

Deep Brain stimulation for cognitive disorders: Insights on targeting Nucleus basalis of Meynert in Alzheimer's dementia

Asem Salma, M.D*, Michail Vasilakis, M.D., Patrick T. Tracy, M.D.

Department of Neurosurgery, Illinois Neurological Institute, University of
Illinois College of Medicine at Peoria, IL

* Corresponding author:

Department of Neurosurgery, Illinois Neurological Institute, University of
Illinois College of Medicine at Peoria, IL

530 NE Glen Oak

Peoria, IL 61637

Phone: 309-655-2700

Fax: 309-655-4728

Email: dr.asalma@hotmail.com or asem.salma@gmail.com

To the Editor: With great interest we read the Hardenacke, et al article entitled, "Stimulate or degenerate: Deep brain stimulation of the Nucleus basalis Meynert in Alzheimer's dementia" published online recently in your journal (3). In their paper, Hardenacke et al presented a review, yet a theoretical article, by searching the literature on translational data, human studies and the pathophysiology of Alzheimer's dementia (AD) to generate a fundamental hypothesis that advocated the Nucleus basalis of Meynert (NBM) as a target for deep brain stimulation (DBS) which aims to treat AD. Even though, we believe that the article of Hardenacke et al is interesting, and they successfully highlight the importance of the acetylcholine system in large in the etiology of AD, as well as the potential role of modulating this system by DBS to control the symptoms of AD. However, we would like to provide comments on their paper mainly for two reasons. First, DBS for dementia has become a hot topic in DBS field; since Hamani et al reportedly observed improvement in memory function in a patient who initially underwent DBS of the hypothalamus for obesity (2), The number of clinical trials that are being conducted to explore the possible role of DBS as a treatment option for Alzheimer's disease evidences this interest (1). Obviously, if this treatment is successful, it will have an enormous impact on future medical polices given the fact that during our modern medical era, the population age has increased dramatically and it is expected to increase even more in the future. That means we are going to see more patients with AD in the future and the burden of AD is going to expand. Secondly, the type (or what we could call the style) of the article of Hardenacke et al itself, which is a theoretical article and not yet supported by strong empirical evidence or at least a mathematical model (which usually is extremely difficult to provide in medicine as opposed to a theoretical article in theoretical physics for example. Despite that we personally believe that this type of article should be encouraged as it could open the door

for new advances and new ideas; however, these types of articles should always undergo a strict critique (from both the reviewers and the readers) to keep us standing in the realm of real science.

Briefly our comments on this article are directed towards the following concerns and raises the following questions:

- **Is NBM really is the best target?** Even though, we have to wait to see the results in the clinical setting. However, the logic that Hardenacke et al used to hypothesize that NBM is a good optional target is questionable, and because the degeneration of NBM is not enough to consider it as the best target for AD. To clarify this point here, let us use DBS for Parkinson (PD) disease (PD) as a model. Although it is well known that substantia nigra is degenerated in PD, we are still not targeting it in DBS for PD; instead we target undegenerated structures such as STN and GPi. This point should be addressed at the theoretical level and should be included in any discussion before we further proceed by the proposal of considering NBM as the best target.
- **What exactly are the pathological sequences of the development of neuro circuit of AD?** Hardenacke et al highlight the acetylcholine system in general and NBM in particular in the etiology of AD. However, the fundamental question is still unanswered. The authors assume that in AD the postsynaptic cholinergic system is intact in AD (this may be always correct in PD associated dementia as this dementia is subcortical by definition). However, because it has shown variability and timing of cholinergic changes during the course of AD (4). Until now the exact pathological process of the cognitive decline is still controversial, is it started at the presynaptic neuron of NBM level or postsynaptic neuron at hippocampus and neo cortex levels (5).

Addressing this question is important because, it determines if we should expect the same result in PD's dementia and AD's dementia. Also, it could give us an idea at what stage of AD we could apply the DBS.

- **What are the potential side effects?** The cholinergic system is a complicated system phylogenetically and anatomically (5). Its dysfunction is involved in several neurological disorders such as epilepsy, schizophrenia, depression as well as dementia. Manipulating this system could be risky and could be associated with serious side effects. Furthermore, the anatomical location of NBM (close to the optic tract and hypothalamus) raises the possibility of another group of side effects. Discussing these possible side effects deserve more.

Finally, at least to some extent, the concepts of the above-mentioned concerns could be applied for almost all published articles dealing with DBS for cognitive disorders, making Hardenacke et al article a good reflection of the current status, as well as to the future directions and challenges of DBS for cognitive disorders. Even though extending the application of DBS to control the cognitive symptoms of AD is attractive, important and deserved exploration, we believe the theoretical foundation is still somehow weak. As we still need to learn more in terms of understanding the structure (or the structures) of the pathophysiology of AD. The mechanism of action of brain stimulation itself, the logic of stimulating a specific anatomical target and the optimal stimulation parameters, and also we need to do more works with regard to the patients' selection as we should define from the beginning. If we are going to target patients with advanced AD or patients with mild AD, we should avoid to make the same mistakes that were done in DBS for depression trials.

References

1. Clinicaltrials.gov.<http://www.clinicaltrials.gov/ct2/results?term=deep+brain+stimulation%2C+dementia>. Accessed March 26, 2013.
2. Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, Wennberg RA, Lozano AM: Memory enhancement induced by hypothalamic/fornix deep brain stimulation. *Ann Neurol*. 63(1):119-123, 2008.
3. Hardenacke K, Kuhn J, Lenartz D, et al. Stimulate or degenerate: deep brain stimulation of the Nucleus basalis Meynert in Alzheimer dementia. *World Neurosurg*. Dec 12.
4. Nixon RA: Cell and molecular neuropathology of Alzheimer disease. in: Davis KL , Charney D, Coyle JT, Nemeroff C (ed). **Psychopharmacology - 5th Generation of Progress**. Lippincott, Williams, & Wilkins, Philadelphia, 2002
5. Reiner PB, Fibiger H C: Functional heterogeneity of central cholinergic systems. In: Bloom FE , David JK (ed). **Psychopharmacology - 4th Generation of Progress**, New York: Raven Press, 1995