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Searching for the Mechanism(s) of ECT's Therapeutic Effect

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The last 10 years have seen significant developments in the science of electroconvulsive therapy (ECT), including clarification of the differential effects of right unilateral (RUL), bitemporal (BL) and bifrontal (BF) stimulating electrode placement (1, 2) and stimulus parameters (3), the role of ECT in improving quality of life in depressed patients (4), the role of concomitant medications in improving ECT outcomes (5, 6), the importance of ECT in the treatment of schizophrenia (especially in countries in the Eastern hemisphere) (7), and the role of ECT in maintaining the benefits achieved during an acute course (8).

The understanding of the mechanism of ECT has also advanced during this time, but evidenced-based mainstream summaries of its mechanism have been lacking, while evidence-poor papers with an anti-ECT agenda have suggested that the mechanism of ECT is through brain damage (9, 10) or via placebo effects (11). These theories are wrong, and join a long list of discredited theories of ECT's mechanism. The notion that ECT produces brain damage was disproven in both in vivo studies of anatomical brain imaging and in post mortem studies of patients after lengthy courses of successful ECT (12, 13). There was no aberrant gliosis nor hypoxic changes in the hippocampus, cerebellum, or other brain structures. A 89-year-old woman received more than 1250 documented ECTs and a further, unsubstantiated 800 ECTs across 26 years for bipolar disorder. Gross and microscopic brain changes at post-mortem were actually less than those that could have been expected on the basis of her age (14).

The idea that placebo effects play a role in ECT is neither original nor relevant as it is widely accepted that non-specific treatment effects are active in most antidepressant treatments (15, 16). However, there is no evidence that the non-specific effects play anything other than a minor role in ECT, as (1) non-specific effect are increasing irrelevant in serious illness (17), and (2) sham-controlled clinical trials of ECT in depression and schizophrenia favor ECT (18). Therefore, the role of non-specific effects, even if present, does not explain the efficacy of ECT. So, mechanistic theories promoting the brain damage

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and placebo effects fall along with antiquated theories that it is amnesia that is responsible for ECT's therapeutic effects.

Psychoanalytic theory of depression posited that depression was a result of inward-turned anger, and that ECT satisfied a need for punishment (19). The introduction of anesthesia in ECT did not remove the efficacy of ECT, despite removing awareness of the procedure along with any idea that the procedure satisfied any unconscious need. Another analytic theory proposed that conflict-laden sexual drives led to depressive neurosis, and this tension was resolved with unmodified convulsive therapy (19). This theory, too, fell away with the implementation of muscle relaxants which eliminated the convulsive movements, but which did not diminish the effectiveness of ECT.

An old and yet persistent misunderstanding among lay persons is that the transient amnesia associated with ECT was efficacious because ECT caused patients to “forget their troubles.” This misconception was no doubt borne out of the more intense amnesia that was associated with older, now-abandoned forms of ECT, such as bilateral sine wave ECT. However, the emergence of brief pulse ECT, then RUL ECT, then ultra-brief pulse ECT has led to a form of efficacious treatment with nearly invisible cognitive side effects in most patients, and with the finding that the efficacy of ECT is unrelated to the degree of cognitive side effects (20, 21).

So, which mechanistic theories have merit? There are many, including antidepressant effects, anti-psychotic effects (22), anti-convulsive effects (23), anti-catatonic effects (24), neurotransmitter effects (25), neuroendocrine effects (26) and powerfull effects on neurogenesis (27). There is no shortage of potential mechanism, largely because ECT has so many measurable effects on the brain. Detractors of ECT would like to say that the mechanism of ECT is not known, implying that students of ECT do not know what ECT does. This is not correct. The truth is that ECT has so many actions that it is difficult to identify which one action is the therapeutic action. The search for one and only one therapeutic mechanism may prove to be misdirected, as it is certainly possible that the mechanisms for antidepressant effects may be distinct from antipsychotic effects, which maybe distinct from its anti-Parkinson's Disease effects (28). Additionally, it is possible that ECT's efficacy may require the simultaneous coordination of two or more different mechanisms of action to produce its therapeutic effects. The search for the most critical therapeutic effects might be advanced by animal models of electroconvulsive shock (ECS) which isolate the effects of ECT one element at a time. This could be accomplished through knock-out mice or chemical interruption of a single process, while allowing other processes of ECT to still unfold.

