Brain Stimulation 8 (2015) 851–854

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Editorial

Is the Seizure an Unnecessary Component of Electroconvulsive Therapy? A Startling Possibility

Electroconvulsive therapy (ECT) is, of course, a misnomer. Convulsive movements are a by-product of eliciting seizures that generalize to the motor cortex. Commonly, convulsive activity is strongly reduced or eliminated by administrating a muscle-paralyzing agent, such as succinylcholine, prior to the electrical stimulus and while the patient is anesthetized. Thus, convulsive motor activity is irrelevant to the therapeutic and cognitive effects of the treatment. Rather, the procedure might more properly be labeled electroseizure therapy (EST), since the goal, at least until now, in applying the electrical stimulus is the elicitation of a cerebral seizure, and not the production of convulsive movements.

Regardless of its label, ECT is the most effective treatment available for episodes of major depression. No other treatment, biological or psychological, matches ECT in terms of short-term rates of antidepressant response and remission [1]. The efficacy of ECT is especially noteworthy since it is usually reserved for patients who are resistant to other treatments. Besides unipolar and bipolar depression, ECT can be of remarkable benefit in other select disorders. There is convincing evidence regarding its clinical utility in disorders as diverse as acute mania [2], some forms of schizophrenia [3], catatonia [4], and Parkinson's disease [5].

Soon after its introduction in 1938, the view was advanced that the generalized seizure provided both the necessary and sufficient conditions for ECT's efficacy [6]. The belief was that the method of seizure induction was irrelevant to the therapeutic process. Rather, there was strong evidence that chemical induction of generalized seizures with Flurothyl, a seizure-inducing inhalant gas, was just as effective in treating major depression and schizophrenia as standard ECT [7]. Indeed, the chemically-induced seizure treatment appeared to have less severe cognitive side effects relative to standard ECT. Despite seeming equivalent efficacy and superior side effects, the chemical-induction approach was abandoned because of impracticality. Understandably, medical personnel were reluctant to work with an inhalant that produced seizures. Regardless, the idea that the seizure was central to efficacy, independent of its mode of induction, provided the conceptual basis for Magnetic Seizure Therapy (MST), which induces seizures via application of a time-varying magnetic field [8,9].

The efficacy equivalence of chemical and electrical induction techniques supported the view that elicitation of the generalized seizure provided sufficient conditions for efficacy. Classic research by Ottosson [10] promoted the idea that the generalized seizure was also necessary for efficacy. Ottosson co-administered lidocaine with the ECT electrical stimulus, producing diminished seizure expression. This combination had inferior efficacy, supporting the view that full expression of the generalized cerebral seizure was necessary to guarantee efficacy. In subsequent decades, starting with Nobler et al. [11], several studies have reported significant correlations between measures of seizure expression (e.g., the timing and amplitude of ictal slow wave activity, degree of postictal EEG suppression, etc.) and ECT efficacy. Furthermore, work mostly in the 1950's suggested that stimulation techniques that did not result in a seizure ("subconvulsive" stimulation) lacked the efficacy of traditional ECT [12].

Thus, there appeared to be strong grounds for arguing that the generalized seizure provided the conditions both necessary and sufficient for ECT's efficacy in major depression. Ottosson [10] also conducted research in which he manipulated the intensity of the ECT electrical stimulus. He reported that high intensity stimulation aggravated the cognitive side effects of the intervention, with little impact on efficacy. Taken together, these findings led to the view that the electrical stimulus was largely responsible for the adverse cognitive effects of the treatment, while the induction of the generalized seizure was responsible for its efficacy. For example, in 1983 d'Elia et al. [13] stated, "Because the therapeutic effect is a result of the cerebral seizure, and the organic side effects partly consequences of the electrical stimulation, the aim should be to induce maximal seizure activity using minimal electrical energy (p. 577)."

