Defining Core Concepts and Measurements in Suicidology

By: Lars Mehlum, University of Oslo & Jill Harkavy-Friedman, AFSP

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American Foundation for Suicide Prevention

Lars Mehlum

Professor of psychiatry and suicidology
Director
National Centre for Suicide Research and Prevention
Faculty of Medicine
University of Oslo, Oslo
Norway

Immediate Past President IASR

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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

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Associations between PTSD symptoms and suicide risk: A comparison of 4-factor and 7-factor models

Methods: 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.

ividuals, we evaluated dels.

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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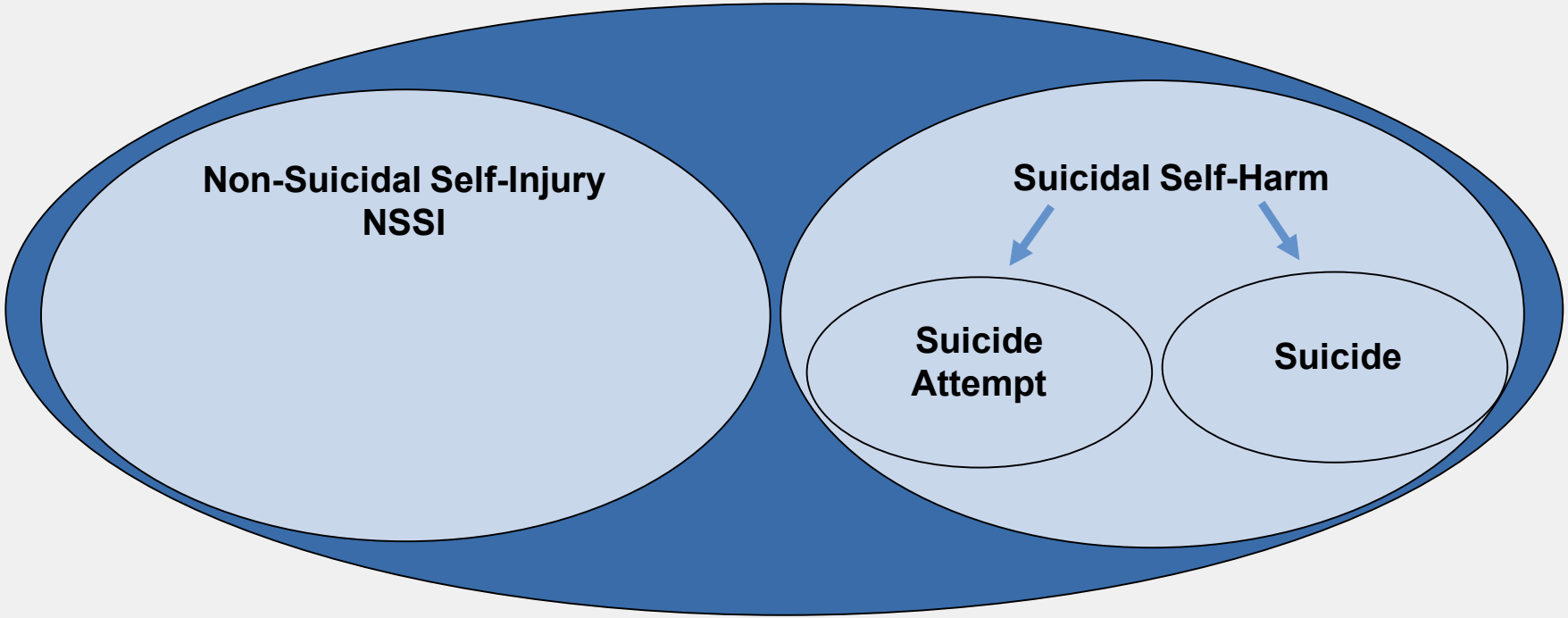
Self-Harm (SH)



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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

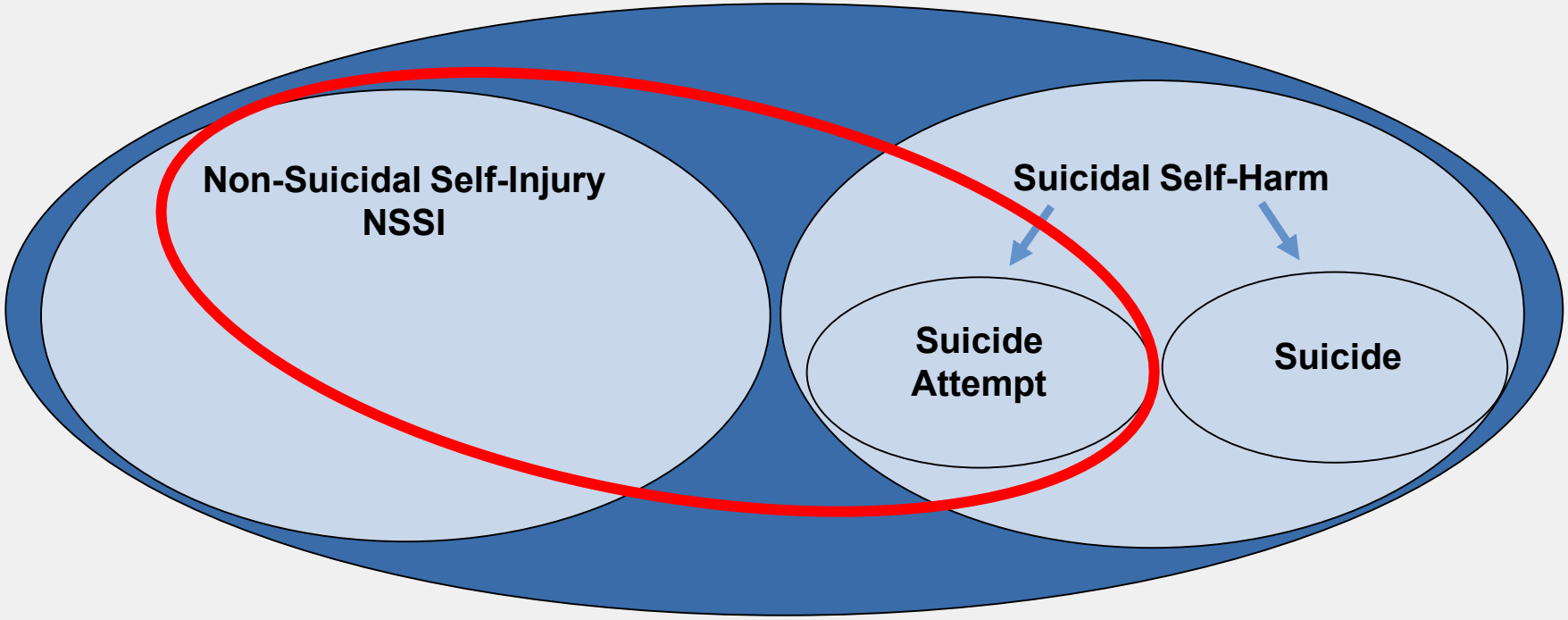
Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Posner et al, *Am J Psychiatry 2011* https://doi.org/10.1176/appi.ajp.2011.10111704

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 3 months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* 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. ***There does not have to be any injury or harm***, 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. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***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)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

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:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
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:	**Yes** ☐ **No** ☐ Total # of aborted or self-interrupted _____	**Yes** ☐ **No** ☐ Total # of aborted or self-interrupted _____
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:	**Yes** ☐ **No** ☐ Total # of preparatory acts _____	**Yes** ☐ **No** ☐ Total # of preparatory acts _____

Self-Harm (SH)



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Clinician-Administered Nonsuicidal Self-injury Disorder Index (CANDI)

Gratz, K.L., Dixon-Gordon, K.L., Chapman, A.L., & Tull, M.T. (2014)

- 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 you 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 ____** (INSERT NUMBER) **times on _____** (INSERT NUMBER) **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?

A. ***Engaged in self-injury 5+ days in the past year?*** ***Self-injury resulted in tissue damage (e.g., bleeding, bruising)?*** ***Without intention or expectation of death?***	**NO YES** **NO YES** **NO YES**
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):

Cutting	_____	Severe Scratching	_____
Biting	_____	Banging or Hitting Self	_____
Burning	_____	Interfering w/ Wound Healing (e.g., picking scabs)	_____
Carving	_____	Rubbing Skin Against Rough Surface	_____
Pinching	_____	Sticking Self w/ Needles	_____
Pulling Hair	_____	Swallowing Dangerous Substances	_____
Other _____,	_____		

Klonsky, E.D. & Olino, T.M. (2008).

INVENTORY OF STATEMENTS ABOUT SELF-INJURY (ISAS) – SECTION II. FUNCTIONS

Name:_____

Date:_____

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 …	**Response**		
1. … calming myself down	0	1	2
2. … creating a boundary between myself and others	0	1	2
3. … punishing myself	0	1	2
4. … giving myself a way to care for myself (by attending to the wound)	0	1	2
5. … causing pain so I will stop feeling numb	0	1	2

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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

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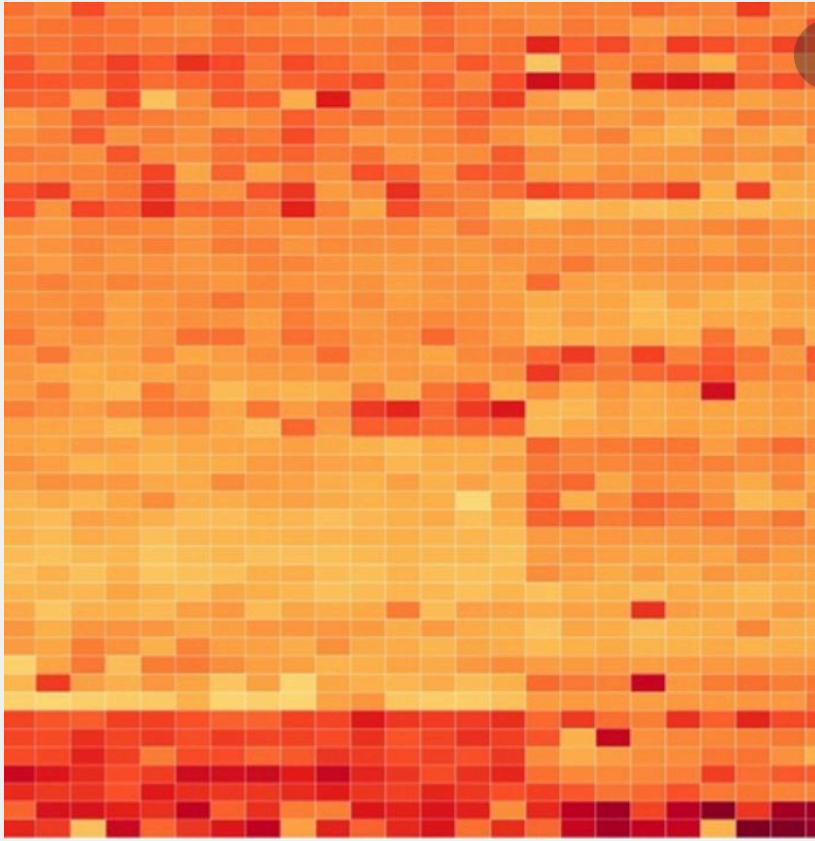
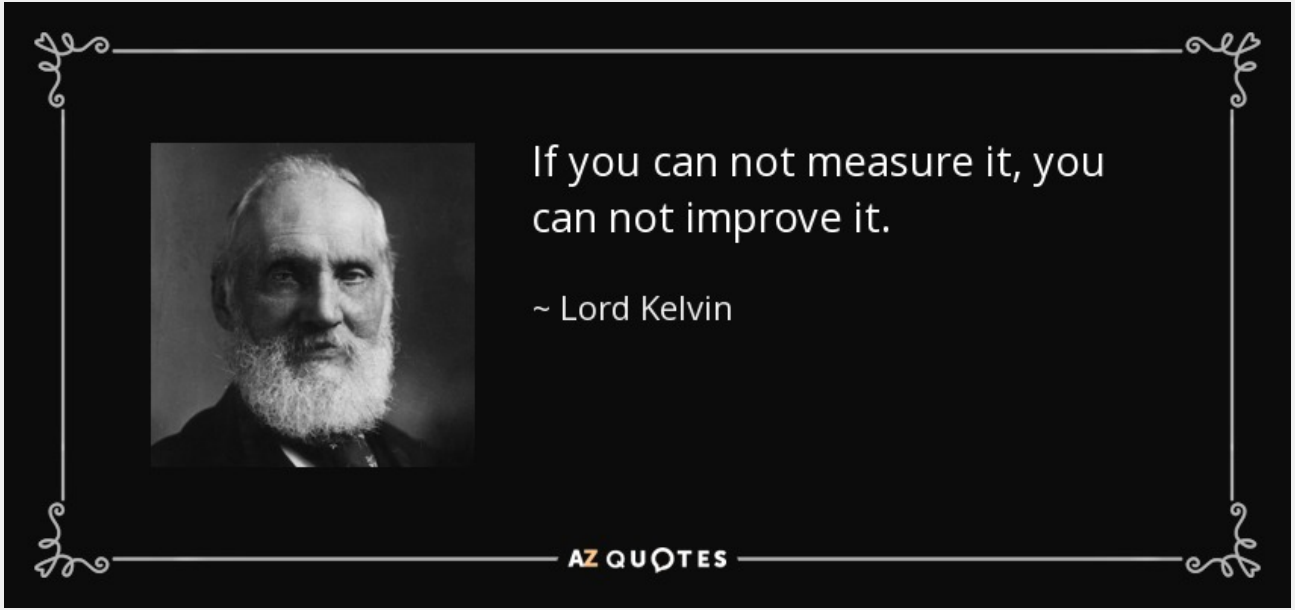
Allows us to study (examples)

- ... 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



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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

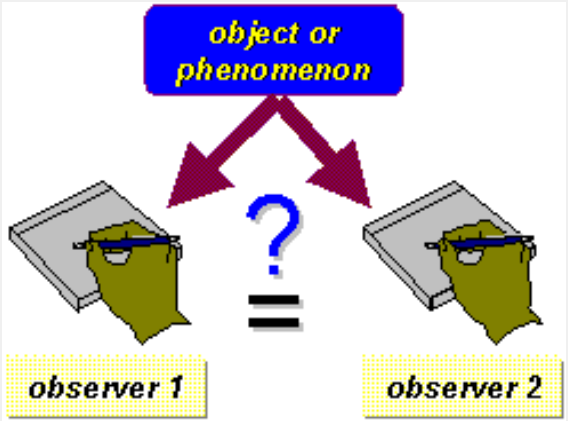
Specificity

Variability

Ceiling and Floor effects

Reliability=Reproducability

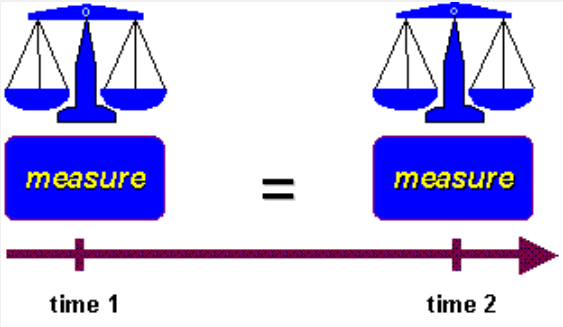
Inter-rater



Kappa

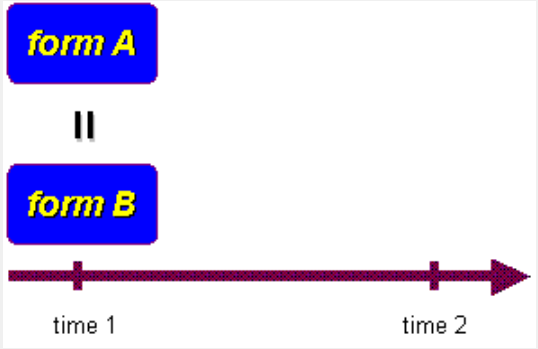
Intra-class correlation

Test-Retest: Over time



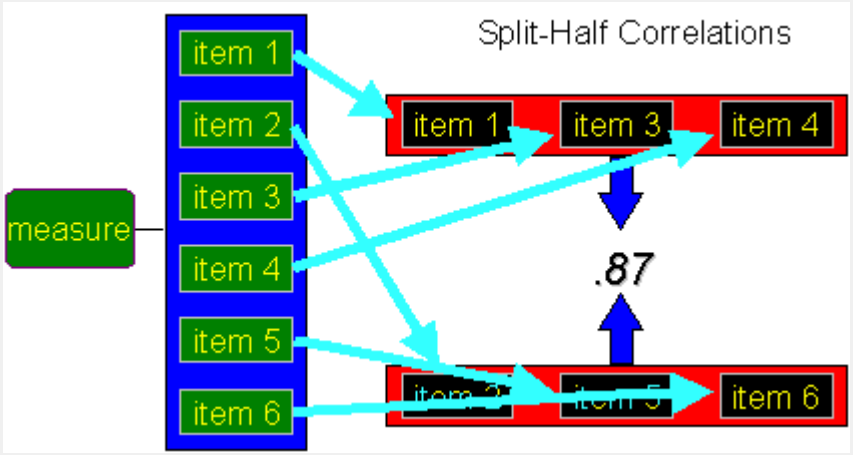
Correlate time 1 and time 2

Parallel Forms: Across Measurements



Correlate forms

Internal Consistency: Within a test



Spearman Brown

Cronbach's Alpha

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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

