Tracking Mood Instability in Bipolar Disorder: Advances in Neuroimaging and Digital Monitoring

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MOOD & MIND LAB

University of Pittsburgh

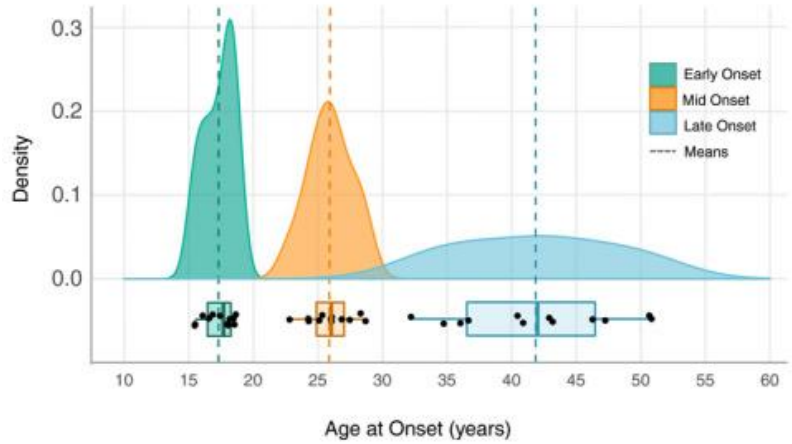
CHILD & ADOLESCENT BIPOLAR SPECTRUM SERVICES (CABS)

Disclosures

- Dr. Hafeman does not report any conflicts of interest.

Bipolar Disorder in Young People

- Affects 1-3% of the population
- Associated with impairment in psychosocial functioning, substance use, and suicidal thoughts & behaviors
- Especially disruptive during adolescence and young adulthood
- Peak onset is during late adolescence & early adulthood
- Diagnostic delays >5 years (even longer in those with earlier onset)



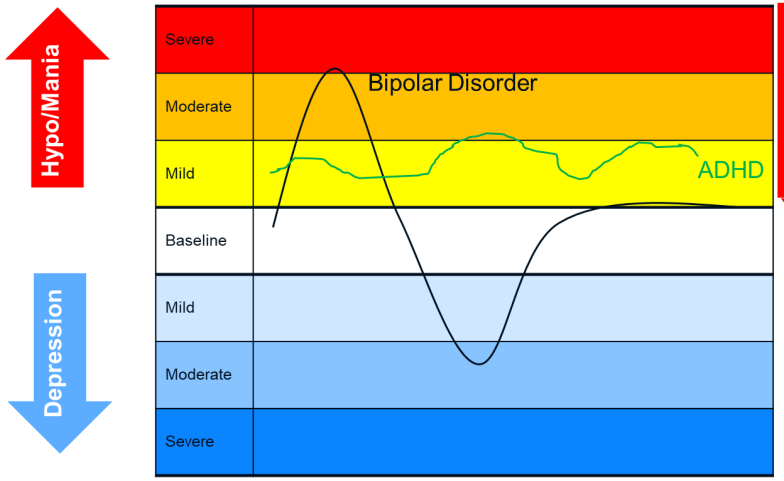
Goal: To recognize BD earlier to avoid treatment delays during important developmental periods

(Goldstein 2022; Goldstein 2013; Bolton 2021; Dagani 2017; Joslyn 2016)

Talk Outline

- Bipolar Disorder + Mood Instability in Young People
- Network instability as a neural marker of mood instability
- Mobile sensing to detect mood shifts?

Bipolar Disorder: Diagnostic Criteria



Elated or irritable mood + ↑ **energy**
+ ≥3 **Criterion B** symptoms (≥4 if irritable):

- ↑ *self-esteem/grandiosity*
- ↓ *need for sleep*
- *Pressured speech/talkative*
- *Racing thoughts*
- *Distractibility*
- ↑ *goal-directed activity*
- ↑ *impulsivity/risk-taking*

How do we distinguish from other disorders, e.g. ADHD?

- Episodic: Different from most other times
- Durable: Lasting for at least 1-2 days for Bipolar Spectrum Disorder
- Concurrent: Occur together in time
- Developmentally Inappropriate: Not acting like a "typical teenager" ("How does the child compare to peers in the same situation?")
- Spontaneous: Occurring even in the absence of obvious stimuli, at least sometimes.

Types of Bipolar Disorder: A Spectrum

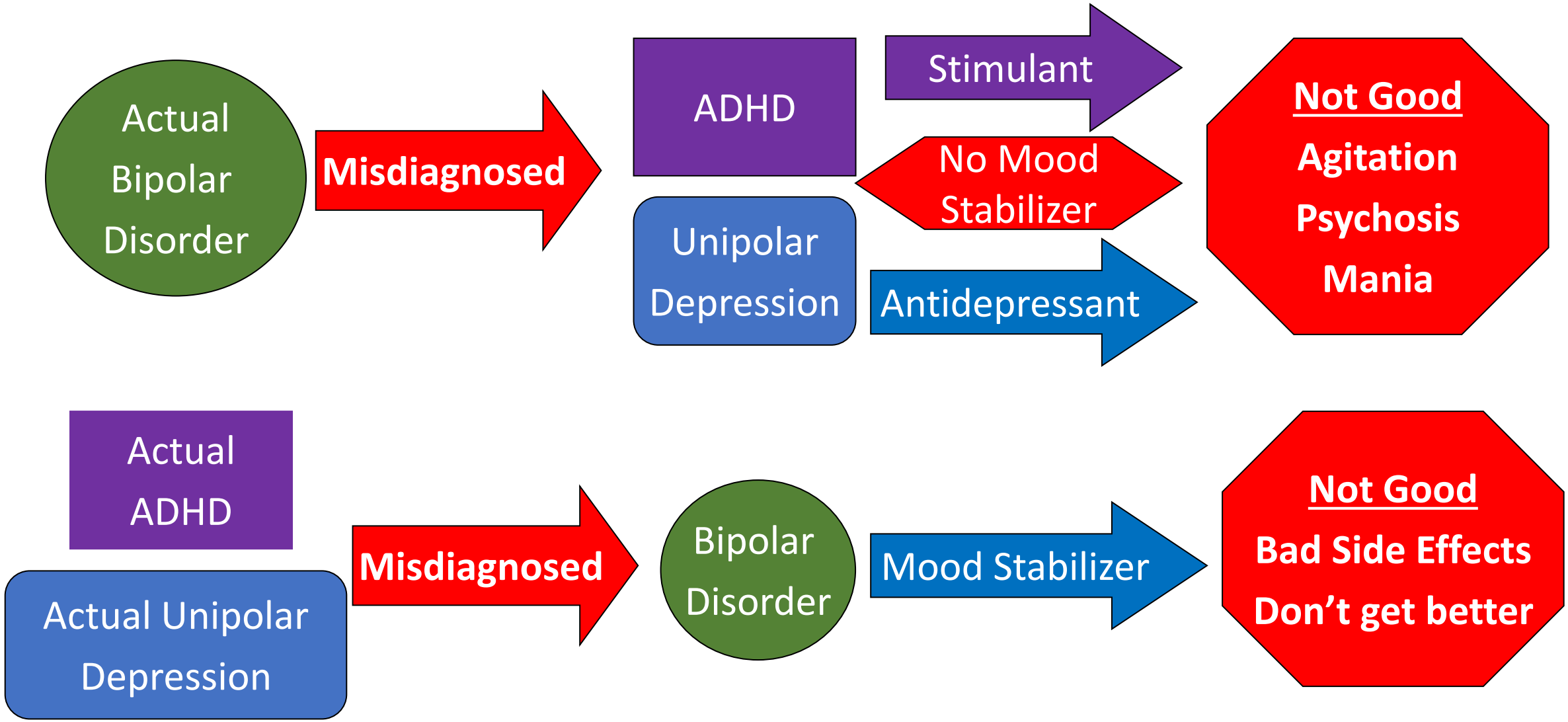
Other Specified Bipolar
- Lasting ≥1 day in a row
- ≥ 4 lifetime days
- Does not meet criteria for BD-I or BD-II

