DOES ECT CAUSE BRAIN DAMAGE?

[Audience, please offer opinions]

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

MISSING LINK

A Primer for the Conceptualization of the Mechanism of Action of Electroconvulsive Therapy, 1: Defining the Question

Chittaranjan Andrade, MD

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

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

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.[1] 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

A Primer for the Conceptualization of the Mechanism of Action of Electroconvulsive Therapy, 2: Organizing the Information

Chittaranjan Andrade, MD

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

Much literature is available on the effects of electroconvulsive therapy (ECT) in the brain. Clinicians need to know how to organize this information when they explain hypotheses about the mechanism of action of ECT to patients and caregivers. One possibility is to classify the data under the headings of delivery

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

Electroconvulsive Therapy, Hypertensive Surge, Blood-Brain Barrier Breach, and Amnesia

Exploring the Evidence for a Connection

Chittaranjan Andrade, MD and Tom G. Bolwig, MD, DMSc†*

Abstract: Preclinical and clinical evidence show that electroconvulsive therapy (ECT)-induced intraictal surge in blood pressure may result in a small, transient breach in the blood-brain barrier, leading to mild cerebral edema and a possible leach of noxious substances from blood into brain tissues. These changes may impair neuronal functioning and contribute to the mechanisms underlying ECT-induced cognitive deficits. Some but not all clinical data on the subject suggest that blood pressure changes during ECT correlate with indices of cognitive impairment. In animal models, pharmacological manipulations of blood pressure during electroconvulsive shocks attenuate electroconvulsive shock–induced amnestic changes; however, the evidence suggests that antihypertensive mechanisms may not necessarily be involved. Clinical studies involving

BP sharply increases by 30% to 40%, with systolic pressure rising more than diastolic pressure. The increase is greater in men than in women and in hypertensive patients than in normotensive patients. In some patients, especially those who receive anticholinergic medications, the systolic hypertensive surge may even exceed 200 mm Hg. There is a sharp drop in BP immediately after the seizure, and baseline or near-baseline levels are attained within a few minutes of the end of the seizure.[1,6]

ECT AND BBB BREACH

The earliest studies of the BBB during pentylenetetrazol (PTZ)- or ECT-induced convulsions were conducted in animal

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 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,[1,2] 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)

show representative coronal sections of the subgranular region of the hippocampus taken at the same level in nonstressed adult male Wistar rats (180–250 g) which received 6 ECSs once daily in each of 3 conditions: sham ECS (n = 3), low-dose (10 mC) ECS (n = 3), or high-dose (40 mC) ECS (n = 3). 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 30 days after the last sham or true ECS and were subsequently sacrificed for the study of new cell formation.

Ten BrdU-stained sections were examined per rat, and the number of new cells identified in these sections was averaged for each rat. The mean number of new cells was significantly greater in rats receiving 40 mC ECS (Fig. 1A) than in those receiving 10 mC ECS (Fig. 1B) and significantly greater in rats receiv-

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[1], Chittaranjan Andrade[2]
Departments of Anatomy, St. John's Medical College, [1]Neuropathology, Electron Microscopy Laboratory, [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 (×11,000) and high (×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,

TO START THE STORY WITH THE ENDING….

- No.
- So, why do people still think that ECT causes brain damage?
- Why did people think that there were weapons of mass destruction in Iraq?
- Lies
- Misinformation.
- ECT and brain damage as a parallel.

QUESTION

What is brain damage?

WHAT BRAIN DAMAGE IS

- CT/MRI evidence of atrophic change?
- Histological evidence of neuronal loss?
  - Question: What is the most powerful inducer of neuroplasticity in the brain?
- Chemical evidence of neuronal damage?
- Evidence of neuropsychological deficits?
  - Comment: Most psychotropic drugs, or even just missing a few hours of sleep, also cause neuropsychological deficits.

DOES ECT CAUSE BRAIN DAMAGE?

- Psychiatrists in the USA: Yes, 41%; No, 26%
  (APA, 1978)
- Psychiatrists in India: Yes, 38%; No, 30%
  (Agarwal and Andrade, 1997)
- Medical students in India: Yes, 19%
  (Andrade and Rao, 1996)

MISSING LINK

REASONS FOR MISINFORMATION

- "Electricity is passed through the brain; surely that must damage the brain."
  - Electric chair imagery.
  - Depiction of ECT effects in movies
  - Amnestic effect of ECT
  - Epilepsy and brain damage
- Peter Breggin sort of testimonies.
- Some historical literature in animals and humans suggests that ECT may result in adverse CNS changes.

REFUTATION: 1

- Animal studies which demonstrated that ECT is associated with adverse structural CNS effects were riddled with methodological shortcomings:
- E.g. Use of nonrepresentative ECT stimuli.
- E.g. Use of faulty tissue fixation techniques.

REFUTATION: 2

- Human data were not longitudinally obtained.
- Consider: Gross and cytoarchitectural brain changes are known to characterize depression, bipolar disorder, and schizophrenia.
- Case reports could have been due to chance co-occurrence.
- In the absence of longitudinal evaluations, brain changes cannot and should not be attributed to ECT.

REFUTATION: 3

- Epilepsy is an inappropriate parallel.
- Epilepsy often develops in children.
- Brain damage may be the cause (and not the result) of the seizures;
- Head injury may result from loss of consciousness and falls.
- There is no oxygenation or airway maintenance during a seizure.
- Status epilepticus may occur.

REFUTATION: 4

- Functional impairments are not an indictment.
- ECT causes cognitive impairments; but so do benzodiazepines, antipsychotics, and most other psychotropic drugs.
- ECT causes transient neurological impairments; but so do antipsychotic drugs (e.g. lateralized neurological signs after UL ECT, EPS with antipsychotic drugs).
- ECT may cause persistent amnesia; but antipsychotics may cause persistent TD.

MISSING LINK

DOES ECT ALTER BRAIN STRUCTURE?

- Cross-sectional CT (Kolbeinsson et al, Acta Psychiatr Scand 1986) and prospective MRI (Coffey et al, Am J Psychiatry, 1988; Pande et al, Biol Psychiatry 1990) studies show no evidence of ECT-induced structural changes.
- Properly conducted animal studies, including studies using quantitative cell counts, show no evidence of neuronal loss even after prolonged courses of ECT (Devanand et al, Am J Psychiatry, 1994)

MISSING LINK

DOES ECT ALTER BRAIN STRUCTURE?

- A large body of literature shows that there is a wide margin of safety between the stimulus intensity and stimulus duration with conventional ECT and the stimulus settings at which irreversible neuronal damage occurs.
- Dozens of closely spaced ECT, or hours of seizure activity if ventilation is supported, are required for brain damage to develop.

Devanand et al, Am J Psychiatry (1994)

OTHER CONCERNS ARE NOT CONCERNS

- Disruption of the blood-brain barrier results in minor, transient edema without neuropathological changes.
- Thermal changes with ECT are negligible and are far less than those during infection.

Devanand et al, Am J Psychiatry (1994)

THOUGHT

- If ECT did cause structural brain damage, it could only do so through hypoxic-ischemic mechanisms. [The brevity of the seizure makes excitotoxicity unlikely.]
- The Purkinje cells in the cerebellum are as sensitive as those in the hippocampus to hypoxic-ischemic mechanisms.
- ECT-treated patients do not develop signs of cerebellar impairment!

GOING FOR THE RECORD

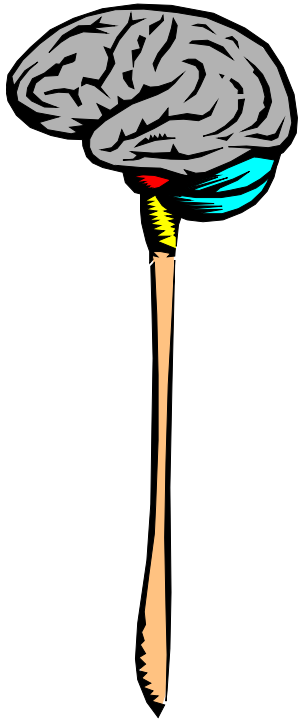
- An 89-year-old bipolar white woman received >1250 documented ECTs and a further, unsubstantiated 800 ECTs across 26 years.
- Gross and microscopic brain changes at post-mortem were actually LESS than those that could have been expected on the basis of her age.
- There was no aberrant gliosis nor hypoxic changes in the hippocampus, cerebellum, or other brain structures.

Lippman et al, Br J Psychiatry (1985)

OTHER STUDIES

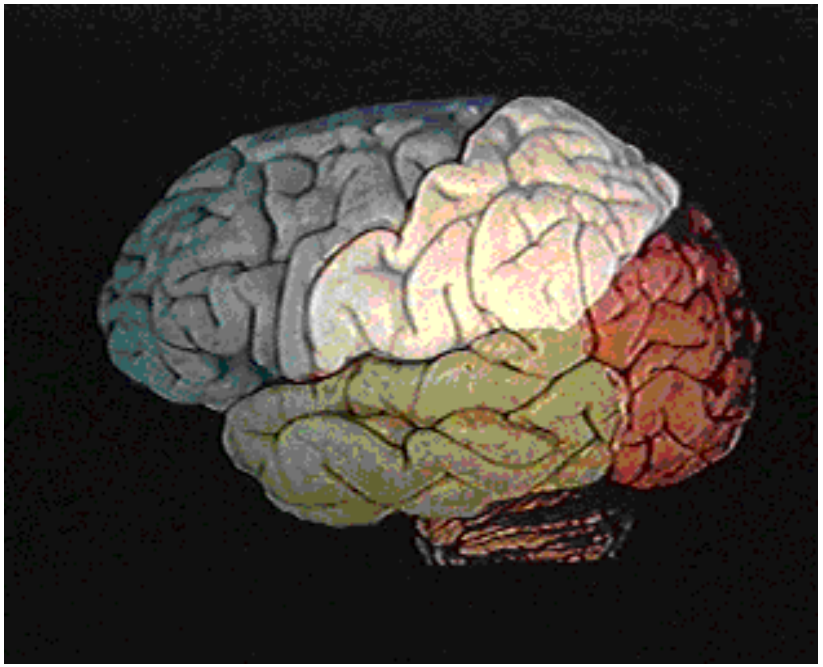
- A 92-year-old woman received 91 ECTs during life. There were no abnormal neuropathological changes evident on postmortem (Scalia et al, J ECT 2007).
- Serum markers of brain cell damage (e.g. CPK-BB) and inflammation (e.g. CRP) are not elevated by a single ECT treatment immediately after ECT and for as long as up to 3 days later (Giltay et al, World J Biol Psychiatry 2008).

