## GROUP 3

### Faculty

<table>
<thead>
<tr>
<th>Group 3</th>
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<tbody>
<tr>
<td>Erika Forbes</td>
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<tr>
<td>Rebecca Ashare</td>
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<tr>
<td>Melissa Brotman</td>
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<tr>
<td>Jay Fournier</td>
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<td>Michael Ostacher</td>
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### Participant | Title

<table>
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<tr>
<th>Abram, Samantha</th>
<th>Brain aging corresponds with trait mindfulness and rumination in people with schizophrenia</th>
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<td>Belleau, Emily</td>
<td>Neural Correlates of Stress and Perceived Control in Adolescent Depression</td>
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<td>Berlow, Yosef</td>
<td>Modeling the Response to Transcranial Magnetic Stimulation using an Exponential Decay Function</td>
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<td>Fries, Gabriel</td>
<td>Deciphering the role of neuronal and peripheral DNA methylation in suicide and bipolar disorder</td>
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<td>Grubisha, Melanie</td>
<td>OMG: Schizophrenia associated adolescent onset dendritic regression</td>
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<td>Vogel-Hammen, Alecia</td>
<td>Dysregulation including positive affect in children predicts impairment in adolescence</td>
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</table>
BRAIN AGING CORRESPONDS WITH TRAIT MINDFULNESS AND RUMINATION IN PEOPLE WITH SCHIZOPHRENIA

SAMANTHA ABRAM, PHD
MIRECC SCHIZOPHRENIA RESEARCH FELLOW
CAREER DEVELOPMENT INSTITUTE FOR PSYCHIATRY, APRIL 2021

BRAIN AGING IN SCHIZOPHRENIA

1. Brahman et al., 2016, American Journal of Psychiatry
2. Abram et al., 2020, Neuroimage: Clinical

TRAITS THAT IMPACT STRESS RESPONSE

- Rumination
- Perceived stress
- Mindfulness

Grierson et al., 2018, Psychological Medicine
Heng et al., 2011, Clinical Psychology Review
Martin et al., 2018, Mindfulness
GOALS OF THE CURRENT STUDY

Assess whether individual differences in trait mindfulness and rumination/stress correspond with advanced aging in schizophrenia.

Does a tendency towards mindfulness provide resiliency in the context of psychosis?

1. Parse high-resolution T1 anatomical scans
2. Feed parcellated metrics into ENIGMA brain age calculator
3. Derive predicted brain age

rSZ = 0.76
rHC = 0.89

"younger" "older"

Higher rumination/stress
Higher mindfulness

p < .001
• Older predicted brain ages in SZ corresponded with more rumination/stress and lower mindfulness.
• Conversely, SZ with PCA scores more similar to HC had relatively younger brain ages.

BENEFITS OF MINDFULNESS ON BRAIN HEALTH

- Mindfulness/low rumination may be protective for SZ
- Meditation found to facilitate telomerase activity

FUTURE DIRECTIONS

- Impact of mindfulness-based interventions
- Coordination across biological aging markers
  - telomere length/activity, inflammatory markers, etc.
SPECIAL THANKS TO…

Brain Imaging and EEG laboratory
Susanna Fryer
Daniel Mathalon
Judith Ford
Jessica Hua
Brian Roach

ENIGMA-Brain Age Working Group
Laura Han
Neural Correlates of Stress and Perceived Control in Adolescent Depression

Emily L. Belleau
McLean Hospital
Harvard Medical School

Sense of Control is Rewarding

Sense of Control Neural Circuitry

Ly et al. 2019
Neural Correlates of Perceived Control

Evidence of Perceived Control Abnormalities in Depression

Lower striatal activation when presented with cues signaling opportunities for exerting control is linked to greater depressive symptoms in a non-clinical sample of older adults.

Reward Positivity = frontocentral event-related potential component, 250-350 ms post-stimulus onset, that is induced when rewarding feedback is presented.
Stress Impacts the Same Frontostriatal Circuitry

Perceived Control

Stress

Depression

K23 Study Design Overview

Female adolescents with (N= 40) and without (N =40) Major Depressive Disorder
Montreal Imaging Stress Task (MIST)

You are performing below criteria we need you to focus!

