SINGING THE BRAIN ELECTRIC

by

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ABSTRACT: Singing the Brain Electric

Brain pacemakers, scientists have found, can treat depression by correcting neural circuitry gone haywire. This thesis examines how such technology - a technique known as deep-brain stimulation, in which electrodes are implanted within the brain - was developed and how it works. We are introduced to a patient who received deep-brain stimulation for her refractory depression, and consider the risks, ethical issues, and questions of humanity and identity the technology raises.

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I. Switches

"Drill, please."

Dr. Emad Eskandar takes the drill to his patient's skull. The patient, a stocky man in his 50s, has his head held fast in a metal frame resembling a birdcage, his scalp shaved and protected by plastic wrap, a five-inch horizontal incision in the flesh exposing the bone beneath. The drill bites, the plastic suction tubing gurgles; within ten minutes, there are two dime-sized holes in the man's skull, from which Dr Eskandar tweezes shreds of flesh and shards of bone.

Then Dr. Eskandar asks his patient, "How do you feel?"

"Oh, I'm fine," the man mumbles, his jaw restricted by the birdcage. "It's an odd feeling."

"To say the least," Eskandar laughs.

The sign on the door of the neurosurgery OR at Massachusetts General Hospital is in bold, all capitals: REMINDER: PATIENT IS AWAKE. It's a first indication that this is no ordinary brain surgery.

Dr. Emad Eskandar is bespectacled and boyish, but has nearly a decade of neurosurgery experience under his belt. His specialty is stereotactic surgery - precisely focused procedures that use 3D coordinates, such as the millimeter and micrometer marks on the metal birdcage frame atop his patient's head, to home in on a target. In the next few minutes, Dr. Eskandar will thread a thin electrical lead into each half of his patient's brain, probing deep into two tiny disc-shaped structures called the subthalamic nuclei, one half of the brain at a time. Then he will turn on an electric current that delivers a pulse into each nucleus. This procedure, called deep-brain stimulation, was approved by the FDA in 2002

to treat Parkinson's disease, the disorder from which Eskandar's patient suffers.

Parkinson's disease appears to be is the result of overactivity in motor-control circuits of the brain. When neurons in the subthalamic nucleus fire too much, they cause the twitching and tremors characteristic of Parkinson's. By running an electric current through his patient's subthalamic nuclei – anywhere from 1 to 3.5 volts at about 150 Hz, depending on the severity of symptoms – Dr. Eskandar is able to calm the neurons and regulate their firing; the electrodes he will implant serve as a pacemaker for the brain.

Before Eskandar can implant the treatment leads, he must insert a test lead, a probe, to pinpoint the precise source of his patient's neural dissonance. The testing and treatment leads are slender, flexible metal tubes nearly a foot long and one-and-a-quarter millimeters in diameter, not much thicker than a bent-out paperclip or the graphite stick in a pencil. Each lead has four tiny notches on each end. These are the electrodes proper, the points of contact through which electricity will flow. And for insertion, each lead has a wire through it, keeping it stiff enough to slide through brain tissue.

"We're putting the electrodes in now," Eskandar says.

When a neuron fires, it sends electric impulses down its axon to the synapse, the space between one neuron and another. Those impulses can be translated into sound - the soft hiss that now issues from a pair of computer speakers set off to the side of Dr Eskandar's operating room. A nurse switches off the overhead lights. The room falls silent. As the lead's first electrode probes deeper into the patient's brain, the static changes. The rustle of leaves. A breathy whisper. When the electrode hits the subthalamic nucleus, right in the midst of neurons wildly misfiring, we hear a noise like raindrops on a tin roof.

Now neurologist John Gale moves the patient's arm and elbow, jerking it around into all sorts of contortions: flexing his wrist inwards, then outwards, extending the arm.

Gale, built like a linebacker, with the skill of a pianist and the bedside manner of a pediatrician, is listening for particular patterns in the static as the electrode is inserted deeper into the subthalamic nucleus. When the electrode hits the misfiring patch of neurons, the static modulates, resolving itself into sudden, irregular bursts of higher activity.

As Gale turns the electrode current up, Eskandar asks the patient, "How are you feeling?"

"My fingers are tingling."

"That's ok. Let's turn the current down a little. Hold out your left hand? Extend it all the way out."

The man's tremor is gone. Earlier in the day, while we were waiting in the hallway after his CT scan, his left hand had taken on a life of its own, twitching and jumping as he spoke. Now it is placid, quiescent.

"Now repeat after me: 'I took a train to Topeka, Kansas'."

"I took a train to Topeka, Kansas." No slurring, which is a good sign.

"Who's the president of the United States?" Eskandar asks, to test the man's recall and alertness. "What about the vice-president? The secretary of state?" The patient gets it right every time. "Great job. I'm impressed."

Then Eskandar turns the current off. In a week's time, he'll operate on this man again, this time under general anesthesia, to implant a pair of domino-sized battery packs for the electrodes. (Every few years, the batteries will run down and need to be replaced, in a repeat of the surgery.) For the time being, the slight temporary swelling caused by inserting the electrode will have a residual effect, and the patient's tremors will remain quiet for a few days.

As Eskandar stitches his patient up, the room breathes again. That's when I ask Gale a stupid question, whispering in the back of the room: How do you tell when the electrode is working? How do you know that the decreased neural activity translates to the tremors going away?

Most of the time, Gale explains, there's a visible and instantaneous improvement. The patient feels better. His fingers stop trembling, and that improvement correlates with more regular neural activity from the deep-brain stimulation. And sometimes, as a kind of placebo test in the operating room, it's possible to turn the current off while the patient *thinks* there's current.

Deep-brain stimulation is not a magic bullet or an instant cure-all for Parkinson's disease patients. Some patients can go off their medication entirely; others must still take half their original doses. Occasionally – this is brain surgery, after all – there are complications like infection and bleeding. The treatment can very occasionally make patients impulsive, prone to rash behaviors like gambling away their savings or moving across the country. (Such impulsive behavior also seems to be a side effect of drug therapies for Parkinson's, so the surgery per se may not be at fault.) Nor does deep-brain stimulation halt the slow march of the disease, only its symptoms. But the improvement in patients' condition is visible in the operating room from the minute the switches are flipped.

Deep-brain stimulation works for Parkinson's disease because the illness stems from an isolated malfunction in the brain, a precise spot where zapping neurons with electricity has a distinct effect. The same is true of other movement disorders like dystonia, where muscle spasms cause twisting and excruciating pain, and essential tremor, where the hands shake so much they interfere with the simplest daily task. For these

illnesses, deep-brain stimulation is also effective. But what of psychiatric illnesses like depression and obsessive-compulsive disorder? These have long been thought to be complicated, whole-brain illnesses, treatable only with endless years of medication and therapy. No one imagined that depression, for instance, could be treated by applying stimulation to a handful of brain areas. No one, that is, till now.

In 2005, Emory University neurologist Helen Mayberg and University of Toronto neurosurgeon Andres Lozano, together with several of their colleagues, published a seminal paper in the journal *Neuron*. The paper described six patients who received deep-brain stimulation in a part of the brain called the subgenual cingulate gyrus, or area 25 in the system of topography that neuroscientists navigate by. The surprise: the patients were receiving DBS for their severe depression.

