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Point of view

Decision under risk: Argument against early deep brain stimulation in Parkinson's disease

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ABSTRACT

Deep brain stimulation (DBS) typically has been delayed until late stage of Parkinson's disease (PD), a mean of 14–15 years after diagnosis. EARLYSTIM study applied DBS in patients with PD presenting motor complications for less than three years, and showed that early stimulation offered greater benefit than best medical therapy in all primary and major secondary end points. Based on the results of EARLYSTIM study, the U.S. Food and Drug Administration recently approved DBS for use in people with PD of at least four years duration and with recent onset of motor complications. However, despite of more benefit from DBS surgery than best medical therapy in early stage of PD, we need to consider the risks of surgery and human nature of risk aversion. Here, we make arguments against early DBS stimulation based on the prospect theory.

1. Introduction

Classical candidates for deep brain stimulation (DBS) in Parkinson's disease (PD) include patients with levodopa induced motor complications that cannot be adequately managed by medical treatment and that limit quality of life (QoL), or with a medically intractable tremor. Levodopa induced motor complications are experienced by approximately 40% of patients after 4–6 years of therapy [1] with tremendous inter-individual variability. DBS has been delayed until the later stage of PD with a mean of 14–15 years after the diagnosis [2,3]. However, there is a position for the earlier timing of DBS in PD.

Recently, the U.S. Food and Drug Administration (FDA) approved DBS for use in people with a PD duration of at least four years and with a recent onset of motor complications [4], meaning not necessarily with motor complications that cannot be adequately managed by medical treatment and that limit QoL. This recent approval by the FDA was based on data from the EARLYSTIM clinical study performing DBS surgery in mid-stage PD patients [5]. This study enrolled patients with a levodopa response of at least 50%, motor fluctuations and dyskinesias for no longer than 3 years, and mild to moderate functional impairment. The EARLYSTIM trial reported a mean improvement of 26% in their disease-related QoL in patients treated with DBS therapy in conjunction with best medical therapy (BMT) at two years compared to a 1% decline in patients treated with the BMT alone. This study showed that early stimulation with BMT offered a greater benefit than that of BMT alone for all primary and major secondary end points, supporting that neurostimulation may be a therapeutic option for patients at an earlier stage rather than what the widely accepted recommendations suggest. An earlier DBS intervention could possibly preserve functional capacity and improve the patient's QoL earlier in the disease course because a significant portion of patients in the advanced stage of PD experience conditions or comorbidities that may make them ineligible for DBS. There was a debate as to lessebo effect in BMT group arguing that benefit from DBS is smaller than reported in the paper [6]. However, even with granting more benefits from DBS therapy than BMT in the early stage of PD, we need to consider the risks of surgery and the risk of unnecessary surgery, which are the key issues when considering early DBS surgery, and human nature of risk aversion.

Here, we aimed to discuss the arguments against early DBS stimulation. First, we will illustrate how people behave under risk by examining patients' hesitation for DBS. Second, we will discuss how people make decisions under risk based on the prospect theory and which factors can predispose a risky choice. Third, we will discuss important risks of early DBS surgery.

2. Patients' hesitation for DBS

The theory of decision began from a correspondence between Pascal and Fermat in the 17th century. Best decision is to maximize the expected value (*EV*), which is defined as probability *p* multiplied by the

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outcome value x. $EV = px$, which is the foundation of utility theory. In utility theory, it is obvious that the best or right decision is to perform DBS surgery in patients with early stage motor complications.

