Neuroimaging-Based Profiling Identifies Distinct Transdiagnostic Subtypes of Youth with Mood and Anxiety Disorders at the Transition to Adolescence

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INTRODUCTION

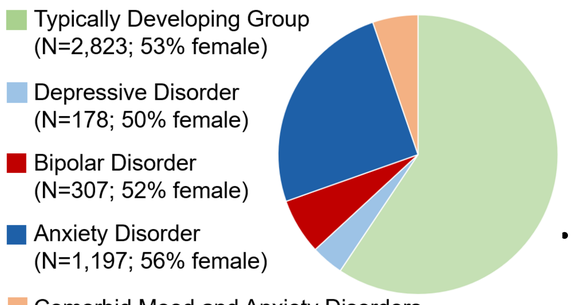
- Clinical overlap between mood and anxiety disorders is pronounced in youth.[1]
- Research into the neurobiological correlates of mood and anxiety disorders has identified transdiagnostic neuroimaging and genetic features.[2]
- Research effort has shifted towards new approaches that use data-driven methods to identify subgroups of individuals with mood and anxiety disorders based on their shared biological properties. This approach has yielded promising findings in adults.[3]

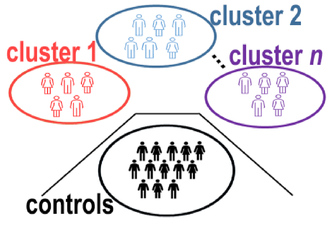
WORKING HYPOTHESIS

Pre-adolescents with mood and anxiety disorders can be partitioned into data-driven biologically informative subtypes based on neuroimaging features.

METHODS

Sample from the ABCD study[4] (N=4,754; 53% female)

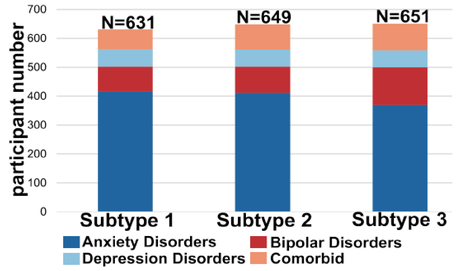




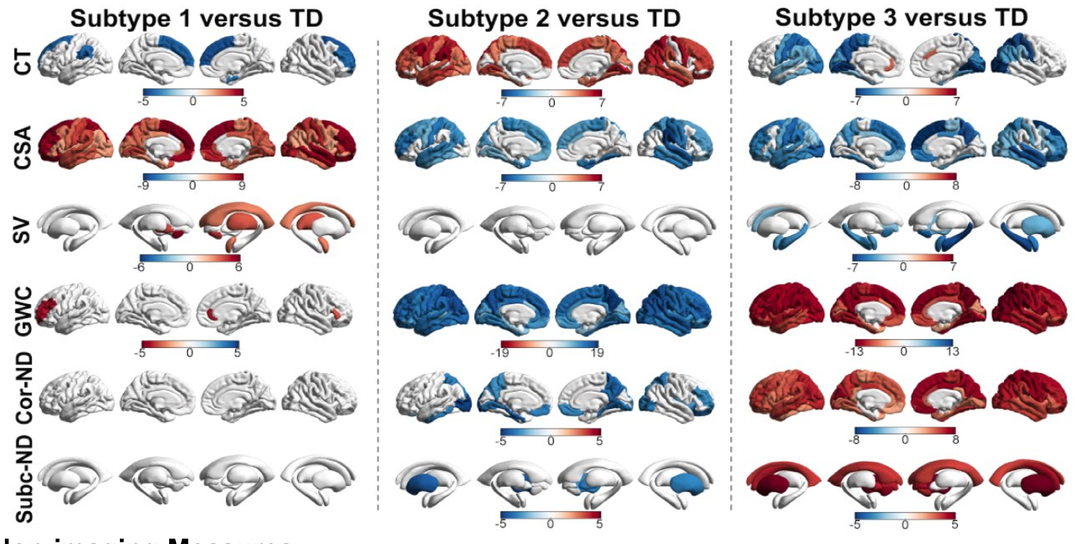
Schematic representation of HYDRA. The HYDRA model uses multiple classifiers that form hyperplanes (black lines) whose segments separate cases from controls into *n* clusters by the largest margin.

- Neuroimaging measures include:
  ① Cortical Thickness (**CT**)
  ② Cortical Surface Area (**CSA**)
  ③ Subcortical Volume (**SV**)
  ④ Gray/White Matter Contrast (**GWC**)
  ⑤ Cortical Neurite Density (**Cort-ND**)
  ⑥ Subcortical Neurite Density (**Subc-ND**)
- **HYDRA** (https://github.com/evarol/HYDRA) was applied to neuroimaging measures to identify homogenous clusters (i.e., subtypes).[5]
- Optimal cluster solution was chosen following 5-fold cross-validation based on the Adjusted Rand Index (ARI).
- Each subtype was compared to the typically developing (**TD**) group in terms of:
  ① neuroimaging features at $P_{FDR}<0.005$;
  ② psychopathology and cognition measures; prenatal and obstetric history; parental socioeconomic status and psychopathology; exposure to adverse life events and quality of family; school and neighbourhood environment at $P_{FDR}<0.005$.[6,7]

RESULTS



- The 3-cluster solution had the highest ARI value and the stability of this solution was supported by permutation testing.
- **Each subtype comprised a mixture of pre-adolescents with mood and anxiety disorders**, which was generally proportional with the diagnostic distribution in the entire clinical sample.
- **Each subtype showed a different brain maturational profile relative to the typically developing (TD) group:**
  ① Subtype 1 showed a pattern of advanced brain maturation;
  ② Subtype 2 showed a pattern of delayed brain maturation;
  ③ Subtype 3 showed an atypical brain maturational pattern.



- **Non-imaging Measures**
  ① Exposure to adverse life events, family conflict and parental psychopathology were higher for all subtypes compared to TD.
  ② Subtype 1 had higher socioeconomic status and higher cognition measures.
  ③ Subtype 2 had greater socioeconomic adversity and lower cognition measures compared to TD and subtype 1 but not subtype 3.
  ④ Subtype 3 had the highest levels of adversity compared to other subtypes and TD across multiple domains of family and neighborhood socioeconomic disadvantage, exposure to maternal drug/alcohol use during pregnancy, and lower cognition measures.

CONCLUSIONS

- **Pre-adolecents with mood and anxiety symptoms are heterogeneous at the neuroanatomical level.**
- **The identified subtypes transcended clinical diagnostic boundaries reinforcing the importance of redefining diagnostic approaches.**

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