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Lindner Center of HOPE | UC Health

Suicide and the Role of Electroconvulsive Therapy (ECT)

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Suicide Risk

- 9.8 million American adults has serious thoughts of suicide in 2015
- 2.7 million made suicide plans
- 1.4 million made non-fatal suicide attempts

  - Substance Abuse and Mental Health Services Association, 2019

Suicide

- Suicide is one of top 10 leading causes of death in the United States, with more than 30,000 deaths per year.
  - Rush, AJ, J Clin Psychiatry 2007; 68, 4-10

Suicide in Doctors

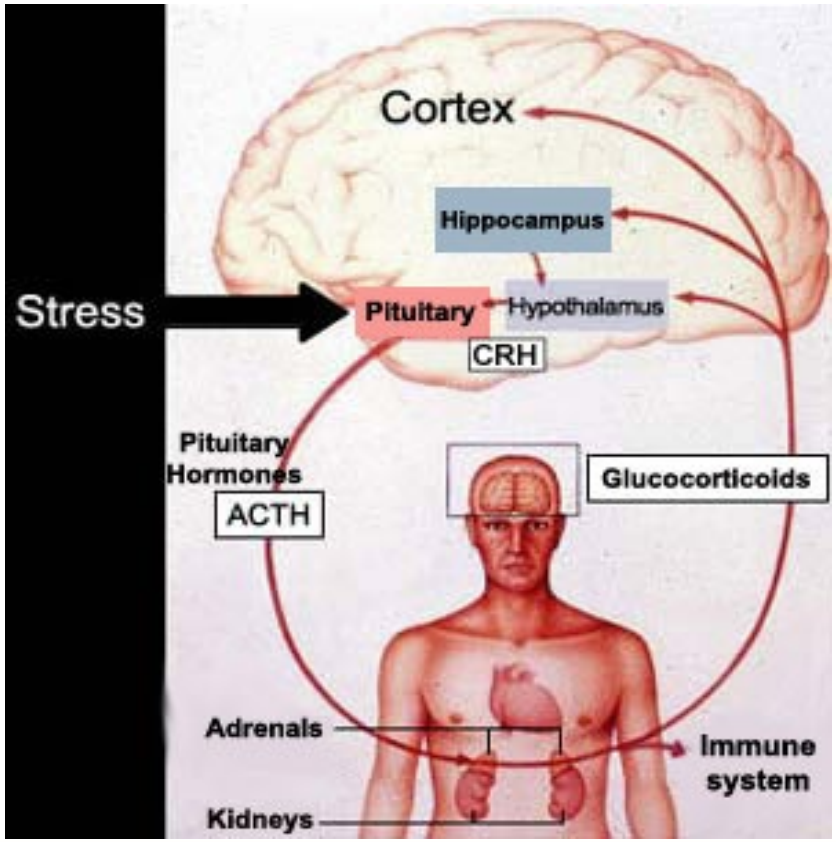
- One doctor per day commits suicide in the US.
- Highest suicide rate of any profession – 28-40 per 100,000 (more than 2 times of the general population)

  - Medscape National Physician Burnout, Depression and Suicide Report, 2019, accessed January 17, 2019

BioPsychoSocial Understanding of Suicide

Stress-Diathesis Model

- Acute Stress
  - Financial, Health, Loss
- Chronic Stress
  - Childhood maltreatment
  - Relationship problems
- Stress modifies disease-relevant biological processes in humans.
  - Depression
  - Cardiovascular disease
  - HIV/AIDS
  - Cancer



Cohen et al, Psychological Stress and Disease, *JAMA* 2007;298(14), 1685-1687

Stress and Neurodegeneration

(Neurotrophic Hypothesis)

Effect of Childhood Maltreatment

Article

Gray Matter Abnormalities in Childhood Maltreatment: A Voxel-Wise Meta-Analysis

Lena Lim

Joaquim Radua, M.D.

Katya Rubia, Ph.D.

Objective: Childhood maltreatment acts as a severe stressor that produces a cascade of physiological and neurobiological changes that lead to enduring alterations in brain structure. However, structural neuroimaging findings have been inconsistent. The authors conducted a meta-analysis of published whole-brain voxel-based morphometry studies in childhood maltreatment to elucidate the most robust volumetric gray matter abnormalities relative to comparison subjects to date.

