Scientific Advancements and New Perspectives on Research in Autism and ADHD

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Prevalence rate of ADHD over time

ADHD diagnosis throughout the years: Estimates from published nationally representative survey data
(Percent of children with a parent-reported ADHD diagnosis)

“ADHD”: ~1,000 per 10,000

https://www.cdc.gov/ncbddd/adhd/timeline.html
ADHD is very commonly observed in autism

- Meta-analysis of 20 years of studies

- The pooled estimate of the current prevalence of ADHD in ASD was 38.5%.

- The pooled estimate of the lifetime prevalence of ADHD in ASD was 40.2%.
Anxiety and mood problems

- Autistic children with ADHD had a 2.2x and 2.7x increase in risk for developing anxiety and mood disorders, respectively
  - When compared to autistic children w/o ADHD
  - Age was the most significant contributing factor to this risk
Lasting adult impairments

- Young adults diagnosed with autism and ADHD were more likely to be unemployed, experience worse sleep quality, have higher risk of severe illness and autoimmune disorders.
ADHD treatments aren’t as efficacious for autistic youths

- 86% of autistic youths with ADHD are prescribed a medication for ADHD symptoms
  - 40% are prescribed two or more psychotropic medications simultaneously
  - 85% of prescribers treating autistic youths with ADHD prescribed stimulants medications
    - Most common symptom targets: aggression and hyperactivity/impulsivity
- Mixed evidence that autistic children with ADHD respond to these ADHD treatments
  - Stimulant response for ADHD symptom reduction (>25%) in autistic youths “well-below” rates in non-autistic youths – 50% vs. 70% response (Handen et al., 2015)
What are the diagnostic challenges around ADHD and autism?
The diagnostic timing for ADHD doesn’t line up with timing of autism diagnosis.
Contending with assessment of ADHD in autism

• Some ADHD symptoms may be due to impairment in social communication and skills, and NOT to underlying difficulties in inattention or hyperactivity/impulsivity
  • E.g., “does not seem to listen when spoken to directly”
  • inattention?
• ...or difficulties in social skills to engage and disengage from an interaction appropriately (i.e., autism)?
New Perspectives and Research in Autism and ADHD

Integrating two emerging mental health perspectives over the past decade
Autism reflects neurodiversity
Deficits, or *differences*?

**TABLE 6.1 | Diagnostic Criteria for Autism Spectrum Disorder**

(A) Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):

(1) Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

(2) Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

(3) Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity based on social communication impairments and restricted, repetitive patterns of behavior.

(B) Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):

(1) Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

(2) Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

(3) Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

(4) Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
Neurodiversity paradigm

• Autism is a part of the range of natural variation in human neurological development

• Typical neurodevelopment is neither superior nor inferior to divergent neurodevelopment

• Neurodiversity helps to create a healthy and sustainable cognitive environment

• There are no right or wrong brains, all forms of neurodevelopment are equally valid

Pelican and den Houting, 2022
Mental health is on a spectrum too!
Existing paradigm

“You have it, or you don’t”

Own symptoms and criteria

Own etiology.

Own treatments for them.
Co-occurring mental health conditions and disorders in autism (based on meta-analysis of 96 studies)
The Hierarchical Taxonomy of Psychopathology (HiTOP)

From a ton of “distinct” categories in the DSM

To a few “spectra” in HiTOP organized by signs and symptoms
The bean count of studies:
554 empirical studies and/or reviews
261 psychometric studies
134 genetic studies
45 neuroscience studies
66 clinical or treatment studies

Figure 2 The bifactor three-factor model in EAs, with factor loadings represented for each pathway. All values are standardized, with standard errors in parentheses. Non-significant pathways are represented by dashed lines.
UW LINK
STUDY
University of Wisconsin
Longitudinal Imaging and
Neurogenetics Study in Kids

NICHD P50HD105353; Research Project PIs: Li and Travers, Site PI: Chang
Which autistic children will and will not go on to have an ADHD diagnosis?

• Cognitive and behavioral features
• Brain structure and microstructures
• Genetics
• Retrospective and prospective treatment history, family environment (e.g., parenting)

**Goal**: Develop earlier and more precise diagnoses and ADHD treatments among autistic youths
• Data collection began in 2021
• 120 autistic youths, ages 4-7
  • 60 with ADHD features (i.e., 3 or more symptoms of either IA/HI)
  • Recruited primarily from local autism clinics
• Followed yearly, over 3 years
• Still recruiting!
Genetics of mental health
Genetics of autism

Fig. 1 | Manhattan plots. The x axis shows genomic position (chromosomes 1-22), and the y axis shows statistical significance as $-\log_{10}(P)$ of z statistics. 

- **a.** The main ASD scan (18,381 cases and 27,969 controls), with the results of the combined analysis with the follow-up sample (2,119 cases and 142,379 controls) in yellow in the foreground. Genome-wide-significant clumps are green, and index SNPs are shown as diamonds. 

