0.59 (±0.93) | **0.034 *** |
| WCST errors, Mean (SD) | -0.82 (±1.34) | -0.59 (±1.81) | 0.252 * |
| Language (ACE), Mean (SD) | 0.18 (±0.72) | 0.29 (±0.84) | 0.519 * |
| Aphasia Battery, Mean (SD) | 0.56 (±1.02) | 0.32 (±0.95) | 0.545 * |
| Visual memory, Mean (SD) | 0.91 (±1.96) | 1.03 (±3.08) | 0.809 * |
| Logical memory, Mean (SD) | 2.41 (±3.21) | 2.32 (±2.65) | 0.877 * |

| | | | |
|---|---|---|---|
| Position discrimination, Mean (SD) | 0.29 (±1.12) | 0.18 (±1.09) | 0.661 * |
| Cube Analysis, Mean (SD) | 0.24 (±0.86) | 0.44 (±1.08) | 0.412 * |

***Analysed using Mann Whitney U test**

****Analysed using unpaired student's t test**

**Table 6: Comparison of decline of the neuropsychological variables between the two groups**

When the temporal change of cognitive variables were compared between the two groups, only measure of decline of verbal fluency was found to be significantly lower on follow up (0.59 ±0.93) when compared to baseline (1.15±1.23). The decline in digit span tended towards statistical significance (p=0.06). Rest of the measures of decline in global cognition, executive function, language, memory and visuospatial function remained stable and comparable over a period of time ($T_1$) in the two groups. Anxiety and depression as measured by NPI and BDI, did not differ significantly between them (Table 6, Figure 11).

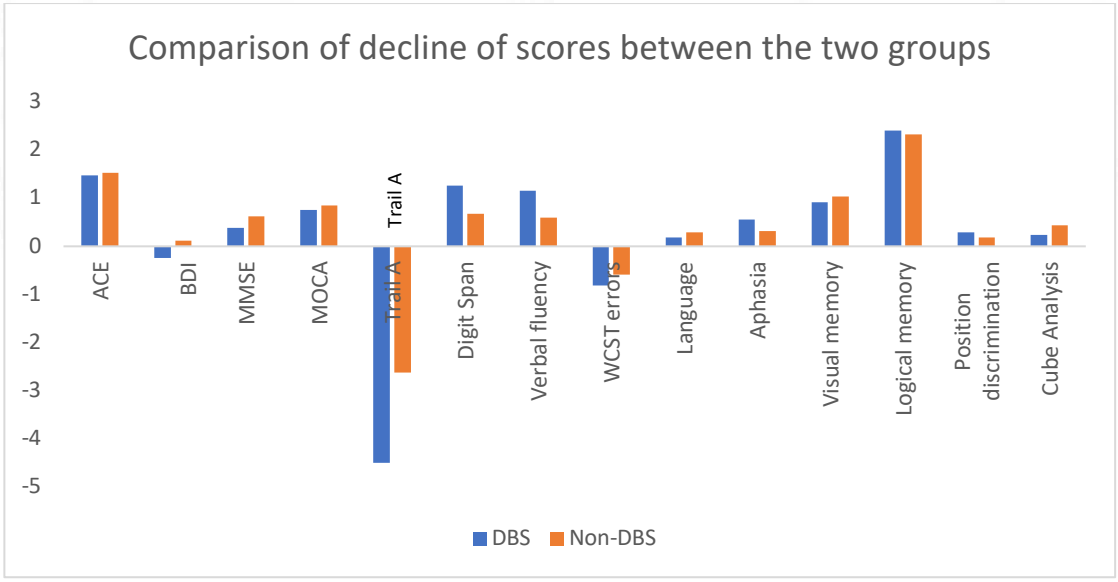


**Figure 11: Comparison of decline of scores between the two groups**

# DISCUSSION

The improvement in motor outcomes after deep brain stimulation (DBS) has been well established in patients with Parkinson's disease. But the cognitive changes in these patients have not been accredited with certainty to DBS or its procedure and it remains controversial. As even small decrements in cognition can lead to profound effects on quality of life, it is important to ascertain the same in this population of patients.

We conducted a comparative observational study to assess the effects of bilateral STN DBS on cognition at minimum two years of neurostimulation when compared to a group of patients with PD on medical management alone. At a mean follow up of around 33 months, compared to medically managed patients, we found a significant decline in verbal fluency scores in the DBS group and a trend for decline was noted in digit span test, both measures of frontal executive function. Though many of the other cognitive scores declined over time, there was no difference between the surgical and medically managed groups, indicating that these are attributable to the natural progression of PD and not the surgical procedure or neurostimulation.

We studied a total of 68 patients; 34 in each group (DBS and non DBS). The DBS group comprised of 26.5% females, with a mean age of 55.53 (±7.36) years and the non DBS group comprised of 29.4% females with a mean age of 58.21 (±6.06) years. This is expected as PD is almost twice more common in men as in women. The mean age and sex ratios between the two groups were comparable.

As age and duration of PD could confound the assessment of neuropsychological functions, we sought to match the two groups for age at assessment and duration of illness. To avoid the confounding effects of education, we selected only patients with a minimum of 10 years of formal education. Age and gender distribution between the two groups were comparable, with no statistically significant difference between them. The mean educational years was

marginally higher (p=0.04) among patients of the DBS group when compared to those in the non DBS group. This may be due to the fact that patients who underwent DBS were more likely to be educated and financially independent to understand the risks and benefits of the procedure and to afford the same.

The UPDRS III (motor) scores assessed in drug off state were similar between the two groups indicating that these two groups of patients who were matched for duration of the disease, had a similar degree of severity of motor deficits of PD. At baseline, the LEDD did not differ significantly between the two groups. Our neuropsychological test battery was composed of tests of global cognitive function (the validated Malayalam versions of ACE, MoCA and MMSE) as well as two tests each, testing each of the five cognitive domains recommended for the cognitive assessment of PD – viz attention and working memory (Trail Making Test A and B (66), digit span test (67–69)); executive function (verbal fluency (63) and Wisconsin Card Sorting Test (70,71)); memory (logical memory and visual recall – subtests of Wechsler Memory Scale (72)); language (subscale of ACE and Frenchay's Aphasia screening test (73)) and visuospatial functions (position discrimination and cube analysis- VOSP battery (74)) - as per the International Parkinson and Movement Disorder Society (MDS) guidelines (58). The baseline neuropsychological testing did not show any significant difference in the test scores, between the two groups. Thus, we had a population of medically and surgically managed patients comparable at baseline, allowing us to study the effect of DBS per se on cognition

Patients were assessed at mean follow up of 32.96 ± 4.097 months. UPDRS II and III scores were significantly lower in the DBS group (11.21 (±3.13); 16.47 ± 4.36) in medication-off state when compared to the non DBS group (26.94 (±3.18); 49.09 ± 5.19; $p<0.0001$). The improvement in motor outcome is expected with DBS as it is the very reason why DBS is undertaken in patients with severe motor symptoms, dyskinesias and/or motor fluctuations. As patients' activities of daily living, measured by UPDRS II are greatly dependent on their motor

outcomes, this too is expected post DBS. This has been asserted by previous randomised trials (75,76). The PD SURG trial reported the 1 year follow-up data of 366 PD patients treated either with surgery or the best medical therapy (75). They found that the mean UPDRS scores decreased significantly between baseline and 1 year follow up in the surgical group and increased in the medical therapy group (attributable to the progression of disease) along with a significant improvement in DBS patient's quality of life.

When the scores were compared at baseline and follow up, for the two groups individually; various neuropsychological scores were found to have significant differences. We found declines in both groups in relation to measures of global cognition (ACE, MOCA), attention, executive function (digit span, verbal fluency) and logical memory. Though the DBS group showed significant increased time for TMT-A, increased errors in WCST (measure of set shifting), worse scores on Frenchay's aphasia scale and visual memory test; the non DBS group also showed trends for worsening in these domains. In addition, the non DBS groups showed decline in visuospatial function. Though found to have significance in the paired statistical tests, the magnitude of most of the declines were small and may not be clinically significant; none of the patients in either groups were demented on follow up. The decline in these scores, occurring in both groups, indicate the natural progression of PD.

York et al., studied neuropsychological outcomes in 23 patients who underwent DBS and 28 patients with PD at baseline and 6 months (11). They found that patients who underwent DBS demonstrated declines from baseline in attention, set shifting and semantic fluency but these changes were similar to the rate of decline seen in the PD group. This was attributed to the natural progression of Parkinson's disease as they were seen in both groups. Similarly, in our study we found minor statistical differences from baseline in both the groups, however, there was no major cognitive decline in these patients. Both the DBS and non DBS group

revealed largely similar intragroup declines on follow up, suggesting that these declines are comparable with the rate of PD progression.

To better ascertain the difference between the two groups, we sought to compare the follow-up neuropsychological scores between the two groups (which were similar at baseline with regard to these scores) and also, the decline in scores over time, between the two groups.

During assessment of follow up scores between the two groups, only measure of decline of verbal fluency (comprising of both phonemic and semantic fluency) was found to be significantly lower (p=0.02) in the DBS group (10.50±1.62) when compared to those who were on medical management alone (11.47±1.71). Patients in the non DBS group performed better on the digit span test with higher scores. However, this did not reach statistical significance (p=0.073).

When the temporal decline between the two groups were ascertained; verbal fluency was again found to be significantly lower on follow up (0.59 ±0.93) when compared to baseline (1.15±1.23, p=0.034). The decline in digit span showed a statistical trend. (p=0.06). Rest of the measures of decline in global cognition, executive function, language, memory and visuospatial function remained stable and comparable over a period of time ($T_1$) in the two groups. The changes in anxiety and depression scores as measured by Beck's Depression Inventory (BDI) and anxiety subscale of Neuropsychiatric Inventory (NPI) , were also comparable, thereby precluding its effects on the cognitive scores.

Our findings are in accordance with most previous studies which have used a control group of PD patients on medical therapy for comparison against patients who underwent bilateral STN DBS (Table 7). The one cognitive adverse event which is consistently reported following DBS is a decrease in verbal fluency (9–11,13,44–47,77–80). Verbal fluency is a complex composite task, with various cognitive subcomponents (e.g. conception and application of a retrieval

strategy, shifting between subcategories, vocabulary access, semantic processing) which may overall be classified as either executive or semantic in nature (14). Neuropsychological and neuroimaging studies, in healthy and clinical subjects, support the involvement of a fronto-temporal system including areas known to be the substrate of executive and semantic processes including (left or bilateral) inferior frontal gyrus, anterior cingulate cortex and superior temporal regions.

