TREATMENT OF ADOLESCENT DEPRESSION:
The Past, The Present and The Future Promise of Experimental Therapeutics

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Disclosures

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Overview – Pros and Cons of Old versus New Approaches to Improving Psychiatric treatments

- NIMH experimental therapeutics
- Research Domain Criteria (RDoC)
- Traditional RCTs – TORDIA, TRYADS, INVEST
- Pilot Studies – Concurrent
- Rumination as a target for experimental therapeutics
- Other experimental approaches to the treatment of depression
Over the past decade, NIMH has supported large-scale, expensive effectiveness trials. These trials were useful for identifying the limits of current treatments, but not helpful for improving outcomes.

In the current climate, with funding tight, we will be shifting to trials that focus on targets as a way of defining the next generation of treatments.

We believe that better outcomes will require a deeper understanding of the disorders. These new clinical trials are designed to provide that.
Why these changes to our clinical trials enterprise?

- Treatment development has stalled. The pharmaceutical industry pipeline for medications is depleted because of an inadequate understanding of the biology of the disorders.

- *Psychosocial interventions may not be disseminated or reimbursed in the new healthcare environment without evidence for the required dose and duration of treatment.*

- Neuromodulatory treatments have seen the most innovation but will need considerably more rigor in terms of establishing mechanisms of action and required dose.
Go/no-go decision point:
Only if the intervention adequately engages the target (mechanism), such as a neural pathway implicated in the disorder, will investigators move on to assess clinical outcomes.
Should we be throwing the baby out with the bathwater?

- **Con:** If we started with demonstrating treatment target/mechanism engagement, there wouldn’t be any of the cognitive psychotherapies we now know and love – would that have been a good thing?

- **Pro:** It is very hard to get decent active psychotherapies to separate

- **Pro:** Can more research really make talking therapies/CBT much better than they are currently?
Someone else thought of this first…

- Why, anybody can have a brain. That's a very mediocre commodity. Every pusillanimous creature that crawls on the earth or slinks through slimy seas has a brain.
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Imaging method</th>
<th>Treatment</th>
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<tr>
<td>Baxter⁶</td>
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<td>18</td>
<td>FDG-PET</td>
<td>BT vs fluoxetine</td>
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<td>Martin⁴</td>
<td>MDD</td>
<td>28</td>
<td>HMPAO-SPECT</td>
<td>IPT vs venlafaxine</td>
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<td>24</td>
<td>FDG-PET</td>
<td>IPT vs paroxetine</td>
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<td>Furmark¹¹</td>
<td>Social phobia</td>
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<td>¹³O-PET</td>
<td>CBT vs citalopram</td>
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<td>OCD</td>
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<td>Xe-CT</td>
<td>BT</td>
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<td>Paquette¹²</td>
<td>Spider phobia</td>
<td>12</td>
<td>fMRI</td>
<td>CBT</td>
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<td>Praško⁹</td>
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<td>12</td>
<td>FDG-PET</td>
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<td>Nakao²⁹</td>
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<td>10</td>
<td>fMRI</td>
<td>CBT vs fluvoxamine</td>
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<td>Sakai¹⁰</td>
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<td>Straube¹³</td>
<td>Spider phobia</td>
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<td>fMRI</td>
<td>DBT</td>
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<td>Schnell¹⁵</td>
<td>BPD</td>
<td>6</td>
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<td>PDT</td>
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<td>Lai¹⁶</td>
<td>BPD</td>
<td>2</td>
<td>SPECT</td>
<td>CBT</td>
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<tr>
<td>Felmingham¹⁴</td>
<td>PTSD</td>
<td>8</td>
<td>fMRI</td>
<td>PDT</td>
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<td>Lehto³⁰</td>
<td>MDD</td>
<td>19</td>
<td>SPECT</td>
<td>PDT vs waiting list</td>
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<td>Beutel¹⁰</td>
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<td>Apostolova²¹</td>
<td>OCD</td>
<td>16</td>
<td>FDG-PET</td>
<td>CBT vs paroxetine</td>
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<td>Karlsson¹⁷</td>
<td>MDD</td>
<td>9</td>
<td>WAY-PET</td>
<td>Short-term PDT vs fluoxetine</td>
</tr>
</tbody>
</table>

OCD, obsessive-compulsive disorder; FDG-PET, [18F]-fluorodeoxyglucose positron emission tomography; BT, behavior therapy; CBT, cognitive-behavioral therapy; MDD, major depressive disorder; HMPAO-SPECT, ⁹⁹mTc-hexamethylpropyleneamine oxime single photon emission CT; IPT, interpersonal psychotherapy; ¹³O-PET, oxygen-15 positron emission tomography; Xe-CT, xenon-enhanced CT; BT, behavioral therapy; fMRI, functional MRI; PD, panic disorder; DBT, dialectic behavior therapy; BPD, borderline personality disorder; SPECT, single photon emission CT; PDT, psychodynamic psychotherapy; PTSD, posttraumatic stress disorder; WAY-PET, positron emission tomography using [carbonyl-¹¹C] WAY-100635.
And in addition to neural pathways.....