Helen Mayberg, a neurologist at Emory University in Atlanta, is a lively, youthful fiftysomething. Her enthusiasm and verve are infectious. She is also the head of one of the first teams in the world to study deep-brain stimulation for depression.

Mayberg has spent her career studying the brain activity of depressed people, hunting for patterns, accumulating evidence. By 2005 she believed she had found a specific target, a part of the brain that seemed to be misfiring when people were depressed. Now she was faced with a test of her theory: six patients, all in a dire state, in what psychiatrists classify as treatment-resistant depression. They had all tried pretty much every other therapy in existence – different combinations of drugs, electroconvulsive therapy, everything – and nothing had worked. They had each been depressed for at least a year – some for as much as a decade. They were at the point where their situations looked most hopeless, and they were all paddling hard in order to merely stay alive – in order to

stay afloat. And they were about to receive deep-brain stimulation at the site of Mayberg's target. The question was not *Would the surgery work?* The question was: *What would the surgery do?*

II. Paddling To Stay Afloat

Liss Murphy had been paddling a long time.

"I remember thinking, I'm going to fail at this as well," she says of her operation. Not 'this treatment's going to fail as well'. It was '*I'm* going to fail', as though she – her will or her brain – were personally responsible for its success.

But sitting in the operating room, with surgeons and neurologists prodding around in her skull, she felt a warm flush rise throughout her as the electrodes were turned on. She began to smile. Then to laugh. "I was really self-conscious about it; it was really strange."

When Liss Murphy does smile now, it is as if she is illuminated by a kind of pale glow. Liss (short for Melissa), 34 this year, is tall and slender, a wan blonde. She seems fragile, as though recovering from a long wasting illness, as, in a way, she is. When I meet her for the first time, she is polished and put-together. Her poise and red lipstick hint at the public-relations career she once enjoyed.

In the summer of 2004, Murphy and her husband Scott had been having marital problems and had been separated since February. She was living in Chicago, enjoying her new job at a public relations firm. Scott was working in Boston, visiting her in Chicago every few months.

That summer, Murphy had had a troubled few weeks: she was anxious, crying a lot, weepy, and on edge. Perhaps those were early warning signs. Perhaps, even then, Liss's neurons were misfiring. But she says, "If I could pick a time in my life that I had been happy, that would have been the time – the most stable, creative time in my life."

Yet one unseasonably damp, grey Friday, August the 13th, 2004, Liss Murphy dropped everything she was doing, walked out of work, and never went back. She still

can't describe the tumult she felt, because the period is a dark blur. She used to run marathons; during her illness she stopped eating or jogging. Her weight dwindled to 90 pounds at 5 feet 6 inches. She began smoking. She didn't leave the house except to go to the doctor. Finally she decided to move back to be with Scott in Boston, where they had met as high-schoolers, where they had lived together for two years while Scott earned his MBA, where their families still live.

"I don't remember packing," Liss says. "I don't remember moving or leaving. I wish I could remember a lot more because I think it would help with the acceptance part of things."

The depression that snared Liss then was not her first episode – she had suffered two briefer episodes, once as a college sophomore and once before getting married in 1999 – but this was her most severe. It would last two years.

"If I had known how bad it was," says Scott, "I would have gone out to Chicago and grabbed her sooner." Sometimes the clearest perspective of depression is an external perspective – that of the spouse or caregiver – and Scott's account is as clear and harrowing as any other. Scott tells his story with the demeanor of an exhausted saint.

"Those were some of the hardest times for her," he says. "It just became a way of life...we just focused on getting her safe and getting her better.

"On the one hand, I was grateful that she was back here and not in Chicago alone, where I was concerned for her safety. But those first couple of months it was alarming to see her – she'd lost a tremendous amount of weight, she was smoking, she wouldn't do her hair. I would spend a lot of time cleaning the house and she'd come home from a walk and track mud through the house. She'd open all the cabinets and leave things out. You want to be supportive, but on the other hand it's like an affront – it's like a lack of respect for you

even though you know your partner's sick.

"I'd just got a new job, and it'd be 10.30am on a Wednesday morning and she'd call me at work and be like 'Scott, I can't get out of bed to walk the dog'. And I would have to leave work and rush home. I literally had my phone with me and was stressing out every time I saw a phone call...I don't think she knew she was doing this, but she'd call me 30 or 40 times a day at work, and every call would have the potential to be a really bad call. And of course I couldn't answer my phone that many times at work.

"As a spouse or significant other [of a depressed person], it's really hard to enjoy time. There were 6 or 8 months when the only time I enjoyed life was when I knew [Liss] was upstairs safe in bed. I didn't go out with friends, go to the gym, or see my family...I didn't want to do those things because even if I went to the movies, I'd sit there with my phone and wait for it to vibrate.

"Every morning before I left for work, I made her promise that she wouldn't hurt herself. But there were at least 20 or 30 days when I came home literally not knowing what I was going to find when I got home – whether she'd be lying in a heap on the bed crying, or whether she'd be totally fine, making dinner. It was literally a crapshoot every night."

The subtext of Scott's speech, of course, seems to be: *or whether I'd come home to find her gone.* Suicide is a very real risk for the severely depressed; half of those with manic depression will make a suicide attempt, and one-fifth of those with major depression will do the same. As a kind of incentive against suicide, Liss Murphy signed life contracts with her doctor, promises to call someone for help if she felt like hurting herself. But to a depressed person, alleviating the pain is sometimes the most urgent imperative. Scott explains that the life contracts were, in a way, spurious. "They were like 'I'll keep my promise...up until the point where I don't keep my promise'," - the point, he says, where the

promise is outweighed by the pain. "At one point she actually wrote me a suicide letter telling me the pain was too much and she didn't want to be a part of this world."

For the next two years, Liss and her doctors experimented with various drug therapies and dosages. Her medical resume reads like a catalogue, a who's who, of antidepressants, antipsychotics, benzodiazepines, and mood stabilizers: Effexor. Risperdal. Klonopin. Lithium. Cymbalta. Abilify. In December of that first year, she started a first round of unilateral, then bilateral electroconvulsive therapy (ECT). (ECT, as used today as a last-resort short-term treatment for severe depression, consists of electric current applied to the temples under general anesthesia and muscle relaxants.) But after two rounds (32 sessions) of ECT, she was not getting any better.

Worse, the therapy left deep crevasses in her memory, rifts that have yet to be smoothed. Today, she apologizes repeatedly for rambling, thanks to the cognitive gaps and memory losses: "I can't string a sentence together to save my life, and sometimes it feels like I have ping-pong balls in my head."

Midway through 2005, the Murphys got Ned, an Old English Sheepdog puppy, now an 80-pound bundle of exuberance who snuffles affectionately through the living room, licking our faces as he goes. Liss developed a routine of going to the doctor, walking Ned, going to the doctor, walking Ned – cobbling together a framework to her days. "[Ned] has been my life," she says. "He's got a great personality, he's very playful."