Castelli et al., conducted a prospective controlled study of 27 PD patients who underwent DBS-STN (DBS group) and a matched control group of 31 PD patients under optimal medical treatment (MED group) who were awaiting surgery themselves (80). The two groups were matched for age, sex, duration and severity of the disease (UPDRS, part III) and levodopa equivalent daily dosage (LEDD). They were followed up for a period of 1 year. At baseline, the two groups were comparable for cognitive scores. On univariate analysis, at follow up, there seemed to be a significant decline in phonemic fluency scores in the DBS group compared to the MED group ($p=0.002$). When these were analysed in a correlation analysis, they did not find any association between change in verbal fluency and demographic-neurological variables. Thus, the decrease in verbal fluency was independent of motor scores, LEDD and natural PD progression. They further found a subgroup of 15% of DBS patients that showed a relevant cognitive decline 1 year after surgery. Even though, the baseline motor scores were not statistically significant, the DBS group ($55\pm11.3$) presented a higher severity of the illness at baseline than the MED group ($49.6\pm11.9$) as evidenced by the UPDRS III scores. The design of our study was similar to this one with 34 patients in each group, using a matched controlled group, though the non DBS group did not comprise of all patients who were waitlisted for surgery. However, both groups were matched at baseline for age at assessment and duration of illness. They had similar severity of motor deficits and equivalent LEDD at baseline. At a longer follow up period, we similarly found a significant

decline in verbal fluency in the DBS group with other neuropsychological variables being comparable between the two. We did not find major cognitive decline or dementia in any of our patients. The subgroup of patients that were found to have dementia in Castelli's groups also had a higher severity of disease at baseline when compared to rest of the DBS group, whereas we did not find such a difference between our study groups.

The three year controlled Italian study by Zangaglia et al., also studied a similar study population to ours with 32 post DBS patients and 33 PD controls, who though were eligible for surgery, denied it for various reasons (9). The groups were matched for various demographic variables at baseline except for age and age at onset of PD (both were greater in the control group). As in our study, they found that between the two groups, at 3 years, with the exception of the FAS score for verbal fluency, which was significantly lower in the DBS group (PD-control: 32.62; PD-DBS: 25.68; P = 0.014), no other significant differences emerged between the two groups. They also assessed within group differences at baseline and at 1, 6, 12, 24, and 36 months for the DBS group, and found that the worse logical executive function task and verbal fluency scores at 1 month, had returned to baseline by 1 year and thereafter, remained stable. This could be attributed to the micro-lesioning effect of the circuits seen in the immediate DBS post-operative period. As at 3 years, the DBS group still showed significant decline in verbal fluency scores, the role of STN neurostimulation on the fronto striatal circuits cannot be completely dismissed. Notably, the WCST score was worse in the control group at 3 years when compared to the baseline. This was potentially attributed to PD progression and they suggested that this was probably not seen in the DBS group, due to a learning effect. We did not see a similar worsening of WCST scores in the non DBS group. The greater age and age at onset of PD in the control group of their study could have accounted for the increased errors.

In their study of 23 DBS PD patients and 28 controls on medical management, York et al., demonstrated that patients who underwent STN DBS experienced declines in verbal delayed recall and verbal fluency when compared to PD controls at 6 months (11). 26% of DBS patients revealed a reliable decline in verbal fluency compared with only 4% of PD controls ($p<0.01$), and 37% of patients who underwent DBS showed a decline on Stroop Color–Word test (SCWT) as opposed to 4% of PD controls after 6 months ($p<0.003$). Several trends were seen in patients who underwent DBS with decline on measures that tap oral information processing speed, including verbal fluency, Symbol Digit Modalities Test and Stroop Word scores. They attributed this to frontostriatal dysfunction rather than due to disease progression alone. Even though verbal and visual memory scores significantly declined from baseline in the DBS group in our population; there was no difference in the declines of the two groups or between the follow up scores. The shorter duration of follow up (6 months vs 33 months), different assessment tests for verbal memory, DBS group having 2 years less educational attainment, a younger age of PD onset, a longer duration of illness and taking more dopaminergic medication could all have been contributing factors.

In one of the earliest controlled studies, Morrison et al., studied cognitive outcomes in 17 patients post DBS in both stimulation on and off states as compared to baseline (mean 13.3±7.8 weeks) and 11 PD matched controls (9.7±7.4 weeks) (10). They went a step further to try and dissociate the effect of the surgical process of implantation and chronic indwelling of electrodes from the STN neurostimulation itself. They also looked at the effects of the procedure as a whole. They assessed composite scores for cognitive domains of attention (digit span forward and backward, brief attention test), execution, language (derived from semantic and phonemic verbal fluency, confrontational naming); learning, recognition, delayed recall and visuospatial function owing to the small sample size and large number of neuropsychological variables being studied. They found mild decline in attention (p-0.031)

and language measures (p=0.05) in stimulation off states when compared to baseline, in the surgical group. As the trajectory of the electrodes passes through the frontal region, these measures of executive function are likely to be affected. When comparing the procedure as a whole in stimulation on state, there were mild significant declines in language and delayed verbal recall from baseline in the DBS group. No significant differences were found between stimulation on and off states in the surgical group, therefore, as a whole, there was no effect of STN stimulation on cognitive and affective functions. Similarly, we found significant declines in verbal fluency tasks and statistical trend in digit span test, both a function of attention and executive function. We did not study the patients in off stimulation state, as many patients are uncomfortable being tested in the off state due to the ensuing disability. Hence, we were not able to dissociate the effects of the surgical process from the high frequency STN stimulation per se.

Williams et al., compared 19 PD patients who had bilateral simultaneous STN DBS to 18 non-surgical PD patients using comprehensive neuropsychological assessment at baseline and at a 2 year follow-up (44). STN DBS patients exhibited impairments on tasks involving processing speed, non-verbal recall and verbal fluency (phonemic and semantic) and a trend was observed for impairment with Stroop Color Word Test. The authors also used RCI to draw conclusions solely based on the effects of DBS on cognition and to demarcate these effects from PD progression. After computing RCIs, patients in both the DBS and PD control groups deteriorated on processing speed, phonemic verbal fluency, semantic verbal fluency, non-verbal recall and executive function (53 vs. 28%, 26 vs. 11%, 29 vs. 29%, 47 vs. 25% and 43 vs. 18%, respectively. The number of STN DBS patients who converted to dementia 2 years following surgery was not significantly different from the control group. Though the two groups were matched in various aspects, the STN DBS group had significantly less education and higher baseline dopaminergic medication usage. Though we also found

declines in information processing (digit span as a measure) and verbal fluency, we did not find any significant differences in verbal and non-verbal memory at follow up between the two groups. This could be attributed to the inherent difference of the tests applied for the same, where we used the Weschler memory scale (WMS) and Williams' group used the RAVLT and BVMT (Brief Visuospatial Memory Test) scores.

Witt et al., carried out a randomised multicentre study with 60 patients randomly assigned to receive STN DBS and 63 patients to have optimal medical treatment (13). After 6 months, impairments were seen in executive function; phonemic verbal fluency and response inhibition (assessed by Stroop Color Word Test) irrespective of the improvement in quality of life. Thus, they concluded that STN DBS does not reduce global cognition but there is a selective decline in frontal executive functions and this was due to the intervention rather than progression of disease. As these changes do not affect improvements in quality of life and, DBS of the STN was considered safe with respect to neuropsychological effects in carefully selected patients. Compared to our study, the advantages of this study were the comparatively larger cohort size and prospective, randomised design which allowed for a comprehensive neuropsychological assessment with increased statistical power.

Recently, Tramontana et al., noted that DBS patients (n=15) had deficits in phonemic fluency (p=0.047) and on several subtests of the Wisconsin Card Sorting Test (WCST, p=0.035) at one year follow up, compared to controls (n=15) in early stage PD patients (H and Y stage II) after withdrawal of treatment (off stimulation/ off medication) (46). Although, the medical therapy group performed better on the phonemic fluency task ($p$ = 0.029) at 2 years, the comparative change from baseline between the two groups was not significantly significant ($p$ = 0.069). In addition, when the authors excluded patients who suffered from an adverse event (one with stroke and one with infected hardware) in the DBS cohort; these findings

were negligible at 2 years follow up. Comparatively, we still found significant differences in verbal fluency at follow up. This could be attributed to our cohort comprising of advanced PD patients with assessment being done in the on stimulation/ on medication states, probably relaying the effect of high frequency bilateral STN stimulation.

In one of the largest studies, Smeding et al., included 99 STN DBS patients and 36 PD controls (47). They found that 6 months after surgery, the STN group showed a greater decline than the control group on measures of selective attention, verbal fluency, speed of color naming and verbal memory. In spite of the apparent differences between the number of participants in each group, longer disease duration and higher baseline LEDD in the DBS group, these baseline differences did not affect the results. Though, we did not find significant differences in measures other than verbal fluency, the other tests mentioned here largely test the executive functioning and connectivity of the fronto-striatal circuits and hence are an extension of our findings.

As evidenced above, verbal fluency commonly declines post STN DBS in PD, but alternating fluency measures using cued and uncued paradigms have been sparingly evaluated. Marshall et al., compared 23 STN DBS patients with 20 non-surgical PD patients with cued and uncued intradimensional (phonemic/phonemic and semantic/semantic) and extra-dimensional (phonemic/semantic) alternating fluency measures at baseline and at 6 months (77). Patients post STN DBS showed a greater decline on the cued phonemic/ phonemic fluency and the uncued phonemic/semantic fluency tasks as compared to the PD patients. For STN DBS patients, verbal learning and information processing speed accounted for a significant proportion of the variance in these declines. Though these results should be interpreted with caution, as the two groups were incompletely matched at baseline for demographic and medical variables. As STN DBS patients demonstrated greater declines over time than the PD

patients, these findings suggested that changes in alternating fluency were not related to disease progression. We did not assess this measure of alternating verbal fluency, but it can be explored in the future, to better delineate the tasks of verbal fluency in which declines are seen in patients after STN DBS surgery.

