New Insights on Depression

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Objectives:

• 1. Understand the new insights on depression.

• 2. Understand the treatment modalities available based on the new concepts.
Stress-Diathesis Model

- Acute Stress
  - COVID19 Pandemic

- Chronic Stress
  - Childhood maltreatment

- 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
**Monoamine Hypothesis of Depression**

- **Monoamine Hypothesis**
  - “chemical imbalance”
  - Reduced availability of monoamines, serotonin and noradrenaline

- Treatment: SSRI/SNRI
Neuroplasticity Hypothesis of Depression

• **Neuroplasticity Hypothesis**
  - Intracellular signaling/mechanisms of gene expression, neurotrophic mechanisms, neurogenesis, synaptic function/neuroplasticity, remodeling of neuronal cells/circuitry

• Treatment: TMS, ECT
**Glutamate Hypothesis of Depression**

- Paradigm shift from “monoamine hypothesis” to “neuroplasticity” and “glutamate hypothesis”, can be traced back to the early 1990s.

- Early findings showed that N-methyl-D-aspartate receptor (NMDA-R) antagonists possess antidepressant-like action. (Trullas and Skolnick, 1990)

- “Brain is in good part a glutamatergic/GABAergic machine.” Glutamate mediates the vast majority of fast excitatory transmission, while gamma-aminobutyric acid (GABA) mediates the vast majority of fast inhibitory transmission.

Epidemiological Triad: Understanding the Impact of COVID-19 Pandemic

The ‘epidemiological triad’ of causal factors

**Agent**
- Virulence, infectivity of a pathogen;
- Addictive qualities of a substance of abuse, etc.

**Environment**
- Sanitary conditions;
- Social context; availability of health care, etc.

**Host**
- Genetic susceptibility;
- Resiliency; nutritional status; behaviour, etc.

*Cf. Fireman’s mantra: a fire requires air, fuel and heat*
Effect of Childhood Maltreatment

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

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 (96 children/adolescents and 235 adults) with a history of childhood maltreatment and 362 comparison subjects (76 children/adolescents and 286 adults). Anatomical effect size-scaled 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 orbital/basal/border temporal gyrus, extending to the amygdala, insula, and part of the hippocampus and middle temporal gyrus and in the left inferior frontal and parietal central gyr. They also had larger gray matter volumes in the right superior frontal and left middle occipital gyri. This was in the left insular/basal/border temporal gyrus and left inferior frontal gyrus, regions that are involved in the processing of affect and cognitive control, which are typically compromised in this population.

Effect of Childhood Maltreatment

Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between childhood maltreatment and these clinically relevant measures of depression.

Method: The authors conducted searches in MEDLINE, PsycINFO, and Embase for articles examining the association of childhood maltreatment with course of illness (i.e., recurrence or persistence) and with treatment outcome in depression that appeared in the literature before December 31, 2010. Recurrence was defined in terms of number of depressive episodes. Persistence was defined in terms of duration of current depressive episode. Treatment outcome was defined in terms of either a response (a 50% reduction in depression severity rating from baseline) or remission (a decrease in depression severity below a predefined clinical significance level).

Results: A meta-analysis of 16 epidemiological studies (23,544 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recency and persistent depressive episodes (odds ratio: 2.27, 95% confidence interval: 1.80–2.87). A meta-analysis of 10 clinical trials (1,945 participants) revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression (odds ratio: 1.43, 95% CI: 1.11–1.83). Meta-regression analyses suggested that the results were not significantly affected by publication bias, choice of outcome measure, inclusion of prevalence or incidence estimates, study quality, age of the sample, or lifetime prevalence of depression.

Conclusions: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression.
Default Mode Network in Discrete Emotions
Management Approaches to Depression

- Stress Management and Resiliency
- Lifestyle Psychiatry
- Psychotherapy
- Medications and Compliance
- Neuromodulation Therapy
Lifestyle Psychiatry
Elements of Lifestyle Psychiatry

- Physical Exercise
- Yoga and Tai Chi
- Mindfulness and Meditation
- Diet and Nutrition
- Managing Sleep
- Lifestyle Interventions
- Helping People Find Synergy
Relationships and Social Integration

• *Need to belong* is one of the most basic human needs.

• Relationships (family, friends, colleagues, and lovers) are essential to well-being: happiness and health.