She also began to read, here and there at first, about depression and other mental health issues. "It became kind of a challenge – can I read all the self-help books, all the books on depression that are out there?" The pamphlets, brochures, leaflets and articles she collected fill more than three magazine folders, while the shelves in the sunroom of the Murphys' West Roxbury home hold over twenty books on the subject. Her favorite,

Andrew Solomon's *The Noonday Demon,* is dog-eared and highlighted, tracked across in pencil, with passages underlined, serving as a kind of security blanket.

"When I was unable to find words to describe how I was feeling, I found it comforting to read how others felt," she says. "There's something calming about it. I go back to them and read them when things aren't going so well."

Then in the spring of 2006, the Murphys heard about a surgical trial at Massachusetts General Hospital for a new treatment called vagus nerve stimulation, or VNS. The vagus nerve runs from brainstem to viscera; stimulating it with a generator the size of a Scotch-tape roll seems (controversially) to alleviate depression, perhaps by increasing blood flow to the brain, though its precise action is not known. At the time, trials for VNS were being carried out at Massachusetts General Hospital, and Liss Murphy with her refractory depression was a potential candidate.

But Liss, in the course of her insatiable reading, had read about a different, more radical therapy: deep-brain stimulation (DBS). Deep-brain stimulation sounded promising, she thought; it would take effect faster and with perhaps more certainty than vagus nerve stimulation. VNS takes several months to work, and even then, its efficacy is debatable. When she asked the surgery team at MGH, the answer was yes: Yes, you are absolutely a eligible candidate for depression DBS. Yes.

When can we do it? she asked.

III. Origins

When she began medical school at the University of California, Los Angeles, in the late 1970s, Helen Mayberg thought she would specialize in psychiatry. But the young medical student soon found that psychiatrists had a poor understanding of the biology behind the psychiatric conditions they sought to treat, and there was little experimentation or quantitative measurement surrounding mental disorders. For instance, the "refrigerator mother" theory of autism had only recently been debunked[1], and schizophrenia was still believed to be the result of childhood trauma or bad parenting.

Frustrated, Mayberg turned to neurology. In her third year of med school, she did a clerkship with neurologist Norman Geschwind at Harvard's Beth Israel Hospital. Geschwind was a pioneer in behavioral neurology. It was with her mentor that Mayberg first encountered the idea that behavior and brain function are correlated, and that the brain works not as a whole, but as a highly coordinated system of different functions. Just as crucially, Mayberg says, Geschwind taught her that being a good listener is essential to being a good neurologist. She tells this story: Geschwind encountered a patient, an architect working on a big project, whom other residents had dismissed as a psychiatric case – "Everyone thought he was a flake" - rather than a neurological case. But by questioning the patient carefully about a specific piece of drafting equipment and observing his comprehension and speech patterns, Geschwind discovered that he had a neurological language deficit, aphasia, caused by an undetected bout of encephalitis. "[Geschwind] was like the ultimate behavioral detective," Mayberg said.

The year she spent with Norman Geschwind had tremendous influence on her, to the point that she began to think about the neurological basis of psychiatric disorders,

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1 Forbonne, E. (2003) Modern views of autism. *Can J Psychiatry 48(8)*:503-505.

particularly depression. Each year, more than 21 million adults in the United States, or about 7 percent of the population, suffer from some form of depression, according to the National Institute of Health. 12 to 15 percent of the population will suffer from depression during their lifetimes. And suicide takes 32,400 lives each year in the US alone. So the disease was a ripe target for an ambitious young neurologist.

"I wanted to think about depression the way people thought about Parkinson's disease at the time – with a localizable centre in the brain," Mayberg said. So with this theme in mind, she spent the next two decades trying to characterize the network of brain regions and functions involved in depression.

The way she could literally peek into the brain was via the new science of neuroimaging. At the time, a technology called positron emission tomography (PET) was becoming widespread as an imaging and diagnostic tool. Patients were given an injection of short-lived, radioactive isotopes, which can be used to measure the activity of brain cells – the more isotopes are taken up by a cell, the more active it is. In 1985, Mayberg was doing PET scans on the brains of Parkinson's patients who also had depression. When she compared her results to brain scans of nondepressed Parkinson's patients, she found that the depressed patients had lower activity in their frontal cortex, the part of the brain associated with 'thinking' and planning. They had lower activity in the paralimbic cortex, which surrounded the 'feeling', emotional part of the brain. And they had overactivity in area 25, a patch of tissue located deep in the brain, near the midline and below the cortex, called the subgenual cingulate gyrus.

Area 25, the subgenual cingulate gyrus, is not *the* one single epicenter of depression. Instead, it's part of the emotional wiring that goes awry when people become depressed. Normally, it helps relay the neural traffic between the frontal cortex and the

limbic region responsible for our emotions. But in depressed people, area 25 seems to interfere with other brain functions elsewhere, as though wrestling with the frontal cortex.

Over the next few years, Mayberg scanned depressed and nondepressed Huntington's patients. Alzheimer's patients. Epilepsy patients. All the depressed patients, regardless of their other illnesses, showed the same pattern. In 1997, she wrote a long paper about her findings, which pointed strongly to a brain network for depression, but barely anyone took notice. Worse, colleagues who did pay attention thought her work was about 'secondary depression', that is, the depression that can accompany other neurological problems like Alzheimer's or epilepsy. But as she recalled in a 2006 profile, "I was saying, 'No, no, *no!* This is about *all* depression.' But it just seemed to annoy people."

Even as Helen Mayberg was scanning patients in the 1980s, the spotlight of mainstream depression research was trained on the neurotransmitters serotonin and norepinephrine. Serotonin is one of the brain's messenger chemicals; it is produced in a ridgelike structure called the raphe nuclei, deep in the brain stem, and one of the most important things it does is regulate our moods. Current theory holds that if the brain doesn't produce enough serotonin, or if the serotonin receptors aren't active enough or there aren't enough of them and the signal doesn't get through, then we become depressed.

But different people are born with different genetic vulnerabilities to brain disorders, just as genetics raises or lowers our likelihood of obesity or high cholesterol when we eat a high-calorie diet. (This gene-environment interaction is known as the diathesis-stress model of illness, and it applies to many other disorders.) Some people are genetically primed to produce less serotonin or fewer serotonin receptors, or be less sensitive to serotonin in the brain. It's these unlucky ones who may be most prone to

depression. In addition, as psychiatrist Peter Kramer writes in his books *Listening to Prozac* and *Against Depression*, "it may not be that a deficit in serotonin causes depression, but serotonin is protective". Think of serotonin as the police – protecting the brain from riots and violent crime, so to speak. A lack of police officers does not directly cause violent crime, but the presence of officers in your neighborhood certainly helps prevent it.

