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STRESS, ALZHEIMER'S & BRAIN STIMULATION

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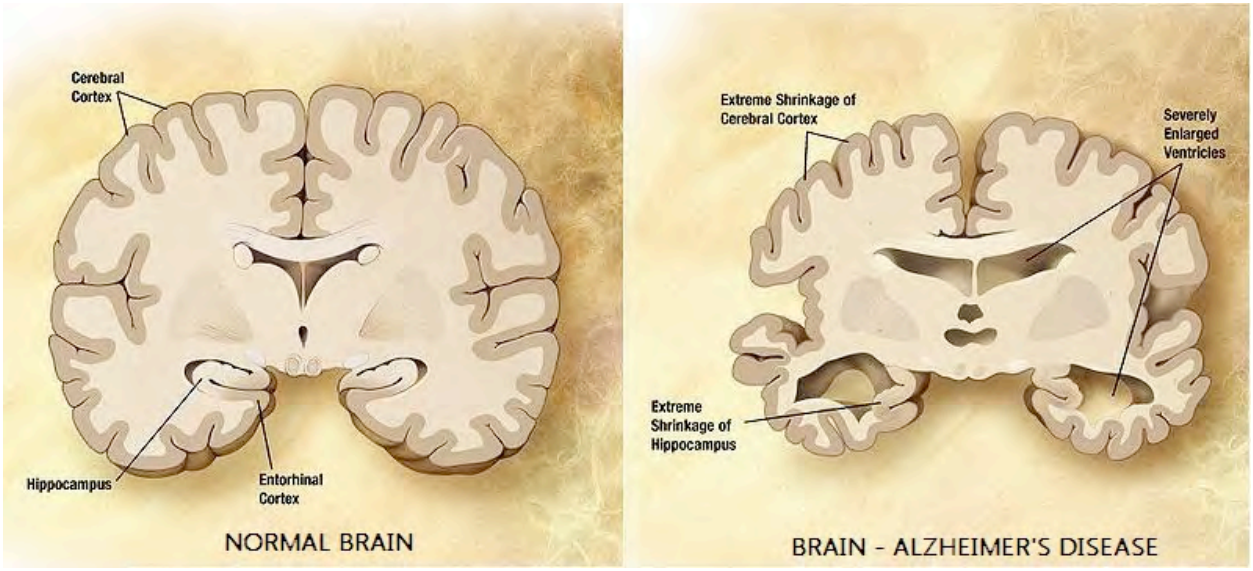
Alzheimer's is the quintessence of stress, because it is a disease over which we have absolutely no control. Save for a small percentage of patients who may have a genetic predisposition, its cause or causes are unknown and there are no effective medications or other interventions. The FDA lists five drugs approved for treating certain symptoms, but they are useless in over half of patients and any slight benefits rarely last longer than a few months.

Also Included In This Issue

Alzheimer's disease (AD) is always fatal, its course is unpredictable, and the order of appearance and severity of different symptoms and signs can vary. Early diagnosis can be difficult, since the first complaint is usually loss of memory for recent events or familiar names. But this also occurs with normal aging, and is now being seen in younger people due to stress.

In one nationwide survey, four out of five doctors reported that baby boomers as young as 35 had complained of mild cognitive impairment (MCI) problems previously seen primarily in senior citizens. These included not only difficulty remembering names, but forgetting where you left your keys or glasses, or the most important thing you went to the supermarket for. In almost 90%, the leading cause of this type of intermittent memory impairment was increased stress from work or personal problems. On the other hand, MCI also seems to increase risk for developing Alzheimer's.

While that doesn't show that stress causes AD, we do know that stress causes a decrease in the size of the hippocampus and that this is also a consistent finding in Alzheimer's. Patients with elevated cortisol due to depression or PTSD complain of memory problems and also show a shrinkage of the hippocampus that is usually not seen until decades later.



