Searching for Biomarkers of Stress-Related Mental Illness, PTSD, and Suicidality

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Brain & Behavior Foundation – Meet the Scientist Webinar
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COI/Disclosures

I have nothing to disclose.

Opinions are my own.
My Journey
My father, the Marine

My father in Montana

My father in Vietnam
“Reality is the leading cause of stress amongst those in touch with it!”

-Jane Wagner
Prevalence of PTSD

- ~8% of US adult population
- Military Veterans ~ 40%
- Refugees ~ 86%
DSM-5 PTSD

- Reexperiencing
- Avoidance
- Negative Mood & Cognitions
- Hyperarousal
- Dissociative Subtype
Suicidality as a Meta Symptom

Hopelessness  Emotional Pain
Worthlessness  Physical Pain
Loneliness  Guilt
Isolation  Regret
Thwarted belonging  Shame
Burdensomeness  Blame
Stress  Anger
Tiredness/Fatigue  Burdensomeness
Impaired decision making  Revenge
Impulsivity
Age-Adjusted Suicide Rates in the United States (2001–2017)

Data Courtesy of CDC

Year:
- 2001: Total Population (4.1), Female (10.7), Male (18.2)
- 2015: Total Population (6.0), Female (13.3), Male (21.0)

Suicide Rate (per 100,000):
- Total Population:
  - 2001: 4.1
  - 2015: 6.0
- Female:
  - 2001: 10.7
  - 2015: 13.3
- Male:
  - 2001: 18.2
  - 2015: 21.0
Suicidality is a Public Health Crisis

Globally, ~800,000 annually
1 death / 40 seconds
~129 / day in the US (47,173)

10th leading cause of death in US across all age groups

2016 →
2nd leading cause for ages 10 - 34
4th leading cause for ages 35 - 54
Veterans elevated risk ~1.5 - 2 times

Bipolar disorder ~5 times

Healthy ~0 risk
9.8 million adults had serious thoughts of committing suicide

2.8 million adults made suicide plans

1.3 million adults attempted suicide

1.0 million adults made plans and attempted suicide

0.3 million adults made no plans and attempted suicide
Trauma Exposure

☑ PTSD, Depression, Anxiety, Substance Abuse, Suicidality...

☑ Problems with family, parenting, friends, employment, education, self-care, finances, housing...
### Suicidality as a Meta Symptom

<table>
<thead>
<tr>
<th>Positive Aspects</th>
<th>Negative Aspects</th>
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</thead>
<tbody>
<tr>
<td>Hopelessness</td>
<td>Emotional Pain</td>
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<tr>
<td></td>
<td>Revenge</td>
</tr>
</tbody>
</table>
Consequences

- PTSD, Depression, Anxiety, Substance Abuse, Suicidality...
- Problems with family, parenting, friends, employment, education, self-care...
- Neurobiological changes...
“There are wounds that never show on the body - that are deeper and more hurtful that anything that bleeds...”

- Laurell K. Hamilton
Regulate emotion and choose action

Fear learning

Interpret emotional context
Averill et al, 2017, Chronic Stress
PTSD

Wrocklage et al, 2017, Eur Neuropsychopharmacology
Suicidality in PTSD

Averill et al., unpublished
Inappropriate persistent fear

Heightened fear/threat processing

Impaired adaptive fear learning and extinction
Negreira & Abdallah, 2019, Chronic Stress
Suicidality in PTSD

Averill et al. Unpublished
Triple Network Model of Intrinsic Connectivity Networks

- **Central executive network**
  - Activity and connectivity
  - Loss of top-down regulation
  - Cognitive deficits

- **Default mode network**
  - Activity and connectivity
  - Dissociation
  - Avoidance
  - Intrusive thoughts

- **Salience network**
  - Activity and connectivity
  - Heightened threat detection
  - Impaired modulation

- **Top-down regulation**

- **Modulation**
Brief timeline of psychopathology standards

Dawn of time to ~1948

Psychopathology 2.0; First DSM/ICD
~1948 (ICD) to ~1952 (DSM)

~2013 (DSM-5/RDoC)

Psychopathology 3.0; Significant changes & transdiagnostic approach
~2019 +

Psychopathology 4.0; Model-based Approach; Biology → Behavior
Science or fiction?
Potential model for psychopathology 4.0

Abdallah et al., 2018, emerge.care
Science or fiction?
Potential model for psychopathology 4.0

Abdallah et al., 2018, emerge.care
Chronic Stress Pathology

Vicious cycle of CSP

Abdallah et al., 2018, emerge.care
Common mechanisms across diagnoses

- High comorbidity (e.g., MDD, PTSD, suicidality)
- Common treatments (e.g., SSRIs, ketamine)
- Common biological pathways (e.g., gray matter deficits)
- Common biopsychosocial predispositions (e.g., genetics, IQ, abuse)
- Common psychological pathology (e.g., chronic stress)
Chronic Stress Pathology
Stress leads to synaptic dysconnectivity
Synaptic dysconnectivity
The canary in the coal mines
In the words of Bonnie Tyler – I’m holding out for a hero.
Ketamine as a treatment AND a tool