In addition to these fundamental mechanistic claims, for decades this perspective guided the search for the neurobiological processes that subserved ECT's efficacy. Thousands of studies focused on the neurobiological consequences of the ictus, and scores of consistent changes were demonstrated in neurotransmitter, peptidergic, and hormonal function as a function of seizure induction. Indeed, because of this plethora of findings, Kety [14] famously bemoaned that the changes in brain neurochemistry following seizure induction were so numerous that it was impossible to separate those subserving efficacy from epiphenomena. The view emphasizing the centrality of the seizure also had anatomic ramifications. To some the emphasis on the generalized seizure argued for a mass action, Hebbian neurobiological effect, in which there was no localization to processes underlying

Dr. Sackeim serves as a consultant to the MECTA Corporation, which manufactures ECT devices. He also holds a patent on Focal Electrically Administered Seizure Therapy (FEAST), and has a patent pending for electrical dose titration in the current domain. He is also the originator of Magnetic Seizure Therapy (MST).

http://dx.doi.org/10.1016/j.brs.2015.07.026
1935-861X/© 2015 Elsevier Inc. All rights reserved.

efficacy [15]. Alternatively to others the need for a generalized seizure focused attention on diencephalic structures that entrain widespread synchronous cortical activity [16].

This fundamental view of ECT mechanisms dictated that lowest dose of electricity should be used to induce the generalized seizure. The generalized seizure would guarantee efficacy, and minimizing electrical dose would minimize cognitive side effects. However, this perspective was never instantiated in practice. For decades, the most common practice was to set ECT devices at the maximum electrical output. Indeed, there was no rationale method for determining electrical dose. In the early 1980's, we developed electrical dose titration to quantify seizure threshold, the minimum electrical charge needed to induce a generalized seizure of adequate duration [17]. Dose titration uses a standard ascending method of limits psychophysical procedure and involves administration of subconvulsive stimulations of increasing intensity until a generalized seizure is produced. A series of studies at Columbia University, using this method to determine dosage, demonstrated unequivocally that the fundamental view of ECT mechanisms was incorrect [18–21].

In the first study [18], patients were randomized to bilateral (BL; bifrontotemporal) or right unilateral (RUL) ECT, with all patients treated just above their seizure threshold (ST) throughout the treatment course. BL ECT was a powerful antidepressant. In contrast, despite producing generalized seizures that met conservative criteria for adequacy, RUL ECT was remarkably ineffective, with only a 17% response rate. By coupling low electrical intensity and the RUL electrode placement, we had inadvertently created a form of ECT that lacked efficacy. This clearly contradicted the premise that the generalized seizure provided sufficient conditions for efficacy.

Because these findings contradicted the fundamental perspective and because the combination of low electrical intensity and RUL electrical held great promise for minimizing side effects, it was critical to attempt to replicate these findings. A second study [19] used a two-by-two design, randomizing patients to electrical dosage just above ST (as in the prior study) or dosage 2.5 times the initial ST (2.5 × ST). Patients were also randomized to BL or RUL ECT. The findings of the first study were strongly replicated. Again low dose RUL ECT was virtually devoid of efficacy. At higher electrical dosage (2.5 × ST), RUL ECT was significantly more effective, though still not equivalent to low or higher dose BL ECT. This study provided the first evidence that RUL ECT displayed a dose–response window that was absent with BL ECT. In other words, the efficacy of ECT was contingent both on the current path of the electrical stimulus (as determined by electrode placement) and the current density within that path (as determined by electrical dosage).

This view was further supported by a third study [20]. Patients were again randomized to 4 ECT conditions: RUL ECT at 1.5, 2.5 and 6 × ST, and BL at 2.5 × ST. The two lower dose RUL ECT conditions (1.5 and 2.5 × ST) were significantly less effective that the high dose RUL (6 × ST) and the BL ECT conditions. Critically, high dose RUL ECT (6 × ST) matched a robust form of BL ECT (2.5 × ST) in efficacy. This led to the conclusion that at sufficient electrical dose relative to ST the efficacy of RUL ECT is equivalent to our most effective forms of ECT. This finding was subsequently replicated in large multi-site trials [22,23] and was of clinical consequence since, despite high dosage, RUL ECT was superior to BL ECT in cognitive side effects.

In a fourth study patients were randomized to RUL ECT at 6 × ST or BL ECT at 2.5 × ST and also to a standard brief electrical pulse width (1.5 ms) or an ultrabrief pulse width (0.3 ms) [21]. This study was predicated on the notion that the traditional brief pulse used in ECT was excessively long in duration and therefore inefficient since it far exceeded the chronaxie of human neurons to depolarize [24]. This study strongly replicated the finding that RUL and BL ECT were equivalent in efficacy when RUL was given at high dosage (6 × ST) regardless of pulse width. This study also documented that use of an ultrabrief pulse width markedly reduced the short- and long-term cognitive side effects of ECT. Since this report, use of high dosage, ultrabrief RUL ECT has become widespread internationally.

