Stereotactic NeuroEngineering (Depression dealt the Techno way)

Rushika Verma, **Neelam Tikone**

Abstract- A study based on the World Health Organization's World Mental Health Survey, 2011 has said that India has the highest rate of major depression condition in the world. Major depression is a kind of neuropsychiatric disorder which can be treated by neural modulation. A region of the human brain called Brodmann area 25 (part responsible for rise of emotion) grows hyperactive, disrupting neural signal causing depression. When anti-depression drugs and Electroconvulsive Therapy (ECT) fail to control the hyperactivity in this region, the condition thereafter is known as Treatment Resistant Depression (TRD). TRD patients can then be treated by Deep Brain Simulation (DBS). DBS system consists of three components - Implanted Pulse Generator (IPG) also called as stimulator, the lead and the extension. The device sends electrical pulses to the brain to interfere with neural activity at target site. Having any part of the device go through the skin would create a risk of infection, so the surgeon typically tunnels a small path under the skin from IPG to the electrode. There was considerable mood upliftment noticed in the patients. DBS is proving to be one of the most recent and novel intervention that involves high end technology for severely disabled patients with TRD.

Keywords: - Treatment resistant depression, Deep brain stimulation, Implanted Pulse Generator, extension, electrode, Brodmann area 25, chest wall surgery, stereotactic frame

1 INTRODUCTION

Major depression is the most common of all psychiatric disorders [1]. It ranks among the top causes of worldwide disease burden and is the leading source of disability in young adults as well as adults in India (World Health Organization, 2011).

Depression is not a disease of a single brain region or neurotransmitter system, it is a systems-level disorder affecting integrated pathways linking select cortical, subcortical and limbic system[2][3]. The mechanism behind system dysfunction is multifactorial, with simultaneous contribution may be related to genetics, developmental problems in the family and environmental [4].

Depression can be effectively treated in majority of the patients by either antidepressants and psychotherapy or Electro Convulsive Therapy [5]. While depression can be effectively treated in the majority of cases, up to 20% of patients fail to respond to standard interventions [6]. These cases are known as treatment resistant patients with major depression. This condition is typically known as Treatment Resistant Depression (TRD).

- *Rushika Verma is currently pursuing Bachelors of Engineering degree program in Computer engineering in University of Mumbai, E-mail: rushika.verma@gmail.com*
- *Neelam Tikone is currently pursuing masters degree program in Computer Science in Indiana University, USA, E-mail: neelam9773@gmail.com*

For this group of patients new treatment strategies with aggressive approach will be more beneficial.

1.1 Area of the brain affected in depression:

A region of the human brain called subgenual cingulated gyrus area 25 or Brodmann's area 25 (BA 25 is a part responsible for the rise of emotion) grows hyperactive, disrupting neural signal causing depression. Also, studies have shown constant involvement of the Brodmann area 25 in both acute sadness and antidepressant treatment effects, suggesting a critical role in modulating negative mood [7] [8].

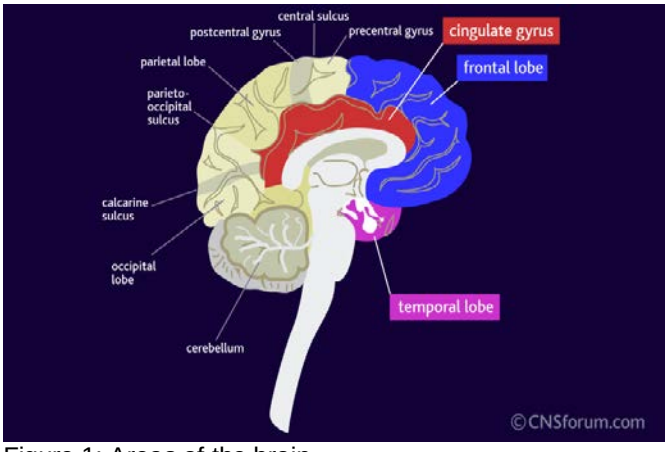

Figure 1: Areas of the brain

2 AIM

Giving an overall outlook of the technology incubated treatment approach like Deep Brain Stimulation (DBS) from the engineering perspective. This is responsive modulation

reducing the neurotransmitter activity of Brodmann's area 25 region of the brain in TRD and which helps in reversing the depressive symptoms in the above said group.