As shown above (left), the hippocampus is located in the temporal lobe on each side of the brain. In Alzheimer's, the hippocampus is the first structure affected and short-term memory starts to deteriorate. The ventricles, chambers in the brain that contain cerebrospinal fluid, become significantly enlarged, followed by an overall shrinkage of brain tissue in the cerebral cortex as the disease progresses as seen above (right).

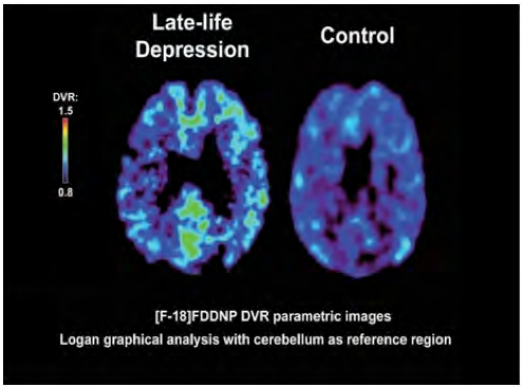
What is of growing concern is the tremendous increase in AD over the past few decades that cannot be attributed solely to longer life expectancy. An estimated 5.4 million Americans, including 200,000 younger than 65 have Alzheimer's and this is expected to rise to 13.2 million by 2050. It was originally thought that drinking out of aluminum cans or cooking in aluminum pots and pans might be responsible. Silver dental fillings were also implicated because they are an amalgam containing about 50 percent mercury, 35 percent silver and 15 percent tin, and certain forms of mercury are known to cause brain damage. Aspartame (Nutrasweet, Equal) was allegedly linked to memory loss and other mental complaints, as were preservatives in flu shots, but there is no proof that any of the above have contributed to the remarkable rise of this deadly disorder. More recently, elevated cholesterol that clogged cerebral arteries with plaque was cited as a possible culprit. The obvious corollary was that statins could prevent or delay Alzheimer's or reduce symptoms. There are not only no clinical studies to support this, but memory loss, amnesia, lack of concentration and other cognitive deficits are such frequent and significant side effects, the FDA

recently mandated that all statins carry a Black Box label warning about this complication as well as increased risk of diabetes.

Depression And Alzheimer's – Cause, Consequence Or Coincidence?

In addition to memory loss and cognitive problems, Alzheimer patients often exhibit apathy, loss of interest in previously enjoyable hobbies or activities, social withdrawal, isolation, and other symptoms that are characteristic of depression. This raises the old chicken or egg enigma, "Which came first?" Some studies suggest that depression is a risk factor for Alzheimer's. One found that people with a history of depression were 2.5 times more likely to develop Alzheimer's and those who had experienced depression before the age of 60 were four times more likely. Others believe that depression is often an early manifestation of Alzheimer's, especially when it surfaces for the first time and is quickly followed by other signs and symptoms of dementia. To explore this, researchers followed over 900 elderly Catholic nuns, priests and monks without dementia for up to 13 years. Their annual evaluation included a neurological evaluation and a battery of 19 tests that were interpreted by neuropsychologists to rate the degree of depression, mild cognitive impairment and Alzheimer's. Of the 190 subjects who eventually developed AD, there was no indication there had been any increase in symptoms of depression before the diagnosis was made. Among those without any baseline cognitive impairment, there was also no increase in depressive symptoms as cognitive deficits later developed. Although not conclusive, these findings suggested that in this population, depression was a prodromal manifestation of Alzheimer's rather than its cause.

If depression did cause Alzheimer's, one would suspect to find deposits of amyloid plaque and tau tangles in the brains of severely depressed patients, since these are the hallmarks of AD at autopsy. These deposits have been associated with memory loss and symptoms of mild depression and anxiety in older individuals who might possibly have gone on to develop Alzheimer's. Researchers investigated this by creating FDDNP, a chemical marker that binds to plaque and tangle deposits so that they can pinpoint where they are accumulating on positron emission tomography (PET) scans, as seen below.