In the first long term controlled study, Merola et al., included 19 DBS and 16 medically treated PD patients (78). They reported phonemic verbal fluency to be significantly worse in STN DBS patients at an average follow up of 6 years (p=0.023). Both groups showed similar progression to dementia during follow-up (25% vs 21%) with no significant differences. This study further affirmed that verbal fluency remains affected even at long term follow up of around 6 years. We did not find any major cognitive decline amounting to dementia in our cohort. This can be explained by the shorter follow up, absence of major cognitive impairments at baseline and no major adverse events being reported in these patients post DBS.

| Authors(s), Year | Population studied | Site of DBS | DBS settings at assessment | Evaluation | Duration of follow up | Neuropsychological outcome (decline in DBS group) |
|---|---|---|---|---|---|---|
| **Moretti et al., 2003 (45)** | 9- DBS<br>9- PD controls | Bilateral STN | ON stim | Stroop Test, Raven Standard Progressive Matrices, digit span backwards and forwards, retrieval of a story, Syntactic comprehension test and Morphological test (from the Bilingual aphasia test, part B, Italian language), | 1, 6, 12 months | Stroop time of execution and number of mistakes, semantic, phonological and syllabic fluency and in the number of intrusions in the syllabic task |

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|---|---|---|---|---|---|---|
| | | | | alternating verbal semantic and phonological fluency, Benton Line Orientation Test . | | |
| **Morrison et al., 2004 (10)** | 17-DBS,<br><br>11-matched PD controls (CPD) | Bilateral STN | ON and OFF stim | Composite scores for attention, execution, language (semantic and phonemic verbal fluency, confrontational naming); learning, recognition, delayed recall and visuospatial domains | For DBS group- 13.3 weeks;<br><br>for CPD group- 9.7 weeks (mean) | OFF- attention and language<br><br>ON- language and delayed verbal recall |
| **Smeding et al., 2006 (47)** | 99- DBS<br><br>36- control | Bilateral STN | ON Stim | DRS; Category fluency, Controlled Oral Word Association Test (COWAT), Alternating fluency, Dutch Adult Reading Test (DART), Paced Auditory Serial Addition Task (PASAT): Auditory Verbal Learning Test (AVLT), Groningen Intelligence Test: Visuospatial reasoning, Stroop Color Word Test, Odd Man Out Test (OMO), TMT-A and B, Boston Naming test (BNT) | 6 months | Verbal fluency, color naming, selective attention, and verbal memory |
| **York et al., 2007 (11)** | 23- DBS<br><br>28- medically treated group | Bilateral STN | ON stim | MMSE, Mattis DRS, Symbol Digit Modalities Test, TMT- A and B, Digit Span, Verbal Fluency, Semantic Fluency, Boston Naming Test (BNT), RAVLT, Brief Visual Memory Test (BVMT), WCST, SCWT, Clock | 6 months | Verbal recall and trends for declines in oral information processing |

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|---|---|---|---|---|---|---|
| | | | | Drawing, BDI, State-Trait Anxiety Inventory (STAI) and Brief Symptom Inventory (BSI) | | |
| **Witt et al., 2008 (13)** | 60- DBS<br><br>63- PD medical group | Bilateral STN | ON stim | Mattis DRS, RAVLT, digit span, verbal fluency, SCWT, Benton test | 6 months | Verbal fluency, Performance on Stroop test |
| **Castelli et al., 2009 (80)** | 27- DBS;<br><br>31- medical management | Bilateral STN | ON stim | Raven Color Matrices, Bi-syllabic Words Repetition test, Corsi's Block Tapping test, Paired Associate Learning and Trail Making B, the Nelson Modified Card Sorting test, Phonemic and Category Verbal Fluency tasks | 1 year | Verbal fluency |
| **Zangaglia et al., 2009 (9)** | 32- PD DBS<br><br>33 – PD control | Bilateral STN | ON stim/ ON med | MMSE, long-term memory, LMT, Verbal span, Digit span, Corsi's Block tapping test, WCST and Raven's Matrices, verbal fluency (FAS) | 3 years | Verbal fluency |
| **Williams et al., 2011 (44)** | 19- DBS<br><br>18- medical management | Bilateral STN | ON stim | MMSE, DRS, RAVLT and the Brief Visual Memory test (BVMT), Symbol Digit Modalities Test oral administration (SDMT), TMT-A, Digit Span from the WAIS-III, verbal fluency, Boston naming test, TMT-B, WCST, SCWT, Clock Drawing | 2 years | Non-verbal recall, oral information processing speed, and lexical and semantic fluency |

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|---|---|---|---|---|---|---|
| **Marshall et al., 2012 (77)** | 23- DBS;<br><br>20- PD non-surgical | Bilateral STN | ON stim | Alternating verbal fluency intra and inter group comparisons for cued and un cued semantic and phonemic verbal fluency tasks within 60s | 6 months | Cued phonemic/ phonemic fluency and the un cued phonemic/semantic fluency tasks |
| **Saez-zea et al., 2012** | 9- DBS<br><br>12- control | Bilateral STN | ON stim | Subscales of WAIS-III, TMT- A and B, Stroop Test, AVLT, tests of executive function, Boston Naming Test, Semantic Verbal Fluency Test (animals), Phonemic Verbal Fluency Test (P/M/R) , constructional praxis tests, WCST, Arithmetic Reasoning, Copy and maintain alternating patterns | 6 months | Phonemic verbal fluency, time to perform the TMT- B, Digit Symbol score of WAIS-III and color-naming score of the Stroop Test. |
| **Merola et al., 2014 (78)** | 19- DBS<br><br>16- Medical control group | Bilateral STN | ON stim/ ON med | Raven color matrices, Bi-syllabic words rep. test, Corsi's block tapping test, Paired associate learning, TMT-B, Nelson MCST, Phonemic verbal fluency, Category verbal fluency, BDI, State Trait Anxiety Inventory | 6.22 years (mean) | Phonemic verbal fluency |
| **Tramontana et al., 2015 (46)** | 15- DBS<br><br>15- optimal drug therapy (ODT)<br><br>(In early PD) | Bilateral STN | OFF stim/ OFF med | Benton Judgment of Line Orientation Test, Boston Naming Test, Verbal Fluency Phonemic (FAS Words), Semantic (Animal Words), WAIS-III Digit Span, PASAT, WMS-III, WCST, Stroop Color and Word Test, Minnesota | 12, 24 months | Attention, executive function, and word fluency at 12 months. These differences were largely diminished at 24 months |

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|---|---|---|---|---|---|---|
| | | | | Multiphasic Personality Inventory-2 | | |
| **Demeter et al., 2017 (79)** | 10- DBS;<br><br>10- PD patients waitlisted for DBS | Bilateral STN | ON stim/ ON med | MMSE, Digit span test, Stroop, TMT-B, Corsi block tapping testy, letter N-back test, phonemic and semantic verbal fluency tasks | 4-6 months | Semantic verbal fluency |

- Stim- stimulation; Med- medication

**Table 7: Previous controlled studies which studied neuropsychological outcomes post DBS surgery**

It is still not known whether post-operative cognitive impairments are solely attributable to PD progression, the effects of the surgery, or both. We demonstrated significant decline in verbal fluency (composite score of phonemic and semantic fluency) in the DBS group from baseline at an average follow up period of 33 months. Statistical trend was also seen with worsening digit span in the DBS group. Our results are concordant with previous studies as detailed in the text above. As these changes were seen only in the DBS group on follow up, these findings cannot be explained by progression of disease. Both verbal fluency and digit span are a measure of frontal executive functions which may be impaired by affection of the fronto-striatal circuitry. This may be due to the effect of the surgical process itself in the form of microlesioning along the trajectory of the electrodes or the high frequency STN stimulation, per se.

There are various theories to postulate how bilateral STN stimulation leads to executive dysfunction. A PET study found that poor verbal fluency during STN stimulation was related to decreased activation as evidenced decreased rCBF (regional cerebral blood flow) in the right orbitofrontal cortex, the left inferior temporal gyrus, and the left inferior frontal/insular cortex

(81). The spread of electrical current from the stimulator is probably not restricted to the sensorimotor part of the STN and may also spread to affect the limbic and cognitive-associative part (81), as well as the medial forebrain bundle, zona incerta, lateral hypothalamus, and other regions that have extensive limbic connections. Another hypothesis may be that stimulation disconnects the basal ganglia, and functions that are normally subserved by the basal ganglia are inadequately taken over by the cortex (82).

We did not study the DBS patients in off stimulation states and thus, could not definitively distinguish between the lesioning effect of surgery versus STN stimulation as the probable cause for the executive dysfunction. However, it could be attributed to STN stimulation as the immediate post-operative effects that lesioning produces may not extend up to our follow up period of 33 months. Furthermore, the reduction of levodopa dose post-surgery often results in apathy which can confound neuropsychological testing or the concomitant use of anticholinergic medications which can worsen cognitive scores. We understand it is a limitation of our study that we did not account for these factors while assessing the neuropsychological variables.

In spite of minor significant differences in selective cognitive tasks, none of our patients showed major cognitive decline in either group or developed dementia. This suggests that the cognitive effects attributable to STN stimulation are minor and very likely to be non-progressive and overall trajectory of global cognitive functions in operated patients follow that of the medically managed group. We also did not find any significant intergroup differences between the anxiety and depression scores at follow up, thereby precluding its effect on the cognitive assessment. Thus, our study demonstrated impairment in selective cognitive task of verbal fluency with no other major significant neuropsychological outcomes.

**Strengths of the study**

Unlike many previous studies, we have employed a control group to compare the cognitive outcome of DBS patients at baseline and follow up so that we could exclude the effect of natural progression of Parkinson's disease. We also matched the two study groups for age, severity of motor deficits and duration of PD at baseline. There was only a minor difference for the mean educational years at baseline.

We followed up patients' long term, for a mean duration of around 33 months, which is a reasonable amount of time for the immediate post-surgical effects of microlesioning of the frontostriatal tracts to wear off.

Our study is the first in the Asian population that explored the cognitive outcome in PD patients undergoing STN DBS when compared to a control group of medically treated patients.

**Limitations of the study**

We recognise that our study had a few limitations. Firstly, ours was not a randomised study. However, given the proven efficacy of the DBS procedure for motor outcomes in idiopathic PD, conducting a randomized controlled study will have major ethical concerns. We could have used a group of patients waitlisted for surgery, to further have a homogenous control group at baseline; however, this will not allow a long follow-up as was possible with the current design. Secondly, we did not assess the patients separately in stimulation -on and stimulation-off states and thus could not definitively determine whether the effects on executive functioning were due to the lesioning from surgical intervention or to neurostimulation itself. However, switching off the stimulation may not immediately withdraw the stimulation effects and prolonged switching off may not be ethically justified. Thirdly, we did not take the LEDD reduction post-surgery into consideration as this also could have contributed to apathy, with

some impact on cognitive testing. Lastly, we had a small sample size which may have affected the statistical power of the tests but given the selectivity of the population in which DBS is undertaken, this may still be a sizeable number.

# CONCLUSION

Our study demonstrated impairment in the selective cognitive task of verbal fluency and a trend towards impairment in attention, with no other major significant neuropsychological outcomes attributable to STN DBS in patients undergoing this neurosurgical procedure for motor complications of Parkinson's disease. None of the patients had any functionally significant cognitive deficits or dementia during the period of follow-up. We postulate that these effects on fluency and attention are attributable to STN stimulation and modulation of the fronto-striatal circuits and not from any acceleration of neurodegeneration resulting from DBS. Thus, DBS of STN can be considered safe from the cognitive viewpoint in patients with idiopathic Parkinson's disease experiencing motor complications of medical treatment. However, patients should be meticulously selected prior to surgery with adequate information regarding the possible cognitive effects of DBS, to minimise the negative effects on quality of life.

