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Shaping plasticity with non-invasive brain stimulation in the treatment of psychiatric disorders: Present and future

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There have been numerous excellent discussions and varying definitions of “plasticity” and how and whether that occurs on different neurobiological levels. There may be confusion about the term. For this chapter, we will talk about neuroplasticity as a broad term, which broadly encompasses plasticity across all cell types and levels of the nervous system. That is, we will not confine the discussion to neuronal or non-neuronal or genetic or behavioral or neurogenetic or synaptic plasticity. I would refer the interested reader to other chapters where the various methods for assessing plasticity have been addressed within specific diseases, for example, the chapter on schizophrenia. This chapter is not a discussion of synaptic plasticity within psychiatric diseases but rather is a focus on the term “plasticity” as a conceptualization of how diseases can be changed over time particularly with brain stimulation methods.

This chapter will view the flexibility and plasticity of psychiatric disease through the prism of clinical depression. We still do not fully understand the pathophysiology of depression or “the clinical depressions.” Clearly, what we lump under the umbrella term “depression” is likely multiple different diseases manifesting with a similar or at least roughly similar phenotype. Although many have tried, there are still no clean ways to divide the depressions into subgroups except in terms of prior disease course and treatment resistance, or the presence or absence of certain symptoms such as psychosis. We will largely focus on unipolar depression and bipolar depression will only be mentioned passingly through this chapter.

What exactly is depression? Roughly considered clinical depression is a state that the brain enters into, often after a loss or trauma, the symptoms of which can be conceptualized by three domains (George et al., 1994; Chapter 21 in Higgins and George, 2007). First, there is a problem with cognitive flexibility and function. Second, there are autonomic or basic bodily problems such as sleep, appetite, and energy. Third, there are more effective problems such as sadness, thoughts of despair, hopelessness, and thoughts of suicide. Although this tripartite grouping describes the illness it does not describe the brain-based mechanisms. There are also neurohormonal changes such as changes in adrenocorticotropic hormone (ACTH), stress hormones, and inflammation. Concerning plasticity, within the last decade, several researchers have speculated that depressions are a disease state characterized by inflexibility or hyper-connectedness. Depression is a disease that lacks plasticity or flexibility, which can be studied using neuroimaging. Dr. Andrew Leuchter and others

have shown with electroencephalography (EEG) connectivity and more recently with resting-state functional connectivity via functional magnetic resonance imaging (fMRI) that when patients are depressed the regular flexibility of the brain shifting from one state to the other is lost (Leuchter et al., 2009, Leuchter et al., 2013). Several lines of evidence suggest that neurophysiologic plasticity is impaired in depression. That is, there is a lack of plasticity in terms of moment-to-moment changes in activity in different circuits. Dichter and colleagues performed a systematic meta-analysis of the imaging studies assessing resting-state fMRI in depression (Dichter et al., 2014). The literature consistently showed that hyperconnectivity of the default mode network and hypoconnectivity of the cognitive control network differentiated treatment-resistant from treatment-sensitive MDD patients. Thus, it appears that depressed patients have maladaptive plasticity or inflexibility in certain circuits.

Another way to measure plasticity in depression is to take neurophysiologic measurements via single pulses of transcranial magnetic stimulation (TMS) delivered over the motor cortex and collect motor evoked potentials (MEPs) from electrodes placed on the contralateral hand. Researchers can test the efficacy of a brain stimulation treatment by acquiring MEPs before and after an intervention, such as pairing single pulses of TMS with median nerve stimulation in a technique called paired associative stimulation (PAS). PAS has increased the corticomotor plasticity by pairing the timing of the TMS pulse and median nerve stimulation to create long-term potentiation (LTP)-like plastic changes in the motor tract (Alder et al., 2019). Colleen Loo and colleagues have shown that in depression, the brain is less plastic as defined by the PAS protocol (Player et al., 2013). Loo and colleagues compared neuroplasticity using PAS in 23 subjects with DSM-IV major depressive episodes and 23 age- and gender-matched healthy controls. MEPs were acquired before and after PAS. After PAS, MEP amplitudes significantly increased in healthy controls compared with depressed subjects ($P = 0.002$). These neurophysiologic changes were further substantiated with a motor learning task (rotor pursuit), which showed that healthy controls also performed better on motor learning ($P = 0.02$). This study provided one of the first direct demonstrations of reduced neuroplasticity in depressed subjects, using an objective test. The EEG and functional connectivity studies set the stage for the idea that in terms of dynamic theory and systems and health the brain is flexible and plastic in health. In contrast, in depression, the brain becomes stuck in a rut perhaps due to the lack of plasticity. We are all familiar with patients who are hyper-ruminative and are fixated on one or two usually pathologic bad thoughts and cannot think flexibly about the array of different options. If one understands depression as a hyper-rigid inflexible or lack of plastic disease, then one can begin to understand and utilize brain stimulation approaches that have the promise of altering neuroplasticity and remediating psychiatric diseases.

