14 Psychiatric Disorders

Cortical targets represent important nodes within the neural networks that subserve psychiatric disorders. Although more invasive, surgical cortical stimulation allows for stimulation with increased spatial specificity. Current paradigms utilize electrodes implanted epidurally rather than subdurally, as the dura provides a barrier that increases the activation threshold of neural tissue, and reduces the risk of induced seizure (Bezard et al., 1999). Furthermore, the implantation of electrodes epidurally significantly decreases the risk of irritating or damaging underlying brain tissue, and eliminates the risk of subdural hematoma as well as cerebrospinal fluid leak. The mechanism of action of ICS is still poorly understood, particularly for psychiatric disorders in which neurophysiologic underpinnings are often ill defined.

14.1 Depression

14.1.1 Review of Studies

We conducted a prospective, longitudinal single-blinded analysis of the effect of epidural stimulation of the left DLPFC in patients with severe treatment-resistant depression (Kopell et al., 2011). The study included 12 patients, followed over the course of 104 weeks with the main outcome measure defined as at least a 40% decrease in the Hamilton-Depression Rating Scale - 28 (HDRS). As this was primarily designed to be a safety and feasibility study, only the subjects were blinded to the stimulation state during an 8-week sham-controlled phase. Patients selected were limited to those with the most severe, refractory depression and met a rigid series of inclusion and exclusion criteria (Table 14.1). Electrodes were implanted unilaterally through a small craniotomy, and consisted of a paddle with two platinum-iridium contacts 3.75 in diameter and spaced 15mm apart (Fig.14.1A). In addition to HDRS, the study also measured response in the Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Function (GAF), and Quality of Life Enjoyment and Satisfaction (QLES) questionnaire. Subjects were followed every two weeks from implantation to week 16, and subsequently every four weeks until week 104 with a variety of the above tests and, at pre-set intervals, the addition of a Mini-Mental Status Exam (MMSE) and repetition of the baseline neuropsychological battery. Moreover, PET scanning was performed at baseline, and in a treated state. Of note, one patient was excluded from the analysis because of a violation in study-protocol during the baseline period. After 8 weeks of active, *continuous stimulation* (week 8 for the study group, and week 16 for the sham-controlled stimulation group), the subjects entered an “adaptive protocol” and settings were adjusted based on subject response with

attention to prolonging battery-life. All subjects were stimulated at 50Hz, with a pulse width varying from 150-250 μ s, and an amplitude setting of 5.5-6.5mA using either a bipolar or unipolar montage. In the evaluation of the 11 remaining patients over the 104-week period, 5 were randomized to the sham group and 6 were randomized into the active group. After week 8, all subjects received active stimulation. During the 8-week single-blinded sham controlled phase, a 20% mean improvement in HDRS scores was noted compared to a 3% improvement in the sham group, however this trend did not reach statistical significance ($p>0.1$). The fact that in this period of time outcomes were not significant may be a reflection of the small sample size, the variability in lead placement, and the short time course. In a post-hoc analysis of this data, it was determined that 20 weeks of stimulation are necessary to approach a 50% response probability (Pathak et al., 2013). During the first several months, it was noted that electrode placement was significantly correlated to response, and at week 52, patients with electrodes deemed to be sub-optimally located were offered revision surgery. Of the 6 patients identified, 3 underwent lead revision (see “Refining Techniques”). During the first 21 months of treatment, a significant improvement was noted in HDRS, MADRS, and GAF scores, however response rates in the QLES questionnaire remained unchanged. Overall, 6 patients (55%) achieved a greater than or equal to 40% improvement on the HDRS, the primary outcome measure, at some point during the trial and 5 patients (45%) achieved a greater than 50% improvement. Four subjects (36%) achieved remission at some point during the trial, defined as an HDRS score <10 (Table 14.2). Of the 3 patients that underwent revision surgery, there was an average of a 4-point improvement in the HDRS and a 0.1-point improvement in the MADRS; however, ultimately, none of these patients met the preset criteria for responsiveness. It is notable that despite the revision surgery, the electrode leads in these patients may still have been in a position posterior to the desired target cortex. Due to the dissolution of the parent company at the end of the trial (104 weeks), the study subjects were explanted per FDA mandate. During the active study phase, there were no reported surgical complications, however upon explantation, one patient developed a bone-flap infection necessitating further surgery for removal, antibiotic treatment, and eventual replacement with a synthetic prosthesis. One patient, who was initially excluded from the study secondary to violation of the protocol during the first 8 weeks (the patient was receiving concurrent TMS therapy), underwent a suicide attempt requiring hospitalization during the period of active stimulation, and completed suicide prior to explantation. This suicide attempt was thought to be caused by a myriad of extenuating personal circumstances, however the pending explantation of the ICS may have served as an additional constituent in her psychological decline.

