JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

LITERATURE REVIEW Open Access

Treatment of Memory Disorders – III. Brain Electromagnetic Neuro Stimulation

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Received date: March 12, 2024, **Accepted date:** March 18, 2024, **Published date:** March 24, 2024.

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Abstract

In rare cases where patients may not improve using standard approaches, surgery can be an option including electroconvulsive therapy, transcranial electrotherapy stimulation, continuous theta burst stimulation, repetitive transcranial magnetic stimulation, vagus nerve stimulation, magnetic seizure therapy, and deep brain stimulation. Brain stimulation is a means to potentially remediate symptoms in a range of neurological and psychiatric diseases. After a brief chronicle of the development and modeling of brain circuits, I will discuss in their several particulars the principle and application of these several procedures, which still need to be further investigated and used only at centers with expertise in them.

Abbreviations

AAN: American Academy of Neurology; ACS: Alternating current stimulation; ADHD: Attention-deficit/hyperactivity disorder; AE: Adverse effects; BDD: (FDA's) Breakthrough device designation; BST: Brain stimulation therapy; cTBS: continuous TBS; cETS: cranial ETS: DBS: Deep brain stimulation; DCS: Direct current stimulation; ECT: Electroconvulsive therapy; EEG: Electroencephalogram; ET: Essential tremors; ETS: Electrotherapy stimulation; FDA: (U.S.) Food & Drug Administration; GABA: Gamma-aminobutyric acid; GPi: Globus pallidus internum; HDE: Humanitarian device exemption; IPG: Implantable pulse generator; IRB: Institutional review board; LEC: Local ethics committee; lMA: lateral motor area; MDS: Movement Disorders Society; mGPi: medial GPi; MA: Motor area; MNS: Median nerve stimulation; MST: Magnetic seizure therapy; NIMH: (U.S.) National Institute for Mental Health; NINDS: (U.S.) National Institute for Neurological Disorders & Stroke; OCD: Obsessive-compulsive disorder; PD: Parkinson's disease; PTSD: Post-traumatic stress disorder; RCT: Randomized clinical trial; RNS: Random noise stimulation; rTMS: repetitive TMS; sEEG: stereoEEG; sMA: supplementary MA; tACS: transcranial ACS; TBS: Theta-burst

stimulation; tDCS: transcranial DCS; tETS: transcranial ETS; TMS: Transcranial magnetic stimulation; TNS: Trigeminal nerve stimulation; tRNS: transcranial RNS; TS: Tourette's syndrome; tUSS: transcranial USS; tVNS: transcutaneous VNS; USS: Ultrasound stimulation; VNS: Vagus nerve stimulation.

Keywords

Brain electromagnetic stimulation; Continuous theta burst stimulation; Deep brain stimulation; Magnetic seizure therapy; Median nerve stimulation; Memory disorders; Transcranial electrotherapy; Transcranial magnetic stimulation; Vagus nerve stimulation.

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In rare cases where patients may not improve using standard approaches, surgery can be an option. Surgeries include electroconvulsive therapy (ECT), transcranial electrotherapy stimulation (tETS), continuous theta burst stimulation (cTBS), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), magnetic seizure therapy (MST), and deep brain stimulation (DBS). Brain stimulation is a means to potentially remediate symptoms in a range of neurological and psychiatric diseases, however, precise targeting of stimulation is necessary to ensure efficacy. In this article, I will discuss the principle and application of these several procedures, which still need to be further investigated and used only at centers with expertise in them.

Brief chronicle of the development and modeling of brain circuits

Understanding the brain circuitry underlying movement-related symptoms, particularly Parkinson's disease (PD) and other movement disorders, contributed significantly to the development of the above procedures. It can be traced back several decades. Thus:

In 1947: Development of the stereotactic frame apparatus to target specific brain areas based on the knowledge of brain anatomy and function known at the time and refinement through trial- and-error.

In the 1950s: Various movement disorders including PD, essential tremors (ET), and dystonia were treated surgically by inactivating or lesioning brain regions involved in motor control. Overall, surgical lesions improved motor symptoms for many patients, though sometimes at the expense of irreversible deficits in other functions.

In the 1960s: Several reports noted that high-frequency stimulation of target regions mimicked surgical lesions, while lower-frequency stimulation worsened motor symptoms.

In 1972: Russian neurophysiologist Natalia Bekhtereva suggested that brain stimulation might itself be used as a treatment for movement disorders instead of permanent lesions.

In the mid-1970s: Mahlon DeLong used electrical stimulation to meticulously characterize the functions of neurons in different brain areas as animals performed movements.

In the 1980s: Technological advances made chronic stimulation suitable for broad clinical application.

During the 1980s: French physician-scientist Alim Louis Benabid and others developed the deep brain stimulation (DBS) procedure, involving the surgical implantation of electrodes into parts of the brain.

In the mid-1980s: Investigators supported by the (U.S.) National Institute for Neurological Disorders & Stroke (NINDS) were among the first to use an implanted device for deep brain stimulation in the thalamus as a treatment for chronic pain.

In 2000: Deep brain stimulation is introduced as an alternative and promising treatment option for patients suffering from severe Tourette's syndrome (TS).

In 2001: The magnetic stimulation therapy (MST) procedure is introduced.

In 2008: The (U.S.) Food & Drug Administration (FDA) clears the first repetitive transcranial magnetic stimulation (rTMS) device to treat several types of depression, including depression with comorbid anxiety and depression with suicidality.

In 2018: The FDA cleared rTMS for severe obsessive compulsive disorder and, more recently, a rapid-acting form of it for treatment-resistant depression.

In 2022: Deep brain stimulation received an FDA's Breakthrough Device Designation (BDD) to investigate its use for treatment-resistant depression.

With growing evidence for the safety of neurostimulation and results suggesting earlier intervention may be beneficial, researchers further examined its use for targeting different brain areas.

Further innovations are emerging with advances in neuroscience and technology. For example, while traditional DBS delivers constant stimulation, newer adaptive devices can self-tune stimulation in response to certain features of a person's brain activity or behavior.

One such closed-loop device had been approved for the treatment of medically-refractory epilepsy. Nonetheless, questions remain about exactly how some such procedures work, and new directions are likely to emerge through research on the mechanisms that underlie their benefits.

What are brain stimulation therapies?

Brain stimulation therapies (BSTs) treat serious mental illnesses and can play an important role in treating mental disorders. They are often used when a person with a serious mental illness is experiencing dangerous circumstances, such as not responding to the outside world or being at risk of self-harm. The therapies operate by activating or inhibiting the brain with electricity, which can be given directly through electrodes implanted in the brain or indirectly through electrodes placed on the scalp. The electricity can also be induced by applying magnetic fields to the head.

Research is ongoing to determine the best use of these therapies and if they are effective treatments for other disorders and conditions. The FDA has authorized certain such therapies to treat specific mental disorders, including depression, bipolar disorder, and obsessive-compulsive disorder (OCD). Other newer therapies may still be considered experimental.