- Research Domain Criteria – transform diagnosis by incorporating genetics, imaging, cognitive science, and other levels of information to build a new classification system.

- Genes
- Molecules
- Cells
- Circuits
- Physiology
- Behavior
- Self-report

From bench to bedside
RDoC approach began with several assumptions (T. Insel):

- A diagnostic approach based on the biology as well as the symptoms must not be constrained by the current DSM categories,
- Mental disorders are biological disorders involving brain circuits that implicate specific domains of cognition, emotion, or behavior,
- Each level of analysis needs to be understood across a dimension of function,
- Mapping the cognitive, circuit, and genetic aspects of mental disorders will yield new and better targets for treatment.
RDoC DOMAINS & CONSTRUCTS

- **Negative Valence** - acute threat (fear); potential threat (anxiety); sustained threat; loss; frustrative nonreward
- **Positive Valence** – reward learning; reward evaluation
- **Cognitive Systems** - attention
  - Perception – visual, auditory perception
  - Cognitive (effortful) Control – response selection, inhibition, or suppression
  - Working Memory
- **Arousal and Regulatory Systems** - arousal; sleep
- **Systems for Social Processes**
  - Affiliation and attachment
  - Social Communication
  - Perception and understanding of self
  - Perception and understanding of others
### Depression-related RDoC Construct

#### Domain: Negative Valence Systems
- **Construct:** Loss

#### Units of Analysis

<table>
<thead>
<tr>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Reports</th>
<th>Paradigms</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOA, COMT, DAT1, 5HTTR,</td>
<td>Downregulation of glucocorticoid receptors; Upregulation of CRH; Estrogens;</td>
<td>Sustained amygdala reactivity; Decreased DLPFC recruitment; Decreased vmPFC (incl. rostral</td>
<td>Increased amygdala reactivity; Decreased DLPFC recruitment; Decreased</td>
<td>ANS &amp; HPA &amp; neuroimmune dysregulation; Prolonged psychophysiological reactivity</td>
<td>Rumination; Withdrawal; Worry; Crying; Sadness; Loss-relevant recall bias; shame; Attentional</td>
<td>Change in attributional style; Hopelessness</td>
<td></td>
</tr>
<tr>
<td>5HTTRs</td>
<td>Androgens; Oxytocin; Vasopressin; Inflammatory molecules</td>
<td>cingulate); Increased insula activation; Increased posterior cingulate activity; Decreased R</td>
<td>vmPFC (incl. rostral cingulate); Increased insula activation;</td>
<td></td>
<td>bias to negative valenced information; Guilt; Morbid Thoughts; Psychomotor retardation;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>parietal; PVN; Hippocampus; Orbitofrontal cortex; Habit systems (striatum/caudate/accumbens);</td>
<td>Increased posterior cingulate activity; Decreased R parietal; PVN;</td>
<td></td>
<td>Anhedonia; Increased self-focus; Deficits in executive function (e.g., impaired sustained</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased default mode activity; Dysregulated reward circuitry</td>
<td>Hippocampus; Orbitofrontal cortex; Habit systems (striatum/caudate/</td>
<td></td>
<td>attention); Loss of drive (sleep, appetite, libido); Amotivation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>accumbens)</td>
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</tbody>
</table>

The table above outlines the units of analysis for the Depression-related RDoC Construct, focusing on the domain of Negative Valence Systems with a specific construct of Loss. It details the genetic, molecular, cellular, and circuitry aspects, along with the physiological and behavioral responses, and self-reports associated with the construct. The paradigm shift towards understanding depression through an attributional and hopeless perspective is highlighted at the end.
A Potential Cognitive Target: Rumination underlying Hopelessness

How would you target it?
Major Depressive Disorder/Dysthymia

**Lifetime Prevalence of 13 to 18 year olds**
- Lifetime Prevalence: 11.2% of 13 to 18 year olds
- Lifetime Prevalence of “Severe” Disorder: 3.3% of 13 to 18 year olds have a “severe” depressive disorder

**Demographics (for lifetime prevalence)**
- **Sex and Age**
- **Race: Not Reported**

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CBT response rates

Response rates for CBT appear to be between 60-66%
How do we treat the most difficult depressed adolescents?