Table 14.1: Inclusion Criteria

	Nahas, et al., 2010	Kopell, et al., 2011
Inclusion Criteria	HDRS score ≥ 20 DSM IV diagnosis of MDD without psychotic features OR a major depressive episode as part of Bipolar Type I or II Failed response to ≥ 4 antidepressant treatments, with a minimum of 6 weeks of prior psychotherapy Current treatment regimen unchanged for at least 4 weeks prior to implantation	HDRS score ≥ 20 DSM IV Diagnosis of MDD without psychotic features Failed response to ≥ 4 antidepressant treatments* Current treatment regimen unchanged for at least 8 weeks prior to implantation At the time of the study, in a major depressive episode for >2 years, or >1 year with 4 or more lifetime episodes GAF <60
Exclusion Criteria		L- handed dominance** Pre-existing neurological disease (including epilepsy) Active comorbid Axis I psychiatric disorders Borderline or histrionic personality disorder MMSE < 24 or other evidence of cognitive disorder Active suicidal ideation ECT within 6 months of implantation Medical condition that may interfere with completion of the study

* Treatments include medications, ECT, VNS, or psychotherapy

** Defined as at least 75% dominance on the Edinburgh Handedness Inventory

Nahas et al (2010) submitted five patients with treatment resistant depression to open-label ICS. Notably different from the previous study, this study implanted two paddles with 4 electrode contacts each (Fig.14.1B), bilaterally, targeting the anterior and mid-lateral prefrontal cortices corresponding to Brodmann's areas 10 and 46 (Fig.14.2). All subjects underwent pre- and post-operative analysis using the HDRS and MADRS. Response was defined a priori as a greater than 50% reduction in mean HDRS and remission was defined as a score of 10 or lower. As in the prior study, a post operative CT scan was obtained and fused to the pre-operative MRI to evaluate electrode placement. No revision surgeries were deemed necessary, likely owing

to the fact that there were 8 contact electrodes placed per side and more ability for programming across anatomical substrates. After an average of 2-3 weeks post-operatively, stimulation commenced and was tested for “optimal settings,” guided by acute, subjective observations by the patients. The stimulation paradigm used differs from the previous study and more closely emulates rTMS protocols. Patients generally underwent chronic, intermittent bilateral stimulation of all four paddle leads at 60Hz, 2-4V, 30' ON 2.5 hours OFF from 8AM to 10PM. The group of five patients was followed for 7 months, after which patients showed a mean improvement in HDRS of $55 \pm 38\%$ ($p=0.009$). Statistically significant improvements were also shown in the MADRS, Inventory of Depression Symptoms – Self Report (IDS-SR), and Clinical Global Impression (CGI). Interestingly, similarly to the previous study, no significant improvement was observed on the QLES. This may be a reflection of the lasting psychosocial effects in severe chronic depression, even after depressive symptoms have improved (Kopell et al., 2011). Of the 5 patients, 4 showed a greater than 40% improvement in HDRS scores at 7 month follow-up (80%), 3 showed a greater than 50% improvement and went on to achieve remission (60%) (Table 14.2). Increased time (28 weeks vs 16 weeks) was associated with improved HDRS scores and increase in likelihood to achieve remission (Table 14.3). Extensive neuropsychological testing was performed pre- and post-operatively and revealed no changes in cognitive functioning with the extensive pre-frontal stimulation. Two adverse events were noted. One was intraoperative and clinically insignificant, where the advancement of a paddle led to a small dural tear with no subsequent leakage of cerebrospinal fluid. The second event was a superficial purulent scalp infection 12 weeks post-operatively, which required debridement and explantation of the leads with no subsequent clinical consequence. Of note, this patient went on to achieve a 42% decrease in HDRS at 7 months follow-up despite explantation.