WHAT THE LAST DECADE OF RESEARCH HAS SHOWN

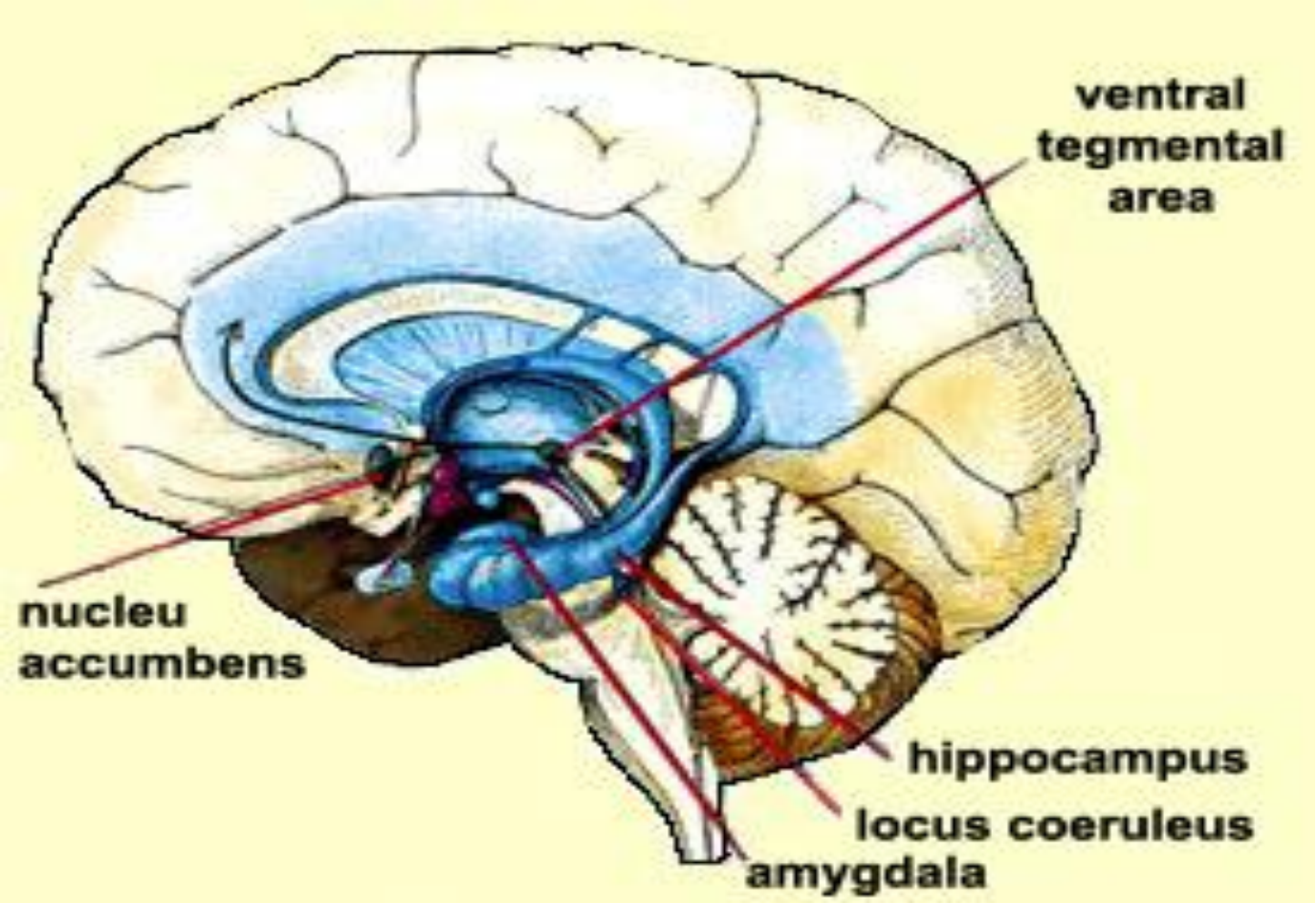


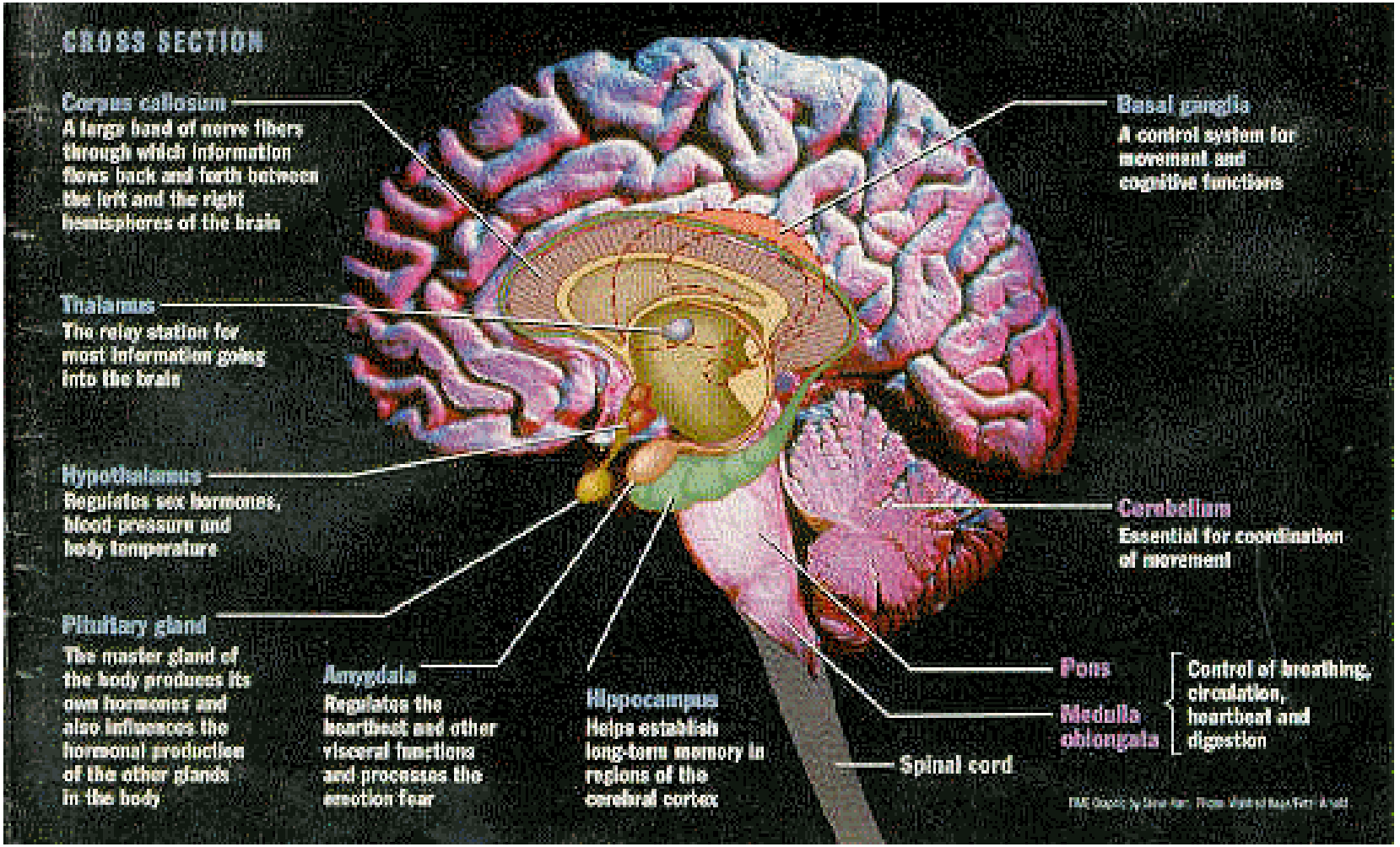
- Rather than induce neuronal damage, ECT actually stimulates neuroplasticity.
- ECT, in fact, may be the most potent inducer of neuroplasticity in psychiatry.

