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## Pre- and Post- GPi DBS Neuropsychological Profiles in a Case of X-Linked Dystonia-Parkinsonism

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### Abstract

We present the pre to post bilateral globus pallidus interna (GPi) deep brain stimulation neuropsychological profiles of a 69-year-old patient with a 12-year history of X-linked dystonia-Parkinsonism (XDP). Pre-operative cognitive function was impaired in almost all domains and this impaired performance was not dependent on his medications. Following DBS, changes in neuropsychological functioning were examined using Reliable Change Indices and standardized z-score comparisons. Results showed reductions in processing speed in the context of stable performance in language and visuospatial domains. Postoperative improvements occurred on a cognitive screening measure, verbal memory, and a test of problem-solving skills. This is the first report on an individual with XDP who was cognitively impaired, but had good outcome following GPi bilateral stimulation to treat debilitating motor symptoms. The possible mechanisms for his stable cognitive performance include the target of his DBS, reduced medication dosage, and improvement in dystonia that may in turn have reduced patient's pain.

### Keywords

XDP; Lubag; X-linked dystonia-Parkinsonism; Neuropsychological assessment; Dystonia; Parkinson disease

## INTRODUCTION

“Lubag syndrome”, or X-linked recessive dystonia Parkinsonism (XDP), is a neurodegenerative condition that primarily impacts men with maternal ancestry from the Island of Panay in the Philippines (Evidente et al., 2002; Lee, Pascasio, Fuentes, & Viterbo, 1976). It is one of the monogenic primary dystonias (Bruggemann & Klein, 2010), and is caused by mutation in the TATA-binding protein-associated factor-1 (TAF1). XDP is a very rare condition with a prevalence rate of 0.34 per 100,000 in the general population of the Philippines (Lee et al., 2002). Age of onset is typically between 12 and 48 years (Lee, Kupke, Caballar-Gonzaga, Hebron-Ortiz, & Muller, 1991). The first symptom is usually

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dystonia, such as blepharospasm, torticollis, and distal limb dystonia. Some individuals first show an action or resting tremor, and have been misdiagnosed with Parkinson's disease (PD) or essential tremor (Evidente et al., 2002). Pharmacological treatment response is generally poor. Levodopa typically fails to improve dystonia symptoms and may even exacerbate them, with a combination of benzodiazepines and anticholinergic agents mildly assisting in the early phases (Evidente et al., 2002). Deep brain stimulation (DBS) surgeries, however, may be beneficial, for there are two reports of motor symptom improvement with pallidal stimulation in patients with XDP (Evidente et al., 2007; Martinez-Torres et al., 2009). However, neither case report discusses pre- or post-surgery cognitive changes associated with this surgery. This is the current focus of the present case report.

Cognitive functioning of patients with XDP has not been extensively described in the literature, and there does not seem to be a consensus in terms of an expected cognitive profile. However, it has been reported that patients with XDP show severe atrophy of the caudate and putamen late in the disease course (Lee et al., 2002). As atrophy of the caudate has been often associated with cognitive deficits in Huntington's disease (Peinemann et al., 2005), one may speculate that patients with XDP show executive dysfunction similar to those reported in Huntington's disease.

DBS is an invasive procedure in which a stimulating lead is placed in one of multiple brain targets, with stimulation then applied that is tailored to individual patient's needs. Although the mechanism of therapeutic effects of DBS has not been fully elucidated, it appears to disrupt abnormal neuronal activities of the affected brain structures (Okun et al., 2007). Stimulator placement in the subthalamic nucleus (STN) or the globus pallidus internus (GPi) is most effective for individuals with PD. The STN site is typically chosen for midline symptoms, with the GPi associated with dyskinesia (Anderson, Burchiel, Hogarth, Favre, & Hammerstad, 2005). Although alleviation of motor effects following DBS is well documented, there are reports of suboptimal non-motor side effects (Daniele et al., 2003; Limousin et al., 1998; Okun et al., 2009). A total of 5% to 33% of individuals reportedly experience changes in cognitive function or mood following DBS (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001; Limousin et al., 1998; Pinter et al., 1999). Cognitive decline appears to be most prominent in the domains that are subserved by the frontal lobe and its network, with declining performance on measures requiring verbal fluency and inhibition, word recall, and processing speed (Daniele et al., 2003; Mikos, Zahodne, Okun, Foote, & Bowers, 2010; Okun et al., 2009; York et al., 2008; Zahodne et al., 2009). Mood difficulties can increase (Herzog et al., 2003; Houeto et al., 2002), or decrease (Daniele et al., 2003; Funkiewiez et al., 2003). Very little is known about how cognitively compromised patients respond to stimulation, although there is evidence that stimulation to the GPi may have less cognitive impact relative to STN placement (Okun et al., 2009).