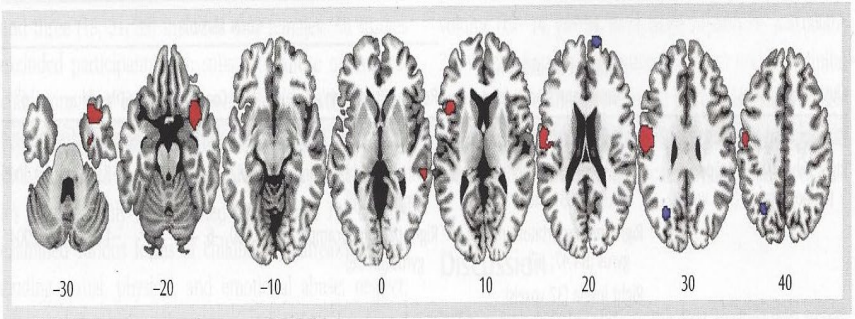
Method: Twelve data sets were included, comprising 331 individuals (56 children/adolescents and 275 adults) with a history of childhood maltreatment and 362 comparison subjects (56 children/adolescents and 306 adults). Anisotropic effect size-signed differential mapping, a voxel-based meta-analytic method, was used to examine regions of smaller and larger gray matter volumes in maltreated individuals relative to comparison subjects.

Results: Relative to comparison subjects, individuals exposed to childhood maltreatment exhibited significant smaller gray matter volumes in the right orbitofrontal/superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyri and in the left inferior frontal and postcentral gyri. They had larger gray matter volumes in the right superior frontal and left middle occipital gyri. Deficits in the right orbitofrontal-temporal-limbic and left inferior frontal regions remained in a subgroup analysis of unmedicated participants. Abnormalities in the left postcentral and middle occipital gyri were found only in older maltreated individuals relative to age-matched comparison subjects.

Conclusions: The findings demonstrate that the most consistent gray matter abnormalities in individuals exposed to childhood maltreatment are in relatively late-developing ventrolateral prefrontal-limbic-temporal regions that are known to mediate late-developing functions of affect and cognitive control, which are typically compromised in this population.

(Am J Psychiatry 2014; 171:854–86

FIGURE 1. Regions of Gray Matter Volume Differences in Participants Exposed to Childhood Maltreatment Relative to Unexposed Comparison Subjects[a]



[a] Slices are shown in axial view and marked with the z coordinate as distance in millimeters from the anterior-posterior commissure. The right side of the image corresponds to the right side of the brain. Smaller volumes are indicated in red and larger volumes in blue.

Effects of Childhood Sexual Abuse

Article

Decreased Cortical Representation of Genital Somatosensory Field After Childhood Sexual Abuse

Christine M. Heim, Ph.D.

Helen S. Mayberg, M.D.

Tanja Mletzko, M.S.

Charles B. Nemeroff, M.D., Ph.D.

Jens C. Pruessner, Ph.D.

Objective: Sexual dysfunction is a common clinical symptom in women who were victims of childhood sexual abuse. The precise mechanism that mediates this association remains poorly understood. The authors evaluated the relationship between the experience of childhood abuse and neuroplastic thinning of cortical fields, depending on the nature of the abusive experience.

Method: The authors used MRI-based cortical thickness analysis in 51 medically healthy adult women to test whether different forms of childhood abuse were associated with cortical thinning in areas critical to the perception and processing of specific behavior implicated in the type of abuse.

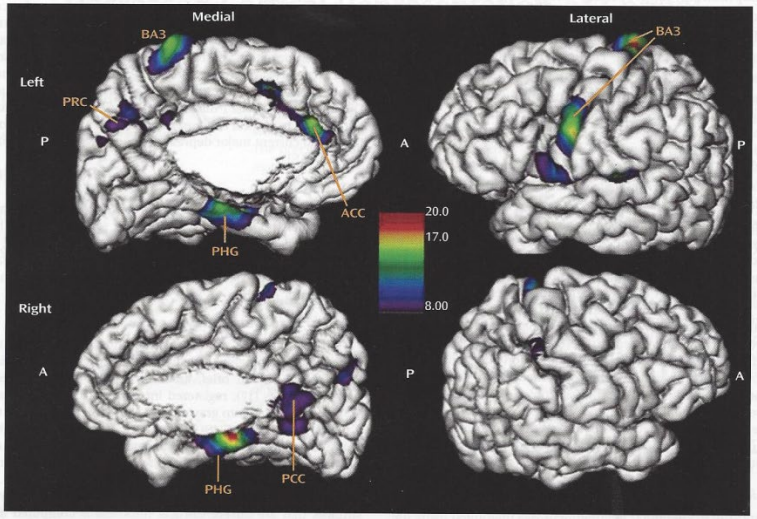
Results: Exposure to childhood sexual abuse was specifically associated with pronounced cortical thinning in the genital representation field of the primary somatosensory cortex. In contrast, emotional abuse was associated with cortical thinning in regions relevant to self-awareness and self-evaluation.

