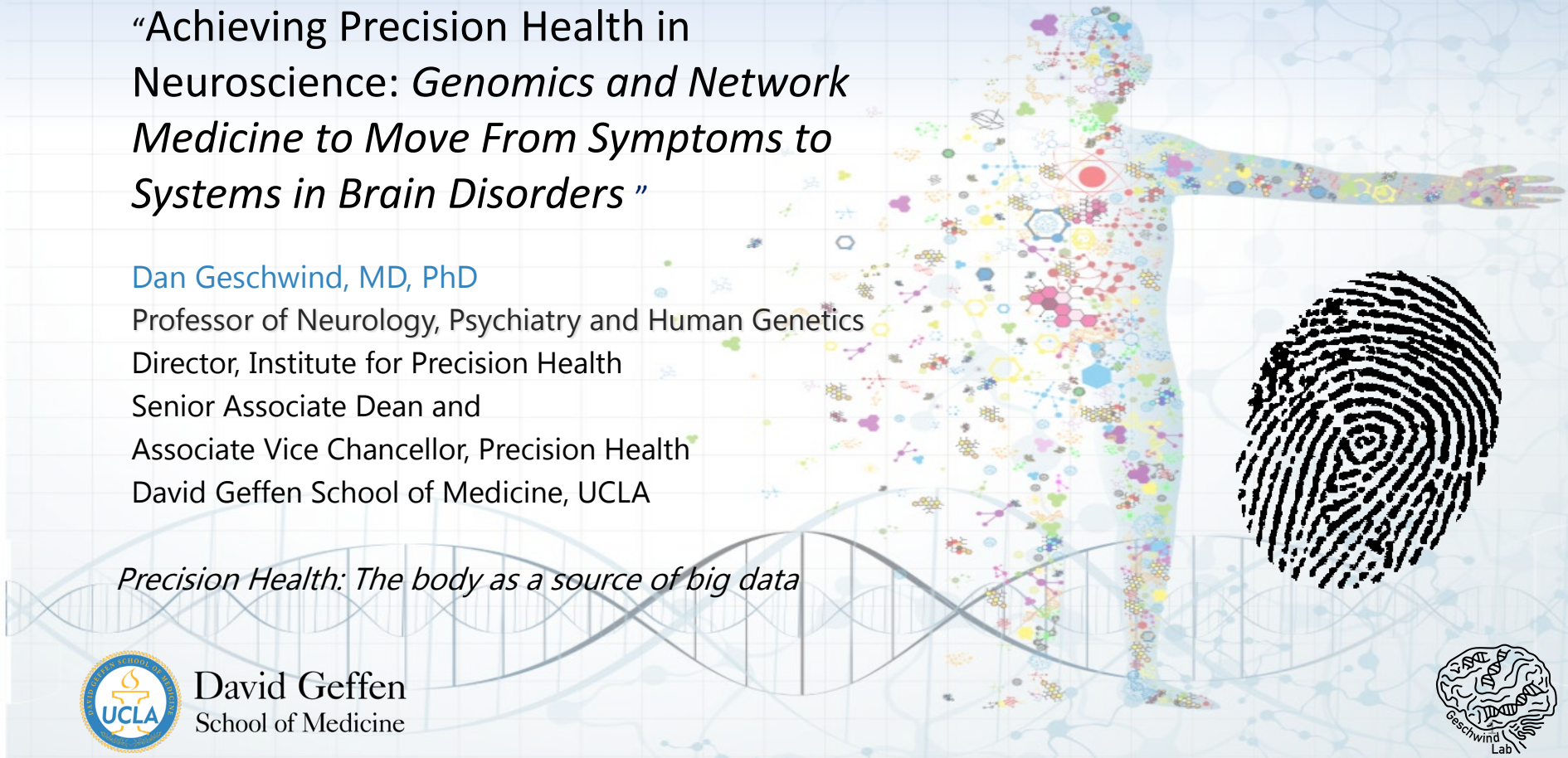
"Achieving Precision Health in Neuroscience: *Genomics and Network Medicine to Move From Symptoms to Systems in Brain Disorders* "

Dan Geschwind, MD, PhD
Professor of Neurology, Psychiatry and Human Genetics
Director, Institute for Precision Health
Senior Associate Dean and
Associate Vice Chancellor, Precision Health
David Geffen School of Medicine, UCLA



Precision Health: The body as a source of big data

David Geffen School of Medicine

Geschwind Lab

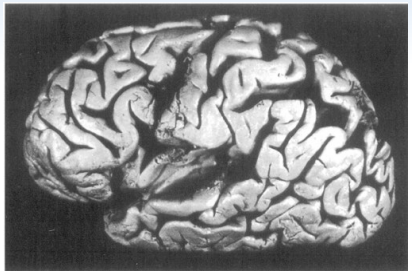
Are We Treating Syndromes as Diseases?