There are now three US Food and Drug Administration (FDA)-approved brain stimulation treatments for depression: Electroconvulsive therapy (ECT), TMS, and cervical vagus nerve stimulation (VNS). We will not have the space to discuss as well transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), or pulsed ultrasound. Another important theme of the discussion about plasticity in psychiatric diseases is the focus on the time to respond and the maintenance of effect or durability of the various brain stimulation techniques that induced plastic changes of the brain (Sackeim, 2016; Caulfield, 2020). The

brain stimulation methods vary sharply in the amount of time that they take to get people well, and in their ability to sustain wellness and not have patients relapse. It seems obvious that these differences across the different brain stimulation methods in terms of speed of response and maintenance of effect are likely due to the underlying neurobiologic changes that they caused in terms of either synaptic changes versus scaffolding changes or changes to the neuron such as myelination versus rewiring. There is a lot more to understand about the translational neurobiology of these methods, specifically with respect to their speed of onset and durability of effect. The prior chapters are some of the best works available in understanding what may be going on in the brain as patients are treated with these brain stimulation methods.

Electroconvulsive Therapy: The oldest brain stimulation method known to treat depression is ECT, which has now been available and in widespread use for over 80 years (Caulfield and George, 2018). ECT involves the willful generation of 8–12 convulsions by passing electricity into the brain. These sessions are typically for 4–6 weeks. In the modern era, the response and remission rates with ECT are on the order of 80%–90%. Remission means that most depressed symptoms are no longer present and implies the ability to sustain a healthy state longer than mere response, which is defined by at least a 50% reduction in depression symptoms. Although ECT is our most effective treatment for acute depression, on its own it is not durable. Given no other treatments after ECT, well over 80% of depressed patients will relapse within several months. Thus, in the modern era, ECT patients are often treated while staying on medications even though the medications alone were not able to get them undepressed. Following the ECT course, patients are maintained on medications or maintenance ECT is used.

For decades, the efficacy of ECT was believed to depend only on the generalized seizure, while its cognitive side effects were determined largely by the intensity of electric stimulation (Ottosson, 1960; Kalinowsky and Hoch, 1961; Fink, 1979; Fraser, 1982; d'Elia et al., 1983; NIH, 1985). It is now becoming clear that seizure initiation in the prefrontal cortex (PFC) is fundamental to efficacy, whereas seizure expression in medial temporal lobe (MTL) regions is widely thought to contribute to amnestic effects. Furthermore, by applying physiologic electric stimuli, especially narrowing the pulse width (PW), thus avoiding the deposit of energy long after depolarization (Ranck, 1975; Geddes, 1987; Sackeim et al., 1994), studies have shown that high dose right unilateral (RUL) ECT delivered at 6 times the seizure threshold (6 × ST) matches the efficacy of traditional bilateral (BL) ECT and substantially reduces cognitive side effects. This is evident by the recent widespread adoption by the clinical community of ultra-brief pulse (UBP) stimulation (0.3 ms) over standard wide pulse or sine wave ECT.

A major theme in the refinement of ECT has been focusing on the area of stimulation and trying to limit the electric current density to brain regions that need to be changed or have plasticity induced while sparing areas that involve memory and cognition particularly the hippocampus. Carrying this idea even one step further our group at MUSC along with Professor Harold Sackeim at Columbia University in New York have pioneered yet another refinement in ECT called Focal Electrically Administered Seizure Therapy (FEAST) (Nahas et al., 2013; Sahlem et al., 2016, Sahlem et al., 2020). This approach uses rapid on and

off Direct Current and smaller electrodes to focus the seizure over the right prefrontal and orbitofrontal cortex. FEAST appears to be again as effective as conventional ECT but reduces the time to reorient and the degree of overall amnestic side effects because of the ability to restrict the focus of electric stimulation to the prefrontal cortex while avoiding the temporal lobe and hippocampus.