The authorized therapies to be covered here are:

- Electroconvulsive therapy (ECT);
- Repetitive transcranial magnetic stimulation (rTMS); and
- Vagus nerve stimulation (VNS)

whereas the experimental therapies covered are:

- Magnetic seizure therapy (MST); and
- Deep brain stimulation (DBS).

Other brain stimulation therapies may also hold promise for treating mental disorders, including:

- Transcranial direct current stimulation (tDCS);
- Transcranial alternating current stimulation (tACS);
- Transcranial random noise stimulation (tRNS);

and

- Transcranial ultrasound stimulation (tUSS).

(**Note:** See the FDA website for the latest information, warnings, and guidance on brain stimulation devices and announcements about new ones.)

The FDA commonly gives two types of authorization to devices like BSTs:

- **Approved:** This means that the FDA has decided that the benefits of the device outweigh the known risks, as demonstrated by the results of clinical testing. Approval is usually required for devices that might have a significant risk of injury or illness, including devices implanted in the body.

- **Cleared:** It means that the device is substantially equivalent to a similar device that the FDA has already cleared or approved. Clearance is usually given to lower-risk devices used outside of the body.

How do brain stimulation therapies work?

In most cases, BSTs are used only after other treatments have been tried. Although less frequently used than medication or psychotherapy, BSTs hold promise for people with certain mental disorders who have not responded to other treatments. They should be prescribed and monitored by a health care provider with specific training and expertise together with a trained medical team. Most BSTs involve using anesthesia to sedate the patient and a muscle relaxant to prevent the patient from moving. If so, an anesthesiologist will monitor breathing, heart rate, and blood pressure throughout the procedure.

A BST treatment plan is based on a person's individual needs and medical situation, and usually also includes medication, psychotherapy, or both, which should usually be continued during and after therapy to maintain clinical improvement.

How do brain electroconvulsive therapies work?

Electroconvulsive therapy (ECT) is a noninvasive procedure that treats serious mental disorders by using an electrical current to induce seizure activity in the brain. It has the longest history of use for depression and is one of the most widely used BSTs. The procedure has been cleared to treat severe depressive episodes in people aged 13 years and older with depression or bipolar disorder and, in some cases, to treat schizophrenia, schizoaffective disorder, and mania. ECT is still considered the "gold standard" for treatment-resistant depression.

ECT is usually considered only if a person's illness has not improved after trying other treatments like medication or psychotherapy. To be eligible for ECT, a person must have severe, treatment-resistant depression or require a rapid response due to life-threatening circumstances, such as being unable to move or respond to the outside world (e.g., is catatonic), being suicidal, or being malnourished. ECT can be effective when medications have not worked, cannot be tolerated, or are undesirable due to physical illness, which is often the case in older adults. ECT also begins working more rapidly than antidepressant medications, usually taking effect within the first week of treatment.

How does ECT work?

A typical course of ECT is administered three times a week until a patient's symptoms improve (usually within 6–12 treatments). Frequently, a patient who undergoes ECT also takes an antidepressant or mood-stabilizing medication. Before a doctor performs ECT, the patient is sedated with a short-acting general anesthetic and given an intravenous muscle relaxant to prevent movement. During the procedure:

• Electrodes are placed at precise locations on the patient's head.

• An electric current is sent through the electrodes into the brain, causing seizure activity that lasts under a minute. Anesthesia ensures that the patient does not experience pain or feel the electrical pulses. Often, a blood pressure cuff is used on an arm or leg to block the muscle relaxant and allow movement of that limb to confirm that the seizure activity is adequate.

• The patient awakens 5–10 minutes after the procedure ends, feeling groggy at first as the anesthesia wears off, but after about an hour, be usually alert and able to resume normal activities.

Modern ECT devices can deliver electrical signals using brief or ultra-brief pulses. These short pulses are as effective as the traditional form of ECT but are given at a lower dose, helping further reduce cognitive side effects.

Although ECT is effective in treating depressive episodes, follow-up treatment—either antidepressant medication or 'maintenance ECT' —is usually required to sustain clinical improvement and reduce the chances that symptoms return. Maintenance ECT varies depending on the patient's needs and may range from one session per week to one session every few months.

ECT Side Effects

The most common side effects associated with ECT include:

- Aches (head, muscles).
- Disorientation or confusion.
- Memory loss.
- Upset stomach.

Some patients may experience memory loss, especially of memories around the time of treatment. The memory problems are more severe, but usually improve over the days and weeks following the end of a treatment course. Also, memory problems are more common with the traditional form of ECT, known as 'bilateral ECT', in which electrodes are placed on both sides of the head. In comparison, 'unilateral ECT' involves placing an electrode on only one side of the head, typically the right side, because it is opposite the brain's learning and memory areas, with another electrode placed on top of the head.

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive therapy that uses a magnet to deliver repeated low-intensity pulses to stimulate the brain. The magnetic field it creates is about the same strength (1 Tesla) as an MRI scan.

rTMS uses

The FDA cleared the first rTMS device in 2008 to treat several types of depression, including depression with comorbid anxiety and depression with suicidality in people who did not respond to at least one antidepressant medication in the current depressive episode. Although ECT is still considered the "gold standard" for treatment-resistant depression, strong clinical evidence supports the effectiveness of rTMS in reducing depressive symptoms. rTMS is now used to treat moderate-to-severe depression in cases where medications have proven ineffective or intolerable.

In 2018, the FDA also cleared rTMS for severe obsessive compulsive disorder (OCD) and, more recently, a rapid-acting form of rTMS for treatment-resistant depression. Accelerated protocols that act more quickly than standard rTMS show similar effectiveness while shortening treatment length. Thus, patients benefit from receiving an entire course of treatment in much less time and getting relief from their symptoms more rapidly.

Newer rTMS forms involving magnetic pulses with other parameters are also under investigation to treat depression, OCD, and other mental disorders.

How does rTMS work?

Rather than electric currents, rTMS uses low-intensity magnetic pulses to stimulate the brain. Unlike ECT, in which stimulation is generalized, in rTMS, magnetic stimulation is targeted to a specific brain site. Also, in contrast to ECT, the procedure does not require anesthesia and can be performed in a clinical or office setting. A typical rTMS session lasts 30–60 minutes. A typical course of rTMS treatment consists of daily sessions, 5 days per week for 4–6 weeks. Accelerated rTMS protocols work much faster (within seconds to minutes). In this case, multiple sessions are delivered on a single day, with short breaks in between.

During the procedure:

• An electromagnetic coil is held against the head near an area of the brain thought to be involved in mood regulation, cognitive control, or both. These brain areas include the left prefrontal cortex (for depression) and the dorsomedial prefrontal cortex or anterior cingulate cortex (for OCD). In deep TMS, two coils may be used to deliver more stimulation to the region and target larger structures deep in the brain.

• Short electromagnetic pulses are repeatedly administered through the coil or coils. The patient usually feels a slight knocking or tapping on the head as the pulses are administered.

• The magnetic pulses pass easily through the skull and cause small electric currents that stimulate nerve cells in the targeted brain region.