- In Neurology we call AD, ADRDs, ALS, MS and PD “diseases”
- But, clinically and biologically they behave as **heterogeneous syndromes** that vary across individuals due to many factors including genetic and environmental contributions.
- Clinical labels group together biologically distinct processes with different causes
- This likely contributes to repeated therapeutic failures

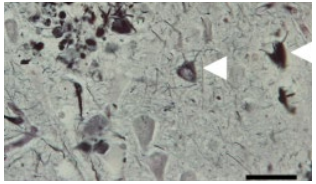
Value and limits of postmortem neuropathology

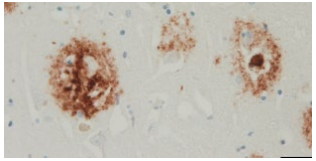
- Neuropathology (microscopic or macroscopic) is a core defining feature of neurologic diseases
  - Provides key information on the cellular and molecular alterations in patients
  - Has shifted psychiatric illness towards a more neurologic/biomedical framing
  - A potential starting point for exploring disease mechanisms
- But, we often assume shared pathology = shared causality; *but it doesn't*
  - This is largely informed by genetic discoveries have transformed our understanding of causality across the spectrum of neurologic disorders (and psychiatric disorders)
    - Dominant familial forms ≈ sporadic forms pathologically, but they have different causes.
    - PD = Lewy body pathology; but, rare *PARK2* and *LRRK2* cases lack Lewy bodies and/or are tau+.
- We are grouping convergent endopoints, rather than mechanistic origins
- Does not automatically dictate therapeutic choice

Neurological disorders like stroke and Alzheimer's disease have visible macroscopic and microscopic pathology



Stroke (Broca 1860s)





Alzheimer's tangles and plaques (DeTour and Dickson 2019)

But, psychiatric disorders are considered differently because of their lack of defining pathology……

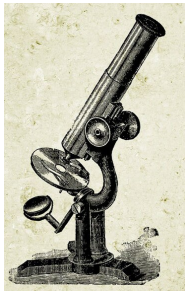
We reasoned that we could use modern genomic methods to identify and define a molecular pathology in post- mortem brain from subjects with ASD and other psychiatric conditions.

PSYCHIATRIC GENOMICS

Gandal et al., Science 359, 693–697 (2018)

Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap

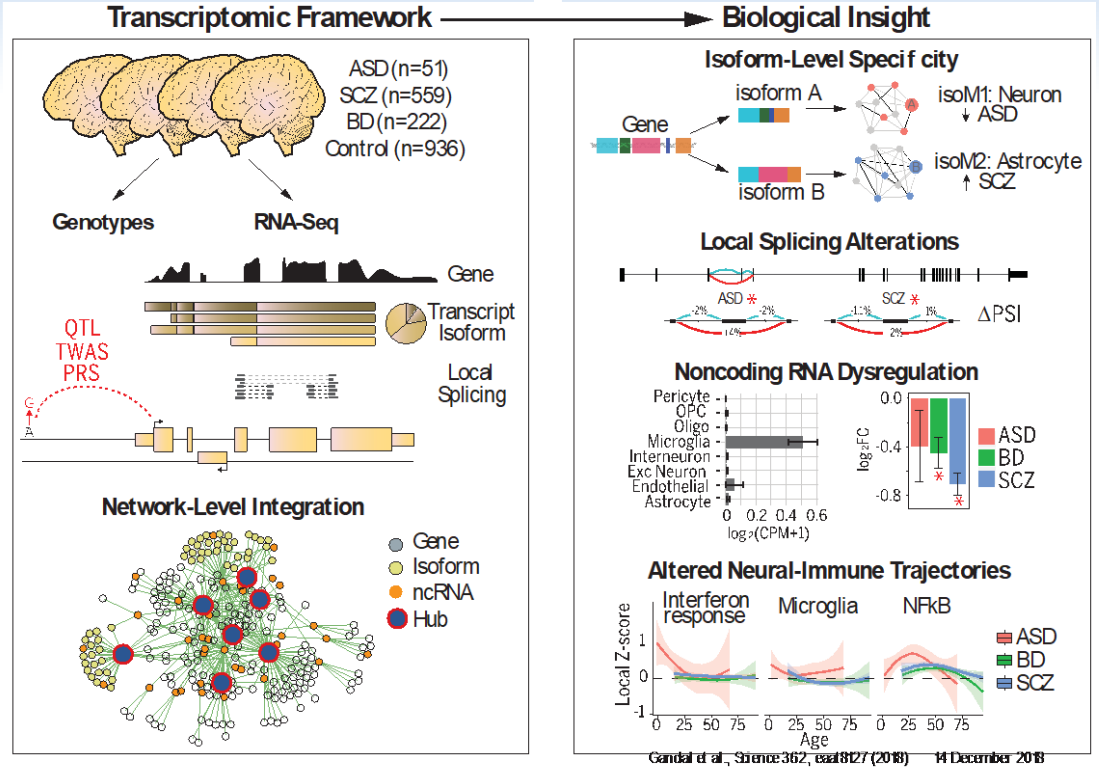
Michael J. Gandal,[1,2,3,4] Jillian R. Haney,[1,2,3] Neelroop N. Parikshak,[1,2,3] Virpi Leppa,[1,2,3] Gokul Ramaswami,[1,2,3] Chris Hartl,[1,2,3] Andrew J. Schork,[5] Vivek Appadurai,[5] Alfonso Buil,[5] Thomas M. Werge,[5,6,7] Chunyu Liu,[8,9] Kevin P. White,[10,11] CommonMind Consortium,* PsychENCODE Consortium,* iPSYCH-BROAD Working Group,* Steve Horvath,[3] Daniel H. Geschwind[1,2,3]†



Laser Scanning Confocal Microscope

Automated sequencer

Integrative Genomics and Gene Networks Map the Molecular Pathology of Psychiatric Disorders



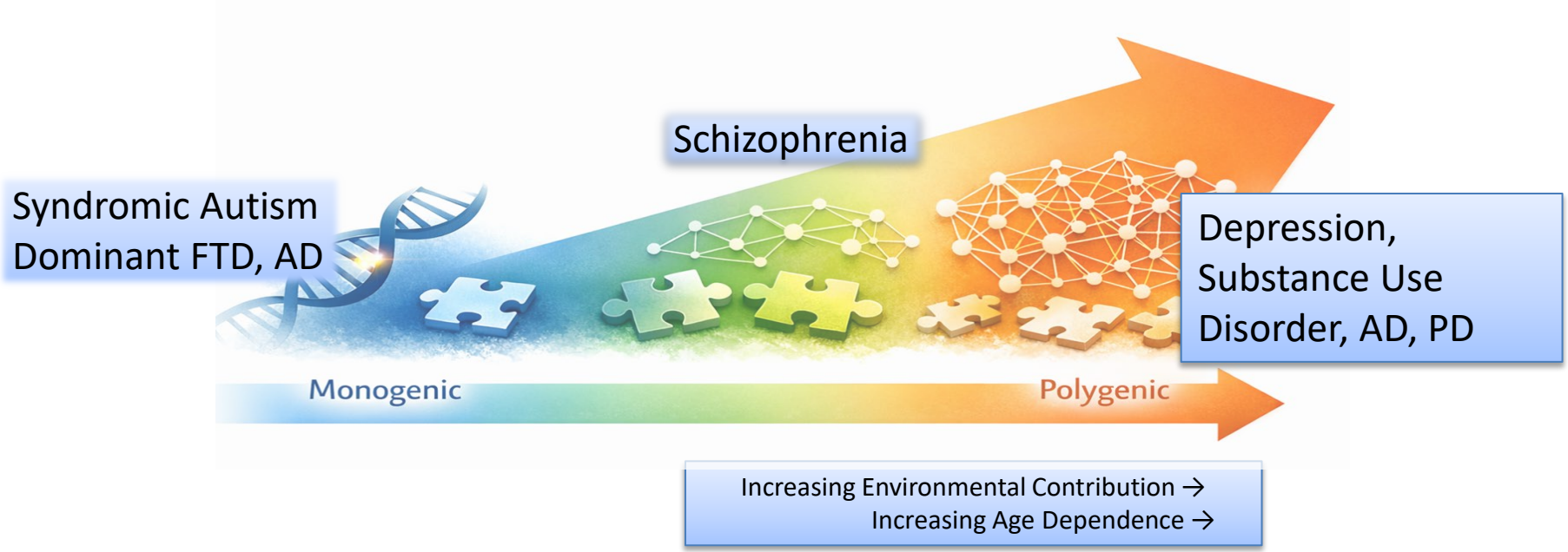
- **Genomic profiling defines starting points for mechanistic understanding and therapeutic development.**
- **Gene-network approaches provide organizing principles for understanding molecular phenotypes in the brain.**
- **Serves as a basis for use of in vitro and in vivo models to understand how genetic risk percolates through development to lead to these patterns (mechanisms).**

