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Abstract:
The arsenal of effective, standardized treatment options for major depressive disorder (MDD) is shockingly low considering one in three individuals in the United States will experience clinical depression during their lifetime (American Psychiatric Association, 2013). MDD is usually limited to drug therapy and cognitive therapy, and alternative treatment methods are often disregarded as ineffective or unethical. This review explores the possibility of electroconvulsive therapy (ECT) as an alternative standard treatment for MDD. ECT has been used for decades for the treatment of mood disorders, but only recently has the medical community begun to understand how ECT affects the brain. With advancements in methodology, ECT has become a safe, efficient, and more permanent treatment option compared to drug therapy. This research discusses proposed causes of depression in the pathways of the brain, as well as specific areas of the brain affected by drug therapy and ECT. With recent research demonstrating the possibility of neurogenesis in the hippocampus being related to depressive symptoms, new perspectives on old treatment options must be explored. This review will propose the possibility of ECT as a standard treatment for MDD.

USE OF ECT

Despite its controversial history, electroconvulsive therapy (ECT) is gaining respect as a treatment for intractable cases of major depressive disorder (MDD). Popular in the 1970s, ECT was used to treat a variety of disorders until its adverse effects restricted further use (Friedberg, 1977). Currently ECT is rarely used as a long-term treatment, but it is used in cases with high risk of suicide. However, recent studies suggest that neurogenesis occurs in the brain following electroconvulsive therapy. This growth of new neural tissue, specifically in the hippocampus, has been linked to long-term alleviation of depressive symptoms (Rotheneichner et al., 2014). Therefore, ECT should again be reviewed as a more standard treatment option for MDD.

Critical assessment of common current treatments for MDD reveals significant weaknesses. The most popular treatment is based on the theory that depression is linked to increased uptake of serotonin (Mann, 1999; Meyer et al. 2006). To reduce reuptake and allow serotonin to bind more on the postsynaptic receptors, selective serotonin reuptake inhibitors (SSRIs), such as sertraline (also known as Zoloft) or fluoxetine (also known as Prozac), are prescribed. These medications have many adverse side effects including heightened suicidal

tendencies in low dosage (Ludwig & Marcotte, 2005). In stark contrast, modern ECT has little visible damage, both biologically and psychologically (Anderson, Wollman, & Dinwiddle, 2013). Over the course of thirty years and many studies, ECT has become sophisticated, controlled, targeted, and better understood (Hanson, Owens, & Nemeroff, 2011). Unlike SSRIs which treat systemically, ECT is a localized treatment that produces minimal systemic side effects (Eschweiler et al., 2007; Gomez, 1975). Both SSRIs and ECT appear to promote positive change in brain chemistry and structure, each modality having its own advantages and weaknesses (Madsen et al., 2000; Rotheneichner et al., 2014). Both modalities are based on the monoamine theory of depression, which dictates that serotonin is key to regulating mood.

Serotonin is thought to be regulated by the dentate gyrus, specifically the CA3 region of the hippocampus (Banasr, Hery, Printemps, & Daszuta, 2004). Recent research suggests that certain types of stimulation of the brain trigger the generation of neural precursor cells (NPCs) which are correlated to neurogenesis within the dentate gyrus and the CA3 region (Banasr et al., 2004; Hanson et al., 2011; Hellsten et

al., 2002). Some stimuli include exercise, hypoxia in controlled doses, ECT, as well as conventional drug therapy, such as SSRIs (Kempermann, Kuhn, & Gage, 1997; Zhu et al. 2010; Malberg, Eisch, Nestler, & Duman, 2000). Due to the pronounced effect ECT has on the brain in regard to NPCs, many neuroscientists are now suggesting ECT as a more regular form of therapy for MDD (Hellsten et al., 2002; Bauer, 2003; Inta & Gass, 2015). Research has shown that ECT and conventional drug therapy promote NPC generation in the area of the brain that regulates serotonin, which suggests stimulating this area of the brain can treat depression.