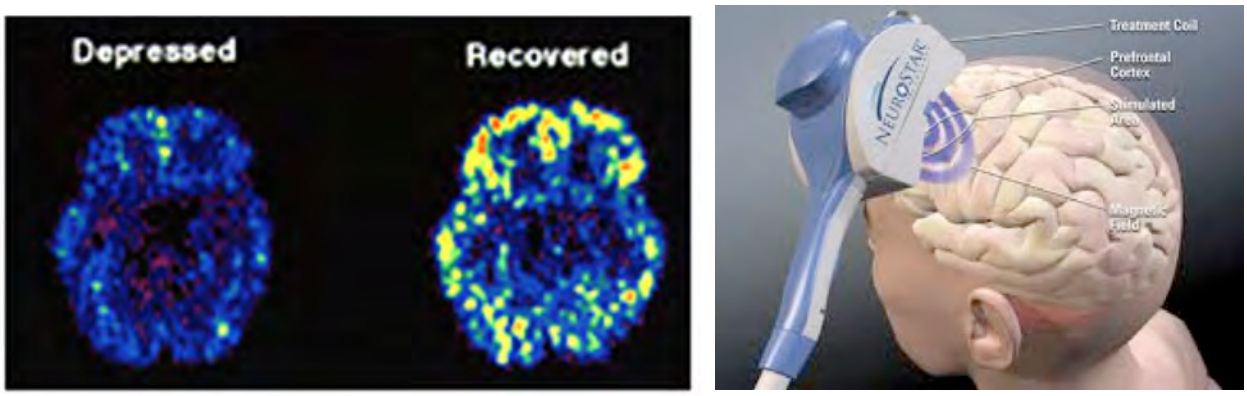


They compared the FDDNP brain scans of 20 depressed adults aged 60 to 82 with the scans of 19 healthy people of similar age, education and gender. As can be seen to the left, FDDNP binding was higher throughout the brain in depressed patients, and especially in critical brain regions that are involved in decision-making, complex reasoning, memory and emotions.

This "window into the brain" technique may demonstrate a correlation between areas of the brain where increased binding is taking place and certain symptoms, which could improve treatment. It may also be useful in evaluating new drugs designed to delay the onset of AD, and to delineate the role of depression in this disorder. The problem is that depression is not a discrete diagnosis like diabetes, nor can it be confirmed by a simple blood test. Depression is merely the description of a patient with a combination of specific symptoms and signs that have no obvious organic basis. There are no diagnostic blood tests and although abnormalities may sometimes be found on sophisticated imaging studies, these are not consistent findings. These same signs and symptoms may have different causes, which is why we have so many different types of treatment: drugs (monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors, lithium); supplements (St. John's wort, melatonin, SAMe); psychotherapy; ultraviolet light; cranioelectrical stimulation therapy (CES), repetitive transcranial magnetic stimulation (rTMS); transcranial direct current stimulation (tDCS); deep brain stimulation (DBS); vagal nerve stimulation (VNS); and electroconvulsive (shock) therapy (ECT). Save for bipolar disorder and SAD syndrome (Seasonal Affective Disorder), there are few ways to predict which of the above will work best in any given patient. SSRI antidepressants, the most popular drugs, are not significantly better than placebos in most clinical trials, can have serious side effects such as suicide, and may be difficult to discontinue. Most electrical stimulation approaches are expensive and also have significant side effects. Some may not be FDA approved or cleared for depression, but can be used off label if a physician believes it will be beneficial. Cranial electrotherapy stimulation (CES) is the only exception. It has been in use for over 30 years, is so safe that it does not require a prescription in any other country, and is extremely cost effective. In addition to depression, it is also recognized by the FDA as being effective in insomnia and anxiety, which often accompany depression.

Why Does Shock Therapy Or Mild Electrical Stimulation Relieve Depression?

Since we don't know what causes depression, it's difficult to explain why any of the above modalities might possibly work. The newer antidepressants are presumably efficacious because they boost serotonin and/ or dopamine etc. but there are no studies to support this hypothesis. Electroconvulsive (shock) therapy (ECT) is the most effective treatment for depression when drug therapy fails and transcranial stimulation (rTMS and tDCS) have also benefited patients resistant to antidepressant drugs. Here again, there is no evidence that this is associated with a rise in serotonin or changes in the levels of other neurotransmitters. What is of great interest is that in many patients, imaging studies show a progressive increase in energy levels at specific sites that do correlate with clinical improvement as shown below.