There is currently no consensus on the best way to position the coil on the head or deliver the electromagnetic pulses. It has also yet to be determined if rTMS works best when delivered as a single treatment or when combined with medication, psychotherapy, or both. Research is underway to establish the safest and most effective uses of rTMS, the optimal brain sites to target, and the best follow-up approach to sustain clinical improvement.

rTMS side effects

Despite being considered a safe technique, rTMS carries the risk of inducing seizures among other milder adverse events and, thus, its safety should be continuously assessed. Several research groups conducted studies of the safety and tolerability of rTMS in patients. They estimated the risk of seizures and other adverse events during or shortly after rTMS application. They concluded that the atypical seizure happened during high-frequency rTMS with maximum stimulator output for speech arrest, clinically arising from the region of stimulation.

Further, the risk of seizure induction in patients undergoing rTMS is small whereas the risk of other adverse events is similar to that of rTMS applied to other conditions and to healthy subjects. Nonetheless, these results should be interpreted with caution. The similarity between the safety profiles of rTMS supports further investigation of rTMS as a therapy. Overall, rTMS is safe and well tolerated by patients. Its side effects include:

- Discomfort at the site on the head where the magnet is placed.
- Contraction or tingling of scalp, jaw, or face muscles during the procedure.
- Mild headaches or brief lightheadedness.
- Dizziness.

Using magnetic pulses and targeting a specific brain site results in a milder stimulation than in ECT, avoiding most seizure activity. Although it is possible for the

procedure to cause seizures, the risk is rare. Most side effects appear to be mild and short-term when expert guidelines are followed. Long-term side effects have not been determined, and more research is needed to establish the long-term safety of rTMS.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is a surgical procedure that involves a device implanted under the skin. The device sends electrical pulses through the left vagus nerve that runs from the brainstem through the neck and down the side of the chest and abdomen. The nerve carries messages from the brain to the body's major organs, including the heart, lungs, intestines, and between areas of the brain that control mood, sleep, and other functions. More recently, this therapy has been simplified by the introduction of noninvasive VNS (known as transcutaneous VNS [tVNS]), which uses a portable device to send electrical stimulation through the skin to activate the vagus nerve. Although tVNS is still experimental, the approach may offer advantages over surgical VNS, such as greater accessibility and affordability, while avoiding surgical complications.

VNS to improve behavioral control

Non-invasive electrical stimulation of the vagus nerve via tVNS has been studied for its effects on cognitive functions, and inhibitory control in patients. Taking into account the role that gamma-aminobutyric acid (GABA) plays in inhibitory control, the alteration of GABA neurotransmission and the possibility to increase its release with tVNS may improve behavioral control in movement disorders.

VNS other uses

VNS was initially developed as a treatment for epilepsy. Research using brain scans showed that the procedure also affected areas of the brain involved in mood regulation, with favorable effects on depression symptoms. In 2005, the FDA approved surgical VNS for depression when the following conditions are met:

- The patient is 18 years of age and older.
- The depression has lasted for 2 or more years.
- The depression is severe or recurrent.
- The depression has not eased after trying at least four other treatments.

However, despite FDA approval for depression, VNS is not intended as a first-line treatment and remains infrequently used. The results of studies examining its effectiveness for depression have been mixed. Whereas a review of clinical trials of VNS for treatment-resistant depression found a sustained reduction in depression symptoms and enhanced quality of life, other studies did not report meaningful improvements.

A portable VNS device has been cleared by the FDA to treat post-traumatic stress disorder (PTSD) under a 'Breakthrough Device Designation (BDD)", given to medical devices with preliminary evidence of clinical effectiveness compared to other available treatments. Research is ongoing to test the efficacy and safety of tVNS for depression, PTSD, and other mental disorders.

How does VNS work?

VNS is traditionally a surgical procedure:

• A device about the size of a stopwatch called a pulse generator is implanted in the upper left side of the chest while the patient is under anesthesia.
• Connected to the pulse generator is an electrical lead wire, which is then connected from the generator to the left vagus nerve.
• Typically, 30-second electrical pulses are sent every five minutes from the generator to the vagus nerve. The duration and frequency of the pulses may vary depending on how the generator is programmed.

• The vagus nerve, in turn, delivers those electrical signals to the brain.

The pulse generator, which operates continuously, is powered by a battery that lasts around 10 years, after which it must be replaced. Patients usually do not feel pain or discomfort as the device operates. It may be several months before a patient notices any benefits, and not all patients respond to VNS. Some patients have no improvement in symptoms, and some may even get worse.

The device can be temporarily deactivated by placing a magnet over the chest where the generator is implanted. A patient may want to deactivate the device if side effects become intolerable or before engaging in strenuous activity or exercise because it can interfere with breathing. The device reactivates when the magnet is removed.

Noninvasive forms of VNS consist of a device worn around the neck or ears or a handheld device. There are many questions about the most effective stimulation sites, parameters, and protocols for tVNS, and research is ongoing to determine the optimal conditions to achieve the greatest clinical benefits.

VNS side effects

VNS is not without risk. There may be complications, such as infection or pain from the implant surgery, or the device may come loose, move around, or malfunction, all of which can require additional surgery to correct. Other potential side effects include:

- Discomfort or tingling in the area where the device is implanted.
- Voice changes or hoarseness.
- Cough or sore throat.
- Neck pain or headaches.
- Breathing problems, especially during exercise.
- Difficulty swallowing.
- Nausea or vomiting.

If cleared by the FDA, tVNS devices may help overcome some of these surgical issues. Nonetheless, mild side effects of tVNS have been reported, including:

- Tingling, pain, or itchiness around the stimulation site.
- Nausea or vomiting.
- Dizziness.

The long-term side effects of all forms of VNS are unknown.

Other brain stimulation therapies are actively being explored for specific mental disorders. The following therapies are still considered experimental and have not yet been authorized by the FDA to treat mental disorders.

Magnetic Seizure Therapy

Magnetic seizure therapy (MST) is a noninvasive procedure that uses high-powered magnetic stimulation to induce seizures. The seizures are targeted to a specific site in the brain. In the U.S., MST is available only as part of a clinical trial or research study.

How does MST work?

MST combines aspects of both ECT and rTMS. Like rTMS, MST uses magnetic pulses to stimulate a specific brain site. The pulses are given at a higher intensity and frequency than in rTMS to induce a seizure. Like in ECT, the patient is anesthetized and given a muscle relaxant to prevent movement during the procedure. The goal is to retain the effectiveness of ECT while reducing the risk of cognitive side effects.

During the procedure:

• An electromagnetic coil is held against the head,

typically targeting the brain's prefrontal area.

• Rapidly alternating strong magnetic pulses pass through the coil into the brain to induce a seizure. Anesthesia is used to ensure that the patient does not experience pain or feel the electrical pulses.

• The magnetic dosage is individualized for each patient by finding the patient-specific seizure threshold.

There is not agreement on MST's optimal dosing, coil size, and stimulation site, and researchers are actively conducting studies to determine those specifications.

MST uses

Introduced in 2001, MST is currently in the early stages of investigation and clinical use for treating mental disorders.