Returning to the concept of plasticity, does ECT, which produces a disruptive seizure, cause changes in plasticity? Some evidence may come from blood serum levels of brain-derived neurotrophic factor (BDNF), which is a key molecule involved in neuroplasticity. ECT increases serum BDNF production, suggesting that ECT can induce neuroplastic changes that underlie response and remission in depression scores (Brunoni et al., 2014). Additionally, several neuroimaging studies measuring functional connectivity suggest that ECT is switching the brain out of a hyper-connected rigid state into a more flexible plastic model. Leaver and colleagues measured resting-state functional connectivity (RSFC) in patients with treatment-resistant depression (n = 30), using fMRI acquired before and after completing a treatment series with right-unilateral ECT. Using independent component analysis, they assessed changes in RSFC with (1) symptom improvement and (2) ECT regardless of treatment outcome in patients, with reference to healthy controls (n = 33, also scanned twice). After ECT, they found consistent changes in RSFC within targeted depression-relevant functional networks in the dorsal anterior cingulate (ACC), mediodorsal thalamus (mdTh), hippocampus, and right anterior temporal, medial parietal, and posterior cingulate cortex in all patients. Both ECT and clinical change were associated with RSFC modulation in dorsal ACC, mdTh, and hippocampus, which may indicate that these regions underlie the mechanisms of clinical outcome in ECT and may be effective targets for future neurostimulation therapies. There are also studies documenting that ECT results in increased size of various brain regions over the month and a half of treatment, particularly the hippocampus (Wade et al., 2016). Thus, ECT, which is the most effective acute treatment for depression, is producing plastic changes in the brain clearly that induce a therapeutic response.

Transcranial Magnetic Stimulation: As we discussed above, ECT works by inducing a convulsion in the brain and does not work if it is applied sub convulsively. However, could repeat sub convulsive stimulation also causes plastic changes and treat depression? (Sackeim, 1994). The idea was quite controversial in the early 1990s when first proposed (George, 1994; George et al., 1994; George and Wassermann, 1994). TMS uses capacitors that rapidly send electricity through coiled wires to create an electromagnetic field. When the TMS coil containing these coiled wires is placed close to the head, the electromagnetic field can induce excitatory cortical activity, particularly when using patterns of pulses such as high-frequency repetitive TMS (rTMS).

Why depression? rTMS has had the biggest clinical success as a therapy in treating treatment-resistant depression. Many have wondered why we moved rTMS into the clinic for depression, and not some other neuropsychiatric illness with a better understanding of the circuits involved, like stroke recovery, Parkinson’s disease, or tinnitus (Ridding and Rothwell, 2007). There was clear evidence from ECT that regional electromagnetic stimulation could treat depression (Nobler et al., 1993, Nobler et al., 1994). Additionally,

beginning in the early 1990s there was an emerging consensus about key cortical and subcortical regions involved in depression, some of which could be directly stimulated with TMS (George et al., 1994, George et al., 1995a, George et al., 1999). Additionally, activity in some of the regions correlated with improvements in symptoms following sleep deprivation (cingulate) (Wu et al., 1992) or ECT (prefrontal cortex) (Nobler et al., 1994, Nobler et al., 2001). Ironically, some ECT practitioners and researchers were among the most ardent early opponents of TMS. Their incorrect logic concern was that TMS was not causing seizures (true), and seizures were necessary for the antidepressant effects of ECT (also true), so a non-seizure-producing intervention device could not work (false) (Fink, 1990). [We did not then have the exquisite tools of today where we can show changes in regional functional connectivity that mediate the clinical effects of rTMS (Avissar et al., 2017)]. Luckily, depression turned out to be a superb initial choice. Methodically uncovering the details required for clinical use, the community of TMS researchers made initial educated guesses about many issues (coil location, intensity, frequency, pulse width, train length, total number of pulses in a day, dosing schedule, and the number of pulses in a treatment course). We were likely both lucky and relatively clever, and the initial choices proved clinically effective (George et al., 1995b, George et al., 1996a, George et al., 1997). Importantly, it took over a decade of work refining these choices in incremental small trials before we were “ready” to launch the first pivotal studies (O’Reardon et al., 2007; George et al., 2010). A TMS industry was born, and this led to FDA approval in 2008 (O’Reardon et al., 2007; George et al., 2010) and now widespread insurance coverage for rTMS to treat acute major depressive episodes.

