Defining Core Concepts and Measurements in Suicidology

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Immediate Past President IASR
Outline

• Clarity of concepts and definitions – why is this important?
• Defining suicide, attempted suicide, self-harm and non-suicidal self-injury
• Some examples of instruments to measure these behaviours
• More core concepts in suicide research and how to measure
• Repeated measures, time windows
• Ecological momentary assessment
Associations between PTSD symptoms and suicide risk: A comparison of 4-factor and 7-factor models

2018), or firefighters (Boffa et al., 2017). To the best of our knowledge, no study has investigated the associations between PTSD symptoms and suicide risk using a national survey database. Therefore, we aimed to investigate the associations between suicide risk using both 4- and 7-factor models of PTSD symptom clusters in the general Japanese population.
Many studies of suicidal behaviour fail to provide clear definitions of what they are studying

- Creates big problems for referees, readers and for those who want to conduct systematic literature reviews and meta-analyses
- This is a waste of resources and impedes scientific progress
- Core concepts in any study should be clearly defined
- If you are going to study suicidal behaviour, you should describe and define these behaviours clearly and in behavioural terms
- Far too many ways of defining suicidal behaviours already exist, so unless you are making development of definitions the focus of your research, don’t add yet another one
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Definitions

• **Self-harm**
  Any act of self-poisoning or self-injury carried out by an individual irrespective of motivation

• **Suicide**
  Death caused by injuring oneself with the intent to die

• **Suicide attempt**
  A potentially self-injurious act carried out with at least some wish to die, as a result of act. There does not have to be any injury or harm, just the potential

• **Non-suicidal self-injury**
  Intentional destruction of one’s own body tissue without suicidal intent and for purposes not socially sanctioned
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COLUMBIA-SUICIDE SEVERITY RATING SCALE

(C-SSRS)

Lifetime Recent - Clinical

Version 1/14/09m


**SUICIDAL BEHAVIOR**
*(Check all that apply, so long as these are separate events; must ask about all types)*

<table>
<thead>
<tr>
<th>Actual Attempt:</th>
<th>Lifetime</th>
<th>Past 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A potentially self-injurious act committed with at least some wish to die, <em>as a result of act</em>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <strong>There does not have to be any injury or harm</strong>, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you made a suicide attempt?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>Have you done anything to harm yourself?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What did you do?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you_____ as a way to end your life?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you want to die (even a little) when you_____?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were you trying to end your life when you_____?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Or Did you think it was possible you could have died from____?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?</strong> (Self-Injurious Behavior without suicidal intent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
</tbody>
</table>
Interrupted Attempt:
When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*
Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

*Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*
If yes, describe:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Total # of interrupted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aborted or Self-Interrupted Attempt:
When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

*Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*
If yes, describe:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Total # of aborted or self-interrupted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Preparatory Acts or Behavior:
Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one’s death by suicide (e.g., giving things away, writing a suicide note).

*Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*
If yes, describe:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Total # of preparatory acts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Total # of preparatory acts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Self-Harm (SH)

Non-Suicidal Self-Injury (NSSI)

Suicidal Self-Harm

Suicide Attempt

Suicide

American Foundation for Suicide Prevention

International Academy of Suicide Research
Clinician-Administered Nonsuicidal Self-injury Disorder Index (CANDI)


- Evaluates the 6 criteria (A-F) for DSM-V NSSI disorder

- First: Administer a 17-item self-report questionnaire – Deliberate Self-Harm Inventory (DSHI) for Criterion A

- Second: Conduct structured interview for Criterion A and the rest of the criteria
DSHI (Past-Year Version)

This questionnaire asks about a number of different things that people sometimes do to hurt themselves. Please be sure to read each question carefully and respond honestly. Often, people who do these kinds of things to themselves keep it a secret, for a variety of reasons. However, honest responses to these questions will allow us to better help you. Please answer yes to a question only if you did the behavior intentionally, or on purpose, to hurt yourself. Do not respond yes if you did something accidentally (e.g., you tripped and banged your head on accident). If you don’t know the exact number of times you engaged in a certain behavior or on how many different days you did it, simply provide your best estimate.

1. **In the past year (12 months)**, have you ever intentionally (i.e., on purpose) cut your wrist, arms, or other area(s) of your body (without intending to kill yourself)? (circle one):
   1. Yes  
   2. No

   If yes,
   a. How many *times* have you done this **in the past year (12 months)**? ________________
   b. On how many different *days* have you done this **in the past year (12 months)**? ________________
ADMINISTER PAST-YEAR DELIBERATE SELF-HARM INVENTORY (PAGE 4), THEN REVIEW ANY ITEMS ENDORSED.

FOR EACH ITEM ENDORSED, CONFIRM THE FOLLOWING:

You indicated that in the past year, you intentionally (METHOD: cut, burned, carved, etc.) yourself ____ times on ____ days, is that correct?

Did you have any intention of killing yourself at those times?

To what extent did you expect this behavior to result in death?

- 0 No expectation of death
- 1 Some expectation of death
- 2 Definite expectation of death

IF “OTHER” IS ENDORSED, CONFIRM:

What did you do?

QUERY AS NECESSARY TO ENSURE DESIRE FOR AND EXPECTATION OF PHYSICAL HARM:

Did you engage in this behavior specifically to harm yourself physically, without intending to kill yourself?

<table>
<thead>
<tr>
<th>A.</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engaged in self-injury 5+ days in the past year?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-injury resulted in tissue damage (e.g., bleeding, bruising)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without intention or expectation of death?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALL OF THE ABOVE “A” ITEMS MUST BE CODED “YES” TO MEET CRITERION A

| A Criterion met? | NO | YES |

INVENTORY OF STATEMENTS ABOUT SELF-INJURY (ISAS) – SECTION I. BEHAVIORS

This questionnaire asks about a variety of self-harm behaviors. Please only endorse a behavior if you have done it intentionally (i.e., on purpose) and without suicidal intent (i.e., not for suicidal reasons).