Performance

You

Group

Worse

Better

\[ 6 + 10 - 9 + 1 = ? \]

Dedlovic et al, 2005

Measuring Perceived Control with Value of Control Task

Wang et al. 2019

NIMH K23 Hypotheses

Compared to health adolescents before stress, adolescents with MDD:

\[ \text{mPFC} \]

\[ \text{VS} \]
Compared to healthy controls, adolescents with MDD from before to after stress:

Thank You!
- Diego Pizzagalli
- Erika Forbes
- Mauricio Delgado
- Kate Harkness
- Blaise Frederick
- Ellen Hedstrom

National Institute of Mental Health
MAJOR DEPRESSIVE DISORDER

- Leading cause of disability worldwide
- Depression affects:
  - Mood
  - Cognition
  - Behavior
  - Psychosocial Functioning
  - Quality of Life
Noninvasive neuromodulation technique
- Pulsed magnetic fields
- Efficacious for pharmacoresistant MDD
- Standard TMS is delivered five days a week for five to eight weeks*

It is expensive! (~$15,000)
- It has an extensive time commitment (~36 treatments)
- Only 60-80 patients can be treated on a single device per year
- TMS is a limited resource!
- Response to TMS is heterogenous

Understanding the pattern of treatment response to TMS could help identify which patients are more likely to respond and help guide treatment decisions to optimize successful treatments.
ANTIDEPRESSANT TREATMENT RESPONSE PATTERN

- Nonlinear!
- Large initial improvements followed by smaller but continued improvements.
- This decrease in symptoms has been shown to follow an exponential decay model.


TMS TREATMENT RESPONSE PATTERN

- TMS also appears to follow this nonlinear pattern of treatment response.
- The objective of this study was to investigate whether TMS follows an exponential decay function and explore the implications of this model.

Blumberger et al. 2018

METHODS 1: NATURALISTIC SAMPLE

- Symptom rating data were collected at baseline and after every five TMS treatment sessions from a naturalistic sample of 97 patients treated with left-sided, high-frequency, TMS.
- Self-report ratings (PHQ9) were collected at baseline and after every five TMS treatment sessions.

Noah Philip and Emily Aiken
Methods 1: Naturalistic Sample

- Nonlinear mixed-effects model (NLME):

$$D(t) = A * e^{-Bt} + C$$

- $A$ and $C$ are treated as random effects at the patient level.
- $A$, $B$, and $C$ are fit as fixed effects at the group level.
- Compared to the corresponding linear mixed effects model using the Akaike information criterion (AIC) and likelihood ratio test (LRT).

Methods:

$$D(t) = A * e^{-Bt} + C$$

Methods 2: Group Level Data

- This exponential decay model was also extended to published group-level data from large clinical trials:
  - Left-sided 10 Hz repetitive TMS ($n_1=205$, $n_2=165$)
  - Left-sided standard ($n=209$) and accelerated ($n=22$) Theta-Burst Stimulation (TBS)
  - Right sided 1 Hz TMS ($n=150$)
- Corresponding linear models were compared to the nonlinear exponential decay models using the AIC.
METHODS 3: SYMPTOM TRAJECTORIES

- Unique group-level symptom trajectories in subjects receiving either left-sided 10 Hz TMS or left-sided TBS (n=388) were fit with this same exponential decay model using NLME.
- Resulting NLME model was compared to the corresponding linear model using AIC and LRT.

Kaiser et al. 2019

RESULTS 1: NATURALISTIC STUDY

- Total of 97 patients
- 562 observations with each individual contributing 2 to 9 (Median 6) measurements
- Remission (PHQ-9 < 5) was achieved by 24% of the patients.
- Response (50% reduction in symptoms) was achieved by 44% of the sample.

Berlow
RESULTS 1: NATURALISTIC STUDY

Providence VAMC (n = 97)

Phorbol Myristate Acetate (THREE-D) (n = 204)

Standard Left 10 Hz (n = 59)

Blumberger et al. 2018

Fitzgerald et al. 2020

RESULTS 2: GROUP LEVEL DATA 10 Hz

10 Hz (THREE-D) (n = 204)

Standard Left 10 Hz (n = 59)

Parameters:

Blumberger et al. 2018

Fitzgerald et al. 2020

Parameters:
RESULTS 2: GROUP LEVEL RIGHT 1 Hz

High Dose Right 1 Hz (n=93)

Standard Right 1 Hz (n=57)

Parameters:

|   | Estimate | Std. Error | t value | Pr(>|t|) |
|---|----------|------------|---------|----------|
| A | 13.700   | 3.739      | 3.664   | 0.0671   |
| B | 10.287   | 6.539      | 1.573   | 0.2563   |
| C | 11.909   | 3.883      | 3.067   | 0.0919   |