Fig. 14.1: Electrode design (A. Northstar Neuroscience Renova © B. Medtronic Resume ©)

In both studies, ICS appears to have a potentially robust antidepressant effect in this patient population previously refractory to most forms of treatments. The combined 10/16 patients (62.5%) met criteria for a 40% decrease in HDRS score and 8/16 patients

(50%) met more rigid criteria for responsiveness with a greater than 50% decrease in score. Seven of 16 patients (43.8%) met criteria for remission. The relatively low surgical complications in both studies highlight the potential advantage of ICS over other surgical procedures, by its nature precluding the need to penetrate dura or brain parenchyma and thus decreasing the risk of hemorrhage and other potential complications. Both studies have proven to be prone to a dramatic variability in individual patient response, which may at least in part be attributed to the anatomical target chosen as well as individual anatomic variability, stimulation parameters as well as device limitations.

Fig. 14.2: Targeting the frontal pole and midlateral prefrontal cortex (BA 10 and 46)

Table 14.2: Clinical Outcomes

		Nahas, et al (n=5)	Kopell et al (n=11)
Partial Responders	>40% decrease in HDRS 4 (80%)		6 (55%)
Responders	>50% decrease in HDRS 3 (60%)		5 (45%)
Remitters	HDRS<10	3 (60%)	4 (36%)

Table 14.3: Average HDRS Scores Over Time

	Baseline (SD)	7 months (SD)	21 months (SD)	p-Value
Nahas et al	28.4 (4.8)	13 (11.4)	N/A	0.009
Kopell et al	34.25 (4.99)	N/A	15 (7)	<0.001

14.1.2 Surgical Technique

Good quality, pre-operative MR imaging is of paramount importance in the pre-surgical planning phase during which the target areas are localized. In the study conducted by Nahas et al (2010), the targets, which included the anterior frontal pole (BA10) and mid-lateral prefrontal cortex (BA46) were defined using an online atlas (MRIcro, <http://mccauslandcenter.sc.edu/mricro>) co-registered to the patients MRI (Fig.14.2). In the study performed by Kopell et al (2011), the target (L DLPFC – BA 9/46) which was localized to the mid-portion of the middle frontal gyrus, was identified using standard anatomic landmarks defined as 2cm anterior to the precentral sulcus, inferior to the sulcus frontalis superior, and superior to the sulcus frontalis inferior (Fig.14.3). Once the targets are identified, the patient is brought to the operating room and the MRI is co-registered with the patient's head using a stereotactic frameless system. The patient may be intubated and sedated, or minimally sedated if awake-intraoperative testing is deemed necessary. In the study conducted by Nahas et al, in which bilateral electrodes were placed, a coronal incision was made behind the hairline and slit-shaped craniotomies (3x0.5cm) were performed bilaterally to allow epidural insertion of the paddle leads. In the study conducted by Kopell et al, a 4-cm round craniotomy was performed centered directly over the predetermined area guided by stereotactic navigation. After insertion, the electrode leads are anchored by suture to the underlying dura. Subsequently, under general anesthesia a separate linear incision is made below the clavicle and a subcutaneous pocket is made for insertion of the pulse generator. Using standard procedures, the electrode extension leads are tunneled subcutaneously behind the ear and over the clavicle, and connected to the infraclavicular pulse generator. The system's impedance is then generally tested prior to the closing of the incision. The patients remain in the hospital for 24-48 hours post-operatively, and a post-operative CT scan without contrast is obtained and fused to the pre-operative MRI to ascertain the final lead placement and rule out intra-cranial hemorrhage.

Fig. 14.3: Targeting the DLPFC (BA9/46)

14.1.3 Refining Techniques

Of the many sources of variability among studies and between patients, electrode location, stimulation settings and duration of stimulation are likely to play vital roles in the efficacy of this treatment modality.