Consequently, much research on the development of antidepressants centers on helping the brain increase its serotonin activity. For example, at the junction between neurons, called a synapse, serotonin is passed from an upstream cell to a downstream one. Part of the serotonin is taken back up by the upstream neuron; in the depressed brain, this happens too fast, depriving the downstream partner of the chemical. A class of antidepressants called selective serotonergic reuptake inhibitors (SSRIs) stops the presynaptic upstream neuron from retrieving the neurotransmitter too soon, helping serotonin hang around longer in the gap between neurons and thus making more of it available for the brain to use. However, new evidence from the University of Hull in England, published in February 2008, suggests that due to the placebo effect, SSRIs may not work as well as previously thought.[2]

Likewise, the neurotransmitter norepinephrine is also implicated in depression; some antidepressants which inhibit norepinephrine reuptake as well as serotonin reuptake seem to be effective in treating the illness. But the relationship between the two neurotransmitters, as well as their relationship to depression, is complex and not well

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2 BBC Health: Antidepressants 'little effect'. http://news.bbc.co.uk/1/hi/health/7263494.stm Accessed Feb 28, 2008.
Kirsch, I. et al. (2008) Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration. PLoS Medicine 5(2):0260-0268

understood. And lack of serotonin or norepinephrine, or any other brain chemical, is only one tiny piece of the vast puzzle – a massively complicated puzzle that includes multiple neurotransmitters, many genes, and an intricate interaction between genes, environment, and individual experience.

All the attention on the neurochemistry of depression meant that few people paid attention to Helen Mayberg's work. Scientific citations – having other people reference your papers in their own – is an indicator of how much attention your work is getting. The more your paper gets cited, the more people are sitting up and taking notice. In the summer of 1997, Mayberg wrote a paper proposing a depression circuit[3]. The interest began as a trickle: Mayberg's paper was cited only 44 times in the first four years after it was published, out of the 305 times it has been cited to date. Four years is a long time in a fast-moving field like neuroscience, especially if people are not paying attention to your work. Other discoveries are made, interest and money go elsewhere, science hurtles on.

Mayberg kept plodding, undeterred. She asked healthy people to "think about something sad" and measured their brains' blood flow patterns using a technique called PET – and found a decrease in frontal-lobe activity and a more active area 25. And she scanned patients who were being treated with the antidepressant drug Paxil or placebos, finding that people who recovered showed an increase in frontal-lobe activity and a corresponding decrease in area 25 activity. All signs pointed to area 25 being implicated in depression: "We knew it was doing something when people were sad," she said

Exactly how area 25 modulates brain function is not known. Most of us can cast

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3 Mayberg, HS (1997) Limbic-cortical dysregulation: A proposed model of depression. *JOURNAL OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES* 9(3):471-481.

off our ordinary sadness. But people suffering from depression seem to sink into a downward spiral – feeling like they can't do anything to resolve their sadness or grief. Mayberg believed a hyperactive area 25 might be suppressing normal thinking and letting depressive thought 'loops' ("I'm sad and I'll never get out of this blue funk") take over. Alternatively, it might be overactive *because* it was working hard to throw off such depressive loops.

But then, in 2004, Mayberg seemed to hit a dead end. She studied patients who were undergoing cognitive-behavioral therapy (CBT), and found that when CBT worked, area 25 calmed down – but so did the frontal lobe. This seemed to contradict her previous findings that frontal lobe underactivity was associated with depression. What was the frontal lobe doing?

Then she realized what was going on: "CBT affects *complementary* areas of the brain to the regions targeted by drugs," Mayberg said. Cognitive-behavioral therapy acts by helping patients modulate their depressive thoughts. For example, someone who is depressed might be prone to thinking, "I'm useless and will never do anything right" whenever she makes a mistake at work. The therapist teaches the patient that she should think instead, "I made a mistake, but I can be more careful in future". In the initial stages of CBT, the frontal lobe must work *harder* – that is, the patients must actively think more to correct her negative self-thoughts – to make CBT work. So the drop in frontal-lobe activity that Mayberg was seeing wasn't due to the patients' depression lifting, it was due to the fact that after several CBT sessions, they were working less hard to control their thoughts, and the frontal lobe could 'relax'.

Those findings fit in with Mayberg's other work on depression circuits, so she kept working, piecing together the patterns of brain changes in depressed patients. At the same

time, the tide of research on depression was beginning to turn in Mayberg's direction.

In June 1999, a young psychiatrist named Yvette Sheline was studying two groups of women: one group which had suffered depression and one which had not. Sheline focused her attention on a part of the brain called the hippocampus, so named for the Latin word for 'seahorse', as the hippocampus has vaguely seahorse-like knots and curves. When she compared two women of the same age with and without depression, the hippocampus of the depressed woman was invariably smaller: depression made it shrink.

The hippocampus is responsible for memory and spatial navigation; what might cause it to shrink in depression? The answer, perhaps, is stress. The influential biologist Robert Sapolsky demonstrated that chronic stress leads to the production of stress hormones, which damage hippocampal cells when the cells are exposed to those hormones for long periods. Normally, the hippocampus signals the adrenal glands to end the stress response and stop the production of stress hormones, but a damaged hippocampus cannot send that feedback, perpetuating the cycle. Chronic stress – such as living in a war zone or being the victim of domestic abuse – is known to trigger depression. In turn, depression acts much like a chronic stressor.

The work of a neuroanatomist named Grazyna Rajkowska in 1999 offered another line of evidence to suggest the connection between depression, stress, and physical changes in the brain. Some scientists pick their field of study, their life's work – cancer research, or schizophrenia, or depression – because they have a personal stake in it. Helen Mayberg picked depression because it was a fascinating problem that had a big impact on lots of people; Rajkowska picked depression because it had haunted her family.

Rajkowska asked: If diseases like Alzheimer's and schizophrenia produced specific

patterns of brain changes, why not depression? To study this, she would need the brains of depressed people. So she arranged with coroner's offices to preserve and give her the brains of depressed people who had died abruptly – of suicide, homicide, accidents and natural causes like heart attacks. In the prefrontal cortex, she discovered differences between depressed brains and healthy brains. In the brains of depressed people, there were decreases in cortical thickness, cell size, and cell density. The changes Rajkowska observed were unique to depression, when depression was compared with other neurodegenerative disorders like Alzheimer's disease. Crucially, part of the prefrontal cortex is the cingulate cortex – the same area that Helen Mayberg was working on. Not just that: in Rajkowska's study, the extent of the damage was directly correlated with how long the patients had been depressed.

Perhaps all these findings are linked – stress is linked to neurotransmitters like serotonin and norepinephrine, which may be linked to overactivity in area 25 and other parts of the depression circuit, which is linked to cell death and hippocampal shrinkage. Depression makes for a complicated neurological picture – a little like a million-piece jigsaw of the sea. Sometimes, the best that scientists can do is work on one piece of the puzzle at a time.

In 1999, Mayberg accepted a professorship in neuropsychiatry at the University of Toronto. One of her new colleagues at Toronto was the surgeon Andres Lozano, who had already won acclaim for his deep-brain stimulation operations on Parkinson's patients. Because Parkinson's disease has its origins in a clearly defined, well-studied brain circuit, it made an ideal target for deep-brain stimulation.

When parts of the neural network that modulates body movements are hyperactive,

their out-of-control buzzing produces the tremors characteristic of Parkinson's. Removing overactive portions of brain tissue such as the globus pallidus or the subthalamic nucleus seemed to dampen the tremors. But rather than excising brain tissue, Lozano and other neurosurgeons found that deep-brain stimulation – inserting an electrode in the hyperactive tissue and applying current – seemed to have the same effect. What's more, deep-brain stimulation could be reversed by just switching off the current, which made it somewhat safer than removing a chunk of brain.