- NIH Budget doubles – 1999-2004
- Big Trials to get more definitive answers
- TORDIA is funded
- 6 site national study
Depressed adolescents who had failed an adequate trial of an SSRI ($n = 334$)
- Randomized to 1 of 4 treatments in a $2 \times 2$ balanced design
- Switch to another SSRI
- Switch to venlafaxine (SNRI – novel at time)
- Switch to another SSRI plus CBT
- Switch to venlafaxine plus CBT
- Follow up at 6, 12, 24, 48, and 72 weeks
CBT Components

- Brent and Poling (1997) Cognitive restructuring and behavioral activation
- Lewinsohn, Clarke, and Hops – Social skills and behavioral activation
- TADS family component
- Added emotional regulation and distress tolerance
- Flexible use of modules
- 12 sessions of individual CBT and 3 family sessions
CLINICAL RESPONSE BY TREATMENT GROUP

CBT: $P = .018$
Predictors of treatment response

- Severity of depression
- Duration of depression
- Suicidal ideation
- Hopelessness
- Family conflict
Take home message

- A lot of papers were published from TORDIA data, but...

- Take home message: getting therapy when you have treatment-resistant depression works better than just meds.

- In the back rooms at NIMH: Couldn’t we have figured that out for a lot less money?
Another example from early 2000s

- Still developing treatments the old fashioned way
- Based on the literature and observations from clinical care
- Treating depressed, suicidal adolescents
- Some were binge drinking
TORDIA Findings are also relevant here

- Baseline suicidal ideation was higher among the subjects who progressed to high substance-related impairment (Q75th percentile) versus those whose substance-related impairment remained low (<75th percentile).

- The MDD response was best among the adolescents with low 12-week substance-related impairment scores regardless of whether they had high or low baseline substance-related impairment.

- Parental depressive symptoms predicted persistence of high substance-related impairment during the study.
Alcohol and Suicidal Behavior

- The relation between suicidality and SUDs, especially alcohol use disorders, appears to strengthen as each problem increases in severity (Esposito-Smythers & Spirito, 2004)
- If diagnosed with SUD and Mood Disorder by age 14, 17 times greater chance of attempting suicide later in adolescence (Reinherz et al., 1995)
- Adolescents with SUD and Mood Disorder at greater risk for completed suicide (OR: 17.0) than those with SUD alone (OR: 3.3) (Brent et al., 1993)
Mitigating factors:

- Preadolescent age of onset
- Severity of use
Disconfirming studies after controlling for covariates

- 2090 young (ages 12-13) Canadian adolescents (Afifi et al, 2007)
- 73,183 adolescents - substance use was not related to SAs that did or did not require medical attention (Wong et al., 2013)
- 180 adolescents followed up to 13 years post-psychiatric hospitalization (Goldston et al., 2009)
- 1,420 children and adolescents, ages 9 to 16 years (Foley et al. 2006)
Substance use, particularly alcohol, primarily confers risk for a suicide attempt in the presence of other mental health symptoms.
Why SUDs and SAs related?

- Adolescents share many common precipitants and life experiences (e.g., psychiatric disorders, trauma history, etc.)
- May also stem in part from commonalities in altered neurobiological processes
Why SUDs and SAs related?

- Means to escape and/or achieve relief from perceived insurmountable stress, consistent with the self-medication hypothesis (Khantzian 1997).

- Co-occur with other health risk behavior among many youth, suggesting a common underlying set of traits (e.g., sensation seeking, impulsivity) or unifying syndrome, consistent with problem behavior theory (Donovan and Jessor 1985).
Marijuana specific findings:

- Conclusions: Modest association between heavy or problematic use of cannabis and depression in cohort and well-defined cross-sectional studies in the GENERAL population.
- Little evidence of this link with infrequent cannabis use.
- Modest association of early-onset, regular cannabis use and later depression (Degenhardt et al., 2003).
THC appears to be related to regulation of emotional experience including depression, i.e. a neurobiological effect of cannabinoids.

Alternatively, or more likely concurrently, the association is linked to common shared social, personality and environmental risk factors.
Directionality may vary by individual

- Alcohol/substance use leads to a SA,
- SA lead to alcohol/substance use,
- Or a bidirectional relationship at varying time points.
Integrated Treatment Approach (Esposito-Smythers, Spirito, et al., 2011)

- Manualized modular treatment
- CBT techniques used to remediate maladaptive cognitions and behaviors that underlie alcohol/drug abuse and suicidality
- CBT techniques shown effective for co-occurring conditions
- Motivational interviewing techniques used to improve motivation and treatment adherence
- Weekly monitoring of suicidality and substance use to help prevent relapse
Treatment Protocol Schedule

- Three treatment phases
  - Active: 6 months of weekly sessions
  - Maintenance: 3 months of bi-monthly sessions
  - Booster: 3 months of monthly sessions
- Two therapists assigned to each case
  - Adolescent therapist
  - Parent/family therapist
Treatment Protocol Design