Bipolar II=HYPOMANIA (+ DEPRESSION)
- Lasting 4 days or more
- Change in functioning
- NOT "marked" impairment (during hypomania)

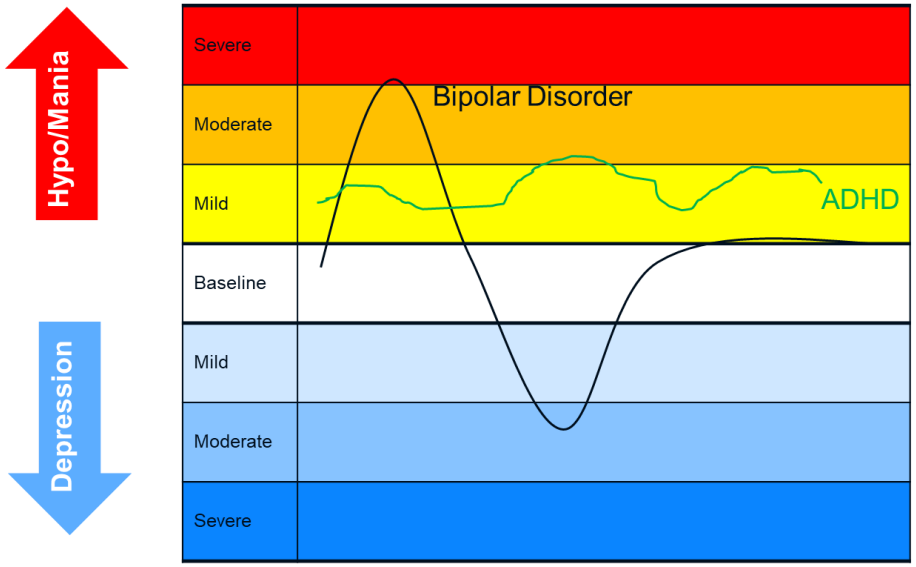
Bipolar I=MANIA
- Lasting a week or more
- Mania causes "Marked" impairment

- OSBD and BD-II also associated with significant impairment (often during depression)
- 50% of youth with OSBD convert to BD-I/II over ~5 years
- All subtypes can benefit from mood stabilizing medications

The Importance of Proper Identification of BD in Youth



(Axelson, 2010)



Mood Instability is key to Bipolar Disorder

Questions central to our research program:

- What are the neural markers underlying mood instability?
- Can we use mobile sensing to detect or even predict mood shifts?

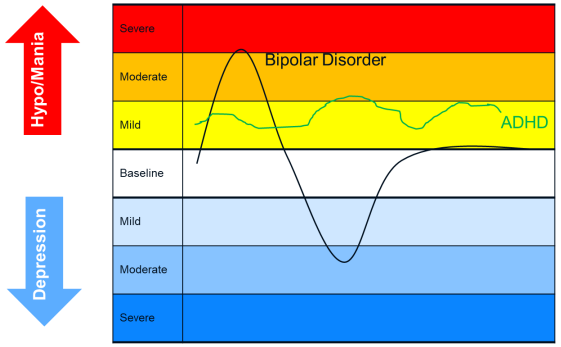
Talk Outline

- Bipolar Disorder + Mood Instability in Young People
- Network instability as a neural marker of mood instability
- Mobile sensing to detect mood shifts?

BD Longitudinal Imaging Study (BDLONG)

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

Mood Instability



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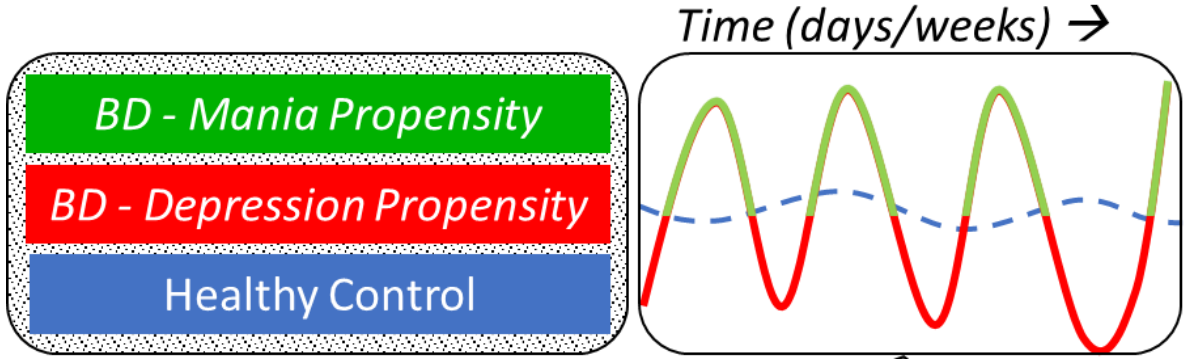
Network Instability