This body of research demonstrated that the generalized seizure was insufficient to guarantee efficacy. Seizures could be reliably evoked that lacked antidepressant properties. Kety's conundrum regarding ECT mechanisms could now be resolved because theoretically one could contrast the neurobiological effects of effective and ineffective forms of ECT, with each resulting in generalized seizures. Only those changes unique to effective forms of ECT were likely relevant neurobiological processes. More specifically, this work indicated that efficacy was contingent on the current path of the electrical stimulus and the current density within that path. In contrast, to the original perspective on mechanisms, this view emphasized localization. The findings dictated that there must be localization in the neural systems that subserved efficacy.

Indeed, our understanding of why low dose RUL was ineffective centered on the notion that prior to generalization such seizures were first triggered from the motor strip, which has a very low threshold for initiating seizure activity. Increasing the electrical dose of RUL ECT resulted in increased current density in prefrontal regions and at sufficient dosage these regions participated in seizure initiation [25]. The view was offered that, like secondarily generalized seizures in epilepsy, the anticonvulsant (inhibitory) effects of seizure induction were spatially targeted more at sites of seizure initiation as opposed to seizure generalization [25–27]. Imaging studies supported this perspective. Patients who had superior antidepressant response to ECT showed greater reductions in regional cerebral blood flow [28] and glucose metabolism [29] and greater increases in the amplitude of slow wave (delta) electroencephalographic (EEG) activity [30] than patients who had inferior clinical response. These physiological correlates of clinical outcome had a strong topography. The associations were most marked in prefrontal regions.

This evolution in our understanding of fundamental ECT mechanisms has also strongly influenced clinical and neurobiological investigation. Traditional ECT, using a bidirectional pulsed electrical stimulus and symmetrically shaped stimulus electrodes, is intrinsically limited in its focality of stimulation. Yet, this new perspective emphasizes the possibility that seizure initiation in spatially delimited regions is key to efficacy. Consequently, we have recently witnessed concerted efforts to develop more focal forms of ECT, capable of eliciting seizures from prespecified neuronal aggregates. This includes magnetic seizure therapy (MST), which takes advantage of the fact that the scalp and skull are transparent to the magnetic field, allowing theoretically for spatially precise and restricted seizure induction [9,31–33]. The promise of MST may be limited by electrical engineering limitations, as the energy transfer between current in a coil and in neural tissue is highly inefficient, and it is difficult to achieve with MST the intracerebral current density that can is easily achieved with electrical stimulation. In contrast, Focal Electrically Administered Seizure Therapy (FEAST) capitalizes on knowledge of optimal methods for focal electrical stimulation [34], and uses a unidirectional pulsed stimulus (creating an anode–cathode arrangement), coupled with asymmetrically-sized electrodes [25,35,36]. In its current instantiation the electrode and stimulation configuration is intended to maximize and restrict current density to right orbitofrontal cortex. Preliminary research suggests that both MST and FEAST have reduced cognitive side effects compared to traditional ECT. As yet, the evidence is not convincing that they match the efficacy of ECT.

This new perspective retains the seizure as a necessary component of the ECT therapeutic process. While not all seizures may be therapeutic, initiating seizure activity in the proper region with

appropriate dosage is fundamental to efficacy. In addition to emphasizing localization, this perspective emphasizes the spatial distribution of inhibitory and perhaps neuroplastic [37,38] changes as mediating efficacy.

The paper by Regenold et al. in this issue [39] could be the start of another revolution in our understanding of ECT. They treated 11 patients with the bifrontal (BF) electrode placement and traditional ECT methods, except that electrical stimulation was dosed below the seizure threshold (ST). In this open clinical series, 73% of patients were responders and 55% were remitters, clinical outcomes close to what one might expect with traditional ECT. What is exceptional about this work is that Regenold et al. claim that no seizures were induced. The strong clinical improvement was instead due to electrical stimulation alone, coupled with the BF placement. The implications of this study contradict our previous understanding of ECT.

Of course, before the implications of this study are accepted, it must be replicated and then studied relative to ECT under strict randomized and blinded conditions. It should be noted that the sample consisted of outpatients whose average level of depression, as indexed by the Hamilton Ratings Scale for Depression, was only moderate in severity. These patients continued to receive psychotropic medications throughout the course of brain stimulation and the clinical team was quite likely eager to see the success of this novel intervention. Thus, there are many reasons the results could have obtained other than the claim that subconvulsive stimulation may be therapeutic.