In the current paper we present a case report of a cognitively compromised Filipino gentleman with XDP who recently underwent DBS of the GPi (Oyama et al., 2010). The patient, named here as "RA", was initially discussed in 2009 during our report on his neuropsychological profile (Howe, Kellison, Fernandez, Okun, & Bowers, 2009). At the time of those pre-operative evaluations in 2008, RA was found to be markedly cognitively impaired. Specifically, he was impaired in recent memory for verbal material, visuospatial skills, language, processing speed, abstract reasoning, and problem solving. Although cognitive impairment is commonly used as exclusion criteria from DBS, RA was approved for surgery due to the severity of his motor symptoms. RA is therefore a unique individual for pre- to post-surgery DBS comparison. We compare the pre cognitive profile reported by Howe et al. (2009) to RA's recent post-operative cognitive and emotional profiles 1 year following bilateral DBS implantation (27 months after the initial evaluation).

## CASE PRESENTATION

At the time of our post-operative evaluation, RA was a 69-year-old right-handed bilingual Filipino gentleman with a 12-year history of XDP and status post bilateral globus pallidus internus deep brain stimulation (GPi DBS) implantation (the left implantation followed by the right, 14 days apart). The current 1 year post-DBS neuropsychological assessment was his third assessment, with his first two pre-operative testing sessions reported previously (see Howe et al., 2009). RA was born in the island of Panay in the Philippines. He obtained a bachelor's degree in the Science of Commerce in the Philippines. He reported acquiring English after he came over to the United States, where he has resided since the age of 34.

### Symptom Progression (Pre-DBS)

RA presented at age 57 with a pill-rolling tremor of his right hand. He then developed tremor that included his entire right arm, dystonic posturing of his right arm, and stiffness of his right leg when walking. Two years later, constant involuntary movement of his hands and odd posturing of his upper right extremity developed. He was initially misdiagnosed clinically with PD, but was later confirmed to have XDP following genetic testing. At the time of the pre-DBS neuropsychological evaluations at age 67, his physical symptoms included (1) dystonia, (2) tremor, (3) constant right hand dyskinesias, (4) rigidity of the neck, bilateral upper extremities, and face, (5) bradykinesia, (6) pain in both wrists, (7) numbness, tingling, and mild aching in his feet, (8) freezing with occasional falling, (9) occasional choking while eating, (10) night-time drooling, and (11) slightly excessive salivation. Cognitively, he complained of memory difficulties, decreased attention, decreased concentration, and problems with speech. Affectively, he reported apathy and decreased initiative of a recent onset. His wife reported observing brief episodes of agitation and irritability.

RA's previous two neuropsychological evaluations (Howe et al., 2009) were conducted 27 months prior to the current evaluation. The first evaluation noted concerning cognitive impairment across multiple domains, including processing speed, mental flexibility, verbal episodic memory, language-related tasks (naming and fluency), and problem solving. His medications at the first evaluation were trihexyphenidyl (Artane, 7.5 mg per day), lorazepam (Ativan, 3mg per day), carbidopa/levodopa immediate-release (25/100 two tablets, three times per day), carbidopa/levodopa sustained-release (50/200 two tablets, three times per day), and ropinirole (12 mg per day). A second evaluation was conducted 6 months later after discontinuing medications with anticholinergic properties (trihexyphenidyl and lorazepam) to confirm that his cognitive performance was not largely compromised by these medications. Performance change was minimal; he continued to perform at impaired levels. Of note, across both evaluations, memory for visually presented stimuli and simple auditory attention were his relative strengths.

### DBS Surgery

After extensive discussions with the DBS interdisciplinary team, a decision was made to proceed with bilateral GPi DBS to reduce dystonic symptoms. Surgery was without complication. There was no post-operative delirium. See Oyama et al. (2010) for more detailed surgical information.

### Symptom Progression (Post Bilateral GPi DBS)

Per RA and his wife, DBS stimulation improved the majority of his extremity motor symptoms and particularly his tremor and dystonia. Freezing and falling difficulties remained, however. Slurred speech was also problematic.