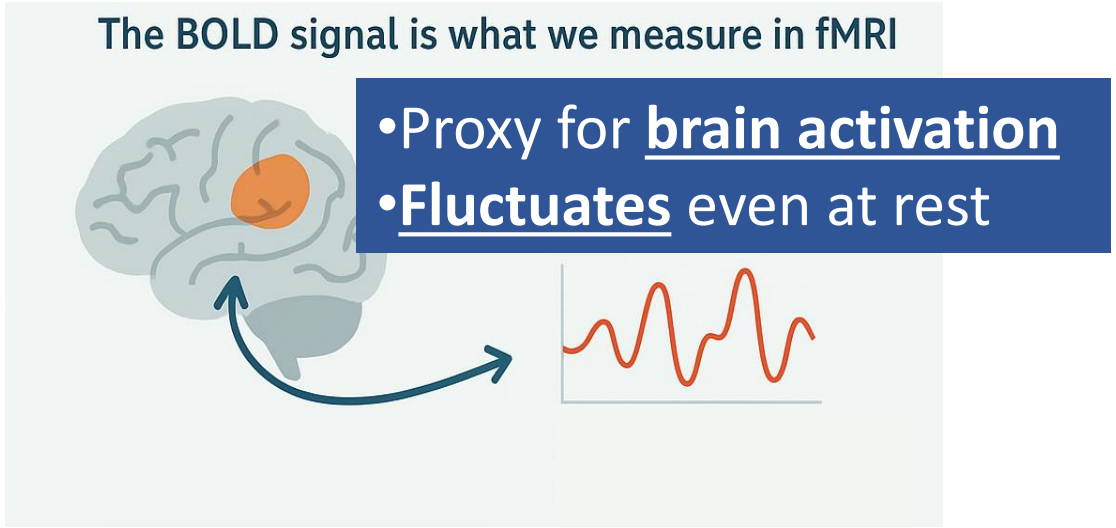


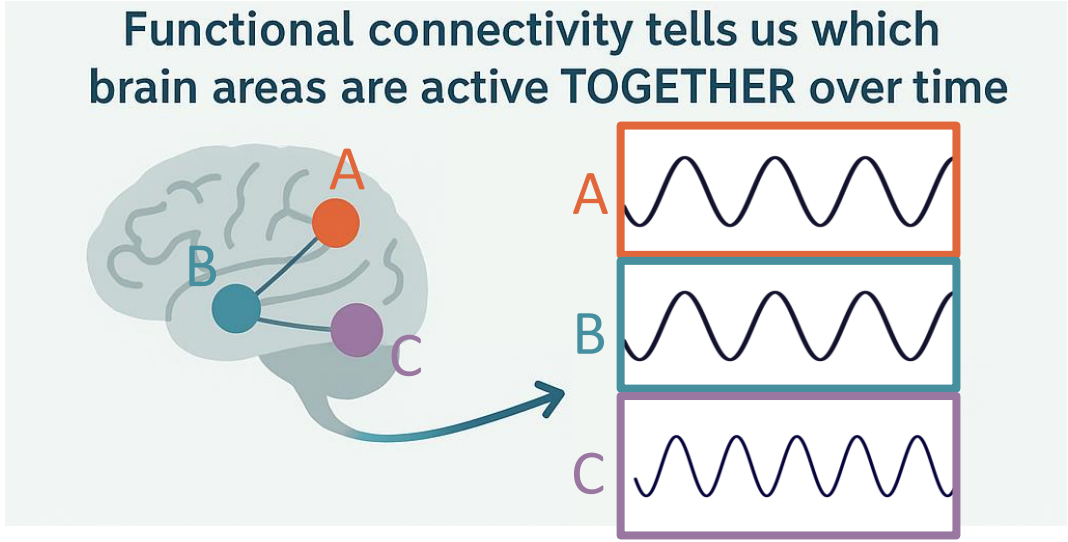
Goals:

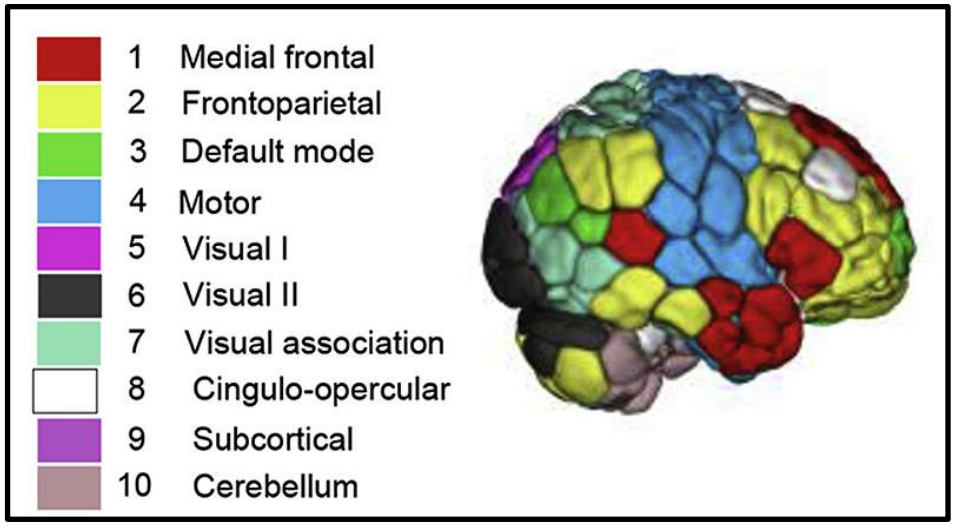
1. To test whether relevant functional networks are **less stable** in BD
2. To assess how functional network connectivity changes with mood state

(Hafeman et al., Translational Psychiatry, 2025)

Principles of Functional Connectivity (FC)

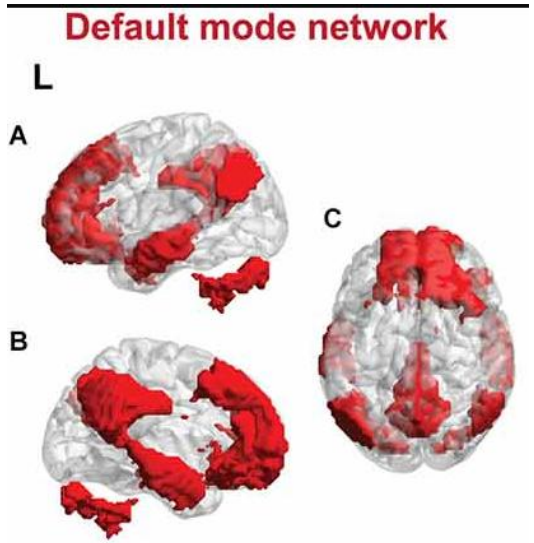






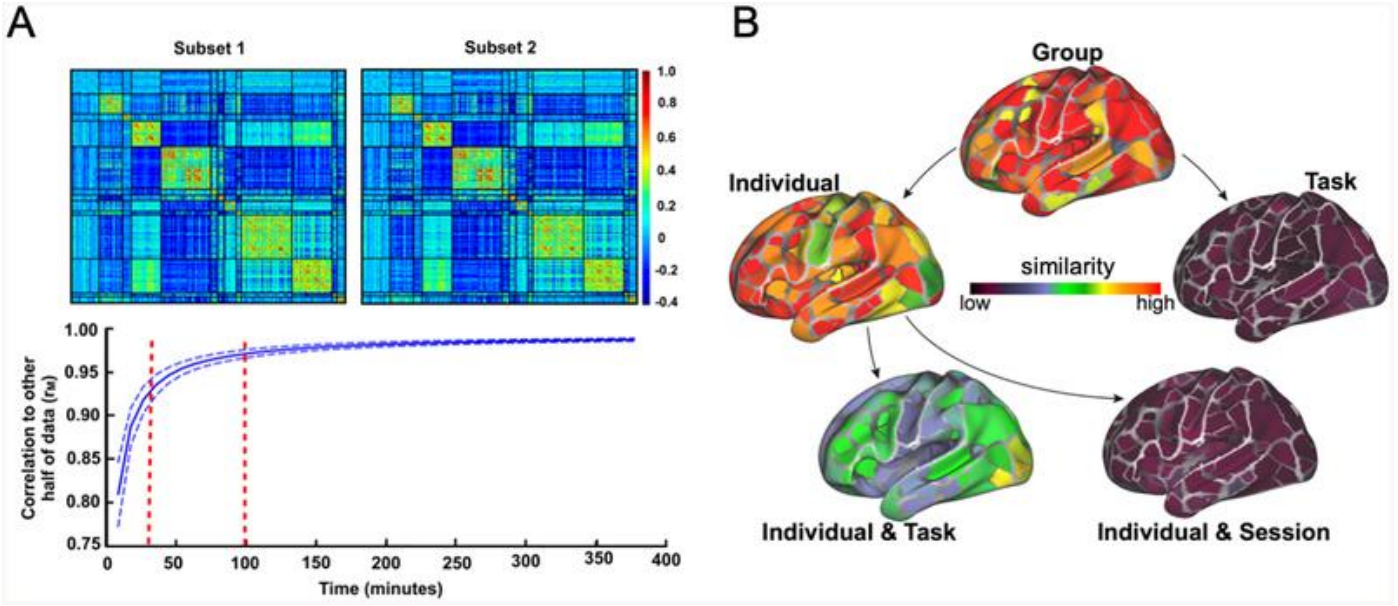
Brain can be divided into parcels based on FC patterns