However, we frequently meet patients with advanced PD who are hesitant to undergo DBS even when operation is clearly indicated. Previously, we studied the reasons for the hesitation to have subthalamic nucleus (STN)-DBS in advanced PD patients. In this study, 186 PD patients who were recommended to have DBS were surveyed whether they proceeded to have surgery without much hesitation or delay. Forty-five percent of the patients (n = 84) were included in the hesitant group, which was defined as patients who answered that they were hesitant to undergo DBS operation, and required multiple discussions before surgery [7]. Fear of complications (n = 62) was the most important reason for the hesitation to not have DBS surgery followed by economic burden (n = 42). The hesitant and the non-hesitant groups did not differ in preoperative characteristics except for the duration between the pre-surgical evaluation and STN-DBS surgery. In our survey, despite the prolonged suffering from motor complications and data clearly showing the benefit of DBS in this advanced PD stage, patients hesitated toward getting STN-DBS surgery out of fear, which shows that we behave or make decisions differently under risk.

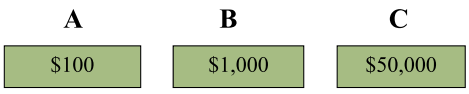
3. Prospect theory and decision making under risk

Daniel Kahneman, a psychologist and Nobel prize winner in Economics, presented a critique of expected utility theory as a descriptive model of decision making under risk and developed an alternative model called prospect theory [8]. There are three key ideas in this theory: 1) Risk aversion means that in most decisions, people tend to prefer smaller variance in outcomes; 2) Loss aversion means that everyone prefers gains over losses and that losses are felt more intensely than gains of equal magnitude; and 3) Endowment effect means that things you own are intrinsically valued more highly. Framing decisions as gains or as losses affects choice behavior. The examples are given in supplementary material.

According to the loss aversion, people are more sensitive to the loss than the gain. In the health domain, the report by Horvath et al. is a good example who examined minimal clinically important differences (MCID) in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [9]. The MCID thresholds for the MDS-UPDRS Parts I and II were −2.64 and −3.05 points for revealing improvement or 2.45 and 2.51 points for observing deterioration. The MCID thresholds for the MDS-UPDRS part I + part II scores were 5.73 points for improvement and 4.70 points for deterioration. Here, we note that the numbers for improvement is larger than those for deterioration, meaning that deterioration is felt more acutely than improvement.

How data are framed and presented are important in decision. In their article “The framing of decisions and the psychology of choice”, Tversky and Kahneman illustrated the effect of framing as follows. In the imaginary outbreak of an unusual disease which is expected to kill 600 people, two alternative programs are proposed [10]. Program A will save 200 people. Program B has 1/3 probability of saving and 2/3 probability of not saving. In this framing, majority chose Program A. In other framing of the programs, 400 will die in Program C; and Program D will save 1/3, and will not save 2/3. In this presentation, majority chose Program D. However, Program A, B, C, and D have the same output. In the case of DBS, how benefit and risks are framed and presented will affect decision. The communication style of the physician consulting and advising patients on DBS may influence how the DBS benefit and risk are presented to patients, although this issue has not drawn much attention until now.

Personality also matters in decision-making. Suppose that there are ticket A, B, and C and that each ticket costs 50 cents, but they each have a different chance of winning (Fig. 1). The individual choosing ticket A is risk averse, and the individual choosing ticket C is risk seeking. The



Ticket A, B, and C has 1 % chance of winning 100 $, 0.1 % chance of winning 1,000 $, and 0.002 % chance of winning 50,000 $, respectively
(modified from https://kevinbinz.com/2016/10/26/prospect-theory/)

Figure 1. Personality on decision making. Ticket A, B, and C has 1% chance of winning 100 $, 0.1% chance of winning 1,000 $, and 0.002% chance of winning 50,000 $, respectively (modified from https://kevinbinz.com/2016/10/26/prospect-theory/).

uneven gender distribution in neurosurgery for PD might be due to behavioral differences between men and women [11–14]. Hariz et al. reported an uneven gender distribution (Male vs Female; 65% vs 35%, respectively) in the surgical treatment of PD including pallidotomy, thalamotomy and DBS [13]. This finding was relatively consistent regardless of the procedure and geographic origin of the publication. And in their subsequent study regarding STN-DBS conducted between 2000 and 2009, 63% (68% in North America, 62% in Europe, 69% in Australia, and 50% in Asia) were men [14]. This male predominance in the distribution of STN-DBS seems to exceed the usual male/female ratio of PD in community-based studies [14,15]. Age might matter in risk attitudes, with younger people being on average more risk taking than older people [16]. Dopamine agonists might affect decision making processes. It is well known that dopamine agonists can enhance risk taking behaviors in PD patients with impulse control disorders [17–19]. However, it has been not studied yet whether dopamine agonists affect decisions on receiving DBS surgery in patients with PD.