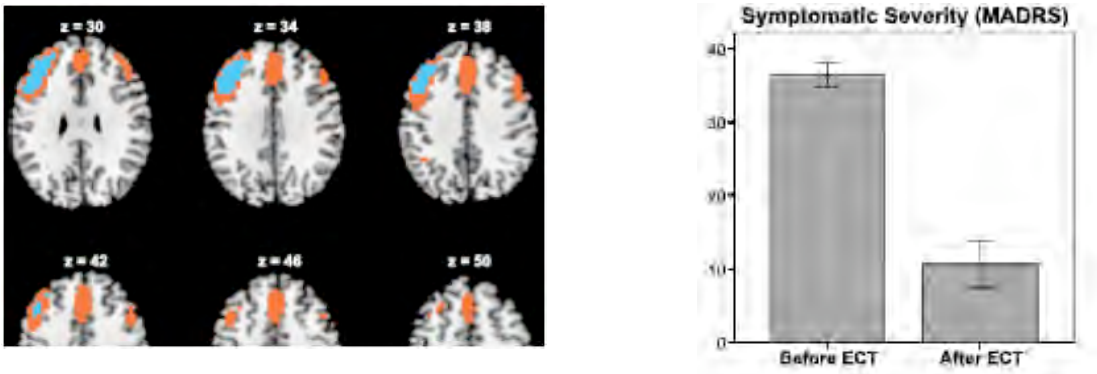


Positive Emission Tomography (PET) scan at left of a depressed patient's brain prior to rTMS treatment. After successful treatment (right), scan reveals greatly increased activity in the left prefrontal cortex (top of scan). This is the area targeted by the magnetic field (right illustration)

There is good reason to believe that future advances in the diagnosis and treatment of depression will depend on developing novel ways to detect and correct disturbances in energy communication pathways, rather than drugs for hypothetical biochemical disturbances. For example, electroconvulsive therapy is the most effective treatment for severe depression, with an impressive success rate of 75% to 80%. Although it has been used for over seven decades, we still don't know why it works. It was originally suggested that the convulsions damaged the brain so that it was no longer sensitive to emotions or stressors that might have precipitated depression. The anticonvulsant theory proposed that during the first few shock treatments, the patient's seizure threshold increases, so that it takes more ECT stimulus to produce a seizure. Certain adaptive responses are initiated to stop the seizures, which affect blood flow and the release of neurotransmitters and chemicals that also relieve depression. Another theory proposes that ECT treatments adjust the regulation of stress hormones that affect energy, sleep, appetite, and mood. Treatment may be unilateral, with one electrode on the right temple and one on the crown of the head, or it may be bilateral. The intensity, number and duration of treatments can also vary.

Little progress had been made in this area until a few weeks ago, when Scottish researchers reported that ECT treatments reduced abnormal communication between certain areas of the brain. They had theorized that depressed patients had a "hyperconnection" or "over connection" between brain areas involved in emotional processing and mood changes, and other sites that focused on concentration and cognitive skills. This disrupted the orderly communication of information that was manifested clinically by varied signs and symptoms depending on the sites most affected. It was proposed that shock therapy removed this blockage in communication and to evaluate this, fMRI (functional magnetic resonance imaging) was used to scan the brains of patients with severe clinical depression who had failed to

respond to antidepressant drugs. The patients were then treated with 2 sessions of ECT per week until they were clinically improved (average 4.2 weeks). The fMRI was then repeated, with the results shown below.