The anatomical target of choice as well as the precise localization at that target has been postulated to be of utmost importance, possibly necessitating sub-centimeter accuracy to achieve optimal results (Herbsman et al., 2009; Kopell et al., 2011; Pathak et al., 2013). Given that the different targets chosen likely function within similar, if not interconnected, networks, *it is conceivable that differing anatomic locations will yield similar clinical outcomes*. Nonetheless, within a chosen anatomic location such as the DLPFC (see [Box 14.1](#)), targeting the lateral and anterior regions has correlated with better clinical outcomes (Herbsman et al., 2009; Pathak et al., 2013). In an analysis done at 16-weeks during the study conducted by Kopell et al, HDRS scores were significantly correlated with electrode distance from the pre-central sulcus with electrodes placed posterior to the initially defined target (2cm anterior to the pre-central sulcus) appearing to be less efficacious than those placed at or anterior to the target ($p = .03$) (Kopell et al., 2011). This distribution was so striking that it prompted the authors to offer revision surgery to the subjects in the cohort with electrodes deemed to be placed sub-optimally; however, those patients that underwent revision surgery did not ultimately yield the same distribution pattern of efficacy at the 104-week analysis. The use of functional imaging, specifically diffusion-tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and magnetoencephalography

(MEG) may play a critical role in localizing cortical targets and accounting for inter-individual variability. The use of diffusor tensor imaging (DTI) may be of particular benefit in its capacity to delineate individual variability in circuitry (Fig.14.4). DTI has been investigated in the localization of sub-cortical targets in DBS for depression and successful placement with reference to tractographic findings has been shown to correlate with improved clinical outcome (Bhatia et al., 2012). DTI analysis with electromagnetic modeling has also been performed in TMS targeting of M1 (Nummenmaa et al., 2014).

In another source of variability, *stimulation sources and parameters varied significantly in between studies and among patients*. In the study conducted by Kopell et al, the stimulation was unilateral and sourced from two electrode contacts, was constant, and varied in montage with mixed polarity (anode/cathode) and full anodic modes found to be most effective (Kopell et al., 2011; Pathak et al., 2013). In contrast, the study by Nahas et al utilized stimulation delivered intermittently, bilaterally, and with a considerably more anterior target with 8 electrode contacts per side (Nahas et al., 2010). Nonetheless in both studies, stimulation was found to be effective.

Not secondarily, the devices themselves have significant limitations. The device used in one study (Fig.14.1A) incorporated only 2 contacts that were not independent in their capacity to stimulate (Kopell et al., 2011). These electrodes stimulated at a maximum of 6.5 mA and were not capable of providing a “burst” pattern of dosage. An improved electrode design would provide more avenues for personalized treatment protocols, and may obviate the need for revision surgery based on small discrepancies in anatomical targeting.

On average, effective stimulation parameters necessitated battery usage resulting in an average battery life of 9 months in one study (Kopell et al., 2011). However, rechargeable batteries may obviate this limitation.

Fig. 14.4: Diffusion Tensor Imaging (DTI)

S Canavero

Current targets of stimulation for depression (DBS: subgenual cingulate cortex; CS: left DLPFC) have resulted from an emerging understanding of the neurophysiological basis of the disorder utilizing data from neuroimaging as well as neuropsychological studies to elucidate anatomical interconnectivity (Rogers et al. 2004). Several targets, postulated to be connected to centers of cognitive and emotional processing, have been implicated in the prefrontal cortex including: the frontopolar region (BA 10), midlateral prefrontal region (BA 46), and the dorsolateral pre-frontal cortex (DLPFC). The DLPFC lies at the junction of the lateral aspect of Brodmann's areas 9 and 46 (BA 9/46), makes up 10% of the surface of the frontal lobe and is functionally connected to the anterior cingulate cortex, the orbitofrontal cortex as well as having strong thalamic and other cortical connections (Fuster 2009). Imaging studies have revealed a consistent pattern between the right and left DLPFC, demonstrating hypometabolism of the left side and hypermetabolism of the right side in the resting state of patients suffering from MDD (Grimm et al., 2008). BA 10 has also shown a robust anatomic relationship to other limbic-related cortical and subcortical circuitry with connections to the anterior cingulate cortex, precuneus, posterior cingulate, orbitofrontal cortex and DLPFC (Fuster 2009). BA 46, which encompasses the DLPFC as well as ventral regions maintains connections to temporal areas, as well as to paralimbic circuitry (Fuster 2009). *Because it is thought to be an interconnected network, it is feasible that stimulation at a various number of anatomical points may yield similar effects.* Actually, resting state fMRI studies have identified about 20 cortical networks in man: in depression, these are all dysfunctional. Thus, applying CS to any given node within these networks is expected to modulate the activity of other nodes via their shared anatomical connections: stimulating DLPFC also engages ACC, subgenual CC and basal ganglia, among others. The question whether CS restores cognitive control over limbic brain areas or enhances connectivity between them appears to have been answered.

