Mapping Neural circuitry of Risk and Resilience for Suicidal Behavior and Mood Disorders

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Talk Outline

• Describe a model of decision making explaining how the patient makes the initial decision regarding suicide and how he/she may review that decision through the course of treatment.

• Link decision making to neural circuits that are abnormal in the patient subgroup at risk for suicide and nonfatal suicidal behavior.

• Consider clinical implications.
Who Dies by Suicide? A Stress Diathesis Model

- 90% or more suicides occur during a psychiatric illness
- 60% of the illnesses are a mood disorder.
- Most depressed patients never attempt suicide.
- Depressed suicide attempters differ from depressed nonattempters in having a diathesis or predisposition for suicidal behavior.

- **Diathesis components:**
  1. mood dysregulation/greater subjective distress,
  2. reactive aggressive traits (greater delayed discounting),
  3. impaired problem solving/learning,
  4. social distortions.

General Decision-Making Pathway

- Learning: Update the representation, valuation and action-selection processes
- Representation: Set of feasible actions? Internal states? External states?
- Valuation: What is the value of each action (given the internal and external states)?
- Action selection: Choose actions based on valuations
- Outcome evaluation: How desirable are the outcomes and states that followed the action?

vPFC & Hippocampus

Ventral Prefrontal Cortex

Anterior Cingulate

Ventral Striatum

Nature Reviews Neuroscience

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PROSPECT THEORY: AN ANALYSIS OF DECISION UNDER RISK

BY DANIEL KAHNEMAN AND AMOS TVERSKY

This paper presents a critique of expected utility theory as a descriptive model of decision making under risk, and develops an alternative model, called prospect theory. Choices among risky prospects exhibit several pervasive effects that are inconsistent with the basic tenets of utility theory. In particular, people underweight outcomes that are merely probable in comparison with outcomes that are obtained with certainty. This tendency, called the certainty effect, contributes to risk aversion in choices involving sure gains and to risk seeking in choices involving sure losses. In addition, people generally discard components that are shared by all prospects under consideration. This tendency, called the isolation effect, leads to inconsistent preferences when the same choice is presented in different forms. An alternative theory of choice is developed, in which value is assigned to gains and losses rather than to final assets and in which probabilities are replaced by decision weights. The value function is normally concave for gains, commonly convex for losses, and is generally steeper for losses than for gains. Decision weights are generally lower than the corresponding probabilities, except in the range of low probabilities. Overweighting of low probabilities may contribute to the attractiveness of both insurance and gambling.

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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.
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.
• Mood modulates this decision-making process. More pessimistic means considers chances of responding to medication is even lower.
• Kahneman: “the operations of System 1 are typically fast, automatic, effortless, associative, implicit (not available to introspection), and often emotionally charged; they are also governed by habit and are therefore difficult to control or modify.

• Operations of System 2 are slower, serial, effortful, more likely to be consciously monitored and deliberately controlled; they are also relatively flexible and potentially rule governed”.

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A Revised Model of Decision Making and Suicidal Behavior

Emotional pain → Value of relief by suicide or relief by antidepressant treatment

- Low lethality impulsive suicidal behavior
- High lethality planned suicidal behavior

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

System 1 & System 2
• **Ventral striatal (reward)** is a major target of the dopamine reward system and its activity is higher when subjects chose a smaller, **immediate monetary reward** compared with a larger, delayed reward (McClure et al., 2004).

• Selection of larger, **delayed** rewards is associated with activity in the lateral orbital PFC and dorsolateral PFC. **This indicates that better tolerance of delayed gratification is associated with higher activity in these two brain regions (lateral oPFC and dlPFC).**
Anterior Cingulate Cortex Instigates Adaptive Switches in Choice by Integrating Immediate and Delayed Components of Value in Ventromedial Prefrontal Cortex

- ACC tracks short-term and long-term reward options in making choices.
- Interacts with ventromedial PFC and striatum for short-term reward and dorsal lateral PFC for long-term reward.