Brain parcels that have higher FC form functional networks



Network Stability in Healthy Volunteers

Given enough fMRI data (>20 minutes), within-person stability of FC is high:



Similar to a fingerprint…

<u>Next question:</u> Do individuals with BD show less within-person stability, particularly in a **mood-related network**?

(Gratton et al., 2020)

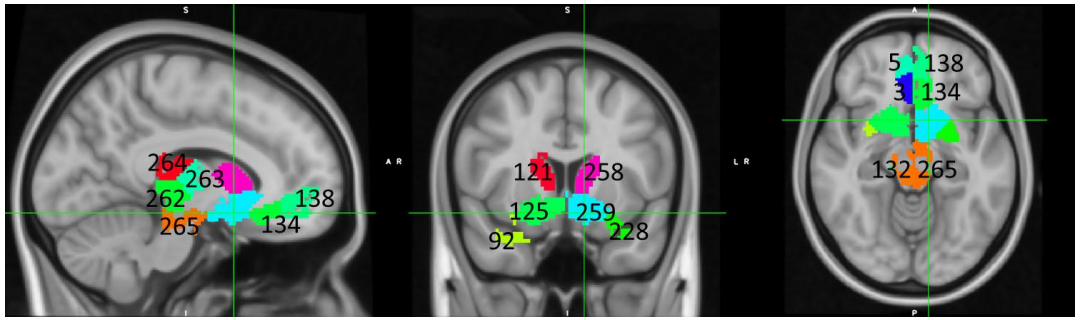
Mood-Related Network: A starting point

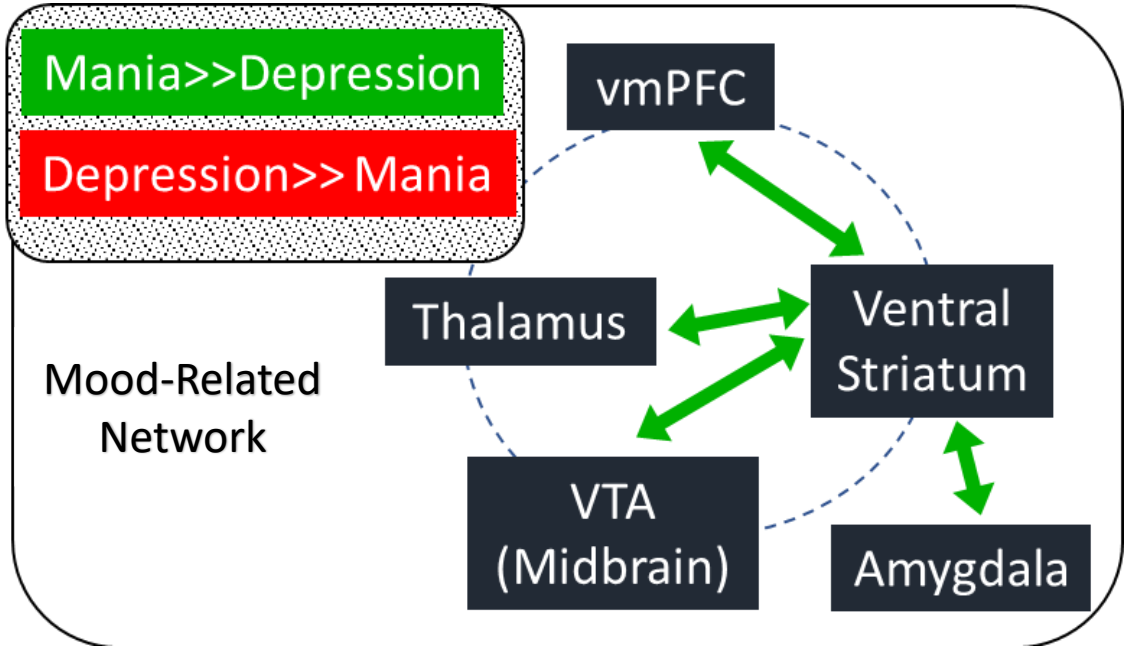
Based on previous cross-sectional studies in adults with BD, <u>mania</u> associated with ↑ FC in a **mood-related network**:

- *Ventral striatum & midbrain* (Altinay, 2018)
- *Amygdala, midbrain, & frontal cortex* (Spielberg 2016)
- *Thalamus & frontal cortex* (Guo, 2021)

<u>Depression</u> associated with ↓ FC in network regions:

- *Thalamus and vmPFC* (Satterthwaite 2016)





BDLONG: Sample & Methods

	BD (n=11)	HC (n=5)
Age: Median [Min, Max]	19.2 [17.1, 23.3]	19.4 [16.3, 21.2]
Sex: n (%) Female	8 (72.7%)	4 (80.0%)
Gender Identity n (%) Women	6 (54.5%)	4 (80.0%)
Race		
Asian	2 (18.2%)	1 (20.0%)
White	7 (63.6%)	4 (80.0%)
Biracial	2 (18.2%)	0 (0%)
Ethnicity		
Hispanic	1 (9.1%)	0 (0%)
Non-Hispanic	10 (90.9%)	5 (100%)

Bipolar Disorder Subtype	
Bipolar I	6 (54.5%)
Bipolar II	5 (45.5%)
Medications	
Lithium	4 (36.4%)
Lamotrigine	5 (45.5%)
Atypical Antipsychotic	10 (90.9%)
Antidepressant	7 (63.6%)
Benzodiazepine	4 (36.4%)
Stimulant	3 (27.3%)
Comorbid Disorders	
ADHD	3 (27.3%)
GAD	6 (54.5%)
Panic Disorder	1 (9.1%)
Social Anxiety Disorder	4 (36.4%)
PTSD	2 (18.2%)
OCD	2 (18.2%)