Parameters:

|   | Estimate | Std. Error | t value | Pr(>|t|) |
|---|----------|------------|---------|----------|
| A | 14.608   | 2.737      | 5.336   | 0.0334   *
| B | 6.007    | 3.036      | 1.979   | 0.1864   |
| C | 11.110   | 2.274      | 4.886   | 0.0394   *

RESULTS 2: GROUP LEVEL TBS

Theta-Burst (THREE-0) (n=209)

Accelerated Theta-Burst (n=22)

Parameters:

|   | Estimate | Std. Error | t value | Pr(>|t|) |
|---|----------|------------|---------|----------|
| A | 12.510   | 1.857      | 6.738   | 0.00253  **
| B | 12.020   | 4.746      | 2.533   | 0.06446  .
| C | 11.035   | 1.859      | 5.934   | 0.00404  **

Parameters:

|   | Estimate | Std. Error | t value | Pr(>|t|) |
|---|----------|------------|---------|----------|
| A | 14.5234  | 0.4761     | 30.508  | 7.74e-05  ***
| B | 22.9591  | 1.8813     | 12.204  | 0.00118  **
| C | -0.3287  | 0.4927     | 0.667   | 0.55241   |

RESULTS 2: GROUP LEVEL DATA AIC

<table>
<thead>
<tr>
<th>Study</th>
<th>Linear Model AIC</th>
<th>Nonlinear Model AIC</th>
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</thead>
<tbody>
<tr>
<td>Left 10 Hz</td>
<td>25.62</td>
<td>14.41</td>
</tr>
<tr>
<td>High Left 10 Hz</td>
<td>23.18</td>
<td>21.47</td>
</tr>
<tr>
<td>Right 1 Hz</td>
<td>28.28</td>
<td>24.04</td>
</tr>
<tr>
<td>High Right 1 Hz</td>
<td>28.28</td>
<td>24.04</td>
</tr>
<tr>
<td>Left 10 Hz</td>
<td>32.66</td>
<td>24.61</td>
</tr>
<tr>
<td>High Left 10 Hz</td>
<td>32.60</td>
<td>26.34</td>
</tr>
<tr>
<td>Right TBS</td>
<td>26.30</td>
<td>3.72</td>
</tr>
<tr>
<td>High Right TBS</td>
<td>26.30</td>
<td>3.72</td>
</tr>
<tr>
<td>Left HF</td>
<td>25.18</td>
<td>3.30</td>
</tr>
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</table>

Berlow
RESULTS 3: SYMPTOM TRAJECTORIES

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponse (N=43)</td>
<td>2.7</td>
<td>37.89</td>
<td>24.07</td>
</tr>
<tr>
<td>High Baseline Linear Response (N=118)</td>
<td>13.9</td>
<td>19.19</td>
<td>11.61</td>
</tr>
<tr>
<td>Low Baseline Linear Response (N=154)</td>
<td>13.04</td>
<td>12.2</td>
<td>9.45</td>
</tr>
<tr>
<td>Rapid Response (N=43)</td>
<td>14.47</td>
<td>5.62</td>
<td>6.29</td>
</tr>
</tbody>
</table>

TMS demonstrates a nonlinear pattern of improvement that follows an exponential decay function.

The greatest improvements in symptom reduction occur early in the TMS treatment course.

CONCLUSIONS

- TMS demonstrates a nonlinear pattern of improvement that follows an exponential decay function.
- The greatest improvements in symptom reduction occur early in the TMS treatment course.

CONCLUSIONS

- The nonlinear model provides fitted parameters that have real-world meaning!
- A is the total magnitude of response
- B is the time constant of the response
- C is the expected symptom rating at the end of treatments.
CONCLUSIONS

- Treatment response defined as a 50% reduction in symptoms would occur when \( A \) is greater than or equal to \( C \).
- Remission would occur when \( C \) is below a rating scale threshold (e.g., PHQ9<5).
- \( B \) defines the treatment session at which 63% of response occurs!
- \( 3^\ast B \) equals the session at which 95% of response occurs!

\[ D(t) = A \cdot e^{\left(\frac{-t}{B}\right)} + C \]

This modeling also provides a parsimonious method to describe a variety of TMS treatment response trajectories.