Mayberg thought the same approach might work for depression. She knew that the cingulate gyrus, area 25, was implicated in depression. And she knew that other teams were removing tiny parts of the brain around the cingulate gyrus in people with depression, in an operation known as a cingulotomy – and that this surgery seemed to be effective. She asked Lozano: could deep-brain stimulation of area 25 be a substitute for cingulotomies? Would inserting an electrode into area 25 calm it down the way it calmed the globus pallidus down in Parkinson's?

They decided to find out. They couldn't test their procedure on rats or monkeys, because there is no way to accurately simulate depression in an animal. Scientists have created animal models that look a little like depression: rats or monkeys simply give up trying to complete a task under prolonged, chronic stress. But, Mayberg argues, true depression is a uniquely human illness. Hopelessness is one of its symptoms, but in order to be hopeless you need to have the capacity to think about your future, and animals just don't appear to have that capacity. In order to best help people, Mayberg had to work with people. So Mayberg's team looked for the most severely ill people, the ones for whom the surgery was an absolute last resort.

The day of the very first surgery, in 2003, Mayberg was intensely nervous. Even

though all her theoretical evidence told her the procedure should work, she didn't yet fully trust it. She anticipated bad side effects: because area 25 is part of a brain pathway that regulates autonomic functions such as blood pressure and body temperature, she thought that stimulating area 25 might affect those things. In fact, she was so stressed that Lozano had to calm *her* down. He said, you know more than anyone else in the world about the science behind this. And he asked her, knowing what you do, would you let your mother or sister go through this procedure?

Yes, she said at once. The surgery proceeded.

Lozano inserted the electrodes, then turned them on one by one to relay a steady four-volt current into the brain of Patient 1. He switched on the first electrode – no reaction. He switched on the second electrode. The woman on the operating table, who had been an avid gardener before her depression, suddenly spoke up. She had felt her mood shift, as if it was "the first day of spring," she said, "when you see the crocuses popping up outside". Mayberg was ecstatic. She had braced herself for bad side effects, just in case stimulation of area 25 interfered with other functions in the same network. She was monitoring the patient's blood pressure, pulse, temperature for changes, and watching for anxiety, agitation or motor and sensory deficits caused by the stimulation. But there were none.

The next five operations were equally dramatic successes. All of Mayberg's patients had their symptoms alleviated instantly when the electrodes were turned on, while four out of six went into remission and two took lower levels of medication. According to her and other doctors like Emad Eskandar, when the current comes on, the surge in patients' mood is spectacular. Even as they sit on the operating table, patients describe how the "noise lifts", the "colors come back", "an enormous weight goes away". One

patient described his illness as a vortex; he felt as though he had to paddle to stay afloat, and when the switches were flipped he felt buoyant. Another patient commented that the room seemed, physically, much brighter.

That deep-brain stimulation worked was the result of more than just theoretical plodding. It was also partly good fortune, Mayberg said. "It was being in the right place at the right time. Twenty years ago when DBS was around for Parkinson's, we didn't know enough about the brain circuitry of depression to try it."

Neuroethicist Steven Hyman, who before his appointment as Harvard provost was also the director of the National Institute of Mental Health, believes that DBS in general is on the right track, and Mayberg's studies are a step in the right direction. "I think this is a treatment which is scientifically feasible," he says. "The good news about DBS is that it really does permit systematic testing and controls."

Mayberg's team published data from the first six patients as 'proof of principle' – evidence that their idea worked, that it was possible. In that seminal 2005 paper, they discussed the technique, its safety, and patients' outcomes after six months. Spurred by Helen Mayberg's initial success, other hospitals' teams – who themselves often had plenty of experience in experimental neurosurgery – began to carry out small DBS trials for mental illnesses like depression or obsessive-compulsive disorder.

IV. Scars and Old Ghosts

One of those groups was the Massachusetts General Hospital neurosurgery team that operated on Liss Murphy. Liss believes she was lucky to be where she was when she was, lucky to hear about the treatment and lucky to be living near enough to make it feasible. "[Moving back to Boston in 2004] was the best decision I've ever made," she says.

As soon as Liss found out that she was eligible for DBS, she could hardly wait. In the three months leading up to her surgery, she would phone the MGH surgical team, even at home, begging them to move it forward. "I barely read the consent form till months after the surgery," she admits. "My biggest worry was that it wasn't going to happen soon enough."

Finally, in June 2006, after an eternity of waiting, Liss underwent a grueling, 10-hour procedure that began at 6.30 in the morning and ended at 4.30 in the afternoon. Instead of implanting the electrode in Liss' subgenual cingulate cortex (the target that Helen Mayberg used), Liss' surgeons placed it in a dense bundle of fibers called the internal capsule, deep in and toward the back. The internal capsule is near to the cingulate cortex, but more importantly, fibers in the internal capsule carry signals from the cingulate cortex to other parts of the brain's depression circuits, the way optical fibers carry light along communications cables.

Dr Darin Dougherty of Massachusetts General Hospital, part of the team that operated on Liss Murphy, explains that the MGH team is deliberately studying targets besides area 25 in the hope of finding the best target for each DBS patient. "Ideally, people who don't respond to one might respond to the other," he says. "We're not like kids chasing the soccer ball – I'm glad people are running around the field doing different things."

Spurred by Helen Mayberg's initial success, other teams are trying deep-brain stimulation on depressed patients, targeting different overactive brain areas in the same network and looking for the most effective targets. Or they're looking for patterns: which patients respond best to which targets? The Cleveland Clinic, collaborating with Brown University's Butler Hospital, places electrodes in patients' internal capsule or their ventral striatum, which is a kind of way-station for brain communication. The procedure, however, is still rare: fewer than 50 people in North America are walking around with electrodes in their brains to treat their depression.

It's now, while DBS for mental illness is still new, that the time is ripe for ethical reflection. Any experimental brain surgery is haunted by the old ghosts of lobotomy, electroconvulsive therapy and psychosurgery (brain surgery to treat psychiatric conditions). In fact, Liss Murphy's regular psychiatrist at McLean Hospital resisted the idea of her undergoing deep-brain stimulation at first, precisely because he had lived and practiced through the 1960s, while much psychosurgery was still uncharted and unregulated – a Wild West gold rush.

But the practice and technology of DBS is being refined and made safer, just as electroconvulsive therapy has been. ECT is no longer the violent, bone-breaking electric shock applied to the first patients in the 1930s and 40s, though its reputation still bears those scars. Today, administered under general anesthesia, it is much more benign. Many neurologists and psychiatrists, including Helen Mayberg, consider electroconvulsive therapy the "best available" therapy for depressed patients – meaning that it has the highest effectiveness in treating patients. And it is: it has a 60-65% response rate, meaning that 60 to 65% of ECT patients have their depression lifted by more than half (as measured by

standardized rating scales). But it is not without side effects – for instance, memory losses and cognitive gaps like Liss Murphy's are fairly common.

Certainly, psychosurgery has a checkered past of ice-picks and damaged patients: famously, Rosemary Kennedy, the sister of US President John F. Kennedy, received a frontal lobotomy in 1941 at the age of 23 for her 'moodiness'. Instead of being cured, she spent the rest of her life in an infantilized state of mental retardation. In popular culture, Ken Kesey's 1962 novel *One Flew Over the Cuckoo's Nest* portrayed lobotomy as brutal and violently abusive, inflicted on patients in a mental hospital as a means of stemming their aggression.