LOBES OF THE BRAIN

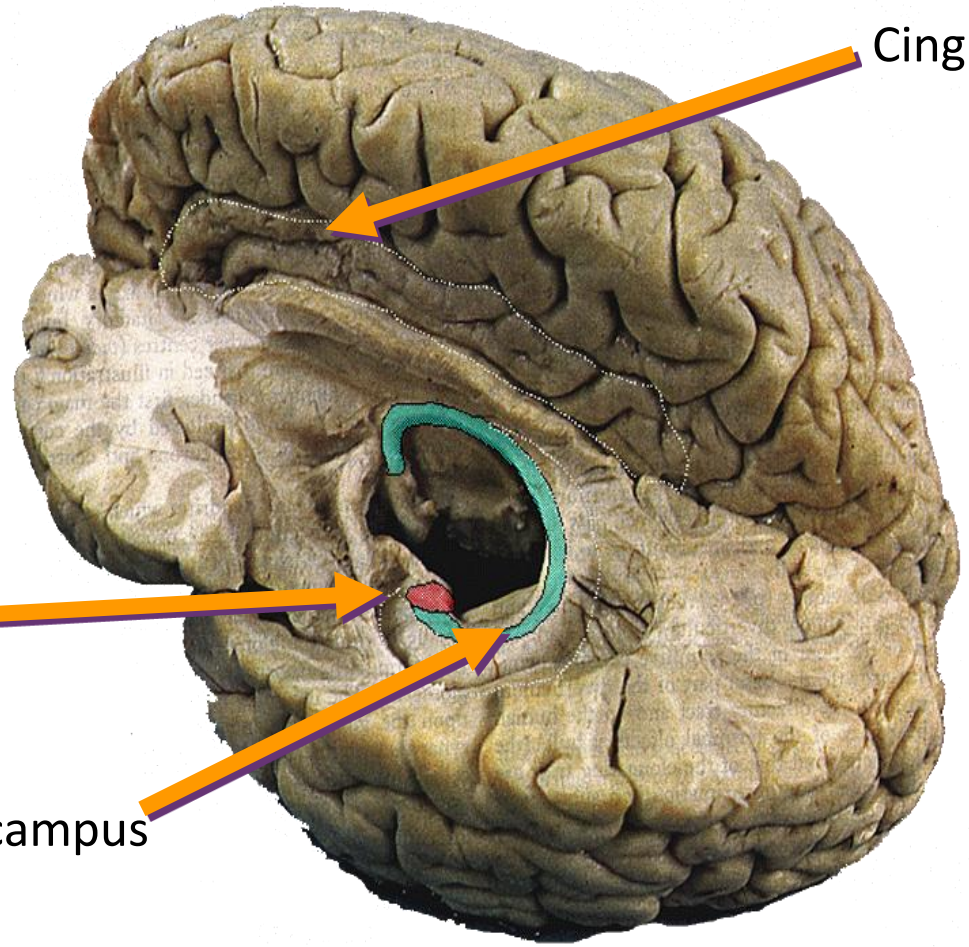


- Prefrontal cortex (PFC)
- Dorsolateral PFC
- Ventromedial PFC
- Orbitofrontal PFC


ventral
tegmental
area
nucleu
accumbens
hippocampus
locus coeruleus
amygdala


CROSS SECTION
Corpus callosum
A large band of nerve fibers through which information flows back and forth between the left and the right hemispheres of the brain
Basal ganglia
A control system for movement and cognitive functions
Thalamus
The relay station for most information going into the brain
Hypothalamus
Regulates sex hormones, blood pressure and body temperature
Cerebellum
Essential for coordination of movement
Pituitary gland
The master gland of the body produces its own hormones and also influences the hormonal production of the other glands in the body
Amygdala
Regulates the heartbeat and other visceral functions and processes the emotion fear
Hippocampus
Helps establish long-term memory in regions of the cerebral cortex
Pons
Medulla oblongata
Control of breathing, circulation, heartbeat and digestion
Spinal cord

AMYGDALA AND HIPPOCAMPUS



SOME BASIC CONCEPTS

- Hippocampus = dentate gyrus + Ammon's horn (CA4, CA3, CA2, CA1) + subiculum + presubiculum and parasubiculum.
- Neurogenesis occurs in the subgranule layer of the dentate gyrus; the new cells migrate into the granule layer.
- Granule cells of the DG send their axons (called "mossy fibers") to CA3.

INTRODUCTORY NOTE

- There are about 1011 neurons in the human brain.
- On average, each neuron synapses with about 1000 other neurons.
- There are about 1014 synapses in the human brain.
- The brain is more socialized than homo sapiens is!

MISSING LINK

NOTE

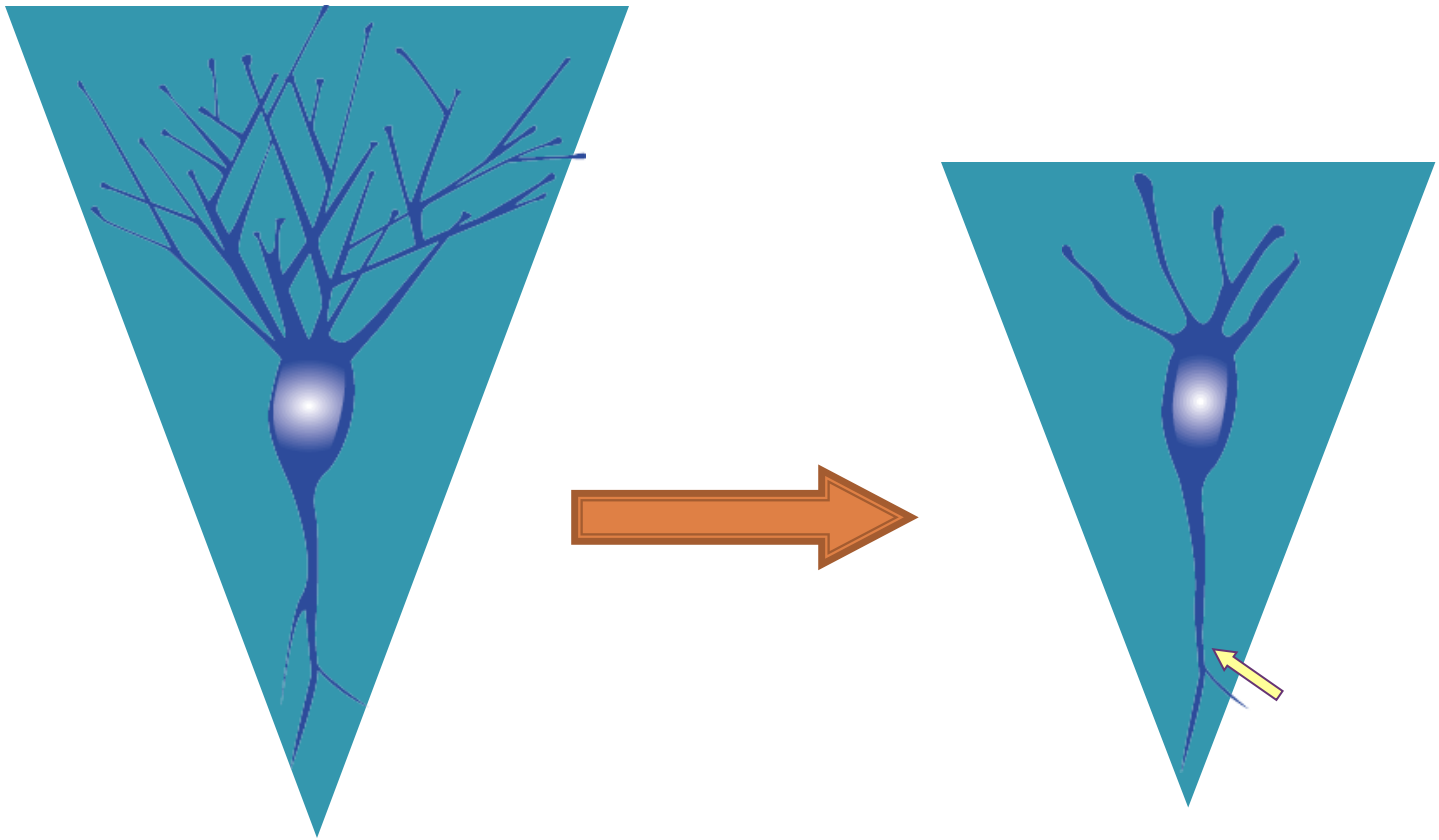
- We are more powerful, and less vulnerable, when we are more socialized.
  - When there are more of us
  - When we are better connected
- Likewise, the functional capacity of the brain depends on
  - The number of nerve cells
  - The connectivity of these nerve cells

