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FINAL REPORT

Improving Treatment for Major Depression by Identifying Predictors of Response and Relapse in Electroconvulsive therapy (ECT): A Paradigm for All Neuromodulation Procedures

Daniel Maixner, M.D., Principal Investigator; Roseanne Armitage, Ph.D.; Mona Goldman, Ph.D.; Scott Langenecker, Ph.D.

Major Depressive disorder (MDD) is a common, recurrent disorder affecting nearly 14 million adults in the United States each year. It is associated with marked impairment in social relationships and functioning, and with a diminished quality of life[1]. Yet one-third of patients remain symptomatic even after four courses of treatment with antidepressants and/or psychotherapy[2]. Neuromodulation, the use of electrical or magnetic current to modulate brain activity, is an alternative approach to treating depression and several new therapies based on this approach (e.g., deep brain stimulation, transcranial magnetic, vagus nerve stimulation) are currently under study at the UM Depression Center. However, the oldest neuromodulation treatment, electroconvulsive therapy (ECT), is still one of the most effective and rapidly acting therapies for severe depression, and is the treatment of choice for individuals who fail to respond to conventional treatment with medications and psychotherapy. Although ECT, as currently administered, is safe and acceptable, its use is limited by stigma, concern about memory side effects, and cost (about $15,000-$20,000 for a course of ECT). The identification of predictors of response and remission could enhance the appropriate use of ECT. These predictors can guide clinical decisions on how, when, and for whom to use ECT.

The purpose of this study was to identify physiological predictors of effectiveness and side effects of ECT in order to improve clinical practice and direct treatment to those who would benefit most from the treatment. A secondary aim was to develop a model for conducting community-based studies to identify predictors of response to the promising new neuromodulation-based treatments. Many studies, including our own, have shown that depression is associated with abnormalities in stress hormones (such as cortisol), sleep architecture[3], and cognitive functioning. These, therefore, are among the most promising predictors of response, and were the focus of this study.

Subjects

Study participants were recruited from the population of patients starting a course of ECT therapy at the University of Michigan between August 1, 2007 and August 8, 2009. Potential participants were identified during the weekly review of all ECT cases conducted by Dr. Maixner and the ECT team. Of the approximately 160 patients who began ECT during this period, 16 (10%) met the inclusion/exclusion criteria established for the study and consented to participate in the study – a rate that was lower than we anticipated. The most common reasons for exclusion from the study were having a

concurrent psychiatric diagnosis (29%) or medical condition (14%), being younger than 18 years of age (13%). Only 4% of potential participants declined to participate.

Of the 16 patients enrolled in the study, 25% were male, 75% were female; the average age was 57 years (range: 31-77 years). Thirteen participants completed the course of treatment; the average number of treatments was 9 (range 7-12). (One subject was withdrawn because she could not follow the protocol; a second subject could not produce an adequate seizure during ECT, and a third could not be scheduled for sleep studies.)

Results

Effect of ECT on Symptoms

Symptoms of depression, measured with the Hamilton Rating Scale for Depression (HAMD), significantly improved by an average of 44% after three ECT treatments and by 47% at the end of a course of treatments (Appendix, Figure 1). Of the thirteen subjects who completed the course of treatment, 10 (77%) achieved remission as judged by the clinical team.

Effect of ECT on Sleep

Using a procedure called polysomnography, which simultaneously measures brain activity, muscle tone, and eye movement, sleep can be divided into two distinct states: rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM sleep consists of 4 stages, starting with the lightest sleep (stage 1) through the deepest and most restorative sleep (stages 3 and 4, also known as slow-wave or delta sleep). Dreaming occurs during REM sleep, although, paradoxically, voluntary muscles are paralyzed at this time. Normally there are 4 to 5 90-minute cycles of NREM /REM sleep throughout the night. Disruption in the pattern of sleep is a key component of depression, reported in 90% of patients[4]. To examine the effect of ECT on sleep patterns, overnight sleep studies were performed just before treatment began (at baseline) and after the third ECT treatment. Seven subjects completed the studies at both timepoints. ECT led to significant improvement in several sleep measures. The amount of deep restorative sleep (also called slow-wave sleep) increased –especially in the early cycles of sleep (Appendix, Figure 2). This measure is thought to be the most important for biological recovery and reflects the basic drive for sleep. In addition, total sleep increased, time to fall asleep (sleep latency) was shorter, and the amount of time spent in light non-restorative (stage one) sleep was decreased. Finally, rapid eye movement (REM) latency (the time from sleep onset to the first REM period), which was high at baseline in most subjects, normalized (Appendix, Figure 3). Together these changes suggest that ECT treatment is associated with an overall normalization of sleep. We also examined whether any of these changes in sleep were associated with improvements in symptoms. The most promising relationship appears to be with REM latency; normalization of REM latency was significantly related to improvement in symptoms after three ECT treatments and at the end of treatment (Appendix, Figure 4). These results offer insight into a putative mechanism of action of

ECT, and if correlations with outcome are confirmed, could be early predictors of response to ECT.