Regenold et al. [39] took the antidepressant efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as supporting the possibility that the seizure is not a necessary component of ECT. Indeed, the same argument was made early in the development of rTMS as an antidepressant treatment. The success of rTMS was taken as negating the necessity of the seizure for the antidepressant effects of ECT [40]. In my view, then and now, this perspective is faulty [8]. Antidepressant treatment with rTMS involves application of multiple trains of stimulation within any session. In contrast, the defining feature of ECT is the administration of a single electrical train. At issue is whether a single train of stimulation, electrical or magnetic, can produce robust antidepressant effects without producing a seizure.

In support of Regenold et al. it should be recognized that many neurobiological effects of ECT may be due solely to the electrical stimulus, with seizure production irrelevant. For example, microdialysis studies show that electroconvulsive shock (ECS) in rodents reliably results in a massive release of dopamine. The extent of this acute release is modulated by the intensity of the electrical stimulus. In contrast, seizures induced with Flurothyl, do not result in a dopamine surge [41–43]. The implication is that the dopamine surge is a result of electrical sitmualtion, with the intervening seizure irrelevant. One can imagine development of a treatment for Parkinson's disease using single high intensity trains of electrical stimulation, with seizure provocation blocked pharmacologically. The larger point is that we lack as yet an academic subfield devoted to the study of stimulation-induced pharmacology. It is conceivable that important effects of ECT may be attributable to the nature of the electrical stimulation without mediation from seizure induction. Indeed, the dramatic progress made in reducing the adverse cognitive side effects of ECT resulted purely from refinement of the electrical stimulus, moving from sine wave stimulation to brief pulse stimulation, to ultrabrief stimulation, along with improvements in dosage protocols. Thus, it is conceivable that the seizure is also irrelevant with respect to efficacy.

The most direct evidence that supported the necessity of the seizure came from studies in the 1950's comparing traditional ECT to various forms of subconvulsive stimulation [44,45]. This work was characterized by numerous methodological shortcomings and can hardly be considered definitive on this issue. Indeed, as Regenold et al. [39] noted, no study has directly compared the efficacy of single trains of subconvulsive electrical stimulation with ECT.

There are good reasons to be skeptical of the possibility raised by Regenold et al. Low dose RUL ECT involves administering an electrical intensity above the ST, and yet is remarkably ineffective. This phenomenon is well replicated. For this to be true and for the argument of Regenold et al. to be accepted, one must posit that electrode placement (current path) is key. Stimulation below the ST may be effective with the BF placement, but highly ineffective with RUL ECT. Modeling of the electrical current suggests that the two placements do have important differences in current density patterns, besides the obvious difference in laterality. BF involves greater concentration of current density in prefrontal structures [46,47]. Regenold et al. must assume that this difference in current paths is fundamental in why subconvulsive stimulation proved to be efficacious in their study.

Another reason for skepticism about these results is the method of stimulus dosing. When subconvulsive stimulation is used, the intracerebral stimulation intensity should be key to neurobiological and behavioral effects. Regenold et al. [39] used a crude and highly inexact method of determining electrical dosage. There are marked individual differences in the extent to which the electrical stimulus is shunted away form the brain, and in intracerebral current density given the same stimulus [48]. Regenold et al. dosed their patients on the basis of their age, despite the fact that age shows only a modest relationship with the electrical intensity needed to evoke seizures. Future research of this type needs to develop a better method of insuring that electrical stimulation is just below ST.

Regardless of the reasons for skepticism, Regenold et al. have presented an important challenge to the field of ECT. They contend that electrical stimulation below the ST, coupled with the BF electrode placement, can match the efficacy of traditional ECT. Consequently, they argue that the seizure is irrelevant to the therapeutic process (at least with this electrode placement). Clinically, this could be a great advance since the seizure undoubtedly contributes to some of the morbidity of the treatment. Conceptually, it could mean that the field of ECT has been barking up the wrong tree since the 1930's. Of note, the name Regenold et al. suggest for this intervention, nonconvulsive electrotherapy (NET), is also a misnomer. As pointed out at the beginning, we can all agree that convulsions have nothing to do with the therapeutic process. At issue is whether nonseizure electrotherapy (with a single train of stimulation) is efficacious.