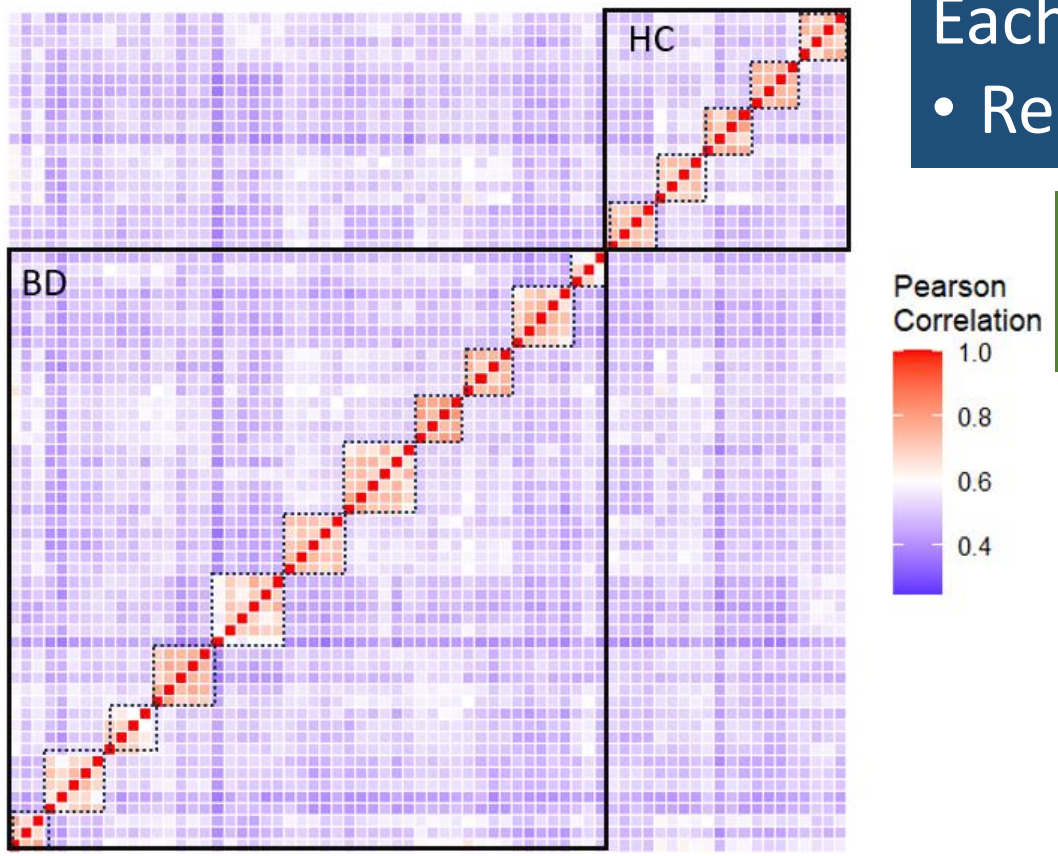
Protocol:

- Scanned longitudinally over 9 months
  - BD: Scanned 4-6x, different moods
  - Healthy Volunteers (HC): Scanned 4x
- 20 min of fMRI data (10 min Rest; 10 min Inscapes)

(Hafeman et al., Translational Psychiatry, 2025)

How similar is FC within vs. between people?

Whole-Brain:



Each square=similarity between FC of 2 scans

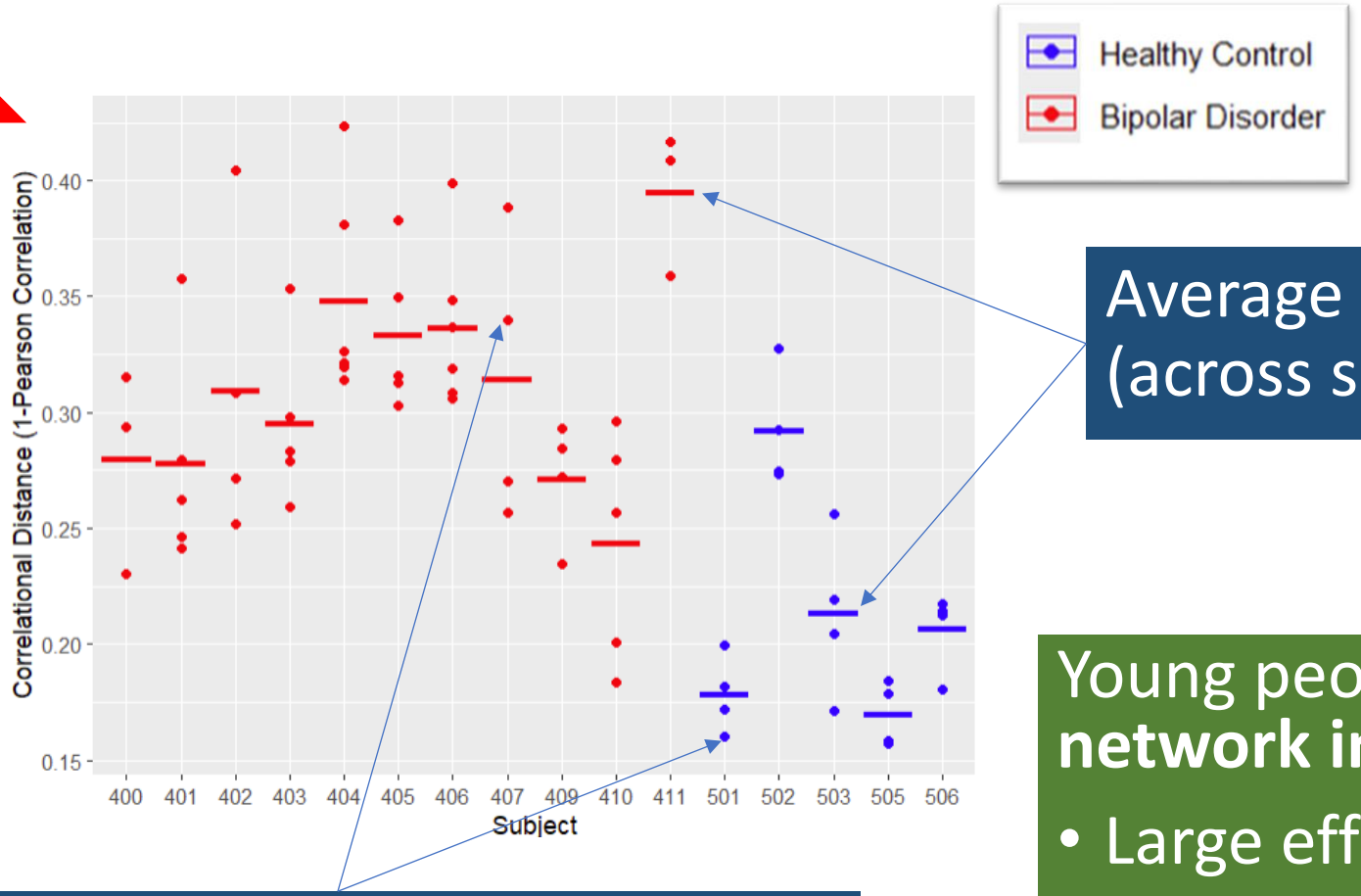
- Red=higher similarity, Blue=lower similarity

Scans within-person show much higher similarity than between people ($p<.0001$)

Similar to a fingerprint…

FC Mood-Related Network Instability in BD

More FC Network Mood Instability



Average "correlational distance" (across scans) for each person

Each circle: How different is each scan from that person's other scans?