We will present these findings in a poster titled "Early Effects of Electroconvulsive Therapy (ECT) on Polysomnography Measures in Major Depression," at the annual meeting of the Society of Biological Psychiatry, May 20-22, 2010 in New Orleans.

Effect of ECT on Neuropsychological Measures

Neuropsychological testing was performed at baseline and at about one week after the last ECT treatment. Several neuropsychological measures changed over this time, although none of these changes attained statistical significance. Not surprising was the suggestion that short-term memory and a related function – the ability to plan - declined during ECT. This is a common, and often transient, side effect of ECT. However, the data also appear to suggest that there were improvements in attention, psychomotor activity, and the consolidation of learning. These interesting findings need to be confirmed with a larger sample.

Effect of ECT on Salivary cortisol

Cortisol is a hormone secreted into the blood in response to stress. Normally, the levels of cortisol cycle during the day, with highest levels occurring about 8:00 a.m. and the lowest during the night. This cycle is often disrupted in depression such that the levels of cortisol might be consistent all the time or highest in the middle of the night. To examine the effect of ECT on cortisol cycling, we measured cortisol at baseline and after the third ECT treatment. Three samples were taken at each timepoint: in the evening and just before and just after breakfast the next day. Overall, we found a normal pattern of cortisol at both timepoints (low in the evening and high in the morning). However, the variation in pattern between individuals was very high. This, combined with the small sample size, precluded any conclusions about the effect of ECT on cortisol levels.

Summary

ECT was an effective treatment for depression in most of the patients in this study. In addition ECT had a significant effect on sleep, with several dimensions of sleep architecture showing improvement after only three treatments. Furthermore, normalization of REM latency after ECT was significantly associated with a decrease in the depressive symptoms. These results, along with the suggested effects of ECT on neuropsychological function need to be confirmed in a larger sample. With this in mind, a next step is to leverage our results by combining our data with those from previous studies on sleep and neuropsychological function in depression conducted by Dr. Armitage and Dr. Langenecker.

Lessons learned about naturalistic studies

In a naturalistic study investigators do not interfere with normal clinical schedules or activities. The advantage of this design is that it produces data that are directly applicable to how a treatment works in the "real world." However, this often presents problems to researchers in terms of patient scheduling, tracking, and follow-up, and the diversity of

patients. Indeed, these were all problems we faced in the current study. For example, our research protocol called for sleep studies to be done on the inpatient unit. But in several instances patients were well enough to be discharged before the second sleep study could be completed, necessitating an overnight study in the sleep lab – a procedure that was more costly and more disruptive for patients. Problems in scheduling all of the baseline assessments before a patient began treatment led to the loss of several potential subjects. In addition, severity of illness prevented several subjects from completing sleep or neuropsychiatry testing. One of the greatest obstacles in this naturalistic study, was getting subjects to complete follow-up surveys after leaving the UM system – very few did. Lastly, the variation between subjects in terms of symptoms and concomitant illnesses in this community-based sample made it more difficult to detect the effects of ECT. We will use the experience gained in conducting this study to improve future protocols.

In summary, despite the problems noted, this study produced some noteworthy findings. The results suggest that ECT may have important clinical effects on sleep and neuropsychological functioning in people with depression. In addition, some of the early effects of ECT, such as the normalization of REM latency, may be useful predictors of response to treatment. We will be able to combine these results with those from other data we have collected on persons with depression to confirm these findings and examine further the role these variables play in depression.

REFERENCES

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4. Szuba MP, O'Reardon JP, Evans DL. Physiological effects of electroconvulsive therapy and transcranial magnetic stimulation in major depression. Depression and Anxiety 2000;12:170-177.