- ~50% of TR patients respond
- It’s RAAD (others are SAAD)
- Mechanistically interventional biomarker testing while improving lives
- Optimization for reproducibility
- Identify neural correlates (drug and psychopathology)
Ketamine stimulates rapid regrowth of synaptic connectivity
Duman and Aghajanian Science 2012
Abdallah et al., 2017, Neuropsychopharmacology

B

\[ \text{Cohen's } d = 0.95 \]

\[
\text{Pre-Ketamine GBCr}
\]

\[
\text{PFC of HC}
\]

\[
\text{PFC of MDD}
\]

C

\[ \text{Cohen's } d = 0.46 \]

\[
\text{Post-Ketamine GBCr}
\]

\[
\text{PFC of HC}
\]

\[
\text{PFC of Responders}
\]
PTSD might be a “synaptic disconnection syndrome...”

Abstract

Purpose of Review

Studies of the neurobiology and treatment of PTSD have highlighted many aspects of the pathophysiology of this disorder that might be relevant to treatment. The purpose of this review is to highlight the potential clinical importance of an often-neglected consequence of stress models in animals that may be relevant to PTSD: the stress-related loss of synaptic connectivity.

Recent Findings

Here, we will briefly review evidence that PTSD might be a “synaptic disconnection syndrome” and highlight the importance of this perspective for the emerging therapeutic application of ketamine as a potential rapid-acting treatment for this disorder that may work, in part, by restoring synaptic connectivity.

Summary

Synaptic disconnection may contribute to the profile of PTSD symptoms that may be targeted by novel pharmacotherapeutics.

Keywords: PTSD, Synapse, Glutamate, NMDA, Ketamine, Plasticity, Connectivity
Ketamine for Veterans with PTSD

- Treatment resistant
- US Veteran
- Able to travel to CT
  - funds for travel/accommodation
- Safety, efficacy, durability of effects & dose response
Evidence of ketamine for suicide

Hot Topics in Neuroscience

USE OF KETAMINE IN ACUTE CASES OF SUICIDALITY

by Jae Lee, DO; Puneet Narang, MD; Manasa Enja, MD; and Steven Lippmann, MD


EFFECTS OF KETAMINE ON EXPLICIT AND IMPLICIT SUICIDAL COGNITION: A RANDOMIZED CONTROLLED TRIAL IN TREATMENT-RESISTANT DEPRESSION

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Abstract

Background—Preliminary evidence suggests intravenous ketamine has rapid effects on suicidal cognition, making it an attractive candidate for depressed patients at imminent risk of suicide. In the first randomized controlled trial of ketamine using an anesthetic control condition, we tested ketamine’s acute effects on explicit suicidal cognition and a performance-based index of implicit suicidal cognition (Implicit Association Test; IAT) previously linked to suicidal behavior.

Method—Symptomatic patients with treatment-resistant unipolar major depression (inadequate response to ≥3 prior antidepressant trials) were randomized using a computer-generated list of explicit suicidal ideations (Beck Scale for Suicidal Identities, Montgomery-Asberg Rating Scale suicide item, Quick Inventory of Depressive Symptom Scales suicide item) and the IAT to assess suicidality implicitly.

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The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis

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Presentations: The results of this meta analysis will be presented in abstract form at the annual meeting of the Society for Biological Psychiatry in May 2017.

Materials

Dr. Winklowski receives research support from Takeda Bioscience and Janssen Pharmaceuticals. In the past three years, Dr. Winklowski has provided consultation services to Johnson & Johnson Research and Development, and documents the current position of the principal investigator or a company in which he holds a financial or nonfinancial interest. Beth Israel Deaconess Medical Center, Massachusetts General Hospital, and the Massachusetts Mental Health Center have all received grants from companies with financial interests in ketamine. Dr. Winklowski is a member of the mental health association of Boston. The Massachusetts Mental Health Center, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, and the Harvard Medical School have received funding from the National Institute of Mental Health. Certain of the authors of this article also have financial or nonfinancial interest in the companies that support ketamine research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
In progress, Upcoming Work and Future Directions

- Symptom improvement in PTSD and SI/SA, and parallel brain changes
- Sex/gender and aging differences in SI/SA and ketamine response
- Sleep
- PET scans to better identify synaptic strength/density
  - SV2A
  - [11C]UCB-J tracer
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NIMH

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**Brief Take Aways**

- Trauma & chronic stress have far reaching consequences
- Death by suicide is tip of the iceberg; need to investigate ideation, especially in context of PTSD
- Chronic stress pathology may be paramount as common underlying insult
- Synaptic connectivity may be critical in prevention, diagnosis, and treatment
- Ketamine is a valuable tool and RAAD
- Research & clinical practice are progressing rapidly - there is HOPE! There is HELP! Don’t go it alone.

**Resources**

- www.ptsd.va.gov
- www.afsp.org
- www.thetrevorproject.org
- suicidepreventionlifeline.org 1-800-273-8255
- emerge.yale.edu lynnette.averill@yale.edu
- www.ptsd.va.gov