Endorsed cognitive changes primarily included reduced spontaneous speech and slower responding to questions. RA continued to require assistance with all instrumental activities of daily living (medication management, finances, and all housework); he was unable to self-monitor for successful task completion. Daily events were minimal: frequent sitting and watching television. Basic activities of daily living (bathing, dressing) were reportedly normal.

Apathy and mood were reportedly similar to pre-DBS status; he continued to be described as “not very upbeat” although irritability and aggression towards his wife was reportedly lessened. Physical aggression, extended periods of dysphoric mood, and tearfulness were all denied.

During the time of the post-DBS neuropsychological evaluation, the patient’s wife indicated increased sleep (“sleeps all the time”) but no night-time difficulties such as thrashing/hitting that are associated with a REM sleep disorder. Appetite was reportedly good. He reported a weight gain of five pounds in 3 months. There were no reported changes in olfaction, taste, hearing, or vision.

### Neurological Examinations

Formal post-DBS neurological exams confirmed lessened dystonia, but continued Parkinsonism with frequent freezing, as well as bradykinesia and rigidity. His post-DBS (12 months follow-up) scores on the Unified Parkinson’s Disease Rating Scale were 43 for both on- and off-stimulation compared to 48 (off-medication) and 43 (on-medication) at a preoperative examination. His post-DBS Burke-Fahn-Marsden Dystonia Rating Scale (Burke et al., 1985) while on stimulation was 4.5, compared to 14 preoperatively. The higher scores on those two scales reflect greater motor impairment.

### Medical History

There were no new medical conditions since the DBS surgeries. The patient’s medications at the time of the post-DBS evaluation were lorazepam 1 mg, carbidopa/levodopa 25/100 mg two pills at 8 am, 11 am, 2 pm, 5 pm, and 8 pm, coenzyme Q10 300 mg daily, vitamin B6, vitamin B12, calcium 600 mg, and vitamin D, and multivitamins. Compared to his pre-DBS medications there has been a reduction in antimuscarinic agent (i.e., trihexyphenidyl). In addition, dopaminergic medications (i.e., ropinirole and levodopa) were reduced by 700 mg (41% reduction) in levodopa equivalent daily dose. This was calculated based on a formula (i.e., levodopa equivalent dose = regular levodopa dose  $\times$  1 + levodopa sustained release dose  $\times$  0.75 + ropinirole dose  $\times$  16.6) that is previously recommended and has been used by numerous studies (Hobson et al., 2002).

### Post-DBS Behavioral Observations

RA had moderately stooped posture, and required a U-step walker as well as assistance moving to and from a chair. Facial expression was minimal to nonexistent; he did not smile during casual conversations nor did he show frustration when he was asked over and over to repeat his statement or when he was performing a challenging task. Answers to questions were short and slurred, and he had striking hypophonia that made his answers difficult to understand. He was able to follow simple commands suggesting adequate comprehension. There was no evidence of delusions or hallucinations. RA was cooperative throughout the session and put forth adequate effort on testing. Embedded measures of effort were adequate (e.g., reliable digit span = 7), and his presentation was consistent with his previous evaluations.

## TEST PROTOCOL

*Cognitive screening:* Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), Dementia Rating Scale-2 (DRS-2; Mattis, 2001); *Attention, processing speed, executive monitoring:* Wechsler Adult Intelligence Scale-Third Edition Digit Span, Letter Number Sequencing subtests (WAIS-III; Wechsler, 1997a), Trail Making Test Part A and Part B, Color Trails Test (D'Elia & Satz, 1989); Stroop Color-Word Test (Golden, 1978); *Learning and memory:* Hopkins Verbal Learning Test-Revised (HVLTR, Form 1; Benedict, Schretlen, Groninger, & Brandt, 1998), Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997b). *Language and related skills:* Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), Controlled Oral Word Association Test and Category Fluency (Tombaugh, Kozak, & Rees, 1999), Writing sample (Boston Diagnostic Aphasia Examination; Goodglass & Kaplan, 1983), Ideomotor Praxis. *Visuoperceptual, spatial, and constructional skills:* Benton Facial Recognition Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), Benton Judgment of Line Orientation (Benton et al., 1994), Clock Drawing; Wechsler Abbreviated Scale of Intelligence Block Design subtest (WASI; Wechsler, 1999). *Abstract Reasoning and Problem Solving:* WASI Matrix Reasoning and Similarities (Wechsler, 1999), Wisconsin Card Sorting Test-64 (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000); *Frontal-executive motor:* Luria Motor Sequence; Luria Contrasting & Go-No Go Motor Programmes (Luria, 1976). *Mood status:* Geriatric Depression Scale (GDS; Yesavage, 1988), State-Trait Anxiety Inventory (STAI; Spielberger, 1977, 1983), and Apathy Scale (Marin, Biedrzycki, & Firinciogullari, 1991).