PsychEncode

See also: Voineagu et al, 2011 *Nature;* Parikshak et al. 2016 *Nature*; Gandal et al. *Science* 2018, *Nature* 2022; Wang et al. *Science 2018;* Wamsley et al. *Science* 2024

Genetic Architecture Matters

Different brain disorders may have fundamentally different genetic architectures, which may inform how we study, stratify and treat them



How genetic architecture might inform study design

Monogenic Disorders

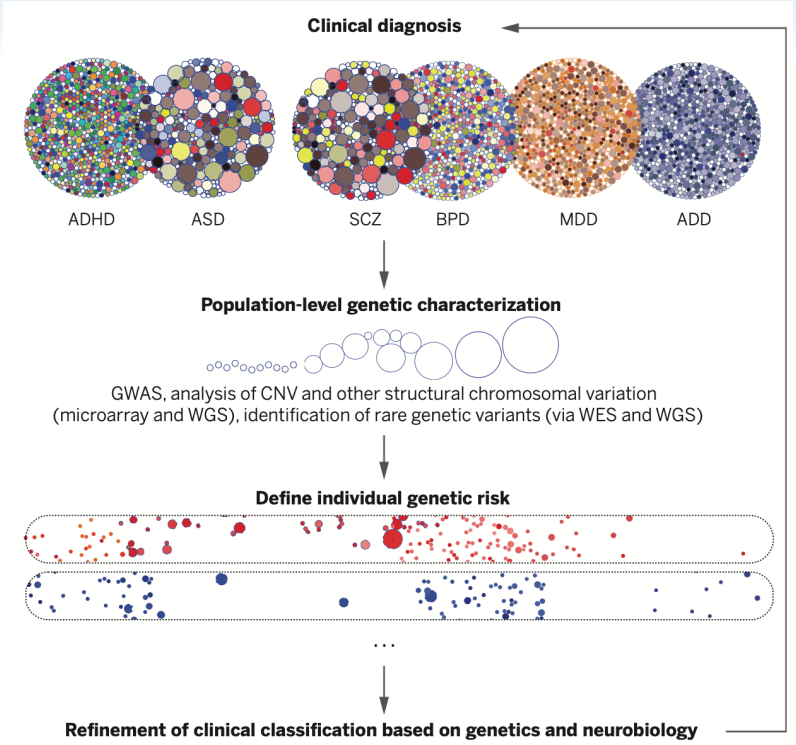
- **Biology:** High effect mutations can lead to clear mechanistic entry point.
- **Study Design:** Small genetically defined cohorts with deep phenotyping.
- **Clinical Trials:** Mutations specific trials and targeted therapies.
- Low hanging fruit for precision approach currently (e.g. nucleic acid therapeutics).

Oligogenic/Polygenic

- **Biology:** Network level vulnerability and potential for more environmental modulation. Disease may occur when resilience thresholds are crossed.
- **Study Design:** Large cohort, EHR integration and real-world longitudinal data, repeated biomarker/biochemical measures…identify subtypes.
- **Clinical Trials**: Biomarker/PGS-guided enrollment. Subgroup-based efficacy.