3 DISCUSSION

The study done by Mayberg [9] proved the use of electrical stimulator on BA25 gray matter, interconnected frontal and subcortical regions in reversing the pathological metabolic activities in these areas of the brain. This produced favourable clinical changes in the symptoms in patients with TRD.

In this study, six patients were taken met DSM IV-TR (Diagnostic and Statistical Manual of Mental Disorders) criteria for major depressive disorder (MDD) with a major depressive episode (MDE) of at least 1 year duration diagnosed by structured clinical interview for DSM IV-TR [10], and all had severe depression with a minimum score at entry of 20 on the 17 item Hamilton Depression Rating Scale

(HDRS) [11]. Each met stringent criteria for treatment resistance defined as failure to response to a minimum of four different antidepressant treatments, including medications, evidence based psychotherapy, or electroconvulsive therapy, administered at adequate doses and duration during the current episode [6][12][13]. Subjects' demographic characteristics are presented in table 1 and table 2.

TABLE 1: Before Surgery Reading:

Table 1. Patient Demographics

Patient #	1	2	3	4	5	6
Gender	F	M	F	M	M	F
Current age	48	59	45	48	37	39
Age MDD onset	18	45	21	40	19	34
Current episode (yrs)	1.5	3	6	8	10	5
# Lifetime episodes	12	9	3	1	2	1
Hamilton depression score (17 item)	29	20	27	24	26	25
Past ECT	no	yes	yes	yes	yes	yes
Past psychotherapy	yes	yes	yes	yes	yes	yes
Family history MDD	yes	no	yes	yes	yes	yes

TABLE 2: After Surgery Reading:

Table 2. Hamilton Depression Rating Scale, HDRS-17, Scores over Time for Each Subject

Time	Hamilton Score[a]					
	Pt 1[b]	Pt 2[c]	Pt 3[b]	Pt 4[c]	Pt 5[b]	Pt 6[b]
Preop baseline	29	22	29	24	26	25
1 week postop (acute stimulation)	5	10	12	18	17	12
2 weeks postop (DBS off)	9	13	23	18	22	n/a
1 month	10	14	17	20	22	12
2 months	13	11	12	18	10	12
3 months	2	15	14	25	7	14
4 months	4	9	12	24	6	12
5 months	5	18	7	23	8	n/a
6 months	5	15	9	23	6	12

[a] Clinical response: decrease HDRS score >50%. Clinical remission: absolute HDRS score <8.
[b] Clinical responders.
[c] Clinical nonresponders.

The above result suggests that, DBS proved to be an effective technological advancement in order to reduce major depression.

3.1 What is Deep Brain Stimulation (DBS)?

Deep brain stimulation (DBS) is a surgical treatment in which a device called a neurostimulator delivers tiny electrical signals to the areas of the brain that control movement. It's not always for depression, doctors use DBS for treatment of other disorders such as Parkinson's and essential tremor as well.

4 WORKING MECHANISM:

The deep brain stimulation system consists of three components: Namely the Implanted Pulse Generator (IPG), the lead, and the extension.

DBS typically involves two separate surgeries:

- **Brain surgery -** Initially, the doctors have to identify the region of the brain where the electrodes will be placed. Analysis of an MRI scan helps find the region. Pre-surgery a stereotactic head frame is fixed to ensure that the patient's head remains still throughout the procedure. Local anaesthesia is used to numb the scalp, and a thin wire with electrodes is implanted into the brain. Next, a neurostimulator is implanted near the collarbone. The patient must be awake during the procedure so that the neurologist or surgeon can ask questions to make sure the correct areas of the brain are being stimulated.
- **Chest wall surgery –** The chest wall surgery is done following the brain surgery. Here, a pulse stimulator is implanted within the patient's chest. A small opening is made behind the ear and the extension wire is made to pass from under the skin, connecting to the neurostimulator. The stimulator is programmed to send electrical pulses to the brain.

5 THE 3 COMPONENTS OF THE DEVICE

The electrode is a small tip-shaped device (imagine the plug for a pair of headphones) that is implanted deep into the region of the brain involved with the disease symptoms. The surface of the electrode has four metal pads used to transmit pulses of electricity. These pulses of electricity are small and only stimulate the brain tissue within close range of the electrode. This allows the electrical stimulation to specifically target only the brain region closest to where the electrode is implanted.