Dysfunctional monoamine neurotransmitter systems are likely just downstream effects of another underlying disorder leading to the symptoms of depression and rTMS effects do not depend critically upon the central serotonergic tone.

Although the left DLPFC has been emphasized in imaging studies, actually both DLPFCs are dysfunctional and clinical studies evince no differences in depression after lesions to the right or left hemispheres. So either high-frequency (but also low frequency) left DLPFC or low-frequency right DLPFC (which is hyperactive) show antidepressant effects. Symmetrical DLPFC stimulation is thus an option, with an eye towards stimulating the brain broadly.

BA 10 has recently been affirmed to be the master-key in frontal lobe function, and this is an important new target for ICS.

Another potential target would be the rostral premotor cortex (rPMC:BA6/8). RPMC has fiber connections with both BA46 and caudalPMC/SMA, acting as a gateway between motor and cognitive networks (Hanakawa 2011).

Box 14.1: The DLPFC and Beyond

Closed-loop ICS will be available in the future for the treatment of psychiatric (and other) disorders. In order to make this possible, biomarkers are needed. It appears that increased interleukin 6 and decreased BDNF levels are among the most promising biomarkers of depression, decreased serum folate of treatment resistance, reduced ACC activity of treatment compliance and decreased total cholesterol of suicidal behavior. However, EEG based markers are required for closed loop systems to “kick in” when needed. CS effects can actually alter neuroplasticity, neurotransmission and CBF through an effect on cerebral oscillatory activity. Integration of brain activity across greater distances is coordinated by alpha or theta activity, while shorter-distance coordination is achieved by beta (12-20 Hz) and gamma (20-40Hz) oscillations. Synchronized alpha oscillations in particular play a key role in global top-down control of brain cognitive processes, probably via inhibition (8-10 Hz). Severity of depression correlates with degree of decrease of PFC rCBF and power of low frequency EEG. Yet, synchronization of rTMS to individual alpha frequency may be less effective than standard stimulation

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14.1.4 Comparison of Outcomes with Nonimplantable Cortical Stimulation

Both noninvasive (e.g. TMS, tDCS) and ICS treatment modalities appear to be effective and safe methods in the adjunctive treatment of major depression. Clear benefits of rTMS and tDCS include their relative ease of use and very low risk profile, as well as the absence of need for anesthesia and surgery. Although there is less data supporting its use, tDCS in particular is cost-effective and is easily attainable. ICS, on the other hand, provides the opportunity for a more potent, consistent, and accurate stimulus delivery to the target cortex. Once implanted and programmed, it obviates the need for repetitive treatment encounters or adherence to a treatment regimen. More importantly, despite stronger or accelerated dosing regimens, longer treatment courses, bilateral stimulation protocols, individually tailored stimulation frequencies, new coil geometries, application of neuronavigation and more accurate targeting, rTMS has not proved superior to ICS (30-35% remission vs 43%). Both, however, appear to fare better than medications (23-33%) and cognitive therapy (22%).