TMS thus represented a paradigm shift in psychiatry. It is not a talking therapy, does not involve taking medications by mouth or an IV, does not involve seizures, and modulates circuit activity in the brain. Because it is focal and non-invasive, there are no systemic side effects and no drug–drug interactions. It thus is a good choice in medically complicated patients and does not involve anesthesia or have deleterious cognitive effects. Below we highlight several key questions in TMS that are ongoing areas of research promising to further improve and refine TMS for depression.

Who to treat? The initial studies involved only treatment-resistant patients, and TMS (like all our treatments) works less well in patients who are more treatment-resistant. Studies are now enrolling patients with less treatment resistance. For reasons of both safety and scientific integrity, the early trials only enrolled patients who were weaned from their antidepressant medications (George et al., 2010). Now, most patients are treated safely and with good efficacy while staying on antidepressant medications (Carpenter et al., 2012; Yesavage et al., 2018).

Where to stimulate? This is an exciting area of research. George and others initially proposed the “5 cm rule,” where treaters placed the TMS coil 5 cm anterior to the location found to induce a thumb twitch (George et al., 1995b, George et al., 1996a, George et al., 1996b). Unfortunately, in perhaps 1/3 of patients, this does not reach the prefrontal cortex (Herwig et al., 2001, Herwig et al., 2003; Herbsman et al., 2009) and most clinicians now typically place the coil based on an EEG grid system that accounts for differences in head size as the best estimate of where the prefrontal cortex is (Beam et al., 2009). The

search is on for the best cortical location, either at a group level or individually guided via functional connectivity. In a fascinating line of research, it may be that the clinical interview corresponds with the “proper” TMS coil location (Drysdale et al., 2017; Weigand et al., 2018). Fox and colleagues have performed meta-analyses of many TMS trials with differences in the method of coil placement and a range of clinical effects (Fox, 2018). Merging this information with data from the human connectome, they find that certain coil locations do better for certain symptoms. More anxious and neurotic patients tend to do better with the 5 cm location, while anhedonic and dysphoric symptoms tend to do better with a more anterior and medial location.(Siddiqi et al., 2019) This raises the possibility that a good clinical exam might be able to parse the depressions into different disease subtypes with differential circuit activity requiring a different coil location.

Conventional TMS can only stimulate the surface of the brain but a new series of coils can stimulate deeper, and broader (Roth et al., 2002; Deng et al., 2013, Deng et al., 2014, Deng et al., 2015). These H-coils are now approved in depression (as well as in obsessive–compulsive disorder (OCD) and smoking cessation) (Levkovitz et al., 2015). It is unclear if they are more effective at treating depression than the other coils. This manufacturer and others also have multiple coils that can be used jointly or independently (Roth et al., 2014). We now can stimulate multiple different regions of the brain with different patterns, exciting some regions and inhibiting others. Remarkable technologies are already here with TMS. What’s lagging is the translational clinical neuroscience informing us how to best use these tools, and how to make them change plasticity.

How to stimulate in terms of patterns and frequencies. One of the most remarkable aspects of TMS is that the brain affects are frequency dependent. Slow, low-frequency rTMS delivered at 1 pulse per second can temporarily inhibit regional brain activity. In contrast, faster high-frequency patterns (typically 10–20 pulses per second) tend to be excitatory. This has enabled various studies to use inhibitory patterns to block or turn down a region or excitatory patterns to boost a region. A fascinating new development is theta-burst stimulation (TBS), which was long known to basic neuroscientists but only recently rediscovered by the TMS research community (Di Lazzaro et al., 2005). An important recent study (Blumberger et al., 2018) showed that iTBS for under 3.5 min was equally effective in treating depression compared to the standard FDA treatment, which takes 37.5 min. One can treat many more patients in a clinic if the time is reduced fivefold, so this may be an important step forward in improving the efficiency of TMS.