Young people with BD have **more network instability** across scans

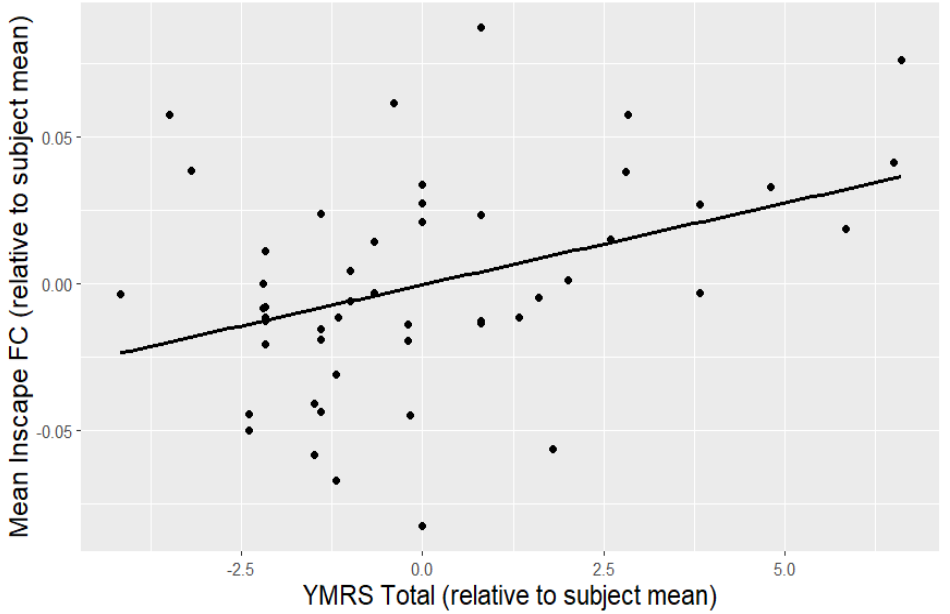
- Large effect size (d=1.4, p=.0005)
- Distinguishes BD vs. HC (AUC=0.93)

(Hafeman et al., Translational Psychiatry, 2025)

Network FC & Mood Symptoms

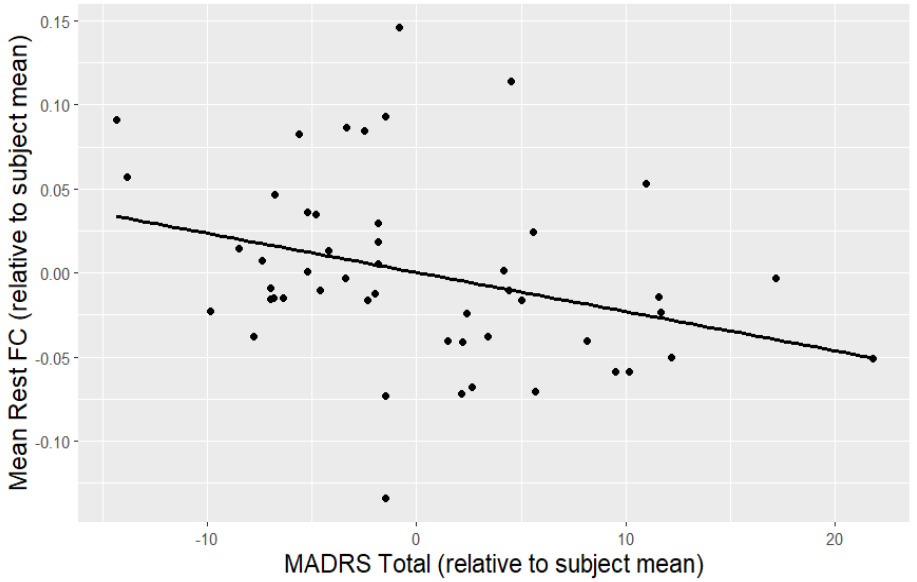
Are mania symptoms at time of scan associated with mood-related network FC?

- Manic symptoms associated with higher network FC, *esp. during Inscapes* (r=.38, p=.006)



Are depressive symptoms at time of scan associated with mood-related network FC?

- Depressive symptoms associated with lower network FC, *esp. during Rest* (r=-.32, p=.02)



Findings driven by within-person, not between-person relationships

Potential Confounds

Comorbid Disorders: Group findings remained significant after removing participants with each comorbidity (i.e., ADHD, GAD, PTSD, OCD)

Medications: Group findings remained significant after (1) removing scan-pairs with discordant medications & (2) adjusting for each med class

Observed sleepiness during scan (eyes closed >5s): Group findings remained significant with adjustment for observed sleepiness

- *Observed sleepiness associated with ↓ within-person stability of mood-related network and whole brain*

Findings were not specific to the Shen atlas: Replicated in the Tian subcortical atlas (d=-1.05, p=.02)

BDLONG: Summary & Future Directions

Summary

- Mood-related Network Instability is a novel marker that builds on recent advances in **precision imaging**.

Next Steps (pending funding…)

- Test this marker of network instability in a **larger sample**
- Include youth with BD, but **without recent hypo/manic symptoms**
- Test **specificity to BD** (vs. MDD)

Longer Term Questions

- Could this be a **marker of risk** as well?
- Could mood-related FC be a **target of neuromodulation** (e.g. ultrasound, neurofeedback)?

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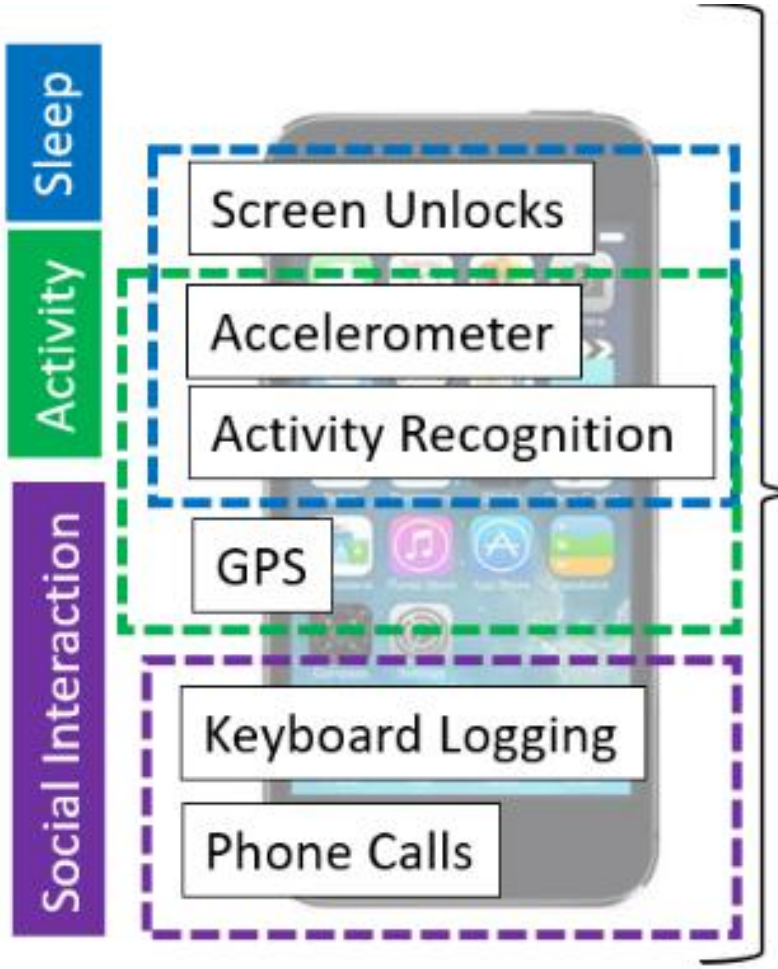
Mobile Sensing: Early Signal for Mood Changes?