STRESS AND DEPRESSION

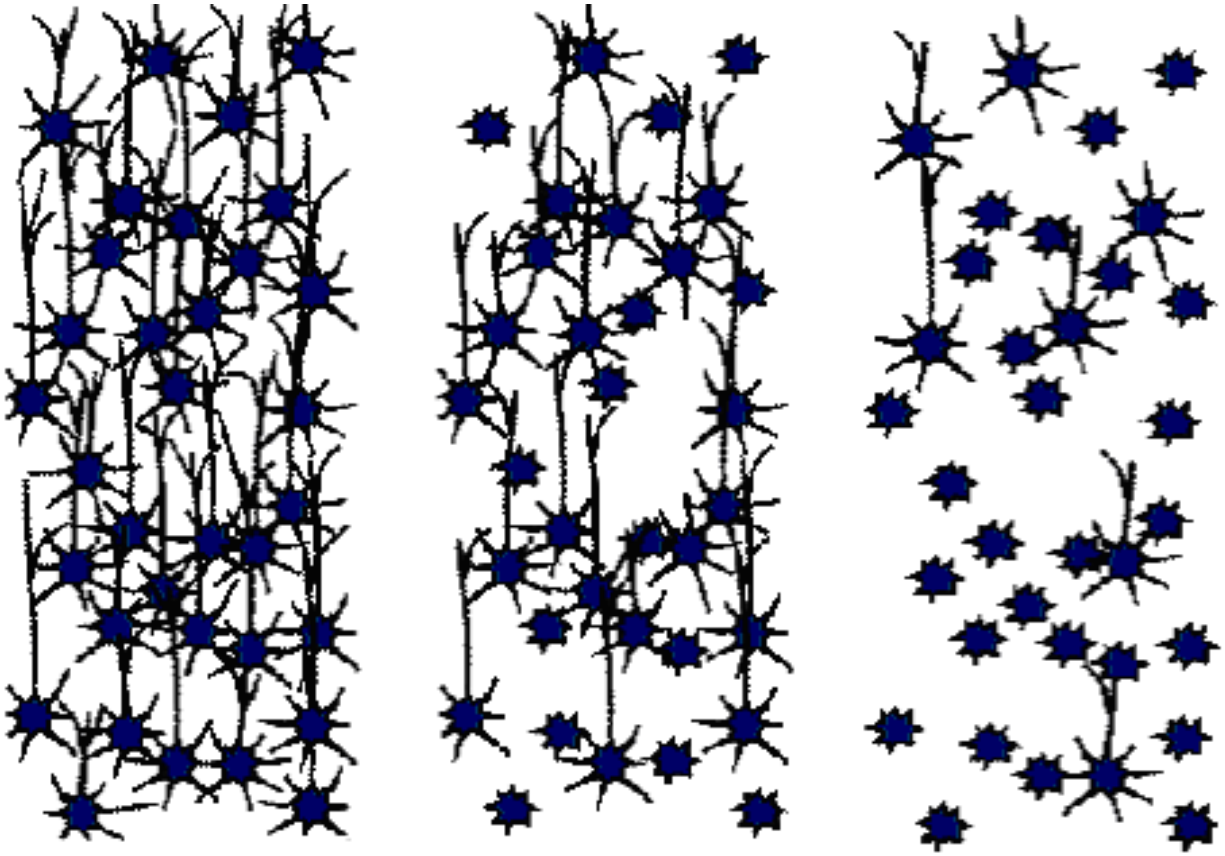
(Andrade and Rao, Indian J Psychiatry 2010)

- Stress and depression are associated with decreased neuroplasticity in the hippocampus and PFC, and increased neuroplasticity in the amygdala.
  - Preclinical and clinical evidence
  - Gross and microscopic evidence
- Antidepressants reverse most of these changes.
  - Neurogenesis
  - Dendritic arborization, new synapse formation
  - Gliogenesis
  - Implications

EFFECTS OF EXCESSIVE STRESS:
DECREASED DENDRITIC ARBORIZATION



EFFECTS OF EXCESSIVE STRESS: REDUCED SYNAPTIC DENSITY



ECT AND NEUROPLASTICITY
Hippocampus: 1

- ECS induces nerve cell proliferation in the hippocampus.
- The number of new neurons formed increases with an increase in the number of ECT.
- The new neurons differentiate and survive for at least 3 months.

(Scott et al, Exp Neurol 2000; Madsen et al, Biol Psychiatry 2000; Hellsten et al, Eur J Neurosci 2002)

ECT AND NEUROPLASTICITY
Hippocampus: 2

- Whereas glucocorticoids inhibit neurogenesis, ECS-induced hippocampal neurogenesis occurs even after chronic treatment with cortisol.
- This implies that ECT would stimulate hippocampal neurogenesis even in the presence of stress-induced hypercortisolemia.

(Hellsten et al, Eur J Neurosci 2002)

ECT AND NEUROPLASTICITY
Hippocampus: 3

- Whereas glucocorticoids also inhibit gliogenesis, ECS-induced hippocampal gliogenesis occurs even after chronic treatment with cortisol.
- This implies that ECT would stimulate hippocampal gliogenesis even in the presence of stress-induced hypercortisolemia.

(Wennstrom et al, Biol Psychiatry 2002)

ECT AND NEUROPLASTICITY
Hippocampus: 4

- ECS also stimulates vascular endothelial proliferation in the hippocampus.
- This probably supports the new neurons and glia that are formed after ECS.

  (Hellsten et al, Biol Psychiatry 2004; Newton et al, Eur J Neurosci 2006)
- This endothelial response is due to the ECS itself, and not to the hypoxia associated with unmodified ECS

  (Hellsten et al, 2005).

ECT AND NEUROPLASTICITY
Amygdala

- Repeated ECS induces glial cell proliferation in the amygdala.
- The proliferation remains evident 3 weeks later, when some of the new cells show differentiation into mature oligodendrocytes

(Wennstrom et al, Biol Psychiatry 2004)

ECT AND NEUROPLASTICITY
Prefrontal cortex and hypothalamus

- Repeated ECS stimulates vascular and glial (but not neuronal) proliferation in the frontal cortex

  (Madsen et al, Neuropsychopharmacol 2005).

- Repeated ECS-induced increase in neuronal activation and associated endothelial proliferation has also been recorded in the paraventricular nucleus, the supraoptic nucleus, and the ventromedial nucleus of the hypothalamus (Jansson et al, Biol Psychiatry 2006).

AFTER 10 ONCE-DAILY ECT: 1

(Chen et al, Eur Neuropsychopharmacol 2009)

- ECT increased the volume of the granule cell layer and hilus of the dentate gyrus.
  - [No change in the volume of the pyramidal cell layer in CA1 and CA2/CA3, or of the stratum radiatum in CA1.]
- ECT increased the number of neurons in the granule cell layer.
  - [No change in the number of neurons in CA1 and CA2/CA3.]

AFTER 10 ONCE-DAILY ECT: 2

(Chen et al, Eur Neuropsychopharmacol 2009)

- ECT increased the total number of synapses in CA1.
- ECT increased the number and percentage of spine synapses in CA1.
  - [No change in the number of shaft synapses; decrease in the percentage of shaft synapses, indicating synaptic remodelling.]
  - Note: Excitatory synapses are mostly formed on dendritic spines; and spine synapses are architecturally more efficient than shaft synapses.

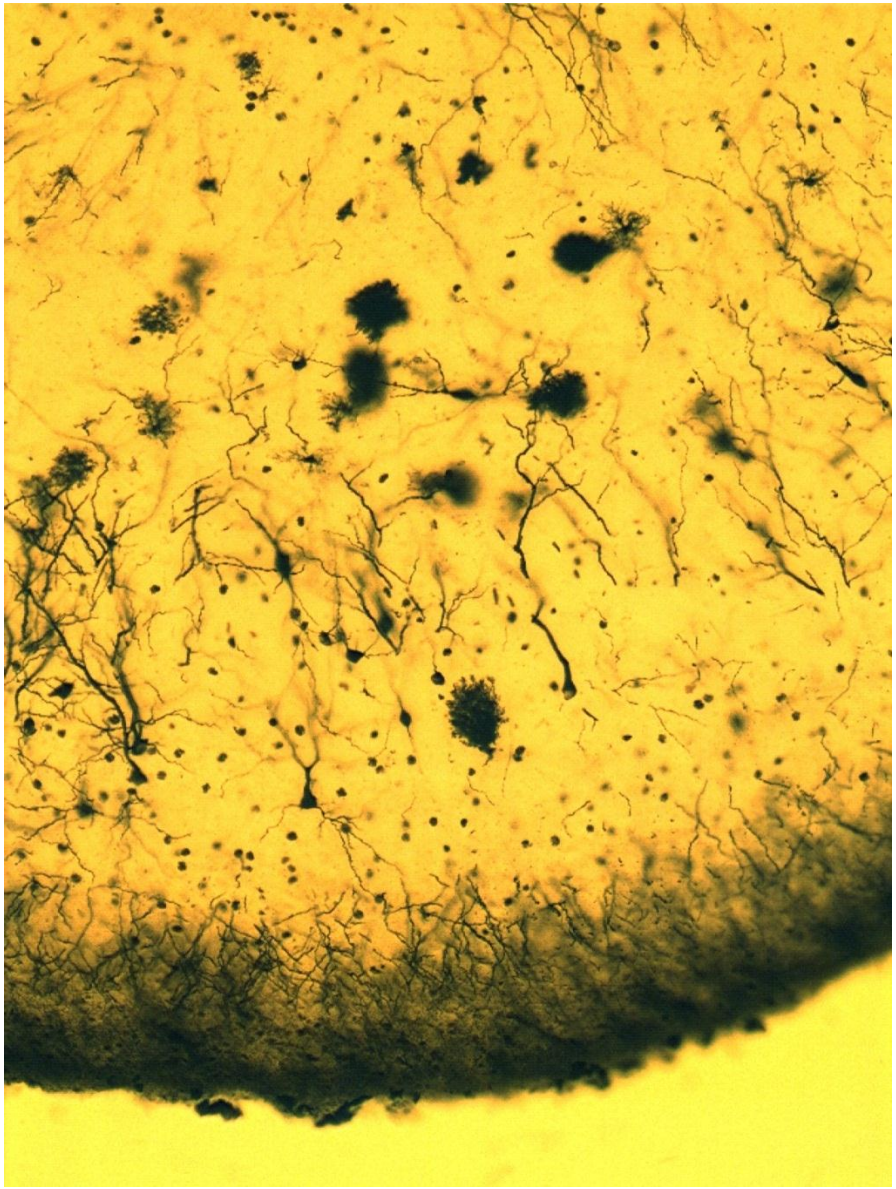
AFTER 10 ONCE-DAILY ECT: 3

(Chen et al, Eur Neuropsychopharmacol 2009)