What is the optimal TMS dose? Over the past 25 years, with mounting assurances about TMS safety, there has been a gradual increase in the number of TMS pulses are given in a day, or week, or treatment course. However, some recent studies have shown that more pulses alone may not be better (Fitzgerald et al., 2019). Can one give more treatments in a day and create a more rapid response to TMS? The jury is still out about this, with some case series producing rapid responses (Williams et al., 2018; Cole et al., 2020), and other controlled trials using similar results not getting effects (Fitzgerald et al., 2020). It is unclear if there is a tradeoff between the acute changes and longer-term durability or maintenance (Caulfield, 2020). That is, is a quicker response less durable? That’s a most interesting concept concerning the theme of this book and plasticity. It could be that with the

hyper-accelerated intensive dosing we get rapid plasticity changes, but they are not nearly as durable as when we spread out the course of treatment over 6 weeks (Caulfield, 2020; Cole et al., 2020). Further research about this fascinating question is needed. It appears that the initially determined daily treatment pattern is not sacred and one can deliver TMS treatment sessions in a more creative and flexible pattern than was done in the pivotal clinical trials.

What is the brain doing during treatment?—Another exciting area of research involves manipulating what the brain is doing while TMS is being delivered. This research marries the rich tradition in psychiatry of talk and behavioral therapies, with the new technology of brain stimulation. In 1949, Donald Hebb wrote that neurons that fire together, wire together (as paraphrased by Lowell) (Hebb, 1949). Applied to TMS, it suggests that the activity, behavior, or state of the person being treated may matter in terms of whether TMS can induce long-term synaptic plasticity changes. Thus, researchers are manipulating brain activity during TMS. In many applications, particularly treating OCD or smoking cessation, what the patient is doing during stimulation appears important if not critical (Amiaz et al., 2009; Li et al., 2013; Dinur-Klein et al., 2014; Gorelick et al., 2014). To date in relation to treating depression, no one has shown that a consistent manipulation of state during TMS treatment produces better outcomes. However, this may be because almost all depressed patients, during treatment, are likely obsessing about their depression and activating these mood-regulating circuits naturally; during TMS treatments, many patients may be engaging in “activation” of their internal thoughts and beliefs that are dysphoric or sad. Alternatively, they might be trying to contain these emotions with cognitions, which is activating the relevant brain circuits. If TMS works through the principles of synaptic plasticity and LTP and LTD, it should be possible to add certain medications and boost these effects. However, there is no convincing evidence that any medication enhances or blocks the antidepressant effects of TMS, although work has been done in the motor cortex (Brown et al., 2020). Some have argued that benzodiazepines may block the antidepressant effect of TMS, although this has not always been found (Caulfield and Stern, 2020) and there is a large confound where those patients taking benzodiazepines are anxious. Furthermore, comorbid anxiety is itself a negative response predictor for antidepressant treatment response to TMS and other interventions (Lisanby et al., 2009). Interestingly, pretreatment with naloxone blocks the antipain effects of TMS, suggesting the prefrontal rTMS releases endogenous opiates (Taylor et al., 2012, Taylor et al., 2013). It is not clear if this is related to its antidepressant actions.

What is the evidence of changes in plasticity? Neuroimaging studies have shown remarkable increases in brain volume in depressed patients after a course of treatment. The key regions are the DLPFC and the anterior cingulate (Liston et al., 2014; Boes et al., 2018). Some studies have found that patients with greater improvements in mood tend to have larger increases in regional brain size. It is still unclear exactly what is happening in the brain to cause these regional brain increases.

In summary, TMS continues to rapidly evolve as an antidepressant, with research into the translational neurobiologic effects and re-examination of the initial parameters to improve its efficiency. In patients with depression who have failed to respond to at least one or two conventional antidepressant medications and talking therapy, approximately 1/3 of the TMS

treated patients will receive remission, another third will achieve response and, unfortunately in 1/3, there will be no response (Carpenter et al., 2012; Sackeim et al., 2020a). TMS for depression is now available throughout the United States and most major cities have several providers. As TMS is covered by most insurance providers, it is slowly making a dent in the overall treatment for depression.