4. Other risks in early surgery: it is difficult to predict especially about the future

4.1. Atypical parkinsonism can mimic PD during the early stage of the disease

One of the reasons to advocate early surgery is that early surgery will extend the period of the DBS benefit. However, some patients may not get the expected long-term benefit even with the best DBS. Diagnostic accuracy is limited during the first years of the disease because atypical parkinsonism can mimic PD for a long period of time [20]. Although the FDA limited the disease duration to at least four years as one of the DBS indications, it is not enough to rule out atypical parkinsonism. More than 30% of DBS failures can be ascribed to inappropriate indications for surgery [21]. In fact, 3 cases (0.8%) had been rediagnosed as non-idiopathic PD in the EARLYSTIM cohort 8 years after the first randomization and approximately 15 years after the diagnosis [22]. Atypical parkinsonism can have a young age at onset and present levodopa induced dyskinesia (LID) [23,24]. There have been other reports regarding DBS in MSA mimicking idiopathic PD [25], where incorrect preoperative PD diagnoses showed positive initial responses to surgery followed by a rapid decline secondary to the progression of MSA and subsequent death or severe disability from complications arising from the MSA. Thus, early surgery increases the risk of atypical parkinsonism patients to be included who will not get the expected long-term benefit even though they may get short-term improvement.

4.2. Can we predict who will need DBS?

The rate of progression for PD is variable. Not all patients with motor complications need DBS surgery. For example, motor complications may not necessarily get worse or be disabling. In a prospective

population-based 5-year longitudinal study following 189 incident PD patients, motor fluctuations and dyskinesia were observed in 42.9% and 24.3%, respectively. In a substantial proportion of patients, however, motor fluctuations (37%) and dyskinesias (49%) reversed on pharmacotherapy alone and remained generally mild in those with persistent complications [26]. In the Sydney multicenter study of PD which did a follow-up for over 15 years, only 12% of the patients experienced severe dyskinesia although 94% experienced dyskinesia [27]. A population-based cohort study in Olmsted county, Minnesota from 1976 to 1990 also showed that the troublesome dyskinesia requiring medication changes was present in 17% of the patients after 5 years and in 43% after 10 years, although dyskinesias of any severity were observed in 60% of the patients by 10 years [28]. Thus, the development of motor complications does not necessarily mean that they will become troublesome and does not justify surgery as the new recommendation by the FDA implies.

5. Discussion

We believe that decisions for early DBS surgery should be made carefully. “Surgery is always second best. If you can do something else, it's better.” This is a quote made by John Kirklin, chair of Surgery at the Mayo Clinic who designed the Heart-Lung machine which was pivotal in making open heart surgery possible. He made this remark to temper Walton Lillehei, who was a pioneer of open heart surgery. Earlier DBS intervention may offer the opportunity to improve the QoL and functional ability of PD patients, providing potential significant symptomatic relief over a longer period of time [29]. Currently, however, there is limited knowledge on patient progression and the long-term outcomes of early DBS patients. These limitations should be brought up when treatment options are offered to patients, so that they can make an informed decision. The adverse event associated with DBS is an important issue in consideration for early DBS surgery. Although the surgical techniques for implanting DBS devices are constantly evolving, DBS surgery is obviously more invasive than medical treatment. Therefore, we need to dampen the enthusiasm for early DBS stimulation and establish regulations for early surgery.

In conclusion, we propose that DBS surgery in patients with early stage PD should be decided very carefully and is always the second option.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.008.