A review of randomized clinical trials (RCT) examining MST for treatment-resistant depression showed promising results. However, more confirmatory evidence is needed to draw conclusions about MST's effectiveness in treating depression and other mental disorders.

MST side effects

Like ECT, MST carries the risk of side effects caused by anesthesia and the induction of a seizure. These side effects can include the following:

- Headaches or scalp pain.
- Dizziness.
- Nausea or vomiting
- Muscle aches or fatigue.

A systematic review and meta-analysis found that MST produced fewer memory problems and other cognitive side effects and caused less confusion and shorter seizures compared to ECT.

Magnetic Seizure Therapy

At the present time, deep brain stimulation (DBS) is still in its infancy. Due to differing legal jurisdictions and treatment facilities in different countries, guidelines issued by regulatory or/and other organizations and professional societies should be understood as recommendations of experts to be used in treatment-resistant, and severely affected patients. Further, it is highly recommended to perform DBS in the context of controlled trials.

DBS therapy is a surgical procedure that aims to improve memory that could not be accomplished with medication, and where surgery to treat the cause is not possible. It has become a valid option for individuals with severe symptoms that do not respond to conventional therapy and management, although it is an experimental treatment. It uses electricity to directly stimulate sites in the brain and can be used to treat severe OCD or depression in patients who have not responded to other treatments. It is available for other mental disorders only as part of a clinical trial. Selecting candidates who may benefit from DBS is challenging, and the appropriate lower age range for surgery is unclear. It is potentially useful in less than 3% of individuals. The ideal brain location to target has not yet been identified.

How does DBS work?

DBS works by sending electrical pulses to specific brain areas. It requires surgery to implant electrodes in the brain. The specific brain area depends on the disorder being treated. For depression, the brain area was initially the subgenual anterior cingulate cortex, which can be overactive in depression and other mood disorders, and now includes several brain areas. For OCD, the brain area is usually the ventral capsule/ventral striatum or the bed nucleus of the stria terminalis.

Prior to the procedure, scans of the brain are taken using

MRI as a guide to determine where to place the electrodes during surgery. Once a patient is ready for surgery:

• The head is numbed with a local anesthetic so the patient does not feel pain.

• The surgeon drills one or two small holes into the patient's head; threads a thin insulated wire, usually a pair of wires, through the hole(s) and into the brain; and places electrodes into a specific brain area (Figures 1-3).

• The patient is awake while the electrodes are implanted to provide feedback on their placement but does not feel pain because the head is numbed and the brain itself does not register pain.

• After the electrodes are implanted, the patient is put under general anesthesia.

• The electrodes are attached to wires that run inside the body from the head, through the neck and shoulder, and down to the chest where a small battery-operated generator (about the size of a pacemaker) is implanted. The pulse generator is placed under the skin in the upper chest. Whereas early DBS models used two pulse generators, one wired to each of the two implanted electrodes, most newer models use a single pulse generator to stimulate both electrodes.

• From the pulse generator, electrical pulses are delivered through the wires to the electrodes in the brain. Stimulation is applied continuously, and its frequency and level are customized to each patient. Although it is unclear exactly how DBS works to reduce symptoms, researchers believe that the pulses help "reset" the malfunctioning area of the brain so that it works normally again.

After the procedure, the patient may be given a device-based tool (like a hand-held controller or smart phone app) to help them monitor and manage their symptoms at home or provide feedback to their clinical care team.

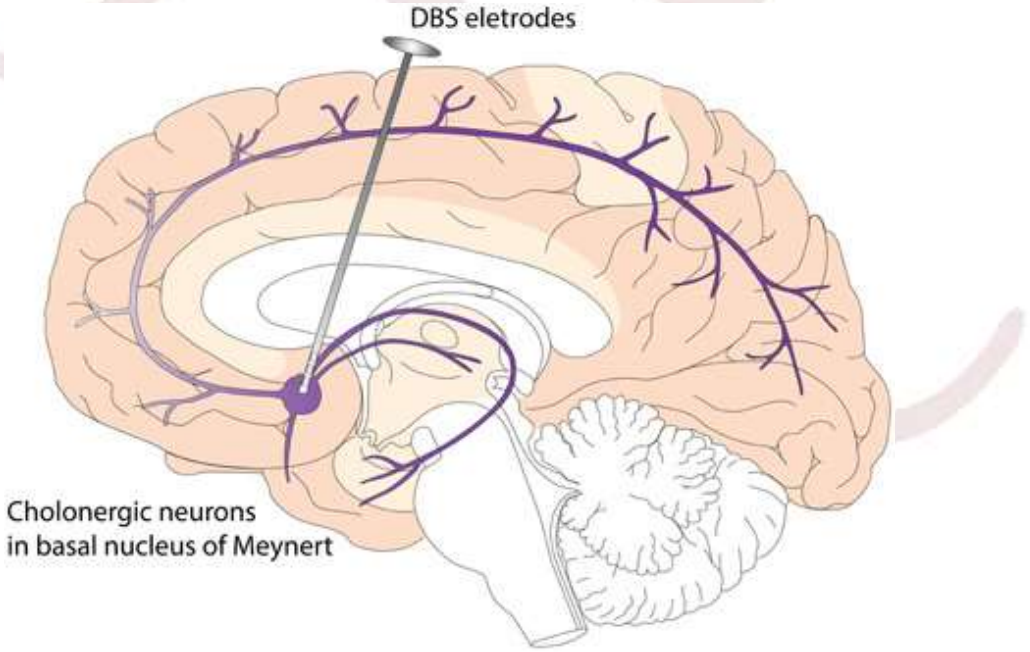


Figure 1: Pictorial showing an inserted deep brain stimulation electrode

Once the system is in place, and after a period of post-surgery healing, the device is programmed and tuned to sets of parameters that work best for each person over several visits with a neurologist.

The therapy works by delivering electrical pulses from the implantable pulse generator (IPG) along the extension wire and the lead, and into the brain.These pulses change the brain's electrical activity pattern at the target site to reduce motor symptoms.

The DBS system

The DBS system consists of three components: the lead, the extension, and the IPG. The "lead" (also called an electrode)—a thin, insulated wire—is inserted through a small opening in the skull and implanted into the brain (Figures 1-3).