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# ANNEXURES

# ABBREVIATIONS

| | |
|---|---|
| PD | Parkinson's Disease |
| DBS | Deep Brain Stimulation |
| STN | Subthalamic Nucleus |
| GPi | Globus Pallidus interna |
| VIM | Ventral Intermediate Nucleus |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| ACE | Addenbrooke's Cognitive Examination |
| MMSE | Mini Mental State Examination |
| MOCA | Montreal Cognitive Assessment |
| BDI | Beck's Depression Inventory |
| TMT-A | Trail Making Test – A |
| TMT-B | Trail Making Test – B |
| SCWT | Stroop Color Word Test |
| WCST | Wisconsin Card Sorting Test |
| WMS | Weschler Memory Scale |
| RAVLT | Ray's Auditory Verbal Learning Test |
| CDR | Clinical Dementia Rating scale |
| VOSP | Visual Object Space Perception |
| GABA | Gamma amino butyric acid |
| L- Dopa | Levodopa |
| RCI | Reliable Change Index |
| NMS | Non-Motor Symptom |
| N/n | Number of |
| SD | Standard deviation |
| LEDD | Levodopa Equivalent Dose |
| H and Y | Hoehn and Yahr stage |

# PROFORMA

Title: **"Cognitive Outcome Following Bilateral Subthalamic Nucleus Deep Brain Stimulation In Parkinson's Disease: A Comparative Observational Study In The Indian Population"**

Serial Number: Date:

Name of the patient: Age:
Gender:

Hospital Number: Education:

Past Medical history: (DM/HTN/CAD/DLP/CVA):

DBS/ Non DBS:

If post DBS surgery, Target of DBS: Date of surgery:

Age at onset of PD: Duration of PD :

First motor symptom noted at onset:

Side of onset:

Motor Fluctuations: YES / NO

Dyskinesias:

Time to ON: Duration of ON: OFF time dystonia:

Type of PD:

Current Medications:

LEDD:

Non-motor symptoms:

Hoehn and Yahr Stage:

UPDRS II and III Score (Off medication) :

## NEUROPSYCHOLOGICAL EVALUATION TOOLS

1. MONTREAL COGNITIVE ASSESSMENT-M (MoCA-M)

2. ADDENBROOKES COGNITIVE EXAMINATION(ACE)

3. BECK DEPRESSION INVENTORY(BDI)

4. WECHSLER MEMORY SCALE (WMS):

   Visual Reproduction (VR) & Logical Memory (LM)

5. TRAIL A AND TRAIL B

6. WISCONSIN CARD SORTING TEST

7. DIGIT SPAN FORWARD AND BACKWARD

8. NEUROPSYCHIATRIC INVENTORY (NPI)

9. FRENCHAY APHASIA SCREENING TEST

10. CLINICAL DEMENTIA RATING SCALE(CDR)

11. VISUAL OBJECT AND SPATIAL PERCEPTION(VOSP):

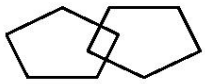
    Position discrimination & Cube analysis

# NEUROPSYCHOLOGICAL TESTS

## Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions: Score one point for each correct response within each question or activity.***

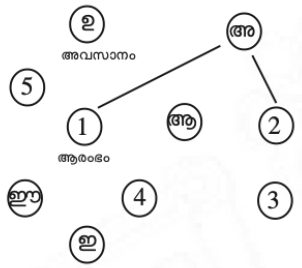
| Maximum Score | Patient's Score | Questions |
|---|---|---|
| 5 | | "What is the year? Season? Date? Day? Month?" |
| 5 | | "Where are we now? State? County? Town/city? Hospital? Floor?" |
| 3 | | The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. |
| 5 | | "I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …)<br>Alternative: "Spell WORLD backwards." (D-L-R-O-W) |
| 3 | | "Earlier I told you the names of three things. Can you tell me what those were?" |
| 2 | | Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them. |
| 1 | | "Repeat the phrase: 'No ifs, ands, or buts.'" |
| 3 | | "Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.) |
| 1 | | "Please read this and do what it says." (Written instruction is "Close your eyes.") |
| 1 | | "Make up and write a sentence about anything." (This sentence must contain a noun and a verb.) |
| 1 | | "Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)<br>  |
| 30 | | TOTAL |

# MONTREAL COGNITIVE ASSESSMENT- MALAYALAM (MOCA-M)

**മോൺട്രിയാൽ ബൗദ്ധിക പരിശോധന-മലയാളം (MOCA - M)**
**MONTREAL COGNITIVE ASSESSMENT - MALAYALAM**

പേര് :
വിദ്യാഭ്യാസം : ജനനതീയതി :
സ്ത്രീ/പുരുഷൻ : തീയതി :

**വിഷ്വോ സ്പേഷ്യൽ/എക്സിക്യൂട്ടിവ്**

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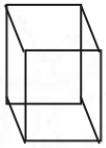
ക്യൂബിന്റെ ചിത്രം പകർത്തുക



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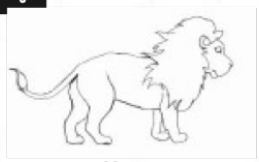
ഘടികാരം വരയ്ക്കുക (സമയം പതിനൊന്നു മണി കഴിഞ്ഞ് പത്ത് മിനിറ്റ്) (മൂന്ന് പോയിന്റ്)

[ ] ആകൃതി [ ] സംഖ്യകൾ [ ] സൂചികൾ

പോയിന്റുകൾ _/5

**പേര് പറയുക**



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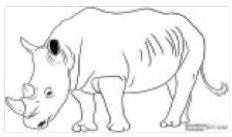

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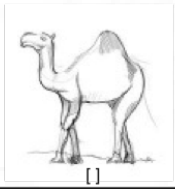

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**ഓർമ്മ :** വാക്കുകളുടെ പട്ടിക വായിക്കുക. പരിശോധിക്കപ്പെടുന്ന വ്യക്തി അവ ആവർത്തിക്കണം. ആദ്യത്തെ ശ്രമം തന്നെ വിജയകരമായാലും രണ്ടു ശ്രമങ്ങളും നടത്തുക. അഞ്ച് മിനിട്ടിനു ശേഷം ഓർമ്മിക്കാൻ ശ്രമിക്കുക.

| | മുഖം | കമ്പിളി | അമ്പലം | മുല്ല | നീല |
|---|---|---|---|---|---|
| ആദ്യ ശ്രമം | | | | | |
| രണ്ടാമത്തെ ശ്രമം | | | | | |

പോയിന്റുകൾ ഇല്ല

**ശ്രദ്ധ :** അക്കങ്ങളുടെ പട്ടിക വായിക്കുക. (ഒരു സെക്കന്റിൽ ഒരു അക്കം എന്ന നിരക്കിൽ)
പരിശോധിക്കപ്പെടുന്ന വ്യക്തി ഇതേ ക്രമത്തിൽ ആവർത്തിക്കണം [ ] 2 1 8 5 4
പരിശോധിക്കപ്പെടുന്ന വ്യക്തി വിപരീതക്രമത്തിൽ ആവർത്തിക്കണം [ ] 7 4 2

_/2

അക്ഷരങ്ങളുടെ പട്ടിക വായിക്കുക. ഓരോ "അ" അക്ഷരത്തിനും പരിശോധിക്കപ്പെടുന്ന വ്യക്തി കൈകൊണ്ട് മേശയിൽ കൊട്ടണം. ഒന്നിൽ കൂടുതൽ തെറ്റുകൾക്ക് പോയിന്റ് ഇല്ല.
ഇ, ഉ, അ, എ, ഐ, ഒ, അ, അ, ഔ, ഓ, അം, ഉ, അ, ഇ, അ, ഒ, ഷ, ശ, അ, അ, അ, ഔ, അ, ഐ, പ, ഷ, അ, അ, ഉ

_/1

നൂറിൽ നിന്ന് ഏഴ് കുറച്ച് പിന്നോട്ട് എണ്ണുക [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
നാലോ അഞ്ചോ ശരിയായ കിഴിക്കലിന് മൂന്ന് പോയിന്റ്, രണ്ടോ മൂന്നോ ശരിക്ക് രണ്ട് പോയിന്റ്, ഒരു ശരിക്ക് ഒരു പോയിന്റ്, എല്ലാം തെറ്റ്: പോയിന്റ് ഇല്ല.

_/3

**ഭാഷ :** ആവർത്തിക്കുക : ഇന്ന് സഹായിക്കുവാനായി ഉള്ളത് ജോണിയാണെന്ന് മാത്രം എനിക്കറിയാം. [ ]
മുറിയിൽ പട്ടികൾ വന്നപ്പോഴൊക്കെ പൂച്ച കട്ടിലിനടിയിൽ ഒളിച്ചു. [ ]

_/2

ഒഴുക്ക് : ഒരു മിനിട്ടുകൊണ്ട് "പ" എന്ന അക്ഷരം വച്ച് തുടങ്ങുന്ന പരമാവധി വാക്കുകൾ പറയുക [ ] പതിനൊന്നിൽ കൂടുതൽ വാക്കുകൾ പറയുന്നതിന് ഒരു മാർക്ക്

_/1

**അബ്സ്ട്രാക്ഷൻ** സമാനത വ്യക്തമാക്കുക. ഉദാ: വാഴപ്പഴം, ഓറഞ്ച് - രണ്ടും പഴങ്ങളാണ് [ ] ട്രെയിൻ - സൈക്കിൾ, [ ] വാച്ച് - സ്ക്കെയിൽ

_/2

**ഓർമ്മിച്ചെടുക്കൽ** വാക്കുകൾ സൂചനയില്ലാതെ ഓർമ്മിച്ചെടുക്കണം

| | മുഖം [ ] | കമ്പിളി [ ] | അമ്പലം [ ] | മുല്ല [ ] | നീല [ ] | സൂചനയില്ലാതെ ഓർമ്മിച്ചാൽ മാത്രം പോയിന്റ് നൽകുക |
|---|---|---|---|---|---|---|
| ഓപ്ഷനൽ: വിഭാഗത്തെപ്പറ്റിയുള്ള സൂചന | | | | | | |
| ഓപ്ഷനൽ: മൾട്ടിപ്പിൾ ചോയ്സ് സൂചന | | | | | | |

_/5

**സ്ഥലകാലബോധം** [ ] തീയതി [ ] മാസം [ ] വർഷം [ ] ദിവസം [ ] സ്ഥലം [ ] പട്ടണം/ഗ്രാമം

_/6



നോർമൽ: 25 -ൽ കൂടുതൽ

**ആകെ** _/30

12 വർഷത്തിൽ താഴെ വിദ്യാഭ്യാസം ഉള്ളവർക്ക് ഒരു പോയിന്റ് ചേർക്കുക.