Authors’ role

Kim HJ: (1) acquisition of data and interpretation of data, (2) drafting the article.

Jeon B: (1) conception and design of the study, (2) revising the article, (3) final approval of the version to be submitted.

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References

[1] J.E. Ahlskog, M.D. Muenter, Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature, Mov. Disord. 16 (2001) 448–458.
[2] J.L. Houeto, P. Damier, P.B. Bejjani, C. Staedler, A.M. Bonnet, I. Arnulf, B. Pidoux, D. Dormont, P. Cornu, Y. Agid, Subthalamic stimulation in Parkinson disease: a multidisciplinary approach, Arch. Neurol. 57 (2000) 461–465.
[3] J. Volkmann, Deep brain stimulation for the treatment of Parkinson's disease, J. Clin. Neurophysiol. 21 (2004) 6–17.
[4] Metronic, FDA Approves Medtronic Deep Brain Stimulation for People with Parkinson’s Disease with Recent Onset of Motor Complications, Metronic, 2016, http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=2139957 , Accessed date: 11 November 2017.
[5] W.M. Schuepbach, J. Rau, K. Knudsen, J. Volkmann, P. Krack, L. Timmermann, T.D. Halbig, H. Hesekamp, S.M. Navarro, N. Meier, D. Falk, M. Mehdorn, S. Paschen, M. Maarouf, M.T. Barbe, G.R. Fink, A. Kupsch, D. Gruber, G.H. Schneider, E. Seigneuret, A. Kistner, P. Chaynes, F. Ory-Magne, C. Brefel Courbon, J. Vesper, A. Schnitzler, L. Wojtecki, J.L. Houeto, B. Bataille, D. Maltete, P. Damier, S. Raoul, F. Sixel-Doering, D. Hellwig, A. Gharabaghi, R. Kruger, M.O. Pinsker, F. Amtage, J.M. Regis, T. Witjas, S. Thobois, P. Mertens, M. Kloss, A. Hartmann, W.H. Oertel, B. Post, H. Speelman, Y. Agid, C. Schade-Brittinger, G. Deuschl, E.S. Group, Neurostimulation for Parkinson's disease with early motor complications, N. Engl. J. Med. 368 (2013) 610–622.
[6] T.A. Mestre, A.J. Espay, C. Marras, M.H. Eckman, P. Pollak, A.E. Lang, Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease-the EARLYSTIM trial: early is not always better, Mov. Disord. 29 (2014) 1751–1756.
[7] M.R. Kim, J.Y. Yun, B. Jeon, Y.H. Lim, K.R. Kim, H.J. Yang, S.H. Paek, Patients' reluctance to undergo deep brain stimulation for Parkinson's disease, Park. Relat. Disord. 23 (2016) 91–94.
[8] D. Kahneman, Prospect theory: an analysis of decisions under risk, Econometrica 47 (1979) 278.
[9] K. Horvath, Z. Aschermann, M. Kovacs, A. Makkos, M. Harmat, J. Janszky, S. Komoly, K. Karadi, N. Kovacs, Minimal clinically important differences for the experiences of daily living parts of movement disorder society-sponsored unified Parkinson's disease rating scale, Mov. Disord. 32 (2017) 789–793.
[10] A. Tversky, D. Kahneman, The framing of decisions and the psychology of choice, Science 211 (1981) 453–458.
[11] K. Hamberg, G.M. Hariz, The decision-making process leading to deep brain stimulation in men and women with Parkinson's disease - an interview study, BMC Neurol. 14 (2014) 89.
[12] J.M. Pavon, H.E. Whitson, M.S. Okun, Parkinson's disease in women: a call for improved clinical studies and for comparative effectiveness research, Maturitas 65 (2010) 352–358.
[13] G.M. Hariz, M.I. Hariz, Gender distribution in surgery for Parkinson's disease, Park. Relat. Disord. 6 (2000) 155–157.
[14] G.M. Hariz, T. Nakajima, P. Limousin, T. Foltynie, L. Zrinzo, M. Jahanshahi, K. Hamberg, Gender distribution of patients with Parkinson's disease treated with subthalamic deep brain stimulation; a review of the 2000-2009 literature, Park. Relat. Disord. 17 (2011) 146–149.
[15] M. Picillo, A. Nicoletti, V. Fetoni, B. Garavaglia, P. Barone, M.T. Pellecchia, The relevance of gender in Parkinson's disease: a review, J. Neurol. 264 (2017) 1583–1607.
[16] T. Rouyard, A. Attema, R. Baskerville, J. Leal, A. Gray, Risk attitudes of people with 'manageable' chronic disease: an analysis under prospect theory, Soc. Sci. Med. 214 (2018) 144–153.
[17] D.O. Claassen, W.P.M. van den Wildenberg, K.R. Ridderinkhof, C.K. Jessup, M.B. Harrison, G.F. Wooten, S.A. Wylie, The risky business of dopamine agonists in Parkinson disease and impulse control disorders, Behav. Neurosci. 125 (2011) 492–500.
[18] V. Voon, J. Gao, C. Brezing, M. Symmonds, V. Ekanayake, H. Fernandez, R.J. Dolan, M. Hallett, Dopamine agonists and risk: impulse control disorders in Parkinson's disease, Brain 134 (2011) 1438–1446.
[19] A. Djamshidian, S.S. O'Sullivan, A. Tomassini, T. Foltynie, P. Limousin, I. Aviles-Olmos, T.T. Warner, A.J. Lees, B.B. Averbeck, In a rush to decide: deep brain stimulation and dopamine agonist therapy in Parkinson's disease, J. Parkinson's Dis. 4 (2014) 579–583.
[20] G. Deuschl, Y. Agid, Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits, Lancet Neurol. 12 (2013) 1025–1034.
[21] M.S. Okun, M. Tagliati, M. Pourfar, H.H. Fernandez, R.L. Rodriguez, R.L. Alterman,