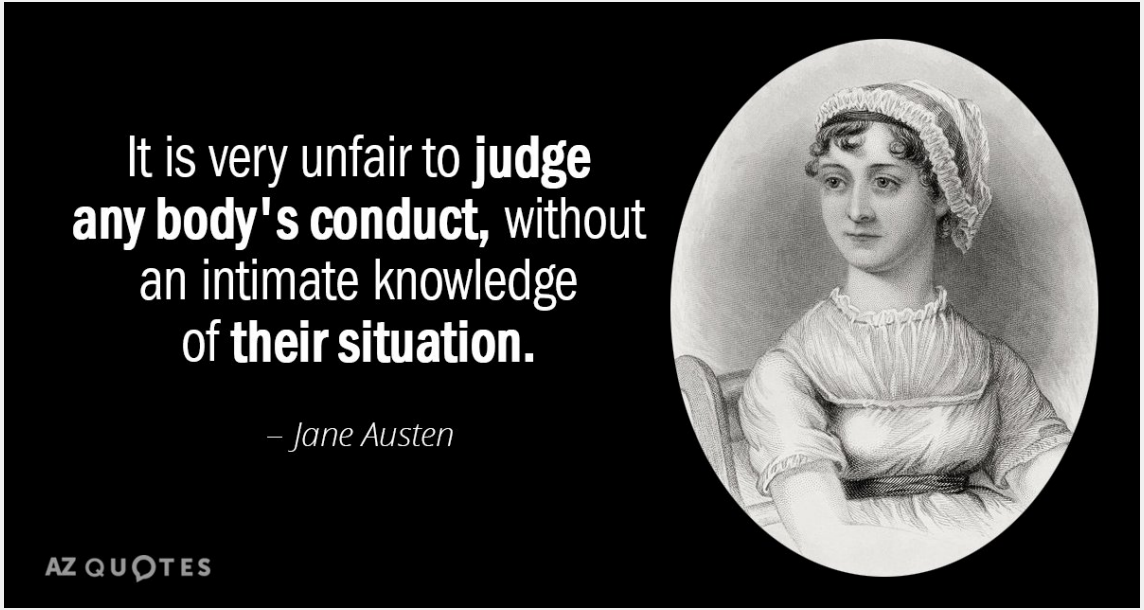
Suicidal ideation and behavior

Risk

Treatment effect

Population risk

No matter the goal, suicide is complex, and you will likely have to measure multiple variables



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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

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What needs to be measured?

Demographics

Suicidal ideation and behavior

Outcome

Confounders

Mediators and Moderators

Context

Current Measures of Outcome

- Knowledge
- Attitudes
- Suicidal Ideation
- Suicide Attempts
- Completed Suicide
- Lethality of attempt
- Suicide Intent
- # crisis calls
- Associated symptoms
- Impact of suicide
- Hospitalization
- School completion
- # referrals
- Social Skills

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!

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Clinical Trial Methods: Specific Considerations for Suicide Research

Gregory K. Brown, PhD

Barbara Stanley, PhD

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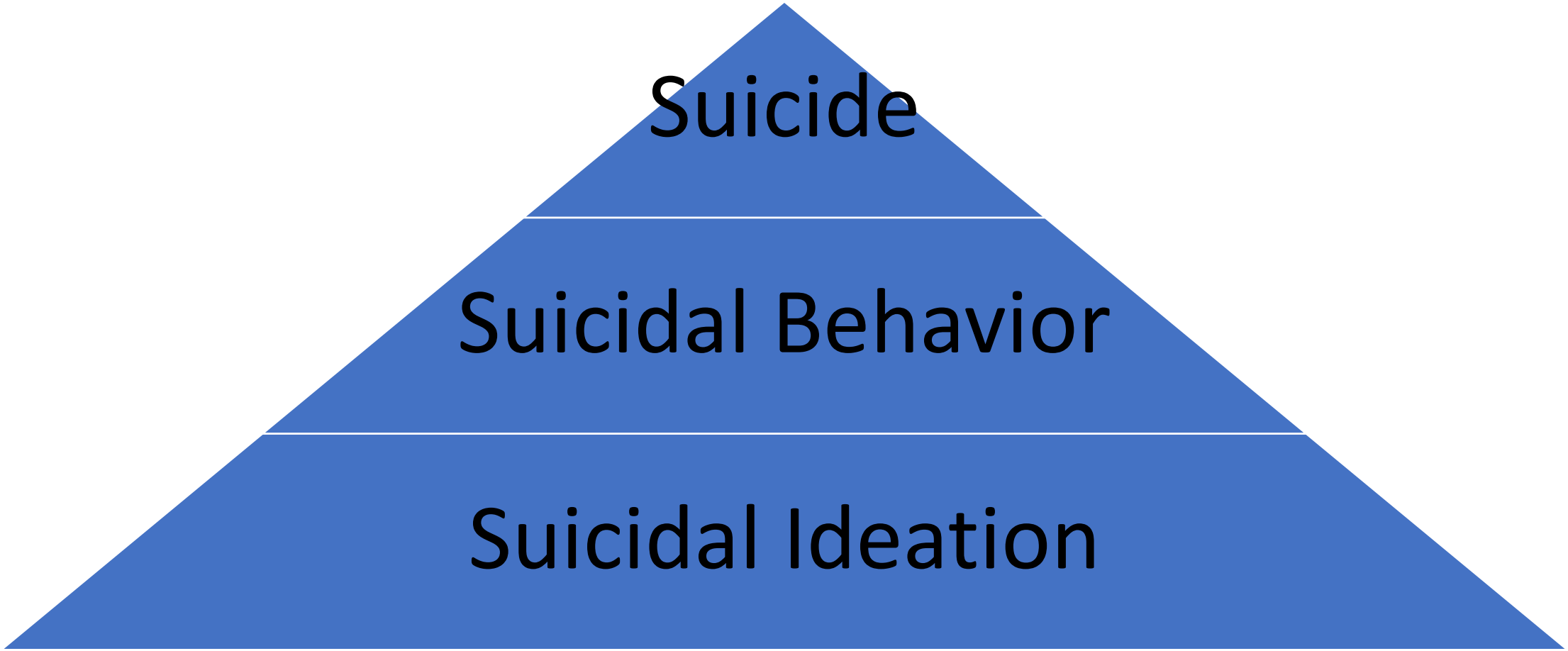
Common design questions to consider when conducting clinical trial research with at risk samples

- 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



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Use an Established Nomenclature of Suicidal Behavior

Self-directed Violence Surveillance: Uniform Definitions

Crosby, A. E., Ortega, L., & Melanson, C. (2011). Self-directed Violence Surveillance: Uniform Definitions and Recommended Data Elements (Version 1.0). Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Columbia Suicide Severity Rating Scale (C-SSRS) Definitions

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., … Mann, J. J. (2011). The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. American Journal of Psychiatry, 168(12), 1266–1277.

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

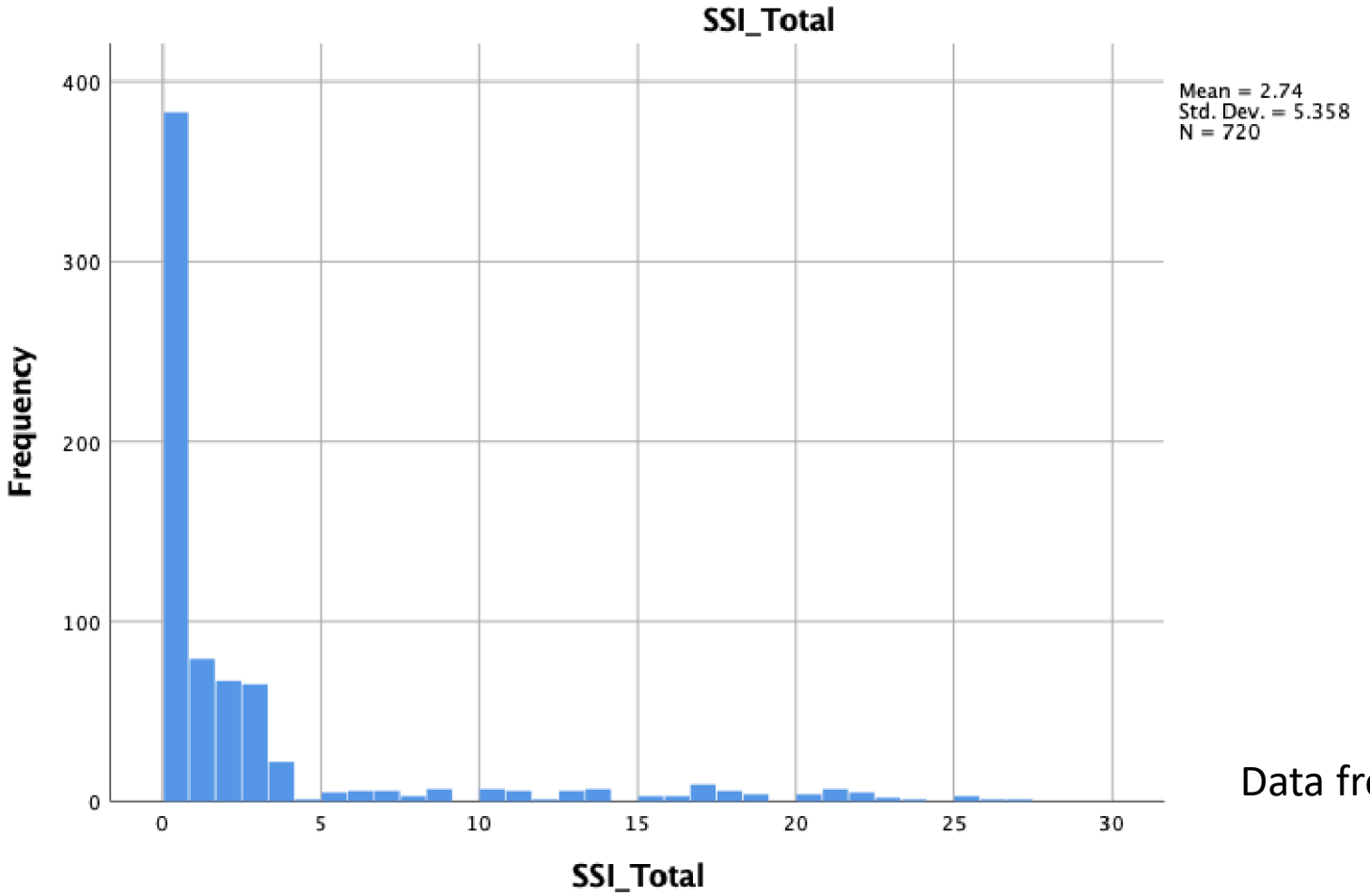
Suicidal Ideation as Outcome

- 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

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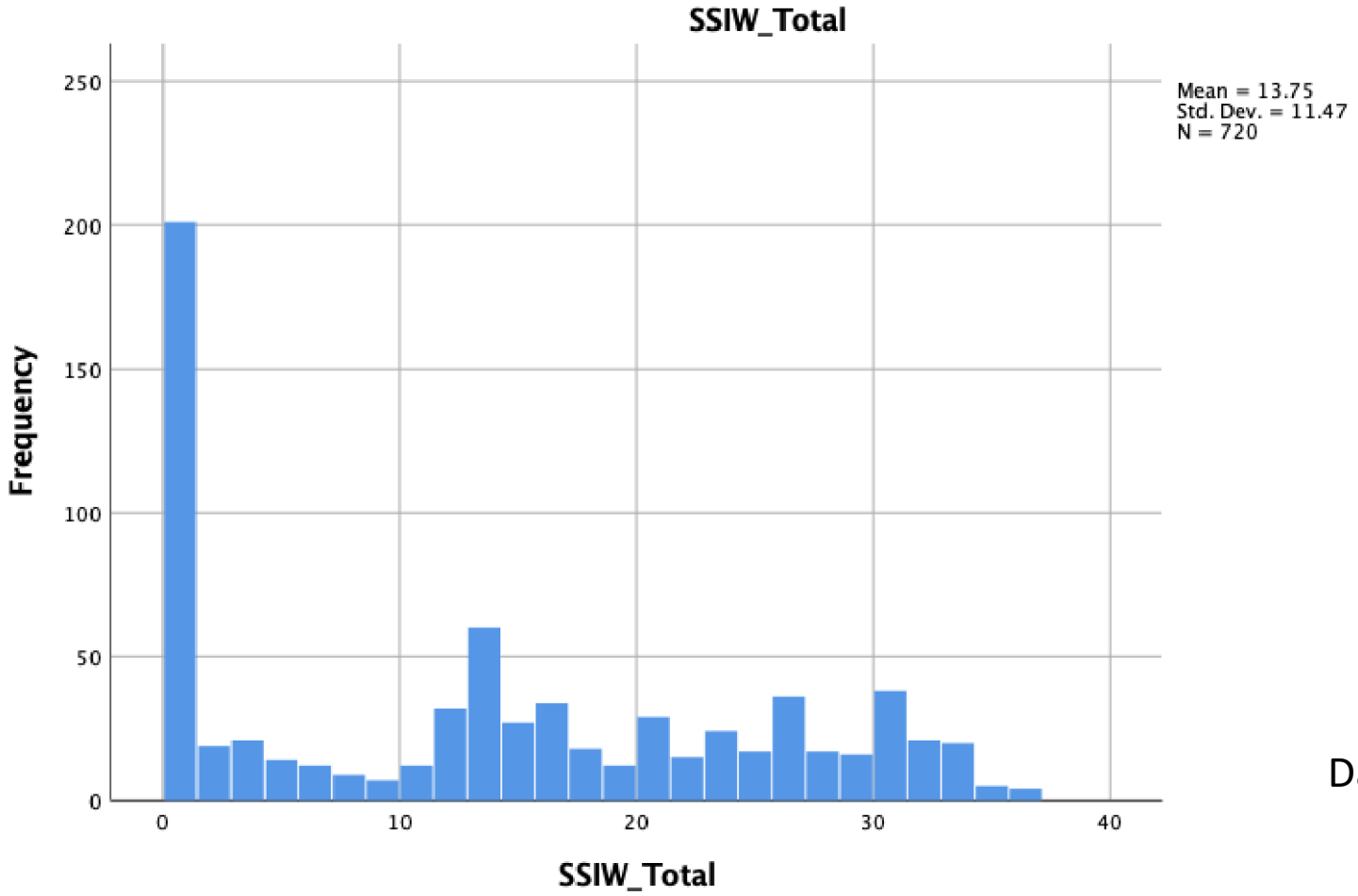
Frequency Distribution of the Scale for Suicide Ideation (Worst) During Follow-up



Data from Brown et al., JAMA, 2005

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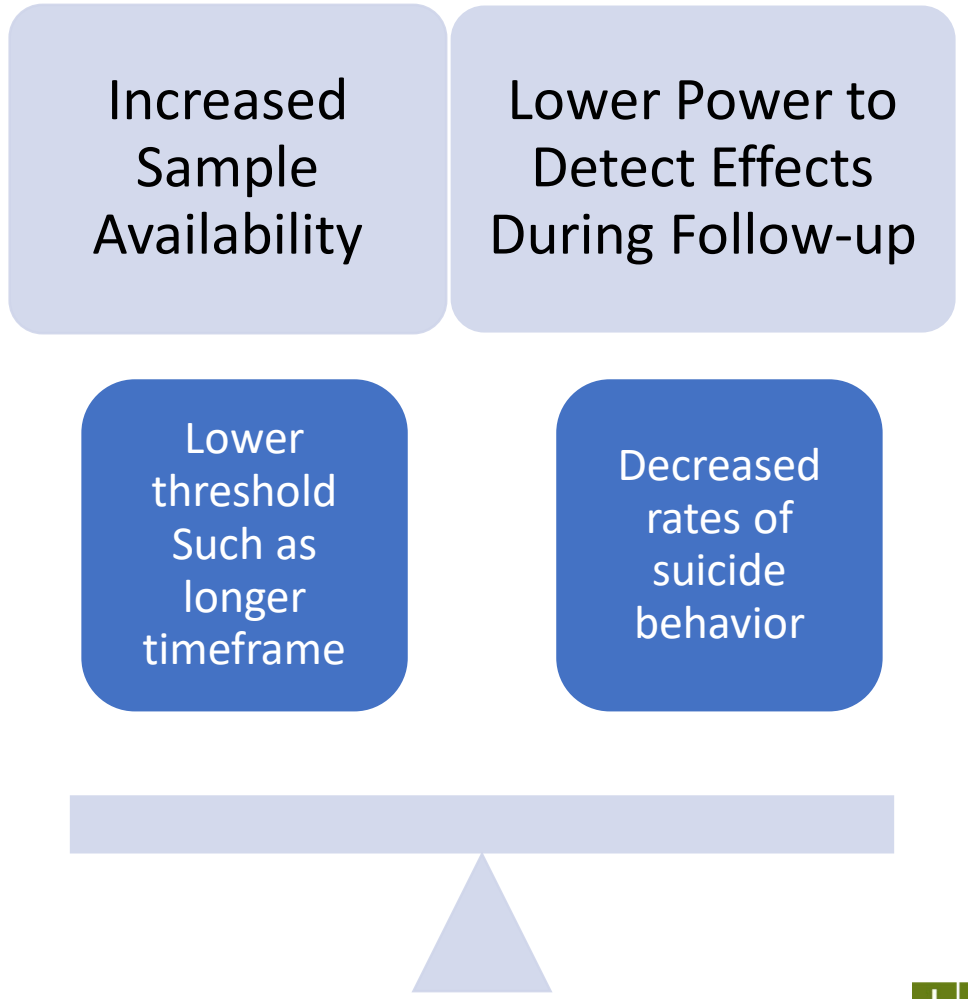
Determining Inclusion Criteria