1. Please estimate the number of times in your life you have intentionally (i.e., on purpose) performed each type of non-suicidal self-harm (e.g., 0, 10, 100, 500):

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutting</td>
<td></td>
</tr>
<tr>
<td>Severe Scratching</td>
<td></td>
</tr>
<tr>
<td>Biting</td>
<td></td>
</tr>
<tr>
<td>Banging or Hitting Self</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td></td>
</tr>
<tr>
<td>Interfering w/ Wound Healing</td>
<td></td>
</tr>
<tr>
<td>(e.g., picking scabs)</td>
<td></td>
</tr>
<tr>
<td>Carving</td>
<td></td>
</tr>
<tr>
<td>Rubbing Skin Against Rough Surface</td>
<td></td>
</tr>
<tr>
<td>Pinching</td>
<td></td>
</tr>
<tr>
<td>Sticking Self w/ Needles</td>
<td></td>
</tr>
<tr>
<td>Pulling Hair</td>
<td></td>
</tr>
<tr>
<td>Swallowing Dangerous Substances</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
# Inventory of Statements About Self-Injury (ISAS) – Section II. Functions

**Instructions**
This inventory was written to help us better understand the experience of non-suicidal self-harm. Below is a list of statements that may or may not be relevant to your experience of self-harm. Please identify the statements that are most relevant for you:

- Circle **0** if the statement *not relevant* for you at all
- Circle **1** if the statement is *somewhat relevant* for you
- Circle **2** if the statement is *very relevant* for you

### When I self-harm, I am ...

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ... calming myself down</td>
<td>0 1 2</td>
</tr>
<tr>
<td>2. ... creating a boundary between myself and others</td>
<td>0 1 2</td>
</tr>
<tr>
<td>3. ... punishing myself</td>
<td>0 1 2</td>
</tr>
<tr>
<td>4. ... giving myself a way to care for myself (by attending to the wound)</td>
<td>0 1 2</td>
</tr>
<tr>
<td>5. ... causing pain so I will stop feeling numb</td>
<td>0 1 2</td>
</tr>
</tbody>
</table>
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Ecological Momentary Assessment (EMA)

- AKA Event Sampling Methodology
- Repeated collection of data via mobile devices on subjects' current behaviours and experiences in real time, in participants' natural environments.
- Minimizes recall bias
- Maximizes ecological validity
- Allows more careful study of processes influencing behaviour in real-world contexts
- For example, if you aim to study mechanisms of change during treatment
- Or you wish to study highly volatile phenomena such as suicidal ideation or hopelessness or frequently occurring events such as NSSI
Ecological Momentary Assessment (EMA)

• Example from my own lab: MinEMA (‘MyEMA’)

• App is password protected (!)

• The app will prompt participants to respond to a set of questions six times daily (between 10 AM and 10 PM) for seven consecutive days, yielding data from a maximum of 42 measurement points

• Each data collection takes 2-3 minutes

• Data are delivered directly and fully encrypted to and stored in the project database in the dedicated project area within our research server
Allows us to study (examples)

- ... sequential orders – what comes first?
- ... temporal patterns in more detail – in what situations or times of day?
- ... individual / group patterns
- ... changes in patterns over time and between intervention groups
- and many more
Defining Core Concepts and Measurements in Suicidology

Jill Harkavy-Friedman, PhD
If you can not measure it, you can not improve it.

~ Lord Kelvin
Plan

Basic measurement considerations
Suicide specific considerations
What is the variable of interest?

Based on level of interest and literature
- ideation, plan, intent, behavior, death
- knowledge, attitude, skill, behavioral change

Level of analysis
- person, family, institution, population
- candidate genes/genome screen

Absolute value or change score
- reduction, response, recovery

Multiple measures vs. single measure
- data reduction, redundancy
Administration Considerations

Format

- Face-to-face interview, self-report, behavioral observation, telephone, computer, biological

Source of information

- Self, parent, other informant, observer, records, epidemiological information

Instrument for repeated measures

- Same form, alternate forms
Who should measure?

Self-report vs. other report
Clinical vs. lay raters
Open vs. blind measurement
Technician vs. computer/lab equipment
Investigator
How to decide on a measure

Reliability
Validity
Sensitivity
Specificity
Variability
Ceiling and Floor effects
Reliability = Reproducability

Inter-rater

Kappa

Intra-class correlation
Test-Retest: Over time

Correlate time 1 and time 2
Parallel Forms: Across Measurements

Correlate forms
Internal Consistency: Within a test

Spearman Brown
Cronbach’s Alpha
Validity

Face Validity: Does it look like it measures what it is supposed to?

Content Validity: Is the content representative?

Criterion Validity: Predictive, Concurrent

Construct Validity: Accrual of meaning through convergent and discriminant validity
Reliability is the upper limit of validity
Can you find an effect?

Sensitivity and Specificity

Variability

Ceiling and Floor effects
Determine Goal of Assessment

Suicidal ideation and behavior
Risk
Treatment effect
Population risk

No matter the goal, suicide is complex, and you will likely have to measure multiple variables
It is very unfair to judge any body's conduct, without an intimate knowledge of their situation.

– Jane Austen
Variables for measurement

• Suicidal Behavior: ideation, attempts, completion details
• Clinical Measures: diagnosis, clinical characteristics, mood
• Psychological measures: depression, hopelessness, impulsiveness, emotion regulation
• Social History: trauma, stress, social functioning, school experience
• Cognitive functioning: decision-making, implicit bias,
• Psychophysiological measures: HRV, GSR, EEG
• Biological measures: neurotransmitters, hormones, metabolomics, inflammation, gut biome
• Environment: access to means, support, housing, food security
What needs to be measured?

Demographics
Suicidal ideation and behavior
Outcome
Confounders
Mediators and Moderators
Context
### Current Measures of Outcome

<table>
<thead>
<tr>
<th>Knowledge</th>
<th># crisis calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitudes</td>
<td>Associated symptoms</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>Impact of suicide</td>
</tr>
<tr>
<td>Suicide Attempts</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>Completed Suicide</td>
<td>School completion</td>
</tr>
<tr>
<td>Lethality of attempt</td>
<td># referrals</td>
</tr>
<tr>
<td>Suicide Intent</td>
<td>Social Skills</td>
</tr>
</tbody>
</table>
For Intervention studies outcomes must:

- Measure the target of intervention
- Be standardized
- Be “not average” at baseline
- Be expected to change within the time frame
- Be Sensitive to change
- Be present in all groups
- Have a measurable effect size
- Have demonstrated reliability and validity
- Be feasible
Measurements, observations, descriptions can only be considered scientific when they are independently confirmed by other people.