Diagnosing and Treating Depression

Over 14 million American adults (6.7% of the U.S. population) struggle with MDD (Heo, Murphy, Fontaine, Bruce, & Alexopoulos, 2008). The prevalence of MDD suggests that almost everyone has either experienced depression or known someone who has. Physicians use a standardized assessment to diagnose and then prescribe treatment, generally either medication, therapy, or both. There are many different medications, each with different properties and adverse side effects which range from fatigue or insomnia to increased risk

of suicide or erectile dysfunction (Ferguson, 2001). Serotonin regulation occurs systemically, so side effects from SSRIs also manifest systemically (Camilleri, 2009). Many people experience adverse reactions to antidepressants because the standard starting dose may be excessively strong (Cohen, 2003). On the other hand, too low of a dose has been shown to lead to increased risk of suicide (Grunebaum et al., 2004; Ludwig & Marcotte, 2005). Because of this life-threatening risk, physicians generally take a cautious approach and prescribe a higher dose than necessarily needed (Cohen, 2003). Although depression is a prevalent problem in the US population, current treatment practices have many negative side effects and are not easy to prescribe in the proper dosage.

The Diagnosis of Major Depressive Disorder

No physical tests exist for the diagnosis of depression (National Health Service, 2014). Instead, a general practitioner uses one of the common rating scales to determine whether or not treatment should be administered. One such scale is the Hamilton Rating Scale for Depression (HAM-D), which outlines the major symptoms of depression (Khan, Khan, Shankles, & Polissar, 2002; Leucht et al. 2005). These symptoms

include sadness, feelings of guilt, suicidal tendencies, insomnia, difficulty at work, and paranoia (Khan et al., 2002). The strength of the medication and treatment is determined by the evaluation and suggestion of the physician or psychologist.

Serotonin within the Hippocampus and its Biological Uses

Treatment for MDD focuses on the physical manipulation of serotonin. However, levels of serotonin rarely vary from an individual with depression from an individual without depression (Marken & Munro, 2000). The monoamine theory relates to synapses with transporters in the synaptic cleft and the effectiveness of serotonin within the brain, not with the actual amount of serotonin (Hirst, Price, Rattray, & Wilkin, 1998). Serotonin is involved in a number of functions, including digestion, mood, appetite, sleep, sexual desire and function, and memory (Buhot, Martin, & Segu, 2000; Labbate, Grimes, Hiaes, Oleshansky, & Arana, 1998; Portas, Bjorvatn, & Ursin, 2000; Zhu et al. 2010). This complex system is monitored within the hippocampus and functionally responds to the precursor to serotonin, 5-HT (Laplante, Diorio, & Meaney, 2002). The precursor 5-HT is derived from tryptophan, an amino acid that is obtained solely through diet (Smith, Fairburn, & Cowen, 1997). This only adds to the complexity

regarding diagnosing and understanding mood disorders, where everything—from diet and exercise to brain chemistry—could have a major effect.

The hippocampus regulates serotonin, which is central to the limbic system and associated with memory processing (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011). This critical area of the brain also acts as a hub for communications across cortexes in the brain (Battaglia et al., 2011). Studies suggest that serotonin can affect the shape of the hippocampus, and that the shape of the hippocampus can affect its functioning (Voineskos et al., 2015; Smolders, Loo, Sarre, Ebinger, & Michotte, 2001). This could mean that the hippocampus's development, size, or shape may play a key role in understanding depression. This plasticity allows for subtle changes in brain chemistry and functioning. These modifications are often associated with the creation of new neuronal connections and neurons, known as neurogenesis.

In recent years, research has shown that neurogenesis is possible in adults (Gabriel et al., 1999; Hellsten et al., 2002; Malberg et al., 2000). Although studies are still ongoing on how neurogenesis occurs and how it can be stimulated, there have been a number of studies proposing that stress can decrease

neurogenesis in the hippocampus (Schloesser, Manji, & Martinowich, 2009). Because the hippocampus is fundamental to the regulation of serotonin, some scientists speculate that the effect of stress on the hippocampus is linked to depressive behavior (Campbell & MacQueen, 2004). This theory opens the door to new ideas regarding treating depression through stimulating neurogenesis (Hellsten et al., 2002; Malberg et al., 2000). In particular, ECT is a promising option.