# ADDENBROOKE'S COGNITIVE EXAMINATION – MALAYALAM (M-ACE)

## Addenbrooke's Cognitive Examination - Malayalam

| | |
|---|---|
| NAME: _____ | HOSP. NO.: _____ |
| D.O.B.: _____ | TESTING DATE(S): _____ |
| AGE: _____ | EDUCATION (YEARS): _____ |
| Handedness: _____ | Tested in (Language): _____ |
| Gender: | Urban / Rural: |

**ORIENTATION**

*Ask the subject the following questions and score a point for each correct answer. Record all errors.*

Total Score for Orientation (0 - 10) ☐ O

1 a) **What is the**

**year** ഇത് / ഇന്നു ഏതു വർഷമാണ് ☐

**season** ഏതു കാലമാണ് (സീസൺ) ☐

**month** ഏതു മാസമാണ് ☐

* **date** തീയതി എത്രയാണ് ☐

**day** ആഴ്ചയിലെ ഏതു ദിവസമാണ് ☐

b) **Where are we** ഇത് ഏതാണ് / എത്രാമത്തെ

** **country** രാജ്യം ☐

**state** സംസ്ഥാനം ☐

**city** നഗരം ☐

*** **hospital (or street/road)** ആശുപത്രി (റോഡ്) ☐

*** **floor (or house name/no.)** നില (വീട്ട് പേര്/നമ്പർ) ☐

**Allow an error of ± 2.*

*** Give the example of **SriLanka** if the subject gives the name of the state when asked the country*

**** The items in the brackets are to be used if the subject is being tested in his/her house*

**ATTENTION/CONCENTRATION**

2 *Tell the subject* **I will name three objects and you have to remember and repeat them after I finish.** *Taking one second for each, say aloud*: lemon, key, ball.
*Say them only once and ask the patient to repeat all three. Give one point for each correct answer at first attempt only. If score <3 repeat all three items until the patient learns all 3. Maximum trials allowed = 5.*

ഞാൻ നിങ്ങളോട് മൂന്ന് സാധനങ്ങളുടെ പേര് പറയും.
പറഞ്ഞ് നിർത്തുമ്പോൾ അത് ഓർത്ത് വച്ച് ഏറ്റുപറയുക.
നാരങ്ങ, താക്കോൽ, പന്ത്.

Score (0 - 3) ☐

Number of trials administered = _____

3 *Ask the patient to* **subtract 7 from 100.**
നൂറിൽ നിന്ന് ഏഴ് കുറയ്ക്കുക

Step 1 *Give one point only for the right answer (93).*
Step 2 *If the subject's answer is wrong then tell the correct answer.*
Step 3 *Ask the subject to* **now subtract 7 from** *the correct answer* **(93).**
അതിൽ നിന്ന് വീണ്ടും ഏഴ് കുറയ്ക്കുക (93).

*Repeat steps 1 to 3 for a total of 5 subtractions (93, 86, 79, 72, 65).*
*Score the total number of correct subtractions*

Score (0 - 5) ☐

**Spell 'WORLD' backwards:** This test is not scored for m-ACE.
Score the number of letters in the correct order, e.g., dlorw = 3.
'പരിശോധന' എന്ന വാക്കിന്റെ അക്ഷരങ്ങൾ, എതിർക്രമത്തിൽ (പിറകിൽ നിന്ന് മുന്നോട്ട്) പറയുക. 'ആന' എന്ന് ഞാൻ പറഞ്ഞാൽ നിങ്ങൾ ' നആ ' എന്ന് പറയണം.

**MEMORY**

4 *Ask the subject to* **recall the names of the 3 objects learnt earlier** *in question 2. Score a point for each correct recall.*
നേരത്തെ പറഞ്ഞ മൂന്ന് സാധനങ്ങളുടെ പേര് ഓർമ്മിച്ച് പറയുക

Score (0 - 3) ☐


Reference: *Int J Geriatr Psychiatry* 2004;19:1188-1194.

5 *Anterograde Memory*: *Tell the subject* **I will read a name followed by an address and ask you to repeat it when I have finished.** *Now read aloud the following name and address which has a total of seven elements in it. Score one point for each element recalled correctly. Regardless of the score after the first trial, repeat the instruction and the task twice in exactly the same way. Record scores for each of the three trials. Record errors.*

ഞാൻ പറയുന്ന പേരും, വിലാസവും കേട്ടിട്ട് ഓർത്തു പറയുക.

| | | Elements | Trial 1 | Trial 2 | Trial 3 | Delayed |
|---|---|---|---|---|---|---|
| Velayuthan Thambi | വേലായുധൻ തമ്പി | 2 | | | | |
| 42 Kovil Road | 42 കോവിൽ റോഡ് | 3 | | | | |
| Chengammanad | ചെങ്ങമനാട് | 1 | | | | |
| Elanji | ഇലഞ്ഞി | 1 | | | | |
| | Total | /7 | /7 | /7 | /7 | /7 |

Trial 1-3: Score (0 - 21) ☐
Delayed: Score (0 - 7) ☐ **M**

6 *Retrograde Memory: Score one point for each correct answer to the following questions and record errors.*

| | | |
|---|---|---|
| **Tell me the name of** | മുഴുവൻ പേര് പറയുക | Score (0 - 4) ☐ |
| **the capital of India** | ഇന്ത്യയുടെ തലസ്ഥാനം | _____ |
| **the Indian currency** | ഭാരതത്തിന്റെ നാണയം | _____ |
| **the Chief Minister of Kerala** | കേരളത്തിന്റെ മുഖ്യമന്ത്രി | _____ |
| **the town where Taj Mahal is** | താജ്മഹൽ എവിടെ സ്ഥിതി ചെയ്യുന്നു | _____ |

**VERBAL FLUENCY**

7 *Letter: Ask the patient to* **tell me all the words you can think of, but not people or places, beginning with the letter P.** *Time the subject for 1 minute and record all answers in the space provided below. Error types: perseverations and intrusions.*

'പ' കൊണ്ടു തുടങ്ങുന്ന കുറച്ചു വാക്കുകൾ പറയുക,
സ്ഥലത്തിന്റെയോ, ആളിന്റെയോ പേര് ആകരുത്.

8 *Category: In the same way ask the patient to generate and* **now tell the names of as many animals as you can beginning with any letter of the alphabet.** *Time the subject for 1 minute & record all responses in the space provided below. Errors: perseverations and intrusions.*

അറിയാവുന്ന മൃഗങ്ങളുടെ എല്ലാം പേരു പറയുക. അവ ഏത് അക്ഷരം കൊണ്ടും തുടങ്ങാം

| P പ | Animals മൃഗങ്ങൾ | Scoring | | |
|---|---|---|---|---|
| | | Raw Score | | Scaled |
| | | P | Animals | Score |
| | | >12 | >15 | 7 |
| | | 11 to 12 | 13 to 15 | 6 |
| | | 8 to 10 | 10 to 12 | 5 |
| | | 5 to 7 | 7 to 9 | 4 |
| | | 3 to 4 | 4 to 6 | 3 |
| | | 2 | 2 to 3 | 2 |
| | | <2 | <2 | 1 |

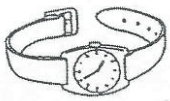
Raw Score = ☐ ☐
Scaled Score = ☐ /7 ☐ /7

Total Scaled Score (0 - 14) ☐ **V**

## LANGUAGE

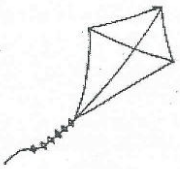
9 *Observe the subject's spontaneous speech and record the following*
*Fluency (phrases > 5 words)*
*Paraphasic errors (phonemic or semantic)*
*Word finding difficulties*

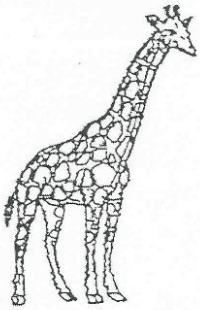
10 *Naming: Show the subject the following two line-drawings and ask him/her to* **name each of the these**. *Record responses and errors. Give one point for each correct response.*
ഓരോന്നിന്റെയും പേരു പറയുക.

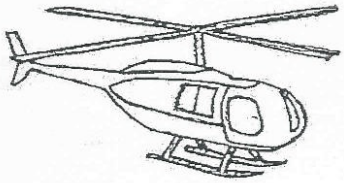


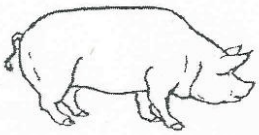
Score (0 - 2) ☐ L

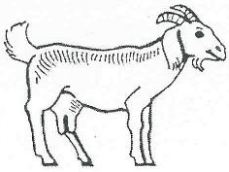
*Naming: Show the subject the following ten line-drawings and ask him/her to* **name each of these**. *Record responses and errors. Give one point for each correct response. If response is different from expected then ask them if it resembles anything else.*
ഓരോന്നിന്റെയും പേരു പറയുക.

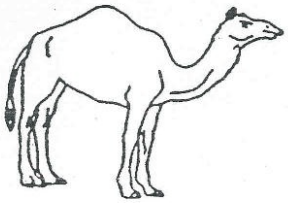


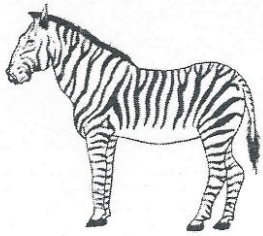












Score (0 - 10) ☐ L

11 *Comprehension (one -stage): Request the subject to* **obey the following simple commands.**

Score (0 - 2) ☐ L

താഴെ പറയുന്ന നിർദ്ദേശങ്ങൾ അനുസരിക്കുക.

**point to the door** വാതിൽ ചൂണ്ടി കാണിക്കുക
**point to the ceiling** തട്ട് ചൂണ്ടി കാണിക്കുക

12 *Show the subject the instruction in the box below and ask him/her to* **read this aloud and obey it.**

താഴെ എഴുതിയിരിക്കുന്നത് വായിക്കുക എന്നിട്ട്, അത് അനുസരിക്കുക

*Score one point if performed correct.* Score (0 - 1) L

**CLOSE YOUR EYES**

**കണ്ണുകൾ അടയ്ക്കുക**

13 *Comprehension (3-stages): Give the subject a piece of paper and tell him to* **take this paper in your right / left hand. Fold the paper in half. Then put it on the floor.**

ഈ കടലാസ് വലതു / ഇടതു കയ്യിൽ എടുക്കുക നേർ പകുതി മടക്കുക എന്നിട്ട് അത് തറയിൽ വയ്ക്കുക.

*Score one point for each correctly performed step* Score (0 - 3) L

14 *Comprehension (complex grammar): Request the subject to* **obey the following commands.**

ഈ നിർദ്ദേശങ്ങൾ പാലിക്കുക Score (0 - 2) L

| | |
|---|---|
| **point to the ceiling then the door** | തട്ടിലേയ്ക്കു ചൂണ്ടിയ ശേഷം വാതിലിലേയ്ക്കു ചൂണ്ടുക |
| **point to the door after touching the bed/desk** | മേശയോ, കിടക്കയോ തൊട്ടിട്ട് കതകിലേയ്ക്കു ചൂണ്ടുക. |

*Score one point only if entire command is performed correctly .*

15 *Repetition (single words): Ask the subject to* **repeat each of these words after me.**

*Score one point for each correct repetition. Allow only one repetition* Score (0 - 3) L

ഞാൻ പറഞ്ഞു കഴിയുമ്പോൾ നിങ്ങൾ അത് ആവർത്തിക്കുക

| | |
|---|---|
| **Brown** | വ്രണം |
| **Conversation** | കാലവർഷം |
| **Articulate** | അറകുറാം |

16 *Repetition (phrases): Ask the subject to* **repeat each of these phrases after me.**

ഞാൻ പറയുന്ന വാചകങ്ങൾ നിങ്ങൾ ആവർത്തിക്കുക.