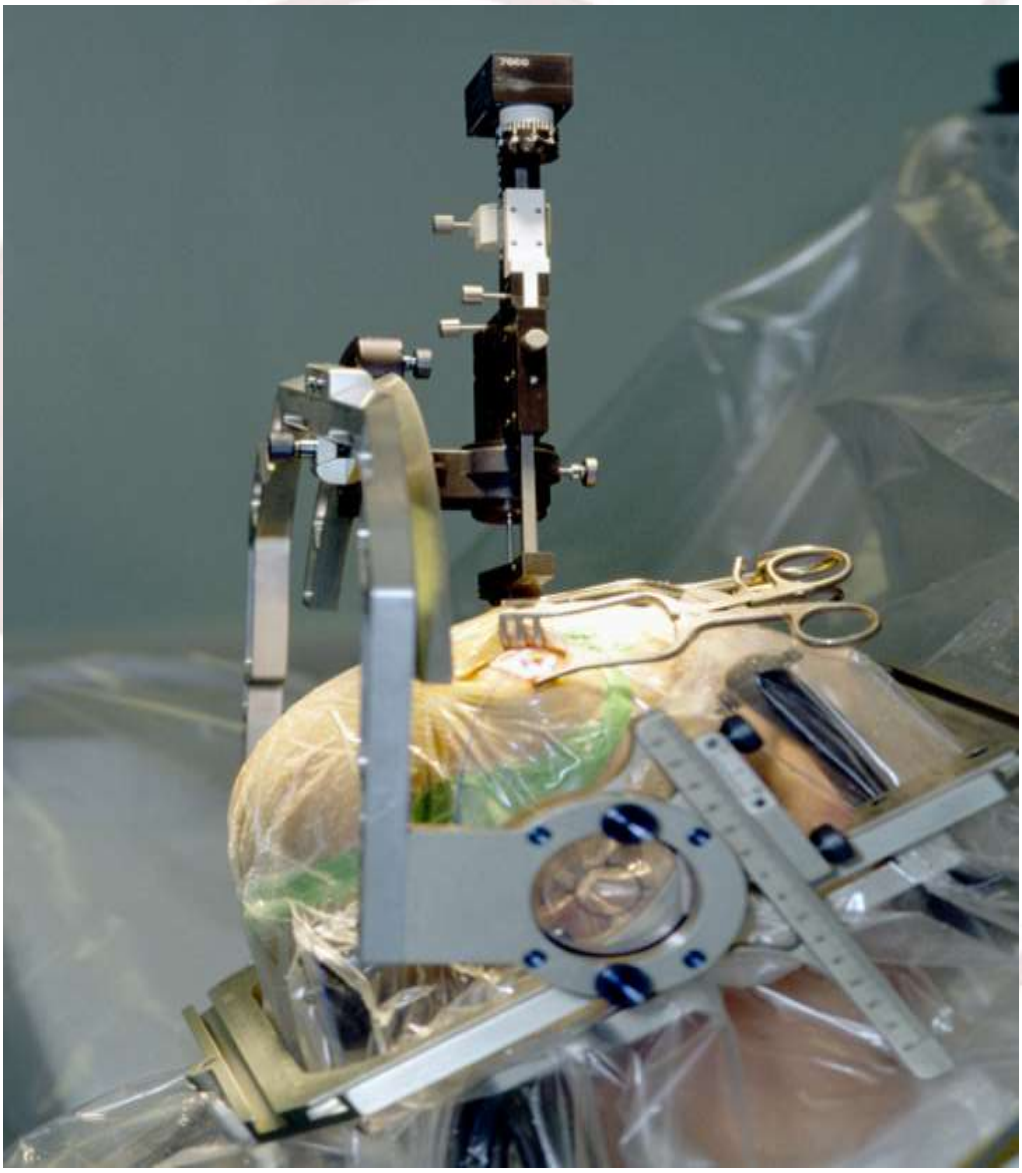


Figure 2: Placement of an electrode into the brain (The head is stabilized in a frame for stereotactic surgery)

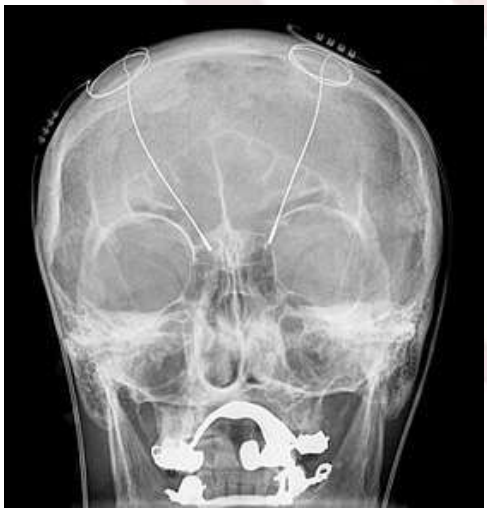
The tip of the electrode is positioned within the specific brain area depending on the disorder. The “extension” is an insulated wire that is passed under the skin of the head, neck, and shoulder, connecting the lead to the IPG. The IPG is a surgically-implanted, battery-operated medical device (the "battery pack") that is similar to a heart pacemaker and has the approximate size of a stop-watch. It delivers electrical stimulation to specific areas in the brain, blocking the abnormal nerve signals that cause symptoms. The IPG is usually implanted under the skin near the collarbone; in some cases, it may be implanted lower in the chest or under the skin over the abdomen.

Treatment rationale

Patients with severe memory loss and resistant to medical and other therapy may benefit from the application of DBS. An important challenge and limitation in evaluating the evidence related to this procedure is that, even in expert DBS centers, extremely few if any operations per year are performed. Furthermore, there is limited information from randomized clinical trials for analysis and interpretation (see the Sidebar).

DBS uses

DBS was first developed to treat movement disorders, including tremor and Parkinson's disease (PD). The FDA has since cleared DBS for severe OCD under a 'Humanitarian Device Exemption (HDE)', which is a provision for rare diseases or conditions experienced by relatively few patients among whom it has been difficult to gather evidence to demonstrate effectiveness. However, there is still much to be learned about optimizing DBS treatment. Similarly, in 2022, DBS received an FDA's Breakthrough Device Designation (BDD) to investigate its use for treatment-resistant depression.



(Bright white areas around the maxilla and the mandibles represent metal dentures that are unrelated to the DBS device)

Figure 3: DBS-probes are shown in an X-ray of the skull

Although a systematic review found that DBS improves OCD symptoms, other review articles have called for more confirmatory evidence before drawing conclusions about its effectiveness. A systematic review and meta-analysis showed favorable effects of DBS in treating depression symptoms. Nonetheless, it remains an experimental treatment for depression until more data from high-quality studies are available.

DBS side effects

DBS carries risks associated with any brain surgery. For example, the procedure may lead to:

- Bleeding in the brain or stroke.
- Device-related discomfort, pain, or infection around the incision.
- Infection near the incision site.
- Headaches.
- Disorientation or confusion.
- Cognitive impairment.
- Lightheadedness, dizziness, nausea, or vomiting.
- Trouble sleeping, agitation, or restlessness.

Because the procedure is still being studied, other side effects not yet identified are possible. Long-term benefits and side effects are unknown.

Surgery candidates and patients' selection

Surgery candidates should have the appropriate DSM-5 diagnosis with severe impairment despite exhaustive medical and other treatment trials. DBS should be offered to patients only by experienced DBS centers after evaluation by a multi-disciplinary team. Rigorous pre-operative and post-operative outcome measures and associated co-morbidities should be used. A local ethics committee (LEC) or institutional review board (IRB) should be consulted. While successes and failures have been reported for multiple brain targets, the optimal surgical approach remains unknown. Though still evolving, DBS is a promising approach for a subset of medication-refractory and severely-affected patients. The sidebar retraces the surgical evaluation phases.

Appropriate patient selection is one of the most important predictors of success of DBS treatment, making multi-disciplinary evaluation essential. Because of the complexity of the patient population, centers performing DBS have been encouraged to screen candidates pre-operatively and to follow them post-operatively. There has been concern about high risk of suicide and other negative psychiatric sequelae in patients not screened and monitored for depression, anxiety, and bipolar tendencies.