Neurogenesis within the Hippocampus

The hippocampus is a dynamic part of the brain (Abe, 2001). Stress, anxiety, depression, and other factors can cause atrophy in the hippocampus and lead to problems within the limbic system (McEwen, 1995). To combat this, the body regulates neural precursor cell growth and decay within the hippocampus through environmental cues given by neuronal pathways that pass through the hippocampus (Abe, 2001; McEwen, 1995). Some specific activities have been identified that encourage growth in the hippocampus, including aerobic exercise. One study done by Kempermann, Kuhn, and Gage, (1997) demonstrated that the dentate gyrus of adult rats increased in size when exposed to an environment with

colors, toys, and other activities to keep the rats engaged. This example demonstrates that it is not necessary to induce neurogenesis through artificial means. However, when negative cues persist, such as chronic stress or depression, damage to the hippocampus can effectively wipe out the body's ability to self-regulate (Campbell & MacQueen, 2004). In these cases, antidepressants, ECT, and other treatment options for depression become necessary because it may be difficult to overcome depression without assistance.

Stress doesn't only affect the hippocampus. The effects of stress extend beyond the hippocampus, dampening the relationship between the hippocampus and the main stress hormone system, the hypothalamo-pituitary-adrenal (HPA) axis (Schloesser et al., 2009). Severe chronic stress impairs HPA axis activity, which mutes the ability of the hippocampus to modulate downstream brain areas involved in stress response. In essence, the brain protects itself by destroying pathways that are overworked, and one of the damaging side effects is MDD (Schloesser et al., 2009). Of course, this type of manipulation of the HPA has damaging side effects, most notably MDD, but is primarily in place to protect the longevity of the brain. Although all the mechanisms and processes involved are as yet

unclear, the importance of neurogenesis in the hippocampus to regulate stress and serotonin has become widely recognized.

ECT as a Treatment for MDD

Developed in 1938, ECT was found effective for treating a number of mood disorders, including depression (Endler, 1988). In its early development, however, ECT was done without precise measurements of voltage or any form of anesthetic by inducing seizures in patients (Endler, 1988). Over the course of the next decades as various forms of treatment began to appear, most notably drug therapy which had less severe side effects, ECT fell out of favor. Today ECT has advanced in sophistication, with more precise voltage calculation and use of anesthesia to literally eliminate the pain involved (Loo, Schweitzer, & Pratt, 2006). Although it has been recognized as one of the most effective treatments (Kellner et al., 2015), its general scope of use is focused on the most severe cases. Recent studies have begun to demonstrate why ECT is a valuable form of treatment. The use of ECT has been expanding over the past decade and continues to grow as research continues.

Although understanding of the mechanism of ECT

has increased, there are still many concerns regarding its safety; these stigmas continue, even among professional psychiatrists (Carney & Geddes, 2003). Though death from ECT was a considerable risk thirty years ago. Refuting this fear, one study suggests that ECT in the mid-1990s was ten times safer than childbirth and that approximately six times as many deaths annually in the U.S. are caused by lightning than by ECT (Abrams, 1997). The most common side effects are temporary confusion and memory loss. Uppal, Dourish, and Macfarlane (2010) suggest that the most dangerous aspect of ECT treatment is being under anesthetic, and not the actual treatment. They argue that most concerns regarding ECT are mostly stigmatic superstition from decades ago.

Current ECT Use

ECT is generally viewed as a last resort for treatment-resistant depression by the psychiatric community (Al-Harbi, 2012). Although there are cases when ECT is regularly administered, its use is far from standard practice. Individuals that receive ECT usually have experienced adverse effects from medication or have been unresponsive to therapy (Al-Harbi, 2012). These individuals range from those who simply need a more rapid

response than medications can provide, such as those suffering from delusions or suicidal tendencies, to those who suffer from catatonia (Al-Harbi, 2012). Those who receive ECT are highly likely to continue to receive treatment in the form of drug therapy (Bauer, 2003). The application of ECT is not limited to MDD, and is used to treat other mental disorders in similar circumstances. Regardless, the universal goal is to stabilize the patient so medications can be started or resumed.