Vagus Nerve Stimulation: ECT and TMS are effective acute treatments that can also be given in a spaced-out approach for maintenance treatment. In contrast, cervical vagus nerve stimulation (VNS) does not work acutely but has remarkable durability and maintenance of effect. When one stimulates the vagus nerve the afferent fibers go into the brain and most of those fibers go to the nucleus solitary tractor (NTS). The next synapse is in several locations but one of the key projections is the locus coeruleus (LC). The LC is the projection for many of the norepinephrine neurons in the brain (Krahl et al., 1998). The LC is critical for the anticonvulsant, antidepressant, cognitive-enhancing effects of VNS and for VNS directed cortical plasticity (Adkins et al., 2006; Hulsey et al., 2019). Thus when one stimulates the vagus nerve one is essentially sending a pulse of norepinephrine into the brain and critically changing attention and learning and memory (Smith et al., 2005).

Cervical VNS was first approved for treating epilepsy in 1997 (Handforth et al., 1998; Schachter and Saper, 1998). Subsequently, we carried out early open-label studies (George et al., 2000; Rush et al., 2000; Sackeim et al., 2001), followed by double blind work in patients with chronic recurrent treatment-resistant depression (George et al., 2000; Rush et al., 2000; Sackeim et al., 2001; George et al., 2005; Rush et al., 2005) resulting in FDA approval in 2008. Unfortunately, the double-blind acute phase study was underpowered and although there was a mathematic difference in favor of active treatment it was not statistically significant. The numbers of patients who responded were also relatively low at the time point of 6–8 weeks. What we've learned in the years since then is that the full effects of cervical VNS for treating depression do not really begin to appear until at least 6 months and perhaps a year after implantation (Nahas et al., 2005). The other thing that is quite remarkable with VNS for either depression or epilepsy is that the responses once they are gained in patients continue for many years. There is a lack of tolerance of the long-term effects of VNS for depression or epilepsy and the clinical effects build and build over many years (Sackeim et al., 2020b). For example, Scott Aaronson and colleagues studied the 5-year outcomes of depressed patients with VNS in and on. Their depression improved year after year up to 5 years (Aaronson et al., 2017).

One of the major clinical problems with treating depression is there is both the acute response and then in people with treatment-resistant illness, there is the propensity to relapse or become tolerant. Harold Sackeim showed this quite dramatically (Sackeim, 2016).

He examined the STAR*D trial data and showed that the different levels of STAR*D have both an acute response and then a maintenance response at 1 year. The conditional probability of finding an antidepressant medication that works for a patient and that will continue for 12 months drops off dramatically after not responding to the second antidepressant medication. In fact, the chances of finding a new medication that worked for an entire year for someone who is treatment-resistant after they failed two other medications

is less than 5%. Concerning plasticity, tolerance to antidepressant medications or tolerance in general to therapies within the brain maybe some form of maladaptive plasticity. If that is the case, then we want brain stimulation treatments that do not have tolerance as a problem. As mentioned earlier, VNS has remarkable durability and does not seem to have tolerance, and has long-term effects in terms of durability. VNS does not produce permanent changes, however, because when patient's batteries die, and their generators need to be replaced, patients often will relapse clinically. However, it is notable that their relapses are not precipitous in the way that, for example, tremor immediately returns after a deep brain stimulation for Parkinson's wire breaks or the battery stops. It can take several weeks to months for depression to return in someone who has had VNS in and on for many years for depression and has done quite well. Luckily, patients who are reimplanted almost always regain the effect. There has been less work done in terms of understanding the neurobiologic changes associated with cervical VNS for depression or epilepsy. There are a series of brain imaging studies showing the involvement of relevant mood-regulating circuitry although the documentation of changes over time has not been well researched (Chae et al., 2003). In a remarkable story about the confluence of clinical medicine and science, the United States Centers for Medicare and Medicaid Services (CMS) has launched a large clinical trial for cervical VNS for treatment-resistant depression (n = > 1000; RECOVER trial: https://clinicaltrials.gov/ct2/show/NCT03887715). In the first years after FDA approval, Medicare-approved some depressed patients to be implanted with VNS. After about a year that ruling was changed and so there were no more CMS patients implanted. However, Medicare can follow these patients down through their lives and noticed that those patients who had cervical VNS in and on for treatment-resistant depression did remarkably better than similar patients without VNS. The VNS treated patients cost the healthcare system much less in terms of the need for rehospitalization, frequent doctor visits, or ECT (Table 33.1).

