ECT FOR PTSD

- Efficacy, mechanisms, and a hypothesis for new directions

- Chittaranjan Andrade, MD
  Professor in Psychopharmacology
  National Institute of Mental Health and Neurosciences
  Bangalore, India
ECT FOR PTSD

- What PTSD is
- PTSD is not a recognized indication for ECT
- Scope
  - Section 1: Efficacy of ECT in PTSD: Evidence
  - Section 2a: Possible clinical mechanisms
  - Section 2b: Possible neurohistological mechanisms
  - Section 3: Hypothesis for new direction for treatment
SECTION 1: EVIDENCE

- 3 case reports (4 cases)
- 2 retrospective studies
- 1 uncontrolled, prospective study
- Plus one recent, innovative case report
Efficacy: Case Report 1
(Helsley et al, Am J Psychiatry 1999)

- 35-year-old woman
- Severe medication- and psychotherapy-resistant, combat-related PTSD
- Substantial improvement with 6, thrice-weekly unilateral ECT
EFFICACY: CASE REPORT 2
(Hanretta and Malek-Ahmadi, J ECT 2006)

- 38-year-old woman
- Medication-refractory depression and PTSD.
- Complete remission from depression and PTSD with 8 bilateral ECT
Two men (age 40, 42 y) with combat-related PTSD and comorbid psychosis.

Received 8-10 ECTs

BPRS and CAPS scores each reduced by about a third.
26 patients with major depressive episode and comorbid PTSD

Received a mean of 9.7 RUL and bilateral ECT

Substantial improvement in depression

Small but statistically significant improvement in PTSD
EFFICACY: CHART REVIEW 2
(Watts and Groft, J ECT 2010)

- 32 patients with major depressive episode and comorbid PTSD
- Received a mean of 10 mostly RUL and bilateral ECT
- Modest improvement in depression
- Small but statistically significant improvement in PTSD
In both studies, PTSD in slightly more than a third of patients was considered to have ‘responded’ to ECT.

Both studies rated PTSD with an instrument that might have been insufficiently sensitive to identify improvement (Andrade et al, J ECT 2011)
20 outpatients
- Mean age, 38 years; 50% male
- Severe, chronic, refractory PTSD
  - Mean duration of illness, 3 years
  - Comorbid depression, if present, did not antedate PTSD
  - At least 4 failed antidepressant trials, 12 CBT sessions
- 6 twice-weekly bilateral ECT
- 3 (15%) drop outs
PROSPECTIVE STUDY: 2
(Margoob et al, Brain Stim 2010)

- ITT analysis:
  - CAPS scores decreased by 34%
  - Comparable improvement on re-experiencing, avoidance, numbing subscales of CAPS
  - MADRS scores decreased by 51%
  - Evidence of improvement by 3\textsuperscript{rd} ECT (Day 10)
  - Improvement in CAPS independent of baseline MADRS
  - Improvement in CAPS independent of improvement in MADRS ($r=0.42$, NS)
PROSPECTIVE STUDY: 3
(Margoob et al, Brain Stim 2010)

- ITT analysis:
  - Response to ECT (30% decrease in CAPS): 70%
  - Remission (endpoint CAPS <20): 0%

- Post-ECT treatment gains maintained at 4-24 month follow up
  - Maintenance treatment with antidepressants
  - Functional improvements subjectively reported
SECTION 2: HYPOTHETICAL MECHANISMS

- Clinical mechanisms
- Neurohistological mechanisms
MECHANISMS: CLINICAL

- Major depression is commonly comorbid with PTSD
- There is symptom overlap between depression and PTSD
- When depression improves with ECT, some PTSD symptoms could also improve
  - Not true improvement in PTSD
MECHANISMS: NEUROHISTOLOGICAL

- Nonspecific
  - Hippocampal/PFC neuroplasticity and learning adaptative skills
  - Hippocampal neuroplasticity and forgetting

- Specific
  - Amygdalar neuroplasticity and forgetting
HIPPOCAMPAL, PFC NEUROPLASTICITY: 1a

- ECS upregulates neuroplasticity in the hippocampus and in the PFC.
- In the hippocampus, there is an increase in neurogenesis, dendritic arborization, new synapse formation, and oligodendroglialosis.
- These changes are evident even when cortisol, the stress hormone, is concurrently administered.
- Andrade and Rao, Indian J Psychiatry 2010; Smitha et al, J ECT 2014a&b
ECS stimulates endothelial cell proliferation in the hippocampus, which change is independent of hypoxia related to ECS.