Jose Padilha
Thank You!

suicideresearchsummit.org
Clinical Trial Methods: Specific Considerations for Suicide Research

Gregory K. Brown, PhD
Barbara Stanley, PhD
Common design questions to consider when conducting clinical trial research with at risk samples

• What is the research question (study hypotheses)?
• What is the study intervention and how does it lower risk (mechanism)?
• Is the intervention safe?
• How will you know if the intervention was provided as indicated?
• Who is eligible to receive the intervention?
• What is the outcome domain?
• How will you measure the outcome?
• What is the control intervention?
• How many participants will you need?
• Is the study feasible?
Choose an Appropriate Suicide Outcome Domain

- Suicide
- Suicidal Behavior
- Suicidal Ideation
Use an Established Nomenclature of Suicidal Behavior

Self-directed Violence Surveillance: Uniform Definitions

Columbia Suicide Severity Rating Scale (C-SSRS) Definitions

Avoid terms that are infrequently used or poorly defined: “suicide gesture” or “suicidality”
Suicide as Outcome

• Pros
  • High ecological validity
  • State and national datasets are available: National Death Index, National Violent Death Reporting System

• Cons
  • Suicide is a rare event even among high risk populations and requires very large samples
  • Ascertaining death by suicide can take a long time
  • Discerning cause of death can be challenging (suicide vs accidental overdose)
Suicidal Behavior as Outcome

• Pros
  • May serve as a valid proxy measure of death by suicide
  • May be assessed by self-report, clinician interview, informant (such as a family member) or by using medical record data such as using ICD-10 codes
  • Occurs more frequently than suicides but are still rare events unless high risk samples are used

• Cons
  • May be especially rare events among older populations who often kill themselves on the first attempt
  • Suicidal attempts can be difficult to identify (questionable lethality/potential lethality or questionable intent to die)
    • Importance of using blind assessors to prevent biased assessments
    • Often difficult to maintain the blind
Suicidal Behavior as Outcome

• Determine the types of suicidal behavior to assess:
  • Suicide attempts
  • Interrupted attempts?
  • Aborted attempts?
  • Preparatory behavior toward imminent suicide behavior?
  • Is an ED visit for a suicide-related concern a positive or negative outcome?

• Use validated measures of suicidal behavior that correspond to the nomenclature
  • See PhenX Toolkit
  • Consider value of Common Data Elements so that data can be harmonized across studies

• Establish interrater reliability; consider using blinded adjudication boards for difficult to classify behaviors
Suicidal Ideation as Outcome

• Pros
  • Often more frequent than suicidal behavior
  • May be assessed by clinical interview or self-report
  • Validated measures of suicidal ideation are available
    • See Phenx Toolkit or recent reviews
    • Consider measures for the appropriate age group
  • Severity of suicidal ideation can be classified: (wish to die, active suicidal thoughts, active suicidal thoughts with general method, suicidal intent, suicidal intent with plan)
Suicidal Ideation as Outcome

• Cons
  • Suicidal ideation can be highly variable over time
    • Fleeting, short or long duration, or can be chronic
  • Subject to recall bias if assessed retrospectively
    • Consider “real time monitoring” such as Ecological Momentary Assessments
  • Secondary gains (or loses) can influence self-report
    • Desires hospitalization for reasons other than suicide risk; fears hospitalization or loss
Frequency Distribution of the Scale for Suicide Ideation (Current) During Follow-up

Data from Brown et al., JAMA, 2005
Frequency Distribution of the Scale for Suicide Ideation (Worst) During Follow-up

Data from Brown et al., JAMA, 2005
Determining Inclusion Criteria

• Measurement of Suicidal Ideation
  • Consider enrolling patients with history of ideation
    • What is the timeframe for the ideation: day/hour of assessment, past week, past month, or lifetime?
  • Use clearly defined and reliable threshold for severity of ideation
    • Use measures with evidence-based cut-off scores or validated types of ideation
    • Avoid vague or unreliable nomenclature: “significant suicidal ideation”
Sample Size Considerations – Suicidal Behavior

• Need to estimate the rates of behavior during follow-up in the intervention condition and the control condition

• Larger sample sizes are needed when measuring suicide behavior to determine if the intervention prevented the behavior than when using measures to assesses changes in severity (such as continuous depression scales)
Consider Recruitment Feasibility when Establishing Thresholds on Suicide Measures

- Increased Sample Availability
- Lower Power to Detect Effects During Follow-up
  - Lower threshold Such as longer timeframe
  - Decreased rates of suicide behavior
Managing Participants in Suicide Intervention Trials

- What to monitor
- How to monitor
- What should be done if risk is detected?
- Participants in the control condition---what is an adequate control?
Managing Risk Occurs throughout the Trial

• Points of managing risk
  • Initial contact—screening phone contact
  • Between screening and in-person visit/consent
  • Prior to randomization
  • During trial
  • Disposition

• Procedures are similar throughout

• Control conditions can vary but monitoring of risk should be the same across conditions
Tension between Safety Procedures and “Best” Research Methods

• Prior to discussing Safety procedures, important to discuss their impact on methods throughout the trial
• This impact has to be considered carefully
• Balance between safety and methods that will answer the research question being asked
Case Example: Trial Comparing Paroxetine with Placebo in Suicide Attempters

• Research question—is paroxetine effective in preventing the recurrence of suicide attempts
• Outcome---Suicide attempts
• Trial length---12 months
• Safety procedures: Remove if suicide attempt occurs during trial or if suicide ideation becomes “too significant”
• Minimizes risks
• May lead to inaccurate conclusions from biased withdrawal
• May not be clinically necessary
“The time from baseline to first recurrence of a suicide attempt was considered to be the primary endpoint.”

“Paroxetine appeared to be effective in the prevention of recurrent suicide attempts. This effect was observed (only) in minor repeaters.” Verkes et al. 1998
What should be done if suicide attempts occur during a trial?

• Removal and referral
• Maintain in trial with standard monitoring procedures
• Maintain in trial with increased monitoring in place
What should be monitored with suicidal participants?

• Suicide risk---but how is it determined?
  • Increasing suicidal ideation
    • Level of ideation that we typically identify as problematic—ideation with intent; ideation with intent and plan
  • Suicidal behavior
    • Increasing symptoms associated with suicidal behavior e.g. depression, hopelessness

• Need to define and set criteria at the outset of the trial
• Need to set procedures for monitoring at the outset
• Need to define what will be done if criteria are met
Defining and intervening on suicide risk

• This is may seem *simple but it is not*

• Has an impact on:
  • Participant safety if too minimal
  • Participant willingness to disclose if too strict
  • Study outcomes if occurs too frequently or at too low a bar
    • Why do we care if safety is at stake if study outcomes are adversely affected?
    • Participants may endure a trial for no reason; waste of time, money and possible risk exposure

• Obtaining risk by: 1. asking participants directly; 2. monitoring how they are responding via EMA; 3. losing contact (participant stops attending appointments, stops answering calls)
Risk determination: How and by Whom

• Obtaining risk by:
  • 1. asking participants directly
  • 2. monitoring how they are responding via EMA
  • 3. losing contact (participant stops attending appointments, stops answering calls)

• Who assesses risk
EMA as Tool to Measure SI: Comparison of SSI and EMA SI

- Worst-point EMA ideation was positively related to the retrospective post-EMA SSI ($r=.729$, $p < .001$)

- EMA ideation severity was also positively related to the retrospective post-EMA SSI; participants with one point higher on the post-EMA SSI had on average .85 higher scores on each EMA ideation item (SE=0.10)

- However, **58% of participants reporting ideation with EMA denied past week ideation when assessed retrospectively** over the same timeframe on the SSI
Demographic and clinical characteristics by whether or not post EMA SSI = 0