While lobotomy did earn its shady reputation, however, deep-brain stimulation as it exists today has not. Jeffrey Schwartz, a researcher at the University of California, Los Angeles medical school, called deep-brain stimulation for depression "the new lobotomy" when the technique surfaced in 2005. Helen Mayberg calls Schwartz's comment "irresponsible" and factually inaccurate. The most striking difference between DBS and lobotomy is that DBS is reversible, she says. You can switch the electrodes off at any time, and their effect will disappear. (That's why neuroethicists prefer the term 'neuromodulation', rather than the irreversible 'psychosurgery', to describe deep-brain stimulation.)

Still DBS could be confounded with unethical surgical practices – such as the ones at Tulane University from the 1950s to the 1970s. The somewhat bioethically-challenged surgeon Robert Heath led a research team that put deep-brain electrodes in fifty-two patients to treat their schizophrenia, intractable pain or epilepsy. But Heath and his team ventured beyond the therapeutic use of stimulation, studying the pleasure and aversion responses that stimulation elicited in at least three different patients. The patients were

wired up to equipment that delivered current when they pressed a button; in one case, it was reported that stimulation of a particular brain region was so unpleasant that the subject jammed the button with a hairpin so it could not be pushed again. And in one notorious case, the Tulane researchers tried to change the sexual orientation of a 24-year-old homosexual man by implanting electrodes into half a dozen subcortical sites, including the septal region – demonstrating an alarming lack of respect for the dignity and volition of their subject. (Did it work? In the year after the procedure, the man reported engaging in both heterosexual and homosexual activities.)

The Tulane studies defied a couple of key bioethics principles. For one thing, the researchers trespassed beyond therapy into the realm of curiosity. As one journal article put it, "The operant conditioning studies appear to have been motivated more by scientific curiosity than therapeutic considerations." Worse, subjecting patients to aversive stimulation for the sake of research seems inhumane, and there was no clear scientific or clinical justification for doing so. (Though the Tulane research was carried out before federal policies about using human subjects were implemented, it was controversial from the start and the scientists drew criticism from their peers.) And whenever deep-brain stimulation patients ask Dr Eskandar questions like, "Can you stimulate the brain's pleasure centers?", he responds with this legend: Once, there was a prison in Bar Harbor, Maine, where the prisoners were fed only lobster, because it was so plentiful there at the time. Lobster all day, every day. Eventually the prisoners revolted *against* the rich seafood. "It's like too much of any good thing," Dr Eskandar says. Yes, you probably could, but what would be the point?

Like any other form of experimental surgery, deep-brain stimulation is subject to basic ethical constraints, such as the medical mantra "First do no harm". Cleveland Clinic

bioethicist Paul Ford argues that the procedure must benefit the patient in some way, unlike the Tulane experiments, and it must respect the patient's autonomy, he says. It should not take advantage of a patient's desperation to coerce him or her into treatment.

In the case of depression DBS, the screening process for the first trials was so rigorous that many more patients applied than were accepted; finding willing subjects is rarely a problem. In fact, Ford says, the real problem with selecting the most severely depressed patients was not an ethical one. It was an issue of experimental design: running the risk of false-negative results.

"DBS could have been effective on moderately depressed patients. If it didn't work on refractory patients, what would it tell us about how it worked on someone with moderate depression? Nothing," Ford says.

"Also, these are the most desperate patients. On the good side, these patients stand to benefit the most, and you're not exactly going to make their depression worse. The other way to think about it is that you should select those who are less depressed, because they have the best chance of getting better." This is a general problem with experimental treatments, which are often tried on those with most at stake: the sickest patients. At the same time, those patients, the ones who are furthest-gone, may be too ill to respond.

Ford is a mild-mannered, bearded man with a thoughtful gaze, first encountered deep-brain stimulation ethics when a patient undergoing a DBS procedure for movement disorder turned out to have an anxiety disorder as well, and refused – right in the operating room – to let the surgery continue. In a kind of ethical SWAT operation, Ford was called down to the OR, where he conferred with the patient's family and the surgeons; they decided that the patient was capable of informed decision-making, and brought the surgery to a halt. Now Ford sits on the Cleveland Clinic's depression-DBS review committee,

assessing the suitability of potential patients.

A 2004 paper from the Netherlands documents another case: that of a 62-year-old man who chose to set his stimulation at levels that stopped his Parkinson's tremors but left him manic. Such tradeoffs have not occurred in depression DBS yet, but as the surgery becomes more common, who knows what other dilemmas could ensue? If for some reason the opposite happened – depression DBS leaving a patient unable to walk, but alleviating his depression – should doctors permit that choice? What physical or mental side effects, what cost to themselves should patients be permitted to endure for the sake of lifting their primary illness, depression? Doctors should always anticipate such complications – no matter how rare.

The most realistic problem is that deep-brain stimulation might become a victim of its own success. Helen Mayberg has already seen an increase in the number of people who approach her team and want to participate in the study. Often, however, potential patients haven't exhausted all their other options, and want to skip therapies like ECT. Sometimes, they haven't considered that the surgery often entails moving to be near the hospital and returning for follow-up visits and battery replacements. Occasionally, she says, they haven't even considered that it entails surgery, and are worried about it leaving a scar. That's when she discusses other treatments with them. "If you're worried about a scar, you're not as sick as you think you are," says Mayberg.

Another issue that might stem from DBS' success is that rogue surgeons looking to profit might begin doing the procedure without proper training or support. There are at least 300 surgeons in the United States are trained in the necessary surgical techniques, according to the American Society for Stereotactic and Functional Surgery; many of them could potentially carry out the procedure. In theory, if a hospital is equipped and surgeons

are already trained to perform the sort of stereotactic surgery used in Parkinson's deep-brain stimulation, they can just as easily perform a DBS operation for depression – it's essentially the same procedure, using the same equipment and slightly modified electrodes.

But Dr. Eskandar argues that this fear is misplaced. . More likely there will be neurosurgeons who are leery of performing depression DBS. Most of the time their reluctance is practical: besides the surgery itself, patients need a support team of neurologists and psychiatrists, and many hospitals can't dedicate the doctors, money and time to such specialized teams.

For the time being, there are more prosaic, more tangible worries. For one thing, depressed patients tend to be somewhat younger than Parkinson's patients, and the effects of having electrodes in one's head for thirty, perhaps forty years is still unknown. At the moment, the first patients to receive DBS for depression have been followed for less than five years. The limits of current technology mean that the batteries run down every four to six months and must be replaced; the higher the patient's stimulation voltage, the faster they are depleted. Liss Murphy, for instance, is already on a stimulation level of 8 volts – in the top quartile of the device's capacity – and has to have her batteries surgically replaced twice a year. The biggest question: no one knows how long the effects of DBS will last, or whether the patient's brain will become acclimatized to them and dampen them over time.