Several years ago, largely led by work out of a group in Dallas TX (Hays et al., 2014; Khodaparast et al., 2014; Hays, 2016), people began to understand that one could pair a behavior with stimulation of the vagus nerve and amplify the plasticity associated with that behavior. This was dramatically shown in some early work in tinnitus where pairing VNS with tones around the tinnitus tone caused remodeling of the brain such that the abnormal plasticity of tinnitus was resolved by pairing VNS with tones above and below the tinnitus tone (Hays, 2016; Shekhawat et al., 2016). This ability to use VNS to change maladaptive plasticity was shown as well in teaching rats how to learn a new language. In this, quite humorous study rats were taught to listen to the language and were taught to respond to the words' dad, da, or RA (Engineer et al., 2011; Shetake et al., 2012; Borland et al., 2016). The more recent human follow-up of this study has shown that pairing VNS with learning a new language drastically improves the ability to speak a new language. Thus, we have now come full circle where brain stimulation treatments can induce plasticity and overcome or undo maladaptive plasticity in clinical diseases like tinnitus.

A drawback to cervical VNS is that it is expensive and requires surgery, which can have side effects. Researchers have been developing a non-invasive cervical approach where one can stimulate the vagus nerve with a handheld device (Cerbomed). Yet another intriguing way to get into the vagus nerve is through a branch in the ear called the transauricular branch of the vagus nerve. Badran and colleagues at MUSC showed that one can stimulate the vagus

nerve in the ear and cause acute changes in heart rate. We systematically explored which parameters consistently caused changes in heart rate (Badran et al., 2018a) and produced these changes inside the MRI scanner, showing that noninvasive taVNS produces changes in brain regions that the control condition does not (Badran et al., 2018b). There is now a rapid growth of studies using either cervical VNS or taVNS paired with behaviors to produce therapeutic change. A potential landmark study was published recently in The Lancet by a company called Micro Transponder. They have a device that is a cervical invasive device that they can pair with physical rehabilitation for upper extremity stroke (Dawson et al., 2021). In 100 patients who had suffered a stroke and had upper extremity paralysis or hemiplegia, they were able to triple the movement scores when they paired VNS with physical therapy as opposed to no pairing of VNS. This is currently being evaluated for potential FDA approval. In another interesting clinical use of this pairing of taVNS with behavior, Jenkins and colleagues at MUSC have been pairing taVNS with bottle feeding in infants who were damaged at birth. Patients with hypoxic–ischemic encephalopathy (HIE) often struggle to gain motor milestones after their brain injury. They often are not able to bottle feed. One of the most common reasons why newborn infants are still in a hospital is that they are unable to breast or bottle feed and they cannot be sent home. The normal treatment for these children after they have tried for several weeks is to insert a gastrostomy tube or G tube where food is inserted directly into the stomach. Then they are sent home. In pioneering open-label work Jenkins and colleagues have paired taVNS with infant bottle feeding. They have shown that they can speed up improvement of feeding and obviate the need for a G tube in approximately 60% of these infants who would otherwise have had to have a G-tube (Badran et al., 2020). A double-blind study is underway now, and many other noninvasive VNS trials are underway.

Summary

Brain stimulation is an intriguing tool that can be used to alter neuroplasticity. ECT and TMS can treat depression acutely and reverse the lack of plasticity that characterizes acute depression. Cervical VNS can slowly produce changes that are quite durable and lasts for many years, improving the disease course in many patients. We do not fully understand the translational neurobiology of how these tools are interacting with the nervous system to produce plastic changes. However, brain stimulation has had robust clinical effects, with few side effects. The exciting new work with VNS paired with behavior shows that we can now use stimulation to reverse maladaptive plasticity particularly in diseases like tinnitus. We can also use it to overcome a stroke and other diseases in the brain like HIE-induced feeding problems in infants. As we better understand how the brain works and how plasticity or maladaptive plasticity occurs, brain stimulation methods can be used to change plasticity or reverse maladaptive plasticity. The future is extremely bright for deriving increasingly effective and precise methods of stimulating the brain.

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Table 33.1.

Table of treatment-resistant outcomes over time by Sackeim, 1 year probability (Sackeim, 2016).

	Acute remission rate (%)	Probability of remaining well for 12 months after acute remission (%)	Probability of sustained benefit (%)
Level 1	36.8	69.9	25.72
Leve] 2	30.6	44.7	13.68
Leve] 3	13.7	35.4	4.85
Level 4	13	28.9	3.76