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total sample (n=51)</th>
<th>Post-EMA SSI=0 (n=30)</th>
<th>Post-EMA SSI&gt;0 (n=21)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>SSI (Baseline)</td>
<td>4.2 (6.2)</td>
<td>1.8 (5.6)</td>
<td>7.3 (5.7)</td>
<td>.0085</td>
</tr>
<tr>
<td>Ham-D</td>
<td>16.0 (6.3)</td>
<td>14.1 (6.1)</td>
<td>18.7 (5.8)</td>
<td>.0104</td>
</tr>
<tr>
<td>BDI</td>
<td>21.6 (9.8)</td>
<td>17.6 (8.7)</td>
<td>27.0 (8.6)</td>
<td>.0005</td>
</tr>
<tr>
<td>BHI</td>
<td>10.5 (6.2)</td>
<td>7.4 (5.8)</td>
<td>14.6 (3.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EMA SI Worst Point</td>
<td>14.2 (9.8)</td>
<td>7.9 (4.7)</td>
<td>23.2 (7.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EMA SI Mean</td>
<td>7.2 (5.7)</td>
<td>3.6 (3.2)</td>
<td>12.4 (4.4)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Comparing EMA SI and SSI=0

Individual EMA suicidal ideation trajectories for participants with post-EMA SSI scores of zero
Mixed effects model of EMA suicidal ideation item endorsement on having non-zero post-EMA SSI

<table>
<thead>
<tr>
<th>EMA Ideation Items</th>
<th>Post-EMA SSI=0 (n=29)</th>
<th>Post-EMA SSI&gt;0 (n=21)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>P-value</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>(1) Thoughts about dying</td>
<td>0.1 (0.1)</td>
<td>.3965</td>
<td>0.6 (0.1)</td>
</tr>
<tr>
<td>(2) Wish to live*</td>
<td>0.9 (0.2)</td>
<td>&lt;.0001</td>
<td>3.0 (0.2)</td>
</tr>
<tr>
<td>(3) Wish to die</td>
<td>0.0 (0.1)</td>
<td>.7256</td>
<td>0.9 (0.1)</td>
</tr>
<tr>
<td>(4) Wish to sleep/not wake</td>
<td>0.2 (0.2)</td>
<td>.1976</td>
<td>1.5 (0.2)</td>
</tr>
<tr>
<td>(5) Wish to escape</td>
<td>0.9 (0.2)</td>
<td>&lt;.0001</td>
<td>2.5 (0.2)</td>
</tr>
<tr>
<td>(6) Reasons for living*</td>
<td>1.3 (0.2)</td>
<td>&lt;.0001</td>
<td>3.0 (0.2)</td>
</tr>
<tr>
<td>(7) Thoughts about hurting self</td>
<td>0.0 (0.1)</td>
<td>.5825</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>(8) Urge to hurt self</td>
<td>0.0 (0.0)</td>
<td>.5178</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>(9) Thoughts about killing self</td>
<td>0.0 (0.1)</td>
<td>.6309</td>
<td>0.3 (0.1)</td>
</tr>
</tbody>
</table>

*Note. + items were reverse-coded.*
EMA Monitoring and Intervening

• Sometimes we do not know enough about when to intervene
• Intervening can have a significant impact on future responding making the assessment meaningless
• Suggested approach---to monitor EMA remotely
  • How often will EMA be monitored? Daily? 24/7?
  • Suicidal crises often last only minutes to a few hours in escalation from ideation to attempt
  • Identify point at which intervention will occur
  • Determine what will the intervention be
• Alternative approach---no EMA monitoring
  • Inform participants that EMA will not be monitored; that it is not a communication method
  • Provide emergency contact information as you would if assessments were done in the usual way—clinician interviews, weekly self ratings
In the past 15 minutes, how strongly have you felt or experienced the following:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>1. A wish to live</td>
<td></td>
<td></td>
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<tr>
<td>2. A wish to die</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. A wish to escape</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Thoughts about dying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Thoughts about suicide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Urge to commit suicide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Thoughts about hurting self</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. An urge to hurt yourself</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Like there were reasons for living</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Individual with Highly Variable Suicidal Ideation: When to Intervene?
Individual with Elevated, Stable Suicidal Ideation
Participant Safety Procedures

• Phone contacts—-at beginning obtain phone number to recontact and physical location

• Develop a safety plan---clinical tool

• Have full discussion with participants about emergency procedures with study staff should they become suicidal—research tool
  • Provide a written document with emergency procedures and study-specific contact information
  • Set the stage where investigators encourage rather than discourage contact if participants are struggling

• Suicide risk should be assessed *clinically* on a routine basis in addition to study assessments
Staff Safety Procedures

• *All* staff should have specific risk assessment training
• Specific safety procedures should be clearly laid out for all study staff
• For phone interactions, staff should have a way to connect with senior staff or emergency rescue *without* ending the call with the participant
• A senior investigator should always be available to assessors and research assistants for consultation; set the stage---better to consult than try to handle matters alone; let staff know to say that they have an emergency
Emergency Procedures

• Obtain emergency contacts at time of enrollment and permission to use them

• Identify conditions to participants when you will use emergency contacts

• Describe limits to confidentiality—if imminent suicide risk, confidentiality cannot be maintained
  • This discussion takes place during consent process but it is good to reinforce this periodically so participants are not surprised

• Describe emergency rescue procedures and how collaboration and cooperation can mitigate their use

• Transparency is crucial
Postvention

• Establish procedures in advance should a suicide or highly lethal attempt occur during the trial
  • Identify to whom events are reported

• Provide support for staff

• Determine how contact with family will be handled
Final Points to Consider

• Ensure adequate staff time
• Ensure adequate funding
• Ensure support for all staff including senior investigators
• Use consultation with peers extensively
• Keep in mind that the work is hard but the goal is extremely rewarding
  • Safety planning feedback from users
The Pathophysiology of Suicidal Behavior

J. John Mann, MD

IASR/AFSP Workshop 2020
Disclosures:

1. This talk is based on research funded by NIMH & BBRF.

2. Recipient of royalties from Research Foundation for Mental Hygiene for commercial use of the C-SSRS.
A Brain-Centric Model of Suicidal Behavior: Mann and Rizk, AJP 2020.
Stress Diathesis Model of Suicidal Behavior

- **Internal Stress of Major Depression**
- **External Stressful Life Events**
- **Perception of Stress (depression & social cues)**
- **Response to Stress**
Subjecive Depression Associated with Anterior Cingulate Cortex Hyperfunction and dlPFC Hypofunction

<table>
<thead>
<tr>
<th>Beck Depression Inventory</th>
<th>Positive correlations</th>
<th>Negative correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<td><img src="image3.png" alt="Image" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hamilton Depression Rating Scale</th>
<th>Positive correlations</th>
<th>Negative correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Subjective depression, and clinician-rated depression are associated with different brain regions.
Brain Blood Flow Predicts Suicide in Major Depression

Dorsolateral PFC and insula hypofunction are seen in future suicides.