ECS stimulates vascular and glial proliferation in the frontal cortex, as well.

Some of the changes are dose-dependent; that is, greater with higher ECS dose, larger number of ECTs.

Andrade and Rao, Indian J Psychiatry 2010; Smitha et al, J ECT 2014a&b
Implications:

Upregulated neuroplasticity may promote improved cognitive and hence adaptative functioning.

Hence, assisting in recovery from conditions such as depression and PTSD.

Andrade and Rao, Indian J Psychiatry 2010; Smitha et al, J ECT 2014a&b
HIPPOCAMPAL NEUROPLASTICITY: 2a

- This change, along with other neuroplasticity changes, may result in formation of connections that disturb existing hippocampal networks.
- Possible result: interference with established memories, particularly recent memories.
HIPPOCAMPAL NEUROPLASTICITY: 2b

- Amnesiogenesis is undesirable in depressed patients.
- In PTSD, it may help if stress-laden memories are weakened.
- In infant and adult rats, hippocampal neurogenesis (induced by exercise or fluoxetine) attenuates fear memories (Akers et al, Science 2014).
- Pyramidal neurons showing dendritic arborization.

- 6 once-daily sham ECS

- 10x magnification
- Pyramidal neurons showing dendritic arborization.

- 6 once-daily 10 mC ECT

- 10x magnification
- Pyramidal neurons showing dendritic arborization.

- 6 once-daily 40 mC ECS

- 10x magnification
BrdU stained new cells formed in the subgranular zone of the dentate gyrus.

6 once-daily sham ECS

40x magnification
BrdU stained new cells formed in the subgranular zone of the dentate gyrus.

6 once-daily 10 mC ECS

40x magnification
• BrdU stained new cells formed in the subgranular zone of the dentate gyrus.

• 6 once-daily 40 mC ECS

• 40x magnification
AMYGDALAR NEUROPLASTICITY: 1

- ECS decreases
  - Dendritic arborization
  - Number of nodes
  - Excitatory synapses
- ECS increases
  - Inhibitory synapses
- Net effect
  - ECT downregulates amygdalar neuroplasticity
The amygdala is involved in fear learning (Benarroch, Neurology 2015).

The amygdalar response to ECS suggests that ECT may weaken the negative affect attached to stress-laden memories (Andrade, J Clin Psychiatry 2014 a&b).
AMYGDALA CHANGES AFTER 6 ECS: Sham, 10 mC, 60 mC
AMYGDALA CHANGES AFTER 6 ECS: Control, 10 mC, 60 mC

- Squares/rectangles: Excitatory synapses
- Circles: Inhibitory synapses

[Differentiation based on shape – circular vs elliptical or flattened]
Sham ECS
10 mC ECS
60 mC ECS
MDD: ECT AND THE AMGYDALA
fMRI study: 1 (Redlich et al, Psychol Med 2017)

- Antidepressant (n=23), ECT (n=24) and healthy control (n=22) groups
- Pre-post, 6-week non-randomized study design
- Pre-treatment, both patient groups:
  - Increased amygdalar reactivity to sad faces
- Post treatment, both patient groups:
  - Reduced amygdalar reactivity to sad faces.
  - Decreased amygdalar activity was associated with symptomatic improvement (significant with ECT, trend with medication)
MDD: ECT AND THE AMGYDALA

fMRI study: 2 (Redlich et al, Psychol Med 2017)