- 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



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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

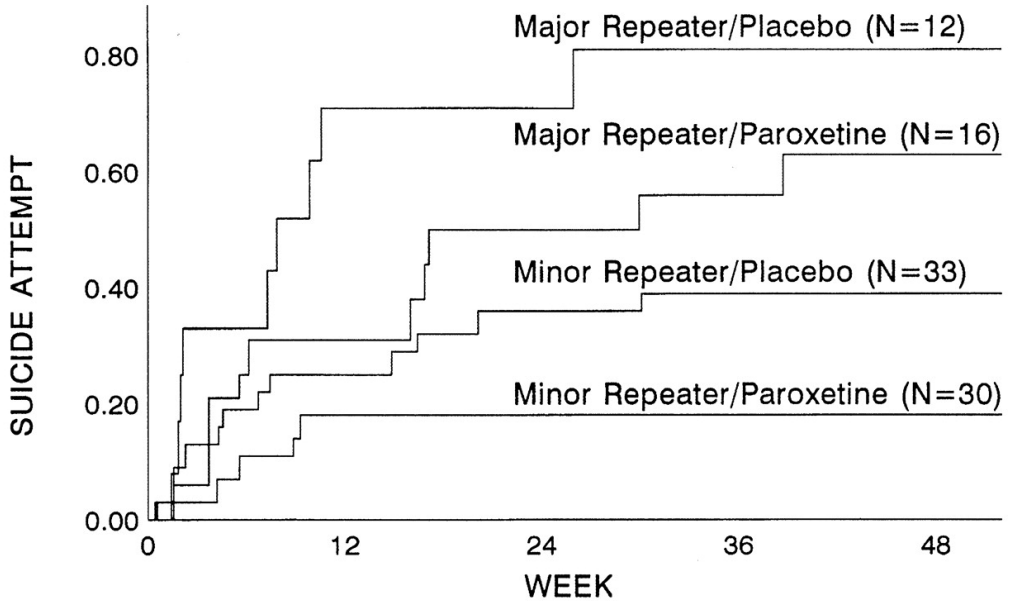
Tension between Safety Procedures and "Best" Research Methods

- 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*

FIGURE 1. Kaplan-Meier Curves for Probability of Another Suicide Attempt by Patients With Five or More Previous Suicide Attempts (Major Repeaters) or One to Four Previous Suicide Attempts (Minor Repeaters) Who Received Paroxetine or Placebo[a]



[a]With adjustment for being a minor or major repeater, there was a significant difference between treatment groups (χ^2=4.86, df=1, p=0.03, stratified log-rank test).

"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

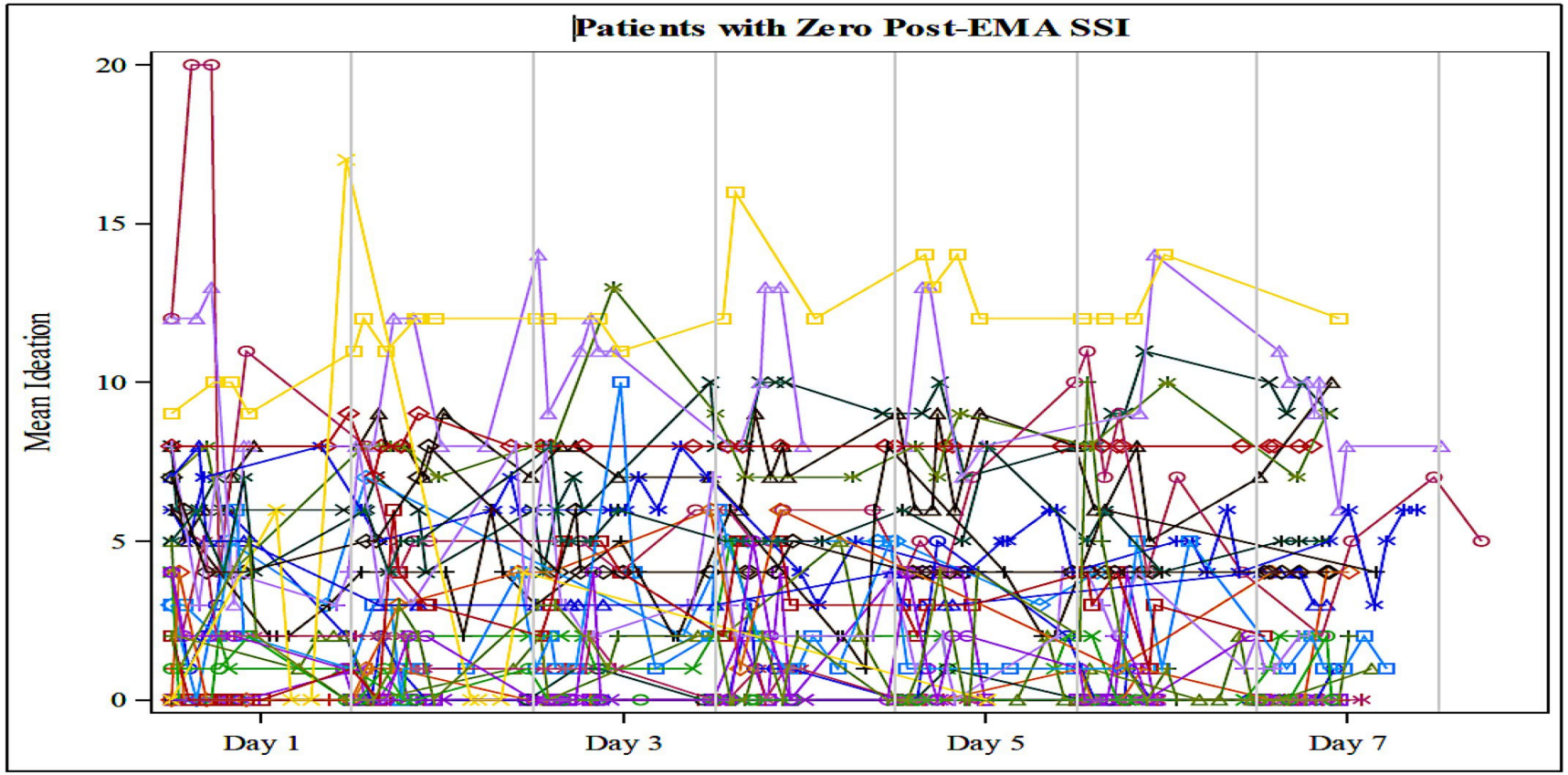
- Worst-point EMA ideation was positively related to the retrospective post-EMA SSI (r=.729, $p < .001$)
- EMA ideation severity was also positively related to the retrospective post-EMA SSI; participants with one point higher on the post-EMA SSI had on average .85 higher scores on each EMA ideation 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

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

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

	Post-EMA SSI=0 (n=29)		Post-EMA SSI>0 (n=21)		Difference
EMA Ideation Items	Mean (SE)	P-value	Mean (SE)	P-value	P-value
(1) Thoughts about dying	0.1 (0.1)	.3965	0.6 (0.1)	<.0001	<.0001
(2) Wish to live+	0.9 (0.2)	<.0001	3.0 (0.2)	<.0001	<.0001
(3) Wish to die	0.0 (0.1)	.7256	0.9 (0.1)	<.0001	<.0001
(4) Wish to sleep/not wake	0.2 (0.2)	.1976	1.5 (0.2)	<.0001	<.0001
(5) Wish to escape	0.9 (0.2)	<.0001	2.5 (0.2)	<.0001	<.0001
(6) Reasons for living+	1.3 (0.2)	<.0001	3.0 (0.2)	<.0001	<.0001
(7) Thoughts about hurting self	0.0 (0.1)	.5825	0.3 (0.1)	<.0001	<.0001
(8) Urge to hurt self	0.0 (0.0)	.5178	0.3 (0.1)	<.0001	.0005
(9) Thoughts about killing self	0.0 (0.1)	.6309	0.3 (0.1)	<.0001	.0002

Note. **+ items were reverse-coded.**

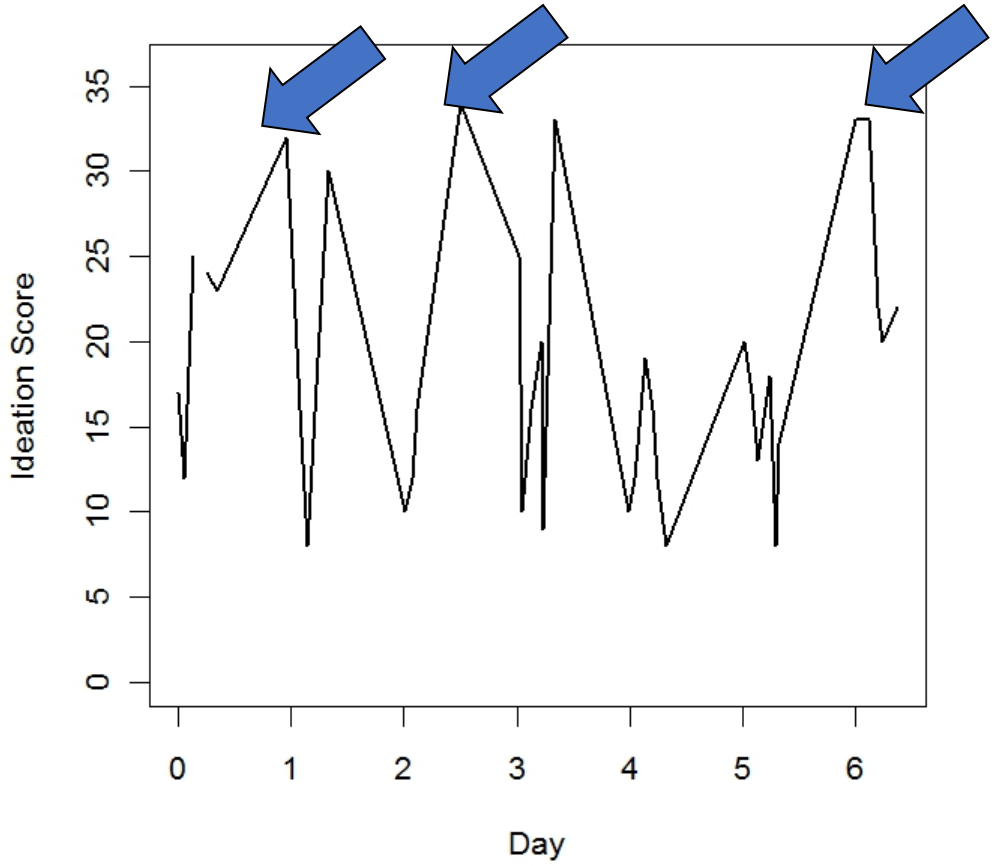
EMA Monitoring and Intervening

- 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

Case Example: Real time monitoring studies of suicidality: When to intervene

In the past 15 minutes, how strongly have you felt or experienced the following:					
1. A wish to live	0	1	2	3	4
2. A wish to die	0	1	2	3	4
3. A wish to escape	0	1	2	3	4
4. Thoughts about dying	0	1	2	3	4
5. Thoughts about suicide	0	1	2	3	4
6. Urge to commit suicide	0	1	2	3	4
7. Thoughts about hurting self	0	1	2	3	4
8. An urge to hurt yourself	0	1	2	3	4
9. Like there were reasons for living	0	1	2	3	4

Individual with Highly Variable Suicidal Ideation: When to Intervene?



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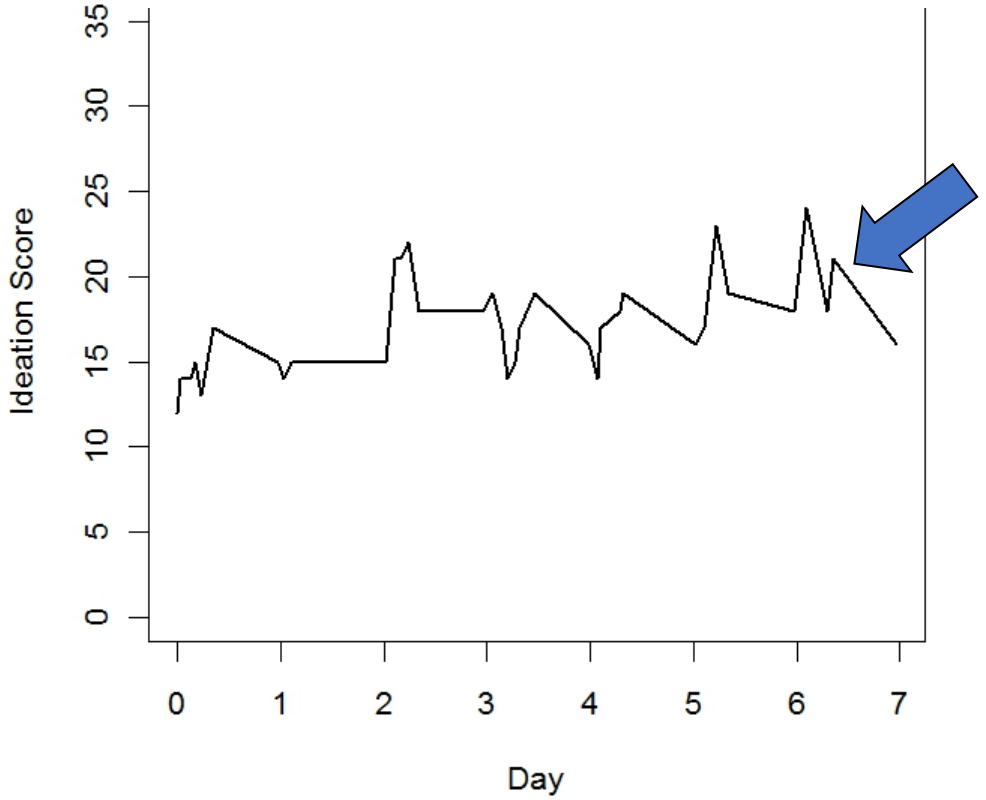
Individual with Elevated, Stable Suicidal Ideation



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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

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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.

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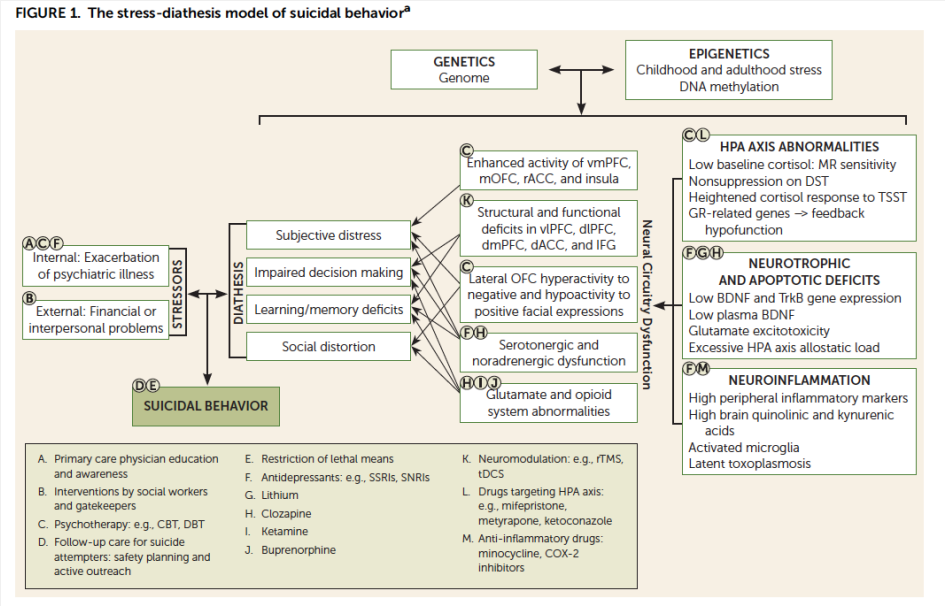
A Brain-Centric Model of Suicidal Behavior: Mann and Rizk, AJP 2020.