<table>
<thead>
<tr>
<th>Treatment Response Trajectories</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponse (N=43)</td>
<td>2.7</td>
<td>37.99</td>
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<td>5.62</td>
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</tr>
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</table>

FUTURE DIRECTIONS

- Replication
- Predicting treatment course from initial response
  - Solving for \( A \) and \( C \) at individual level
  - Predictions using the mixed-effects model

\[ D(t) = A \cdot e^{\left(\frac{-t}{B}\right)} + C \]
ACKNOWLEDGMENTS

- Noah S. Philip
- Amin Zandvakili
- Lawrence Price
- William Rooney (OHSU)

Funding:
- NIMH R21 MH101078
- VA RR&D Center for Neurorestoration and Neurotechnology

All models are wrong, but some are useful.
- George Box
Deciphering the role of neuronal and peripheral DNA methylation in suicide and bipolar disorder

Gabriel R. Fries, PhD
Assistant Professor
Department of Psychiatry & Behavioral Sciences, McGovern Medical School
Center for Precision Health, School of Biomedical Informatics

Background and Significance

- Suicide: leading cause of death in most societies.
- More frequent among patients with BIPOLAR DISORDER (BD).
- BD: 8-fold higher risk of suicide.
- Identification of biomarkers of suicidal behavior.

Background and Significance

- Suicide: complex multifactorial event.
- Family history of suicide
- Higher risk for suicide attempts
- DNA sequence variants explain only part of the variability in suicidal behavior
- Only partially explained by liability to mental disorders

Background and Significance

- Shared genetic risk between suicidal behavior and BD.


Background and Significance

- Premise: need for disentangling the risk of suicide from that of BD and characterizing the clinically heterogeneous phenotype of suicide in BD.

EPIDEMIOLOGY

- Suicide-related epigenetic alterations in blood and brain.

EPIGENETICS


McGovern Medical School

Aims of the study

1. To identify a DNA methylation biomarker of suicidality in post-mortem prefrontal cortex (BA9/46) from patients with BD.
2. To determine how the association between genetic risk for BD and suicide attempt and DNA methylation alterations in post-mortem prefrontal cortex.
3. To identify a DNA methylation biomarker of suicidality in peripheral blood from patients with BD who have attempted suicide.
**Aims of the study**

- Genetic risk for BD and suicide attempt
- DNA methylation alterations
- Suicide attempt

---

**Aim 1**

- **To identify a DNA methylation biosignature of suicidality in post-mortem prefrontal cortex (BA9/46) from patients with BD.**

  - **Hypothesis #1:** Predictive neuronal methylation markers, primarily in pathways related to the stress response, will discriminate patients who died of suicide from controls and patients who died of other causes.

  - **Sample 1:** 514 post-mortem dorsolateral prefrontal cortex (BA 9/46) samples
  - **Sample 2 (replication):** 50 post-mortem dorsolateral prefrontal cortex (BA 9/46) samples from the UTHealth Brain Collection for Research in Psychiatric Disorders

  - **Genotyping:** Polygenic Risk Score (PRS) for BD and suicide attempt
  - **Genome-wide DNA methylation.**

---

**Aim 2**

- **To determine the association between genetic risk for BD and suicide attempt and DNA methylation alterations in post-mortem prefrontal cortex.**

  - **Hypothesis #2:** Increased polygenic burden for BD and/or suicide attempt will be associated with distinct methylation variation in the prefrontal cortex.

  - **Sample 1:** 514 post-mortem dorsolateral prefrontal cortex (BA 9/46) samples
  - **Sample 2 (replication):** 50 post-mortem dorsolateral prefrontal cortex (BA 9/46) samples from the UTHealth Brain Collection for Research in Psychiatric Disorders

  - **Genotyping:** Polygenic Risk Score (PRS) for BD and suicide attempt
  - **Genome-wide DNA methylation.**
Aim 3

- To identify a DNA methylation biosignature of suicidality in peripheral blood from patients with bipolar disorder that have attempted suicide.

Hypothesis #3:

- previous suicide attempt is associated with a higher polygenic load for BD and suicide, as well as with significant blood DNA methylation alterations.