- Amygdala as the seat of fear learning
- Implications of the findings:
  - ECT, antidepressants may dampen emotional associations with anxiogenic memories
- Findings support the use of both ECT and ADs for both depression and PTSD.
- Limitations:
  - ECT patients also received antidepressants
  - Generalization from a lab experiment to real life events
SECTION 3: HYPOTHESIS FOR NEW DIRECTIONS IN TREATMENT

- Using ECT as a tool to disrupt specific memories
MEMORY IS LABILE

- Animal and human data show that when memories are awakened, they are transiently labile and can spontaneously distorted or weaken before they are reconsolidated.
  - Examples from everyday life
  - Not applicable to rehearsing
- Weakening can be effected by the same agents that can impair the acquisition of new memories.
  - E.g. drugs, ECT
USE OF ECT TO INACTIVATE SPECIFIC MEMORIES: Findings

- A single ECT administered immediately after the activation of a (recently created, laboratory-type) unpleasant memory can weaken that memory.
  
- Evident when that memory is tested one day (but not one hour) later.

- ECT does not disturb memories that are not reactivated immediately before the treatment.


- Implications for patients with PTSD
USE OF ECT TO INACTIVATE MEMORIES: Challenges

- PTSD memories are real, not laboratory-created.
- PTSD memories are longstanding, not recent.
- PTSD memories are well-rehearsed
TESTING THE HYPOTHESIS: Case report: 1

- Gahr et al, J Neuropsychiatry Clin Neurosci 2014
- 47-year old male
- 7-year h/o antidepressant- and CBT-refractory PTSD related to traffic accident, childhood sexual abuse
- Comorbid severe major depressive episode
- Treatment: 8 RUL ECT, thrice-weekly
TESTING THE HYPOTHESIS: Case report: 2

- Before each ECT, he was asked to recall the accident and to describe his recollections.
- The duration of reactivation was about 10 min.
- The ECT procedure commenced 10 min later.
- Depression and PTSD both improved.
- After the ECT course, recall of the accident memories was much weakened and PTSD symptoms related thereto were attenuated.
- CSA memories, PTSD symptoms persisted.
TESTING THE HYPOTHESIS: Case report: 3

- Usual ECT-induced amnestic mechanisms
  - Show a temporal gradient
  - Lack specificity for an event

- Implication: Reactivation/reconsolidation interference, mediated by ECT, was responsible.
USE OF ECT TO OBLITERATE TRAUMATIC MEMORIES IN PTSD

Challenges: Several variables will need to be manipulated and studied
- The nature of the memory that is activated
- The extent to which it is activated
- The duration for which it is activated
- Reassurance provided, if any, during reactivation
- Timing of the ECT with regard to the reactivation
- Etc.
A Primer for the Conceptualization of the Mechanism of Action of Electroconvulsive Therapy, 1: Defining the Question

Chittaranjan Andrade, MD

Clinical Problem

Mr D, a 35-year-old man with major depressive disorder, has been severely depressed for the past 6 months. He has failed 2 adequate antidepressant trials, one of which was with a dual-acting antidepressant drug. He has also failed 1 trial of antidepressant augmentation with an atypical antipsychotic drug. Presently, he has severe social and occupational impairment as well as active suicidal ideation. Electroconvulsive therapy (ECT) has been suggested to him. Mr D is doubtful; he wants to know why electricity needs to be passed into his brain and how ECT acts. How should the clinician respond?

ECT is arguably the most effective treatment available for major mental illness. ECT is commonly advised when the patient is catatonic, suicidal, very severely ill, or unresponsive to medications. When ECT is discussed, a common question addresses the mechanism of action of the treatment: How does ECT work?