- Experimental (EXP)
  - Medication management
  - Case management
  - Comprehensive baseline assessment and follow-ups
  - Integrated treatment delivered by study staff

- Enhanced SC (ESC)
  - Medication management
  - Case management
  - Comprehensive baseline assessment and follow-ups
  - Treatment as usual in the community

Esposito-Smythers et al, 2011
Inclusion/Exclusion Criteria

- Inclusion criteria
  - Clinically significant suicidal ideation or a recent suicide attempt
  - Used alcohol over the last month
  - Meets current diagnostic criteria for an Alcohol Use Disorder or Cannabis Use Disorder

- Exclusion criteria
  - IQ < 70
  - Current psychosis
  - Dependence on substance other than alcohol or cannabis
Study Participants

- 36 adolescents (19 in EXP and 17 in ESC); 12 M, 24 F
- 72% on medication at study entry
- Prior therapists: 0-5, mean = 2
- Depressed for an average of 2.8 years
- Average of a 2.9 year treatment history
- Suicidality: 100% suicidal ideation; 75% suicide attempt
Diagnoses

- 36% alcohol abuse; 28% alcohol dependence
- 25% marijuana abuse; 58% marijuana dependence
- 86% Major Depressive Disorder
- 17% GAD; 33% Social Phobia
- 19% PTSD
- 33% ADHD
- 33% Conduct Disorder
Integrated Treatment Protocol: Sessions addressing suicidality

- **Rapport Building / Goal Setting**
- **Problem-solving**
- **Cognitive restructuring**
- **Affect regulation (cognitive)**
- **Affect regulation (behavioral)**
- **Skill review**
Integrated Treatment Protocol: Alcohol/Drug Sessions

- Motivational Interview
- Increasing Healthy Pleasant Events
- Enhancing Social Support Networks
- Alcohol/Drug Refusal Skills
- Coping with Cravings
- Planning for Suicide and Alcohol Related Emergencies
Model

Brief MI intervention targeting substance use and suicidality

- Increase in negative expectancies
- Increase in situational confidence
- Increase in mental health and substance abuse treatment engagement

Decrease in substance use

Decrease in substance-related suicidal thoughts and behaviors

O’Brien, 2013
Intervention:
Decisional Balance

- Reasons to stay the same?
  - “Helps me be more sociable”
  - “Meet new people”
  - “Helps numb the pain”

- Reasons to make a change?
  - “Too much makes you an idiot”
  - “Losing memory”
  - “Losing control”

- Not so good things about cutting down or stopping drinking?
  - “Not having something to numb the pain”
  - “Less fun drinking”

- Good things about cutting down or stopping drinking?
  - “More control”
  - “Less humiliation after”
The changes I want to make are: “Coping better with life”

The most important reason I want to make these changes are: “To be happier and use my emotions for positive things rather than negative things”

The steps I plan to make in changing are:
- “Going to groups and therapy to learn coping skills and work on self-acceptance”
- “To continue using art and guitar as my go to skills”
- With the migraines, accept where I’m at, take meds and go to sleep even in times when I want to be a normal teenager”

The ways people can help me are: “listening, understanding, accepting me for who I am, not showing pity”

The things that could interfere with my plans are:
- “If the depression gets bad, self-esteem goes down, and lose the motivation to try”
- “Migraines”
Integrated Treatment Protocol: Family Sessions

- Family Communication
- Family Problem-Solving and Compromise
- Contingency Management
- Increasing Positive Family Interactions
Integrated Treatment Protocol: Parent Training Sessions

- MI for Treatment Engagement
- Parental Monitoring
- Parent Belief Systems
- Parent Affect Regulation
- Parent Problem-Solving
- Attending to Child and Self
- Contingency Management
## Integrated CBT

<table>
<thead>
<tr>
<th>Phase</th>
<th>Adolescent sessions</th>
<th>Parent sessions</th>
<th>Family sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Tx (1-6 months)</strong></td>
<td>Core skills: cognitive problem-solving, cognitive restructuring, affect regulation, and behavioral activation, with an emphasis on working through problems related to MDD, suicidal behavior, and substance use</td>
<td>Parental MI, monitoring, positive attending, contingency management, problem-solving, cognitive restructuring, affect regulation</td>
<td>Family problem-solving, communication, positive interactions, contingency management</td>
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<tr>
<td>1x per week</td>
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<td>2x per week if needed in 1st 6 weeks</td>
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</tr>
<tr>
<td>Maintenance Phase (7-12 months)</td>
<td>Skill strengthening &amp; generalization as well as relapse prevention with respect to suicidal behavior and substance use</td>
<td>Parental skill strengthening &amp; generalization</td>
<td>Family skill strengthening &amp; generalization</td>
</tr>
</tbody>
</table>
Attempted Suicide 18M