BD-I patients

(attempters)

N = 50

BD-I patients

(non-attempters)

N = 50

Genome-wide methylation

Pyrosequencing

Integration with
polygenic risk scores
(McGovern Medical School)

Machine learning

Controls

N = 100

Data analysis plan – Aim 3

- Differential methylation analyses (controlling for blood cell type composition);
- Pathway analysis;
- Association with clinical and neuroanatomical variables:

- Manic and depressive symptoms (YMRS and MADRS)
- Suicide attempt history and severity
- Number of acute episodes
- Neuroanatomical (MRI) data
- Number of hospitalizations
- Functionality (FAST and GAF)
- Impulsivity (BIS)

Expected outcomes

- Overlap between neuronal and blood suicide-related DNA methylation
- Neuronal DNA methylation biosignature of suicidality in BD
- Blood DNA methylation biosignature of suicidality in BD

(flying subjects)
Follow-up functional investigation of significant suicide-related genes

McGovern Medical School

Future studies and directions

McGovern Medical School

UTHealth

McGovern Medical School

School of Biomedical Informatics (UTHealth)

Zhongming Zhao

Peilin Jia

Max Planck Institute of Psychiatry

Theo Rein

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Jair Soares

Benson Fronger

Elisabeth Vinson

Alexandre Paim

McGovern Medical School
A schizophrenia-relevant model of dendritic regression across adolescence

Melanie J Grubisha, MD, PhD
Department of Psychiatry, University of Pittsburgh
CDI Class of 2020

Schizophrenia

Clinical Pathology
• Positive
• Negative
• Cognitive
• Adolescent/early adulthood symptom onset

Postmortem Pathology

Dynamic Equilibrium
(re)sequencing + serendipity = KALRN-PT

- Increased risk of schizophrenia
- PT mutation present in KAL9 and KAL12 isoforms
- OMGp increases across adolescence
- OMGp + NGR1 + KAL9 → dendritic regression

Hypothesis:
Schizophrenia-relevant reductions in dendritic length and complexity arise from enhanced regression across adolescence

Pre-adolescence Early Adult
10 Kalrn-WT & 10 Kalrn-PT
10 Kalrn-WT & 10 Kalrn-PT

Grubisha 2
Summary

- OMGp+NGR1+KAL9 → dendritic regression
- KAL9-PT → gain-of-function
- KALRN-PT stimulates dendritic regression across adolescence
Precise quantification of >5400 phosphopeptides from 1,936 proteins
>900 unique proteins were differentially phosphorylated

Summary
• OMGp → differential phosphorylation of Trio and Cacna1g
• OMGp + Kalrn-PT → ???
• Phosphomutant constructs of Trio and Cacna1g
  • Functional assays
  • Effect on dendritic architecture
Acknowledgements
Dysregulation including positive affect in children predicts impairment in adolescence

Alecia Vogel-Hammen, MD PhD
Career Development Institute

Emotion Dysregulation

A pattern of emotional responses or expressions that interfere with appropriate goal-directed behavior (Beauchaine, 2015).

Emotion dysregulation, like riding ocean waves
Dysregulation of negative affect (irritability) is impairing.

- Irritability
  - Tonic: grouchy, grumpy mood
  - Phasic: Outbursts
- Irritability in preschoolers is linked to internalizing and externalizing diagnoses and poor school functioning.
- Irritability in older children also predicts poor global functioning and health.

Having big waves of negative affect and chronic negative affect (irritability) is impairing.

Are big waves impairing even if they include positive affect?

Increased positive affect can be impairing.

- High positive affect in 6-12 month old infants predicts externalizing symptoms at age 2 (Putnam & Stifter, 2005).
- The frequency and intensity of positive affect predicts anger and externalizing behaviors (Putnam et al., 2000).
- Children with higher positive anticipation have higher rates of aggression (Deater-Deckard, et al., 2010).
Defining dysregulation including positive affect.

- Data-driven approach
  - Exploratory Factor Analysis
- Emotion related symptoms from a standardized clinical interview
- Preschool Age Psychiatric Assessment (PAPA; Egger & Angold, 2004)
  - Items from parent report mania and depression modules
  - Parent report tantrum items from conduct module
- Preschool Depression Study: 14 year longitudinal study of children with preschool onset psychiatric symptoms.
  - N=306 (145F) enrolled between ages 3-6 years
  - Enriched for children with increased affective and behavioral symptoms

EFA of PAPA emotion dysregulation items at baseline (age 3-6 years) defined 4 factors:

1. **Irritability**
   - Irritability intensity: 0.646*
   - Irritability frequency: 0.429*
   - Irritability spontaneity: 0.414*
   - Irritability concern to caretakers: 0.580*
   - Tearfulness & crying: 0.457*
   - Touchy or easily annoyed: 0.376*
   - Angry or resentful: 0.510*
   - Temper tantrums: 0.433*
   - Mood cycling intensity: 0.697*
   - Mood cycling frequency: 0.502*
   - Easily frustrated: 0.395*