Willeumier et al Trans Psychiatry (2011)
Responses to Emotional Faces in Euthymic Suicide Attempters *versus* Nonattempters Show Social Distortion

Jollant et al, AJP 2008, 165
Stress Diathesis Model of Suicidal Behavior

- External Stressful Life Events
- Internal Stress of Major Depression
- Perception of Stress (depression & social cues)
- Response to Stress

J Mann 2020
Delayed Discounting

* Value of rewards are discounted in proportion to delay.

* Value of uncertain rewards are even more discounted.

* Degree of discounting is a trait.

* Delayed discounting is an unconscious mechanism.
Clinical implications for decision to die by suicide or not?

• Suicide offers *immediate certain* relief from pain associated with life.
• Treatment offers *uncertain future* benefit.
• Treatment is a harder sell to a patient prone to delayed discounting and because of uncertainty of response.
A Revised Model of Decision Making and Suicidal Behavior

Emotional pain

Value of relief by suicide or relief by antidepressant treatment

Need for rapid relief even if survives attempt or value of certainty of death

Low lethality impulsive suicidal behavior

High lethality planned suicidal behavior

Treatment
Brain Blood Flow Predicts Suicide in Major Depression

Dorsolateral PFC and insula hypofunction is associated with severity of subjective depression and more pronounced in future suicides.

Willeumier et al Trans Psychiatry (2011)
Dorsolateral PFC Regulates Risk-taking Behavior

* Healthy men, increase risk-taking choices on a gambling task when transcranial magnetic stimulation inhibits dorsolateral PFC presumably because top down effect on orbital PFC is compromised (Knoch et al 2006).
* Imaging of MDD at risk for suicide shows hypoactive dlPFC.
* **Dorsolateral PFC impaired > orbital PFC > risky decisions and suicidal behavior**
Impaired Learning During Iowa Gambling Task by Suicide Attempters: failure to improve problem solving

![Figure 2: Changes in Performance During the Iowa Gambling Task for Violent and Nonviolent Suicide Attempters, Affective Control Subjects, and Healthy Comparison Subjects (Intermediate Scores)](image)

Jollant et al. AJP, 2005
Neurobiology of Suicide: seven pathways

1. High $5$-HT$_{1A}$ autoreceptors $\rightarrow$ low serotonin release $\rightarrow$ low activity $\rightarrow$ loss of trophic effect
2. Low CSF MHPG = low noradrenergic activity
3. Low GABA = low GABAergic activity
4. High glutamate $\rightarrow$ neurotoxicity
5. High HPA axis activity $\rightarrow$ neurotoxicity
6. Inflammation $\rightarrow$ neurotoxicity
7. Low omega $3/6$ PUFA ratio, stress $\rightarrow$ neuroinflammation and altered brain activity/ neurotoxicity
Stress and Inflammation

• Inflammation is how the body defends against infection and cancer.
• Inflammation is how the body repairs after trauma.
• Inflammation is a response to stress.
Inflammation in the Brain

- Inflammation outside the brain affects the brain and produces “sickness” behavior or state.
- Inflammation in body can cross the BBB and affect the brain by producing inflammation in the brain.
- Infections can cross the BBB and produce inflammation in the brain.
- COVID-19 has not been shown convincingly to get into the brain but does affect brain blood vessels and cause strokes.

J Mann.2020
Inflammatory Response is Triggered by Emotional Stress
A PET Scan of Inflammation in Brain: TSPO binding
ER176 $V_T$ (not adjusted for genotype)

- anterior cingulate
- orbital PFC
- medial PFC

$y = 7.569x - 4.888$
$R^2 = 0.692$

$y = 6.991x - 4.672$
$R^2 = 0.692$

$y = 7.695x - 6.943$
$R^2 = 0.691$

J Mann. 2020
SUICIDAL IDEATION

ER176 $V_T$ (not adjusted for genotype)

$y = 1.709x - 2.763$
$R^2 = 0.199$

$y = 1.497x - 2.378$
$R^2 = 0.179$

$y = 1.875x - 3.787$
$R^2 = 0.231$

- anterior cingulate
- orbital PFC
- medial PFC

J Mann.2020
Stress Diathesis Model of Suicidal Behavior

- **Internal Stress of Major Depression**
- **External Stressful Life Events**

**Perception of Stress (depression & social cues)**

**Response to Stress**
Dranovsky and Hen, 2006:
Stress in mice > fewer cells and smaller cells in hippocampus
Antidepressants > more and bigger cells
More Time in a Major Depression Produces Smaller Hippocampus

Fig. 3. Correlation between left hippocampal gray matter volumes and total days of major depression.

Sheline et al PNAS, 1996
Antidepressants Appear to Correct Dentate Gyrus Volume Deficit in Depression

n=18
n=18
n=8
n=5
n=4

p<.001

Boldrini et al, BP 2012
Fewer **Mature** Neuronal Granule Cells in Dentate Gyrus in Untreated MDD Suicides.

**SSRI-Treated MDD Are Same as Controls**

Boldrini et al, BP 2012.
Process Length/Synapses In MDD Suicides

Process retraction in MDD suicides indicates synapse loss

Boldrini et al, unpublished
Shorter Serotonin Neuron Process Length in PFC of Suicide Decedents

Process length is shorter in some layers of Brodmann Area 46 in dIPFC.

Austin et al. Neuroscience 2002
Brain BDNF Lower in Depression and Suicide If History Of Childhood Adversity

Figure 5. 5-HT1A receptor mRNA in situ hybridization in hippocampus from subjects with and without childhood adversity (ELA). 5-HT1A receptor mRNA is more in anterior DG in suicide vs non-suicide MDD.

Figure 6. FKBP5 Levels in Prefrontal Cortex. Subjects with a history of early life adversity have higher FKBP5 levels in both dorsolateral and cingulate prefrontal cortex.

Figure 7. HDAC levels in prefrontal cortex. In dorsolateral prefrontal cortex (BA 9) suicides with early life adversity had reduced HDAC6 levels compared to suicides with no history of early life adversity. In anterior cingulate cortex (BA 24) suicides had lower HDAC6 levels than nonsuicides, independent of adversity status.

Figure 8. BDNF Protein. Western blots were analyzed by autoradiography. Both suicide groups as well as controls exposed to adversity had lower ratios than controls.
HPA Axis Over-activity and Neuroinflammation in Suicide

Figure 6. FKBP5 Levels in Prefrontal Cortex. Subjects with a history of early life adversity have higher FKBP5 levels in both dorsolateral and cingulate prefrontal cortex.