\( X^2(1) = 5.17, \ p < .05 \)

\( d = .82, \text{ large effect} \)
Other Psychiatric Outcomes 18M

**Percentage Requiring ER Services**

- EXP: 16%, ESC: 59%
  - Sample size: EXP = 3, ESC = 10

**Percentage Requiring Inpatient Services**

- EXP: 16%, ESC: 53%
  - Sample size: EXP = 3, ESC = 9

\[ \chi^2(1) = 7.20, \ p < .01 \]
\[ d = .93, \text{ large effect} \]

\[ \chi^2(1) = 5.57, \ p < .05 \]
\[ d = .81, \text{ large effect} \]
Summary Points

- Better treatment retention
- Less use of school resources
- Less use of inpatient hospitalization, ER services, and residential services
- Fewer conduct related problems (e.g., arrests, suspensions, running away)
- Fewer suicide attempts
- Greater decline in suicidal ideation
- Greater declines in alcohol and cannabis use
Conclusions

- Adolescents with co-occurring substance use and suicidality can be effectively treated in an outpatient treatment setting.
- Parental involvement may enhance treatment effects for suicidality as well as substance abuse problems.
- Require longer treatment than that provided for either problem alone for optimal treatment outcome.
InVest

- Two group randomized controlled trial - Integrated CBT versus standard care (SC)
- Rounding out the NIMH portfolio
- NIMH Mantra – Faster and Cheaper
- More than one risk factor – NSSI, prior suicide attempt, and/or substance abuse
New cohort, even worse patients

- 140 adolescents completed baseline measures
- Suicide Ideation Questionnaire (SIQ) Cut-off 30
  - $M = 51.84$, $SD = 21.0$
  - Number of days in the past 30 with SI $M = 17.8$, $SD = 11.3$
- Columbia Suicide Severity Rating Scale (C-SSRS)
  - 65.6% lifetime SA (Mean age at 1st attempt = 13.4, $SD = 2.1$)
  - 19.0% lifetime interrupted attempts
  - 33.9% lifetime aborted attempts
- Children’s Depression Rating Scale
  - Cut off 40; $M = 73.0$, $SD = 6.7$
WHERE SHOULD WE AIM THIS GOLDEN ARROW OF EXPERIMENTAL MEDICINE?

- **K-SADS diagnoses**
  - **MDD** → 88.2% (remainder had depression NOS)
  - Concurrent diagnoses
    - GAD 39.4%
    - SUD 25.8%
    - ODD 24.2%
    - PTSD 23.4%

- **NSSI**
  - Lifetime 87.3%
  - Past 30 days 70.3%

- 68.3% had at least 1 suicide attempt in social network
Another “new” approach in 2008

- Noticed in the two therapist trial that many parents were on meds and we were referring many parents for therapy

- Literature: Links Between Parental and Adolescent Psychopathology via
  - Parental modeling
  - Family discord and stress
  - Transactional relationship between parent and child
  - Heritability

Best predictor of youth response to depression treatment is maternal depression
Concurrent Treatment Pilot Study

- Creating synergy that will assist in adolescent’s treatment
  - Parent and teen acquire common language
  - Parents can reinforce teen’s use of skills
- Improved attendance
  - One time and location
  - Increased motivation
- Enhances coordination of care
  - Prevents conflicting treatment goals
Parent & Adolescent BDI Scores
Why no difference?

Small Ns in R34 Treatment Development Studies
Failure of randomization - 14 vs 7

50% of PA-CBT adolescents reported a history of suicide attempt, while none of the AO-CBT adolescents reported a previous attempt.

Five adolescents met screening criteria for BPD, all of whom were randomized to PA-CBT.

<table>
<thead>
<tr>
<th>History of Trauma</th>
<th>PA-CBT</th>
<th>AO-CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>73%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Teen</td>
<td>82%</td>
<td>43%</td>
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</tbody>
</table>
“Developmental and Environmental Aspects”

- Not represented in the matrix per se
- RDoC matrix will enhance the study of both areas by promoting a systematic focus on their relationship to specific circuits and functions.
- Sources of both risk and protection for many different disorders
Familial Expressed Emotion (EE): A Measure of Affective Reactivity

- Critical or hostile attitudes
- Emotional over-involvement: marked over-concern, inordinate self-sacrifice, intrusiveness, overprotectiveness (enmeshment)
What is teen circuit engagement in response to EE? And does it vary?

