

Accuracy of Robotic Guided Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease

Purpose

The purpose of this white paper is to develop an analytical process to compare Deep Brain Stimulation (DBS) lead placement techniques allowing for the simplification and standardization of the procedure. The goal is to achieve high quality, repeatable results which can be applied broadly and economically to the Parkinson's patient population without the need for rationing of care. The first step in achieving this goal is to develop a language by which accuracy of surgical techniques can be discussed and compared and then to introduce the *Denver DBS Technique* combining the best aspects of current practice.

History

Parkinson's Disease

Parkinson's disease is diagnosed in roughly 60,000 individuals in the United States each year. The disease is characterized by slowness of movement (bradykinesia), rigidity, and tremor, but there are many other motor and non-motor symptoms. The cause of Parkinson's disease is the degenerative death of dopamine producing neurons. There is no cure and symptoms typically progress over a period of years. Treatment consists of medications either replacing the missing dopamine or enhancing the effect of the existing dopamine. While medications are effective, the efficacy declines as the disease advances reducing effectiveness and requiring escalating doses. Individuals typically report short periods where the medications are effective ("on periods") followed by periods where their motor symptoms make quality of life difficult ("off periods"). Often, these oscillations combined with other medication side effects become more prominent as the doses are increased. Deep brain stimulation is both an alternative and an adjunctive therapy to medications for the treatment of Parkinson's disease.

Efficacy of DBS

Deep brain stimulation (DBS) systems consist of two components. The first part is a lead placed into one of two targets in the brain, either the subthalamic nucleus (STN) or globus pallidus internus (GPI). The second part is the implantation of an electrical pulse generator similar to a pacemaker.

Leads implanted in either the STN or GPI have been found to be equally effective in to alleviating the motor symptoms of Parkinson's disease including slowness of movement (bradykinesia), rigidity, tremor, lack of facial expression and fine motor impairment.[1-6] Notably balance does not typically respond to DBS therapy as well as most non-motor symptoms. A notable non-motor symptom which does seem to respond is sleep impairment.[7] Placing the lead into the STN may have an advantage over the GPI with a greater medication reduction.[4]

Deep brain stimulation was first used for Parkinson's disease in 1987 by Dr. Alim-Louis Benabid's team. In 2002, DBS was approved by the FDA for use in the United States based on evidence from the DBS Group Study.[1] Including the group study there have been at least five large, randomized controlled trials demonstrating improvements in quality of life for those who receive DBS versus those who receive only best medical management.[2, 3, 6, 8] All of these studies are published in either *Journal of the American Medical Association (JAMA)*, *Lancet*, or *New England Journal of Medicine (NEJM)* with all showing quality-of-life benefits utilizing the validated PDQ-39 survey.[9]

In a high-quality retrospective study, Ngoga, et al. demonstrates a survival advantage and lower risk of nursing home admission for Parkinson's patients with DBS over a 10-year period.[10] They report a hazard ratio (HR) after DBS surgery of 0.29 (95% CI 0.13 to 0.64, $p < 0.002$). This hazard ratio is equivalent to a *3.4-times higher risk of death without DBS than with DBS*. The most likely reason for this increase in risk of death appears to be due to an increased risk of

aspiration pneumonia without DBS. An increased risk of being admitted to a nursing home was similarly found to be associated with not having DBS with an odds ratio (OR) of 0.1 (95% CI 0.0 to 0.3, $p < 0.001$).

In addition to improvements in quality-of-life and life-expectancy, DBS has been shown to be a less costly management strategy for severe Parkinson's disease as compared to medical management. A study conducted in Spain illustrates a two-year return on investment for DBS due to a significant reduction in costly advanced medications.[11]

Current DBS Surgical Techniques

As prolific as DBS efficacy publication has been, there is a nearly equal paucity of information published about the exact techniques. However, all techniques have certain features in common.

The intracranial target can be identified in one of two ways. Either the target can be directly identified using an MRI (direct targeting) or the target location can be calculated based on nearby anatomic landmarks utilizing an atlas (indirect targeting). Until recently it was felt that the target could not be adequately visualized utilizing an MRI alone, but this appears to have largely been dispelled.