*Score one point for each correct repetition. Allow only one repetition.*

**No ifs, ands or buts** Score (0 - 1) L

അവർ ഇവിടെ വന്നിരുന്നുവെങ്കിൽ എനിക്ക് അവരെ കാണാമായിരുന്നു

**The orchestra played and the audience applauded** Score (0 - 1) L

ഒഴിവുകഴിവുകളൊന്നും പറയരുത്.

17 *Reading (regular): Ask the subject to* **read each of these words aloud** *and show him/her the following five words.* Score (0 - 1) ☐ L

താഴെ പറയുന്നവ ഉറക്കെ വായിക്കുക.

| | |
|---|---|
| **SHED** | ശബ്ദം |
| **WIPE** | വെപ്പ് |
| **BOARD** | ബോധം |
| **FLAME** | ഫ്രെയിം |
| **BRIDGE** | ഭൃത്യൻ |

18 *Reading (irregular): Ask the subject to* ***read each of these words aloud*** *and show him/her the following five words.* Score (0 - 1) ☐ L

താഴെ പറയുന്ന വാക്കുകൾ ഉറക്കെ വായിക്കുക.

| | |
|---|---|
| **SEW** | സഞ്ചി |
| **PINT** | സുന്ദരി |
| **SOOT** | ഫലിതം |
| **DOUGH** | ഉത്കണ്ഠ |
| **HEIGHT** | ബ്രഹ്മാണ്ഡം |

19 *Writing: Ask the patient to* **make up a sentence and write it down in the space below.** *If stuck, suggest a topic e.g. weather, journey. Score one point if the sentence has a correct subject and verb and is meaningful.*

ഒരു വാചകം താഴെ എഴുതുക. Score (0 - 1) ☐ L

_____

_____

20 *Now to check delayed recall ask the subject* **Tell me the name and address that I had told you and you had practiced at the beginning of the test**. *Record points, scores and errors as for question 6 in the space provided in question 5 on page 2.*

നേരത്തെ, ഞാൻ പറഞ്ഞു തന്ന പേരും, വിലാസവും നിങ്ങൾക്ക് ഓർത്ത് പറയുക.

**VISUOSPATIAL ABILITIES**

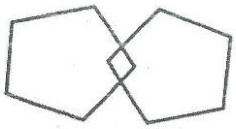
21 *Overlapping pentagons and Wire Cube: Show the subject the two figures in the next page and* ask him/her to **copy these figures in the space provided.** Score as follows

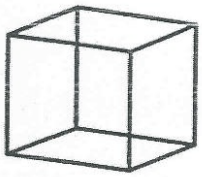
*For the Overlapping pentagons, score one point if both figures have 5 sides and overlap.*

*For the Cube, score one point if the figure is correct.*

താഴെ കാണിച്ചിട്ടുള്ള ചിത്രം ഒന്നു വരച്ചു കാണിക്കാമോ?

Score (0 - 1)





Score (0 - 1)

22 *Clock : Ask the patient to* **draw a clock-face with all the numbers and the hands at 5:10**

*Score 1 point each for- correct circle, numbering of the clock-face & position of the hands*

ഒരു ഘടികാരത്തിൽ /ക്ലോക്കിൽ എല്ല അക്കങ്ങളും വരച്ച്, അതിൽ 5:10 എന്ന സമയം വരച്ച് കാണിയ്ക്കുക.

Score (0 - 3)

23 ***CHECK*** *: Have you recorded the delayed recall for name and address in Q 5 on page 2?*

**OVERALL SCORES :** **MMSE** (0 - 30)

(Enter the sum of the scores in the boxes on each side of the vertical line) +

**ACE** (0 - 100)

**VLOM Ratio**

| V | + | Sum of L |
|---|---|---|
| O | + | M |

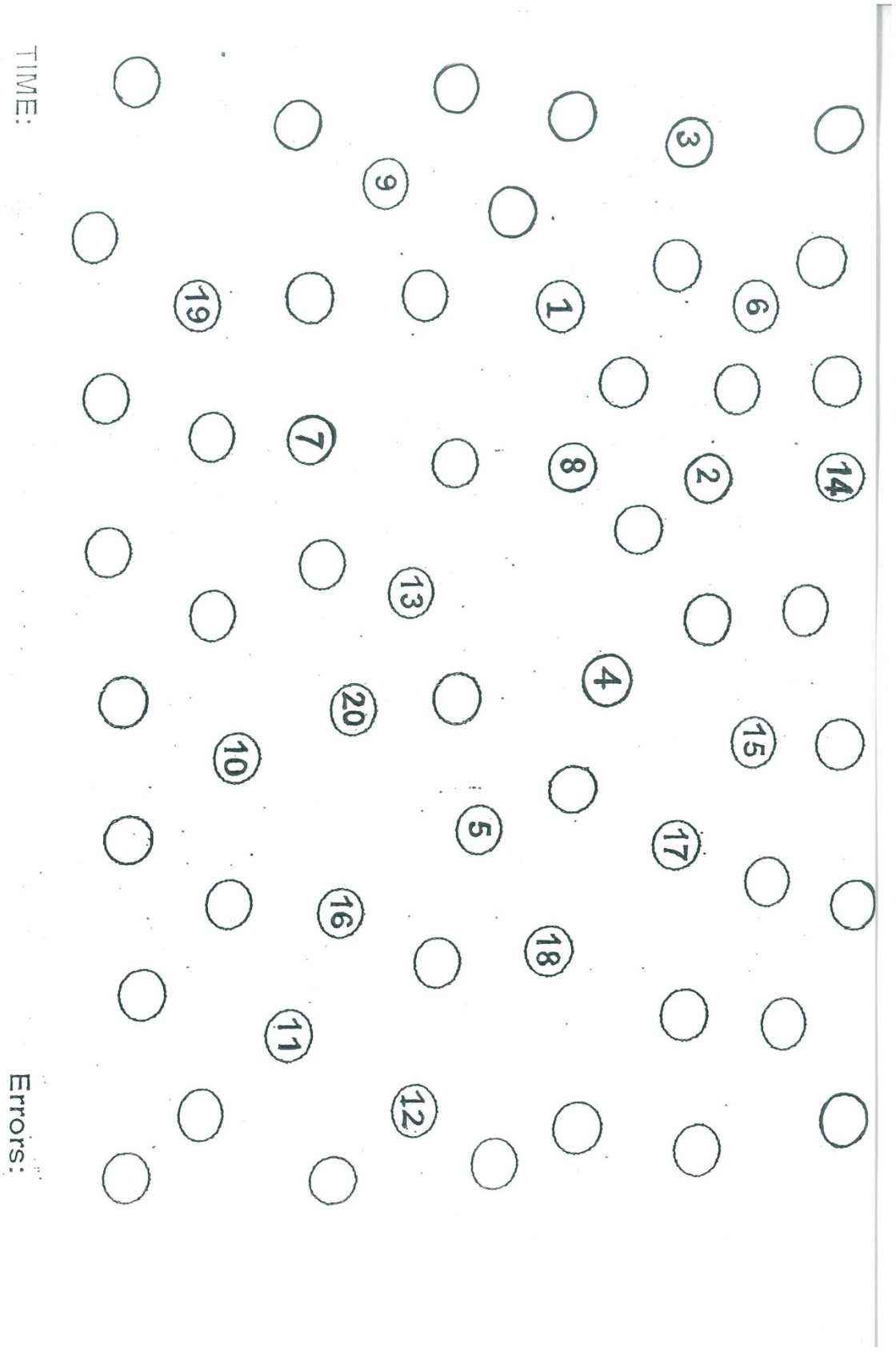
→ → 

| If < 2.2 FTD | If > 3.2 AD |
|---|---|



Reference: *Int J Geriatr Psychiatry* 2004;19:1188-1194.

**TRAIL MAKING TEST - A**



**TRAIL MAKING TEST - B**

# DIGIT SPAN TEST – FORWARD AND BACKWARD

## WMS - R: DIGIT SPAN

| | | | |
|---|---|---|---|
| NAME: | | HOSP. NO.: | |
| D.O.B.: | | TESTING DATE(S): | |
| AGE: | | EDUCATION (YEARS): | |
| Handedness: | | Proficient Language: | |

Instructions for Digits Forward:

Say I am going to say some numbers. Listen carefully, and when I am through say them right after me.

ഞാൻ ചില അക്കങ്ങൾ പറയും. ശ്രദ്ധിച്ചു കേൾക്കണം. ഞാൻ വായിച്ചു കഴിഞ്ഞാലുടൻ താങ്കൾ അത് ഏറ്റു പറയണം.

Read the digits at the rate of one per second. Administer both trials of each item, even if the first trial is passed. Discontinue after failure on both trials of any item. Score 1 point for each trial passed. If subject is unable to repeat 3 digits, go back and test on 2 digits.

| DIGIT FORWARD | | | | | |
|---|---|---|---|---|---|
| Span | Trial I | P / F | Trial II | P/F | Score |
| 2 | 4-7 | | 1-8 | | |
| 3 | 6-2-9 | | 3-7-5 | | |
| 4 | 5-4-1-7 | | 8-3-9-6 | | |
| 5 | 3-6-9-2-5 | | 6-9-4-7-1 | | |
| 6 | 9-1-8-4-2-7 | | 6-3-5-4-8-2 | | |
| 7 | 1-2-8-5-3-4-6 | | 2-8-1-4-9-7-5 | | |
| 8 | 3-8-2-9-5-1-7-4 | | 5-9-1-8-2-6-4-7 | | |

Total Forward (Max. = 12): ____

Instruction for Digits Backward:

Say Now I am going to say some more numbers, but this time when I stop I want you to say them backwards. For example, if I say 2-8-3, what would say?

ഇപ്പോൾ ഞാൻ ചില അക്കങ്ങൾ പറയും. ശ്രദ്ധിച്ചു കേൾക്കണം. ഞാൻ വായിച്ചു കഴിഞ്ഞാലുടൻ താങ്കൾ അത് എതിർക്രമത്തിൽ ( പിറകിൽ നിന്ന് മുന്നോട്ട് എന്ന രീതിയിൽ ) ഏറ്റു പറയണം.

ഉദാ: ഞാൻ 2-8-3 എന്ന അക്കങ്ങൾ പറഞ്ഞാൽ താങ്കൾ എങ്ങനെ ഏറ്റു പറയും?