Treatment recommendations

Treatment recommendations have been made by certain professional societies. For example, the Movement Disorders Society (MDS) recommends that best practices be followed, including: Confirmation of diagnosis; use of multidisciplinary screening; preoperative and postoperative visits for tuning the stimulation parameters and recording stimulation effects; and stabilization of psychiatric co-morbidities inclusive of active suicidality. In 2019, the American Academy of Neurology (AAN) had also issued its own recommendations.

In 2011, 63 patients have received DBS in 19 centers worldwide. As reported in the literature, 59 had a beneficial outcome following DBS with moderate-to-marked movement disorder improvement. However, randomized controlled studies including a larger number of patients are still lacking. Although persistent serious adverse effects (AEs) have hardly been reported, surgery-related (e.g., bleeding, infection) as well as stimulation-related AEs (e.g., sedation, anxiety, altered

mood, changes in sexual function) may occur. Only two studies on just a few patients fulfill some of the evidence-based criteria. DBS for movement disorders such as, for example, Tourette's syndrome (TS) is therefore still highly experimental.

Stimulated brain regions

Different key structures and different brain targets have been defined for DBS:

- Thalamus: Centromedian-parafascicular complex region and subthalamic nucleus.
- Globus pallidus: Internus (ventral and dorsal), externus, and anteromedial (which is probably more likely than sham stimulation to reduce tic severity.
- Nucleus accumbens: Ventral capsular.
- Basal ganglia.
- Vagus nerve.

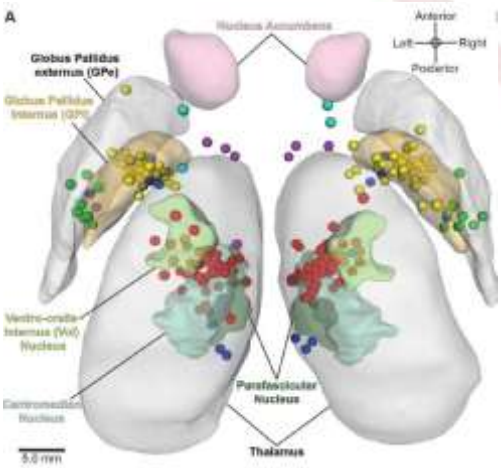
Figure 4 shows the active DBS contact lesions in the bilateral atlas space (3D superior view). The circles represent an active DBS contact colored by its intended structural DBS target region. The active contacts are usually all found to be located relatively near the intended target nuclei.

Treatment complications

Complications of treatment, including infection and removal of hardware, appear more common with DBS than with other neurologic conditions.

Benefits and risks of DBS

DBS is a surgical procedure that involves minimal permanent surgical changes to the brain and is minimally invasive. There is a low chance the placement of the stimulator may cause bleeding or infection in the brain. Nonetheless, it carries some associated risk. Complications may include bleeding and swelling of brain tissue, headaches, seizures, and temporary pain following the surgery. Such complications may result from mechanical stress from the device but are generally reversible. Also, the hardware may erode or break down with use, requiring surgery to replace parts of the device. If the DBS causes unwanted side effects or newer, more promising treatments develop in the future, the IPG can be removed and the DBS procedure halted. Also, stimulation from the IPG is easily adjustable—without further surgery—if the person's condition changes. Data on harms related to the use of DBS can be found in the complete and unabridged practice guideline.



Source: Unknown

Figure 4: Active DBS contact lesions in the bilateral atlas space (3D superior view)

The largest available randomized trials of DBS have revealed benefits on motor and phonic tics for the ventral globus pallidus internus and the centromedian thalamic region target (refer to Figure 4). However, these studies have raised methodological concerns that need to be addressed in future trials. Such concerns include intracerebral hemorrhage (a probability of 0.5%–2.0%), infection (1%–3%), as well as DBS-specific issues such as lead migration and fracture (1%–3%) and device malfunction (1%–3%). There is little information on the effects of DBS on psychiatric co-morbidities.

Prognosis following the procedure

DBS changes the brain firing pattern but does not slow the progression of the neurodegeneration. Despite small patient numbers, the procedure remains a valid option for medically intractable patients. Different brain targets result in comparable improvement rates, indicating a modulation of a common network. Future studies might focus on a better characterization of the clinical effects of distinct regions, rather than searching for a unique target.

International DBS Registry

An international DBS Registry has been developed to collect data on DBS outcomes in patients in various centers. The Registry also collects information about responses to non-standardized selection criteria, various brain targets, differences in hardware, and variability in the programming parameters used.

Transcranial electrotherapy stimulation

Recent imaging data suggest that a disruption in the pattern of functional connectivity in cortico-basal ganglia networks could reflect a defect in brain maturation. However, it is difficult to capture on-line the cortical changes associated with tic generation using imaging techniques due to moving artifacts. The aims of the various TES studies relate to median nerve stimulation (MNS), continuous theta burst stimulation (cTBS), brain stimulation, and vagus nerve stimulation (VNS).

Brain stimulation may help with symptoms such as memory, concentration problems, movement symptoms, and mood in patients with a movement disorder who have mild-to-moderate problems with these mental abilities. The procedure does not involve any surgery or hair removal but places a small amount of electrode gel on the head to hold two electrodes while a small electrical current is generated. While occasionally leading to mild side-effects (e.g. headache, nausea, fatigue, exacerbation of scalp skin conditions), there are no known harmful long-term effects. The positive benefits of brain stimulation can include improving brain functioning with memory problems. It is also possible that mood symptoms (e.g. depressive thoughts) could improve.

As a non-invasive therapy, cranial electrotherapy stimulation (cETS) may be applied in various areas with few side effects.

Continuous theta burst stimulation

Continuous theta burst stimulation (cTBS) is relatively safe and effective, and its efficacy in psychiatric diseases has been gradually recognized. However, the results of current researches in the case of tic disorder treatment are varied and the evaluation method is relatively simple. cTBS under functional MRI-guided stimulation is employed in patients with tics to explore individualized cTBS treatment parameters, including stimulation frequency, intensity, type, time, and stimulation target. Based on DBS studies that reported that the medial globus pallidus internum (mGPi) showed an obvious curative effect, a deep brain area can be modulated indirectly by a superficial target via functional connectivity. Therefore, cTBS stimulates the superficial target in the supplementary motor area (sMA) and the lateral motor area (lMA). Combined with clinical

symptoms and neuroimaging, the therapeutic effect of cTBS may provide a new therapeutic method and a better therapeutic effect for the disease.

Other types of brain stimulation therapy

Other types of brain stimulation therapy are in development. Most are used in combination with other therapies or treatments to optimize clinical outcomes. One emerging therapy that shows promise for treating mental disorders is trigeminal nerve stimulation (TNS), which was FDA-approved to treat attention-deficit/hyperactivity disorder (ADHD) in children, but it has not yet been approved to treat other conditions or for adults.