- **Negative Valence** - acute threat (fear); potential threat (anxiety); sustained threat; loss; frustrative nonreward

- **Positive Valence** – reward learning; reward evaluation

- **Cognitive Systems** - attention
  - Perception – visual, auditory perception
  - Cognitive (effortful) Control – response selection, inhibition

- **Working Memory**

- **Arousal and Regulatory Systems** - arousal; sleep

- **Systems for Social Processes**
  - Affiliation and attachment
  - Social Communication
  - Perception and understanding of self
  - Perception and understanding of others
If we aren’t finding new ways to reduce treatment resistant depression, where do we go from here?

Can we take an experimental approach? How would you target it?

A Potential Cognitive Target: Rumination underlying Hopelessness
Is there a behavioral process emanating from a neural circuit underlying this symptom? Concurrent study data

<table>
<thead>
<tr>
<th>Measure</th>
<th>PA-CBT (n = 16)</th>
<th>AO-CBT (n = 8)</th>
<th>t-value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent Age</td>
<td>14.69 (1.78)</td>
<td>14.00 (1.69)</td>
<td>0.91</td>
<td>.40</td>
</tr>
<tr>
<td>Parent Age</td>
<td>44.94 (7.48)</td>
<td>42.25 (8.68)</td>
<td>0.79</td>
<td>.33</td>
</tr>
<tr>
<td>Adolescent BDI</td>
<td>29.32 (11.76)</td>
<td>19.13 (5.94)</td>
<td>2.82**</td>
<td>1.09</td>
</tr>
<tr>
<td>Parent BDI</td>
<td>28.81 (14.78)</td>
<td>19.00 (10.04)</td>
<td>1.86</td>
<td>.78</td>
</tr>
<tr>
<td>Adolescent Current BSS</td>
<td>9.81 (7.85)</td>
<td>5.75 (6.09)</td>
<td>1.28</td>
<td>.58</td>
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<tr>
<td>Parent Current BSS</td>
<td>4.63 (6.96)</td>
<td>1.00 (1.85)</td>
<td>1.95†</td>
<td>.71</td>
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<tr>
<td><strong>Adolescent HSC</strong></td>
<td><strong>9.25 (4.92)</strong></td>
<td><strong>4.63 (2.77)</strong></td>
<td><strong>2.45</strong></td>
<td><strong>1.16</strong></td>
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<tr>
<td>Parent BHS</td>
<td>9.69 (5.47)</td>
<td>5.38 (4.81)</td>
<td>1.89†</td>
<td>.84</td>
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<tr>
<td>Adolescent CDRS</td>
<td>62.13 (12.78)</td>
<td>52.38 (10.50)</td>
<td>1.86†</td>
<td>.83</td>
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<td>Adolescent MSI-BPD</td>
<td>6.38 (2.13)</td>
<td>4.50 (1.41)</td>
<td>2.25*</td>
<td>1.04</td>
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<tr>
<td>Parent MSI-BPD</td>
<td>5.44 (1.86)</td>
<td>4.00 (2.62)</td>
<td>1.56</td>
<td>.63</td>
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<tr>
<td>Number of Sessions</td>
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<td></td>
<td></td>
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<tr>
<td>Adolescents Attended</td>
<td>11.38 (5.98)</td>
<td>11.88 (6.66)</td>
<td>.19</td>
<td>.08</td>
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<tr>
<td>Adolescent Number of Medications Baseline</td>
<td>1.0 (.82)</td>
<td>.88 (.99)</td>
<td>.33</td>
<td>.14</td>
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<tr>
<td>Parent Number of Medications Baseline</td>
<td>1.25 (1.0)</td>
<td>1.25 (.89)</td>
<td>0</td>
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</tbody>
</table>
Predictors of TORDIA treatment response

- Severity of depression
- Duration of depression
- Suicidal ideation
- \textit{Hopelessness}
- Family conflict
Site differences in multisite trials
Why Site Differences in Multisite RCTS?

I Sampling Factors
Number of participants per site
Recruitment sources – e.g. pediatrics, inpatient psych
Outliers
Participant characteristics
- Demographics
- Clinical characteristics

II Treatment Protocol Factors
- Fidelity to assessment protocol
- Protocol deviations
- Fidelity to treatment protocol
- Differences in therapy modules used by clinicians across sites
- Participant differences in adherence to protocol
- Attrition

Spirito et al, JCCP (2011)
Recursive partitioning based on receiver operating characteristics was used to identify homogeneous subgroups where site variability was diminished (Kraemer, 1992).

Each of the clinical predictors that contributed to site differences and treatment outcomes was examined one at a time by comparing the diagnostic predictability for each of the variable’s cut points.
Is it the Site or the Psychopathology?
334 Total Cases
47.6% Positive Response Rate (RR)

CBQ

N = 165
CBQ
CE - 9
38.2% RR

N = 162
CBQ
LT - 9
57.4% RR

BHS
LT - 10

N = 75
BHS
GE - 10
43.8% RR

N = 87
NHS
LT - 10
67.8% RR
Take home messages

It’s not my fault!