Electroconvulsive therapy is performed with the goal of "as little as possible," both in terms of voltage and number of treatments (Al-Harbi, 2012; Bauer, 2003). Typically, a single procedure will only last five to 10 minutes, not including preparation time and recovery. General anesthesia is administered so that pain is minimized. Patients are given a muscle relaxant to minimize seizure as well. The electrode pads are placed on the head either unilaterally or bilaterally, with location determined to best target the area of interest ("Electroconvulsive Therapy," 2015). Electroencephalogram (EEG) is used to record electrical activity in the brain to make sure the procedure is done correctly and strongly enough to induce the desired seizure. Recovery usually lasts for about one hour before the patient is released. During this time,

confusion and memory loss are a common side effect, either from anesthesia or from the treatment itself ("Electroconvulsive Therapy," 2015). In the United States, ECT treatments are administered in sets of two to three times a week for a month, for a total of six to twelve treatments, depending on severity of the case and the physiological reaction to the treatments.

Due to careful localization of the treatment, most common side effects are temporary and isolated to the parts of the body affected by the procedure. Confusion, memory loss, and headache are common, but they generally subside within 24 hours. Long-term memory loss can take up to a few months to fully recover, but it is rare for memory loss to persist beyond that time (MacQueen, Parkin, Marriot, Begin, & Hasey, 2007). As with any medical procedure, especially those that use anesthesia, there are rare risks of complications, including cardiac arrest or other heart condition, stroke, and even death ("Electroconvulsive Therapy," 2015). Considering the large success rate among patients suffering from depression and the minimal risks of ECT warrant ECT to be considered a potential alternative to conventional drug therapy.

422 ECT treatments: A neuropathological evaluation. Much of the stigma surrounding ECT is unfounded, as

illustrated by the following neuropathological evaluation. In 2013, an autopsy of an 84-year-old man revealed little-to-no brain damage despite his having received 422 ECT treatments over 8.6 years (Anderson, Wollman, & Dinwiddle, 2013). This man had been treated for a severe depressive episode that culminated in a suicide attempt. After many hospitalizations, ECT was prescribed, which continued until the time of his death. The postmortem report was completed immediately after his death, one month after his final ECT treatment. The report showed that there was no link between cause of death and his ECT treatments (Anderson et al., 2013). Although this is an isolated case, the authors linked a large number of similar reports from the past twenty years.

ECT has not been shown to cause brain damage according to this case study and other reports. Stigma regarding ECT and brain damage stems from postmortem reports dating to the 1940s, claiming that ECT causes harmful physical changes to the brain. This stigma remains in part because over the past four decades, few postmortem studies have been done due to the low mortality rate after the immediate treatment period of ECT patients. In the past two decades, computed tomographic brain imaging has shown no changes in brain

structure after ECT (Anderson et al., 2013). Simply put, the notion that ECT causes brain damage is unfounded.

Discussion

MDD poses a problem for treatment because the precise mechanisms that cause MDD are unknown. However, correlations between treatments and behavioral changes spur innovation. Early ECT was done with minimal understanding of why it worked, but half a century later, neuroscientists have a better idea of how the brain is affected by ECT (Endler, 1988). Early monoamine oxidase inhibitors (MAOIs) were discovered serendipitously while trying to treat tuberculosis. Subsequent in vitro work led to a theory of the drug's mechanism of action (Ramachandraih, Subramanyam, Bar, Baker, & Yeragani, 2011). Over the next twenty years, MAOIs were replaced with SSRIs which have fewer side effects and are more potent. Along with these advances, ECT became safer and more controlled. Advanced methods of evaluation, brain scanning technology, and the ability to perform advanced experiments allow for a much deeper understanding of treatment options before ever being released to the general population. As understanding of the brain increases, methods become more refined.

USE OF ECT

Technological improvement has influenced the way antidepressants are manufactured and the way ECT is performed. Studies on rats have demonstrated the effectiveness of ECT in treating induced depression on a biological level (Bauer, 2003; Inta & Gass, 2015; Kempermann, Kuhn, and Gage, 1997). Currently ECT is used as the last resort of treatment, despite evidence it is safe, effective and has few side effects. Antidepressants are more prevalent and have more common side effects that generally are present for as long as the patient is taking the prescription (Cascade, Kalali, & Kennedy, 2009). Antidepressants are an effective treatment, but as with any treatment, have their shortcomings and should not be the only offered solution. This is the precise reason ECT should be taken into consideration as a viable treatment option.