Some measures given during the pre-DBS evaluations were not administered due to time constraints (e.g., WASI Vocabulary, Paced Auditory Serial Addition Test, finger tapping). The Color Trails Test (D'Elia & Satz, 1989) was administered due to the fact that the patient was bilingual and that this test was administered at his second pre-DBS evaluation.

## STATISTICAL CONSIDERATIONS

Table 1 shows pre–post DBS neuropsychological test scores. We discuss the results with use of Reliable Change Index (RCI) adjusted for practice effects on the instruments for which test–retest performance data are available. The RCI method provides us with a tool to identify meaningful difference in test scores, above and beyond what is expected from practice effects, related to age non-disease peers (i.e., Pedraza et al., 2007, for Dementia Rating Scale 2; Dikmen, Heaton, Grant, & Temkin, 1999, for Trail Making Test Part A, Part B, and Boston Naming Test; Basso, Lowery, Ghormley, & Bornstein, 2001, for the Wisconsin Card Sorting Test-64; and Woods et al., 2005, for the HVLTR). Furthermore, to formally quantify the pre-to-post change in each of the cognitive domains, we utilized a composite *z*-score for each domain based on tests' normative published data (see Figure 1).

## RESULTS

### Cognitive performance

MMSE pre–post DBS performance was unchanged. The DRS-2 post-test had a 13-point increase (pre = 113/144; post = 126/144) representing a significant improvement based on reliable change analyses (see Pedraza et al., 2007), yet still scoring at below average levels. Auditory attention span (Digit Span) and working memory (Letter Number Sequencing) remained low average (pre *z*-score composite =  $-0.84$ ; post *z*-score composite =  $-0.50$ ). Processing speed (Trail Making Test-Part A; Color Trail Test 1) declined from baseline with a 50-second increase on the Trail Making Test-Part A (reliable change analyses; Dikmen et

al., 1999). Composite score indicated continued impairment (pre  $z$ -score composite =  $-1.73$ ; post  $z$ -score composite =  $-2.39$ ).

Language performance on formal tests remained at impaired levels (pre  $z$ -score composite =  $-2.17$ ; post  $z$ -score composite =  $-2.10$ ). Visual confrontation naming to line drawings (BNT) was impaired with five more errors relative to pre-surgery score, but did not represent a reliable change per published data (Dikmen et al., 1999). The errors were semantic in nature (e.g., “bread” for pretzel, “boat” for canoe), with 11 items benefiting from phonemic cuing. Verbal fluency was impaired.

The patient’s visuospatial perception (Benton Face Recognition and Judgment of Line Orientation) and visuoconstructional abilities (DRS-2 Construction subscale, clock drawing, WASI Block Design) were within normal limits. There was over half a standard deviation improvement in these domains relative to his previous evaluation (pre  $z$ -score composite =  $-0.89$ , post  $z$ -score composite =  $-0.08$ ).

Learning and retrieval of verbal information (WMS-III Logical Memory and HVLTR) were borderline, with adequate recognition performance at 83% accuracy for the Logical Memory subtest and a five-word increase on the HVLTR recognition trial. The HVLTR recognition performance represents a significant improvement based on Woods et al. (2005). Learning of visual designs was average range (WMS-III Visual Reproduction, immediate recall) with a superior delayed recall and average recognition. Overall, memory retrieval composite scores (pre-DBS composite  $z$ -score =  $-2.04$ ; post-DBS composite  $z$ -score =  $-.89$ ) as well as  $z$ -scores for HVLTR recognition trial (pre-DBS  $z$ -score =  $-2.6$ ; post-DBS  $z$ -score =  $.90$ ) demonstrate that his pre to post abilities improved both in retrieval and recognition of the information.