It is tempting to look for ECT mechanisms that overlap with medication mechanisms, looking for commonalities and differences, showing how ECT builds and expands upon the mechanism of medications. Clinically, ECT may work in the same types of patients as where psychotropics work, yet it is necessary to explain how ECT is superior to medications in most instances. So, ECT may have the same mechanism as psychotropic medications, but must then go beyond the effects of psychotropics. There are mechanisms that exemplify this premise. First, ECT, like selective serotonin reuptake inhibitors (SSRIs) and serotonin-

norepinephrine reuptake inhibitors (SNRIs) potentiates the action of serotonin and norepinephrine (25). However, ECT's effects on biogenic amines goes further than medications, as it also potentiates dopamine (28) – an effect that is largely absent in SSRIs and SNRIs. Second, antidepressants (with a few minor exceptions) suppress the rapid eye movement (REM) sleep abnormalities seen in severe depression (29). However this suppression is temporary with antidepressant medications, and followed by REM rebound upon discontinuation of the antidepressant medication. ECT also suppresses REM sleep (30, 31), but in contrast to medications, the withdrawal of ECT is not followed by REM rebound (32). In effect, the suppression of REM sleep abnormalities is a phenomenon shared between antidepressants and ECT, but the suppression is more complete with ECT (33).

In recent years, recovery from depression has been suggested to result from antidepressant-induced promotion of neuroplasticity in the hippocampus (34, 35). A sizeable body of research in animal models has demonstrated that ECT is a potent inducer of hippocampal neuroplasticity (27, 36), and recent research even shows that, like the efficacy of the treatment, ECT-induced dendritic arborization and new cell formation in the hippocampus is dose-dependent (37, 38); that is, the favorable neurohistological changes are greater when the electrical charge administered is higher.

Even more compelling is research in animal models which demonstrates that ECT reduces dendritic arborization and excitatory synapses in the amygdala (27, 39, 40). Given the importance of the amygdala in the mediation of negative affect, especially anxiety and fear, these findings provide direct neurobiological support for the beneficial effect of ECT on mood. By attenuating aberrant amygdalar responses in depression, ECT may promote recovery from depression.

It is likely that the multiplicity of action of ECT is what makes it so effective a treatment; thus, for example, the hippocampal and amygdalar mechanisms (and other actions, as well) may act additively or synergistically to promote recovery. Similarly, glucocorticoid, lipid signalling, glutamatergic, and other mechanisms may act synergistically to mediate the cognitive adverse effects of the treatment (41-44).

The search for a therapeutic mechanism of ECT is important and deserves support, for several reasons. First, identification of a particular therapeutic mechanism might lead to refinements of ECT technology, or perhaps the discovery of new drugs which capitalize upon what is learned about ECT mechanisms. Second, the understanding of therapeutic mechanisms would provide additional re-assurance to patients who are uncomfortable with the inability to specify one and only one mechanism of ECT. But as ECT practitioners, what do we do until such time as we can more clearly specify a mechanism of action? Can we proceed with confidently providing ECT in the absence of isolating a single, critical mechanism?

The present understanding of ECT's mechanism is similar to what is known regarding other forms of brain stimulation for neuropsychiatric illness. For example, the exact mechanism for vagus nerve stimulation's (VNS) anti-epilepsy effect is not well understood. The same is true of the degree of understanding of deep brain stimulation's (DBS) anti-Parkinson's

Disease effect. So why is ECT held to a different standard than VNS or DBS? We hypothesize it is because the critics of ECT, who demand a simple explanation of ECT's mechanism, fail to appreciate that severe mental illness is disabling, non-trivial, and sometimes deadly. Historically-dated explanations of mental illness as religious problems (45) (as opposed to medical problems) will predictably attack medical treatments of mental illness and will challenge scientific explanations of how psychiatric treatments work and where psychiatric illnesses come from. So, in some measure, the continued refinement of the understanding of ECT's mechanism of action is also a journey into the understanding of the sources of severe mental illness, and a drive to have science replace prejudice in the care of those with mental illness.