Can we identify mobile sensing metrics that imminently predict mood worsening?

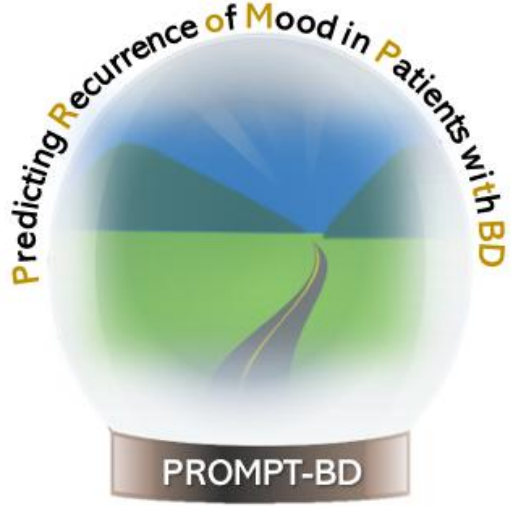
Mood Symptoms (Depression, Hypo/mania)
Mood Recurrence (Polarity-Specific)

Clinical Impact: Could early warning signs eventually help prevent mood recurrence?

Predicting Mood Recurrence in BD *(PI: Birmaher)*

Questions:

1. Does mobile sensing provide a good measure of sleep?
2. Does mobile sensing predict next-week mood symptoms?



Sample:

- Target: 120 young people (14-26 y.o.) with BD-I/II, in remission
- *Current: 59 enrolled so far*

Protocol:

- Target: 24 months of mobile sensing, with assessments + actigraphy q 6 months
- *Current: median 27 weeks (~6 months) of total follow-up*
- *Current: median 24 weeks with usable mobile sensing data (89% of total)*

Mood Recurrences Thus Far:

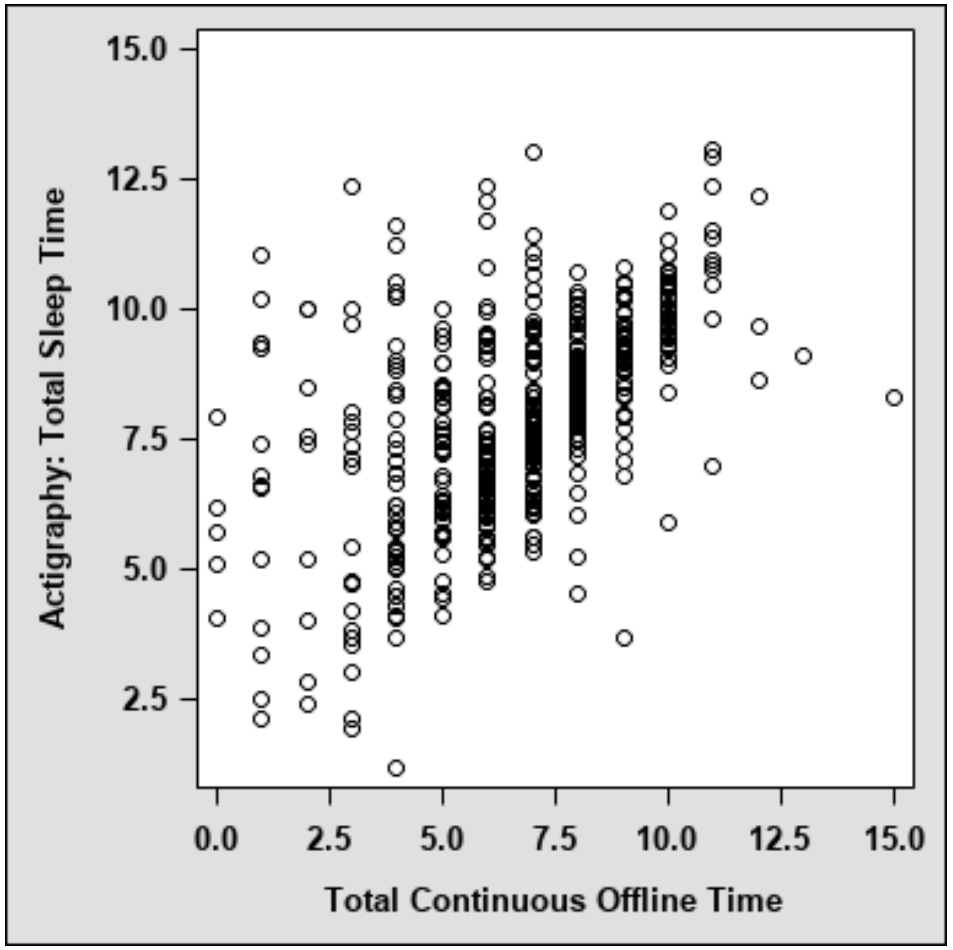
- 20 threshold mood episodes (13 depression, 7 hypo/mania)
- 72 subthreshold or worse mood episodes (47 depression, 25 hypo/mania)

Can Mobile Sensing Approximate Actigraphy?

Total Continuous Offline Time (TCOT): Longest continuous period (7pm-1pm) with no screen unlocks or motion detected >1 minute

Does TCOT approximate actigraphy-derived Total Sleep Time?

- Overall correlation coefficient estimated via linear mixed model: ***r*=0.58**
- On average, TCOT underestimated Total Sleep Time (as measured by actigraphy) by **8 minutes**.



Can Mobile Sensing Predict Next-Week Mood?