In a comparison of results from the randomized controlled trials in rTMS and tDCS with epidural cortical stimulation, it is important to note the variability in inclusion criteria in the studies and between treatment modalities. The two epidural cortical stimulation trials had rigid inclusion/exclusion criteria (Table 14.1) resulting in the most treatment refractory patient population. Furthermore, in the cortical stimulation trials, long-term efficacy and follow-up proved to have significant impact on the results; the same type of data does not exist in the rTMS and tDCS literature for an accurate comparison. Nonetheless, despite the small sample sizes, the two trials using epidural cortical stimulation had higher rates of responders and remitters, with pooled data revealing a 43% remission rate. In comparison, rTMS meta-analyses of high frequency, left DLPFC stimulation reveal lower overall response and remission rates despite a population with a comparatively less severe form of depression (Table 14.4).

A recent meta-analysis (Ren et al 2014) (n=425) found Electroconvulsive Therapy (ECT) superior in terms of remission (52.9% vs 33.6%) to both high and low frequency rTMS. ECT was superior for psychotic but equal for non-psychotic depression (high frequency rTMS). ECT had a nonsignificant advantage over HF rTMS on overall improvement in HAMD scores. However, nothing could be concluded for the longer term for all techniques and ECT is burdened by memory and verbal fluency impairment.

Table 14.4: Selected rTMS Meta-Analyses of High Frequency, Left DLPFC Stimulation

		Berlim et al 2013 (n=1371)*	Lam et al 2008 (n=782)**
Responders	50% decrease in HDRS	29.3% (vs 10.4% sham)	19%
Remitters	HDRS<10	18.6% (vs 5% sham)	16%

* Inclusion criteria ≥ 10 sessions of stimulation, sham controlled

** Inclusion criteria treatment resistant depression

14.2 Future Directions

As noted previously, limitations of ICS in the treatment of depression are in individual patient variability to response. Refining the anatomical target based on functional imaging including the use of DTI, fMRI, and MEG with high-density EEG to customize electrode placement *based on individual anatomic variability* may dramatically improve results. In addition to accurate and preferably individualized anatomical targeting, patient selection is paramount in improving the overall efficacy of ICS. Higher baseline regional cerebral metabolic rate of glucose (rCMRG) in the right DLPFC has been associated with increased responsiveness to ICS for major depression (Kopell et al., 2011) and advances in neuroimaging may provide additional avenues of targeting responders.

In integrating all of these new and improving methods of cortical stimulation, non-invasive methods such as rTMS and tDCS offer the possibility of acting as invaluable screening tools in pre-assessing potential responsiveness to ICS in major depressive disorder, as well as for future psychiatric targets. TMS has already demonstrated to be useful when integrated as a screening tool for other conditions such as neuropathic pain and tinnitus (Chapters 8, 9, 15). However, if results of screening rTMS are to be accepted as a valid proxy for surgical implantation, targeting must be accurate. Recent refinements have moved the TMS field beyond the fit-for-all “5 cm rule” for localizing BA9 (i.e. stimulating the cortex 5 cm anterior to the M1 hand area in a parasagittal line): given significant anatomic variations among individuals, several patients get their stimulation over BA6 or BA8. A “6 cm rule” has been proposed (Johnson et al 2013), covering more frequently BA46. A group proposed a “9 cm rule” / F3 (10-20 EEG coordinates system) (Fitzgerald et al 2009) or F5/6 targeting (Rusjan et al 2010). Parenthetically, fMRI appears superior to neuronavigated TMS in mapping the cortical motor system, especially for the face and leg areas (Weiss et al 2012).

Also, stimulation parameters, including the frequency of stimulation, now widely variable between the methodologies, as well as the magnitude, duration, and pattern of stimulation need to be normalized. For instance, the resting motor threshold (MT) upon which intensity of rTMS stimulation is usually based is NOT the best measure for determining the minimal TMS dose required to stimulate the cortex, and doses up to 120-130% of the MT appear safe (Johnson et al 2013).

Psychiatric disorders amenable to ICS mirror to a large extent those submitted to noninvasive CS: schizophrenia (left, but not right, temporoparietal area, 1Hz rTMS: Slotema et al 2014), obsessive-compulsive disorder, autism, post-traumatic stress disorder, craving and addiction, anxiety, and several others (reviewed in Eichhammer et al 2009).

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