Harold A. Sackeim*
Department of Psychiatry
College of Physicians and Surgeons
Columbia University
2124 Moselem Springs Road
Fleetwood, PA 19522, USA

Department of Radiology
College of Physicians and Surgeons
Columbia University
2124 Moselem Springs Road
Fleetwood, PA 19522, USA

* Corresponding author. Department of Psychiatry, College of Physicians and Surgeons, Columbia University, 2124 Moselem Springs Road, Fleetwood, PA 19522, USA. Tel.: +1 917 273 5379; fax: +1 610 944 5600.
E-mail address: has1@columbia.edu

References

[1] American Psychiatric Association. The practice of ECT: recommendations for treatment, training and privileging. 2nd ed. Washington, D.C.: American Psychiatric Press; 2001.
[2] Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. Am J Psychiatry 1994; 151(2):169–76.
[3] Sackeim HA. Electroconvulsive therapy and schizophrenia. In: Hirsch SR, Weinberger D, editors. Schizophrenia. 2nd ed. Oxford: Balckwell; 2003. p. 517–51.
[4] Kugler JL, Hauptman AJ, Collier SJ, et al. Treatment of catatonia with ultrabrief right unilateral electroconvulsive therapy: a case series. J ECT 2014.
[5] Balldin J, ën S, Granërus A, et al. Electroconvulsive therapy in Parkinson's syndrome with 'on-off: phenomenon. J Neural Transm 1980;47(1):11–21.
[6] Kalinowsky LB, Hoch PH. Shock treatments and other somatic procedures in psychiatry. New York: Grune & Stratton; 1946.
[7] Small JG, Small IF, Sharpley P, Moore DF. A double-blind comparative evaluation of flurothyl and ECT. Arch Gen Psychiatry 1968;19(1):79–86.
[8] Sackeim HA. Magnetic stimulatuion therapy and ECT. Convuls Ther 1994;10: 255–8.
[9] Lisanby SH, Schlaepfer TE, Fisch HU, Sackeim HA. Magnetic seizure therapy of major depression. Arch Gen Psychiatry 2001;58(3):303–5.
[10] Ottosson J-O. Experimental studies of the mode of action of electroconvulsive therapy. Acta Psychiatr Scand Suppl 1960;145:1–141.
[11] Nobler MS, Sackeim HA, Solomou M, Luber B, Devanand DP, Prudic J. EEG manifestations during ECT: effects of electrode placement and stimulus intensity. Biol Psychiatry 1993;34(5):321–30.
[12] Ulett G, Smith K, Gleser G. Evaluation of convulsive and subconvulsive shock therapies utilizing a control group. Am J Psychiatry 1956;112:795–802.
[13] d'Elia G, Ottosson JO, Strömgren LS. Present practice of electroconvulsive therapy in Scandinavia. Arch Gen Psychiatry 1983;40(5):577–81.
[14] Kety S. Biochemical and neurochemical effects of electroconvulsive shock. In: Fink M, Kety S, McGaugh J, Williams T, editors. Psychobiology of convulsive therapy. Washington, DC: V H Winston & Sons; 1974. p. 285–94.
[15] Fink M, Kahn RL, Green MA. Experimental studies of convulsive and drug therapies in psychiatry: theoretical implications. Arch Neurol Psychiatry 1958;80: 733–4.
[16] Fink M. How does convulsive therapy work? Neuropsychopharmacology 1990;3(2):73–82.
[17] Sackeim HA, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. Arch Gen Psychiatry 1987;44(4):355–60.
[18] Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S. Effects of electrode placement on the efficacy of titrated, low-dose ECT. Am J Psychiatry 1987 Nov; 144(11):1449–55.
[19] Sackeim HA, Prudic J, Devanand DP, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 1993;328(12):839–46.
[20] Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 2000;57(5):425–34.
[21] Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 2008 Apr;1(2):71–83.
[22] Kellner CH, Knapp R, Husain MM, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry 2010 Mar; 196:226–34. PubMed PMID: 20194546. Pubmed Central PMCID: 2830057. Epub 2010/03/03. eng.
[23] Sackeim HA, Dillingham EM, Prudic J, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry 2009 Jul;66(7):729–37. PubMed PMID: 19581564. Epub 2009/07/08. eng.
[24] Ranck Jr JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975;98:417–40.
[25] Sackeim HA. The convulsant and anticonvulsant properties of electroconvulsive therapy: towards a focal form of brain stimulation. Clin Neurosci Rev 2004;4:39–57.