Once a target has been identified, the lead must be placed using some type of guide. Traditionally this guide consists of a specialized frame mounted directly to the skull by four pins with the most common design being manufactured by Leksell™ (Electa, Stockholm, Sweden). The NexFrame™ is a plastic gimbal which can be aligned with the use of a camera tracking system (Stealth™) both of which are manufactured by Medtronic (Minneapolis, Minnesota). The StarFix™ (FHC, Bowden, ME) is a plastic guide manufactured using a rapid prototyping process custom-fit for each patient; manufactured using a rapid prototyping process. The StarFix is attached to the skull utilizing three or four registration screws. These screws are placed into the skull several days in advance of surgery. ClearPoint™ (MRI Interventions, Memphis, TN) is an advancement of the NexFrame design specifically made for

use in an MRI suite where the plastic design is advantageous. Lastly, Mazor Robotics (Caesarea, Israel) has introduced a DBS software application and set of operating tools for use with the Renaissance™ Guidance system (aka Mazor robot).

Each of these guides has intrinsic accuracy limitations defined by the probability of deviation from the intended target. Every time a DBS lead is placed, the deviation of the lead can be measured using one of several measurement tools.[12-15] However, all of these measurement tools also have intrinsic accuracy limitations that need to be considered. *It is the combination of a guide with a measurement tool or tools which are the primary basis of any particular surgical technique.*

One of the most popular measurement tool for assessing DBS lead placement accuracy is the use of microelectrode recording (MER). MER is the measurement of small electrical potentials from one or a few neurons at the tip of a fine wire electrode as the electrode is passed through the brain. Variations of these potentials with voluntary and passive movement, as well as sensory input, can be used to confirm the location being probed. While this appears at first to be a fool-proof methodology, new evidence shows that supposedly parallel microelectrodes deviate on average 1.12 ± 0.74 mm from the expected positions leading to possible erroneous information during the MER process.[16] In addition, MER techniques vary wildly from center to center. Some centers use a single brain penetration to simply confirm an adequate tract while other centers use multiple tracts. Even though MER is the most popular measurement tool, there is no Class-I or Class-II evidence that MER improves the accuracy or efficacy of the DBS implantation and the extra brain penetrations may increase the overall risk of hemorrhagic stroke.[17] Furthermore, a 309 patient trial demonstrated that when the lead was actually within the STN patients did better clinically, but only 64% of leads placed utilizing MER hit the intended target.[18]

Testing the clinical changes in an awake patient while still in the operating room may also be considered as a measurement tool for validating DBS lead placement. As awake surgery was the

dominate methodology at the time of initial submission to the FDA, DBS leads by Medtronic are only considered “on-label” when used where the lead is clinically tested prior to the generator being implanted. As with all measurement tools, awake lead testing of the DBS leads has drawbacks. Tests can only be performed while the patient is laying down and relies upon patient feedback. This feedback is prone to vary with fatigue as the procedure can take many hours. While tests of tremor and rigidity improvements are relatively easy, gait testing is impossible. Another less obvious limitation is that there is a fundamental limit to the accuracy of clinical testing. Each lead is placed by a cannula which is typically 1.8 mm in outer diameter. It is not possible in practice to move a lead to another trajectory closer than about 2 mm from a previous trajectory as the cannula and lead will tend to shift into the prior tract. This limits the accuracy of clinical lead testing to ~2 mm. Each time a lead is moved there is additional brain injury and risk of stroke.



Because of the limitations with MER and the lack of acceptance of awake surgery by patients, newer techniques have been developed utilizing imaging to verify lead placement. These alternatives rely either on an intraoperative or preoperative CT or MRI to visually confirm lead location.

Dr. Philip Starr (UCSF) introduced a technique which is performed in an intraoperative MRI suite and is based entirely on anatomic identification without the use awake testing or MER. The choice of guides was limited to only those which were MRI compatible and those which could be utilized the same day as the surgical planning. Initially, he used the NexFrame guide reporting a circular accuracy of 1.2±0.65 mm.[12] This was improved upon by transitioning to the ClearPoint guide. With a small series of just 6 patients the circular

accuracy is reported to be 0.6±0.5 mm as measured by an MRI.[15] It is important to note that these are the accuracies as measured by an MRI which is a measurement tool subject to intrinsic accuracy limitations. This is distinct from the true accuracy as the error in the measurement tool (MRI) still needs to be taken into account. Another criticism is that the surgery must be performed in an MRI suite that is suitable for surgical procedures. This limits the ability to replicate the interpretive MRI technique broadly and increasing the cost of the procedure.