Conclusions: Neural plasticity during development appears to result in cortical adaptation that may shield a child from the sensory processing of the specific abusive experience by altering cortical representation fields in a regionally highly specific manner. Such plastic reorganization may be protective for the child living under abusive conditions, but it may underlie the development of behavioral problems, such as sexual dysfunction, later in life.

(Am J Psychiatry 2013; 170:616–623)

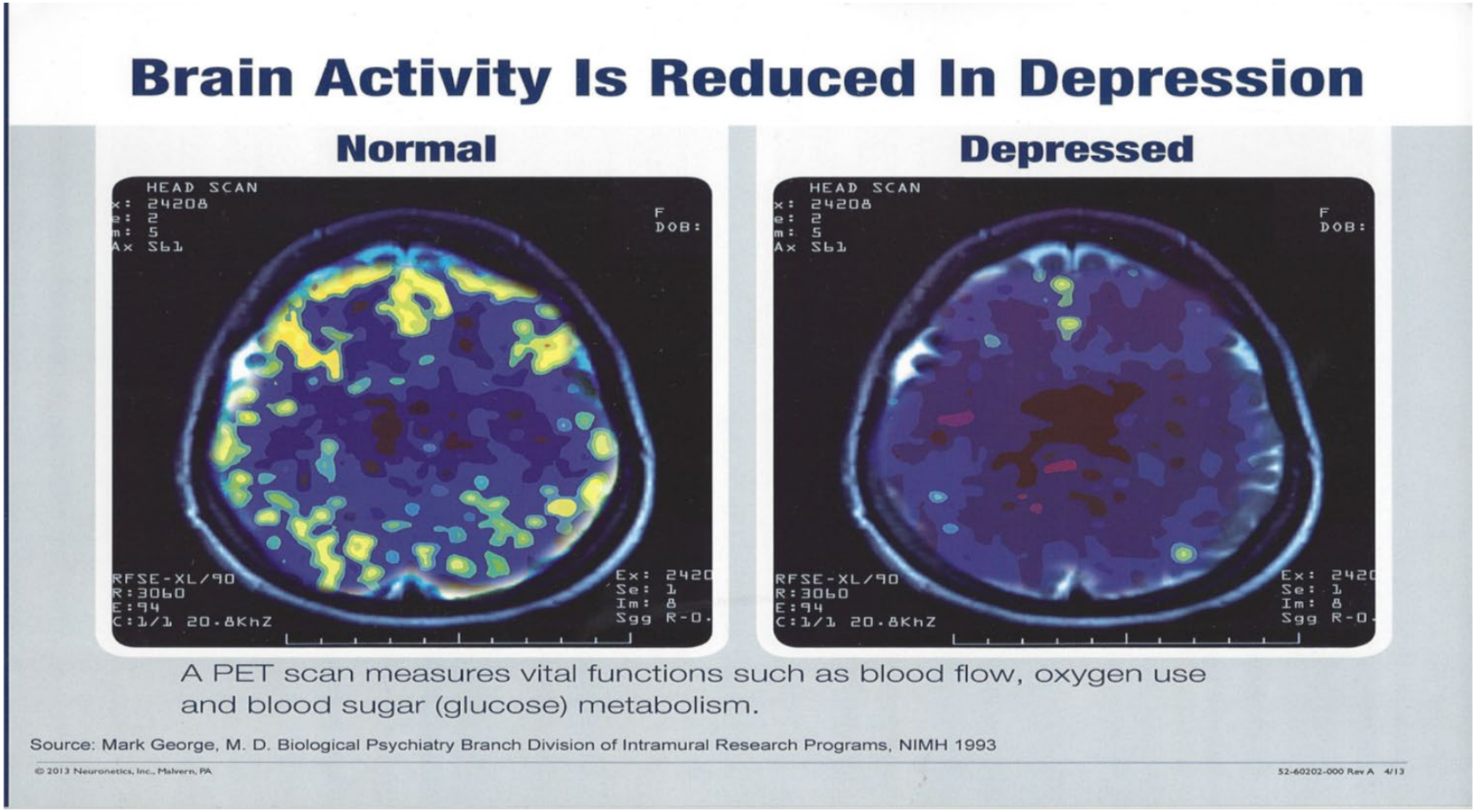
GENITAL SOMATOSENSORY FIELD AFTER CHILDHOOD SEXUAL ABUSE

FIGURE 1. Regression of Childhood Trauma Questionnaire (CTQ) Total Score Against Cortical Thickness in Women With and Without Childhood Sexual Abuse[a]