APPENDIX

Fig. 1

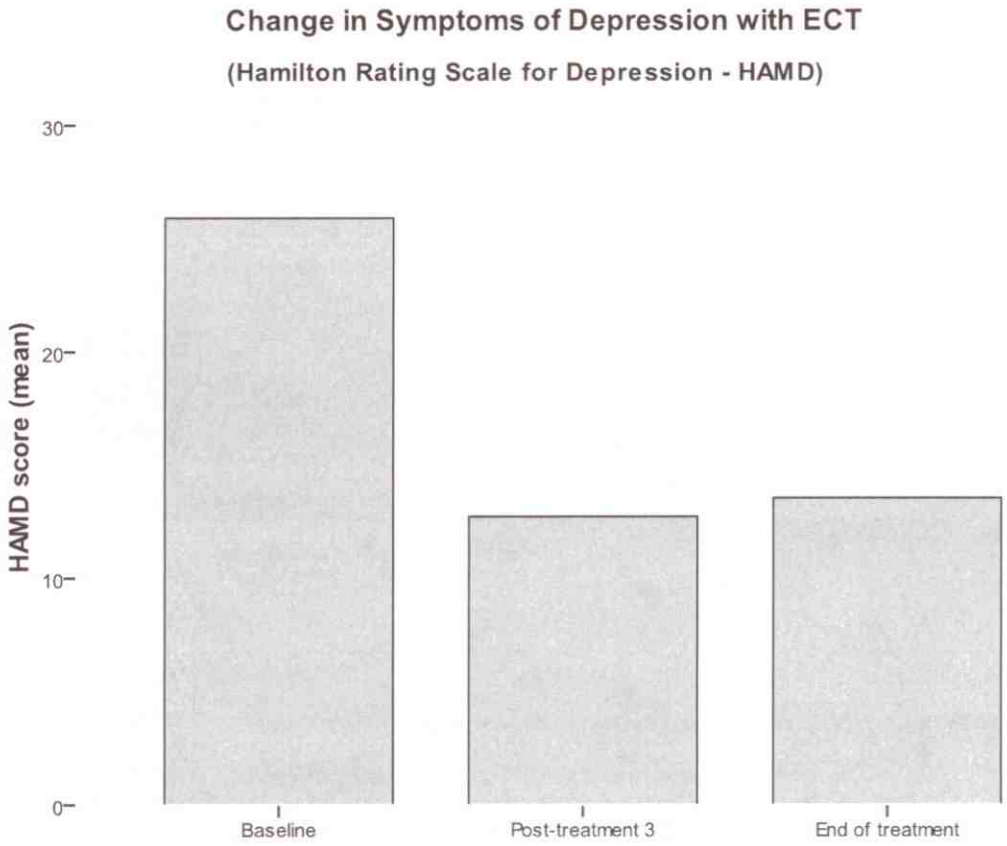


Fig. 2 **Effects of ECT on SWA (Delta) in 1st NREM Period**

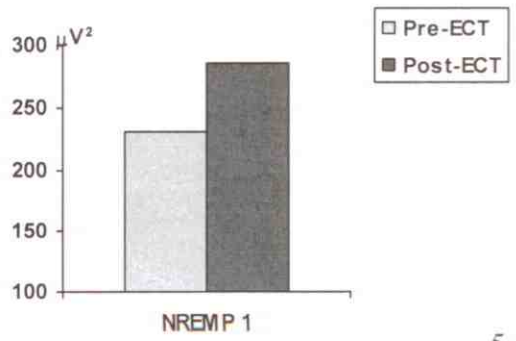


Figure 3 Effects of ECT on REM latency in 1st NREM Period

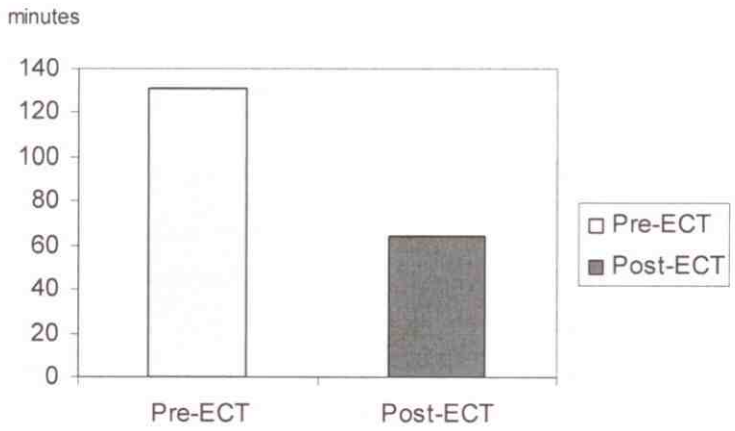
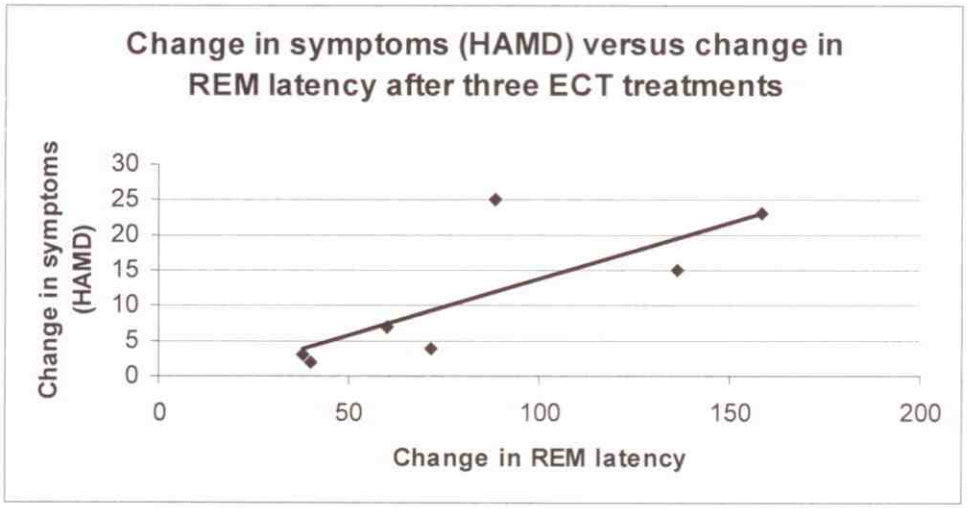


Figure 4



Notes:
1. $R^2 = 0.60$; $p = .04$
2. All change scores: subtract score at baseline from score after third ECT
3. Change in REM latency is absolute change score: higher score = greater normalization
4. Change in HAMD: higher score = greater improvement