The 'Neuromodulation and Neurostimulation Program' and the 'Multimodal Neurotherapeutics Program' at the (U.S.) National Institute for Mental Health (NIMH) support researchers as they develop new therapies and refine existing therapies to treat mental disorders and conditions.

Table 1 is a summary of the several brain stimulation therapies including their therapeutic indication, the brain region(s) they stimulate, and their side effects.

Brain stimulation therapy	Therapeutic indication	Brain region(s) stimulated	Benefits & Side effects
Generally Activating/inhibiting brain with electrical/ magnetic fields	o Serious mental illnesses o Authorized: Depression, bipolar disorder, and OCD		
Electroconvulsive therapy (ECT)* - Unilateral - Bilateral	o Bipolar disorder o Depression ("gold standard") o Rapid response due to life-threatening circumstances *In some cases:* o Mania o Schizophrenia o Schizoaffective disorder	o Precise location(s) on patient's head	o Can be effective when medications have not worked, cannot be tolerated, or are undesirable Side effects: o Aches (head, muscles) - Confusion o Disorientation o **Memory loss** o Stomach upset
Transcranial electrotherapy stimulation (tETS)*	o **Memory** o Concentration problems o Movement symptoms o Mood symptoms (depressive thoughts)	o Corticobasal ganglia networks	o Improvements in brain functioning with **memory problems** o Improvements in mood symptoms (e.g. depressive thoughts) Side effects: o Fatigue o Headache o Nausea o Scalp or/and skin conditions exacerbation o No known harmful long-term effects
Repetitive transcranial magnetic stimulation (rTMS)*	o Depression, including with comorbid anxiety and with suicidality ("gold standard") o Severe obsessive compulsive disorder o Other mental disorders	o Head near area of the brain involved in mood regulation, cognitive control, or both - Dorsomedial prefrontal cortex or anterior cingulate cortex (for OCD) - Left prefrontal cortex (for	Side effects: o Contraction or tingling of scalp, jaw, or face muscles o Discomfort o Dizziness. o Mild headaches or brief lightheadedness o Risk of inducing seizures

		depression) o No consensus on the best approach	
Vagus nerve stimulation (VNS)*	o Behavioral control in movement disorders o Cognitive functions o Depression (not a first-line treatment) o Epilepsy o Inhibitory control o Mood regulation	o Electrical pulses through left vagus nerve from brainstem through neck, side of chest, and abdomen - Invasive (subcutaneous) - Non-invasive (transcutaneous)	Side effects: o Breathing problems o Cough or sore throat o Difficulty swallowing o Discomfort or tingling o Dizziness o Infection o Nausea or vomiting o Neck pain or headaches o Tingling, pain, or itchiness around the stimulation site o Voice changes or hoarseness Long-term side effects of all forms not known
Magnetic seizure therapy (MST)** (In U.S. only in clinical trials and research)	o Mental disorders o Treatment-resistant depression More confirmatory evidence needed	o Specific brain site to induce seizure	o Less confusion **o Fewer memory problems** o Fewer other cognitive side effects o Shorter seizures compared to ECT. Side effects: o Dizziness o Headaches or scalp pain o Muscle aches or fatigue o Nausea or vomiting No agreement on optimal dosing, coil size, or stimulation site
Deep brain stimulation (DBS)** (Experimental)	o Depression in patients not responding to other treatments o Movement disorders (tremor, Parkinson's disease) o Severe **memory loss**, resistant to medical and other therapy o Severe OCD (need confirmatory evidence)	o Basal ganglia o Globus pallidus: Internus (ventral and dorsal), externus, and anteromedial o Nucleus accumbens: Ventral capsular o Thalamus: Centromedian-parafascicular complex region and subthalamic nucleus o Vagus nerve. Direct stimulation of specific brain areas: o For depression: Subgenual anterior cingulate cortex o For OCD: Ventral capsule/ventral striatum or bed nucleus of stria terminalis	o Improves **memory** o Improves other mental disorders (only as part of a clinical trial) o Long-term benefits unknown Side effects: o Bleeding in brain or stroke o **Cognitive impairment** o Device-related discomfort, pain, or infection around incision o Disorientation or confusion o Headaches o Infection near incision site o Lightheadedness, dizziness, nausea, or vomiting. o Trouble sleeping, agitation, or restlessness. o Other side effects not yet identified o Long-term side effects not known
Transcranial alternating current stimulation (tACS)***			

Transcranial direct current stimulation (tDCS)***			
Transcranial random noise stimulation (tRNS)***			
Transcranial ultrasound stimulation (tUSS)***			

Key: *=Authorized; **=Experimental; *=Other promising therapies**

Table 1: The various brain stimulation therapies and their particulars

As seen from Table 1 above, when it comes to memory disorders, electrovonvulsive therapy (ECT), transcranial electrotherapy stimulation (tETS), magnetic seizure therapy (MST), and deep brain stimulation (DBS) are presently of interest for memory disorders consideration.

Conclusions and take-aways

- Surgery can be an optional treatment in those rare cases of severely disabled patients who do not improve using standard approaches. It includes electroconvulsive therapy, transcranial electrotherapy stimulation, continuous theta burst stimulation, repetitive transcranial magnetic stimulation, vagus nerve stimulation, magnetic seizure therapy, and deep brain stimulation.

- Brain stimulation therapies treat serious mental illnesses and can play an important role in treating mental disorders. They operate by activating or inhibiting the brain with electricity. The FDA has authorized certain such therapies to treat specific mental disorders, including depression, bipolar disorder, and obsessive-compulsive disorder. Other newer therapies may still be considered experimental.

- The authorized therapies include: Electroconvulsive therapy, repetitive transcranial magnetic stimulation, and vagus nerve stimulation whereas the experimental therapies include: magnetic seizure therapy and deep brain stimulation. Other brain stimulation therapies may also hold promise for treating mental disorders, including: Transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, and transcranial ultrasound stimulation. Surgical procedures need to be further investigated and used only at expert centers.

- In most cases, brain stimulation therapies are used only after other treatments have been tried. Although less frequently used than medication or psychotherapy, they hold promise for people with certain mental disorders who have not responded to other treatments. The treatment plan is based on a person's individual needs and medical situation, and usually also includes medication, psychotherapy, or both.

- Electroconvulsive therapy is a noninvasive procedure that treats serious mental disorders by using an electric current to induce seizure activity in the brain. It treats severe depressive episodes in people aged 13 years and older with depression or bipolar disorder and, in some

cases, to treat schizophrenia, schizoaffective disorder, and mania. It is still considered the "gold standard" for treatment-resistant depression.

- Continuous theta burst stimulation is relatively safe and effective in psychiatric diseases. Combined with clinical symptoms and neuroimaging, it may provide a new therapeutic method and a better therapeutic effect.

- Repetitive transcranial magnetic stimulation delivers repeated low-intensity pulses to stimulate the brain. It is used to treat moderate-to-severe depression in cases where medications have proven ineffective or intolerable. More recently, a rapid-acting form of it or treatment-resistant depression acts more quickly than the standard form and shows similar effectiveness while shortening treatment length. Despite being considered a safe technique, it carries the risk of inducing seizures among other milder adverse events, and thus, its safety should be continuously assessed.