The pulse generator (also called the stimulator) is a small, box-shaped device that generates the electrical signals that are sent to the electrode. The pulse generator is usually implanted under the skin in a space near the patient's chest. It includes a battery with a lifespan that ranges anywhere from two to seven years. The electrical patterns are generated in quick on-off pulses delivered at very high frequencies -- usually over 100 times per second. Only at these high frequencies does the stimulation help reduce the unwanted symptoms.

The extension is the last component of an implanted DBS device. This is simply an insulated cable that carries the electrical signals from the pulse generator to the electrode implanted in the brain. Having any part of the DBS device go through the skin would create a risk of infection, so the surgeon typically tunnels a small path under the skin from the pulse generator to the electrode.

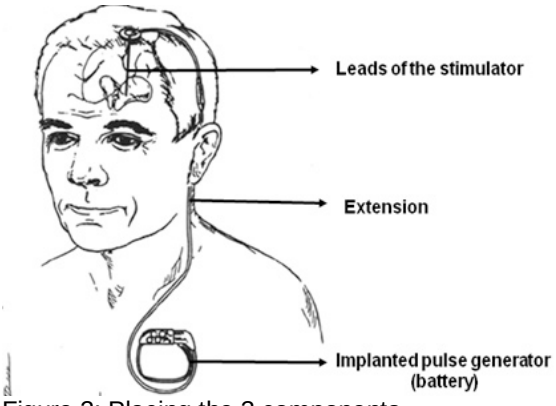

Figure 2: Placing the 3 components

5.1 How the device is used?

A handheld device is given to the patients. This device uses a magnet to communicate through their skin to the pulse generator thereby allowing the patient to control the dosages of electrical stimulation he or she intends to receive. The range of stimulation dosages is set by the doctor, but the fine-tuning of the device based is carried out by the patient depending on their own individual needs.

5.2 Current Scenario

This procedure is used only for patients whose symptoms show no changes while on medications, or whose medications have severe side-effects. The direct effect of this procedure on the physiology of brain cells and neurotransmitters is currently under debate, but by sending high frequency electrical impulses into specific areas of the brain it can reduce the symptoms and/or directly diminish the side-effects induced by medications, allowing a decrease in medications, or making the medications slightly more tolerable.

The most difficult and tricky part of the procedure for a surgeon implanting a deep brain stimulation device is, to safely implant the electrode in the precise target location within the brain. All humans being unique, their brains are also unique making each person's brain structure a little different from the other. The task of locating and accessing a specific brain structure without disturbing the surrounding structures requires the use of special tools and techniques.

The standard tool which is used for most delicate and flimsy brain surgeries is a stereotactic frame. This frame is basically a metal structure that holds the patient's head very still and gives the doctors a stable work area to make their measurements. The surgeon also relies on high resolution imaging techniques to help know the location of specific structures within the brain

DBS can also have certain side effects such as breaks in the extension wire or movement of the stimulating electrode. The above, are also the major causes of device failure. The side effects caused by the electrical stimulation from the DBS electrode vary from patient to patient and commonly include minor sensory problems. Psychological side effects might include sudden mood changes. These pitfalls are usually temporary and can be reversed by switching off the stimulation.