This question is asked by patients, relatives of patients, members

ABSTRACT

With regard to the question of how electroconvulsive therapy (ECT) acts, a common answer is that the mechanism of action of the treatment is not well understood. However, this
Clinical Problem

The previous article in this column\(^1\) presented an antidepressant-refractory, severely depressed patient for whom electroconvulsive therapy (ECT) had been suggested. The patient had asked why it was necessary for electricity to be passed through his brain. He wanted to know how ECT acts. The article\(^1\) explained why the question about the mechanism of action of ECT is a complex one and why it needs to be resolved into specific elements. The article also explained difficulties in the interpretation of research and academic concerns related to the generation of explanatory models. The present article deals with the problem of plenty; that is, how the large body of evidence on the subject may be organized so as to generate coherent explanations about the mechanism of action of ECT.

Much evidence is available on the electrophysiologic, neurochemical, neurotransmitter, neuroendocrine, histologic, and other changes that result with ECT, most or all of which have been offered as explanations for its mechanism of action. A considerable problem that one faces is to understand which of these changes are therapeutic and which are epiphenomena; which of the therapeutic changes are upstream and which
Images in Electroconvulsive Therapy

Electroconvulsive Shocks Dose-Dependently Increase Dendritic Arborization in the CA1 Region of the Rat Hippocampus

Jangama S. M. Smitha, MSc (Medical Anatomy), * Ravindranath Roopa, MBBS, MS (Anatomy), * Nagarchi Khaleel, MSc (Medical Anatomy), * Bindu M. Kutty, PhD, † and Chittaranjan Andrade, MD ‡

Abstract: Stress and depression are associated with impaired neuroplasticity in the hippocampus: there is decreased dendritic arborization and synaptogenesis, which is hypothesized to explain decreased adaptive competence of the organism. Representative light microscopy images are presented that show that 6 once-daily electroconvulsive shocks (ECSs) dose-dependently increased dendritic arborization in the CA1 region of the hippocampus in healthy, adult, male Wistar rats (n = 10 in each of sham, 10-mC, and 40-mC ECS groups). These neuroplasticity changes, identified 1 month after the last ECS, may explain a part of the mechanism of action of electroconvulsive therapy in conditions such as depression.

Key Words: Electroconvulsive therapy, Electroconvulsive shocks, Hippocampus, Neuroplasticity, Depression

(J ECT 2014;00: 00–00)

There is decreased dendritic arborization and synaptogenesis in the hippocampus in stressed animals and in animal models of electroconvulsive shocks (ECSs) on the hippocampus. The images show representative coronal sections of the CA1 region of the hippocampus, taken at the same level, in nonstressed adult male Wistar rats (180–250 g) that received 6 once-daily ECSs in each of 3 conditions: sham ECS (n = 10), low-dose ECS (10 mC) (n = 10), or high-dose ECS (40 mC) (n = 10). All rats receiving true ECS experienced generalized convulsions of adequate duration. No rats were lost to spinal fracture or other reasons. The rats were housed under standard laboratory conditions for 1 month after the last sham or true ECS and were subsequently sacrificed for study of persistent hippocampal changes.

The mean length of the apical dendritic tree was significantly greater in rats receiving 40 mC ECS (Fig. 1) than in those receiving 10 mC ECS (Fig. 2) and significantly greater in rats receiving 10 mC ECS than in those receiving sham ECS (Fig. 3). The implication is that electroconvulsive therapy may dose-dependently restore the hippocampal neuroplasticity that is lost in depression, thereby explaining at least a part of the mechanism of...
Images in Electroconvulsive Therapy

ECS Dose-Dependently Increases Cell Proliferation in the Subgranular Region of the Rat Hippocampus

Jangama S. M. Smitha, MSc (Medical Anatomy), * Ravindranath Roopa, MBBS, MS (Anatomy), *
BK Chandrasekhar Sagar, PhD, † Bindu M. Kutty, PhD, ‡ and Chittaranjan Andrade, MD §

Abstract: Stress and depression are associated with impaired neuroplasticity in the hippocampus; there is a decrease in neurogenesis, which is hypothesized to decrease the adaptative competence of the organism. Representative light microscopy images are presented which show that 6 once-daily electroconvulsive shocks (ECS) once daily, dose-dependently increased new cell formation in the subgranular region of the hippocampus in healthy adult male Wistar rats (10 sections per rat, 3 rats in each of sham ECS, 10 mC, and 40 mC groups). These neuroplasticity changes, demonstrated 1 month after the last ECS, may explain a part of the mechanism of action of electroconvulsive therapy in conditions such as depression.