[26] Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR. Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. Biol Psychiatry 1983 Nov;18(11):1301–10.
[27] Sackeim HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. J ECT 1999;15:5–26.
[28] Nobler MS, Sackeim HA, Prohovnik I, et al. Regional cerebral blood flow in mood disorders, III. Treatment and clinical response. Arch Gen Psychiatry 1994;51(11):884–97.
[29] Nobler MS, Oquendo MA, Kegeles LS, et al. Decreased regional brain metabolism after ect. Am J Psychiatry 2001 Feb;158(2):305–8.
[30] Sackeim HA, Luber B, Katzman GP, et al. The effects of electroconvulsive therapy on quantitative electroencephalograms. Relationship to clinical outcome. Arch Gen Psychiatry 1996 Sep;53(9):814–24.
[31] Cycowicz YM, Luber B, Spellman T, Lisanby SH. Differential neurophysiological effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS) in non-human primates. Clin EEG Neuroscience 2008 Jul;39(3):144–9.
[32] Kosel M, Frick C, Lisanby SH, Fisch HU, Schlaepfer TE. Magnetic seizure therapy improves mood in refractory major depression. Neuropsychopharmacology 2003 Nov;28(11):2045–8.
[33] Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. Neuropsychopharmacology 2003 Oct;28(10):1852–65.
[34] Amassian V, Eberle L, Maccabee P, Cracco R. Modelling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: the significance of fiber bending in excitation. Electroencephalogr Clin Neurophysiol 1992;85:291–301.
[35] Chahine G, Short B, Spicer K, et al. Regional cerebral blood flow changes associated with focal electrically administered seizure therapy (FEAST). Brain Stimul 2014 May-Jun;7(3):483–5.
[36] Nahas Z, Short B, Burns C, et al. A feasibility study of a new method for electrically producing seizures in man: focal electrically administered seizure therapy [FEAST]. Brain Stimul 2013 May;6(3):403–8.
[37] Perera TD, Coplan JD, Lisanby SH, et al. Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. J Neurosci 2007 May 2; 27(18):4894–901.
[38] Perera TD, Dwork AJ, Keegan KA, et al. Necessity of hippocampal neurogenesis for the therapeutic action of antidepressants in adult nonhuman primates. PLoS One 2011;6(4):e17600.
[39] Regenold WT, Noorani RJ, Piez D, Patel P. Nonconvulsive electrotherapy for treatment resistnat unipolar and bipolar major depressive disorder: a proof-of-concept trial. Brain Stimul 2015.
[40] George MS, Wassermann EM. Rapid-rate transcranial magnetic stimulation and ECT [editorial]. Convuls Ther 1994;10(4):251–4.
[41] Zis AP, McGarvey KA, Clark CM, Lam RW, Patrick L, Adams SA. Effect of stimulus energy on electroconvulsive therapy-induced prolactin release. Convuls Ther 1993;9:23–7.
[42] Zis AP, Nomikos GG, Brown EE, Damsma G, Fibiger HC. Neurochemical effects of electrically and chemically induced seizures: an in vivo microdialysis study in the rat hippocampus. Neuropsychopharmacology 1992;7(3):189–95.
[43] Zis AP, Nomikos GG, Damsma G, Fibiger HC. In vivo neurochemical effects of electroconvulsive shock studied by microdialysis in the rat striatum. Psychopharmacol Berl 1991;103(3):343–50.
[44] Ulett GA. Preliminary observations on convulsive and subconvulsivetreatments induced by intermittent photic stimulation. Am J Psychiatry 1953; 109:741–8.
[45] Ulett GA, Gleser GC, Caldwell BM, Smith K. The use of matched groups in the evaluation of convulsive and subconvulsive photoshock. Bull Menninger Clin 1954;18:138–46.
[46] Deng ZD, Lisanby SH, Peterchev AV. Effect of anatomical variability on neural stimulation strength and focality in electroconvulsive therapy (ECT) and magnetic seizure therapy (MST). Conf Proc IEEE Eng Med Biol Soc 2009;1: 682–8.
[47] Lee WH, Deng ZD, Kim TS, Laine AF, Lisanby SH, Peterchev AV. Regional electric field induced by electroconvulsive therapy in a realistic finite element head model: influence of white matter anisotropic conductivity. Neuroimage 2012 Feb 1;59(3):2110–23.
[48] Sackeim HA, Long J, Luber B, et al. Physical properties and quantification of the ECT stimulus: I. Basic principles. Convuls Ther 1994;10(2):93–123.