In terms of executive function, speeded cognitive set-shifting between two colors was average (Color Trails Test 2), but between numbers and letters was impaired (Trail Making Test Part B, four errors) with this time difference representing significant slowing compared to pre-DBS evaluation (Dikmen et al., 1999). Cognitive inhibition (Stroop Color-Word subtest) had three errors but scored in the average range. Regarding verbal reasoning skills, DRS-2 Conceptualization subtest was average, while WASI Similarity subtest was impaired. Visual abstract reasoning (WASI Matrix Reasoning) was borderline. Problem solving was average on the WCST-64 and represented a significant improvement from pre-DBS performances (Basso et al., 2001). Overall, tests associated with speeded executive monitoring skills (pre-DBS composite  $z$ -score of  $-1.90$  to a post-DBS  $z$ -score of  $-2.00$ ) and reasoning skills (pre-composite  $z$ -score =  $-1.12$ ; post composite  $z$ -score =  $-1.07$ ) were stable, while his post Wisconsin Card Sorting Test scores represent a significant and reliable improvement from baseline (pre-DBS composite  $z$ -score of  $-2.85$  to a post-DBS  $z$ -score of  $-0.35$ ).

Frontal motor control was impaired with Luria contrasting movements (five errors) and Luria Go–No–Go motor programs (five errors). Alternate hand movements and motor sequencing task (Fist Edge Palm) were slow but without errors.

### Mood status

The patient’s responses to the measures of depression indicated he was experiencing a moderate level of self-reported symptoms of depression (Geriatric Depression Scale = 10, Beck Depression Inventory = 23). He endorsed clinically significant levels of apathy, situational anxiety (STAI State Anxiety, 89th percentile), and general proneness to anxiety (STAI Trait Anxiety, 74th percentile). Compared to his pre-DBS evaluation, his situational

anxiety was higher this time, but his trait anxiety remained stable. Notably, his apathy levels were significantly increased post-surgery.

## DISCUSSION

This is the first case study reporting on cognitive functioning for an individual with “Lubag” syndrome, or XDP, having bilateral DBS. Despite the potential insult to the brain from the DBS surgery and his pre-DBS diagnosis of dementia, RA’s overall general cognitive abilities as screened by the DRS-2 showed a meaningful improvement in the total score, although they were still below average. He did not show drastic decline in the memory domain. Rather he showed significant improvement in verbal memory, and particularly recognition, that are considered above and beyond practice effects alone. This interpretation is based on our use of published data assessing repeat test performance thereby allowing for RCI analysis. His performance on problem solving (WCST-64) and visuospatial tasks also improved. His continuing deficits remain consistent with a subcortical-frontal disease process; RA demonstrated greater difficulty and variability with tests assessing cortical frontal and frontal-subcortical circuits (i.e., rapid thinking and processing speed, in addition to pre-existing impairment in word retrieval and speech initiation, and abstract reasoning abilities). Although many of these tests are verbal based and he is bilingual, the extent of his verbal retrieval deficits cannot be fully explained by his bilingual status alone. Higher cortical abilities involving abstract reasoning remained despite an improvement on card-sorting task, which is considered a test of concept formation and problem solving. His strengths remain in right hemisphere functions (spatial and perceptual identification and visuospatial construction).

Overall, combined with the improvement in dystonia, we consider these findings a positive outcome of bilateral GPi surgery in an individual with XDP who was significantly cognitively compromised pre-surgery. For individuals who have PD (most often treated with DBS) and are considered intact at baseline, acute confusion and cognitive decline have been reported. Long-lasting cognitive and/or mood decline has been reported in 5% to 33% of patients following DBS (Limousin et al., 1998; Pinter et al., 1999), with this largely associated with reductions in frontal lobe functions such as rapid verbal processing, inhibition, working memory and mental flexibility (Daniele et al., 2003; Okun et al., 2009). For RA, despite his baseline cognitive impairment, he demonstrated stability, if not improvement, in memory functioning, visuospatial skills, and a problem-solving task. Due to the progressive nature of his disease and impact on frontal-subcortical pathway integrity (Lee et al., 1976), his pattern of decline was seen in areas that may have declined despite DBS (i.e., fronto-subcortical pattern). His wife’s concern of reduced facial expression and speech clarity is also unfortunately known to have the least amount of improvement after DBS (Herzog et al., 2003; Okun et al., 2009). His relative benefit in motor symptoms also encourages future consideration of DBS for XDP.