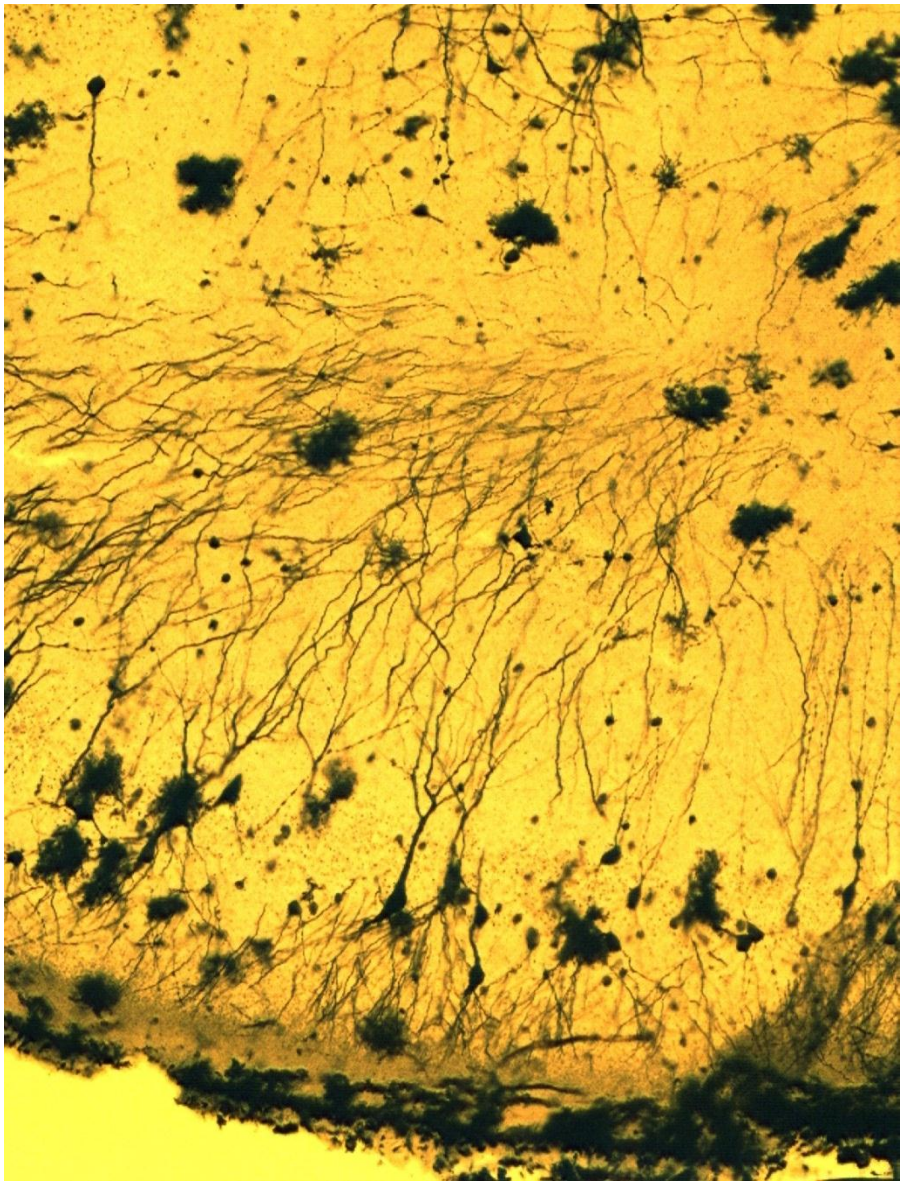
- Both perforated and nonperforated spine synapses were increased in CA1.
  - Note: Perforated synapses show greater synaptic efficiency; and they may split into two or more nonperforated synapses.
- ECT increased synaptic height in CA1.
  - Note: Increased synaptic height may improve the efficiency of synaptic remodelling.

ECT, Hippocampus, and Amygdala

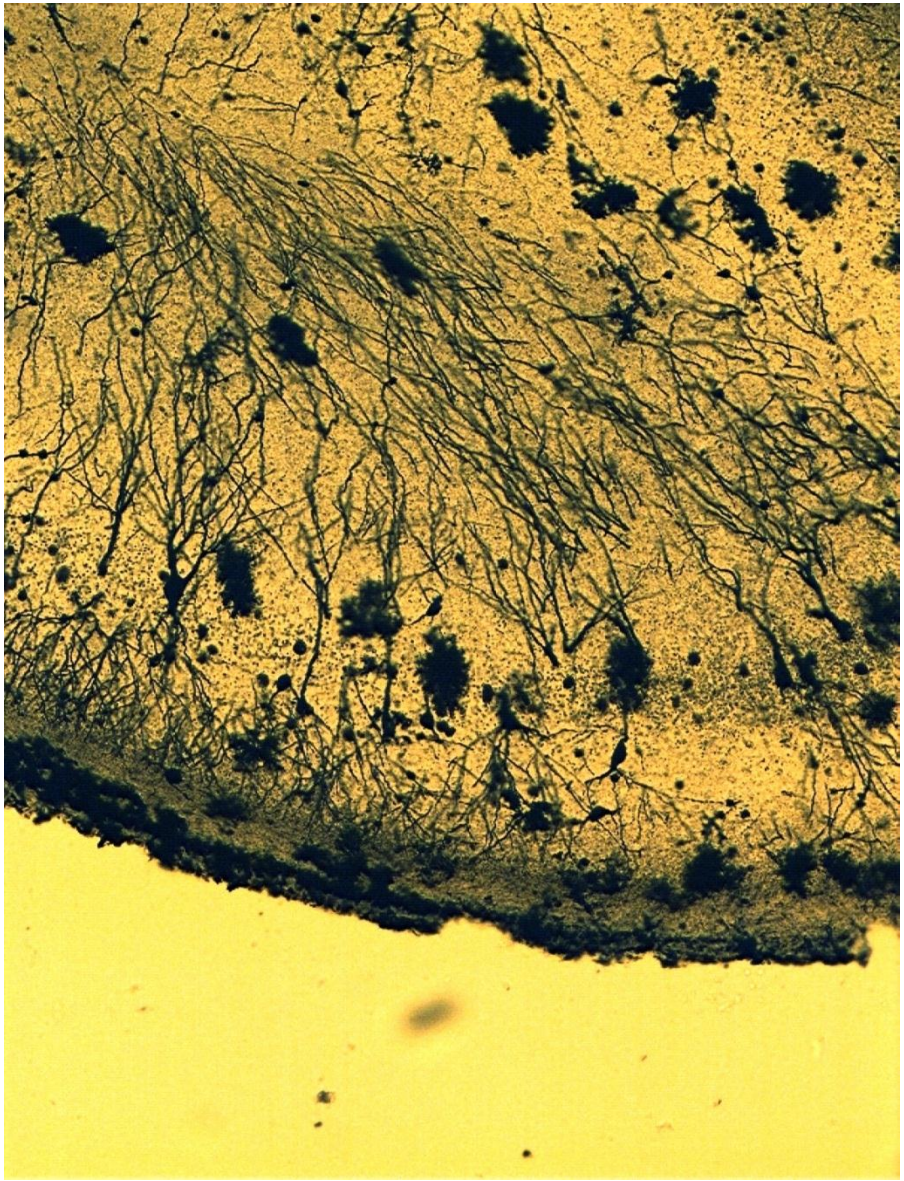
- Adult, male, Wistar rats
- 6 once-daily sham, 10 mC, or 40/60 mC ECS
- Animals sacrificed 1 month after the last ECS
- Hippocampus studied:
  - Pyramidal neurons in CA1: Light microscopy at 10x
  - BrdU staining in subgranular zone of DG: Light microscopy at 40x
- Basolateral amygdala studied
  - Apical dendrite and nodes: Light microscopy at 40x
  - Synapses: Electron microscopy @ 11,000x and 30,000x