[a] Cortical thickness analysis results after regressing CTQ total score against thickness across the entire cortex. Control variables included age and depression scores. Main effects are seen in the somatosensory cortex in the female genital and mouth area on the left, the parahippocampal gyrus (PHG) bilaterally, the left anterior cingulate cortex (ACC), and the precuneus (PRC) bilaterally. For the precise location of the genital sensory field as identified using functional MRI of neural response to stimulation, see references 22 and 23. BA3=Brodmann's area 3; PCC=posterior cingulate cortex; A=anterior; P=posterior. The color scale refers to the F values of the linear regression (significance threshold:

PET Scan in Depression



Management Approaches to a Suicidal Patient

- Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors (American Psychiatric Association, 2003)
  - Psychiatric Management
    - Establish and Maintain a Therapeutic Alliance
    - Patient safety, Setting, Treatment Plan, Education
  - Specific Treatment Modalities
    - Somatic Therapies
      - Lithium
      - Clozapine
    - Electroconvulsive Therapy (ECT)
    - Psychotherapy

Electroconvulsive Therapy in Suicidal Patients

Declining Use of ECT in US General Hospitals

Biological Psychiatry, 2012

ARCHIVAL REPORT

Declining Use of Electroconvulsive Therapy in US General Hospitals

Brady G. Case, David N. Bertollo, Eugene M. Laska, Lawrence H. Price, Carole E. Siegel, Mark Olfson, and Steven C. Marcus

Background: Falling duration of psychiatric inpatient stays over the past 2 decades and recent recommendations to tighten federal regulation of electroconvulsive therapy (ECT) devices have focused attention on trends in ECT use, but current national data have been unavailable.

Methods: We calculated the annual number of inpatient stays involving ECT and proportion of general hospitals conducting the procedure at least once in the calendar year with a national sample of discharges from 1993 to 2009. We estimated adjusted probabilities that inpatients with severe recurrent major depression (n = 465,646) were treated in a hospital that conducts ECT and, if so, received the procedure.

Results: The annual number of stays involving ECT fell from 12.6 to 7.2/100,000 adult US residents, driven by dramatic declines among elderly persons, whereas the percentage of hospitals conducting ECT decreased from 14.8% to 10.6%. The percentage of stays for severe recurrent major depression in hospitals that conducted ECT fell from 70.5% to 44.7%, whereas receipt of ECT where conducted declined from 12.9% to 10.5%. For depressed inpatients, the adjusted probability that the treating hospital conducts ECT fell 34%, whereas probability of receiving ECT was unchanged for patients treated in facilities that conducted the procedure. Adjusted declines were greatest for elderly persons. Throughout the period inpatients from poorer neighborhoods or who were publicly insured or uninsured were less likely to receive care from hospitals conducting ECT.

Conclusions: Electroconvulsive therapy use for severely depressed inpatients has fallen markedly, driven exclusively by a decline in the probability that their hospital conducts ECT.

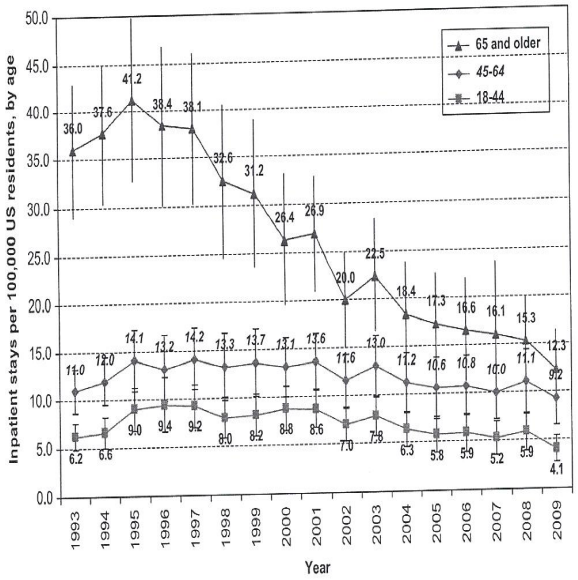


Figure 1. Annual number of inpatient stays in US general hospitals involving electroconvulsive therapy administration/ 100,000 US residents, by age group, with 95% confidence intervals, 1993–2009. See Methods and Materials section for sample description.

ECT Reduces Suicide Risk

- **Consortium for Research in Continuation ECT (CORE Study)**

- Multisite, collaborative, NIMH-funded study
- Compare the efficacy of continuation pharmacotherapy (lithium plus nortriptyline) and continuation ECT

- Remission rate for depression in the 355 patients who completed the course of treatment was 85.6%.