- **b-d.** Manhattan plots for three MTAG scans of ASD together with schizophrenia\(^7\) (34,129 cases and 45,512 controls; **b**), educational attainment\(^8\) (n=328,917; **c**) and major depression\(^9\) (111,902 cases and 312,113 controls; **d**). Full-size plots are shown in Supplementary Figs. 45–48. In all panels, the results of the composite of the five analyses (consisting of the minimal P value of the five for each marker) is shown in gray in the background.
Polygenic scores (PGS)

Polygenic Score = $\sum x_{ij} \beta_j$
Autism genes overlap with lots of other heritable traits

Fig. 2 | Genetic correlation with other traits. Significant genetic correlations between ASD (n = 46,350) and other traits after Bonferroni correction for testing a total of 234 traits available at LD Hub with the addition of several new phenotypes. Estimates and tests were performed with LDSC. The results shown correspond to the following GWAS analyses: IQ* (n = 78,308), educational attainment* (n = 328,917), college* (n = 111,114), self-reported tiredness* (n = 108,976), neuroticism* (n = 170,911), subjective well-being* (n = 298,420), schizophrenia* (n = 82,315), major depression* (n = 480,359), depressive symptoms* (n = 161,460), attention deficit/hyperactivity disorder (ADHD)* (n = 53,293), and chronotype* (n = 128,266). Supplementary Table 5 shows the full output of this analysis. Asterisks indicate values are from in-house analyses of new summary statistics not yet included in LD Hub.
A HiTOP perspective enhances genetic predictive precision

<table>
<thead>
<tr>
<th>Study</th>
<th>ADHD</th>
<th>ASD</th>
<th>BIP</th>
<th>SCZ</th>
<th>MDD</th>
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<tbody>
<tr>
<td>Sample Size</td>
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<td>46,351</td>
<td>51,710</td>
<td>105,318</td>
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<td>18,382</td>
<td>20,352</td>
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<td>170,756</td>
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<tr>
<td>Control</td>
<td>34,194</td>
<td>27,969</td>
<td>31,358</td>
<td>64,643</td>
<td>329,443</td>
</tr>
</tbody>
</table>

Li, He, Wang, Travers, & Lu, under review
The full model...
Enhancing predictive precision in the PGS: ADHD and autism

\[ B = 0.207, \text{se} = 0.025, p = 6.61 \times 10^{-16} \]

\[ B = 0.199, \text{se} = 0.025, p = 6.28 \times 10^{-15} \]

\[ B = 0.067, \text{se} = 0.026, p = 0.009 \]

\[ B = 0.017, \text{se} = 0.025, p = 0.505 \]

Li, He, Wang, Travers, & Lu, under review
Attenuated genetic correlations with other traits

**Optimized ADHD PGS:** 4 of the 13 significant genetic correlations no longer significant (e.g., substance use, neuroticism, Tourette’s Syndrome)

**Optimized Aut PGS:** 3 of the 6 previously significant genetic correlations no longer significant (e.g., loneliness, neuroticism, and anxiety)

**Take home:** Aut and ADHD PGS can be optimized to increase its discriminant validity when accounting for other dimensions of mental health

Li, He, Wang, Travers, & Lu, under review
Leveraging –omics in mental health diagnosis

Caregiver questionnaires
- SDQ
- CBCL
- BRIEF-2
- BASC
- Connor’s

Teacher questionnaires
- See above

Caregiver interview
- Semi-structured

Child assessment
- NEPSY
- WISC

Child observation
- School
- Home

Genomics
- Whole genome sequencing

Brain imaging
- Structural/DTI
- Functional

Psychophysiological
- Eye tracking
- Skin conductance

Language processing
- Social media usage

Passive sensing
- Wearables/health tracking
NIH awards $50.3 million for “multi-omics” research on human health and disease

New research consortium will develop innovative strategies for clinical studies involving ancestrally diverse populations.

The National Institutes of Health is establishing the Multi-Omics for Health and Disease Consortium, with approximately $11 million awarded in the consortium's first year of funding. The new consortium aims to advance the generation and analysis of “multi-omic” data for human health research.

Multi-omics refers to a research approach that incorporates several “omics” data types derived from different research areas — such as genomics, epigenomics, transcriptomics, proteomics and metabolomics. Each of these data types reveals distinct information about different aspects of a biological system, and leveraging all these data types at once is becoming increasingly possible with advances in high-throughput technologies and data science.
Integrating neurodiversity and HiTOP

• Beyond autism, all mental health can also be viewed as spectra (across a few major dimensions)
  • Functional impairments across dimensions may necessitate individual treatment, but so too are accommodations and social environmental changes (e.g., reducing stigma, acceptance)

• Impairment in mental health dimensions are typically exacerbated in autistic populations
  • Instead of treating individual disorders one-by-one and one-at-a-time (e.g., ADHD in autism, anxiety in autism, etc. etc.), researchers and clinicians can create more unified treatments that cut across single disorders
Social and Behavioral Development Lab
Investigating How Biology and Environments Impact Children’s Development

https://lilab.waisman.wisc.edu/

Waisman Center
Advancing knowledge of human development, developmental disabilities, and neurodegenerative diseases.
The UW LINK Research Team

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Questions? Comments?

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