In a similar effort, Dr. Kim Burchiel (OHSU)

Table 1 - Accuracy of DBS Measurement Tools

	σ	σ_{x1-x2}	PE _x	PE _{x1-x2}	PE _c	P _{95%}
MRI Phantom Distortion	0.23	0.33	0.16	0.22	0.27	0.56
CT Phantom Distortion	0.13	0.18	0.08	0.12	0.15	0.31
Fused CT-MRI	0.43	0.61	0.29	0.41	0.51	1.05
MRI w/Leads Distortion*	0.80	1.13	0.54	0.76	0.94	1.96
MER Deviation	0.79	1.12	0.53	0.76	0.93	1.94
Awake Lead Testing**						~2

*RMS error of reported x and y standard deviations
 **A lead cannot practically be placed closer than 2 mm to a previous tract

developed a NexFrame surgical technique utilizing a portable CT scanner (CereTom™, Neurologica subsidiary of Samsung Electronics, Ridgefield Park, NJ) as the measurement tool. This technique has the distinct advantage of being performed in a normal operating room rather than a specialized MRI suite. This techniques has a reported circular accuracy of 1.24±0.87mm.[13]

Both Dr. Starr’s and Dr. Burchiel’s techniques have statistically identical reported circular accuracies when using the NexFrame. This

should not be surprising because what was really being measured was the accuracy of the guide and not the accuracy of the measurement tool. The accuracy of the measurement tool cannot be assessed by the use of the tool itself. Instead, what is needed are independent assessments of the measurement tools. Such assessments exist in the literature, but there so far have been no standardized methods for collecting or reporting data making comparisons difficult. Furthermore, all errors in a chain of measurements must be taken into account to estimate true accuracy.

When utilizing an MRI as a measurement tool, the biggest contribution of error appears to be distortion of the image. Magnetic lines can never be straight no matter how strong or confined the magnetic field. MRI machine software attempts to correct for these distortions, but the distortions change depending on the nature of the material being imaged. Tissue distortion the image is termed

The addition of DBS leads adds significantly to this distortion. This is due both to shift of the image as well as difficulty in manually identifying the true lead location within the artifact.[20, 21] Often these errors are neglected because they are numerically small, but each error in the chain of measurement contributes. The best estimate is one where all of the errors in a chain can be taken into account in one test. In one such test, MRI lead position was compared to ventriculography which, while invasive, has a much higher imaging resolution. In this study, the errors were reported as standard deviations in the x, y, and z axes for the left and right leads respectively.[22] Assuming that the variance is truly the same in all directions, the root-mean-square (RMS) of the reported individual standard deviations is an estimate of the true standard deviation. The RMS error was calculated to be 0.8 mm. In this same study a significant translation to the right side of the head was identified consisting of 0.59 mm (left lead) and 0.46 mm (right lead). It is assumed that anyone utilizing an MRI for lead position measurement would appropriately account for this fixed offset in their targeting.

Table 2 - Accuracy of DBS Guides

	PE _c
Leksell Frame	1.7±0.6
NexFrame MRI-Guided	1.2±0.65
NexFrame CT-Guided	1.24±0.87
ClearPoint	0.6±0.5
Mazor Robot	0.7±0.36

chemical shift. Whereas, when a foreign body such as a DBS lead creates the distortion the effect is called susceptibility artifact. A similar problem of image distortion plagues the field of stereotactic radiosurgery and the best characterizations come from these studies. An MRI without leads in place is reported to have a probable linear two-point distortion of 0.22±0.1mm with the worst distortion near the edges of the image.[19]

CT scanners in contrast to MRIs, do not suffer from distortion but do have resolution limits. With a constant resolution for all imaged substances, phantom studies can easily be used as a measure of accuracy. Again, from the stereotactic radiosurgery literature, CTs have a reported linear two-point resolution of 0.12±0.14 mm.[19] Since the STN cannot be visualized on a CT, an MRI image must be utilized and fused together as one image using a computer algorithm. This fusion process introduces additional error with the linear two-point resolution of a CT-MRI fused image being reported as 0.41±0.30mm.[19] Distortion from DBS leads does not occur as leads are not in place during the MRI imaging process. One criticism of CT methods is that shift of the midbrain structures after making a burr hole cannot be accounted for.[23] This occurs when CSF is lost and replaced with air shifting the brains position. However, a new technique exists where a burr hole is partially created leaving the dura intact prior to passing a cannula directly through with electrocautery. No measurable CSF is lost and shift should not occur. This procedure appears to be unique to

those surgical techniques performed in a standard operating room and not using microelectrode recording.