We speculate that there are primarily two potential factors that might have limited the amount of his cognitive decline post-surgery. The first is the target site of his DBS, and the second is the reduction of his medications and pain secondary to the success of his DBS. There are an increasing number of studies indicating that the GPi appears to be a target for minimizing cognitive side effects after DBS. Studies found stable cognition or improvement on aspects of cognition (Halbig et al., 2005; Pillon et al., 2000; Rouaud et al., 2010), lower rates of adverse events involving cognitive decline after GPi compare to STN DBS (Anderson et al., 2005; Rodriguez-Oroz et al., 2005; Volkmann et al., 2001), and less decline specifically in letter fluency post-operatively (Okun et al., 2009). Moreover, it is reported that post-operative mood issues are also more often observed with STN DBS compared to GPi DBS (Anderson et al., 2005). Because mood status can impact one’s

cognitive performance, the impact of DBS on patient's mood is also an important aspect to consider when evaluating cognitive impact of the DBS. It has been suggested that the larger size of the GPi relative to the STN, combined with the fact that multiple fiber pathways of the limbic, motor, and associative circuits of the STN are contained in a compact area which may result in inadvertent stimulation of limbic and associative circuits, may explain why GPi is a safer target, as there is a smaller chance for tissue around the target area to be affected (Okun et al., 2009; Walter & Vitek, 2004; Wichmann & DeLong, 2006). Although this is a single-case study, we believe that the current case adds to the existing body of evidence that GPi DBS may be an appropriate and better target to consider for DBS candidates with cognitive vulnerability.

The other factor to consider is reduction in medication and pain due to the success of RA's DBS surgery. Medications can play a role in one's cognitive performance. RA's medications were reduced post-surgically. Specifically, levodopa was reduced, and ropinirole and trihexyphenidyl were discontinued. Effects of levodopa on cognition have been controversial but the literature suggests possible adverse effects on aspects of executive function (Cools, 2006). Trihexyphenidyl, due to its anticholinergic properties, can contribute to cognitive deficits (Brooks & Hoblyn, 2007; Campbell et al., 2009). Thus, reduced medication dosage could explain some of the improvement that RA has shown. Furthermore, his dystonia has significantly improved post-surgery, and we speculate that surgery has attenuated his experience of pain. Acute as well as chronic pain has been documented to negatively affect individual's cognitive performance, and severity of pain was shown to have inverse correlation with the neuropsychological performance of older adults who had chronic pain (Weiner, Rudy, Morrow, Slaboda, & Lieber, 2006). It is possible that improvement in his dystonia has reduced the patient's pain thereby resulting in improved performance on some of the cognitive tests. It is also possible that these factors were positive to the extent that they have masked ongoing disease-related cognitive decline. Careful monitoring is needed to confirm if RA's cognitive fluctuation is actually due to changes in pain and medication.

Another interesting presentation is the patient's apathy that was significantly elevated post-surgery. An increasing number of studies are reporting elevated apathy in patients with PD following STN DBS (Kirsch-Darrow, Mikos, & Bowers, 2008; Le Jeune et al., 2009; Thobois et al., 2010). The present case indicates the importance of investigating the effects of GPi DBS on patients' levels of apathy. It is possible that the GPi DBS induced elevation in his apathy level, similar to what has been suggested with the STN DBS. Other possibilities for the increased apathy in the present case include the reduced dosage of his dopaminergic medications, and an interaction of the DBS and reduced medication.

RCIs and composite z-score calculations aided our interpretation of RA's performance. Detecting meaningful changes in individual patients is one of the important contributions that neuropsychological evaluations can provide. When neuropsychological evaluations are used for the purpose of diagnosis, the best normative reference group would be neurologically intact individuals who are demographically similar to the person being evaluated. It has been pointed out, however, that in order for neuropsychologists to properly evaluate meaningful changes in clinical patients, norms based on neurologically normal individuals may not be always adequate (Heaton et al., 2001). Towards this aim, within the area of movement disorders a number of studies have used RCIs in examining meaningful changes in PD population (Mikos et al., 2010; Troster, Woods, & Morgan, 2007; York et al., 2008; Zahodne et al., 2009). Large-scale investigations where Reliable Change Indices can be calculated on neurologically ill patients as well as neurological intact controls appear warranted. One limitation of the current case study would be that the RCI method that



adjusts for practice effects may not fully consider a score change due to regression to the mean.