Key Words: electroconvulsive therapy, electroconvulsive shocks, hippocampus, neuroplasticity, neurogenesis, depression

(J ECT 2014;00: 00–00)
Electroconvulsive Therapy Attenuates Dendritic Arborization in the Basolateral Amygdala

Nagarchi Khaleel, MSc (Medical Anatomy),* Ravindranath Roopa, MBBS, MS (Anatomy),* Jangama S.M. Smitha, MSc (Medical Anatomy),* and Chittaranjan Andrade, MD†

Abstract: Stress and depression are associated with aberrant neuroplasticity in the amygdala: there is increased dendritic arborization and synaptogenesis, perhaps explaining the increased anxiety and fear that are often apparent in depressed patients. Light microscopy images are presented, which show that 6 once-daily high (but not low)-dose electroconvulsive shocks attenuated dendritic arborization in the basolateral amygdala of Wistar rats, which changes were apparent even 1 month after the last electroconvulsive shock. These changes may explain a part of the mechanism of action of electroconvulsive therapy in conditions such as depression and posttraumatic stress disorder.

There is increased dendritic arborization and synaptogenesis in the amygdala in stressed animals and in animal models of depression. It is suggested that these changes represent fear learning and explain the anxiety, fear, and related dysfunctional moods experienced by depressed patients.1 What is the effect of electroconvulsive therapy (ECT) on these changes? Figure 1 displays representative coronal sections of the basolateral amygdala, taken at the same level, in nonstressed male Wistar rats (180–250 g) receiving 6 once-daily electroconvulsive shocks (ECS) in each of 3 conditions: sham ECS, low-dose (10 mC) ECS, or high-dose (60 mC) ECS. The rats were housed under
Images in electroconvulsive therapy: Pilot impressions suggesting that ECT reduces excitatory synapses in the basolateral amygdala

Nagarchi Khaleel, Roopa Ravindranath, B. K. Chandrasekhar Sagar\textsuperscript{1}, Chittaranjan Andrade\textsuperscript{2}

Departments of Anatomy, St. John’s Medical College, \textsuperscript{1}Neuropathology, Electron Microscopy Laboratory, \textsuperscript{2}Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka, India

ABSTRACT

Background: In animal models, stress and depression are associated with excitatory changes in the amygdala; this aberrant neuroplasticity may represent increased fear learning, explaining the anxiety, fear, and related symptoms that characterize clinical depression.

Materials and Methods: In a pilot investigation, we treated adult, male, Wistar rats with sham electroconvulsive shocks (ECS; $n=3$), low-dose ECS (10 mC; $n=3$), and high-dose ECS (60 mC; $n=3$). The rats were sacrificed 1 month after the last of 6 once-daily ECS and, after dissection, sections of the basolateral amygdala were examined using transmission electron microscopy under low ($\times 11,000$) and high ($\times 30,000$) magnification.

Results: In each group, 4 fields were examined under low magnification and 6 fields under high magnification. The number of excitatory synapses and the ratio of excitatory to inhibitory synapses were both numerically lower with ECS than with sham ECS, and the effect was stronger in the high-dose ECS group (statistical analyses were not performed because this was a pilot study).

Conclusions: By reducing the number of excitatory synapses and the ratio of excitatory to inhibitory synapses,
E-LEARNING INITIATIVES

- Send a blank email to:
  - synergytimes-subscribe@yahoogroups.com
    - For Synergy Times, an e-newsletter on psychiatry and the allied medical and mental health sciences
  - eJCIndia-subscribe@yahoogroups.com
    - To join the Journal Club e-group of the Dept of Psychopharmacology and Indian Psychiatric Society.
ENFIN...

- That’s it, folks; thanks for listening!