Figure 7. HDAC levels in prefrontal cortex. In dorsolateral prefrontal cortex (BA 9) Suicides with early life adversity had reduced HDAC6 levels compared to suicides with no history of early life adversity. In anterior cingulate cortex (BA 24) suicides had lower HDAC6 levels than nonsuicides, independent of adversity status.

Figure 8. BDNF Protein. Western blots were analyzed by autoradiography. Both suicide groups as well as controls exposed to adversity had lower ratios than controls.

HPA Axis Overactivity

Neuroinflammation in Suicide MDD

J Mann 2020
Trophic Deficits and Toxic Effects in MDD Suicides

- Lack serotonin/BDNF trophic effects.
- Excessive HPA allostatic load.
- Neuroinflammation.
- All favor process and cell loss.
Summary

• Brain function is abnormal in high suicide risk patients and decedents in brain areas related to emotion regulation, social perceptions, decision-making and learning.
• Stress raises HPA activity, increases inflammation and lowers BDNF.
• Inflammation reduces serotonin function.
• All reduce processes and cell survival and increase risk of suicide.
Genetics and Epigenetics in Suicide Research

Gil Zalsman MD, MHA
President of the IASR
Director of Geha MHC
Chair of Psychiatry, Tel Aviv University, Israel
and Molecular Imaging and Neuropathology Division,
Columbia University, USA
Basic Principals
Chapters: 10-14
Specific for suicide
Suicide runs in families
Suicide runs in families

(A Roy et al 1990, DA Brent et al., 1996)

Ernest Hemingway
Suicide runs in families

A. Families studies

What we do using this method?
- Familial aggregation of suicidal behavior
- Assessing relatives of attempters/died by suicide
- Population registry in Denmark and Sweden (Asberg 2003, Qin 2002)

Strengths and weaknesses of this method
- Most are retrospective
- Environment confounders? No just due to grief (sui>homicide)
- Prospective- lots of years and resources, government will…
Suicide runs in families

B. Adoption studies

What we do using this method?
• Using adoption registry
• Matching adopted subjects who died by sui to those who didn’t looking at their biological vs non biological parents (Schulsinger 1979)
• Controls for environmental confounders

Strengths and weaknesses of this method
• Needs open registry (Denmark)
• Most are retrospective
• Prospective- lots of years and resources, government will…
Suicide runs in families

C. Twins studies

What we do using this method?
- Using twins registry
- MZ vs DZ
- Evaluate magnitude of gene vs environment effects
- Twins registry in Denmark

Strengths and weaknesses of this method
- Needs registry
- Shared and non-shared environment
- Most are retrospective
- Prospective- lots of years and resources, government will...
Suicide runs in families

C. Twins studies

DZ 0.7%

MZ 13%

(Roy A. 1990; Ott J. et al, 2001)
Approaches in research of the medical genetics

Figure 1 | Approaches to psychiatric genetics research. a | The gene-to-disorder approach assumes direct linear relations between genes and disorder. b | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. c | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. d | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.
Association studies in suicidology
Association Studies in Suicidology

What we do using this method?
• Assessing specific candidate genotype frequency in affected vs non affected subjects. Can use intermediate phenotypes (endophenotype)
• Assuming direct main effect by a single allele/SNP/polymorphism
• Chi square statistics

Strengths and weaknesses of this method
• Looking under the light
• Association doesn’t mean effect or causality
• If there is a direct main effect of a single marker it’s a Nobel price…
• Simple PCR technique (learn how to)
• Needs large numbers (n)
• Needs good clinical phenotype (Questionnaires) OR ENDOPHENOTYPE
• Environmental effects are not accounted for
### e.g. 5HTTLPR

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Non suicidal (expected)</th>
<th>Suicidal (finding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>SS</td>
<td>15%</td>
<td>75%</td>
</tr>
<tr>
<td>SL</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Direct main effect approach

TPH1
TPH2
SERT-5HTTLPR
COMT val/met
MAO A
5HT’s
DRD4
NET
BDNF
Wolfram (WFS1)
Etc......

→ Equivocal results
Haplotype Relative Risk (HRR)

TDT

Parents are controls for their suicidal kid

*Avoid Ethnic Stratification
HRR association approach

Transmitted alleles

Non-transmitted allele
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population Description</th>
<th>Polymorphisms</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zalsman et al. (2003a,b)</td>
<td>Family-based study (IBIS): 185 Caucasian adolescents of Jewish origin who recently attempted suicide and both biological parents of 43 subjects and from one parent of 9 subjects</td>
<td>A218C in intron 7 of tryptophan hydroxylase (TPH) gene</td>
<td>HBB method (chi-square = 0.94; P = 0.36), the TDT (chi-square = 0.25; P = 0.61), or association analysis in known population frequencies (chi-square = 1.66; P = 0.19 for Ashkenazi, and P = 0.38 for non-Ashkenazi). Analysis of variance with the 5-HTTLPR demonstrated a significant difference between C/C and A/A genotypes in suicide risk and depression among the patients (F = 8.0). The findings suggest that polymorphisms 5-HTTLPR has no major relevance to the pathogenesis of adolescent suicidal behavior but may have a subtle effect on some related phenotypes.</td>
</tr>
<tr>
<td>Zalsman et al. (2003b)</td>
<td>Forty-eight Israeli adolescent adolescents who recently attempted suicide using the haplotype relative risk (HRR)</td>
<td>5-HTTLPR polymorphism</td>
<td>No significant association of the 5-HTTLPR polymorphism with suicidal behavior was found. Analysis of variance demonstrated a significant difference in violence measures between patients carrying the LL and LL genotype.</td>
</tr>
<tr>
<td>Zalsman et al. (2004)</td>
<td>Sixty-nine Israeli adolescent adolescents who recently attempted suicide and 167 healthy controls</td>
<td>Dopamine receptor subtype 4 (DRD4) gene; serotonin transporter (5-HTTLPR)</td>
<td>No significant association between the DRD4 polymorphism and suicidal behavior was found. Analysis of the suicide-related measure demonstrated a significant difference in depression severity between suicidal and non-suicidal healthy and heterozygous for the DRD4 allele.</td>
</tr>
<tr>
<td>Reference</td>
<td>Population</td>
<td>Polymorphisms</td>
<td>Main Findings</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Zaleman et al. (2005a)</td>
<td>Thirty-two suicidal and 28 non-suicidal Ashkenazi Israeli adolescent psychiatric inpatients</td>
<td>5-HTTLPR polymorphism and platelet transporter binding</td>
<td>The 5-HTTLPR polymorphism was not associated with transporter binding or with suicidality or other clinical phenotypes. However, in the suicidal group, a significant positive correlation between platelet SERT density and anger scores and a negative correlation between platelet count and trait anxiety were observed.</td>
</tr>
<tr>
<td>Zaleman et al. (2005b)</td>
<td>A family-based method (394 J30 families of inpatient adolescents from Jewish Ashkenazi origin, with a recent suicide attempt)</td>
<td>5-HT(2A) receptor gene polymorphism T105C</td>
<td>No difference was found in allelic distribution between transmitted and non-transmitted alleles. There was no significant association of genotype with any of the clinical traits.</td>
</tr>
<tr>
<td>Cicchetti et al. (2010a)</td>
<td>Eight hundred and fifty low-income children (478 maltreated; 372 non-maltreated) with self-reported depressive and suicidal symptoms</td>
<td>5-HTTLPR</td>
<td>Higher suicidal ideation was found among maltreated than non-maltreated children. The groups did not differ in 5-HTTLPR genotype frequencies. Children with one to two maltreatment subtypes and/or 5-HTTLPR had higher suicidal ideation than those with the 11 genotype; suicidal ideation did not differ in non-maltreated children or children with three to four maltreatment subtypes based on 5-HTTLPR variation.</td>
</tr>
<tr>
<td>Zaleman et al. (2010b)</td>
<td>Four groups of adolescents were included: suicidal (N = 33) and non-suicidal (N = 30) psychiatric inpatients, suicide attempts admitted to three psychiatric emergency rooms (N = 51), and a community-based control group (N = 93)</td>
<td>5-HTTLPR, MAOA (1027C) HTR2A (1027C) and plasma serotonin</td>
<td>Haplo-genotype for the T allele of the HTR2A 1027C polymorphism was associated with lower impulsivity and aggression compared to TC carriers. Low activity MAOA genotypes were associated with suicidality. No association was found with 5HTT level.</td>
</tr>
</tbody>
</table>
GWAS in suicidology
Genome Wide Association Studies