• Humans are fundamentally social in nature. (Aristotle)

• **Social integration** – one’s degree of integration into social networks

• **Social support** – the extent to which individuals feel cared for, can receive help from others, and are part of a supportive network.
Spirituality and Suicide Rate

• Nurses’ Health Study, 89,708 women from 1996-2010

• **Attendance at religious services once per week or more** was associated with an approximately **5-fold lower rate of suicide** compared with never attending religious services.
Spirituality and Risk of Death from Despair

• Nurses’ Health Study II with 66,492 female nurses from 2001-2017, and
• Health Professionals Follow-Up Study 43,141 male health care professionals, from 1988-2014
• **Religious service attendance** is associated with **lower risk of death from despair** (deaths from suicide, unintentional poisoning by alcohol and drug overdose, and chronic liver diseases and cirrhosis) among health care professionals (HCP).
  • Chen, Y, Koh, HK et al, JAMA Psychiatry, 2020; 77:737-744
Dialectical Behavior Therapy

• An evidence-based “third wave” of cognitive-behavioral therapy.
• Approach developed by Marsha M Linehan.
• 1980s to treat people with borderline personality disorder and chronically suicidal patients
• Efficacy:
  • Borderline personality disorder
  • Depression
  • Complex post-traumatic stress disorder
Dialectical Behavior Therapy

• Four Modules:
  • Mindfulness
  • Distress Tolerance
  • Emotion Regulation
  • Interpersonal Effectiveness
Role of Genetic Testing

• Personalized Psychopharmacology

• Genetic Testing
  • Genesight Test
  • Genomind Test
Medication Options for Treatment Resistant Depression:

• Antipsychotics:
  • Aripiprazole
  • Brexipiprazole
  • Quetiapine
  • Cariprazine

• Lithium or lamotrigine

• Glutamatergic therapies:
  • Ketamine
  • Repurposed antibiotics
    • Minocycline
    • D-cycloserine

Young, et all, Relative Effectiveness of augmentation treatments for treatment resistant depression: a systemic review and network meta-analysis, Int Review of Psychiatry, 32:5-6, 477-490, 2020
Esketamine (Spravato)

- S-enantiomer of racemic ketamine
- Has a higher affinity for the N-methyl-D-aspartate receptor than the R-enantiomer
- 2019- approved for Treatment resistant depression in adults.
- August 2020, approved by the US FDA with added indication for the short-term treatment of suicidal thoughts.

- Doses: 28 mg; 56 mg; 84 mg
- Self-administered in a staff monitored clinic
- Patient is observed and monitored for 2 hours
Instructions for Use
Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1)

Although esketamine 84 mg/AD was not statistically significant relative to AD/PBO, the treatment differences at day 28 of -3.2 (84 mg) and -4.1 (56 mg) were consistent with positive findings.
Relapse Prevention in TRD (SUSTAIN 1)

- Among patients who achieved stable remission, **26.7%** in esketamine/AD group and **39%** in AD/placebo group experienced relapse.

- Continued treatment with esketamine and AD significantly delayed relapse.
SUSTAIN-2 Study

- Common treatment-emergent adverse events (TEAEs):
  - Dizziness (32.9%)
  - Dissociation (27.6%)
  - Nausea (25.1%)
  - Headache (24.9%)
- Two deaths reported not related to esketamine
- Cognitive performance generally stable
- Treatment emergent dissociative symptoms were transient and generally resolved 1.5 hours postdose.
Neuromodulation Therapy

- Transcranial Magnetic Stimulation (TMS)
- Electroconvulsive Therapy (ECT)
- Vagal Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)
Transcranial Magnetic Stimulation

- A noninvasive procedure that uses highly focused magnetic pulses to target specific mood circuits in the brain.
- Approved by the Food and Drug Administration for Major depressive disorder, 2007
Transcranial Magnetic Stimulation (TMS)

• **Benefits:**
  • Ease of administration of treatment
    • No anesthesia
    • No memory side-effects
    • Mild headache as side-effect.

• **Issues:**
  • Insurance coverage
Transcranial Magnetic Stimulation

- **Standardized Effect size** (Neuronetics and NIMH trials): 0.39-0.55; Efficacy: 40-60%
- Deep TMS/Brainsway Trial (20 sites): At week 16: Response rate: 38.4%; Remission rate: 31.8%
- **Durability studies**: High (64-90%) durability for acute TMS benefits over a 3-12 month period.
- O’Reardon JP et al, 2007; George MS et al, 2010
Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for Treatment-Resistant Depression

• Intermittent theta-burst stimulation (iTBS) – in a noninvasive brain stimulation treatment approved by the FDA
• SAINT – an accelerated, high-dose resting-state functional connectivity MRI (fcMRI)-guided iTBS protocol for treatment-resistant depression
• Fifty iTBS sessions (1,800 pulses per session, 50-minute intersession interval) were delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold (adjusted for cortical depth)
• Response rate: 90.48%; all responders were in Remission after SAINT.
LCOH ECT Service
Lingering Concerns about ECT

• Safety issues

• Stigma
  • “One Flew Over the Cuckoo’s Nest”

• Cognitive or Memory side-effect
Speed of Response and Remission

- 253 patients with MDD received bilateral ECT 3X weekly
- 86% completed acute course of ECT
- Sustained response occurred in 79%
- Remission occurred in 75%
- Over half (54%) had initial first response by ECT #3
- 34% (85/253) of patients achieved remission at or before ECT #6
- 65% (164/253) achieved remission at or before ECT #10 (weeks 3-4)

Brain Volume Increase with ECT

Volume of the Human Hippocampus and Clinical Response Following Electroconvulsive Therapy


ABSTRACT

BACKGROUND: Hippocampal enlargements are commonly reported after electroconvulsive therapy (ECT). To clarify matters, we examined if ECT-induced hippocampal volume change relates to dose (number of ECT sessions) and electrode placement and acts as a biomarker of clinical outcome.