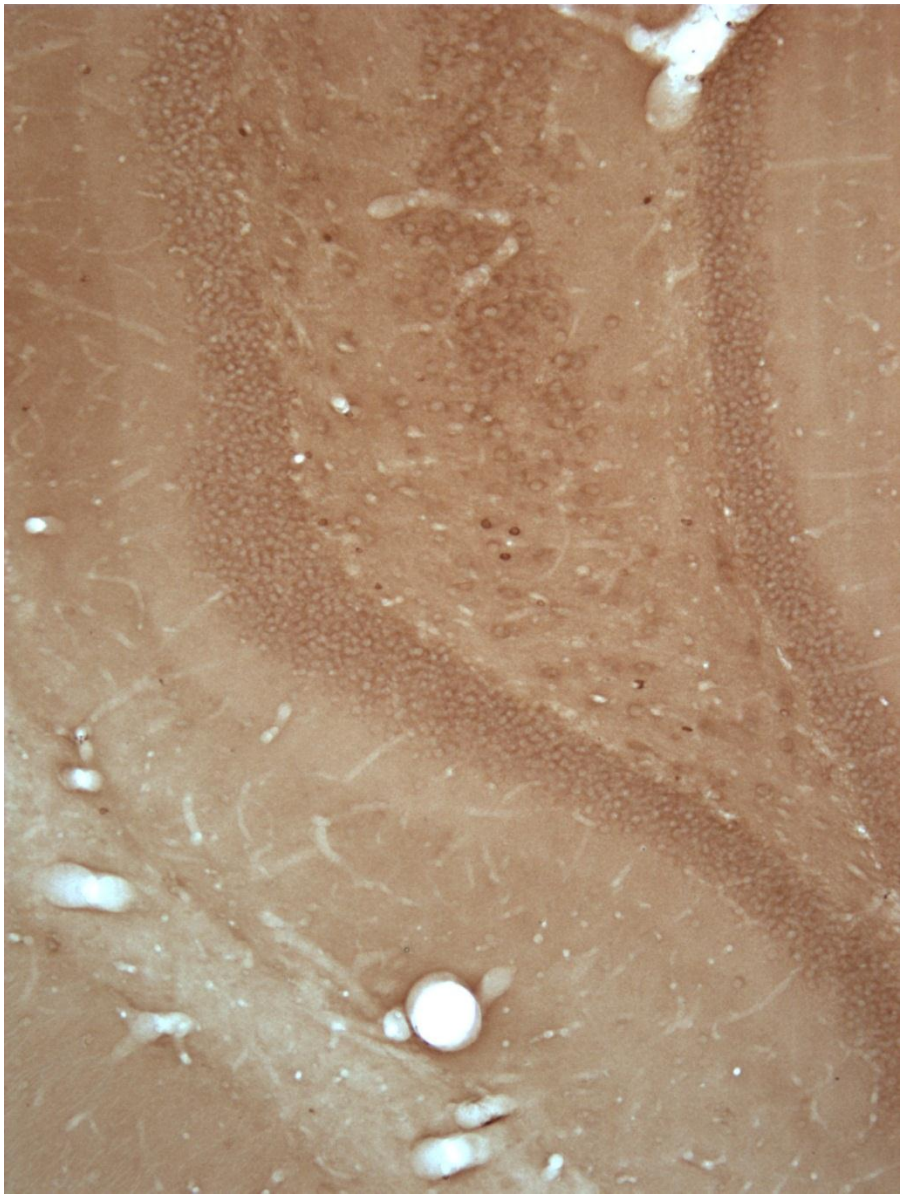
- Pyramidal neurons showing dendritic arborization.
- 6 once-daily sham ECS
- 10x magnification



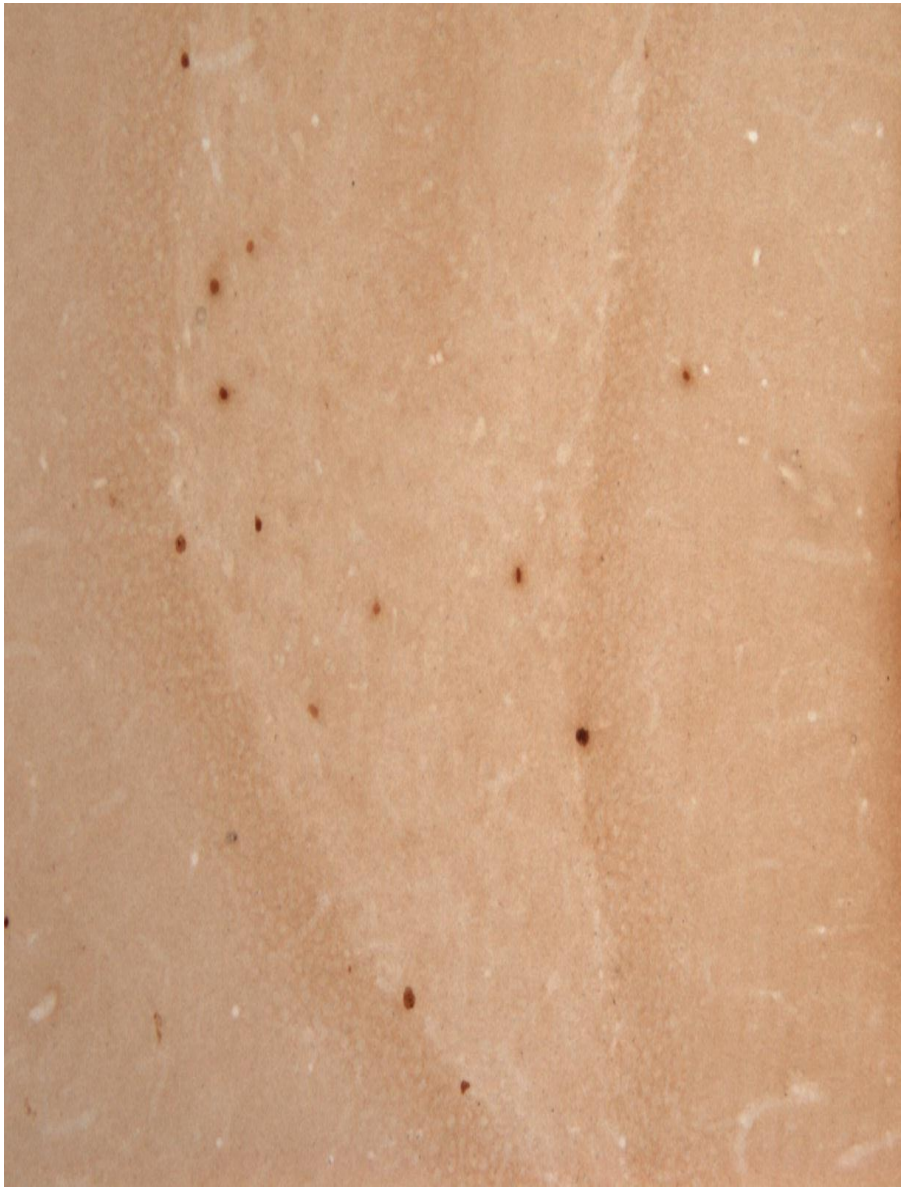
- Pyramidal neurons showing dendritic arborization.
- 6 once-daily 10 mC ECT
- 10x magnification



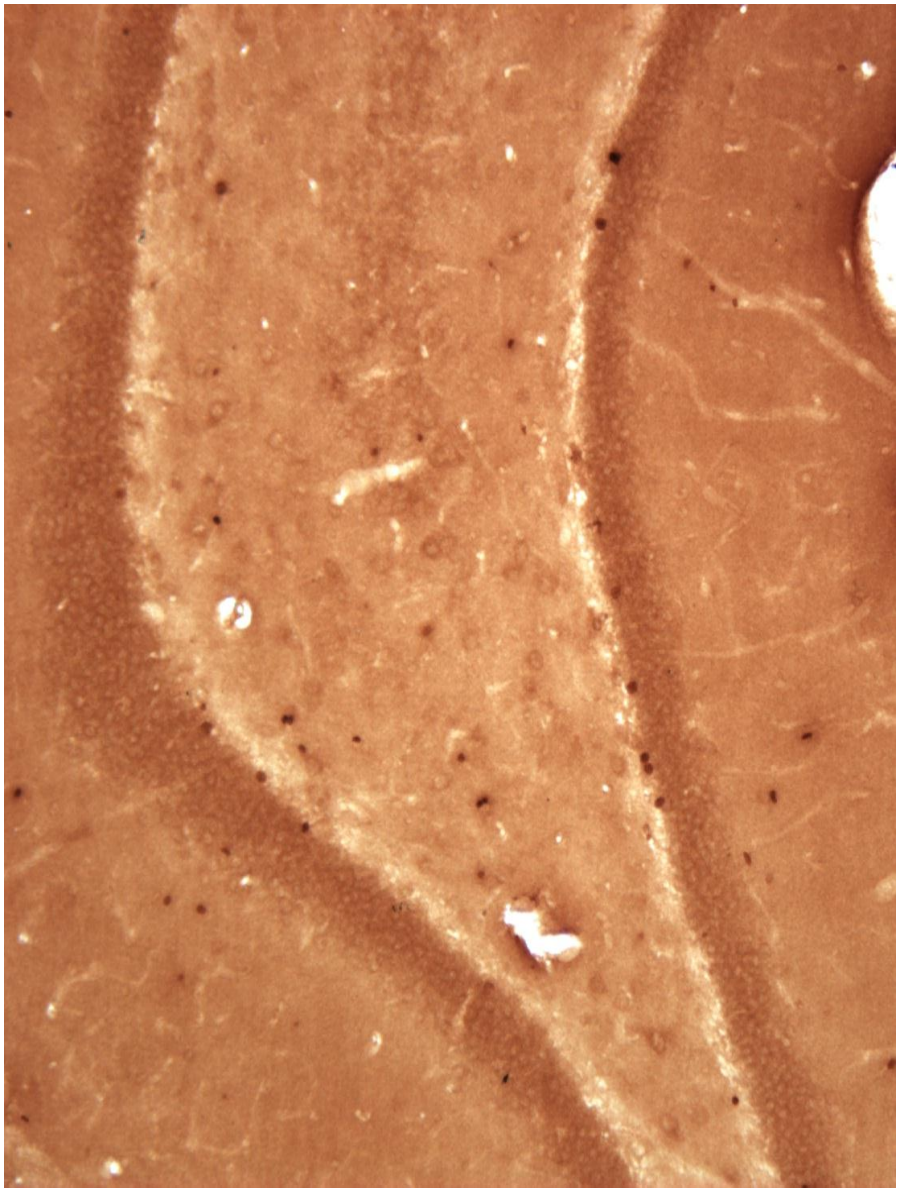
- Pyramidal neurons showing dendritic arborization.
- 6 once-daily 40 mC ECS
- 10x magnification