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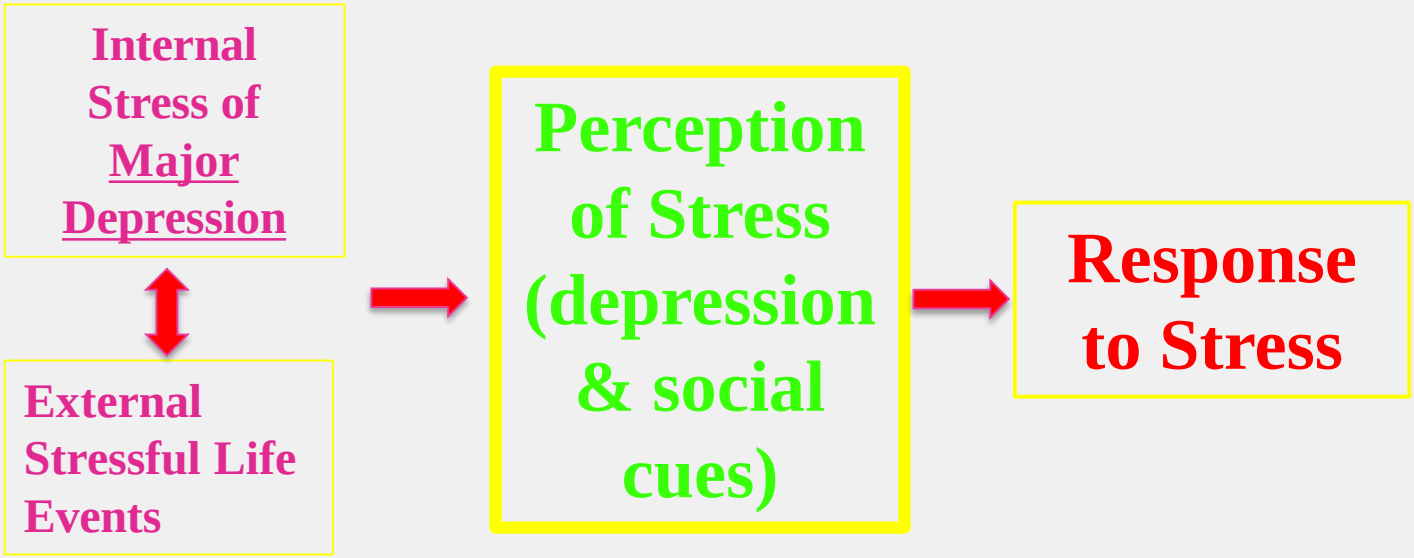
Stress Diathesis Model of Suicidal Behavior



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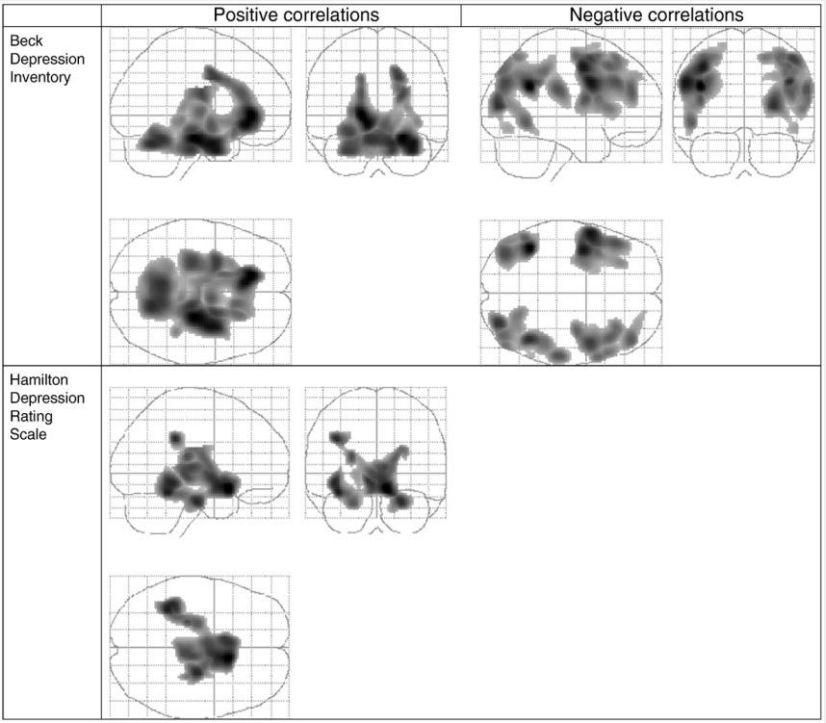
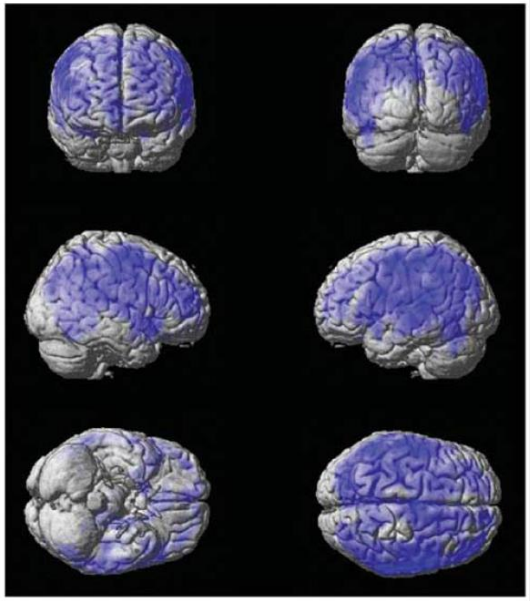
Subjective Depression Associated with Anterior Cingulate Cortex Hyperfunction and dlPFC Hypofunction



Subjective depression, and clinician-rated depression are associated with different brain regions.

Milak et al, J Affective Disorders, 2010

Brain Blood Flow Predicts Suicide in Major Depression



Dorsolateral PFC and insula hypofunction are seen in future suicides.

Willeumier et al Trans Psychiatry (2011)

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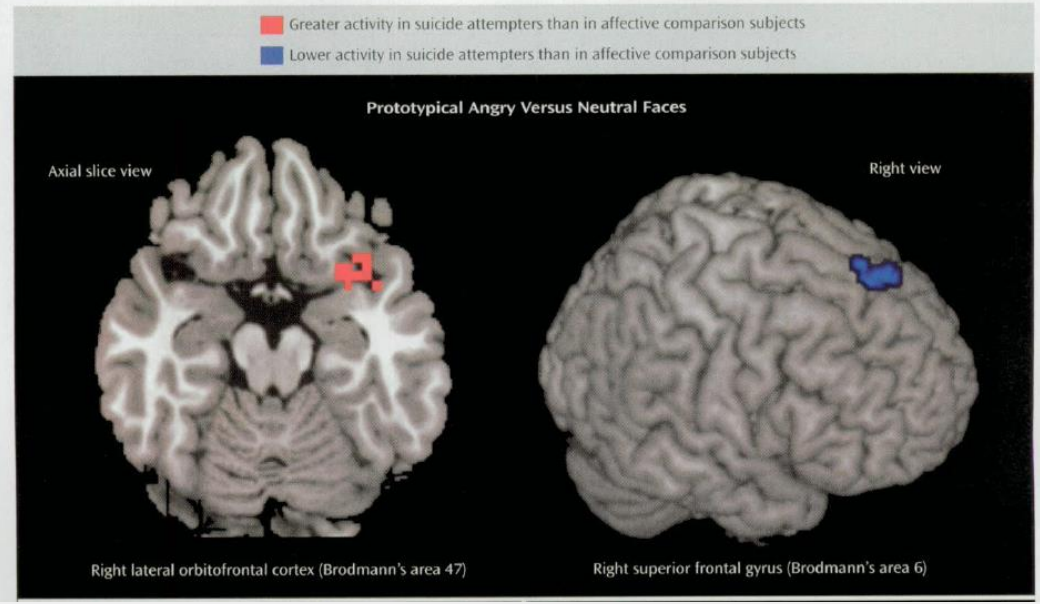
Responses to Emotional Faces in Euthymic Suicide Attempters *versus* Nonattempters Show Social Distortion



Jollant et al, AJP 2008, 165

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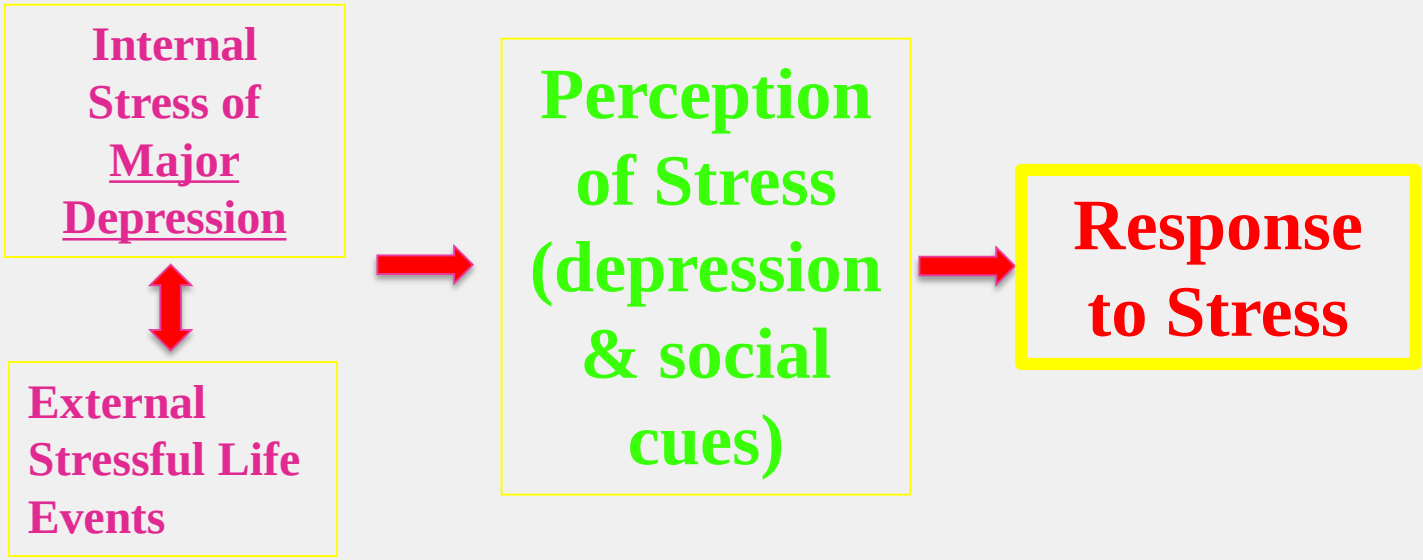
Stress Diathesis Model of Suicidal Behavior



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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.

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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.**

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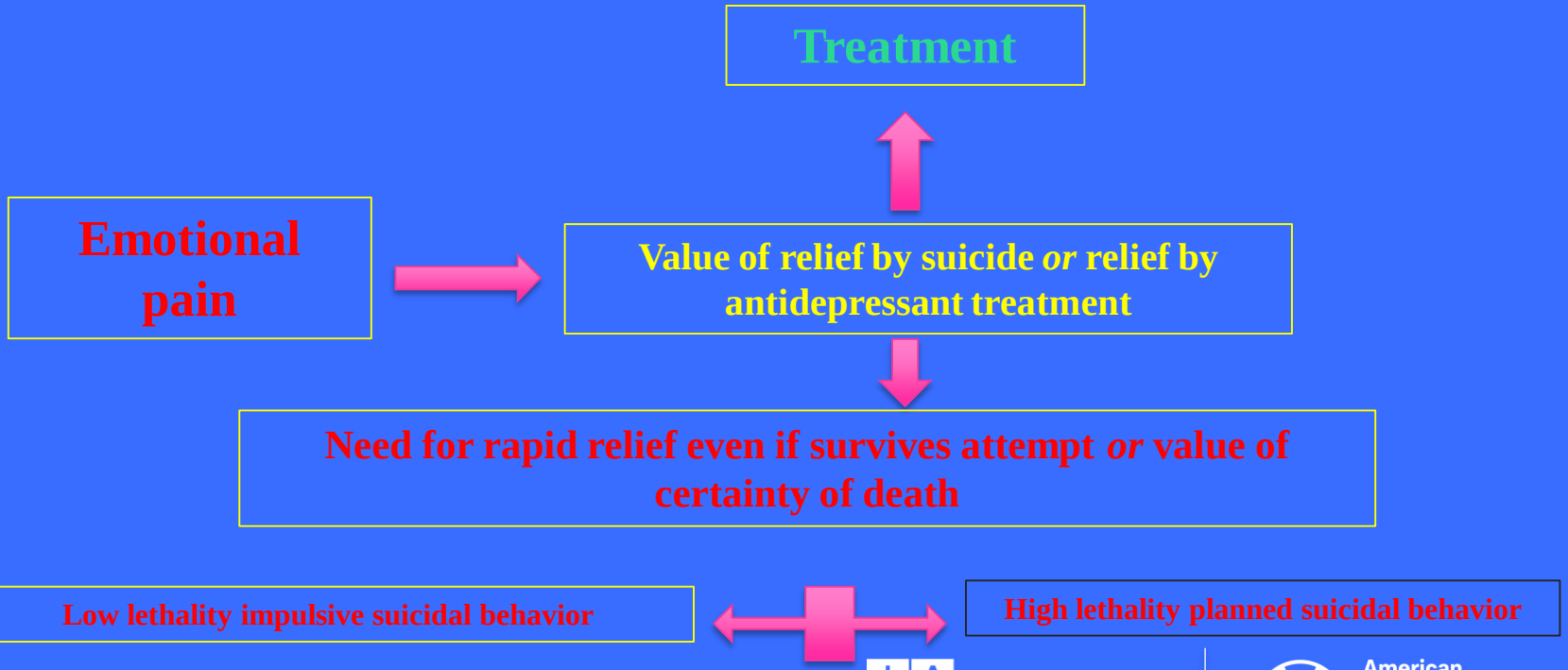
A Revised Model of Decision Making and Suicidal Behavior



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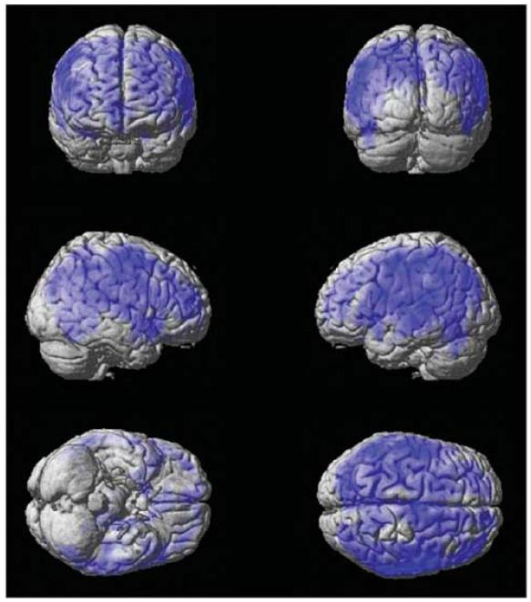
Brain Blood Flow Predicts Suicide in Major Depression



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

Willeumier et al Trans Psychiatry (2011)

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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**

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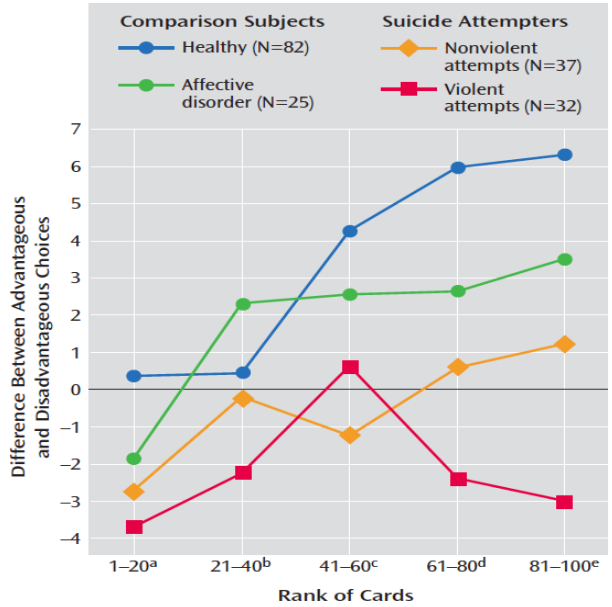
Impaired Learning During Iowa Gambling Task by Suicide Attempters: failure to improve problem solving