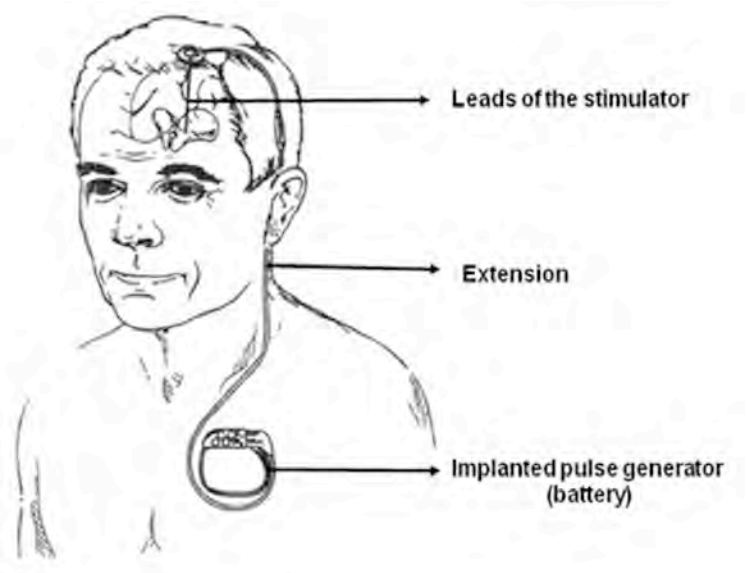


Excessive connectivity in severely depressed patients before ECT (displayed in orange) and persisting connectivity after ECT (displayed in blue) showing a marked decrease following ECT. This was accompanied by a significant decrease in symptoms on the graph to the right. From Perrina JS, Merz S, Bennet M. et al., "Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder." *PNAS*, March 19, 2012 (published ahead of print).

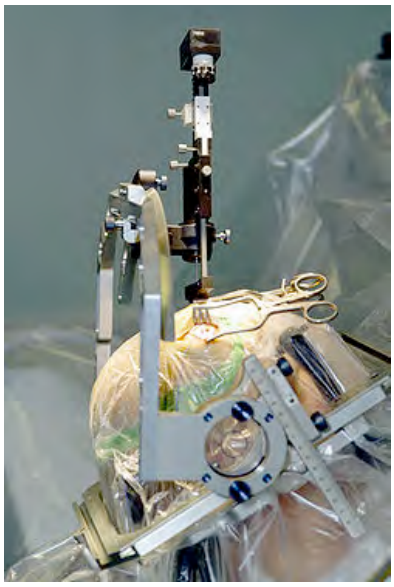
The blue areas in the left prefrontal cortex showed the most improvement and it is interesting that this is the precise region targeted in rTMS. The impressive degree of improvement is evident in the bar graph with a fall from 37, (severe depression) on the Montgomery-Asberg Depression Rating Scale, to 10. (7-17 is mild depression and 6 or less is normal). Antidepressants are considered to be effective if there is a 50% drop in the rating scale after several months. Recent statistics suggest that this happens in only 40% of patients. In this study, the average drop was over 70% in 8 weeks, and 100% of this small group of patients improved. Because of memory loss, headache and other side effects, ECT is usually limited to depressed patients who are severely disabled or believed to be at increased risk for suicide and have not responded to any other intervention. Magnetic Seizure Therapy (MST) is designed to provide the same benefits as ECT with fewer side effects. It induces seizures by using rapidly alternating strong magnetic fields. Since these enter the brain without any significant impedance by the skull, there is improved control over the site of stimulation and seizure initiation compared to ECT. Efficacy appears to be similar to ECT, there are fewer side effects, and patients recover more rapidly.

Deep Brain Stimulation (DBS) may also be a last resort when everything else fails. The FDA has approved DBS for Parkinson's disease, essential tremor, and dystonia (recurrent muscle contractions or spasms), but it is also used to treat OCD, Tourette's syndrome, phantom limb and other chronic pain complaints as well as treatment resistant epilepsy and depression. DBS involves implanting small electrodes into very specific areas of the brain to achieve a desired response. These are connected by a tiny insulated wire to

a battery powered impulse generator placed under the skin usually near the collarbone. The connecting wire runs under the skin, around the ear, and into the top of the head as shown below to the left. This is minor surgery compared to implanting the electrodes in the brain, as shown to the right.