In summary, for our unique gentleman with XDP with pre-existing cognitive impairment documented on two separate occasions at baseline, no further global cognitive decline was observed following bilateral DBS. Rather, there was demonstration of improvement in some memory and problem-solving abilities. Whether pre-operative cognitive impairment should continue to rule out deep brain stimulation needs examination with large sample prospective investigations.

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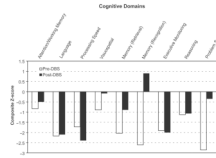
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**Figure 1.**

Composite z-scores pre- and post-DBS for the cognitive domains created only with those tests given both at pre and post time points. For the pre time point, the very first of the two pre-DBS evaluations was used. The composite z-scores consisted of the following: Attention/Working Memory = Dementia Rating Scale-2 (DRS-2) Attention subscale, Digit Span Total; Language = Boston Naming Test, Controlled Oral Word Association, and Animal Fluency; Processing speed = Digit Symbol, Trail Making Test A, Stroop Word Reading, and Stroop Color Naming; Visuospatial = DRS-2 Construction, Wechsler Abbreviated Scale of Intelligence (WASI) Block Design subtest, Facial Recognition test, and Judgment of Line Orientation; Memory (Retrieval) = DRS-2 Memory subtest, Hopkins Verbal Learning Test-Revised (HVLTR) immediate total and delayed recall, and Wechsler Memory Scale-III Logical Memory; Memory (Recognition) = HVLTR recognition; Reasoning = DRS-2 Conceptualization subtest, and WASI Similarities and Matrix Reasoning; Executive Monitoring = Stroop Color Word and Trails B; Problem Solving = Wisconsin Card Sorting Test-64 Total Error and Perseverative Responses.

Table 1

## Neuropsychological test results

Cognitive Domain/Test	Initial test session					Follow-up test session						
	Raw score/Max score	Std. score	SS	T score	%ile	Qualitative descriptor	Raw score/Max score	Std. score	SS	T score	%ile	Qualitative descriptor
<i>General intellectual abilities</i>												
WASI												
Full Scale IQ		79			8	Borderline		N/A				
Verbal IQ		84			14	Low Ave		N/A				
Vocabulary	43/80			39	13	Low Ave		N/A				
Similarities	22/48			39	13	Low Ave	16/48			31	3	Impaired
Performance IQ		78			7	Borderline		83			14	Low Ave
Block Design	11/71	37			9	Borderline	15/71			40	16	Average
Matrix Reasoning	7/32	34			5	Impaired	9/32			37	9	Borderline
WAIS-III												
PSI		N/A						71			3	Impaired
Digit Symbol	19		5		2	Impaired	28		5		5	Impaired
Symbol Search	N/A						8/60		4		2	Impaired
Prorated WMI		N/A						86			18	Average
Digit Span Total	12/30		7		16	Average	11/30		7		16	Average
Forward Span	6/9			48	42	Average	5/9			41	19	Average
Backward Span	3/8			40	16	Average	3/8			40	16	Average
Letter Number Sequencing	N/A						7/21		8		25	Average
<i>Dementia Screening</i>												
MMSE	25/30					Borderline	25/30					Borderline
DRS-2												
Attention	34/37		8		19–28	Average	35/37		10		41–59	Average
Initiation/Perseveration	21/37		2		<1	Impaired	25/37		3		1	Impaired
Construction	6/6		10		41–59	Average	6/6		10		41–59	Average
Conceptualization	34/39		8		19–28	Average	37/39		10		41–59	Average
Memory	18/25		4		2	Impaired	23/25		9		29–40	Average
Total Score	113/144		2		<1	Impaired	126/144		5		3–5	Impaired
Age/Education Corrected			0		<1	Impaired			3		1	Impaired
<i>Attention, executive monitoring, and processing speed</i>												
Trail Making Test Part A	59 sec		5	32*	4	Impaired	99 sec		1	15	1	Impaired
Trail Making Test Part B	198 sec		5	30*	2	Impaired	297 sec		2	17	1	Impaired
Color Trails 1	N/A						85 sec	70		30	2	Impaired
Color Trails 2	N/A						135 sec	80		37	10	Borderline
Color Trails Interference	N/A						.59				>16	Average
PASAT												
Trial 1	23			35	7	Borderline	N/A					
Stroop Color and Word Test												