If the subject responds correctly, say that's right

ശരിയാണ് എന്ന് പറയണം

and proceed to Trial I. If the subject fails the example, say no, I said 2-8-3, so to say them backwards you would need to say 3-8-2. Now try these numbers. Remember you are to say them backwards. Ready? 1-5-8.

അല്ല. ഞാൻ പറഞ്ഞത് 2-8-3 എന്നാണ് അത് എതിർ ക്രമത്തിൽ പറഞ്ഞാൽ 3-8-2 എന്നാവും. ഇനി ഈ അക്കങ്ങൾ ശ്രദ്ധിക്കൂ. എതിർ ക്രമത്തിലാണ് പറയേണ്ടത് എന്ന് ഓർക്കുക. റെഡി?

1-5-8

Give no help on this second example or any of the trials that follow. Whether the subject passes or fails with the second example, proceed to Trial I. Read the digits at a rate of one per second. Administer both trials of each item, even if the first trial is passed. Discontinue after failure on both trials of any item. Score 1 point for each trial passed.

| DIGIT BACKWARD | | | | | |
|---|---|---|---|---|---|
| Span | Trial I | P / F | Trial II | P/F | Score |
| 2 | 5-1 | | 3-8 | | |
| 3 | 4-9-3 | | 5-2-6 | | |
| 4 | 3-8-1-4 | | 1-7-9-5 | | |
| 5 | 6-2-9-7-2 | | 4-8-5-2-7 | | |
| 6 | 7-1-5-2-8-6 | | 8-3-1-9-6-4 | | |
| 7 | 4-7-3-9-1-2-8 | | 8-1-2-9-3-6-5 | | |

Total Backward (Max. = 12): ____

Overall Total (Max. = 24): ____

Highest number of digits for which score on Digits Forward was 1 = DIGIT SPAN FORWARD = ____

Highest number of digits for which score on Digits Backward was 1 = DIGIT SPAN BACKWARD = ____

SCTM&ST, WMS-R Digit Span, rev July 2000

Page 1 of 1

## WISCONSIN CARD SORTING TEST

TRN.....

NAME.....

WCST

DATE.....

| RULES / RESPONSES | | | | | | |
|---|---|---|---|---|---|---|
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| | |
|---|---|
| Errors | |
| Perseverations | |
| TOTAL | |

categorys passed-

# FRENCHAY'S APHASIA SCREENING TEST (FAST)

## FRENCHAY'S APHASIA SCREENING TEST
## ADMINISTRATION FORM

### MATERIALS REQUIRED

ചിത്രവും അതിന്റെ കൂടെയുള്ള വായന കാർഡുകളും, പെൻസിൽ, പേപ്പർ, സ്റ്റോപ്പ് വാച്ച്/സെക്കന്റ് സൂചിയുള്ള വാച്ച്.

ശ്രദ്ധിക്കുക: രോഗി കണ്ണട ഉപയോഗിക്കുന്നുയെങ്കിൽ ധരിച്ചിട്ടുണ്ടോ എന്നു പരിശോധിക്കുക. രോഗിക്ക് നിങ്ങൾ പറയുന്നത് വ്യക്തമായി കേൾക്കാം എന്നു ഉറപ്പുവരുത്തുക.

### Comprehension:

രോഗിയെ നദിയുടെ കാർഡ് കാണിക്കുക, എന്നിട്ട് പറയുക.

ചിത്രത്തിൽ നോക്കി പറയുന്നത് വളരെ ശ്രദ്ധയോടെ കേട്ടിട്ട് സാധനങ്ങൾ ചൂണ്ടിക്കാണിക്കുക.

ശരിയായ ഒരോപ്രതികരണത്തിനും 1 പോയിന്റ് നൽകുക. നിർദ്ദേശങ്ങൾ ആവർത്തിക്കേണ്ടി വന്നാൽ തെറ്റായി അടയാളപ്പെടുത്തുക. സഹായം കൂടാതെ സ്വയം തെറ്റുകൾ തിരുത്തുകയാണെങ്കിൽ ശരിയായി അടയാളപ്പെടുത്തുക.

സ്കോർ പരിധി **0 - 10**

### (a) River Scene

പരിശീലനം: നദി ചൂണ്ടികാണിക്കുക.

ഇതിനു സ്കോർ നൽകേണ്ടതില്ല. ചെയ്യേണ്ട കാര്യം എന്താണെന്നു മനസിലാകുന്നതുവരെ നിർദ്ദേശം ആവർത്തിക്കുക

1. ബോട്ട് ചൂണ്ടിക്കാണിക്കുക
2. ഉയരംകൂടിയ വൃക്ഷം ചൂണ്ടിക്കാണിക്കുക
3. ആളിനേയും ആടിനേയും ചൂണ്ടിക്കാണിക്കുക
4. മനുഷ്യന്റെ ആളിന്റ ഇടതുകാലും പിന്നെ കഷലും ചൂണ്ടിക്കാണിക്കുക
5. പാലത്തിനരികിൽ ഉള്ള താറാവിനെ ചൂണ്ടിക്കാണിക്കും മുമ്പേ മദ്ധ്യഭാഗത്തുള്ള കുന്ന് മല കാണിച്ചുതരുക.

### b) Shapes

പരിശീലനം: (വൃത്തം ചൂണ്ടിക്കാണിക്കുക)

(രോഗിക്ക് മനസ്സിലാവും വരെ ആവർത്തിക്കുക)

1. സമചതുരം ചൂണ്ടിക്കാണിക്കുക
2. കോൺ ചൂണ്ടിക്കാണിക്കുക
3. ആവും സമചതുരവും ചൂണ്ടിക്കാണിക്കുക
4. സമചതുരവും, കോണും അർദ്ധവൃത്തവും ചൂണ്ടിക്കാണിക്കുക
5. കന്നിനെഷോലെ (മല) തോന്നുന്നതും അർദ്ധചന്ദ്രനെഷോലെ തോന്നുന്നതും ചൂണ്ടിക്കാണിക്കുക.

### Expression

രോഗിയെ നദിയുടെ ചിത്രം കാണിച്ചിട്ടു പറയുക, ഈ ചിത്രത്തിൽ കാണുന്ന കാര്യങ്ങൾ കഴിയുന്നതുപോലെ വിവരിക്കുക.

സ്കോർ അളവ്/പരിധി 0-5

**0 -** ഒരു വസ്തുവിന്റെയും പേര് വ്യക്തമായി പറയാൻ കഴിയുന്നില്ല.

**1 -** 1-2 വസ്തുക്കളുടെ പേരു പറഞ്ഞു.

**2 -** 3-4 വസ്തുക്കളുടെ പേരു പറഞ്ഞു.

**3 -** 5-7 വസ്തുക്കളുടെ പേരു പറഞ്ഞു.

**4 -** 8-9 വസ്തുക്കളുടെ പേരു പറയുകയോ വാക്യങ്ങൾ, വാചകങ്ങൾ ഉപയോഗിക്കുകയോ ചെയ്യുക എന്നാൽ അസാധാരണമായ പ്രകടനം (ഉദാഹരണം സംസാരത്തിൽ സ്ഫുടതകുറവ്, ഉചിതമല്ലാത്ത വ്യഞ്ജനങ്ങൾ)

**5 -** വാചകങ്ങളും വാക്യങ്ങളും ഉപയോഗിക്കുക 10 വസ്തുക്കളുടെ പേര് പറയുക, സ്വാഭാവികമായ പ്രകടനം

ചിത്രം മാറ്റിയതിനുശേഷം, ഇനി നിങ്ങൾ വ്യത്യസ്തമായ ഒരു കാര്യം ചെയ്യാൻ പോകുകയാണെന്നു രോഗിയെ അറിയിക്കുക. അതിനുശേഷം ഒരു മിനിറ്റ് സമയത്തിനുള്ളിൽ എത്രത്തോളം മൃഗങ്ങളുടെ പേര് പറയാമോ അത്രത്തോളം പറയാൻ പറയുക. രോഗി സംശയം പറയുകയാണെങ്കിൽ വളർത്തുമൃഗങ്ങളും, വന്യമൃഗങ്ങളും ഉൾപ്പെടുന്ന ഏത് തരത്തിലെയും മൃഗങ്ങളെയും പറയാം എന്നു വിശദീകരിക്കുക. കൂടാതെ കുറച്ച് മുമ്പേ ചിത്രത്തിൽ കണ്ടവയെ മാത്രമായി പറയരുതെന്നും അറിയിക്കുക. രോഗി ആദ്യത്തെ മൃഗത്തിന്റെ പേര് പറഞ്ഞു തുടങ്ങുമ്പോൾ തന്നെ സമയം നോക്കേണ്ടതാണ് 60 സെക്കന്റ് അനുവദിക്കുക.

സ്കോർ പരിധി **0-5**

**0** - ഒന്നും പറഞ്ഞില്ല
**1** - 1-2 പേരുകൾ പറഞ്ഞു
**2** .- 3-5 പേരുകൾ പറഞ്ഞു.
**3** - 6-9 പേരുകൾ പറഞ്ഞു.
**4** - 10-14 പേരുകൾ പറഞ്ഞു.
**5** - 15 അല്ലെങ്കിൽ അതിൽ കൂടുതൽ.

### Reading

രോഗി വായിക്കാൻ ഉപയോഗിക്കുന്ന കണ്ണട ധരിച്ചിട്ടുണ്ടോ എന്ന് സ്ഥിരീകരിക്കുക. രോഗിയെ നദിയുടെ ചിത്രവും വായിക്കുവാനുള്ള ഒന്നാമത്തെ കാർഡും കാണിക്കുക.കാർഡിൽ എഴുതിയിരിക്കുന്ന വാചകം മനസിൽ വായിച്ചിട്ട് (ഉച്ചത്തിൽ അല്ല) അതു ചെയ്തു കാണിക്കാൻ ആവശ്യപ്പെടുക തുടർന്നുള്ള കാർഡും അതേരീതിയിൽ ചെയ്യുക.

സ്കോർ പരിധി **0-5** ശരിയായ പ്രതികരണത്തിന് ഓരോ സ്കോർ നൽകുക.

### Writing

നദിയുടെ ചിത്രം കാണിച്ചിട്ട് പറയുക: ചിത്രത്തിൽ കാണുന്ന കാര്യങ്ങൾ കഴിയുന്നിടത്തോളം വിശദീകരിച്ച് എഴുതുക. രോഗിക്ക് മനസിലാകുന്നില്ലെങ്കിൽ, ചിത്രത്തിൽ കാണുന്ന എന്തെങ്കിലും എഴുതാൻ ആവശ്യപ്പെടുക. എഴുതാൻ ഉപയോഗിക്കുന്ന കൈയ്ക്ക് വൈകല്യം സംഭവിച്ചിട്ടുണ്ടെങ്കിൽ മറ്റേ കൈ ഉപയോഗിച്ച് എഴുതാൻ ശ്രമിക്കാൻ രോഗിയോട് ആവശ്യപ്പെടേണ്ടതാണ്. രോഗി എഴുത്ത് നിർത്തുകയാണെങ്കിൽ എഴുതുവാനുള്ള പ്രോത്സാഹനം നൽകേണ്ടതാണ്.