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)



Jollant et al. AJP, 2005

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Neurobiology of Suicide: seven pathways

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

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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.**

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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.**

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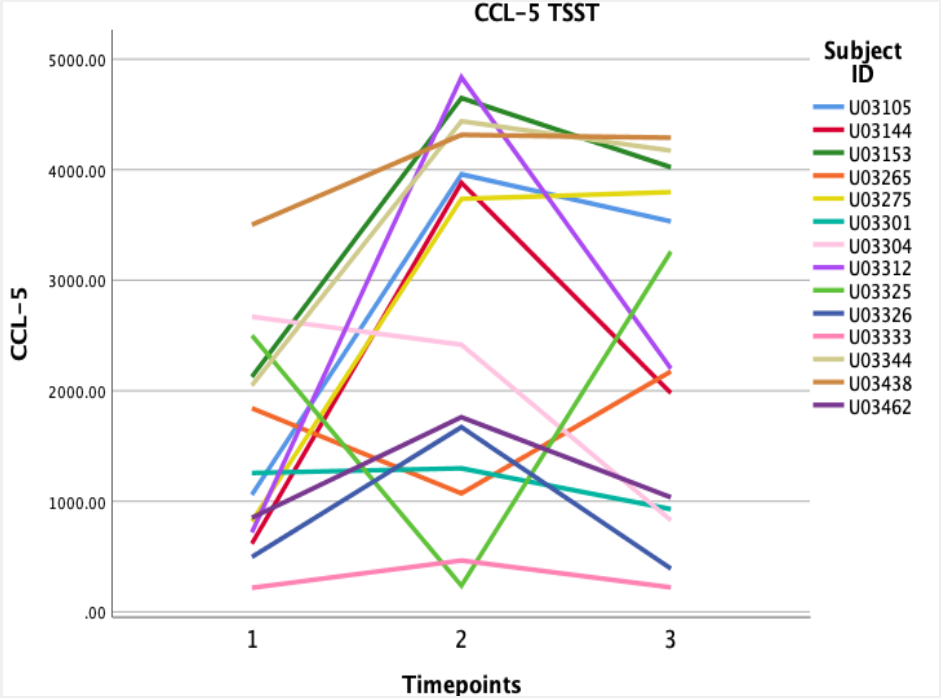
Inflammatory Response is Triggered by Emotional Stress



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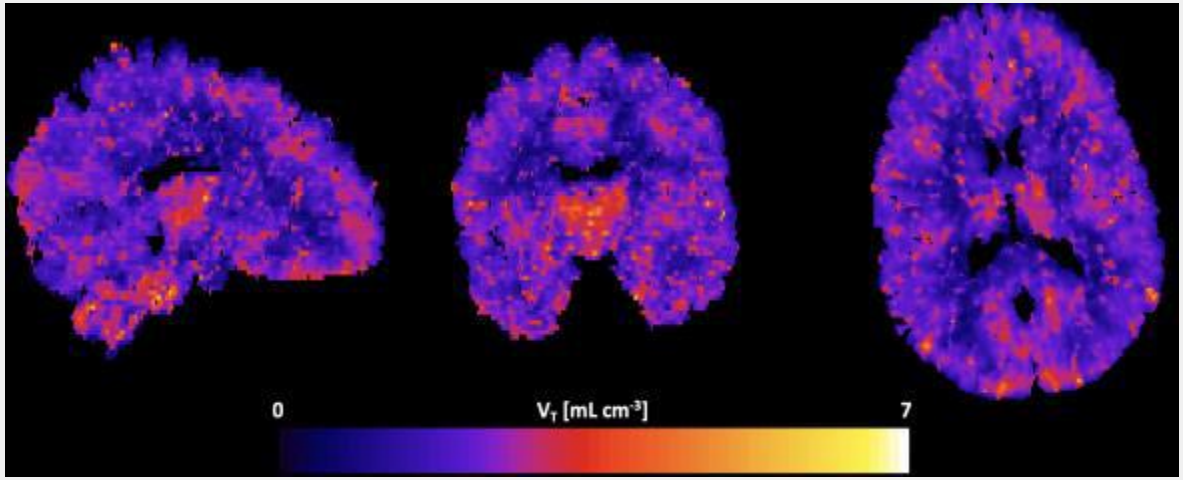
A PET Scan of Inflammation in Brain: TSPO binding



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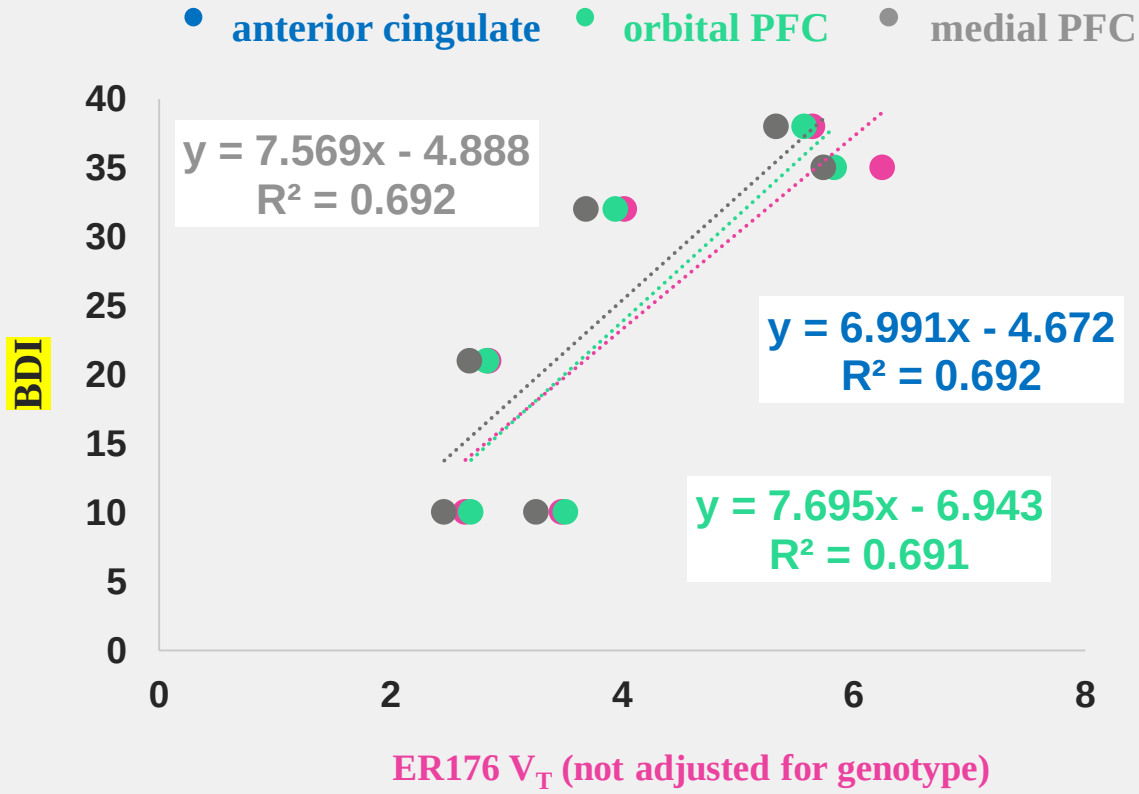

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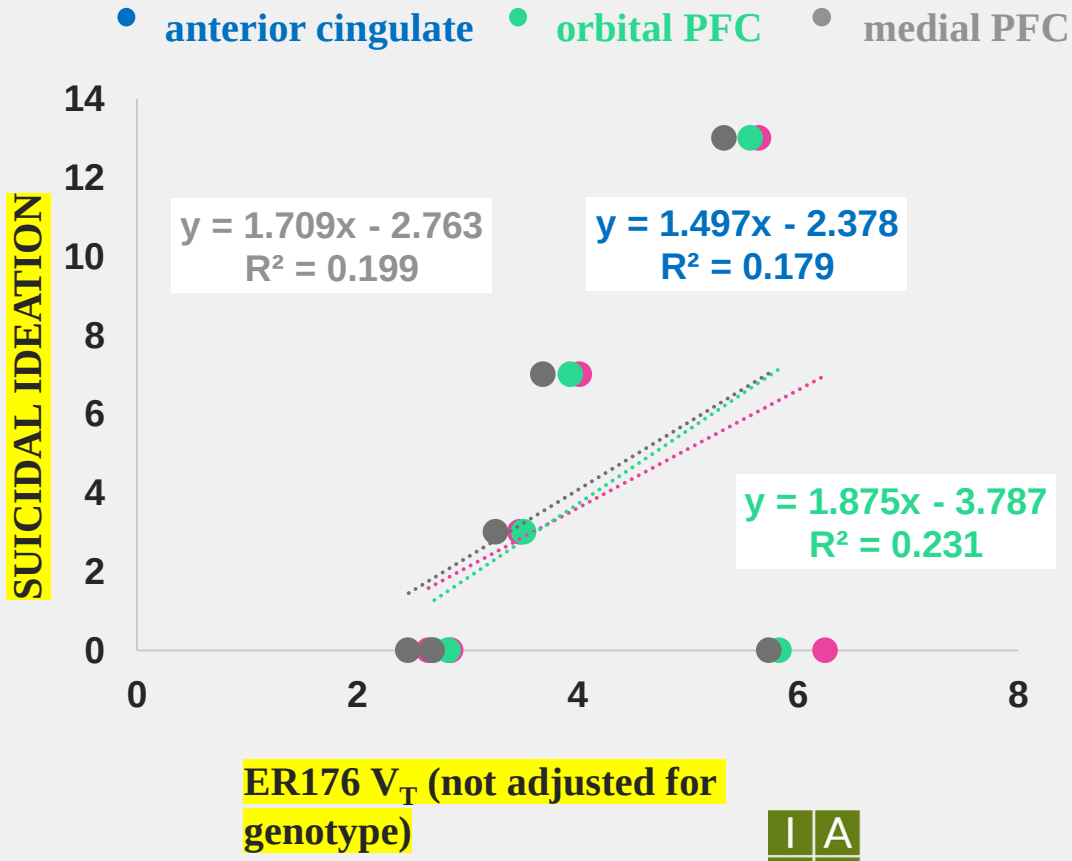

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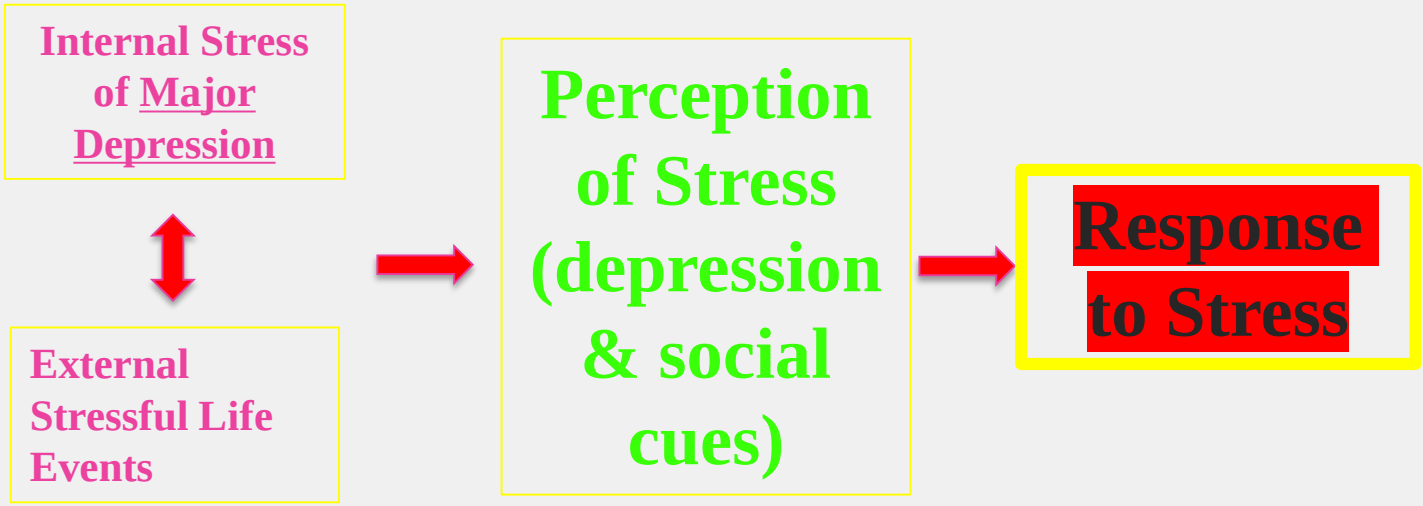
Stress Diathesis Model of Suicidal Behavior



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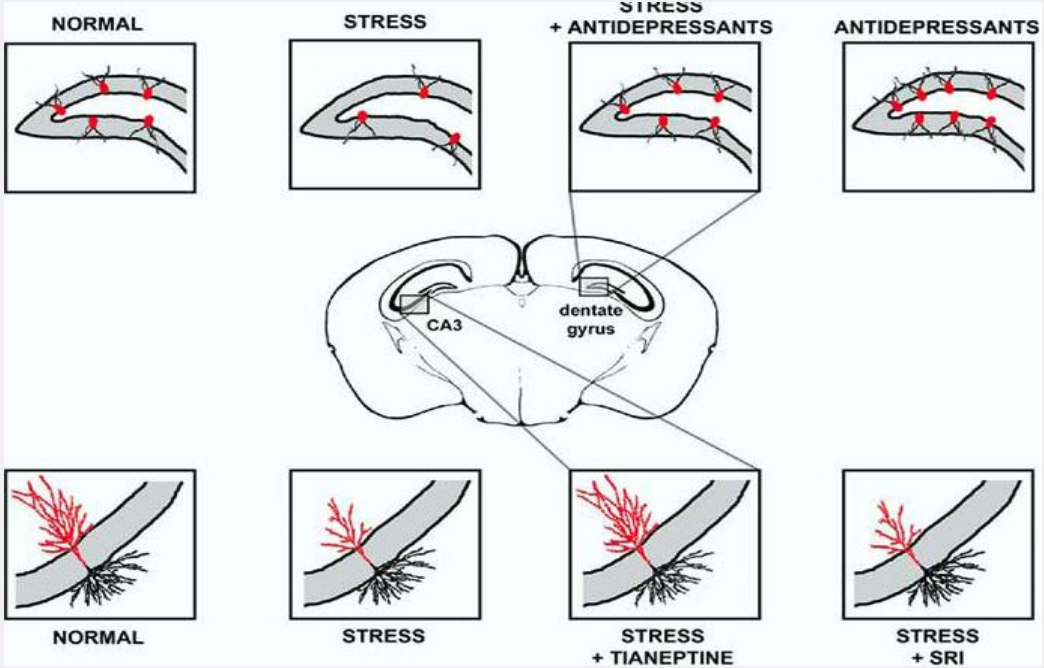
Dranovsky and Hen, 2006:
Stress in mice > fewer cells and smaller cells in hippocampus
Antidepressants > more and bigger cells



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More Time in a Major Depression Produces Smaller Hippocampus