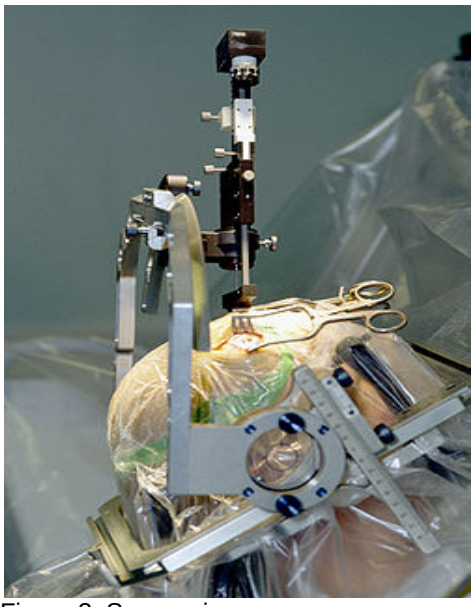

Figure 3: Surgery in progress

6 CLINICAL BENEFITS OF DBS:

1. DBS produces both local and remote regional effects with suppression of abnormally increased baseline BA 25 activity which is similar to the response achieved with antidepressants.
2. The high frequency DBS induces synaptic failure in the target area [14].
3. Acute deactivation of hyperactive BA 25 with DBS produces immediate favourable changes in the mood [15].
4. DBS also produces favourable changes in the activity of hypothalamus and brainstem which are monosynaptically connected to BA 25 resulting in improved level of energy, motivation and sleep complains [15].
5. DBS is responsible to bring about more global changes in functioning of TRD.
6. Vaidya and Duman et al, 2001 have observed that the persistent benefit of DBS in TRD even after cessation of stimulation. The phenomenon of ongoing clinical benefit after DBS discontinuation has been observed in other brain disorders like Parkinson's disease [17], epilepsy and dystonia [18][19].

7 CONCLUSION

DBS is one of the most recent, effective and novel intervention that involves high end technology for severely disabled patients with Treatment Resistant Depression.

ACKNOWLEGMENTS

The authors wish to thank Dr. Chhaya Verma and Mr. Sajid Abdullah for believing in us and the idea and for their extensive support.

REFERENCES

1) Wang, P.S. (2003). National Co-morbidity survey replication. The epidemiology of major depressive disorder: results from the National co-morbidity Survey Replication (NCS-R). JAMA *289*, 3095–3105.
2) Manji, J.K., Drevets, W.C., and Charney, D.S. (2001). The cellular neurobiology of depression. Nat. Med. *7*, 541–547.
3) Nemeroff, C.B. (2002). Recent advances in the neurobiology of depression. Psychopharmacol. Bull. 36 (Suppl.), 6–23.
4) Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., and Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.
5) American Psychiatric Association, A.M. (2000). Practice guideline the treatment of patients with major depressive disorder (revision). Am. J. Psychiatry *157*, 1–45.
6) Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. Biol. Psychiatry 53, 649–659.
7) Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin,R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., and Fox, P.T. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J.Psychiatry 156, 675–682.
8) Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., Goldapple, K.K.,Kennedy, S., Segal, Z., and Rafi-Tari, S. (2004). Limbic-Frontal Circuitry in Major Depression: A Path Modeling Metanalysis. Neuroimage 22, 409–418.
9) Helen S. Mayberg et al, Neuron, Vol. 45, Issue 5, 651–660, March 3, 2005.
10) First, M.B., Spitzer, R.L., Gibbon, M., and Williams, J.B.W. (2001).Clinical Interview for DSM-IVTR (SCID-I): User's Guide and Interview–Research Version (New York: New York Psychiatric Institute Biometrics Research Department).
11) Hamilton, M.A. (1960). Rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
12) Nobler, M.S., Oquendo, M.A., Kegeles, L.S., Malone, K.M., Campbell,C.C., Sackeim, H.A., and Mann, J.J. (2001). Decreased regional brain metabolism after ECT. Am. J. Psychiatry 158, 305–308.
13) Thase, M.E., and Rush, A.J. (1997). When at first you don't succeed: Seuqntial strategies for antidepressant nonrsponders. J. Clin. Psychiatry 58 (Suppl.), 23–29.
14) Davis,K.D., Taub, E., Houle, S., Lang, A.E., Dostrovsky, J.O., Tasker,R.R., and Lozano, A.M. (1997). Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. Nat. Med. 3, 671–674.
15) Barbas, H., Saha, S., Rempel-Clower, N., and Ghashghaei, T. (2003). Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neurosci. *4*, 25.
16) Vaidya, V.A., and Duman, R.S. (2001). Depression–emerging insights from neurobiology. Br. Med. Bull. 57, 61–79.
17) Vidailhet, M., Vercueil, L., Houeto, J.L., Krystkowiak, P., Benabid, A.L., Cornu, P., Lagrange, C., Tezenas du Montcel, S., Dormont,

D., Grand, S., et al. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N. Engl. J. Med. 352,59–67.

18) Hodaie, M., Wennberg, R.A., Dostrovsky, J.O., and Lozano, A.M.(2002). Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43, 603–608.

19) Kumar, R., Lozano, A.M., Sime, E., and Lang, A.E. (2003). Longterm follow-up of thalamic deep brain stimulation for essential and parkinsonian tremor.Neurology 9, 1601–1604.