References

1. Dunne RA, McLoughlin DM. Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression. World J Biol Psychiatry. 2012; 13:248–258. [PubMed: 22098115]
2. Kellner CH, Knapp R, Husain MM, Rasmussen K, Sampson S, Cullum M, McClintock SM, Tobias KG, Martino C, Mueller M, Bailine SH, Fink M, Petrides G. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry. 2010; 196:226–234. [PubMed: 20194546]
3. Spaans HP, K HK, Verwijk E, Kok RM, Stek ML. Efficacy of ultrabrief pulse electroconvulsive therapy for depression: a systematic review. J Affect Disord. 2013; 150:720–726. [PubMed: 23790557]
4. McCall WV, Reboussin D, Prudic J, Haskett RF, Isenberg K, Olfson M, Rosenquist PB, Sackeim HA. Poor health-related quality of life prior to ECT in depressed patients normalizes with sustained remission after ECT. J Affect Disord. 2013; 147:107–111. [PubMed: 23158959]
5. Chanpattana W, Chakrabhand ML, Kongsakon R, Techakasem P, Buppanharun W. Short-term effect of combined ECT and neuroleptic therapy in treatment-resistant schizophrenia. J ECT. 1999; 15:129–139. [PubMed: 10378152]
6. Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, Isenberg K, Garcia K, Mulsant BH, Haskett RF. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry. 2009; 66:729–737. [PubMed: 19581564]
7. Pompili M, Lester D, Dominici G, Longo L, Marconi G, Forte A, Serafini G, Amore M, Girardi P. Indications for electroconvulsive treatment in schizophrenia: a systematic review. Schizophr Res. 2013; 146:1–9. [PubMed: 23499244]
8. van Schaik A, Comijs H, Sonnenberg C, Beekman A, Sienaert P, Stek ML. Efficacy and safety of continuation and maintenance ECT in depressed elderly: a systematic review. American Journal of Geriatric Psychiatry. 2012; 20:5–17. [PubMed: 22183009]
9. Read J, Bentall R. The effectiveness of electroconvulsive therapy: a literature review. Epidemiol Psichiatr Soc. 2010; 19:333–347. [PubMed: 21322506]
10. Fosse R, Read J. Electroconvulsive Treatment: Hypotheses about Mechanisms of Action. Frontiers in psychiatry. 2013; 4:94. [PubMed: 23986724]
11. Blease CR. Electroconvulsive therapy, the placebo effect and informed consent. Journal of medical ethics. 2013; 39:166–170. [PubMed: 23038801]
12. Devanand DP, Dwork AJ, Hutchinson ER, Bolwig TG, Sackeim HA. Does ECT alter brain structure? Am J Psychiatry. 1994; 151:957–970. [PubMed: 8010381]
13. Scalia J, Lisanby SH, Dwork AJ, Johnson JE, Bernhardt ER, Arango V, McCall WV. Neuropathologic examination after 91 ECT treatments in a 92-year-old woman with late-onset depression. J ECT. 2007; 23:96–98. [PubMed: 17548979]