Implanting Pulse Generator And Connecting Wires



Implanting DBS Electrodes

The impulse generator can send either constant or intermittent stimulation to the electrodes at specific frequencies and strengths to affect neurons within a certain range. These signals can also be adjusted to make neurons fire or to suppress firing and precise placement using stereotactic guidance is crucial. Battery packs usually last for three or four years but a new rechargeable unit may extend life to up to 9 years. Most antidepressant drug studies have centered on areas where effects on serotonin, memory, or hippocampal size can be demonstrated. The antidepressant effects of non-invasive transcranial electrical stimulation have focused more on the prefrontal cortex, as illustrated by the PET scan changes during rTMS.

Deep brain stimulation research has instead concentrated on a network of neurons that connects higher cortical structures with those in the limbic system that regulate emotions, known as Brodmann's Area 25, or BA25. The initial study results were very encouraging since the only eligible patients were those completely resistant to all treatments, including ECT. Many were so disabled that they had been hospitalized for psychiatric observation and therapy. However, **one month after the electrodes were implanted in BA25, 60% or 12 of the 20 patients showed a 50% reduction in depression symptoms** and some had a complete remission. While this was encouraging, the other 8 patients had absolutely no benefit and one asked for the electrodes to be removed. And in those who initially responded with a

50% reduction in symptoms, less than one third were able to maintain this improvement 3 months later, suggesting a possible placebo effect.

Subsequent studies, which included not only BA25 but also related areas BA24 and BA32, found that many patients did not improve during the first few months and it could take a year or more to see results. In one study the patients were told that immediately after surgery they would be assigned to two treatment groups, with one receiving immediate stimulation and the other receiving stimulation only after four weeks. In fact, neither group was stimulated during this period and no significant placebo effects were observed. They then received constant stimulation and there was steady improvement over the next six months. **At the end of two years, 92% had a significantly improved response and 58% were in remission.** None of the patients who experienced a remission had a relapse, but other patients quickly reverted to full blown depression if stimulation of their electrodes was discontinued. As the senior author explained, the areas stimulated are a key conduit of neural traffic back and forth between the "thinking" frontal cortex and older limbic structures that give rise to emotions. "In depressed people, the latter appears to be overactive, 'like a gate left open,' allowing negative emotions to overwhelm thinking and mood. Inserting the electrodes closed this gate and alleviated the depression in two-thirds of the patients." This is consistent with the view that ECT is effective because it also dampens "over connected" areas of the brain.

A much larger study called BROADEN, (**BRO**dmann Area 25 **DE**ep brain **N**euromodulation) has been under way to determine if DBS is a safe and effective treatment for depression. Only three centers were initially involved using the St. Jude Medical Libra System, which has been found to be effective in Parkinson's disease. Among 21 patients, 62% reported a 40% reduction in depression and 29% said their symptoms were reduced by 50% after one year. These results were so encouraging that the study is now being expanded to allow 20 sites in the U.S. to enroll up to 125 patients, and if the results are equally impressive, a further increase to 230 is planned. To be eligible, participants must: have been diagnosed with major depressive disorder (MDD); be between 21 and 70 years old; have had their first depressive episode before age 45; have tried at least four treatments in their current episode (for example, different antidepressants, different combinations of medications, and/or electroconvulsive therapy (ECT).

Because severe depression seems to antedate Alzheimer's in so many instances, many believe that it can cause this fatal disease. Support comes from a study of 486 people aged 60 to 90 who had no evidence of dementia. Over the next 6 years, 33 developed Alzheimer's disease and 134 had

consulted a doctor because of depression. Those in this group were 2.5 times more likely to develop Alzheimer's as other participants.

Is Brain Stimulation Or Some Other Cure For Alzheimer's On The Horizon?