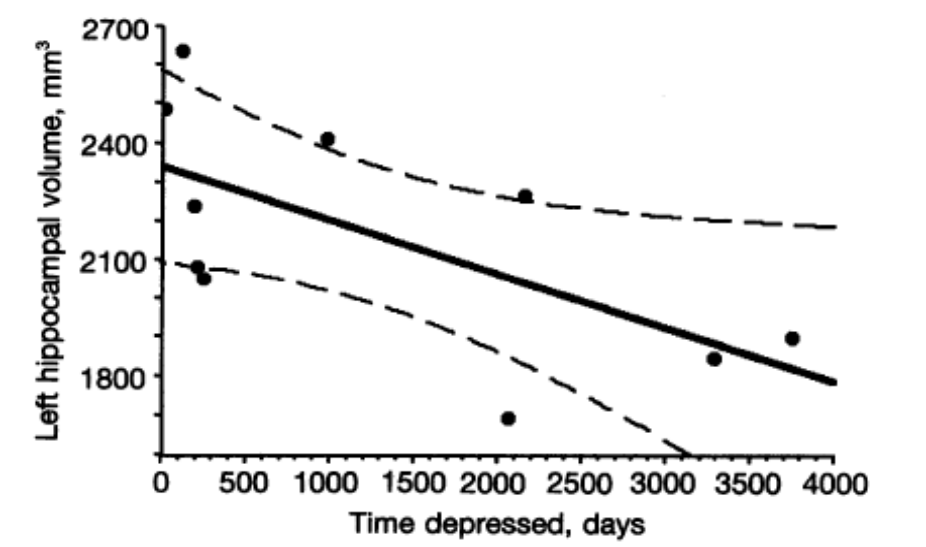
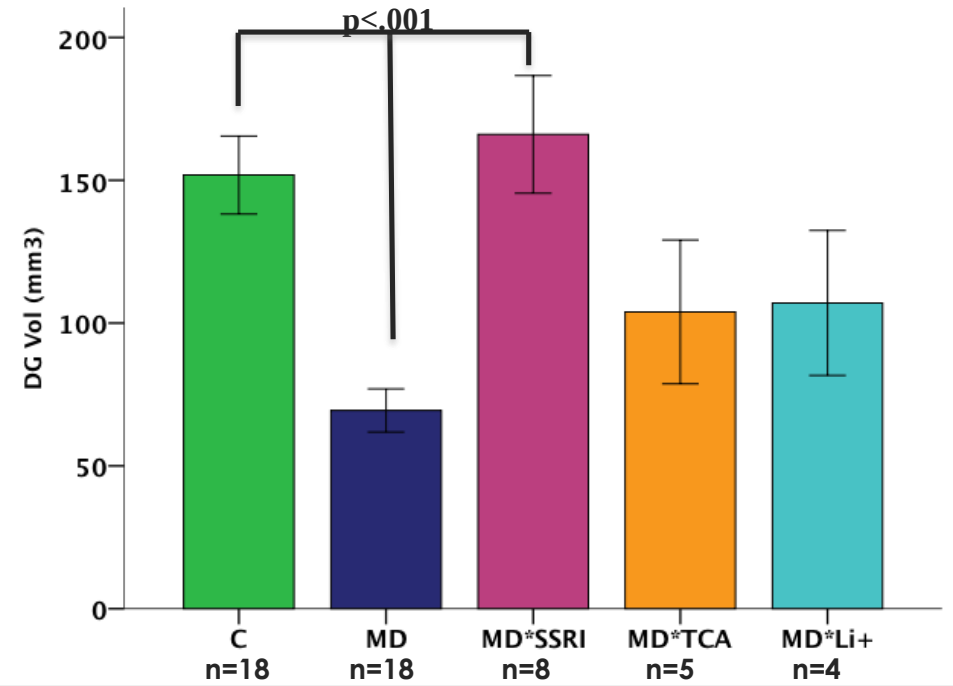
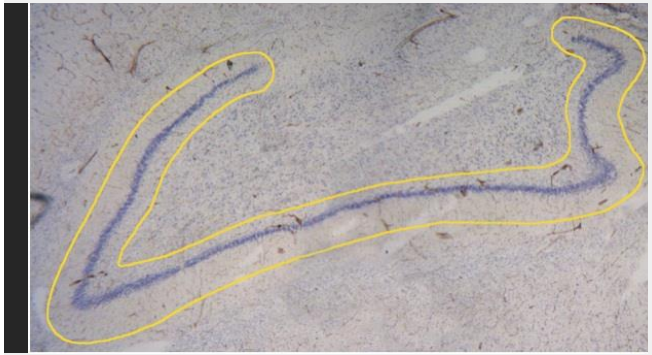


FIG. 3. Correlation between left hippocampal gray matter volumes and total days of major depression.

Sheline et al PNAS, 1996

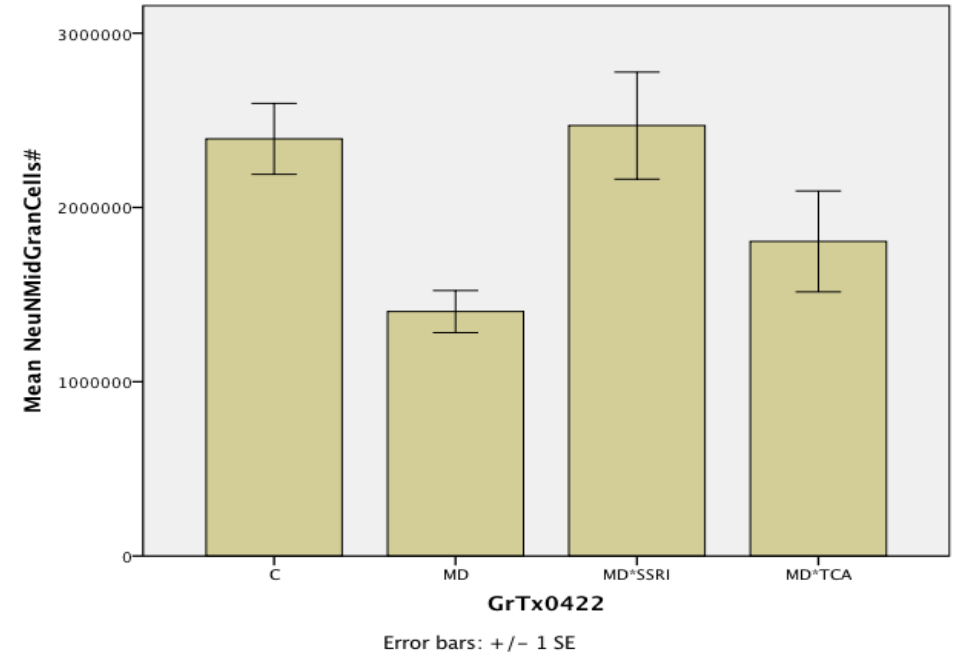
Antidepressants Appear to Correct Dentate Gyrus Volume Deficit in Depression





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.

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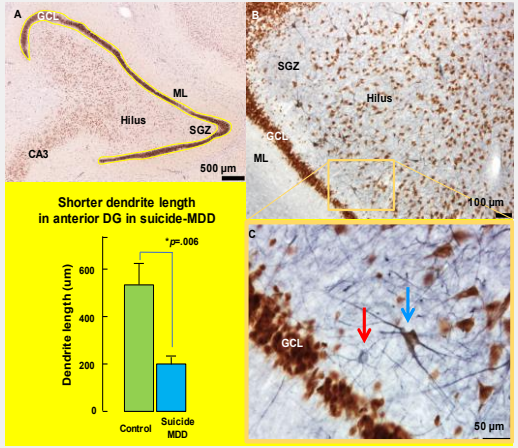
Process Length/Synapses In MDD Suicides



Process retraction in MDD suicides indicates synapse loss

Boldrini et al, unpublished

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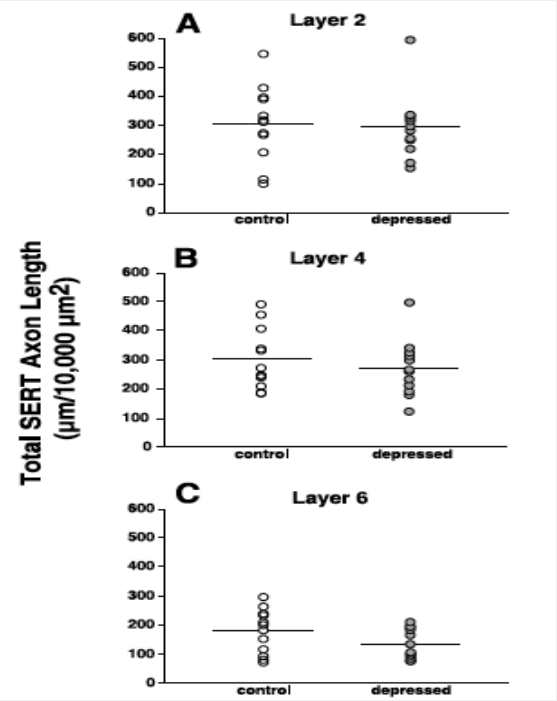
Shorter Serotonin Neuron Process Length in PFC of Suicide Decedents



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

Austin et al. Neuroscience 2002

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Brain BDNF Lower in Depression and Suicide If History Of Childhood Adversity

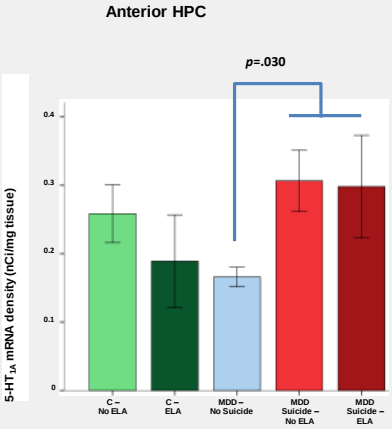

Figure 5. 5-HT_{1A} receptor mRNA *in situ* hybridization in hippocampus from subjects with and without childhood adversity (ELA). 5-HT_{1A} receptor mRNA is more in anterior DG in suicide vs non-suicide MDD.

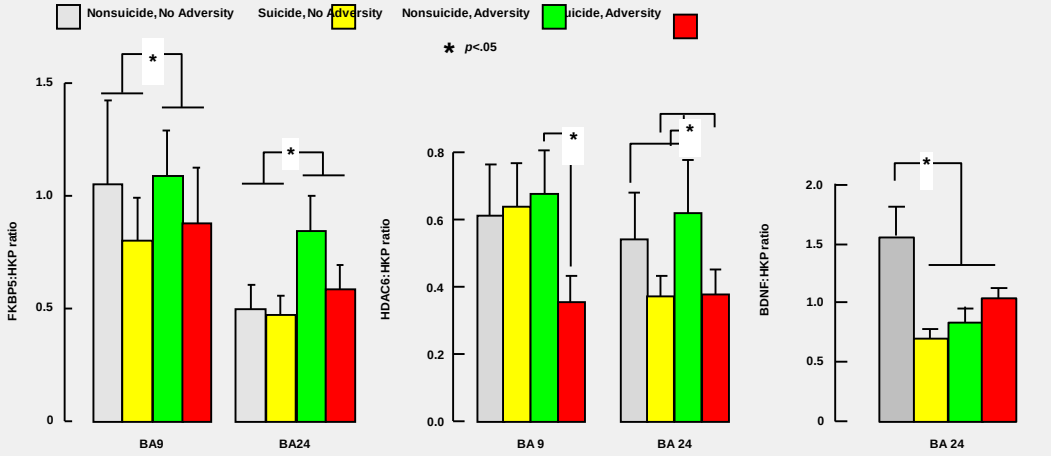

Figure 6. FKBP5 Levels in Prefrontal Cortex. Subjects with a history of early life adversity have higher FKBP5 levels in both dorsolateral and cingulate prefrontal cortex.

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 autoradio-graphy. Both suicide groups as well as controls exposed to adversity had lower ratios than controls.

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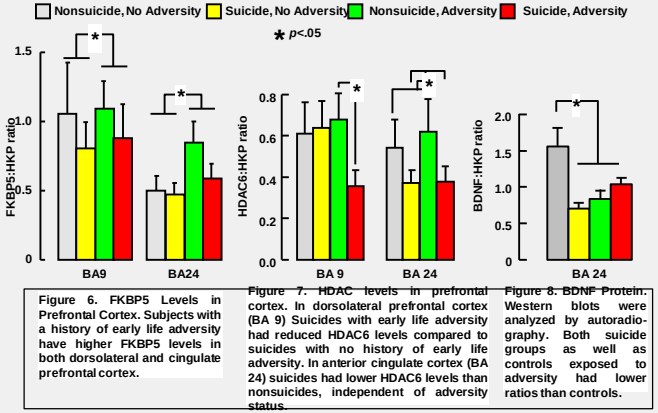
HPA Axis Over-activity and Neuroinflammation in Suicide



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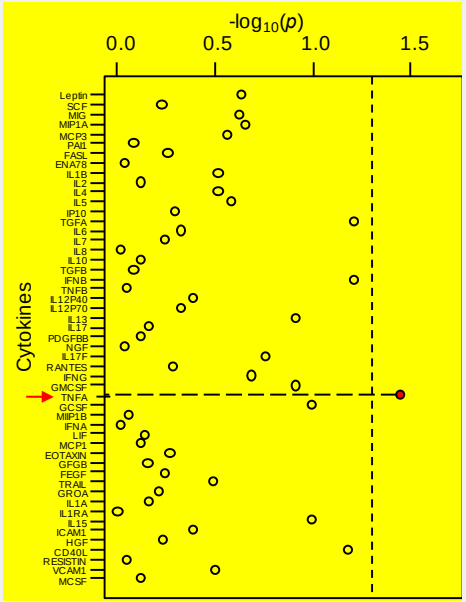
HPA Axis Overactivity



Neuroinflammation in Suicide MDD

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Trophic Deficits and Toxic Effects in MDD Suicides

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

J Mann.2020

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.**

J Mann.2020

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

TEL AVIV UNIVERSITY
Pursuing the Unknown

Columbia University
College of Physicians and Surgeons

Geha
Mental Health Center
Affiliated with the Sackler School of Medicine Tel Aviv University

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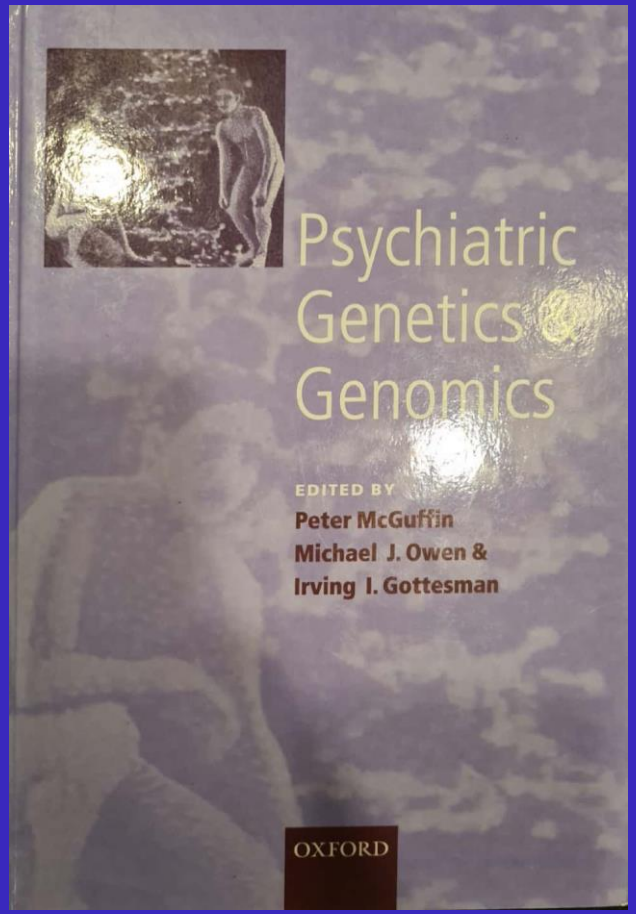

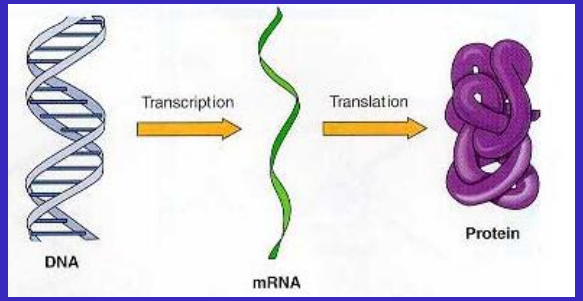

Basic Principals

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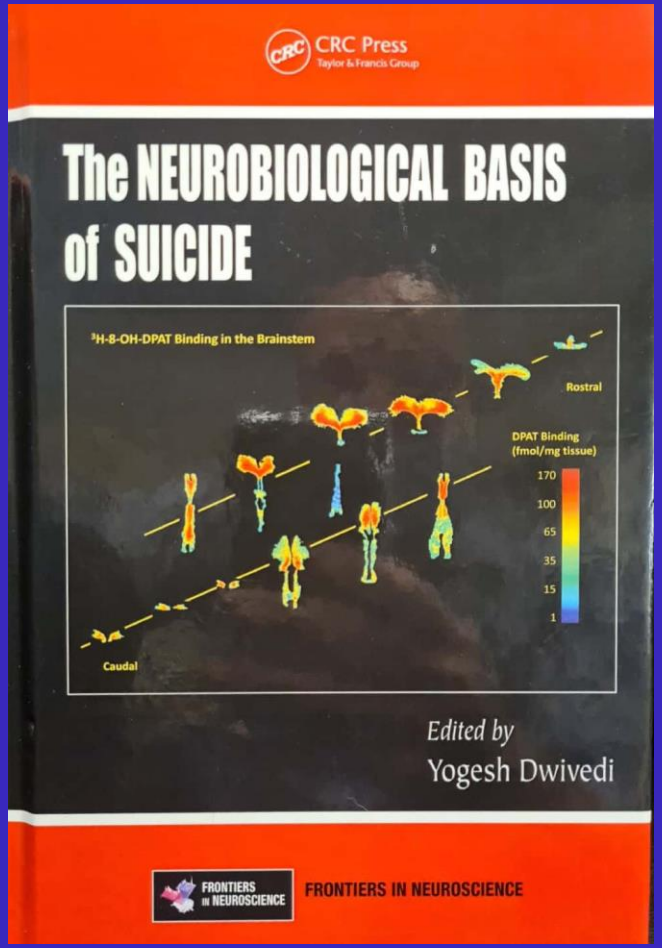