*If you want to have a good success rate, just say no to difficult patients with difficult families*

Any good clinician knows it’s the moderators/predictors that account for the largest amount of variance in the performance of an evidence-based treatment.

At some point in the new frontier, these moderators will move beyond overt symptoms to psychophysiology, brain circuitry, genes, and ..........
Hopelessness reflects a negative view of the future, that nothing will get better.

- Negative Valence Construct – Loss
- Self-report – Hopelessness
- Behavioral process - Rumination
- Neural Circuit
- Cells and Molecules
- Genes
Computer-based sustained attention and working memory tasks

Developed to explicitly target the DLPFC-amygdala circuit implicated in rumination and depression

Theory: increase prefrontal (DLPFC) function to remediate the prefrontal deficits that lead to limbic dysregulation and rumination.

(Siegle et al, 2009)
Cognitive Control Training

- Participants are presented with a continuous stream of auditory digits (1–9) and are instructed to immediately respond to the sum of the last two heard digits by clicking the corresponding response buttons (1–18).
- The speed of number presentation is adapted based on participants’ performance in order to train cognitive control in a frustrating task context.
- Following every four incorrect responses the ISI increases with 100 ms, reducing task difficulty.
- Throughout each session participants are presented with their current ISI and amount of consecutive correct and incorrect responses.
A therapist friendly example: Rumination-focused CBT

- Shift from unconstructive rumination to constructive rumination, through the use of functional analysis, experiential/imagery exercises and behavioral experiments.

- Rumination is conceptualized as a form of avoidance, and functional analysis is used to facilitate more helpful approach behaviors.

- Functional analysis to help individuals realize that their rumination about negative self-experience can be helpful or unhelpful and to coach them in how to shift to a more helpful style of thinking.

- Patients use directed imagery to recreate previous mental states when a more helpful thinking style was active, such as memories of being completely absorbed in an activity (for example ‘flow’ or ‘peak’ experiences), which act directly counter to rumination.

(Watkins et al, 2009)
The brain’s dense thicket of interrelationships, like those of history or art, does not yield to the reductivist’s bright blade.
I can name that brain in 3 (4?) notes circuits!

Are all brains alike?
Can we find a specific circuit for a specific emotional target?

Meta-analysis of 148 fmri studies and PET studies (n = 2,159) of emotion categories - fear, anger, disgust, happiness, and sadness

“The results indicate that emotion categories are not contained within any one region or system, but are represented as configurations across multiple brain networks” (Wager et al, 2015)

Can we find a specific circuit for complex, multidetermined behaviors, like: NSSI vs Suicide Attempts vs Aggressive outbursts?
If we find a circuit in one study will we find it again in the next study?

The project, PsychFileDrawer, dedicated to replication of published articles in experimental psychology, shows a replication rate 3 out of 9 (33%) so far.

But there is some good news.....

- The biotech company Amgen had a team of about 100 scientists trying to reproduce the findings of 53 “landmark” articles in cancer research published by reputable labs in top journals. Only 6 of the 53 studies were reproduced (about 10%).

- Scientists at the pharmaceutical company, Bayer, examined 67 target-validation projects in oncology, women’s health, and cardiovascular medicine. Published results were reproduced in only 14 out of 67 projects (about 21%).
It’s not the circuit that’s posing a problem for researchers, it’s the symptom!

- Is everyone’s hopelessness the same?
  - Alienation (Attachment)
  - Forsakenness (Attachment and Survival)
  - Uninspired (Attachment and Mastery)
  - Powerlessness (Mastery)
  - Oppression (Mastery and Attachment)
  - Limitedness (Mastery and Survival)
  - Doom (Survival)
  - Captivity (Survival and Attachment)
  - Helplessness (Survival and Mastery)

- “Hope in the Age of Anxiety,” Scioli and Biller
It’s not the circuit or the behavior (symptom) that is a challenge, it’s the clinical relevance!

- “A positive impact on clinical symptoms constitutes proof of concept of a role for the target”.

- How much variance does it account for? Is it clinically significant?
Translating findings from experimental psychopathology to clinical psychology: Are we speaking the same language?

Patients are complicated – we need a quiver of arrows

Although he spoke perfect English, there was still a language barrier, and I sensed immediately that no real meaning would ever pass between us - Hunter Thompson, The Rum Diary
A failure of CBT and meds

12 year old, MDD – hospitalized due to NSSI and suicidal ideation
Conflict with best friend started NSSI
Any distress could provoke cutting – couldn’t be left alone
Negative attributional style and rumination
NSSI with high pain tolerance and fascination with blood
No distress secondary to cutting and reported reinforcing pleasant effects after cutting
Learns various CBT skills well and implements them often but not always
Temporary tattoos and other self-soothing strategies
Liz – what accounts for the most variance?