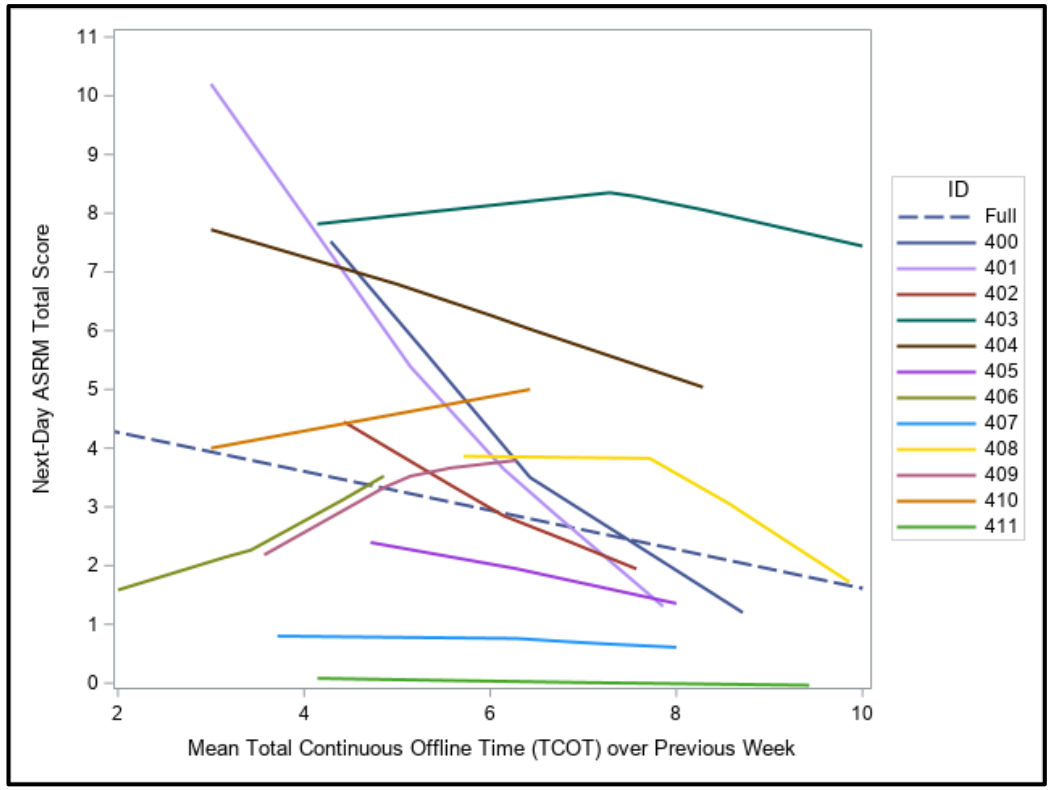
Mobile Sensor	Depression		Hypomania	
	OR	*p-value*	*OR*	*p-value*
Duration Mobile	0.68	**0.0001**	1.25	**0.0145**
Duration Stationary	1.18	0.1033	0.61	**<0.0001**
Time spent at home	1.08	0.3055	0.91	0.3167
Screen Unlocks: Duration	1.44	**0.0001**	0.89	0.2781
Screen Unlocks: Number	1.32	**0.0091**	0.89	0.3993
Incoming Calls: Mean Duration	1.04	0.6677	1.10	0.3172
Incoming Calls: SD Duration	1.02	0.8968	0.94	0.7288
Outgoing Calls: Mean Duration	1.14	0.1287	1.11	0.1772
Outgoing Calls: SD Duration	1.09	0.4451	1.09	0.3802
TCOT: Mean	0.88	0.1534	0.99	0.9308
TCOT: SD	0.92	0.3383	1.34	**0.0072**

Depression associated with:
- Less physical activity
- More screen time

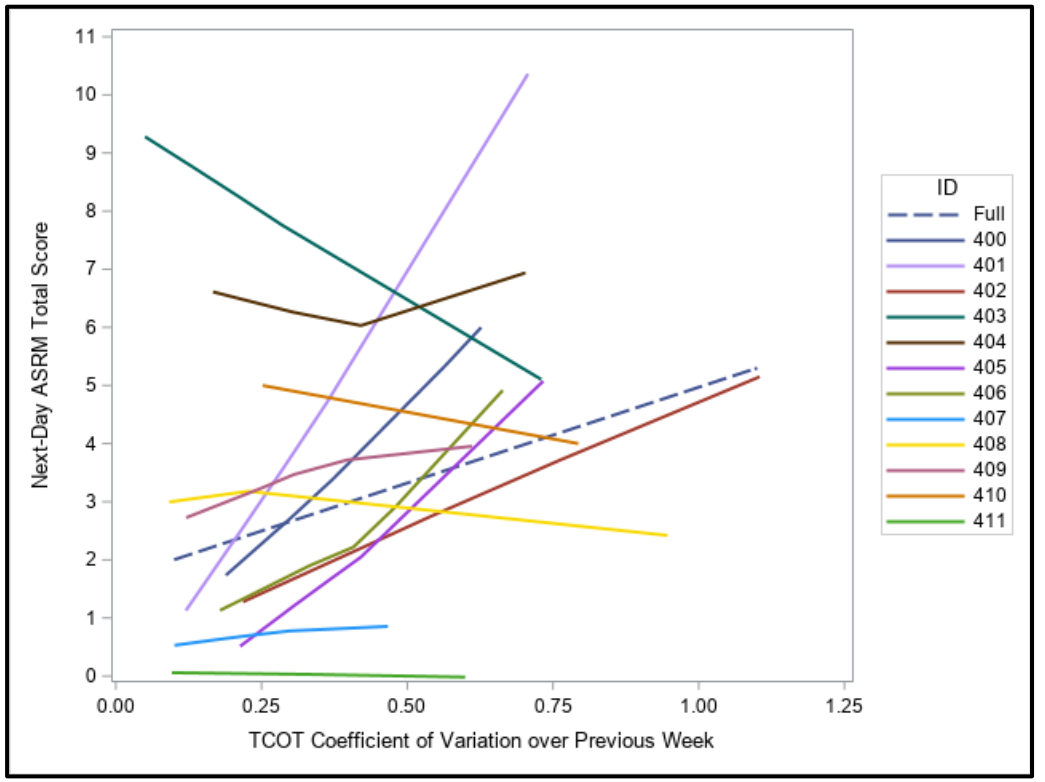
Hypomania associated with:
- More physical activity
- More variable sleep

- *All findings were similar in <u>within-person</u> models*

Similar results found with sleep time in BDLONG…



↓ mean TCOT over past week associated with ↑ manic symptoms (β=-0.15, p=0.01)



↑ variability in TCOT over past week associated with ↑ manic symptoms (β=0.18, p=0.002)

Summary and Next Steps

- ***Promising evidence that mobile sensing metrics of sleep & mobility***
  - Correspond to actigraphy-derived sleep measures
  - Predict next week mood symptoms
- ***Next Steps***
  - Develop personalized models that can predict mood recurrence with acceptable accuracy
  - Build infrastructure for just-in-time assessment, i.e. deliver self-report mood assessments when the personalized model indicates trouble!
  - Eventually… we can intervene, e.g. evidence-based recommendations, alert family members or clinical team, etc.

Conclusions

- BD typically onsets in adolescence, & diagnostic delays interfere with reaching young adult milestones – **early identification is critical**!
- **Network instability**, particularly in a largely subcortical mood-related network, may characterize BD and map onto mood symptoms.
- **Mobile sensing** is a promising direction for imminent prediction of mood symptoms in BD

Acknowledgements

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