Chapters: 10-14
Specific for suicide

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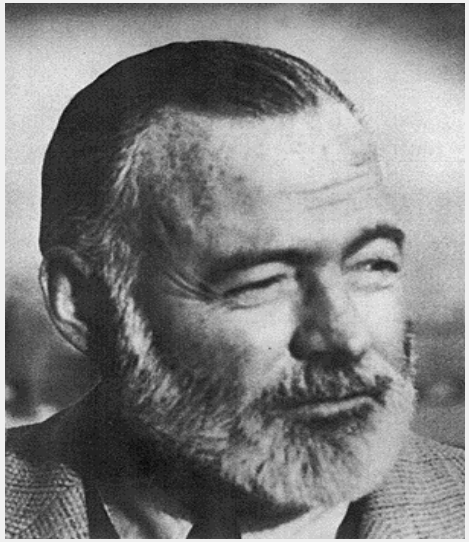
Suicide runs in families

International Academy of Suicide Research

American Foundation for Suicide Prevention

Suicide runs in families

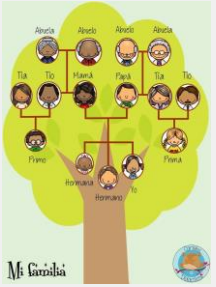
(A Roy et al 1990, DA Brent et al., 1996)



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

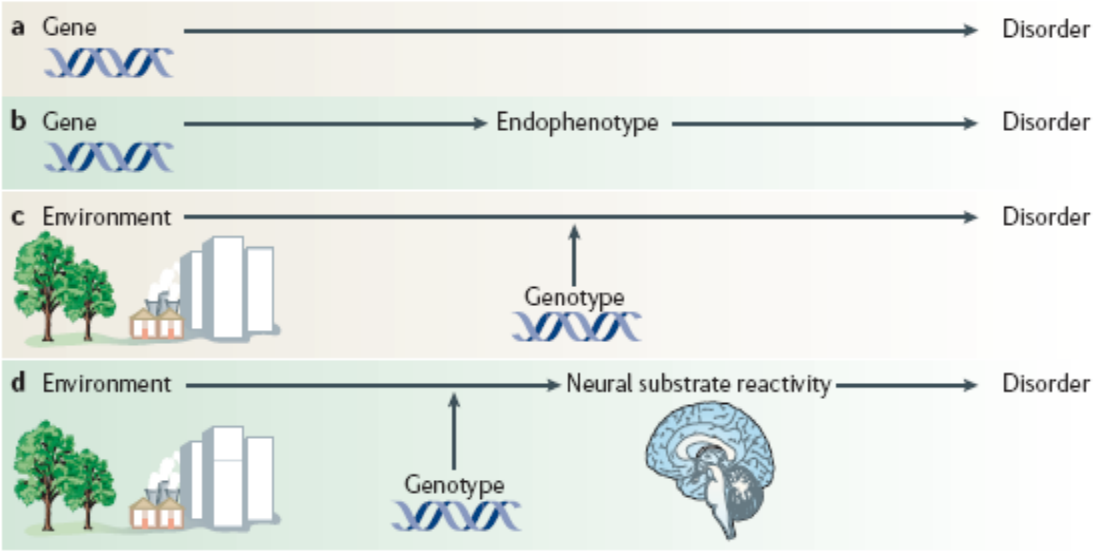


Figure 1 | **Approaches to psychiatric genetics research.** **a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder. **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. **c** | The gene–environment interaction approach 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.

Caspi and Moffitt, Nature Reviews Neuroscience, July 2006, with permission

Association studies in suicidology

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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

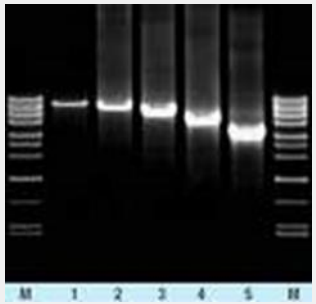
- Looking under the light
- Association doesn't mean effect or causality
- If there is a direct main effect of a single marker it's a Nobel price…
- Simple PCR technique (learn how to)
- Needs large numbers (n)
- Needs good clinical phenotype (Questionnaires) OR **ENDOPHENOTYPE**
- Environmental effects are not accounted for

e.g.5HTTLPR

Genotype	Non suicidal (expected)	Suicidal (finding)
LL	**80%**	20%
SS	15%	**75%**
SL	5%	5%

Direct main effect approach

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



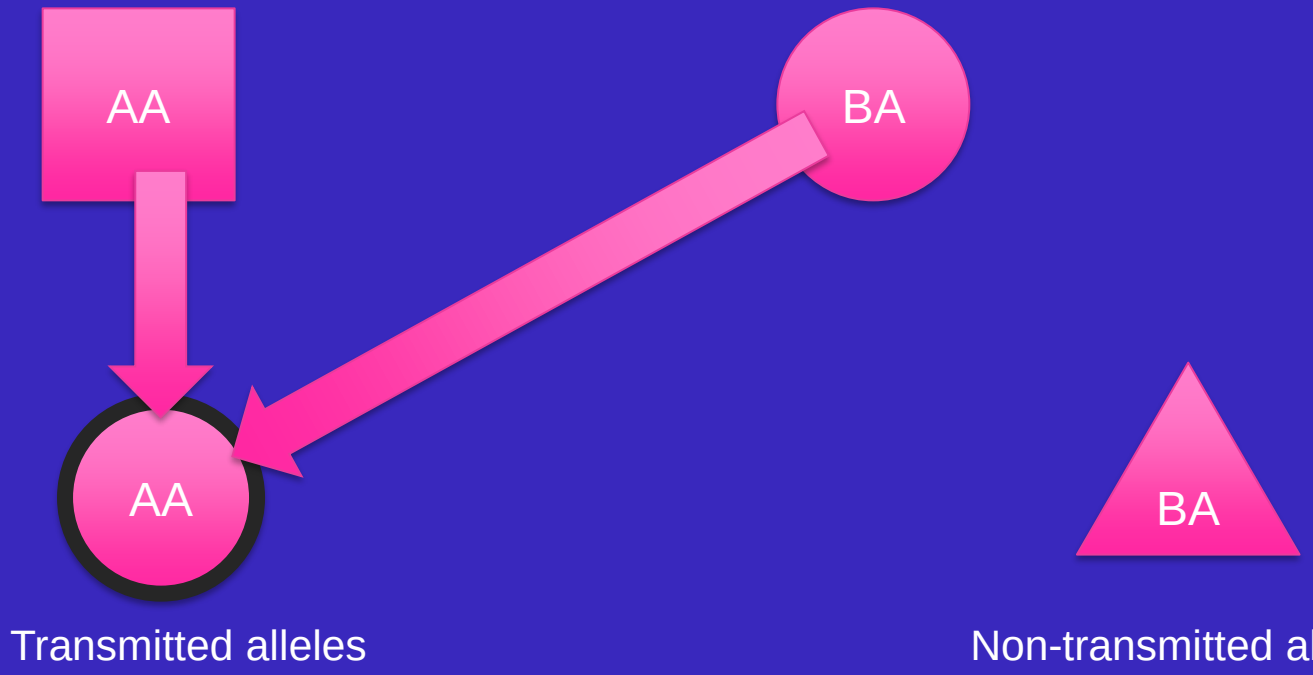
→ **Equivocal results**

Haplotype Relative Risk (HRR) TDT

Parents are controls for their suicidal kid

*Avoid Ethnic Stratification

HRR association approach



Genetics of Suicide in Adolescents

TABLE 14.1
Published Studies on Genetics of Adolescent Suicide

Reference	Population	Polymorphisms	Main Findings
Zalsman et al. (2001a,b)	Family-based study (HRR): 88 inpatient adolescents of Jewish origin who recently attempted suicide and both biological parents of 40 subjects and from one parent of 9 subjects	A218C in intron 7 of tryptophan hydroxylase (*TPH*) gene	HRR method (chi-square = 0.094; $P = 0.76$), the TDT (chi-square = 0.258; $P = 0.61$), or association analysis to known population frequencies (chi-square = 1.667, $P = 0.19$ for Ashkenazi, and chi-square = 0.810, $P = 0.37$ for non-Ashkenazi). Analysis of variance with the Scheffe test demonstrated a significant difference between CC and AA genotypes in suicide risk and depression among the patients ($n = 88$). The findings suggest that polymorphism A218C has no major relevance to the pathogenesis of adolescent suicidal behavior but may have a subtle effect on some related phenotypes
Zalsman et al. (2001b)	Forty-eight Israeli inpatient adolescents who recently attempted suicide using the haplotype relative risk (HRR)	The serotonin transporter-linked promoter region polymorphism (5-HTTLPR)	No significant allelic 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 LS genotypes
Zalsman et al. (2004)	Sixty-nine Israeli inpatient suicidal adolescents who recently attempted suicide and 167 healthy control subjects	Dopamine receptor subtype 4 (*DRD4*) gene exon III 48 bp repeat polymorphism	No significant association between the DRD4 polymorphism and suicidal behavior was found. Analysis of the suicide-related measures demonstrated a significant difference in depression severity between suicidal inpatients homozygote and heterozygote for the DRD4 alleles

(*continued*)

Zalsman G
In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. 2012. Chapter 14.

TABLE 14.1 (continued)
Published Studies on Genetics of Adolescent Suicide

Reference	Population	Polymorphisms	Main Findings
Zalsman et al. (2005a)	Thirty-two suicidal and 28 non-suicidal Ashkenazi Israeli adolescent psychiatric inpatients	5-HTTLPR polymorphism and platelet transporter binding	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
Zalsman et al. (2005b)	A family-based method (HRR): 30 families of inpatient adolescents from Jewish Ashkenazi origin, with a recent suicide attempt	5-HT(2A) receptor gene polymorphism T102C	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
Cicchetti et al. (2010)	Eight hundred and fifty low-income children (478 maltreated; 372 non-maltreated) with self-reported depressive and suicidal symptoms	5-HTTLPR	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 s/s or s/l genotypes had higher suicidal ideation than those with the l/l genotype; suicidal ideation did not differ in non-maltreated children or children with three to four maltreatment subtypes based on 5-HTTLPR variation
Zalsman et al. (2010)	Four groups of adolescents were included: suicidal ($N = 35$) and non-suicidal ($N = 30$) psychiatric inpatients, suicide attempters admitted to three psychiatric emergency rooms ($N = 51$), and a community-based control group ($N = 95$)	HTR2A (102T/C) 5-HTTLPR MAOA) and plasma serotonin	Homozygosity for the T allele of the HTR2A 102T/C 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 p5HT level

GWAS in suicidology

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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 Studie

Taylor & Francis
Taylor & Francis Group

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 Haghighi, Victoria Arango & J. John Mann

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American Foundation for Suicide Prevention

Table 3: Literature review for the 19 significant GWAS candidate genes in suicides (based on OMIM database*)

Gene Symbol	Chro. #	Description	Suggested clinical role*	Similar Genes found by others in expression studies
CDH13	16	cadherin 13, H-cadherin (heart)	Lung tumor recurrence?	CDH12, CDH22 (Thalmeier et al., 2008)
NPR3	5	natriuretic peptide receptor C	Maintenance of blood pressure	
CD300LB	17	CD300 antigen-like family member b	Cell surface localization in B and NK cells	
FOXN3	14	forkhead helix transcription	DNA damage correction?	ADAMTS1, IGF1, VIP, WDR39 (Thalmeier et al. 2008)
DISC1	1	disrupted in schizophrenia 1	Susceptibility for schizophrenia (Millar et al. 2000)	
CYP19A1	15	cytochrome P450, family 19, subfamily A, polypeptide 1	Aromatase deficiency	
MYO3A	10	myosin IIIA	Autosomal recessive deafness	MYR8 (Thalmeier et al. 2008)
SFRS11	1	arginine/serine-rich 11 splicing factors	Pre-mRNA splicing?	
LSAMP	3	limbic system-associated membrane protein	Neuronal surface glycoprotein in limbic system (Pimenta et al., 1996)	
DSC2	18	desmocollin 2	Ca dependent glycoprotein important for cell adhesion	
SPTLC1	9	serine palmitoyltransferase, long chain base subunit 1	Hereditary sensory neuropathy	
ACCN1	17	amiloride-sensitive cation channel 1, neuronal (degenerin)	neurodegeneration? KO-mice reduced sensitivity to mechanic sensation	
FLJ23312	5	Hypothetical protein	Not known	FLJ21616 (Sequeira et al. 2007)
MBNL2	13	muscleblind-like 2	May be associated with Myotonic Dystrophy	
CD44	11	CD44 molecule	Migration , cell fusion, tumorgenesis?	(Thalmeier et al.2008 , Sequira et al.2007)
TUBGCP3	13	tubulin, gamma complex associated protein 3	Associated with gama-tubulin in cells and oocytes	

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. Shabalin, Ph.D., Emily DiBlasi, Ph.D., Eric Monson, M.D., Niamh Mullins, Ph.D., Daniel E. Adkins, Ph.D., Silviu-Alin Bacanu, Ph.D., Amanda V. Bakian, Ph.D., Sheila Crowell, 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 Jerominski, M.S., Caroline Hayward, Ph.D., David J. Porteous, Ph.D., Andrew McIntosh, M.D., Qingqin 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.

rs35518298, rs34053895, rs66828456, rs35502061, and rs35256367). Gene-based analyses implicated 22 genes on chromosomes 13, 15, 16, 17, and 19 ($q<0.05$). Suicide death heritability was estimated at an h^2_{SNP} value of 0.25 (SE=0.04) and a value of 0.16 (SE=0.02) when converted to a liability scale. Notably, suicide polygenic scores were significantly predictive across training and test sets. Polygenic scores for several other psychiatric disorders and psychological traits were also predictive, particularly scores for behavioral disinhibition and major depressive disorder.

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.

Approaches in research of the medical genetics

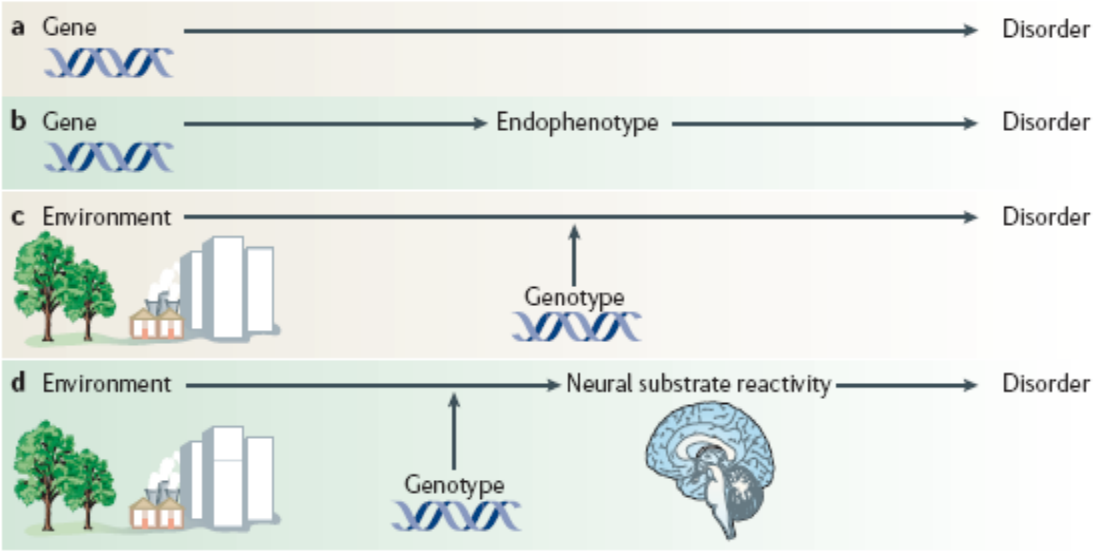
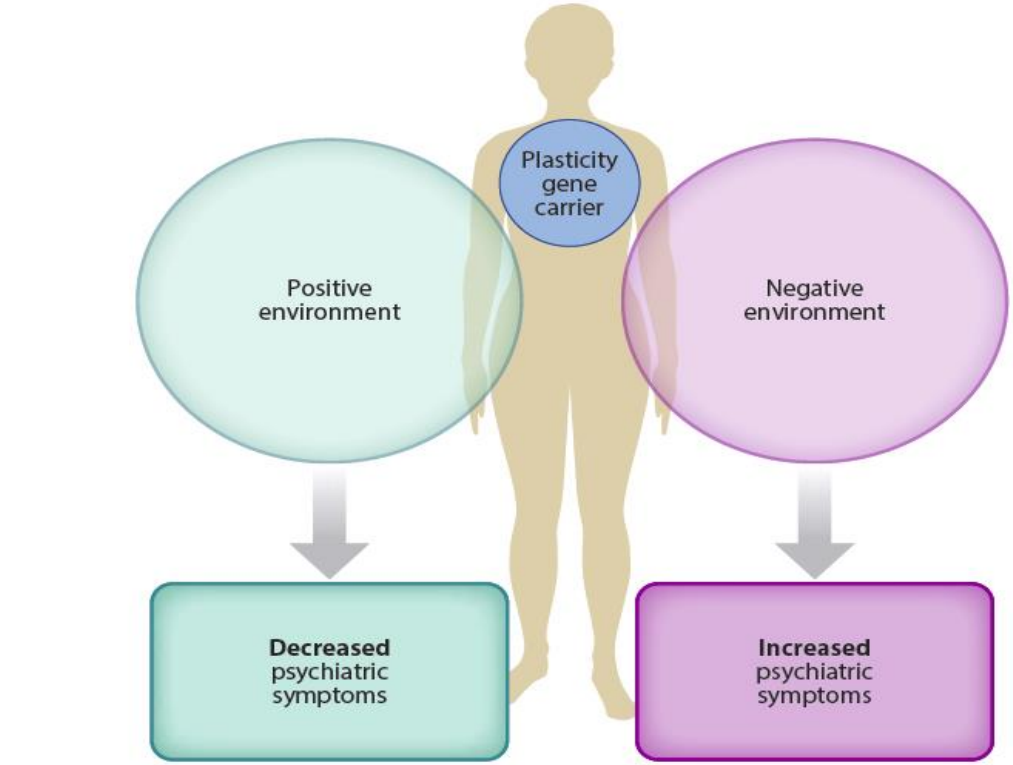


Figure 1 | **Approaches to psychiatric genetics research.** **a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder. **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. **c** | The gene–environment interaction approach 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.