K.D. Foote, Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers, Arch. Neurol. 62 (2005) 1250–1255.
[22] W.M. Schupbach, J. Rau, J.L. Houeto, P. Krack, A. Schnitzler, C. Schade-Brittinger, L. Timmermann, G. Deuschl, Myths and facts about the EARLYSTIM study, Mov. Disord. 29 (2014) 1742–1750.
[23] H.J. Kim, B.S. Jeon, Multiple system atrophy with prolonged survival, Mov. Disord. 27 (2012) 1834.
[24] H.J. Kim, B.S. Jeon, J.Y. Lee, J.Y. Yun, Y.E. Kim, S.H. Paek, Young-onset multiple system atrophy, J. Neurol. Sci. 319 (2012) 168–170.
[25] N. Thavanesan, M. Gillies, M. Farrell, A.L. Green, T. Aziz, Deep brain stimulation in multiple system atrophy mimicking idiopathic Parkinson's disease, Case. Rep. Neurol. 6 (2014) 232–237.
[26] A. Bjornestad, E.B. Forsaa, K.F. Pedersen, O.B. Tysnes, J.P. Larsen, G. Alves, Risk and course of motor complications in a population-based incident Parkinson's disease cohort, Park. Relat. Disord. 22 (2016) 48–53.
[27] M.A. Hely, J.G. Morris, W.G. Reid, R. Trafficante, Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years, Mov. Disord. 20 (2005) 190–199.
[28] J.A. Van Gerpen, N. Kumar, J.H. Bower, S. Weigand, J.E. Ahlskog, Levodopa-associated dyskinesia risk among Parkinson disease patients in Olmsted County, Minnesota, 1976-1990, Arch. Neurol. 63 (2006) 205–209.
[29] G. Suarez-Cedeno, J. Suescun, M.C. Schiess, Earlier intervention with deep brain stimulation for Parkinson's disease, Parkinson's Dis. 2017 (2017) 9358153.