14. Lippman S, Manshadi M, Wehry M, Byrd R, Past W, Keller W, Schuster J, Elam S, Meyer D, O'Daniel R. 1,250 electroconvulsive treatments without evidence of brain injury. Br J Psychiatry. 1985; 147:203–204. [PubMed: 4041696]
15. McCall WV. Electroconvulsive therapy and placebo effects: does full disclosure affect expectancy and satisfaction? J ECT. 2006; 22:161–162. [PubMed: 16957529]
16. Andrade C. There's more to placebo-related improvement than the placebo effect alone. J Clin Psychiatry. 2012; 73:1322–1325. [PubMed: 23140650]
17. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med. 2001; 344:1594–1602. [PubMed: 11372012]
18. Masoudzadeh A, Khalilian AR. Comparative study of clozapine, electroshock and the combination of ECT with clozapine in treatment-resistant schizophrenic patients. Pakistan journal of biological sciences: PJBS. 2007; 10:4287–4290. [PubMed: 19086588]
19. Fink, M. Convulsive Therapy. Raven Press Books, Ltd; 1979.
20. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med. 1993; 328:839–846. [PubMed: 8441428]
21. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects. J Affect Disord. 2010; 122:60–67. [PubMed: 19577808]
22. Rosenquist PB, Miller B, Pillai A. The antipsychotic effects of ECT: A review of possible mechanisms. 2014 THIS ISSUE.
23. Medda P. The mood-stabilizing effects of ECT. 2014 THIS ISSUE.
24. Dhossche D. The rapid relief of catatonia by ECT: what does it learn about ECT's immediate effects. 2014 THIS ISSUE.
25. Lanzenberger R. Neurotransmitters and ECT. 2014 THIS ISSUE.
26. Haskett R. Neuroendocrine hypotheses. 2014 THIS ISSUE.
27. Bouckaert F, Sienaert P, Obbels J, Dols A, Vandenbulcke M, Stek M, Bolwig T. ECT: Its Brain Enabling Effects. A review of electroconvulsive therapy-induced structural brain plasticity. 2014:30. THIS ISSUE.
28. Kellner CH. ECT in Parkinson's disease: ECS and dopamine enhancement. 2014 THIS ISSUE.
29. Kluge M, Schussler P, Steiger A. Duloxetine increases stage 3 sleep and suppresses rapid eye movement (REM) sleep in patients with major depression. Eur Neuropsychopharmacol. 2007; 17:527–531. [PubMed: 17337164]
30. Coffey CE, McCall WV, Hoelscher TJ, Carroll BJ, Hinkle PE, Saunders WB, Erwin CW, Marsh GR, Weiner RD. Effects of ECT on Polysomnographic Sleep: A Prospective Investigation. Convuls Ther. 1988; 4:269–279. [PubMed: 11940976]
31. Lahmeyer HW, Janicak P, Easton M, Smith M, Davis J. ECT's effect on sleep in major depression. Sleep Research. 1989; 18:346.
32. Steiger A, Kimura M. Wake and sleep EEG provide biomarkers in depression. J Psychiatr Res. 2010; 44:242–252. [PubMed: 19762038]
33. Linkowski P, Mendlewicz J, Kerkhofs M, Leclercq R, Golstein J, Brasseur M, Copinschi G, Van Cauter E. 24-hour profiles of adrenocorticotropin, cortisol, and growth hormone in major depressive illness: effect of antidepressant treatment. J Clin Endocrinol Metab. 1987; 65:141–152. [PubMed: 3034952]
34. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology. 2008; 33:88–109. [PubMed: 17851537]
35. Andrade C, Rao NS. How antidepressant drugs act: A primer on neuroplasticity as the eventual mediator of antidepressant efficacy. Indian J Psychiatry. 2010; 52:378–386. [PubMed: 21267376]
36. Chen F, Madsen TM, Wegener G, Nyengaard JR. Repeated electroconvulsive seizures increase the total number of synapses in adult male rat hippocampus. Eur Neuropsychopharmacol. 2009; 19:329–338. [PubMed: 19176277]

37. Smitha JSM, Roopa R, Khaleel N, Kutty BM, Andrade C. Images in ECT: ECS dose-dependently increases dendritic arborization in the CA1 region of the rat hippocampus. J ECT. 2014
38. Smitha JSM, Roopa R, Sagar BKC, Kutty BM, Andrade C. Images in ECT: ECS dose-dependently increases cell proliferation in the subgranular region of the rat hippocampus. J ECT. 2014
39. Khaleel N, Roopa R, Sagar BKC, Andrade C. Images in electroconvulsive therapy: Pilot impressions suggesting that ECT reduces excitatory synapses in the basolateral amygdala. Indian J Psychiatry. 2013; 55:204–205. [PubMed: 23825863]
40. Khaleel N, Roopa R, Smitha JSM, Andrade C. Images in electroconvulsive therapy: ECT attenuates dendritic arborisation in the basolateral amygdala. J ECT. 2013; 29:156–157. [PubMed: 23965605]
41. Nagaraja N, Andrade C, Sudha S, Madan Singh N, Chandra JS, Venkataraman BV. Glucocorticoid mechanisms may contribute to ECT-induced retrograde amnesia. Psychopharmacology (Berl). 2007; 190:73–80. [PubMed: 17072590]
42. Andrade C, Singh NM, Thyagarajan S, Nagaraja N, Sanjay Kumar Rao N, Suresh Chandra J. Possible glutamatergic and lipid signalling mechanisms in ECT-induced retrograde amnesia: experimental evidence for involvement of COX-2, and review of literature. J Psychiatr Res. 2008; 42:837–850. [PubMed: 17937934]
43. Andrade C, Thyagarajan S, Singh NM, Vinod PS, Sanjay Kumar Rao N, Chandra JS. Celecoxib as an in vivo probe of cyclooxygenase-2 mechanisms underlying retrograde amnesia in an animal model of ECT. J Neural Transm. 2008; 115:1063–1070. [PubMed: 18523723]
44. Andrade C, Shaikh SA, Narayan L, Blasey C, Belanoff J. Administration of a selective glucocorticoid antagonist attenuates electroconvulsive shock-induced retrograde amnesia. J Neural Transm. 2012; 119:337–344. [PubMed: 21922193]
45. McCall WV. Psychiatry and psychology in the writings of L. Ron Hubbard. Journal of Religion and Health. 2007; 46:437–447.