For her husband Scott, the worries extend to supporting Liss through the next forty years of biennial surgery. And there's always the fear: *what if the depression comes back?* "We just lived through a multi-year episode," he says. "What if we go a few more months and then we go through a 5-year episode? What if it comes back worse than before?"

When I ask Liss if she's worried about being dependent on electrodes in her brain,

she says, yes, every day. But in his book *The Noonday Demon,* Andrew Solomon likens his dependence on antidepressants to his dependence on contact lenses. Without his lenses, he is virtually blind, but he is not shamed by them or by his need for them; why should antidepressants be any different? Liss feels much the same way about her electrodes. "Having DBS doesn't change me as a person; I'm still astonished the difference it's made." And she is hopeful about new technology that could reduce the need for constant stimulation or replacements: "Who knows what we'll learn in the next several years?"

V. Ever After

Today, while she is still treating new patients, Mayberg is also studying the long-term effects of stimulation in the patients she's treated. So far, the results are positive – a 60 to 65 percent response rate within a year, meaning that 60-65% of these patients are taking less than half of their original medication. (A response rate is defined in medicine as a 50% reduction in previous levels of treatment.) Mayberg has moved from Toronto to Emory University in Atlanta, Georgia, and her team there is in the midst of conducting a larger-scale blind trial.

Mayberg jokes, "The head of neurology at Stanford said to me, 'You know you've got a great idea when it gets the following response stages from other people: 'I don't believe it', 'Oh yeah, it's obvious', and 'Great idea, wish I had it'!' " She adds that the *Neuron* paper documented only the first demonstration that applying stimulation to area 25 would calm depression, and that much more work needs to be done. Ethical, controlled studies need to be carried out on larger patient groups, and long-term studies need to be done on the effectiveness and safety of deep-brain stimulation in situations like depression, when an electrode needs to stay in for decades, even a lifetime.

Harvard provost, National Institute of Mental Health director and neuroethicist Steven Hyman says Mayberg's work to date is some of the cleanest so far, with no confounding factors. But he adds, "If people can do convincing controlled trials – if they can be randomized with sham surgeries – then I think a lot of the ethical concerns about deep-brain stimulation will recede."

Ultimately, Mayberg is rational about the use of deep-brain stimulation, not irrationally exuberant about the technique. Not all patients are going to want brain surgery, and deep-brain stimulation's effectiveness has not been tested on patients whose depression

is less severe. She'd like to figure out the neural wiring of depression circuits. Their genetic basis. She'd like to map their neurochemistry in more detail. These efforts could eventually help doctors figure out the most appropriate treatment for each patient – those who might respond most to DBS should be given that treatment, while others who might be most responsive to drugs should be offered those first.

"There should be some way to identify the most malignant forms of depression early, instead of subjecting patients to electroconvulsive therapy and four different kinds of drugs," Mayberg said. "It should be like Bill Clinton having an angiogram and receiving bypass surgery straight away, instead of the doctors saying 'Well, why don't you try losing weight?'"

There are two major manufacturers of the hardware for DBS; Mayberg and Lozano are now working with one, St. Jude Medical. The other company, Medtronic, is also working with the Food and Drug Administration and several other hospitals to plan the largest study yet of depression DBS, enrolling at least a hundred patients. It may have scientists delay stimulation in half the patients for six months, switch it on in the other half, and compare the results. To be really convincing, the trial should be a double-blind if possible: neither the patients nor the doctors should be told whether the device is on or off. That way, doctors won't have any biases or prior expectations based on their knowledge, and they'll be able to tell how much of patients' improvement is from the DBS and how much is from a placebo effect.

And at the Cleveland Clinic, the Cleveland-Brown team is beginning to investigate second-generation versions of DBS technology. For instance, sensors might sniff out abnormal brain activity and deliver stimulation only then, rather than delivering a continuous stream of electricity. Cleveland Clinic engineers are also trying to fine-tune the

device so that it streams electricity in one direction, allowing doctors to focus its effects.

Liss Murphy's surgery went off without a hitch. In the video footage of her operation, as the electrodes are turned on, Liss looks "tired and uncomfortable, sort of older – pretty lackluster and benign stuff". If there were crocuses for Liss, she doesn't recall them. Nor bright lights or a sensation of floating, of relief – just that shy, initial smile.

But the real breakthrough was her process of recovery. When patients receive DBS for Parkinson's disease, they stop shaking almost instantaneously. For Liss, the recovery was not instantaneous. Her world brightened, though much remained the same. But she started to feel better. She began to smile more. To get out and walk Ned of her own accord. The Murphys went on vacation to Florida with Scott's family. Liss remembers laughing a lot, even at silly things like a waiter's mannerisms or a family member's comment. Scott says, "We could make plans for the weekend, go away, paint the house... She could see the landscape beyond her own toes. As small as that sounds, it's pretty big."

The treatment of depression is a gradual process, even with DBS. Just as someone who undergoes a heart bypass doesn't go home and resume his normal life straight away, but must return for several follow-up visits and monitor his diet and exercise throughout his lifetime, a patient with depression DBS must keep seeing a team of neurologists and psychiatrists – especially because the procedure is so new – and often must remain on medication for some time. Liss Murphy still sees her regular psychiatrist and pharmacologist at McLean Hospital, goes to Massachusetts General Hospital for battery replacement surgery and neurological tests, and is on about half her former dosage of medication. Few others beyond Liss' immediate family know of her surgery. Her fine

blonde hair has grown back to shoulder-length, hiding the scars. Still, she's loath to tell others that she's had DBS, for fear they might misunderstand. She says she has trouble explaining the surgery to others.

Even the media get it wrong sometimes, she says. In November 2007, an article appeared in the Boston Globe about a teenage boy who underwent DBS for a movement disorder called dystonia. A paragraph described the patient, who "beamed with anticipation as he officially began life as a cyborg – part human, part machine." Liss was indignant. "'Machine' seems like a...a techno-edgy, harsh word," she says. "If I was going to be part machine I definitely would have been something different!"

But the word 'cyborg', with its science-fiction echoes of sinister monstrosities, may also raise some misplaced concerns about who she is now – or what. "I'm still the same person – my personality hasn't changed, my values haven't changed, my beliefs haven't changed. [Having DBS] is like having a pacemaker or an artificial leg – you're still the same person." She is insistent that she is still herself – only without the severe depression, as if something had been lifted rather than added or augmented.

What misunderstanding, what prejudice precisely, is Liss Murphy afraid she might encounter from others who hear of her surgery? Why are we squeamish at mental illness, electrodes in the brain, or a simultaneous combination of the two? Perhaps we are reluctant to believe that the motley collection of mental processes, emotions, thoughts, and memories we call selves could be altered by a piece of metal and an electric current. Perhaps we believe that those who have their selves altered in that way are somehow diminished or less than wholly human. The truth is, our brains do not reach adulthood and then become eternal, unchangeable, fully formed. Every experience shapes, adds to and

whittles our brains. Over time, we are flexible: researchers have found that adults do grow new brain cells when they learn new skills[4], even as they lose brain cells to disease or age. And yes, our brains do run on electrical impulses.