- Among 102 patients in the high expressed suicidal intent group who completed acute course of ECT, 87.3% had scores drop to 0.

Kellner CH, Fink M, Knapp R, et al, Am J Psych 2005;162:977-982

Electroconvulsive Therapy (ECT)

Neuromodulation
and
Neurogenesis

ECT and Neuromodulation

- Neurotransmitter Hypothesis:
  - Hypothesis: ECT stabilizes dysregulated intracellular signaling linked to multiple transmitter system.
  - Alterations in Neurotransmitter and Receptor Function
  - NE : Down-regulation and desensitization of *B*-receptors
  - 5HT: Upregulation and sensitization of post-synaptic 5HT2 receptors
  - Ach: Increased brain and CSF acetylcholine concentration
    - Down-regulation of cortical muscarinic receptors
      - *Could be related to ECT-induced amnesia*
  - DA: Increased dopamine-mediated behaviors

Kaplan and Saddock. *Comp Textbook of Psych*, 1995

Other Proposed ECT Mechanisms of Action

- Anticonvulsant Hypothesis:
  - Post-ictal inhibitory response to ECT-induced seizure may be therapeutic.
- Hyperconnectivity Hypothesis:
  - ECT exerts its therapeutic efficacy through modification of the aberrant functional connectivity.
    - Hyperconnectivity in amygdala and cognitive network in depression. (Sheline et al, 2010)
    - ECT attenuates connectivity to the amygdala (2014)
- Connectivity Resetting Hypothesis:
  - ECT exerts its therapeutic efficacy through resetting aberrant neural connectivity, likely mediated through activating thalamocortical pathways and central inhibitory mechanisms, and increasing the possibility of formation of newer and healthier connecting by promoting neurogenesis.

  - Farzan, F , Daskalakis, ZJ et al, *J ECT* 30;2 June 2014, 98-106

ECT and Neurogenesis

ECS and Neurogenesis in Rat Hippocampus

Smitha JSM, Andrade C, et al, J ECT 30;3, Sept 2014:192-194

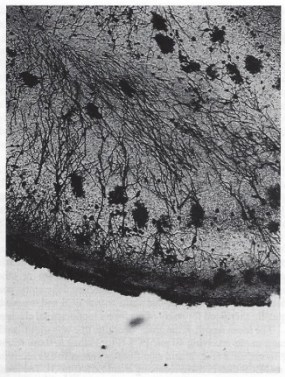


FIGURE 1. Rapid Golgi-stained coronal section of the CA1 region of the hippocampus in a healthy Wistar rat that received high dose (40 mC) electroconvulsive shocks. Light microscopy view was obtained at 10x magnification. Pyramidal neurons are seen, displaying apical dendritic trees.

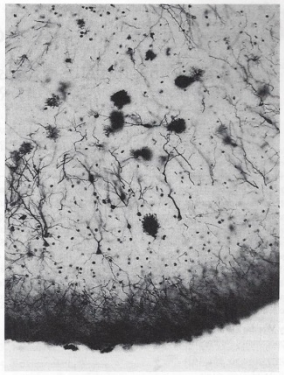


FIGURE 3. Rapid Golgi-stained coronal section of the CA1 region of the hippocampus in a healthy Wistar rat that received sham electroconvulsive shocks. Light microscopy view was obtained at 10x magnification. Pyramidal neurons are seen, displaying apical dendritic trees.

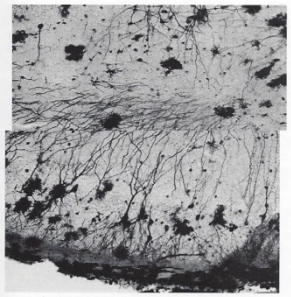


FIGURE 2. Rapid Golgi-stained coronal section of the CA1 region of the hippocampus in a healthy Wistar rat that received low dose (10 mC) electroconvulsive shocks. Light microscopy view was obtained at 10x magnification. Pyramidal neurons are seen, displaying apical dendritic tree.

caveat, however, is that these changes remain to be demonstrated in animal models in which neuroplasticity has been compromised by stress.

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1. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology.* 2008;33:88–109.
2. 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.

N Engl J Med. 1993;328:839–846.