പരമാധി 5 മിനിറ്റ് സമയം അനുവദിക്കുക.

**0-** എഴുതുവാനുള്ള ശ്രമം നടത്തിയെങ്കിലും അനുയോജ്യമായോ/ വ്യക്തമായോ വാക്കുകൾ ഉപയോഗിക്കാതിരിക്കുക.

**1-** അനുയോജ്യമായ 1-2 വാക്കുകൾ എഴുതുക.

**2 -** 3 വസ്തുക്കളുടെ പേര് / രണ്ടോ മൂന്നോ വസ്തുക്കളുടെ പേര് ഉൾപ്പെടുത്തിയുള്ള വാക്യം.

**3 -** അക്ഷരതെറ്റ് വരുത്താതെ 4 വസ്തുക്കളുടെ പേര് എഴുതുക. അല്ലെങ്കിൽ 4 വസ്തുക്കളുടെ പേര് ഉൾപ്പെടുത്തി രണ്ടോ, മൂന്നോ വാക്യങ്ങൾ എഴുതുക.

**4 -** 5 വസ്തുക്കളുടെ പേര് ഉൾപ്പെടുത്തി വാചകത്തിലും, വാക്യത്തിലും എഴുതുക. എന്നാൽ സാധാരണമായ പ്രകടനമായി പരിഗണിക്കാനാകില്ല ഉദാഹരണം ആളുകളെയും പ്രവൃത്തികളെയും സംയോജിപ്പിക്കാതെ എഴുതുക.

**5 -** തീർച്ചയായും സാധരണ പ്രകടനം, ഉദാഹരണം വ്യക്തികളെയും അവരുടെ പ്രവൃത്തികളെയും സംയോജിപ്പിച്ചുള്ള വാചകം.

### Interpretation

താഴെപറയുന്ന കട്ട്-ഓഫ് സ്കോറിൽ കുറവാണ് രോഗിയുടെ സ്കോർ എങ്കിൽഅത് അഫേസിയയെ സൂചിപ്പിക്കുന്നു. (അത്തരം വ്യക്തികളെ കൂടുതൽ രോഗനിർണ്ണയത്തിനായി Speech Therapist ന്റെ അടുത്ത് അയക്കേതാണ്)

| Age | Raw Score |
|---|---|
| Up to 60 | 27 |
| 61 + | 25 |

# LOGICAL MEMORY – WECHSLER MEMORY SCALE- REVISED

## WMS – R: Logical Memory Test

MALAYALAM

| | |
|---|---|
| NAME: _____ | HOSP. NO.: _____ |
| D.O.B.: _____ | TESTING DATE(S): _____ |
| AGE: _____ | EDUCATION (YEARS): _____ |
| Handedness: | Proficient Language: |

Tell the subject ഞാൻ ഒരു കഥ വായിക്കുവാൻ പോകുകയാണ്. ശ്രദ്ധയോട് കേൾക്കണം. ഓർത്ത് വച്ചേക്കണം.അതിനെക്കുറിച്ച് പിന്നീട് ചോദിക്കും. Now read Story-I slowly and clearly only ONCE. Ask the subject to മുമ്പേ പറഞ്ഞ കഥ കഴിയുന്നത്ര ഓർക്കുന്നത് എന്നോട് പറയുക. Record response in the Imm. Recall space. Do the same for Story-II. Test for delayed recall (after passage of appropriate time) by asking the subject മുമ്പേ പറഞ്ഞ രണ്ടു കഥകളും ഓർമ്മയുണ്ടോ? അത് രണ്ടും ഓരോന്നായി പറയാമോ? If the subject is unable to remember the story give the appropriate cue.

### Story-I

തെക്കൻ / പറവൂരിൽനിന്നുള്ള / ആശാകുമാരി / ഒരു കമ്പനി ആഫീസിൽ / പ്യൂണായി / തൊഴിൽ ചെയ്യുന്നു. / തലേ രാത്രി / ചന്തയിൽ നിന്ന് മടങ്ങുമ്പോൾ / തന്നെ തടഞ്ഞു നിർത്തി / അൻപതു രൂപ / തട്ടിയെടുത്തു / എന്ന് ടൗൺ പോലീസ് / സ്റ്റേഷനിൽ / അവൾ പരാതി നൽകി / അവൾക്ക് നാല് / ചെറിയ കുട്ടികളുണ്ട് /വാടക / നൽകിയിട്ടില്ല / രണ്ടു ദിവസമായി / അവൾ ആഹാരം കഴിച്ചിട്ടില്ല / അവളുടെ കഥ കേട്ട് മനസ്സലിഞ്ഞ് / പോലീസുകാർ /അവൾക്ക് / കൂറച്ച് പണം ശേഖരിച്ച് നൽകി. /

/24

### Imm. Recall

_____

_____

_____

_____

_____

_____

_____

/24

### Del. Recall ( minutes)

Cue given: Yes / No

Cue: ഈ കഥ ഒരു സ്ത്രീയുടെ പൈസ മോഷ്ടിക്കപ്പെടുന്നതിനെക്കുറിച്ചായിരുന്നു

_____

_____

_____

_____

_____

_____

_____

PTO

Page 1 of 2

SCTMST, WMS-R Logical Memory, rev July 2000

Story II

ശ്രീലങ്കൻ / യാത്രക്കപ്പലായ / 'സമുദ്ര' /കന്യാകുമാരിയിലേക്ക് / തിങ്കളാഴ്ച / രാത്രിയിൽ / പാറയിൽതട്ടിതകർന്നു / ഭയങ്കര/ മഞ്ഞും കൊടുംകാറ്റും ആയിട്ട് കൂടിയും / ഇരുട്ടത്ത് / പതിനെട്ട് / സ്ത്രീകളടക്കം / അറുപത് / യാത്രക്കാരെയും / നടുകടലിൽ / തിരമാലകളിൽ തടികണക്കെ / ആടിയുലഞ്ഞിരുന്ന / ബോട്ടുകളിൽ / രക്ഷപ്പെടുത്തി / പിറ്റേന്നു രാവിലെ / അവരെ ഇന്ത്യൻ ആവിക്കപ്പലിൽ / തുറമുഖത്ത് / കൊണ്ടുവന്നു.

Imm. Recall /23

Del. Recall ( minutes) /23

Cue given: Yes / No

Cue: ഈ കഥ കൊടുങ്കാറ്റിൽ പെട്ട ഒരു കപ്പലിനെ കുറിച്ചാണ്

Immediate Recall Total Score:

Delayed Recall Total Score:

# VISUAL OBJECT AND SPACE PERCEPTION BATTERY (VOSP)

**Position Discrimination**

| Sl.No | Right option | |
|---|---|---|
| 1 | R | |
| 2 | L | |
| 3 | L | |
| 4 | R | |
| 5 | R | |
| 6 | L | |
| 7 | L | |
| 8 | R | |
| 9 | L | |
| 10 | L | |
| 11 | L | |
| 12 | R | |
| 13 | L | |
| 14 | R | |
| 15 | L | |
| 16 | R | |
| 17 | R | |
| 18 | R | |
| 19 | L | |
| 20 | L | |
| **Total Score** | | |

**Cube Analysis**

| Sl.No | Right option | |
|---|---|---|
| . | 3 | |
| . | 3 | |
| 1 | 6 | |
| 2 | 5 | |
| 3 | 5 | |
| 4 | 4 | |
| 5 | 6 | |
| 6 | 9 | |
| 7 | 9 | |
| 8 | 8 | |
| 9 | 8 | |
| 10 | 10 | |
| **Total Score** | | |

# INSTITUTIONAL ETHICS COMMITTEE CLEARANCE

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
*(An Institute of National Importance under Govt. of India)*
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

## Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1287/OCTOBER-2018

27.11.2018

**Dr. Kshiteeja Jain**
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Kshiteeja Jain,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "COGNITIVE OUTCOME FOLLOWING BILATERAL SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE: A COMPARATIVE OBSERVATIONAL STUDY IN THE INDIAN POPULATION (IEC/1287)" on 26th October, 2018.

**The following documents were reviewed:**

*Original submission*

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Informed Consent Form in English and Malayalam for patient with DBS*
7. *Informed Consent Form in English and Malayalam for patient on medical management*
8. *Patient Information Sheet in English and Malayalam*
9. *CV of Principal Investigator and Co-Principal* Investigators

*Revised submission*

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST date 17.11.2018 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Informed Consent Form in English and Malayalam for patient with PD and DBS*
7. *Informed Consent Form in English and Malayalam for patients with PD on medical management*
8. *Informed Consent Form in English and Malayalam*
9. *Patient Information Sheet in English and Malayalam*
10. *CV of Principal Investigator and Co-Principal Investigators*

**The following members of the Ethics Committee were present at the meeting held on 26th October, 2018 at G. Parthasarathi Board Room, AMCHSS, SCTIMST**

| SL. No. | Member Name | Highest Degree | Gender | Scientific /Non Scientific | Affiliation with Institution(s) |
|---|---|---|---|---|---|
| 1. | Dr. R V G Menon | M Tech, PhD | Male | Lay Person (Chairman) | No |
| 2. | Dr. Rema M. N | MD | Female | Basic Medical Scientist | No |
| 3. | Smt. Sathi Nair | MA (English Literature) | Female | Lay Person | No |
| 4. | Dr. Kala Kesavan. P | MBBS, MD | Female | Basic Medical Scientist | No |
| 5. | Dr. Harikrishna Varma PR | Ph.D( Materials Science) | Male | Medical Technology | Yes |
| 6. | Dr. Christina George | MD Psychiatry | Female | Clinician | No |
| 7. | Dr. S S Giri Sankar | LL.M. Ph.D. | Male | Legal Expert | No |
| 8. | Dr. Aneesh V Pillai | BA. LLB (Hons.), LLM, Ph. D, SET (Law) | Male | Legal Expert | No |
| 9. | Mr. Satheesh Chandran | MSW, PGDPM | Male | Lay person/ NGO/ Social Scientist | No |
| 10. | Dr. Harikrishnan S | MD, DM (Cardiology) DNB (Cardiology) | Male | Clinician | Yes |
| 11. | Dr. Anand Kumar A | MD, DM | Male | Clinician | No |
| 12. | Dr. V. Raman Kutty | M D, M Phil, M P H | Male | Health Sciences Expert/Clinician | Yes |
| 13. | Dr. Mala Ramanathan | PhD | Female | Social Scientist (Member Secretary) | Yes |

**IEC Decision**

The IEC approved the conduct of the study in the present form.

**Remarks:**
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

***Mala Ramanathan***
*Member Secretary, IEC*

# PLAGIARISM CHECK

## Plagiarism Checker X Originality Report

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Cognitive Outcome Following Bilateral Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A Comparative Observational Study in the Indian Population