Gut instincts aside, the issues surrounding depression DBS are very similar to the ones surrounding: medical devices such as hearing aids, pacemakers or artificial limbs, since these also ameliorate physical conditions; drug therapy for depression, which targets the same disease; and deep-brain stimulation for other illnesses like Parkinson's, as it uses the same methods and technology. As an experimental surgery, depression DBS faces the same concerns as any other experimental technique. The point is, DBS for depression is a novel application of an old technique and existing technology.

Whatever the future of deep-brain stimulation for depression – even though it is not a magic bullet, even though there are no fairytale endings – there is no doubt that it is now saving lives, offering hope. Helen Mayberg continues to study deep-brain stimulation, hoping to improve the technique and find new ways of treating human suffering. And Liss Murphy, two years after her DBS surgery, hopes to return to work this year. She is helping a friend out at her hair salon, volunteers in a patient group at the hospital. She'd like to work in mental health – perhaps in patient education and support. "I've been given so much, I'd like to give back," she says. "I never thought I'd still be here at this point."

4 Draganski, B. & May, A. (2008) Training-induced structural changes in the adult human brain. *Behavioural Brain Research* (in press).

Sources and Further Reading

Interviews and emails

Ed Boyden (MIT). Personal communication, October 2007
Suzanne Corkin (MIT). Personal communication, October-December 2007
Darin Dougherty (MGH). Personal communication, 22 December 2007
Emad Eskandar (MGH). Personal communication & surgery observation, February 2008
Paul Ford (Cleveland Clinic). Personal communication, 30 December 2007
Steven Hyman (Harvard). Personal communication, October 2007
Helen Mayberg (Emory University). Personal communication, September 2007-April 2008
Liss Murphy, personal communication, December 2007-April 2008
Scott Murphy, personal communication, 21 January 2008

Depression – general resources and personal accounts

Casey, Nell (ed). (2001). *Unholy Ghost: writers on depression.* New York: Morrow.
Guldberg, Helene. (2008, January 18). *Humanity, thou art sick.* (Review of Lane, Christopher, *Shyness: How Normal Behaviour Became A Sickness).* Retrieved February 2, 2008 from spiked-online, http://www.spiked-online.com/index.php?/site/article/4287/
Knauth, Percy. (1975). *A season in hell.* New York: Harper & Row.
Kramer, Peter. (2005). *Against Depression.* New York: Penguin Books.
Solomon, Andrew (2001) *The Noonday Demon: an atlas of depression.* New York: Scribner.
Styron, William. (1990) *Darkness Visible: a memoir of madness.* New York: Random House.

Depression – etiology, mapping neurological circuits

Mayberg, Helen S. (1997) Limbic-cortical dysregulation: A proposed model of depression. *Journal of Neuropsychiatry and Clinical Neurosciences* 9(3):471-481.
Mayberg, Helen S. (2006). Defining Neurocircuits In Depression. *Psychiatric Annals 36*(4): 258-267
Rajkowska G, Miguel-Hidalgo JJ, Wei JR, et al (1999) Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry* 45(9):1085-1098
Ressler, Kerry J. & Mayberg, Helen S. (2007). Targeting abnormal neural circuits in mood and
anxiety disorders: from the laboratory to the clinic. *Nature Neuroscience 10*(9):1116-1123
Sheline YI, Sanghavi M, Mintun MA et al. (1999) Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience* 19(12):5034-5043

DBS for depression

(2006, January 5). *Deep Brain Stimulation for Treatment-Resistant Depression: An Expert Interview with Helen S. Mayberg, MD.* Retrieved October 5, 2007 from Medscape, http://www.medscape.com/viewarticle/520659

Dobbs, David (2006, April 2). A Depression Switch? *The New York Times Magazine*, p50
Dobbs, David (2006, August/ September). Turning Off Depression. *Scientific American Mind*, pp26-31
MacDonald, Ann (2005, September 1). *Deep Brain Stimulation: A Technique for Mood, Too?* Retrieved October 5, 2007 from The Dana Foundation website, www.dana.org
Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C. et. al. (2005). Deep Brain Stimulation for Treatment-Resistant Depression. *Neuron 45*:651-680
Mone, Gregory (2007, September 13) *Happiness Is A Warm Electrode.* Retrieved October 5, 2007 from Popular Science, http://www.popsci.com/scitech/article/2007-09/happiness-warm-electrode
Wichmannn, Thomas & DeLong, Mahlon R. (2006) Deep Brain Stimulation for Neurologic and Neuropsychiatric Disorders. *Neuron 52:*197-204

Depression – other treatments

BBC Health: Antidepressants 'little effect'. http://news.bbc.co.uk/1/hi/health/7263494.stm Accessed Feb 28, 2008.
Kirsch, I. et al. (2008) Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data. Submitted to the Food and Drug Administration. PLoS Medicine 5(2):0260-0268
Tone, Andrea & Watkins, Elizabeth Siegel. (2007). *Medicating Modern America: prescription drugs in history.* New York: New York University Press.
Charles Barber – The Brain: A Mindless Obsession? (Wilson Quarterly)

DBS for other conditions

Goldberg, Carey. (2007, November 25). He risks deep brain surgery to regain muscle control. *The Boston Globe*, pA1
Lamberg, Lynne. (2007). Interest Surging in Electroconvulsive and Other Brain Stimulation Therapies. *Journal of the American Medical Association 298*(10):1147-1149

Neuromodulation and Psychosurgery: General

Fink, Max & Taylor, Michael A. (2007) Electroconvulsive Therapy: Evidence and Challenges. *Journal of the American Medical Association, 298*(3):330-332
Keiper, Adam. (2006). The Age of Neuroelectronics. *The New Atlantis*, Winter 2006, pp4-41
Marangell, L.B., Martinez, M., Jurdi, R.A. & Zboyan, H. (2007) Neurostimulation therapies in depression: a review of new modalities. *Actia Psychiatrica Scandinavia 116:*174-181
Pandya, Mayur, Pozuelo, Leopoldo & Malone, Donald. (2007) Electroconvulsive therapy: What the internist needs to know. *Cleveland Clinic Journal of Medicine 74*(9):679-685
Szasz, Thomas Stephen (2007) *Coercion as cure: a critical history of psychiatry.* New Brunswick, NJ. Transaction Publishers
Vertusick, Frank T. (1997). Lobotomy's back – controversial procedure is making a comeback. *Discovery, Oct. 1997.*

Neuromodulation and Psychosurgery: Ethics

Baumeister, Alan A. (2000) The Tulane Electrical Brain Stimulation Program: A Historical Case Study in Medical Ethics. *Journal of the History of the Neurosciences* 9(3):262-278
Brower, Vicki. (2003) The ethics of innovation. *EMBO reports 4*(4):338-340
Fins, Joseph J., Rezai, Ali R. & Greenberg, Benjamin D. (2006) Psychosurgery: Avoiding an Ethical Redux while Advancing a Therapeutic Future. *Neurosurgery 59*(4): 713-716
Ford, Paul J. (2006). The Clinical and Research Ethics of Neuromodulation. *Neuromodulation 9*(4):250-252
Visser-Vandewalle V., van der Linden C., Temel Y. et al. (2005) Long-term effects of bilateral subthalamic nucleus stimulation in advanced Parkinson disease: a four year follow-up study. *Parkinsonism & Related Disorders 11*(3):157-165.

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