Smitha et al Journal of ECT • Volume 30, Number 3, September 2014

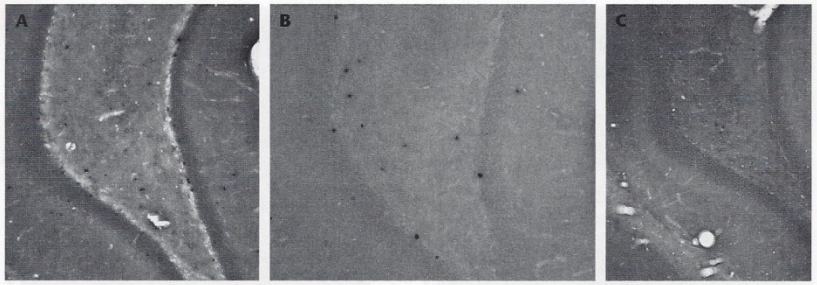

FIGURE 1. Newly formed BrdU immunoreactive cells (DAB technique) seen as dark spots in coronal sections of the subgranular region of the hippocampus. These sections were taken at the same level in healthy adult male Wistar rats receiving high-dose (40 mC) ECS (A), low-dose (10 mC) ECS (B), and sham ECS (C). Light microscopy views were obtained at ×40 magnification.

Epigenetic Effects of Electroconvulsive Seizures

De Jong, JO, Sienart P, Rutten B, et al, J ECT 30:2, 152-159 June 2014

Epigenetics (or Epigenesis) refers to the processes that modify gene expression independent from the primary DNA sequence.

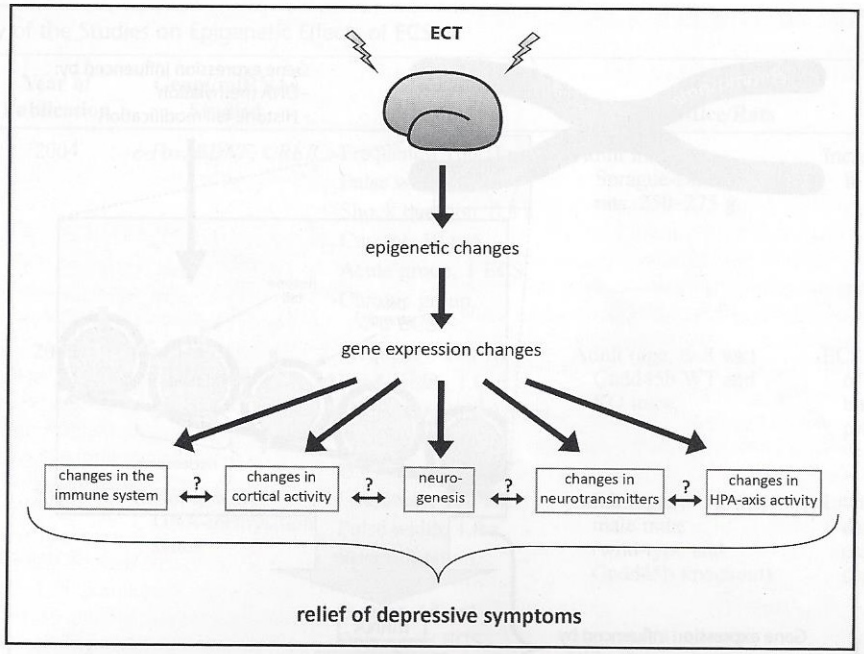

FIGURE 1. Hypothetical model on the working mechanism of ECT at different biological levels. Electroconvulsive therapy may impact different biological systems via epigenetic regulation of gene expression. The different biological systems depicted in the boxes are thought to dynamically interact and interrelate with each other in various straightforward and more complex manners (the question marks illustrate the limited knowledge on these interrelations).

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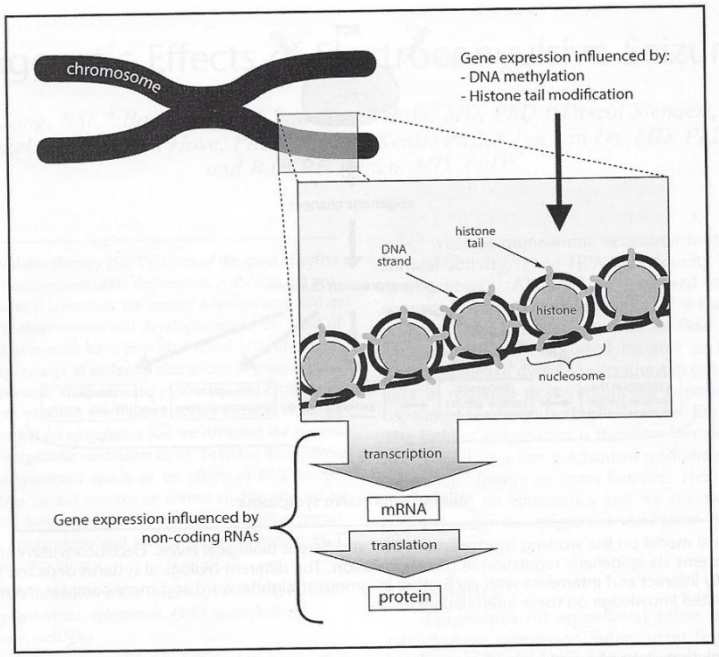