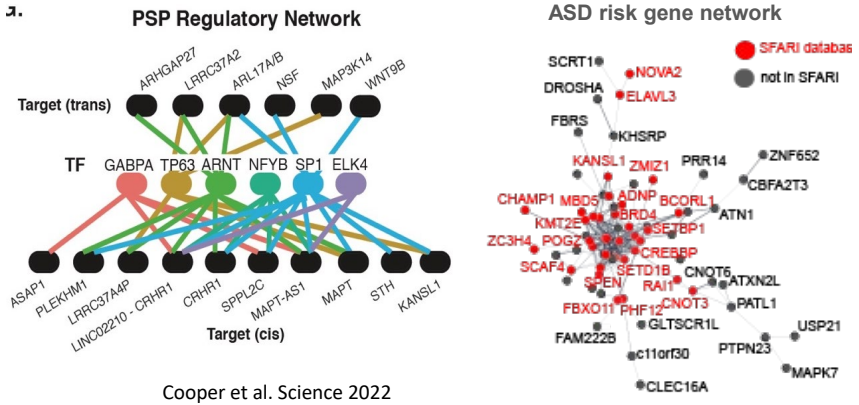
It is necessary to redefine brain disorders as biologically stratified syndromes

- **From Diagnostic Categories → Biological Subtypes**
- Move from symptom clusters to:
  - Genomic signatures and molecular networks
  - Other molecular and physiological biomarkers
  - Longitudinal trajectories
- Genetic characterization is challenged since genetic findings blur disease boundaries and boundaries between disease states and normal variation…
  - **Variable expressivity:** *NRXN1* and 22q11-13 mutations in SCZ and ASD; *C90RF72* in FTD and ALS; *MAPT* in PSP, CBD, FTD.
  - **Reduced penetrance** → What are the modifiers? Environment? Networks? Epigenetics?



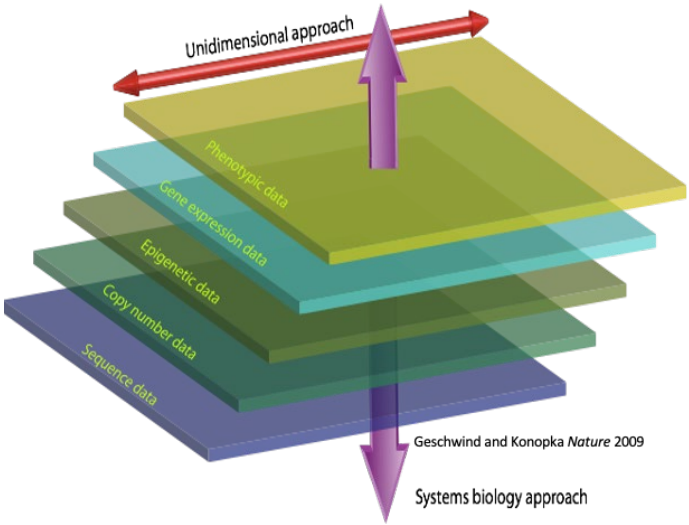
Geschwind and Flint *Science 2015*

Systems-Level View: *Gene Networks, Not Single Genes*



Cooper et al. Science 2022

- Genes don't act alone
- Nervous system diseases can be framed as network failures
- Reduced penetrance suggests buffering systems
  - Variable penetrance occurs in mendelian disease, suggesting that modifiers exist even in these major gene conditions
  - In polygenic disorders variable penetrance is more dramatic.
  - If we can identify the factors that mediate penetrance or disease progression, we may have more therapeutic leverage than focusing only on primary risk genes



Phenotype = genotype + environment

A Genomic Inflection point?

How does diagnosis, prevention and patient sub-grouping change when whole genome sequencing (WGS) costs < $100?

- Genomics becomes a ubiquitous part of standard care…
- Every patient becomes molecularly characterized
- Carrier awareness (high risk individuals who remain stable)
- Disclosure of polygenic scores and integration into clinical care

Stratification by genetic risk and gene networks, not symptoms, becomes commonplace. But genetic risk alone is insufficient.

Need for inclusion of diverse populations to permit interpretation

Ability to study reduced penetrance at scale

- What determines divergence among individuals with similar genetic burden?
- That answer likely resides in longitudinal biology and monitoring.