METHODS: Longitudinal neuroimaging and clinical data from 10 independent studies participating in the Global ECT-Magnetic Resonance Imaging Research Collaboration (GERB-E15) were obtained for 1526 patients. Hippocampal volumes were extracted from structural magnetic resonance images, acquired before and after ECT (n = 291) encompassing a major depressive episode preceded an ECT treatment series using right unilateral and bilateral stimulation. Unrelated nondepressed control subjects (n = 83) were scanned twice.

RESULTS: The linear component of hippocampal volume change was 0.038 mm³ per ECT session (p = .031). Volume change varied with electrode placement in the left hippocampus (right > left > bilateral > control, 1.8 ± 0.1, 1.6 ± 0.1, 1.3 ± 0.1, 1.4 ± 0.4, 1.1 ± 0.1 respectively, p = .001) but not the right hippocampus (1.3 ± 0.1, 1.1 ± 0.1, 1.1 ± 0.1, 1.4 ± 0.4, 1.2 ± 0.4, 1.1 ± 0.1, p > .05). Volume change for electrode placement per ECT session varied similarly by hemisphere. Techniques with greater treatment-related volume increase had lower outcomes. Cerebrospinal-Aquaporin Dependent Regional Social change = -0.038 mm³ per 1% volume increase, p = .003, although the effects were not significant after controlling for ECT number (above DE = 0.38, p = .003).

CONCLUSIONS: The number of ECT sessions and electrode placement impacts the extent and stability of hippocampal enlargement, but volume change is not positively associated with clinical outcome. The results suggest that the high efficacy of ECT is not explained by hippocampal enlargement, which alone might not serve as a viable biomarker for treatment outcome.

Keywords: Antidepressant response, Remission, Brain, Depression, ECT, Neuroimaging

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Research Paper

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 have described increased hippocampal gray matter volume in patients undergoing ECT. However, the exact neural mechanisms of ECT and its effects on grey matter volume have not been elucidated. In order to understand the potential neural mechanisms underlying ECT-induced grey matter volume changes, we examined longitudinal changes in grey matter volume in patients undergoing ECT for treatment-resistant depression.

Methods: Grey matter volume changes were assessed using 3T MRI at baseline and post-treatment (after 5 sessions) in patients undergoing ECT for treatment-resistant depression. The ECT treatment protocol consisted of 10 sessions of ECT with a frequency of twice a week using a 4 Hz square wave stimulation. Patients were divided into two groups based on symptom improvement: responders (≥ 50% symptom reduction) and non-responders (≤ 49% symptom reduction). Grey matter volume changes were assessed using voxel-based morphometry analysis. Results: Grey matter volume changes in the prefrontal cortex were observed in both groups, with an increase in grey matter volume in the left inferior frontal gyrus, left superior frontal gyrus, and right superior frontal gyrus. Conclusions: Our findings suggest that ECT induces grey matter volume changes in the prefrontal cortex, which may be related to antidepressant action. Grey matter volume changes in the prefrontal cortex may be a biomarker of treatment response to ECT. Further studies are needed to determine the clinical relevance of these changes.
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 mechanism 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 analyses 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 3T structural MRI at both time points. We used the VBM8 toolbox in SPM12 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 ± 7.4 yr, 8 men) participated in our study. Patients received a mean of 11.2 ± 4 sessions of ECT. The remission rate was 78.0%. 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 = 0.65, 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 (predominantly) to the stimulation side.
Ultrabrief Pulse Right Unilateral ECT: A New Standard of Care? (Kellner CH 2009)

- Pulse width in milliseconds (msec):
  - Stimuli between 0.5 and 2.0 are called “Brief Pulse” (Standard)
  - Stimuli less than 0.5 msec. are called “Ultrabrief Pulse”

Main advantage: cognitive side effects are greatly reduced.
ECT in the 21st Century: Ultra Brief Stimulation
(Loo C, 2013)

- Ultra brief stimulation is a new advance in electroconvulsive therapy.

- Response rates: 57%-78%

- Cognitive adverse effects are greatly reduced.
TMS, ADM, ECT

Figure. Comparative Effective Sizes: TMC/ADM/ECT

KEY: ADM — antidepressant medication, ECT — electroconvulsive therapy; TMS — transcranial magnetic stimulation
Thank you.

• For inquiries:
  • LCOH Access and Referral Center:
    • (513) 536-0538
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