- 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



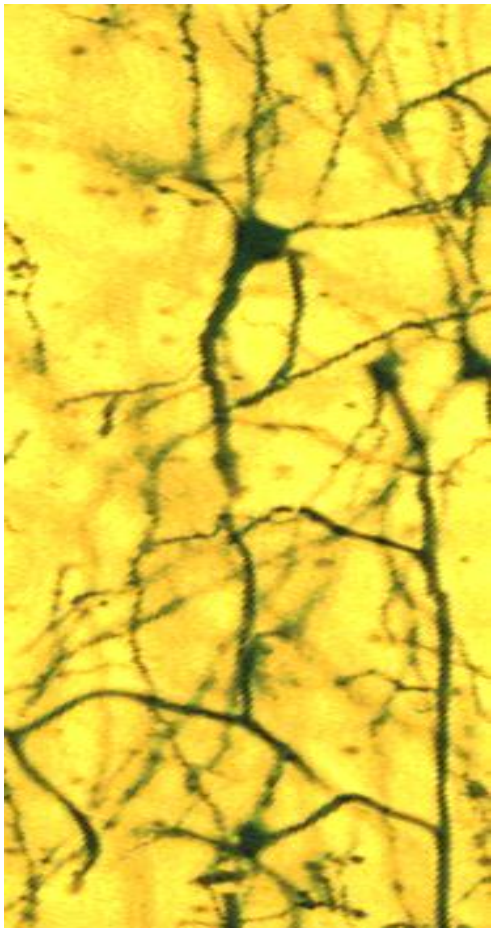
- BrdU stained new cells formed in the subgranular zone of the dentate gyrus.
- 6 once-daily 40 mC ECS
- 40x magnification

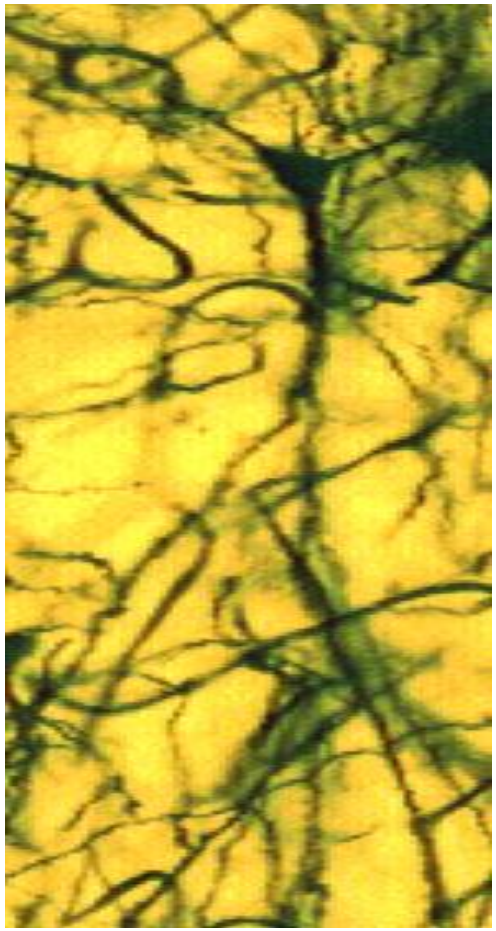
HIPPOCAMPAL CHANGES AFTER 6 ONCE-DAILY SHAM, 10 mC or 40 mC ECS

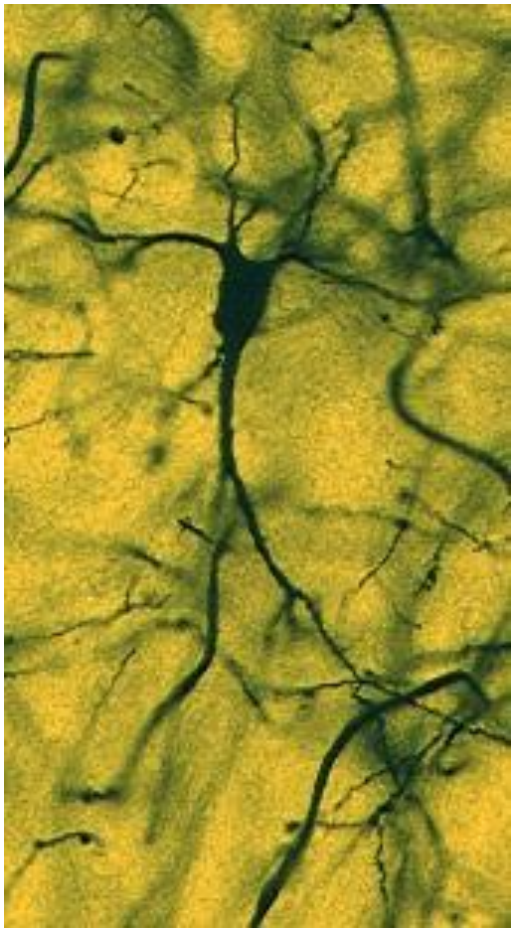
- ECS is associated with dose-dependent:
  - Increase in dendritic arborization
  - Increase in new cell formation
  - [Differentiation of these new cells not studied]
- Implications
  - Favors adaptative learning, coping?
  - Impairs memory by disturbing existing networks?
  - Mossy fibre sprouting may have the same effect

(Lamont et al, Br Res 2001; Akers et al, Science 2014)

