Make Waves
Community Education Day

BREAK THE SILENCE.
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

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

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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-varying 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 significantly smaller gray matter volumes in the right orbitofrontal/superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyrus, and in the left inferior frontal and postcentral gyrus. They had larger gray matter volumes in the right superior frontal and left middle occipital gyrus. Deficits in the right orbitofrontal-temporal-limbic and left inferior frontal regions remained in a subgroup analysis of unmedicated participants. Abnormalities in the left posterior central 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 and limbic-temporal regions that are known to mediate late-developing functions of affect and cognitive control, which are typically compromised in this population.

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

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

Decreased Cortical Representation of Genital Somatosensory Field After Childhood Sexual Abuse

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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.

Results: Exposure to childhood sexual abuse was specifically associated with pronounced cortical thinning in the genitai 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)
PET Scan in Depression

Brain Activity Is Reduced In Depression

Normal

Depressed

A PET scan measures vital functions such as blood flow, oxygen use and blood sugar (glucose) metabolism.

Source: Mark George, M.D. Biological Psychiatry Branch Division of Intramural Research Programs, NIH 1993
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

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.
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.

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

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

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.

REFERENCES
Epigenetic Effects of Electroconvulsive Seizures
Epigenetics (or Epigenesis) refers to the processes that modify gene expression independent from the primary DNA sequence.

![Diagram showing the working mechanism of ECT](image)

**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).
Epigenetic Effects of Electroconvulsive Seizures
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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

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

Grey matter volume increase following electroconvulsive therapy in patients with late life depression: a longitudinal MRI study
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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, amygdalas 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 VBM6 toolbox in SPM6 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.