Cutting evolved into having a noose to hang herself in her room which led to re-hospitalization

Anger and depression worsen secondary to mother’s depression and mother’s suicide attempt

Toxic peer group

Small school with overly involved staff leading to anxiety and angry outbursts
What is the mechanism of NSSI? – Is this why we need research on targeted treatments in order to help Liz in 2017?

- RDoC Negative Valence Construct – Loss
- Self-report – Negative attributional style
- Behavioral process - Rumination
- **Neural Circuit**
- Cells and Molecules
- Genes
rTMS?
fMRI Feedback?

Or something being worked on in a start-up in Cambridge or Silicon Valley?
It’s complicated ....

(Sanford, 1953): “the question is, which people in what circumstances, responding to what psychotherapeutic stimuli”

2017: which circuits, genes, behavioral processes in what circumstances, responding to what psychotherapeutic (medication, device, brain training) stimuli
Open your eyes, step into the light

Music can improve verbal IQ, evoke colors in the mind and even help you see happy faces all around
Circuit, circuit, who engages circuits your circuit?
Depression is associated with excessive connectivity of the brain, and the **default mode network** which is associated with high-level thinking, self-consciousness and introspection becomes over-connected,

The over-connectivity causes depressed people to become locked into rumination and concentrate excessively on negative thoughts about themselves.

Injected 30 healthy volunteers with __________

Positive finding: the brain's "**default mode network,**" was disjointed and less active.

"By disrupting that network with _______ you can liberate them from those depressive symptoms by showing them it's possible to escape those thoughts“.

**SOUNDS GREAT!**
Psilocybin! We used to call it getting high

And for the health conscience, it comes in an organic version, too – magic mushrooms!
There is nothing new in psychology ....
STOOL SAMPLES?!? It’s not your brain, it’s your gut, stupid!

How these differences in our microbial world influence the development of brain and behavior will be one of the great frontiers of clinical neuroscience in the next decade. Insel 2012
Flash back – 39 years – I started my career doing mechanisms research

- **Cognitive impulsivity**

- Verbal self-instructional training plus response cost; Six 20 minute training sessions (Kendall & Finch, 1978)

- Visual scanning plus verbal self-instructional training (Parrish, 1978)

## Units of Analysis

<table>
<thead>
<tr>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Reports</th>
<th>Paradigms</th>
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<tbody>
<tr>
<td>COMT</td>
<td>Glu</td>
<td>Somatostatin</td>
<td>DLPFC</td>
<td>theta, gamma</td>
<td>Impulsive behaviors;</td>
<td>Disorganization Sx on SANS/SAPS/PANSS BRIEF (Gioa)</td>
<td>Simon Stroop Flanker</td>
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<td>CHRM4</td>
<td>DA</td>
<td>PV</td>
<td>VLPFC</td>
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<td>PPC</td>
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<td>DRD4</td>
<td>NE</td>
<td>AcH</td>
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<tr>
<td>MAO-A</td>
<td>Glu</td>
<td>Pyramidial</td>
<td>Ventromedial striatal</td>
<td>Alpha Pupilometry</td>
<td>Impulsive behaviors; off-task behaviors; distractibility</td>
<td>Conners impulsivity scale ADHD Rating Scale (Dupaul) BRIEF (Gioa) ATQ/CBQ Effortful Control</td>
<td>Go/Nogo Stimulus-Resp Incompat Stop-Signal Reaction Time Antisaccade Countermanding Conflicting and contralateral motor response task</td>
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<tr>
<td>DAT1</td>
<td>DA</td>
<td>BA6/8 (FEF)</td>
<td>Pre-SMA</td>
<td>Prolonged interval cortical inhibition (TMS)</td>
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<td>Conners impulsivity scale ADHD Rating Scale (Dupaul) BRIEF (Gioa) ATQ/CBQ Effortful Control</td>
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</tbody>
</table>
Matching Familiar Figures Test
Beware “Methodolatry” and the Magic Arrow: It’s the variance, stupid!

- **Human Genome Project**

  - So far, with only a few exceptions, the genetic contribution to major diseases is small, accounting at most for 10% of all disease causes.

  - And this genetic contribution is usually distributed among large numbers of genes, each with only a very small effect on any specific disease.

Do you have blind faith, no false hopes.
Let’s not devalue our contributions too much

- Psychotherapy in general and CBT in particular, in the hands of a skilled therapist who is cognizant of the literature, is personalized medicine.
- But we do need to be open to ways to improve our treatment outcomes.