The Journal of Neuroscience, February 26, 2014 • 34(9):3340–3349 Economides et al

• 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 (Nock et al 2006).
• Imaging of MDD at risk for suicide shows hypoactive dlPFC.
• **Dorsolateral PFC impaired > orbital PFC > risky decisions and suicidal behavior**
Trait Components of Diathesis for Suicidal Behavior

- Reactive or impulsive aggressive traits—decision-making—delayed discounting.
- Cognitive rigidity and impaired problem solving.
- Misreading social signals from others.
Subjective depression, not clinician-rated depression, is more severe in depressed suicide attempters and is a trait transmitted in families with suicidal behavior. Mann et al. 2015.
Brain Blood Flow Predicts Suicide in Major Depression

Dorsolateral PFC and insula deficits are seen in future suicides.

Willeumier et al Trans Psychiatry (2011)
Thinner prefrontal cortical & anterior cingulate in depressed patients at high-risk for suicidal behavior

- Thinner cortex in the left **dorsolateral, ventrolateral prefrontal cortex and the anterior cingulate** in high risk MDD.

Prefrontal cortex is thinner in depressed patients at high-risk for suicidal behavior

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Decision-Making Neural Circuitry During Response Inhibition is Different in Depressed Adolescent Suicide Attempters

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
Decreased Activation Of Lateral Orbitofrontal Cortex During Risky Choices Under Uncertainty Is Associated With Suicidal Behavior

• Left lateral orbitofrontal cortex hypofunction during risky relative to safe choices in the Iowa Gambling Task in remitted depressed suicide attempters compared to remitted depressed nonattemtpters could explain the decision-making deficits observed in suicide attempters

• Jollant et al NeuroImage 51 (2010) 1275–1281
Responses to Emotional Faces in Euthymic Suicide Attempters versus Nonattempters Show Social Distortion

Jollant *et al.* AJP 2008, 165

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Responses to Emotional Faces in Euthymic Suicide Attempters

Brodmann area 47 may be involved in sensitivity to disapproval and expectation of punishment (Kringelbach et al. 2004).

**Conclusions:** Suicide attempters were distinguished from nonsuicidal patients by responses to angry and happy faces that may suggest increased sensitivity to others’ disapproval, higher propensity to act on negative emotions, and reduced attention to mildly positive stimuli. These patterns of neural activity and cognitive processes may represent vulnerability markers of suicidal behavior in men with a history of depression.

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The Diathesis for Suicidal Behavior

- **Low/altered serotonin activity**
- **Altered HPA dysfunction**
- **Altered decision-making**
  - Negative perceptual sets: Hopelessness/RFL
  - Perception of depression
- **Social distortions**
- **Impaired problem solving and learning**
- **Suicidal ideation/intent**
- **Suicidal act**

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Low Serotonin Transporter Binding (PET with $^{11}$C-DASB) in MDD Suicide Attempters

Controls | MDD non-attempters | MDD attempters

Miller et al (Biol Psych 2013)
5-HT1A Receptor Binding Imaged by PET
Suicides have more $5$-$HT_{1A}$ Autoreceptor Binding in the Rostral DRN

$\text{[^3]H}-8$-OH-DPAT Binding (fmol/mg tissue)

- Controls ($n=10$)
- Suicides ($n=10$)

$\times \ p < 0.05$

DRN Rostrocaudal Levels (mm)

Boldrini et al., J Psychiatric Res. 2007

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Higher 5-HT$_{1A}$ Autoreceptor Binding Means Higher Attempt Lethality
Higher \(5\text{-}HT_{1A}\) Autoreceptor and Prefrontal Cortical Binding Means More Severe Suicidal Ideation
Higher $5\text{-HT}_{1A}$ binding potential of raphe nucleus autoreceptors predicts greater maximal lethality of suicide attempt during follow-up.
Biomarker Prediction of Suicidal Ideation Up To One Year Post Scan
Summary

• Mood regulation, decision-making, learning and problem solving and social perception are altered in suicidal behavior.

• Neural circuits related to these functions show abnormalities in suicide and suicide attempters that favor system 1.

• Clinical and biological knowledge of these processes can help optimize clinical management of suicidal patients.

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