FIGURE 2. Epigenetic regulation of gene expression. Figure 2 illustrates the main epigenetic mechanisms that regulate gene transcription. DNA is located within the chromosomes tightly packaged around the histones. The histone complex is built up from 8 histone subunits (protein dimers named H2A, H2B, H3, and H4), around which 146 base pairs of DNA are wrapped. Histones contain histone tails, which can be covalently modified by attaching a number of different side groups. The DNA can be modified by the attachment of (hydroxy)methyl groups to the cytosine residue. Both DNA methylation and histone tail modification cause a change in the configuration of the DNA around the histones, resulting in either an increase or a decrease in accessibility of the transcriptional machinery, which may result in altered gene transcription. Another mechanism by which cells regulate their gene expression is by using regulatory ncRNAs.

mRNA Changes in ECT

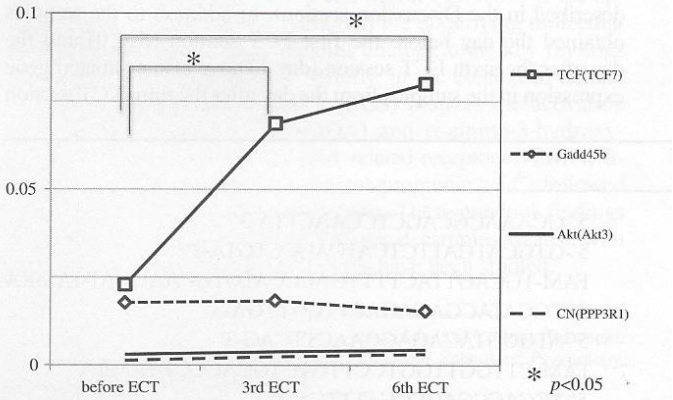


FIGURE 1. Time-dependent mRNA changes in the expression of 4 selected genes (*GADD45B, TCF7, PPP3R1*, and *AKT3*) using qPCR. Analysis of variance was applied for each gene, and a significant difference only on *TCF7* was found ($F = 7.04$, $P = 0.0095$). The comparison between 2 points, such as before the third ECT and sixth ECT indicated the significant difference at $P < 0.05$ level (post hoc analysis by Tukey method). *x* axis: time course, before ECT (day 0), third ECT (day 7), and sixth ECT (day 17). *y* axis: the average of mRNA expression of 5 cases normalized by *GAPDH* expression.

Human Brain Connectome

NEJM, Dec 2018

MAPPING SYMPTOMS TO BRAIN NETWORKS

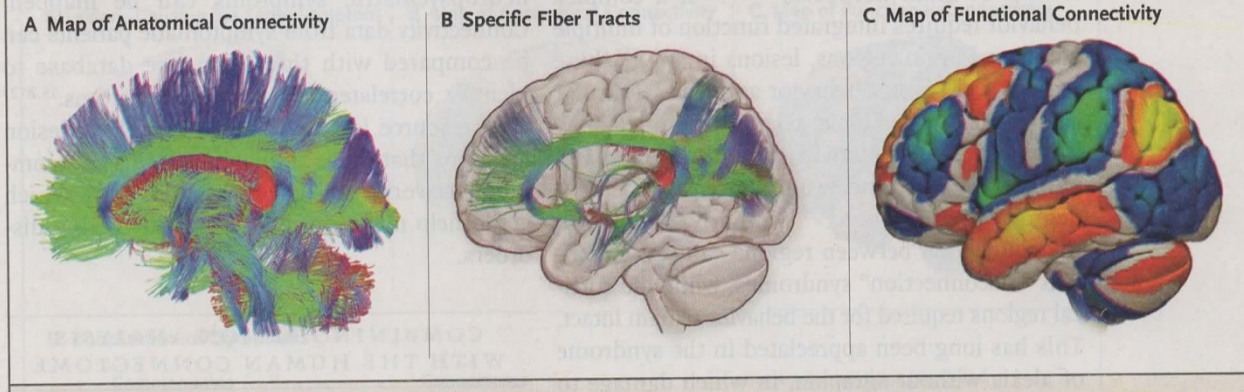


Figure 2. The Human Brain Connectome.