What we do using this method?
- Multiple association studies in one shot
- DNA microarrays
- RNA expression arrays
- Looking for linkage between specific SNPs and suicide phenotypes

Strengths and weaknesses of this method
- Needs large numbers (n)
- $$$ (not anymore)
- University setting-genome center
- Environmental confounders
- Multiple testing: many SNPs are very significant….Use post hoc tests (e.g. Hochberg-Binayminy) or look for candidate SNPs
Genome Wide Association Studies

The World Journal of Biological Psychiatry

ISSN: 1562-2975 (Print) 1814-1412 (Online) Journal homepage: http://www.tandfonline.com/loi/iwbp20

A pilot genome wide association and gene expression array study of suicide with and without major depression

Hanga Galfalvy, Gil Zalsman, Yung-Yu Huang, Lauren Murphy, Gorazd Rosoklija, Andrew J. Dwork, Fatima Haghghi, Victoria Arango & J. John Mann
Table 3: Literature review for the 19 significant GWAS candidate genes in suicides
(based on OMIM database*).

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Chr. #</th>
<th>Description</th>
<th>Suggested clinical role*</th>
<th>Similar Genes found by others in expression studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH13</td>
<td>16</td>
<td>cadherin 13, H-cadherin (heart)</td>
<td>Lung tumor recurrence?</td>
<td>CDH12, CDH2 (Thalmeier et al., 2008)</td>
</tr>
<tr>
<td>NPR3</td>
<td>5</td>
<td>neprilysin peptide receptor C</td>
<td>Maintenance of blood pressure</td>
<td></td>
</tr>
<tr>
<td>CD300LB</td>
<td>17</td>
<td>CD300 antigen-like family member b</td>
<td>Cell surface localization in B and NK cells</td>
<td></td>
</tr>
<tr>
<td>FOXN3</td>
<td>14</td>
<td>forkhead box transcription</td>
<td>DNA damage correction?</td>
<td>ADAMTS1, IGF1, VIP, WDR39 (Thalmeier et al. 2008)</td>
</tr>
<tr>
<td>DISCI</td>
<td>1</td>
<td>disrupted in schizophrenia 1</td>
<td>Susceptibility for schizophrenia</td>
<td></td>
</tr>
<tr>
<td>CYP19A1</td>
<td>15</td>
<td>cytochrome P450, family 19, subfamily A, polypeptide 1</td>
<td>Aromatase deficiency</td>
<td></td>
</tr>
<tr>
<td>MYO3A</td>
<td>10</td>
<td>myosin IIIA</td>
<td>Autosomal recessive deafness</td>
<td>MYR8 (Thalmeier et al. 2008)</td>
</tr>
<tr>
<td>SFRS11</td>
<td>1</td>
<td>arginine/serine-rich 11 splicing factors</td>
<td>Pre-mRNA splicing?</td>
<td></td>
</tr>
<tr>
<td>LXAMP</td>
<td>3</td>
<td>limbic system-associated membrane protein</td>
<td>Neuronal surface glycoprotein in limbic system (Pimenta et al., 1996)</td>
<td></td>
</tr>
<tr>
<td>DSC2</td>
<td>18</td>
<td>desmocollin 2</td>
<td>Ca dependent glycoprotein important for cell adhesion</td>
<td></td>
</tr>
<tr>
<td>SPTLC1</td>
<td>9</td>
<td>serine palmitoyltransferase, long chain base subunit 1</td>
<td>Hereditary sensory neuropathy</td>
<td></td>
</tr>
<tr>
<td>ACCN1</td>
<td>17</td>
<td>aniloid-sensitive cation channel 1, neuronal (degermin)</td>
<td>Neurodegeneration? K.O mouse reduced sensitivity to mechancic sensation</td>
<td></td>
</tr>
<tr>
<td>FLJ33312</td>
<td>5</td>
<td>Hypothetical protein</td>
<td>Not known</td>
<td>FLJ21616 (Sequeira et al. 2007)</td>
</tr>
<tr>
<td>MBNL2</td>
<td>13</td>
<td>muscleblind-like 2</td>
<td>May be associated with Myotonic Dystrophy</td>
<td></td>
</tr>
<tr>
<td>CD44</td>
<td>11</td>
<td>CD44 molecule</td>
<td>Migration, cell fusion, tumorgenesis</td>
<td>(Thalmeier et al. 2008, Sequeira et al. 2007)</td>
</tr>
<tr>
<td>TUBGCP3</td>
<td>13</td>
<td>tubulin, gamma complex associated protein 3</td>
<td>Associated with gama-tubulin in cells and oocytes</td>
<td></td>
</tr>
</tbody>
</table>
Just came out: Ducherty et al.,
AJP October 2020

Genome-Wide Association Study of Suicide Death and Polygenic Prediction of Clinical Antecedents

Anna R. Docherty, Ph.D., Andrey A. Shabalina, Ph.D., Emily DiBlaasi, Ph.D., Eric Monson, M.D., Niamh Mullins, Ph.D., Daniel E. Atkins, Ph.D., Silviu-Attil Bacanu, Ph.D., Amanda W. Baklan, Ph.D., Danli Chen, Ph.D., Todd M. Darlington, Ph.D., William B. Callor, M.S., Erik D. Christensen, M.D., Douglas Gray, M.D., Brooks Keeshin, M.D., Michael Klein, M.S., John S. Anderson, B.S., Leslie Jerominiski, M.S., Caroline Hayward, Ph.D., David J. Porteous, Ph.D., Andrew McIntosh, M.D., Qingge Li, Ph.D., Hilary Coon, Ph.D.