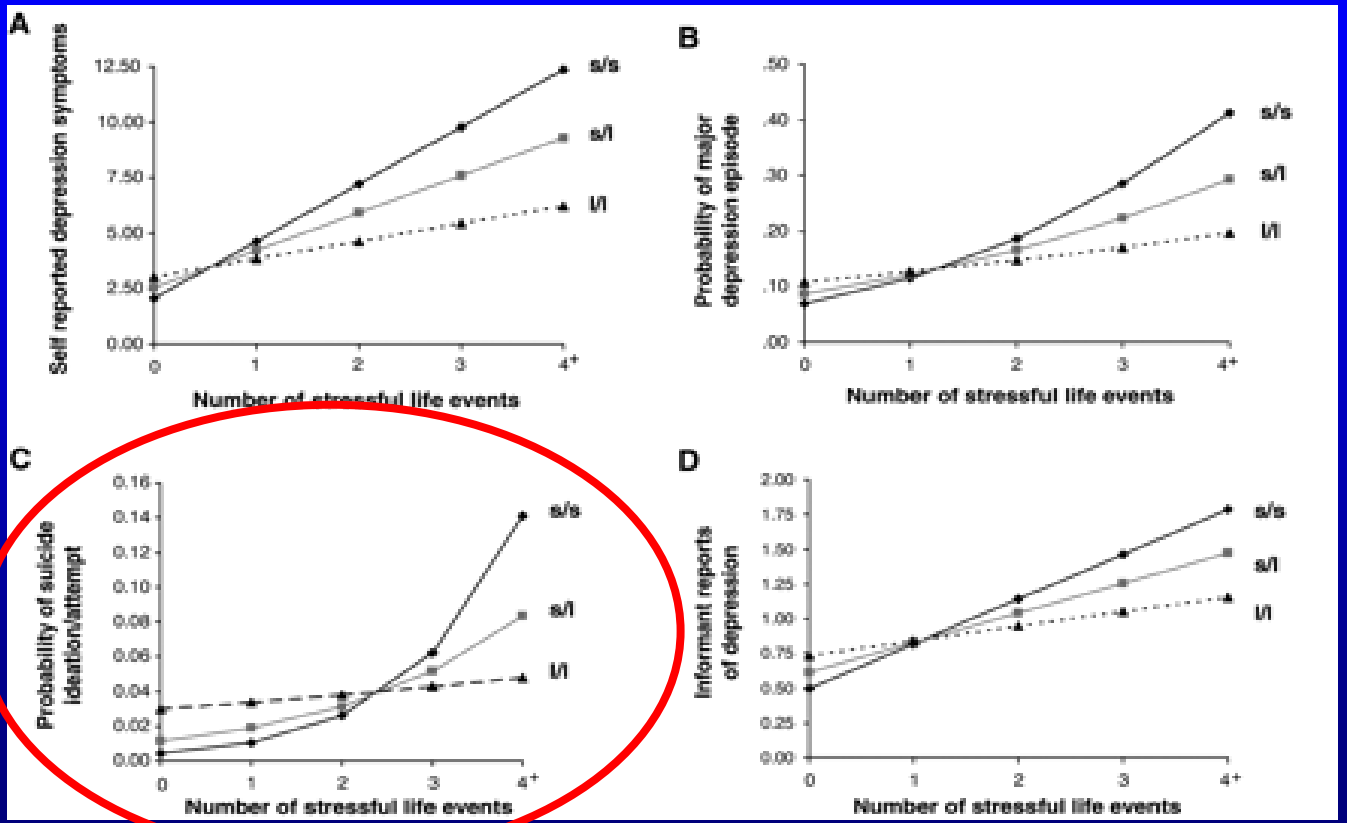
Caspi and Moffitt, Nature Reviews Neuroscience, July 2006, with permission

GxE approach in suicidology


Plasticity gene carrier
Positive environment
Negative environment
Decreased psychiatric symptoms
Increased psychiatric symptoms

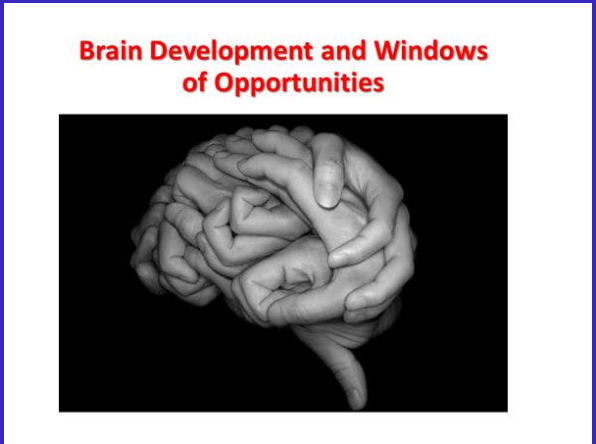
Binder 2016

5HTTLPR Gene X Environment Interaction in suicidal behavior



Caspi et al. Science, 2003

GxExT approach



Suggested Model: GxExT interaction

European Psychiatry 25 (2010) 284–286

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Review

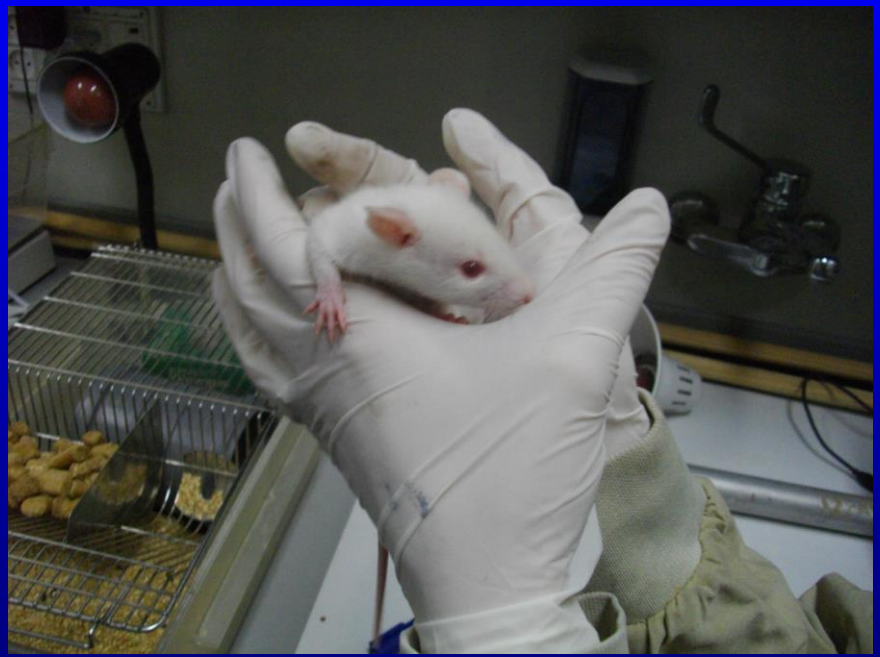
Timing is critical: Gene, environment and timing interactions in genetics of suicide in children and adolescents

G. Zalsman [a,*,b,c]

[a] Child and Adolescent Psychiatry Division, Geha Mental Health Center, PO Box 102, 49100 Petach Tiqwa, Israel
[b] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] Molecular Imaging and Neuropathology Devision, Psychitry Department, Columbia University, New York, USA

Zalsman G. Timing is critical. Eur Psychiatry. 2010;25(5):284-6

WKY Rat
Animal model for depression, despair and anhedonia



GxExT

European Neuropsychopharmacology (2015) 25, 2075-2085

ELSEVIER

www.elsevier.com/locate/euroneuro

Genetic vulnerability, timing of short-term stress and mood regulation: A rodent diffusion tensor imaging study

Gil Zalsman[a,b,*], Avihay Gutman[c,d], Liat Shbiro[d], Ruth Rosenan[d], J. John Mann[b], Aron Weller[d]

Zalsman et al., Eur Neoropsychopharmacology 2015

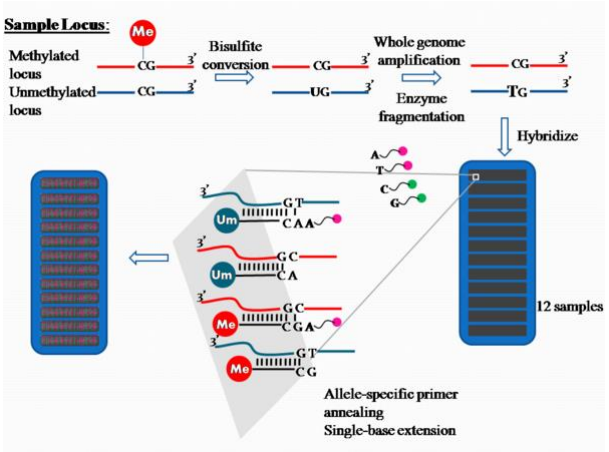
Epigenetics

Epigenetics

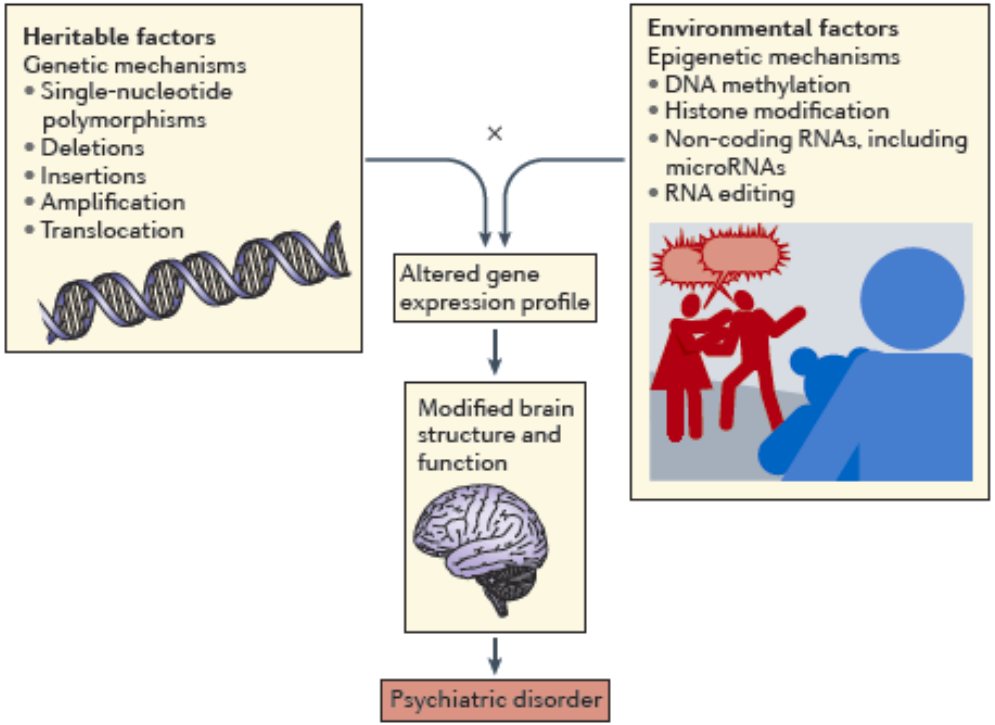
Changes in DNA that change gene expression. These changes can be permanent (cell type) or temporary (developmental window , environmental ques)

Types:

1. Methylation
2. Histones modification
3. Non coding RNAs=MiRNA



Epigenetics in Psychiatry



Issler and Chen, Nature Review Neuroscience 2015

Epigenetics in suicidology

International Academy of Suicide Research

American Foundation for Suicide Prevention

Labonte 2013

Article

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 Szyf, 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.

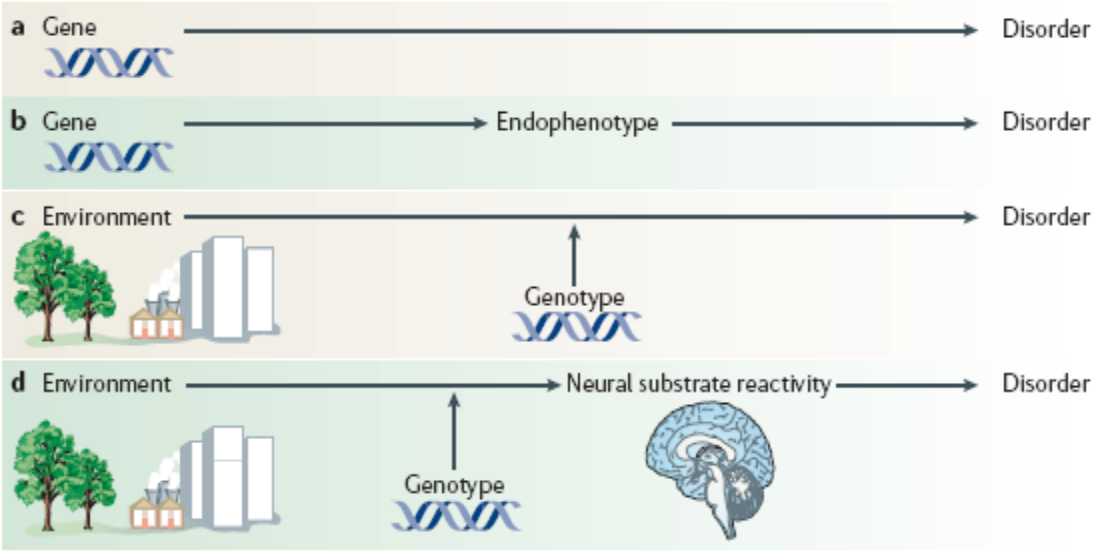
Method: Promoter DNA methylation was profiled using methylated DNA immunoprecipitation (MeDIP) followed by microarray hybridization in hippocampal tissue from 62 men (46 suicide completers and 16 comparison subjects). The correlation between promoter methylation and expression was investigated by comparing 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



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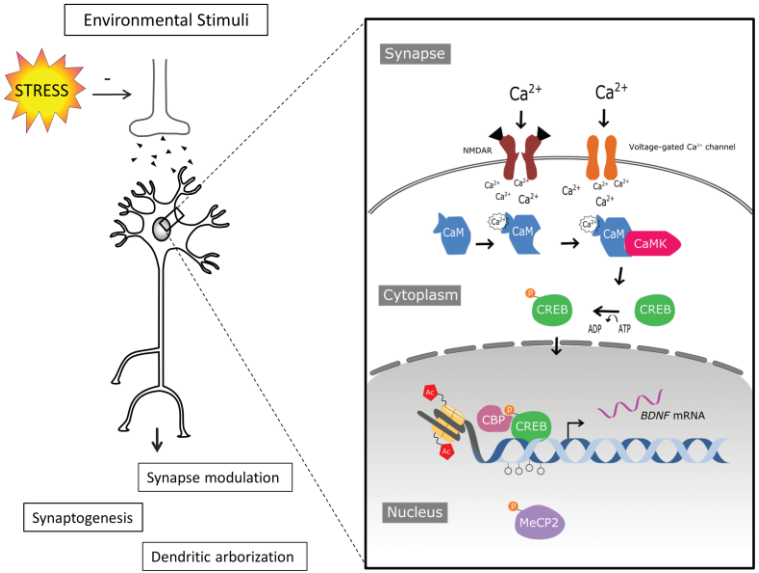
Caspi and Moffitt, Nature Reviews Neuroscience, July 2006, with permission

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.

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Thank You!

zalsman@tauex.tau.ac.il