2. **Excitability**
   - Elated mood: 0.164*
   - More talkative: -0.004
   - Inappropriate laughing, joking: -0.008
   - Uninhibited gregariousness: 0.034
   - Increased energy: 0.160*
   - Agitation: 0.165*
   - Unusually energetic: 0.085
   - Grandiosity: 0.026
   - Grandiosity concern to caretakers: 0.021
   - Bragging: 0.028
   - Racing thoughts: 0.106
   - Flight of ideas: 0.02
   - Poor judgment: 0.113
   - Inappropriate sexual interest: -0.004
   - Inappropriate sexual language: -0.022
   - Decreased concentration: 0.011
   - Motor slowing: -0.150*
   - Sleep duration: -0.052
   - Decreased need for sleep: 0.129
   - Self-hatred: 0.071
   - Suicidality & self injury: -0.012

Preschool excitability predicts later emotion lability, psychopathology, and impairment above and beyond irritability.

Controlling for all factor scores, age 5 social adversity, and maternal history of bipolar disorder

Vogel et al., Development and Psychopathology, 2019
In preschool, having “big waves” of negative AND positive affect predicts later problems with emotion regulation.

Is this specific to early development?

Irritability declines after preschool.  

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Irritability Mean T1 (age 3-6, mean 4.0)</th>
<th>Mean FS T8 (age 10-16, mean 13.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>55.6</td>
<td>36.3</td>
</tr>
</tbody>
</table>

Excitability remains stable through childhood.  

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Excitability Mean T1 (age 3-6, mean 4.0)</th>
<th>Mean FS T8 (age 10-16, mean 13.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40.4</td>
<td>40.8</td>
</tr>
</tbody>
</table>

**Multilevel Modeling**

- **Irritability slope**  
  Range = -4.24 to -0.42  
  mean = -2.026, SD=0.725

- **Excitability slope**  
  Range = -3.95 to 0.48  
  mean = -0.29, SD=0.65
Excitability intercept predicts later problems with emotion regulation, externalizing psychopathology and peer relations using multilevel modeling.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>t</th>
<th>p</th>
<th>FDR p</th>
<th>Estimate</th>
<th>t</th>
<th>p</th>
<th>FDR p</th>
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<tbody>
<tr>
<td><strong>EMOTION REGULATION CHECKLIST</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lability and Negativity</td>
<td>0.44</td>
<td>3.78</td>
<td>&lt;0.001</td>
<td></td>
<td>-0.01</td>
<td>0.17</td>
<td>0.86</td>
<td>0.940</td>
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<td>Emotion Regulation</td>
<td>-0.20</td>
<td>-2.58</td>
<td>0.011</td>
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<tr>
<td>Flow Experience</td>
<td>0.02</td>
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<td>&lt;0.001</td>
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<td>Flow Enjoyment</td>
<td>0.01</td>
<td>3.13</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>0.01</td>
<td>0.35</td>
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<td><strong>GENERIC PSYCHOPATHOLOGY</strong></td>
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<tr>
<td>HBQ Internalizing</td>
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<td>0.024</td>
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<td>HBQ Overall Impairment</td>
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<td>0.04</td>
<td>0.005</td>
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<td>Child CGAS</td>
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<td>-2.03</td>
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<td>0.005</td>
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<td>0.838</td>
<td>0.940</td>
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<tr>
<td>HBQ Peer Relations</td>
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<td>-3.28</td>
<td>0.001</td>
<td>0.003</td>
<td>0.00</td>
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**HBQ** = Health and Behavior Questionnaire, **CGAS** = Child global assessment scale

Models included gender, z-scored adverse childhood experiences, and T9 MDD diagnosis.

Summary

- Data driven analysis supports that “big waves” of negative affect (**Irritability**) and positive affect (**Excitability**) can contribute to impairment and psychopathology.
- The effect of excitability is not limited to early development.
  - **Irritability** declines with age, while **excitability** is stable.
  - Overall **excitability** (intercept) in childhood predicts later problems with emotion regulation and peer relationships.

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Vogel et al., under review
Questions

Next steps: a better understanding of how the components of emotion dysregulation are related.

Are there effects specific to positive and negative valence systems?

Top down (emotion regulation)

Bottom up (emotion generation)

Valence systems

Emotional response

Do problems with top down emotion regulation contribute to both?

Excitability intercept predicts less BOLD activity in inferior frontal gyrus regions during explicit cognitive emotion regulation in adolescence.
Long term goal: helping children better match the size of their waves to the size of their boat

Emotional response

Bottom Up (emotion generation)

Top down (emotion regulation)