AMYGDALA CHANGES AFTER 6 ECS: Sham, 10 mC, 60 mC



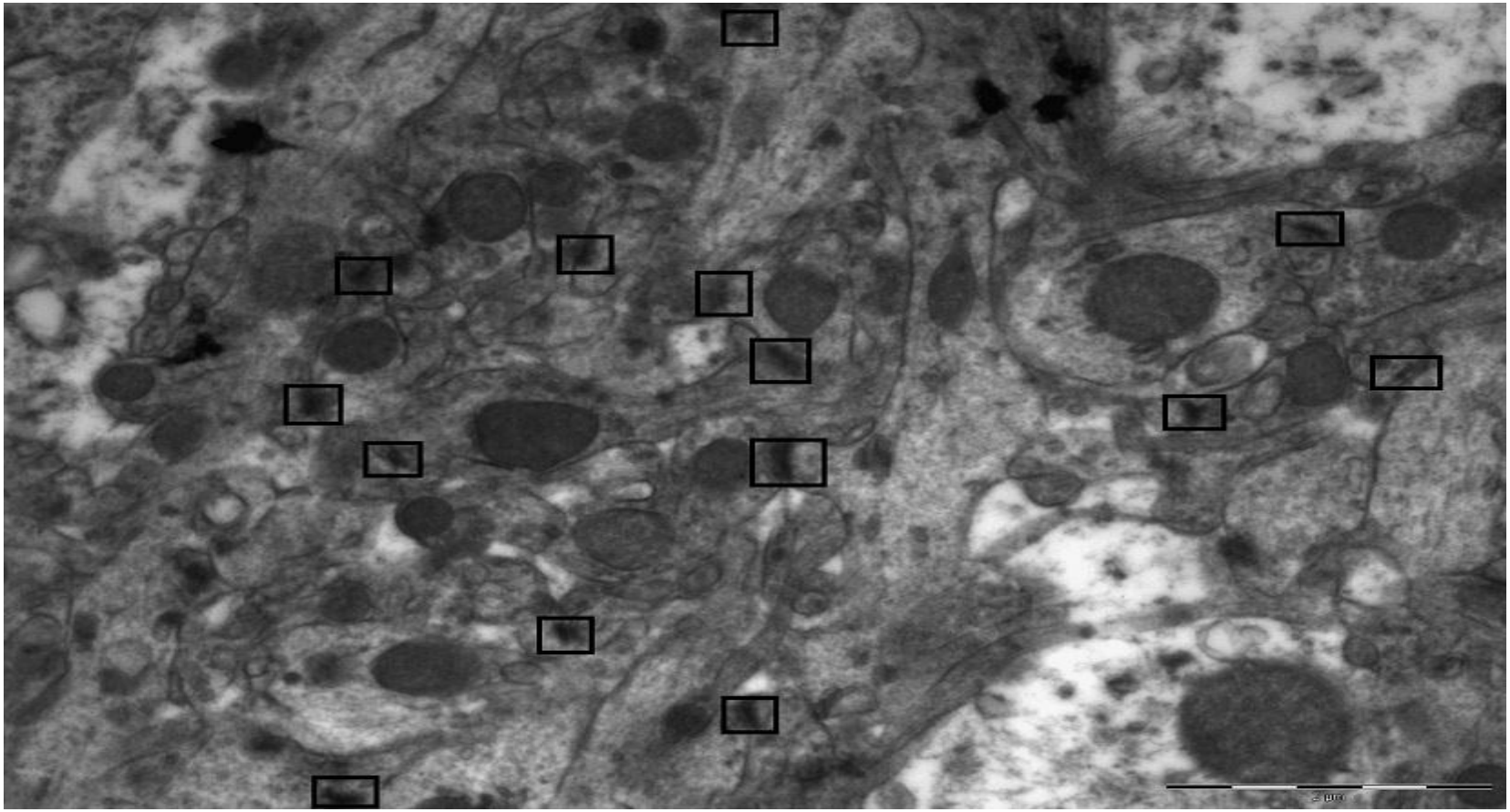




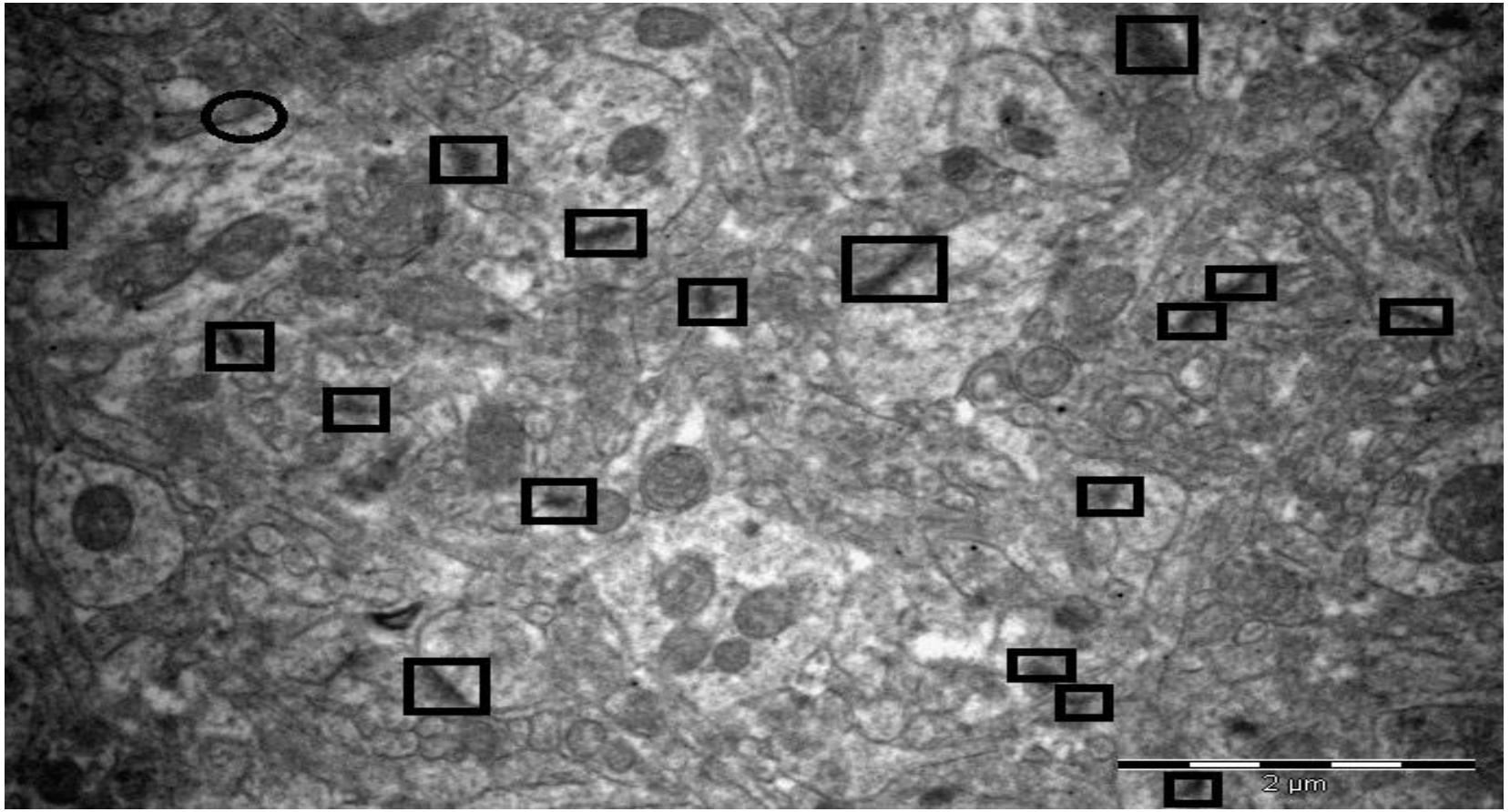
AMYGDALA CHANGES AFTER 6 ECS: Control, 10 mC, 60 mC

- Squares/rectangles: Excitatory synapses
- Circles: Inhibitory synapses
- [Differentiation based on shape – circular vs elliptical or flattened]

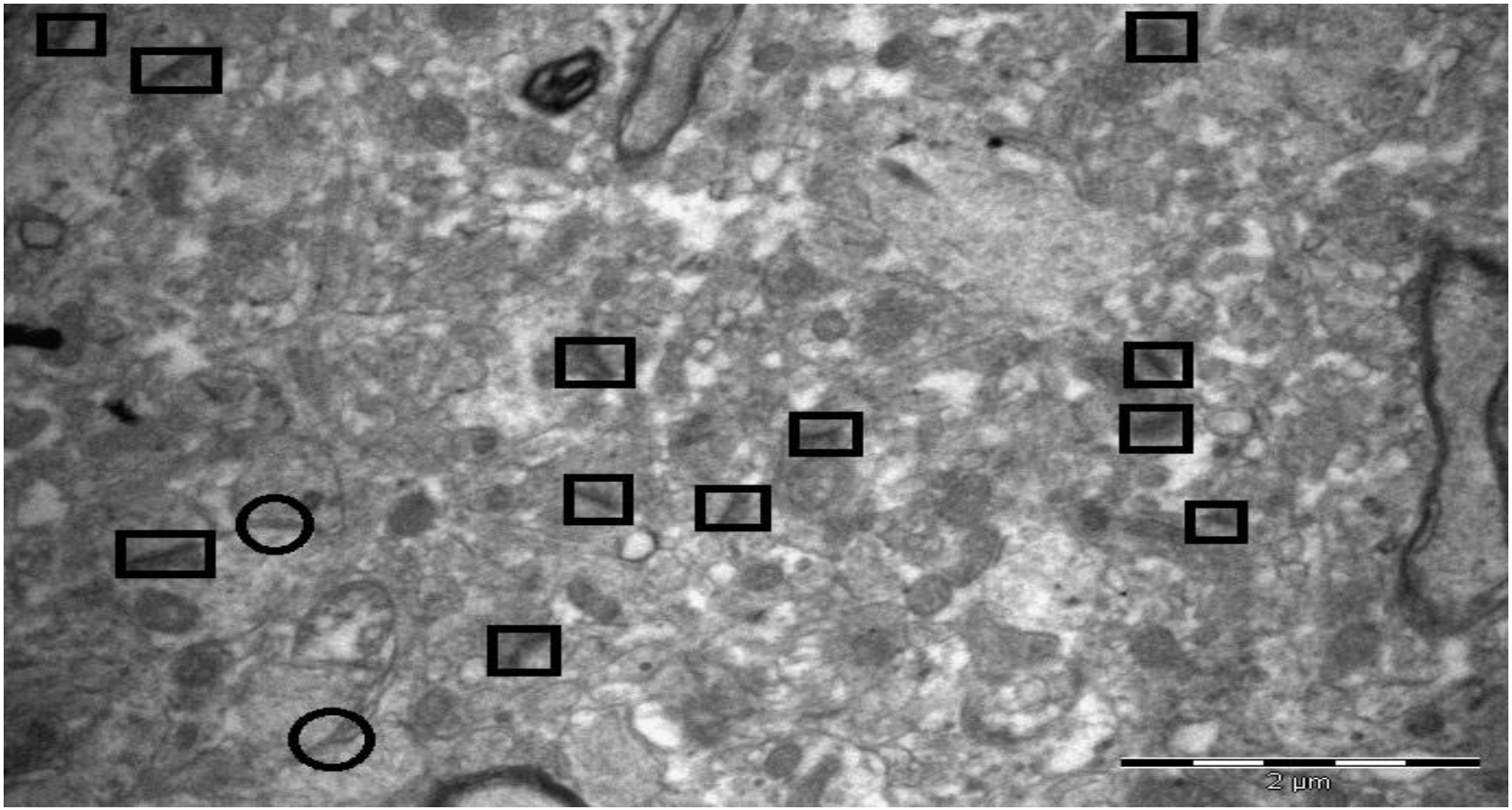
Sham ECS



10 mC ECS



60 mC ECS



AMYGDALA CHANGES AFTER 6 ECS: Control, 10 mC, 60 mC

- Apical dendritic arborization: 60 mC <(10 mC=sham)
- Dendritic nodes: Ditto
- ECS: fewer excitatory, more inhibitory synapses.
- Interpretation
  - High dose ECT may correct the aberrant amygdalar neuroplasticity that mediates fearful affect in depression and PTSD, thereby explaining the efficacy of this treatment in these disorders.
  - High dose ECT may obliterate the fearful affect associated with a stressor without affecting memory of the stressor.

THE BOTTOMLINE

- There is no convincing evidence that ECT induces structural brain damage.
- There is strong evidence that ECT, as clinically practiced, is associated with wide margins of safety in matters such as stimulus parameters and seizure duration.

THE BOTTOMLINE

- ECT is the most potent inducer of neuroplasticity in the brain, reversing the impaired neuroplasticity associated with stress, hypercortisolemia, and depression in critically important brain territories.
  - ECT increases cell proliferation 2.5-4.0 fold, compared with 1.5 fold with antidepressant drugs.
  - ECT induces neurogenesis within 3 days of a seizure; antidepressant drugs can take 2-4 weeks.
  - ECT induces both neural stem cells and neural progenitor cells; fluoxetine induces only the latter.

(Segi-Nishida, Biol Pharm Bull 2011)

MISSING LINK

PARTING NOTE:

- ECT is the only somatic therapy to have survived the advent of pharmacotherapy in psychiatry.
- [Cf psychosurgery, insulin coma therapy etc.]
- ECT remains the gold standard antidepressant treatment.
- Direct current stimulation, rTMS, vagus nerve stimulation, transcranial direct current stimulation and deep-brain stimulation have limitations and may never replace ECT.

FOR E-MAIL UPDATES ON RESEARCH IN PSYCHIATRY

- Synergytimes
- Write to
  andradec@gmail.com
  or
  andrade@nimhans.kar.nic.in

ENFIN…

THAT'S IT, FOLKS; THANKS FOR LISTENING!