Cognitive Domain/Test	Initial test session					Follow-up test session						
	Raw score/Max score	Std. score	SS	T score	%ile	Qualitative descriptor	Raw score/Max score	Std. score	SS	T score	%ile	Qualitative descriptor
Word	66(88 cor)			36	8	Borderline	51(65 cor)			28	1	Impaired
Color	39(50 cor)			30	2	Impaired	37(48 cor)			28	1	Impaired
Color-Word	12(27 cor)			32	4	Impaired	22(38 cor)			43	23	Average
Interference	-3.77			46	34	Average	10.4			60	84	Average
<i>Learning and memory</i>												
Hopkins Verbal Learning Test Revised												
Trial 1	5/12			37	10	Borderline	6/12			43	25	Average
Total Learning	18/36			31	3	Impaired	20/36			42	21	Average
20-min Delayed	7/12			37	10	Borderline	6/12			40	16	Average
Retention	116%			69	96		86%			49	45	Average
Recognition	7/12			24	1	Impaired	12/12			59	81	Average
WMS-III Logical Memory												
Immediate Recall	11/75		2		1	Impaired	14/75		6		9	Borderline
30-min Delayed	3/50		3		1	Impaired	13/50		7		16	Average
WMS-III Faces												
Immediate recognition	40/48		14		91	High Ave	N/A					
30-min Delayed recognition	34/48		9		37	Average	N/A					
WMS-III Visual Reproduction												
Immediate Recall	N/A						70/104		10		50	Average
30-min Delayed	N/A						62/104		14		91	High Ave
Recognition	N/A						40/48		10		50	Average
<i>Language and language-related skills</i>												
Boston Naming Test	43/60		5	28*	1	Impaired	38/60		4	24*	1	Impaired
COWA (letter FAS)	25		6	33*	4	Impaired	24		6	28*	1	Impaired
Category Fluency (animals)	10		4	24*	1	Impaired	15		8	35*	6	Borderline
Writing sample						WNL						WNL
Reading sample						WNL	N/A					
Brief Praxis Assessment												
Right hand						Low	N/A					
Left hand						Impaired	N/A					
Left-right discrimination						Impaired						Impaired
Repetition						WNL						WNL
<i>Visuoperceptual, spatial, and constructional skills</i>												
Benton JLO	15(18 cor)				4	Impaired	22(25 cor)				56	Average
Benton FRT	41(43 cor)				32	Average	45(47 cor)				71	Average
Clock Drawing						Impaired						WNL
<i>Problem solving and abstract reasoning</i>												
WCST-64												
Number of categories	0/6				2-5	Impaired	2/6				11-16	Low Ave

Cognitive Domain/Test	Initial test session					Follow-up test session						
	Raw score/Max score	Std. score	SS	T score	%ile	Qualitative descriptor	Raw score/Max score	Std. score	SS	T score	%ile	Qualitative descriptor
Perseverative responses	62			<20	<1	Impaired	10			44	27	Average
Total errors	48			23	<1	Impaired	15			49	45	Average
<i>Frontal Executive and motor</i>												
Luria recursive writing						Impaired	N/A					
Luria contrasting						WNL						WNL
Luria go-no go tasks						WNL						WNL
<i>Finger Tapping</i>												
Dominant right	30.2					Impaired	N/A					
Non-dominant left	22.8					Impaired	N/A					
<i>Mood Status</i>												
GDS	6/30					Normal	10/30					Mild
<i>STAI</i>												
State	29/80				36	Normal	48/80				89	Elevated
Trait	38/80				71	Normal	39/80				74	Elevated
Apathy Scale	11/42					Not Apathetic	22					Elevated

Max score = maximum score; Std. score = standard score; SS = scaled score; %ile = percentile score; WASI = Wechsler Abbreviated Scale of Intelligence; IQ = intelligence quotient; WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; PSI = Processing Speed Index; WMI = Working Memory Index; MMSE = Mini-Mental Status Examination; DRS-2 = Dementia Rating Scale – 2; PASAT = Paced Auditory Serial Addition Task; WMS-III = Wechsler Memory Scale - Third Edition; COWA = Controlled Oral Word Association; JLO = Judgment of Line Orientation; FRT = Facial Recognition Test; WCST-64 = Wisconsin Card Sorting Test 64-card version; GDS = Geriatric Depression Scale; STAI = State Trait Anxiety Inventory; N/A = not available; sec = seconds; WNL = within normal limits; Ave = Average; cor = corrected score.

\* T-scores are demographically corrected for age, sex, and education based on Heaton, Miller, Taylor, and Grant (2004).