- Vagus nerve stimulation, including its noninvasive transcutaneous form is still experimental but may offer advantages over surgery.

- Magnetic seizure therapy is a noninvasive procedure that uses high-powered magnetic stimulation to induce seizures targeted to a specific site in the brain. In the U.S., it is available only as part of a clinical trial or research study. It produces fewer memory problems and other cognitive side effects, and caused less confusion and shorter seizures compared to electroconvulsive therapy.

- Deep brain stimulation therapy is a surgical treatment that has become a valid option for individuals with severe symptoms that do not respond to conventional therapy and management, although it is an experimental treatment. It delivers electrical stimulation to specific areas in the brain that control movement, blocking the abnormal nerve signals that cause symptoms.

- Deep brain stimulation therapy should be offered to patients only by experienced centers after evaluation by a multi-disciplinary team. The optimal surgical approach remains unknown. Though still evolving, it is a promising approach for a subset of medication-refractory and severely-affected patients.

- Appropriate patient selection is one of the most important predictors of success of deep brain stimulation treatment, making multi-disciplinary evaluation essential. There is no consensus on the optimal brain target. There is little information on the effects on psychiatric co-morbidities.

- An international deep brain stimulation Registry has been developed to collect data on DBS outcomes in implanted patients in various centers.

- Brain stimulation may help with symptoms such as memory, concentration problems, movement symptoms, and mood in patients with a movement disorder who have mild-to-moderate problems with these mental abilities.

- Of the well-known therapies, it would appear from Table 1 that convulsive therapy, transcranial electrotherapy stimulation, magnetic seizure therapy, and deep brain stimulation could be of use in the treatment of memory problems.

Sidebar – Surgical evaluation phases

Pre-surgical non-invasive evaluation – Phase I

Pre-surgical evaluation consists of a one- or two-phase process to determine if surgery is the best option and can improve memory with minimal risk. Phase I involves all non-invasive (non-surgical) tests whereas Phase II involves invasive tests (requiring surgery) that are used in selecting patients.

Phase I evaluation is designed to find the area of the brain that is likely to be generating the memory disorder (the focus), to determine if that area can be safely treated, and to predict what kind of outcome might be expected.

There are generally six tests involved in Phase I, but not every patient requires every test available in this evaluation. For the selection of the necessary and appropriate tests, patients are evaluated by neurologists who determine such tests on an individualized basis. The tests provide separate independent information that can be correlated in order to zero-in on the location of origin of the memory disorder. These tests comprise:

Inpatient video-EEG monitoring

The aim of this test is to identify the likely location in the brain where memory disorders originate. As its name implies, inpatient video-EEG monitoring is a recording with simultaneous video and EEG. It is the most important pre-surgical test and is generally conducted in an inpatient setting in a specialized monitoring unit. It is performed with electrodes attached to the scalp (noninvasive monitoring). All the data are analyzed by a trained neurologist to evidence the likely location where the memory disorders might originate within the brain.

Magnetic resonance imaging (MRI)

The aim of this test is to detect abnormalities in the brain. The test may detect an abnormality that could be the cause of the memory disorders. With more powerful MRI machines and use of special protocols and software, subtle brain abnormalities are increasingly being identified.

Positron emission tomography (PET)

The aim of this test is to localize brain regions with decreased brain function. PET scans record the metabolic activity of the brain to determine if the brain is functioning normally. In patients with memory disorders, decreased brain function is seen in the region where they originate. On the other hand, the scan may show abnormalities even if the brain MRI is normal. PET scans are usually done in the outpatient setting.

Single-photon emission computed tomography (SPECT)

The aim of this test is to identify brain regions with increased blood flow. Single photon emission computed tomography (SPECT) scans can identify the brain regions where blood flow increases and thus indicate where the memory disorders might have begun. SPECT scans are performed when the patient is admitted to the hospital for video-EEG monitoring.

Neuropsychological evaluation and functional MRI

The aim of this combination test is to predict cognitive deficits after surgery. Neuropsychological evaluation and functional MRI (fMRI) are used to assess cognitive functions, especially language and memory function prior to surgery to determine which side of the brain is dominant for language and if there is decreased memory function. This allows prediction of cognitive deficits after surgery. Functional MRI measures blood flow changes in areas of the brain during the performance of specific cognitive tasks.

Intracarotid amobarbital/methohexital (Wada test)

The aim of this test is to predict language and memory function post surgery. Performed in selected cases, the test involves the injection of a medication such as sodium Amobarbital or Methohexital into one carotid artery at a time. The medication causes temporary (1-5 minutes) paralysis of one half of the brain allowing independent testing of language and memory function in the other half. This test is also used to predict post-operative deficits in language and memory function.

If all tests performed point to the same region of the brain, the patient is likely to be a good surgical candidate.

Based on the results of the Phase I evaluation, patients may be deemed good or poor surgical candidates. In some cases, despite all prior tests, surgical treatment may not be advisable so that more testing would be needed (called Phase II evaluation).

Presurgical invasive evaluation - Phase II

Phase II evaluation involves video-EEG monitoring with electrodes that are placed inside the skull (invasive monitoring). As there is more risk from invasive monitoring, the decision about the necessity for a Phase II evaluation is usually made by the neurological team as a whole and discussed in detail with the patient.

There are six surgical implantation options, each involving the implantation of electrodes either on the surface of the brain, or within the brain. The benefit of these electrodes is that they are closer to the area producing the memory disorders than those placed simply on the scalp. After surgical placement of electrodes, neurologists perform video-EEG monitoring in a similar fashion to the phase I monitoring.

The electrode types and implantation arrays differ and may include:

- Subdural electrodes: A subdural electrode grid is a thin sheet of material with multiple small (a couple of millimeters in size) recording electrodes implanted within it. The electrodes are placed directly on the surface of the brain. They have the advantage of recording the EEG without the interference of skin, fat tissue, muscle, and bone that may limit scalp EEG. Shapes and sizes of these sheets are chosen to best conform to the surface of the brain and the area of interest.

- Depth electrodes: These are small wires surrounded by electrodes, which are implanted within the brain itself through small skin pokes. The electrodes are able to record brain activity along the entire length of the implanted wire. They have the advantage of recording activity from structures deeper in the brain. They can be implanted.

- Electrodes combination: In a number of instances, it may be beneficial to implant a combination of subdural and depth electrodes.

Stereoelectroencephalography

Increasingly common, invasive monitoring may be done using stereoelectroencephalography (sEEG). Here, multiple depth electrodes are implanted in a specific pattern individualized to the patient. The three-dimensional space which is covered by the depth electrodes is designed to encompass the seizure focus.

Functional mapping

This is usually performed in patients with implanted subdural electrodes. Brief electrical stimulation is provided through each electrode separately to determine the normal function of the part of the brain underneath that electrode. It is a painless procedure. The purpose is to map out critically important areas of the brain such as

those necessary for motor, sensory, and language functions. This allows tailoring of surgical resections to minimize the risk of major neurological deficits after surgery.

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