It would seem so based on recent media headlines. The November 23, 2011 U.K.'s *Daily Mail* reported, **"Alzheimer's disease eased by the return of electric shock therapy".** The *New Scientist* headline was **"Alzheimer's damage reversed by deep brain stimulation"**. However, instead of offering hope, these claims were little more than the usual hype associated with any hint of a breakthrough in this dreaded disease. This excitement was precipitated by a report on six patients, all of whom had been diagnosed as having Alzheimer's of recent origin (less than two years) and were being evaluated to determine the safety and efficacy of deep brain stimulation. There were no significant safety concerns. The procedure was well tolerated and there were few adverse side effects. The Alzheimer's disease assessment scale (ADAS) and the mini-mental state examination (MMSE) were used to measure the severity and progress of the disease and functional changes such as memory and language assessment. These were administered at the start of the study and after 1, 6 and 12 months of deep brain stimulation. After one month of DBS, three patients showed slight improvement in functioning and three patients showed a slight worsening of functioning. After six months of DBS, four patients showed improvement in functioning and two showed either no change or worsening of functioning. After 12 months of DBS, one patient showed an improvement, and five showed a worsening of functioning. When these results were compared to the expected change in functioning over one year of a typical patient with Alzheimer's disease, it was found that two of the participants had a less severe decline in functioning than expected, one had a more severe decline than expected, and three had the expected changes in function. So what was all the publicity and hype all about?

It should be emphasized that this was a small phase 1 study designed primarily to demonstrate safety and all patients received stimulation to the fornix/hypothalamus area for a 12-month period. One of the characteristics of Alzheimer's disease is that the metabolic activity of affected brain tissue declines, and this can be accurately measured by studying glucose utilization with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). What excited the researchers was the "early and striking" reversal of impaired glucose metabolism in temporal and parietal cortical areas in all patients 1 year after DBS treatment. This correlated with improved neural traffic in memory circuits using low-resolution brain electromagnetic tomography (LORETA). DBS reduced the rate of hippocampus shrinkage in 4 patients, and in 2, the hippocampus actually increased in size, and memory also improved. A phase 2 study involving 50 patients is now being planned.

Other promising new "breakthroughs" include vaccines like bapineuzumab, which may prevent or even reverse amyloid deposits that clog up vital connections between brain cells. It should be available in 2 years, at which time we should also have more information about bexarotene (Targetin). It is currently used to treat certain types of cancer but has been found to dissolve plaque and improve memory in a mouse model of Alzheimer's. There is also CERE-110, an experimental drug that contains the gene for nerve growth factor (NGF), which can be injected directly into damaged brain areas to stimulate the growth of new nerves. Etanercept (Enbrel) is used to treat rheumatoid arthritis, plaque psoriasis and other immune system disorders because it inhibits tumor necrosis factor alpha (TNF-a). Elevated levels of TNF-a have been found in the spinal fluid of Alzheimer's patients and are thought to interfere with transmission of nerve signals in the brain. In one patient, injection of etanercept produced **"a miraculous restoration of memory and markedly improved mood within 10 minutes."** The injection was given between the spinous processes of the C6 and 7 vertebrae in the neck where there are numerous veins that can transport the medication into the brain and spinal fluid. This improvement lasted throughout a 7-week assessment period during which the patient received an injection every week for the first 5 weeks. Since the cost for 12 treatments here is $27,000, patients are flocking to Nicaragua, where physicians can train caregivers to administer 12 treatments for $2,840.

Direct current stimulation (tDCS) has also been shown to improve memory in Alzheimer's and to remarkably enhance focus and concentration in normal people. The Army has been using it to reduce the time it takes to train snipers to be expert sharpshooters. One reporter spent two hours learning how to shoot a close-range assault rifle. She had never held a rifle and described her initial experience in the February 6 *New Scientist* as follows.

> I'm close to tears behind my thin cover of sandbags as 20 screaming, masked men run towards me at full speed, strapped into suicide bomb vests and clutching rifles. For every one I manage to shoot dead, three new assailants pop up from nowhere. I'm clearly not shooting fast enough, and panic and incompetence are making me continually jam my rifle. My salvation lies in the fact that my attackers are only a video, projected on screens to the front and sides. … But I am failing miserably.

She is then hooked up to the dCTS device and tries again.