Methods/Data

A retrospective analysis was performed for the last 10 bilateral STN cases (20 leads) performed using a technique nearly identical to that described by Dr. Burchiel, but utilizing the Mazor robot as guide rather than the NexFrame. The mean circular error was found to be 0.7 ± 0.36 mm as measured using a CereTom portable CT scanner.

Analysis

The Mazor robot is statistically equivalent in accuracy to the ClearPoint guide both of which are superior to other commercially available guides listed in **Table 2**.

Determining which measurement tool is superior is much more difficult as the data is reported as linear standard deviations, linear two-point probable error, and circular probable error depending on the reference source. In **Table 1** the best available information for each measurement tool is tabulated with original source values being stated in bold. Conversion from one type of reported statistical value to another was performed using the following relationships:

$$\sigma_{x1-x2} = \frac{\sigma}{0.7071}$$

$$PE_x = 0.6745\sigma$$

$$PE_c = 1.1774\sigma$$

$$P_{95\%} = 2.4478\sigma$$

Discussion

One way to characterize accuracy is to give a probability of the lead passing through a circle of a specific radius. While errors of the guides are observable by the measurement tools, we are blind to the error inherent in the measurement tool itself. Because of this, errors of the measurement tools are held to a higher standard than errors of the guides. For example it might be reasonable to quote a circular radius

containing 50% (probable error, PE_c) of the leads for a given guide. A measurement tool, however, should be quoted when the lead is within the circle for greater than 95% of the cases ($P_{95\%}$). *Because of the difference between these observable and unobservable errors, overall accuracy is affected much more by the measurement tool than by the insertion guide.*

Despite being considered the standard of care since the inception of DBS, MER appears to be among the least accurate measurement tools available and, at the same time, exposes the patient to greater risk of intracranial hemorrhage. One wonders if this practice should continue. This is not to say that awake surgery has no value as awake lead testing has a nearly identical accuracy compared to intraoperative MRI. There will, however, inevitably be improvements to intraoperative MRI with time. Whether or not these improvements will be the equal of a CT-MRI fusion remains to be seen as both are likely to improve. Clearly, in both cases better and more rigorous characterization is needed.

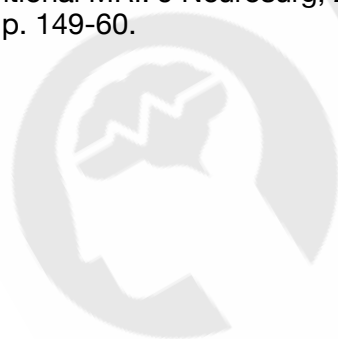
Until now, the best available DBS insertion guide was ClearPoint, but the best measurement tool appears to be CT-MRI fusion. Because a CT based procedure is not compatible with ClearPoint it was unclear which combination of guide and measurement tool would lead to the most accurate surgical technique. This has changed now that the Mazor robot has been shown to be the equivalent of ClearPoint. Overall accuracy of this *Denver DBS Technique*, combining the Mazor Renaissance Guidance system with the CereTom CT image verification, will likely be the most accurate surgical pathway given currently available technology. However, this is only likely to be true with the use of the closed burr hole technique avoiding CSF loss and brain shift.

DBS is clearly efficacious for alleviating disability associated with Parkinson's disease. Once the decision has been made to have the procedure, a surgical technique should be judged solely on accuracy, procedure time, complication rate and costs. On these points we feel that this new *Denver DBS Technique* will be judged favorably.