Objective: Death by suicide is a highly preventable yet growing worldwide health crisis. To date, there has been a lack of adequately powered genomic studies of suicide, with no sizable suicide death cohorts available for analysis. To address this limitation, the authors conducted the first comprehensive genomic analysis of suicide death using previously unpublished genotype data from a large population-ascertained cohort.

Methods: The analysis sample comprised 3,413 population-ascertained case subjects of European ancestry and 14,810 ancestrally matched control subjects. Analytical methods included principal component analysis for ancestral matching and adjusting for population stratification, linear mixed model genome-wide association testing (conditional on genetic-relatedness matrix), gene and gene set-enrichment testing, and polygenic score analyses, as well as single-nucleotide polymorphism (SNP) heritability and genetic correlation estimation using linkage disequilibrium score regression.

Conclusions: Multiple genome-wide significant loci and genes were identified and polygenic score prediction of suicide death case-control status was demonstrated, adjusting for ancestry, in independent training and test sets. Additionally, the suicide death sample was found to have increased genetic risk for behavioral disinhibition, major depressive disorder, depressive symptoms, autism spectrum disorder, psychosis, and alcohol use disorder compared with the control sample.
the first comprehensive genomic analysis of suicide death using previously unpublished genotype data from a large population-ascertained cohort.
Genome-wide association analysis identified two genome-wide significant loci (involving six SNPs: rs34399104, rs35518298, rs34053895, rs66828456, rs35502061, and rs35256367). Gene-based analyses implicated 22 genes on chromosomes 13, 15, 16, 17, and 19 (q<0.05). Polygenic scores for several other psychiatric disorders and psychological traits were also predictive, particularly scores for behavioral disinhibition and major depressive disorder.
Figure 1 | Approaches to psychiatric genetics research. a | The gene-to-disorder approach assumes direct linear relations between genes and disorder. b | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. c | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. d | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.
GxE approach in suicidology
5HTTLPR Gene X Environment Interaction in suicidal behavior

Caspi et al. Science, 2003
Review

Timing is critical: Gene, environment and timing interactions in genetics of suicide in children and adolescents

G. Zalsman\textsuperscript{a,b,c}

\textsuperscript{a} Child and Adolescent Psychiatry Division, Geha Mental Health Center, PO Box 102, 49100 Petch Tikwa, Israel
\textsuperscript{b} Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
\textsuperscript{c} Molecular Imaging and Neuroradiology Division, Psychiatry Department, Columbia University, New York, USA
WKY Rat
Animal model for depression, despair and anhedonia
Genetic vulnerability, timing of short-term stress and mood regulation: A rodent diffusion tensor imaging study

Gil Zalsman\textsuperscript{a,b,*}, Avihay Gutman\textsuperscript{c,d}, Liat Shbiro\textsuperscript{d}, Ruth Rosenan\textsuperscript{d}, J. John Mann\textsuperscript{b}, Aron Weller\textsuperscript{d}
Epigenetics
Epigenetics

Changes in DNA that change gene expression. These changes can be permanent (cell type) or temporary (developmental window, environmental ques)

Types:
1. Methylation
2. Histones modification
3. Non coding RNAs=MiRNA
Epigenetics in Psychiatry

Heritable factors:
- Genetic mechanisms
- Single-nucleotide polymorphisms
- Deletions
- Insertions
- Amplification
- Translocation

Environmental factors:
- Epigenetic mechanisms
- DNA methylation
- Histone modification
- Non-coding RNAs, including microRNAs
- RNA editing

×

Altered gene expression profile

Modified brain structure and function

Psychiatric disorder

Epigenetics in suicidiology
Genome-Wide Methylation Changes in the Brains of Suicide Completers

Benoit Labonté, M.Sc.
Matt Suderman, Ph.D.
Gilles Maussion, Ph.D.
Juan Pablo Lopez, B.Sc.
Luis Navarro-Sánchez, M.Sc.
Volodymyr Yerko, Ph.D.
Naguib Mechawar, Ph.D.
Moshe Szyl, Ph.D.
Michael J. Meaney, Ph.D.
Gustavo Turecki, M.D., Ph.D.

Objective: Gene expression changes have been reported in the brains of suicide completers. More recently, differences in promoter DNA methylation between suicide completers and comparison subjects in specific genes have been associated with these changes in gene expression patterns, implicating DNA methylation alterations as a plausible component of the pathophysiology of suicide. The authors used a genome-wide approach to investigate the extent of DNA methylation alterations in the brains of suicide completers.

Method: Promoter DNA methylation was profiled using methylated DNA immunoprecipitation (MeDIP) followed by microarray hybridization in hippocampal tissue from 62 men (46 suicide completers and 16 comparison subjects). The correlation between promoter methylation and expression was investigated by comparing the MeDIP data with gene expression profiles generated through mRNA microarray. Methylation differences between groups were validated on neuronal and nonneuronal DNA fractions isolated by fluorescence-assisted cell sorting.

Results: The authors identified 366 promoters that were differentially methylated in suicide completers relative to comparison subjects (273 hypermethylated and 93 hypomethylated). Overall, promoter methylation differences were inversely correlated with gene expression differences. Functional annotation analyses revealed an enrichment of differential methylation in the promoters of genes involved, among other functions, in cognitive processes. Validation was performed on the top genes from this category, and these differences were found to occur mainly in the neuronal cell fraction.

Conclusions: These results suggest broad reprogramming of promoter DNA methylation patterns in the hippocampus of suicide completers. This may help explain gene expression alterations associated with suicide and possibly behavioral changes increasing suicide risk.

(Am J Psychiatry 2013; 170:511–520)
Approaches in research of the medical genetics

Figure 1 | Approaches to psychiatric genetics research. 

- **a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder.
- **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes.
- **c** | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder.
- **d** | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.

Caspi and Moffitt, Nature Reviews Neuroscience, July 2006, with permission
How environment and epigenetics interact?

Epigenomic marks can be altered through calcium-dependent signaling cascades in direct response to neuronal activity.

Nagy C et al., Genes Brain Behav. 2018;17(3):e12446.
Thank You!

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