> Initially, there is a slight tingle, and suddenly my mouth tastes like I've just licked the inside of an aluminum can. I don't notice any other effect. I simply begin to take out attacker after attacker. As twenty of them run at me brandishing their guns, I calmly line up my rifle, take a moment to breathe deeply, and pick off the closest one, before tranquilly assessing my next target. In what seems like next to no time, I hear a voice call out, "Okay, that's it." In the sudden quiet amid the bodies around me, I was really expecting more assailants, and I'm a bit disappointed when the team begins to remove my electrodes. I look up and wonder if someone wound the clocks forward.

> Inexplicably, 20 minutes have just passed. "How many did I get?" I ask the assistant. She looks at me quizzically. "All of them."

tDCS has been found to more than double the rate at which people improve other skills, such as objection recognition and mathematical calculations. Many describe it as feeling in the "zone", or "flow", the feeling of effortless concentration that characterizes outstanding performance in all kinds of sports and other skills. While all of the above sounds promising, until there are clinical trials to support the off-label use of tDCS, Targetin and Enbrel, physicians are not likely to prescribe them, since dosages and their frequency have not been determined and there can be serious side effects. It is likely that Alzheimer's may have multiple causes and many miraculous responses could be placebo effects, especially when disturbances in immune system function are involved. As with depression, appropriate treatment and especially prevention depends on identifying the cause of the problem.

Is There A Stress, Homocysteine, Depression And Alzheimer's Connection?

Researchers have increasingly focused on depression as an etiologic factor in Alzheimer's, and particularly the possible role of homocysteine and stress. A recent study of almost 12,000 people undergoing a routine physical examination found that high homocysteine was associated with a 26% increased risk of experiencing symptoms of depression. The homocysteine hypothesis of depression is based on the observation that high homocysteine levels cause cerebral vascular disease and neurotransmitter deficiency, which result in clinical depression. If this were true, then administration of B vitamins (folate, B12 and B6) should help to prevent AD and some studies support this. Higher concentrations of homocysteine have also been reported in AD patients. The long running Framingham study found that a **homocysteine level over 14µmol/L doubled the risk of developing Alzheimer's disease and levels over 10 increased risk of dementia and memory loss 75 percent.** High B12 levels were associated with improved cognitive function and other studies similarly show that B vitamins help prevent the cognitive decline seen with aging. Brain shrinkage or atrophy is a natural part of aging but is accelerated in people with Mild Cognitive Impairment (MCI), half of whom go on to develop Alzheimer's. British researchers used an advanced MRI technique to study brain shrinkage in 168 volunteers over the age of 70 with diagnosed MCI. Half were given a daily tablet containing high doses of folic acid, B6 and B12 and half were given a placebo. After two years, **the B vitamin group averaged a 30% reduction in the rate of brain atrophy and in some patients this was as high as 53 percent.**

We have devoted several Newsletters to a detailed discussion of the role of stress in depression as well as Alzheimer's. Increased cortisol is a frequent finding in depression as well as early Alzheimer's, and in animal studies,

similar hormones can produce the characteristic amyloid plaque and neurofibrillary tangles. Researchers at the Salk Institute have shown that certain types of low grade chronic stress can also do this in the absence of increased cortisol, so other mechanisms may be involved. They have traced the problem to corticotropin-releasing factor receptors, CRFR1 and CRFR2, which are part of a central switchboard that mediates the body's responses to stress. In the absence of CRFR1, stress-induced tangle pathology was abolished, while in mice missing CRFR2, the effect was amplified. Drugs that bind CRF receptors are already in stage 2 clinical trials for depression, and some might also delay the onset or progression of Alzheimer's disease.

Stress can contribute to Alzheimer's in other ways. Acute mental stress (solving mathematical problems under time pressure) can increase homocysteine, and chronic anxiety and hostility are also associated with higher homocysteine levels. And we still don't know why electrical stimulation relieves depression, whether similar approaches might also be effective in Alzheimer's, or if stress can influence such responses. There are many more questions than answers - so stay tuned for more on this enigma!

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