Biological Psychiatry: Celebrating 50 Years

Large-Scale Population-Based Assessment of Psychiatric Comorbidities in Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder

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Understanding the etiologic architecture of neurodevelopmental disorders is critical for the development of better diagnostics and therapeutics for improvement of quality of life. Neurodevelopmental disorders have been shown to have high heritability [e.g., a heritability of ~80% in autism spectrum disorder [ASD] (1)], indicating that they comprise both genetic and environmental components. Recent genetic studies have also shown that assessment, en masse, of individuals with these and other psychiatric disorders can aid in the discovery of common variants underlying these phenotypes (2) and demonstrate a shared heritability (3). Similarly, studies of de novo variants (genetic variants seen in children but not their parents) have identified statistically significant genes by combining individuals with different neurodevelopmental disorders, indicating potential shared molecular pathways (4). There are also known phenotypic overlaps based on studies of clinical cohorts (5). Determining the prevalence of different psychiatric comorbidities is important for providing critical clues to what is overlapping and nonoverlapping concerning inherited influences on neurodevelopmental disorders. These were recently outlined by Hawks and Constantino (6) and include 1) implications for refining genotype–phenotype associations (e.g., ASD in some individuals with 16p11.2 copy number variants), 2) identifying dissociable (endophenotypic) "elements" of genetic liability that might contribute "necessary but insufficient" influence on more than one disorder, and 3) identifying potential targets of intervention (i.e., shared phenotypic underpinnings of disorders). It has also been posited that relational maps of behavioral development features could be built and used clinically (in the manner that height vs. weight tables are used in pediatric practice) to operationalize affection status (6) in a manner that improves upon binary classification. Previous studies have assessed psychiatric comorbidity with neurodevelopmental disorders (5) but have not focused on a cohort consisting of only adults. This has left an appreciable gap in the literature in relation to child-onset neurodevelopmental disorders and their potential co-occurrence with adult-onset psychiatric comorbidities. Big data are revolutionizing the way we assess neurodevelopmental disorders by providing key insights into their epidemiological and genetic features.

In this issue of *Biological Psychiatry*, Solberg *et al.* (7) use nationwide databases containing information on >1.7 million individuals in Norway to determine shared and differing psychiatric comorbidities between ASD and attention-deficit/hyperactivity disorder (ADHD) both overall and in a sex-stratified manner. In contrast to smaller clinical cohorts, the use of an epidemiologic sample specifically enables the assessment of psychiatric comorbidities in individuals with ASD and/or ADHD as well as generally enables insights into their prevalence in the general population. An additional advantage of this study is complementary genome-wide association data, which confirmed from a genetic aspect many of their findings regarding ASD/ADHD and their observed psychiatric comorbidities.

The main subsets of the population assessed were individuals with ADHD only, ASD only, or both ADHD and ASD. Regardless of whether the individual had ASD, ADHD, or both, they were more likely to have a psychiatric comorbidity than the remaining population. Their parents also had a higher prevalence of psychiatric phenotypes. A major finding by Solberg *et al.* (7) was that there were differences in psychiatric comorbidities depending on whether the individual had ASD, ADHD, or both ASD and ADHD. Based on prevalence ratio data, individuals with ASD were more likely to also have schizophrenia, individuals with ADHD were more likely to also have substance use disorder or major depressive disorder, and individuals with both ASD and ADHD were more likely to also have anxiety disorder, bipolar disorder, or personality disorder. These results were robust even when accounting for different covariates and when removing potential confounders. The follow-up genetic correlation analysis also supported the findings regarding schizophrenia and ASD as well as substance use disorder and ADHD. Higher prevalence ratios and genetic correlations of antisocial behavior were seen in individuals with ADHD than those with ASD, which could be important regarding sociopathy.

Solberg *et al.* (7) went yet another step further by stratifying by sex. This is an important consideration because there are known sex biases in many of the neuropsychiatric conditions considered in the analysis [e.g., a male bias in ASD (8)]. While there is debate regarding the reason(s) for sex biases (e.g., genetic [X and Y chromosome], diagnostic, or ascertainment bias), this study provides key insights and an updated point of reference for sex biases in an adult cohort. As with the above analyses, there is a focus on how these sex biases may differ for psychiatric comorbidities in individuals with ASD, ADHD, or both ASD and ADHD. Profiles of sex differentiation for psychiatric comorbidities in individuals with ADHD and/or ASD and in the remaining population are summarized from the

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https://doi.org/10.1016/j.biopsych.2019.08.012
ISSN: 0006-3223

Table 1. Summary of Relative Prevalence Differences for Psychiatric Comorbidities in Individuals With ADHD and/or ASD and in the Remaining Population