The bottleneck will no longer be WGS, but integration and and modeling

The Missing Dimension: Longitudinal Biology in Patients

We have technologies today we didn't have 20 years ago

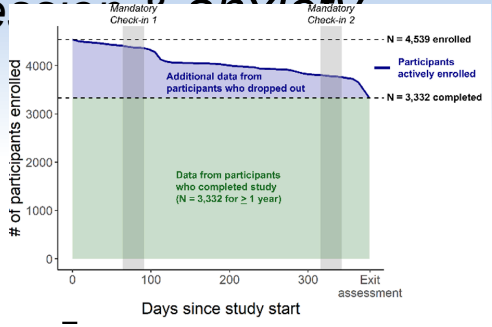
- Wearables (e.g., Apple Watch collaborations)
- Remote monitoring of continuous physiologic data streams
- Electronic medical records (natural habitat data)

We should move from studying research cohorts to studying patients across the spectrum in their real-world environments.

- EHR-based phenotypes are scalable
- Continuous data vs. episodic clinic visits
- Need longitudinal biochemical/physiological data
- Future model: Integrate genomics/multi-omics + wearable data/environment + clinical records into
  - Network-topology-aware classification
  - Genetic architecture-informed subtyping
  - Longitudinal trajectory stratification
  - Mechanism-aligned trials

UCLA Depression Grand Challenge: *built the UCLA-Apple Digital Mental Health Study (DMHS) to advance scalable, longitudinal objective assessment of depression & anxiety*

>4000 participants consented to share 12 months of nearly continuous digital data+ surveys of depression & anxiety



> 900 digital features including novel measures of emotional expression

Phone — Accelerometer, Gyroscope, GPS, Light sensor, Screen interaction, Call records, Microphone

Watch — Accelerometer, Gyroscope, Light sensor, Screen interaction, PPG sensor, ECG, Microphone

Keyboard sentiment
Absolutist words typed
Anger emojis typed
Anger words typed
Anxiety emojis typed
Anxiety words typed
Confused emojis typed
Death words typed
Down words typed
Health feeling emojis typed
Health feeling words typed
Low energey emojis typed
Positive emojis typed
Positive words typed
Sad emojis typed

Socializing
Call contacts count,
Msg contacts count
No. of incoming/outgoing calls
No. of incoming/outgoing msg
Total time in calls

Keyboard
Keyboard usage
Total emojis types
Total words types
Typing error offset
Typing flight time
Typing hold time
Typing interkey delay
Words altered

Location
Visit duration
Staying at home
Staying at work
Staying atother

Sleep
Sleep staging
Sleep start time
Sleep end time

Face
Anger expression
Baseline expression
Disgust expression
Fear expression
Joy expression
Sadness expression
Surprise expression

Vitals
Heart rate
Heart rate variability
Respiratory rate
Blood oxygenation

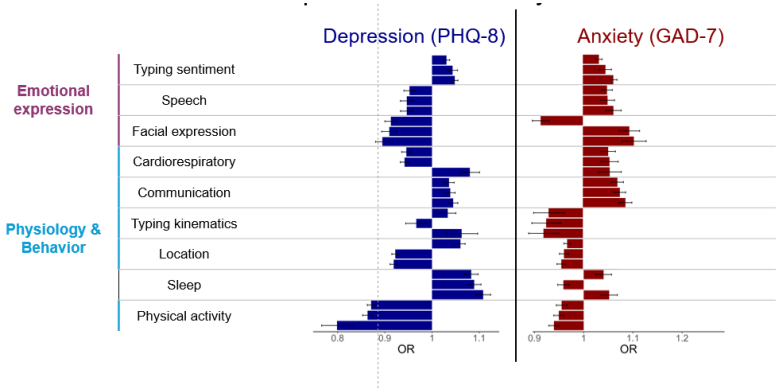
Device usage
App usage
Screen time
No. of unlocks

Mindfulness
Mindful session

Voice
Arousal
Crying
Dominance
Jitter
Laughter
Mood
Pause duration
Shimmer
Shouting
Speaking rate
Utterance duration
Voicing

Physical activity
Active calories burned
Basal calories burned
Exercise time
Stand time
Walking speed

Robust associations to depression and anxiety across all digital domains



UCLA Depression Grand Challenge

Summary

- Precision neuroscience requires better definitions of disease. The failure in brain therapeutics may not be only that our targets are wrong — but that our disease categories are not biologically coherent.
- Nervous system disorders can be framed as failures of interacting gene networks embedded in dynamic biological systems.
- If we can classify diseases by genetic/network architecture and longitudinal biology, we may better align biological mechanisms with therapies.
- Understanding genetic risk and resilience will lead to preventive strategies