References

1. Deep-Brain Stimulation for Parkinson's Disease Study, G., Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med*, 2001. 345(13): p. 956-63.
2. Deuschl, G., et al., A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*, 2006. 355(9): p. 896-908.
3. Weaver, F.M., et al., Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*, 2009. 301(1): p. 63-73.
4. Follett, K.A., et al., Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*, 2010. 362(22): p. 2077-91.
5. Weaver, F.M., et al., Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology*, 2012. 79(1): p. 55-65.
6. Schuepbach, W.M., et al., Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*, 2013. 368(7): p. 610-22.
7. Klingelhofer, L., et al., An update of the impact of deep brain stimulation on non motor symptoms in Parkinson's disease. *J Parkinsons Dis*, 2014. 4(2): p. 289-300.
8. Williams, A., et al., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol*, 2010. 9(6): p. 581-91.
9. Jenkinson, C., et al., The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing*, 1997. 26(5): p. 353-7.
10. Ngoga, D., et al., Deep brain stimulation improves survival in severe Parkinson's disease. *J Neurol Neurosurg Psychiatry*, 2014. 85(1): p. 17-22.
11. Valdeoriola, F., et al., Cost analysis of the treatments for patients with advanced Parkinson's disease: SCOPE study. *J Med Econ*, 2013. 16(2): p. 191-201.
12. Starr, P.A., et al., Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device: technique and application accuracy. *J Neurosurg*, 2010. 112(3): p. 479-90.
13. Burchiel, K.J., et al., Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording. *J Neurosurg*, 2013. 119(2): p. 301-6.
14. Sharma, M., et al., Accuracy and precision of targeting using frameless stereotactic system in deep brain stimulator implantation surgery. *Neurol India*, 2014. 62(5): p. 503-9.
15. Starr, P.A., et al., Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. *J Neurosurg Pediatr*, 2014. 14(4): p. 400-8.
16. Holloway, K. and A. Docef, A quantitative assessment of the accuracy and reliability of O-arm images for deep brain stimulation surgery. *Neurosurgery*, 2013. 72(1 Suppl Operative): p. 47-57.
17. Zrinzo, L., et al., Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. *J Neurosurg*, 2012. 116(1): p. 84-94.
18. Welter, M.L., et al., Optimal target localization for subthalamic stimulation in patients with Parkinson disease. *Neurology*, 2014. 82(15): p. 1352-61.

19. Rahimian, J., et al., Geometrical accuracy of the Novalis stereotactic radiosurgery system for trigeminal neuralgia. *J Neurosurg*, 2004. 101 Suppl 3: p. 351-5.
20. Pinsker, M.O., et al., Accuracy and distortion of deep brain stimulation electrodes on postoperative MRI and CT. *Zentralbl Neurochir*, 2008. 69(3): p. 144-7.
21. Mirzadeh, Z., et al., Validation of CT-MRI fusion for intraoperative assessment of stereotactic accuracy in DBS surgery. *Mov Disord*, 2014.
22. Pinto, S., et al., Comparison of two techniques to postoperatively localize the electrode contacts used for subthalamic nucleus stimulation. *Neurosurgery*, 2007. 60(4 Suppl 2): p. 285-92; discussion 292-4.
23. Ivan, M.E., et al., Brain shift during bur hole-based procedures using interventional MRI. *J Neurosurg*, 2014. 121(1): p. 149-60.



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Appendix
STD and Confidence Circle Relationship

Bivariate probability distribution:

$$P(x,y) = \frac{1}{2\pi\sigma_x\sigma_y} \exp\left\{-\frac{x^2}{2\sigma_x^2} - \frac{y^2}{2\sigma_y^2}\right\}$$

if:

$$\mu_x = \mu_y = 0$$

$$\nu_{xy} = 0$$

$$\sigma = \sigma_x = \sigma_y$$

$$r^2 = x^2 + y^2$$

$$P(r,\theta) = \frac{1}{2\pi\sigma^2} \exp\left\{-\frac{r^2}{2\sigma^2}\right\}$$

$$C(r,\theta) = \int_0^{2\pi} \int_0^r \frac{1}{2\pi\sigma^2} \exp\left\{-\frac{r^2}{2\sigma^2}\right\} r dr d\theta$$

let:

$$\alpha = \frac{r^2}{2\sigma^2}$$

$$\sigma^2 d\alpha = r dr$$

$$C(r) = \frac{1}{2\pi} \int_0^{2\pi} \int_0^\alpha \exp\{-\alpha\} d\alpha d\theta$$

$$C(r) = \frac{1}{2\pi} \int_0^{2\pi} \left[1 - \exp\left\{-\frac{r^2}{2\sigma^2}\right\}\right] d\theta$$

$$C(r) = 1 - \exp\left\{-\frac{r^2}{2\sigma^2}\right\}$$

$$0.5 = 1 - \exp\left\{-\frac{r_{50\%}^2}{2\sigma^2}\right\}$$

$$\sigma = \sqrt{\frac{-r_{50\%}^2}{2\ln(0.5)}} = (0.8493)r_{50\%}$$

$$\sigma = \sqrt{\frac{-r_{95\%}^2}{2\ln(0.05)}} = (0.4085)r_{95\%}$$