Current human brain maps of anatomical connectivity (Panel A) can be used to isolate specific fiber tracts, such as those passing through the posterior cingulate (Panel B). Maps of functional connectivity can be used to identify brain regions with spontaneous activity that is positively correlated (yellow or red) or negatively correlated (blue or green) with any other region, such as the posterior cingulate (Panel C).

Resting-State Functional Connectivity in TRD and Effects of ECT

- Resting-State Functional Connectivity (RSFC) in patients with TRD was measured pre and post- RUL ECT, using functional magnetic resonance imaging (fMRI)
- N= 30 women with TRD; and 33 healthy controls
- Both ECT and clinical change were associated with RSFC modulation in dorsal ACC (dorsal anterior cingulate), mdTH (mediodorsal thalamus) and hippocampus.
- RSFC of these regions did not change in healthy controls.

- Leaver AM, Espinoza R, Pirnia T, Joshi SH, Woods RP, Narr KL, Modulation of intrinsic brain activity by electroconvulsive therapy in major depression, Biol Psychiatry Cogn Neurosci Neuroimaging, 2016, Jan 1; 77-86

Bilateral ECT induces bilateral increases in regional cortical thickness

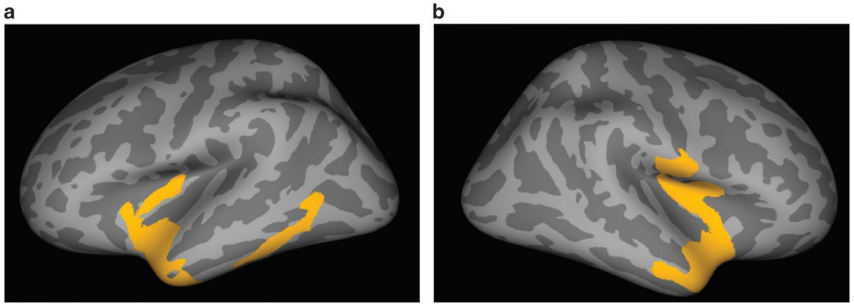
P van Eijndhoven1,2, P Mulders1,2, L Kwekkeboom1, et al

Research Paper

Grey matter volume increase following electroconvulsive therapy in patients with late life depression: a longitudinal MRI study

Filip Bouckaert, MD*; François-Laurent De Winter, MD*; Louise Emsell, PhD; Annemieke Dols, MD, PhD; Didi Rhebergen, MD, PhD; Martien Wampers, PhD; Stefan Sunaert, MD, PhD; Max Stek, MD, PhD; Pascal Sienaert, MD, PhD; Mathieu Vandenbulcke, MD, PhD

Background: The evidence on the mechanisms of action of electroconvulsive therapy (ECT) has grown over the past decades. Recent studies show an ECT-related increase in hippocampal, amygdala and subgenual cortex volume. We examined grey matter volume changes following ECT using voxel-based morphometry (VBM) whole brain analysis in patients with severe late life depression (LLD). **Methods:** Elderly patients with unipolar depression were treated twice weekly with right unilateral ECT until remission on the Montgomery–Åsberg Depression Rating Scale (MADRS) was achieved. Cognition (Mini Mental State Examination) and psychomotor changes (CORE Assessment) were monitored at baseline and 1 week after the last session of ECT. We performed 3 T structural MRI at both time points. We used the VBM8 toolbox in SPM8 to study grey matter volume changes. Paired *t* tests were used to compare pre- and post-ECT grey matter volume (voxel-level family-wise error threshold $p < 0.05$) and to assess clinical response. **Results:** Twenty-eight patients (mean age 71.9 ± 7.8 yr, 8 men) participated in our study. Patients received a mean of 11.2 ± 4 sessions of ECT. The remission rate was 78.6%. Cognition, psychomotor agitation and psychomotor retardation improved significantly ($p < 0.001$). Right-hemispheric grey matter volume was increased in the caudate nucleus, medial temporal lobe (including hippocampus and amygdala), insula and posterior superior temporal regions but did not correlate with MADRS score. Grey matter volume increase in the caudate nucleus region correlated significantly with total CORE Assessment score ($r = 0.63$; $p < 0.001$). **Limitations:** Not all participants were medication-free. **Conclusion:** Electroconvulsive therapy in patients with LLD is associated with significant grey matter volume increase, which is most pronounced ipsilateral to the stimulation side.



Role of ECT in Suicide

- Stress
  - Neurodegeneration
    - Gray matter abnormalities in childhood maltreatment
  - Suicide
    - 10th leading cause of death
- ECT
  - Epigenetic effects
    - Histone tail modification
    - mRNA effect with elevated serum level of TCF -7
  - Neurogenesis
  - 87.3% of patients were relieved of suicide thoughts (CORE Study)

Thank you.