ECT as a Standard Treatment

The general consensus is that it is safer to take a pill than undergo ECT, which may be incorrect in the long-term. A meta-analysis study demonstrated that in severe cases, ECT is the most effective treatment option (Kellner et al., 2015). There is less evidence that ECT would be effective in less-severe cases other than studies on rats with induced depressive states (Madsen et al., 2000; Theilmann et al., 2014). The lack of studies

may be attributed to the limited amount of ECT use in less-severe cases. In rats, ECT has shown to be effective regardless of perceived severity of the depression (Madsen et al., 2000; Theilmann et al., 2014). Although the triggering mechanisms of antidepressants and ECT are primarily different, the effect is primarily the same: encouraging neurogenesis in the dentate gyrus and CA3 region of the hippocampus (Malberg et al., 2000; Warner-Schmidt et al., 2008).

More detailed studies are required to confirm that ECT could be standardized as a treatment for MDD. ECT has been reexamined in a number of studies to advance understanding of the hippocampus and brain function in rats. If ECT were considered ethical and effective, another sophisticated tool would be given to the psychiatric community to better treat and understand depression and other mood disorders. Of course, more research is necessary to realize this possibility. In light of the current research of the effects of ECT on the brain, further research on ECT should be conducted to confirm its viability to become a more standard treatment option as an alternative to drug therapy.

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USE OF ECT
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Appendix A

Tables and Figures

Table 1

Descriptive statistics for critical values

	Mean	Std. Deviation	N
Eating disorders	75.5556	15.59547	63
Stress	23.3333	6.56481	63
Sleep quality	12.0794	7.03746	63

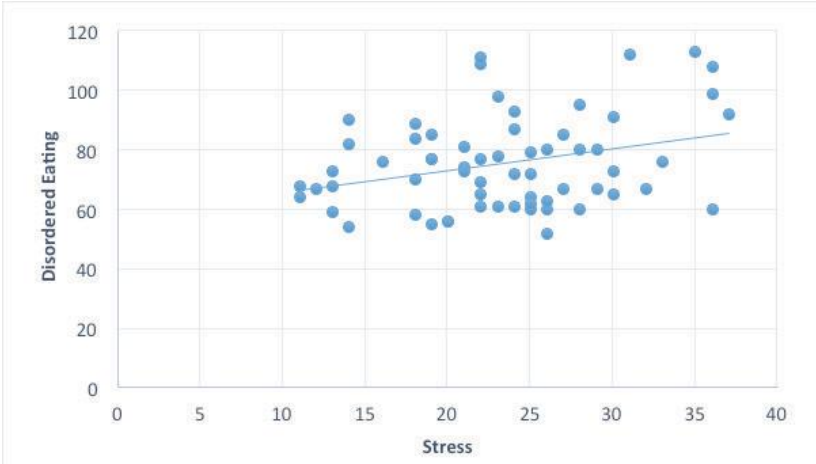

Figure 1. Regression line between stress (x axis) and disordered eating (y axis)

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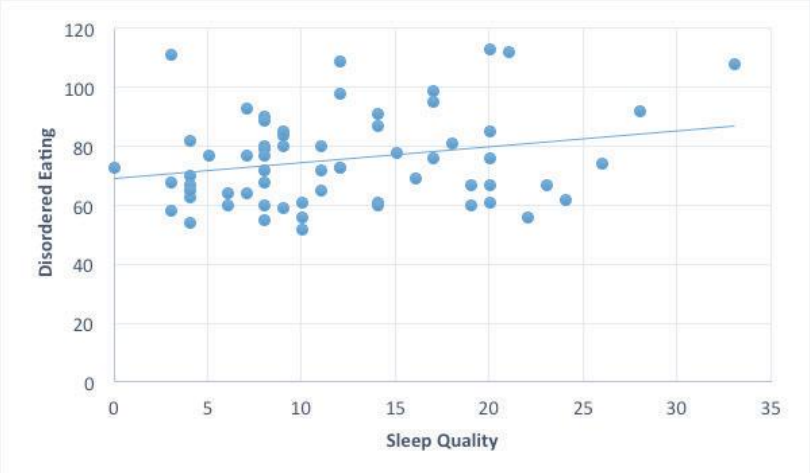

Figure 2. Regression line between sleep quality (x axis) and dis- ordered eating (y axis)