Psychiatric Comorbidity	Remaining Population	ADHD	ASD	ADHD and ASD
Anxiety Disorder	♀ > ♂	♀ > ♂	♀ ≈ ♂[a]	♀ > ♂
Bipolar Disorder	♀ ≈ ♂	♀ > ♂[a]	♀ > ♂[a]	♀ > ♂[a]
Major Depressive Disorder	♀ > ♂	♀ > ♂	♀ > ♂	♀ > ♂
Personality Disorder	♀ ≈ ♂	♀ > ♂[a]	♀ > ♂[a]	♀ > ♂[a]
Schizophrenia	♀ ≈ ♂	♀ < ♂[a]	♀ ≈ ♂	♀ < ♂[a]
Substance Use Disorder	♀ < ♂	♀ < ♂	♀ < ♂	♀ < ♂

Summary values are derived from Solberg *et al.*'s (7) Supplemental Table S4. ♀ > ♂ indicates that the prevalence is greater in females than in males, ♀ < ♂ indicates that the prevalence is greater in males than in females, and ♀ ≈ ♂ indicates that the prevalence is about equal in males and females.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

[a]Categories in which there is a difference when compared with the remaining population.

study's data in Table 1. Some psychiatric comorbidities show the same pattern in the general population as in individuals with ADHD and/or ASD. For example, major depressive disorder is more common in females than males (♀ > ♂), and substance use disorder is more common in males than females (♀ < ♂) in all categories. There are three psychiatric comorbidities, however, that show a difference in the presence of ASD and/or ADHD when compared with the general population. Both bipolar disorder and personality disorder are approximately equal in males and females in the general population (♀ ≈ ♂) but they are more prevalent in females who already have ASD and/or ADHD (♀ > ♂). On the other hand, schizophrenia is approximately equal in males and females in the general population (♀ ≈ ♂), but schizophrenia is more prevalent in males who already have ADHD or both ADHD and ASD (♀ < ♂). This has both scientific and clinical relevance—clinicians should be attuned to the prevalence of comorbidities by sex.

As with all large cohort studies, there are limitations. First, by studying Norway, Solberg *et al.* (7) have focused primarily on a European ancestry cohort (estimated at 91.8%) and a specific health care system. It will be important to see if these findings replicate in other similarly sized cohorts; this should be possible given that other countries also have national registries (1). Second, for the genetic analyses, Solberg *et al.* (7) have focused on common variants (>1% minor allele frequency) via summary statistics from genome-wide association studies. Recent studies of neurodevelopmental disorders, including ASD and intellectual disability, have shown that some genes are enriched for de novo variants in both ASD and intellectual disability (4). There have been few individuals with ADHD studied for de novo variants (9). Another class of genetic variation not studied in this approach are copy number variants, which have also been shown to be shared between different neurodevelopmental and psychiatric disorders (10). One approach that would be able to identify these missing genetic factors would be population-level whole-genome sequencing. This may be possible in the near future with pioneering efforts being led by similar projects like the UK Biobank and All of Us (https://www.researchallofus.org/). This type of work is essential for a comprehensive understanding of the genetic structure of neurodevelopmental and psychiatric disorders, including their potential shared genes and variants. A final area for future investigation is the potential effect of changing diagnostic criteria over time. The findings in this study were robust even when considering individuals who had two separate reports of their diagnosis, but it is possible that comorbidity patterns may change with the inclusion of less severe cases of ASD.

Solberg *et al.* (7) have provided the field with a roadmap for the use of comorbidity patterns to inform understanding of both overlap and nonoverlap of ASD and ADHD in a large adult cohort from one country. Schizophrenia was more common in individuals with ASD and substance use disorder, and antisocial behavior was more common in individuals with ADHD. They have also shown the importance of stratifying their analyses by sex. In the coming years, larger population-scale datasets containing epidemiologic, clinical, and genetic data will continue to refine our understanding of neurodevelopmental and psychiatric disorders and their shared architectures. It is possible that these types of datasets will also be able to integrate information about environmental exposures and social determinants of behavioral and developmental outcome to provide an even richer understanding of causation and opportunity for personalized intervention.

Acknowledgments and Disclosures

Early Career Investigator Commentaries are solicited in partnership with the Education Committee of the Society of Biological Psychiatry. As part of the educational mission of the Society, all authors of such commentaries are mentored by a senior investigator. This work was mentored by John N. Constantino, M.D.

The author reports no biomedical financial interests or potential conflicts of interest.

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Received Aug 6, 2019; revised Aug 19, 2019; accepted Aug 20, 2019.

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