EDITORIAL

Editorial: Several Roads Lead to Anxiety

Chad M. Sylvester, MD, PhD

Traditional attempts to characterize the brain pathophysiology associated with mental illnesses have relied on relating symptoms to a static snapshot of abnormal brain structure or function. Over the last few decades, however, it has become increasingly clear that many or most psychiatric disorders are the consequence of atypical brain development.[1] As such, the pathophysiology of mental illnesses may be better understood by characterizing the dynamic changes in brain structure or function that unfold over time and ultimately result in psychiatric symptoms. One important concept that has emerged out of studies that have examined longitudinal trajectories resulting in mental illnesses is the concept of equifinality—that multiple different trajectories can result in the same symptoms in adolescence or adulthood.[2] If proved to be true, equifinality is a fundamentally important principle because it suggests that even if two patients have the same symptoms, the cascade of brain changes that ultimately resulted in these symptoms differed. Potentially diverse monitoring and treatment strategies would be required to detect and treat patients with the same set of symptoms. There would be no "one-size fits all" approach to screening and treating patients, and clinicians would ultimately have to learn to identify and alter multiple different risk trajectories.

In the current issue of *JAACAP*, Smith *et al.*[3] test whether there are multiple neurodevelopmental trajectories that result in elevated symptoms of anxiety during adolescence. Anxiety disorders are the most common form of psychiatric illness in children,[4] and children with anxiety disorders are more likely than their peers to develop a range of additional psychiatric illnesses as adults, including depression and substance use disorders.[5,6] Thus, studies of aberrant trajectories that result in increased levels of anxiety during adolescence have broad applicability, because similar trajectories may manifest as different disorders later in life. One well-established neurodevelopmental trajectory to increased symptoms of anxiety in adolescence begins with high temperamental behavioral inhibition (BI) in the first few years of life. BI is characterized by high reactivity and distress to novel stimuli,[7] and longitudinal studies indicate that high BI is one of the most potent known risk factors for developing an anxiety disorder later in life.[8] Not all children with high BI go on to develop anxiety disorders, however; children with high BI who also have altered response to errors, increased attention to threat, and decreased cognitive control later in childhood appear to be at especially high risk.[9] Conversely, young children with low BI may also develop symptoms of anxiety in adolescence, although it is not known whether the neurodevelopmental trajectory to anxiety in adolescence is the same for children with high versus low BI in early childhood.

Smith *et al.*[3] tested whether the neurodevelopmental trajectory for high anxiety during adolescence varies depending on degree of BI in the first few years of life. To address this issue, Smith *et al.* examined brain activity in response to making an error in three different groups of children from two different longitudinal cohorts. Children from the first cohort had been assessed for BI at ages 2 and 3 years and were divided into those at ages 12 to 15 years who had low BI (n = 28) and high BI (n = 27) during early childhood. Children from the second cohort (n = 78) had not been assessed during early childhood, but these individuals were seeking treatment for anxiety between the ages of 8 and 18 years. Smith *et al.* compared brain response to error versus correct trials on the Eriksen Flanker Task among the three groups and related error-related activity to symptoms of anxiety. The main result was that the relation between anxiety and brain response to error varied across the three groups. For example, among adolescents with high BI during early childhood, lower ventromedial prefrontal cortex (vmPFC) activity following errors was associated with increased anxiety, whereas among adolescents with low BI during early childhood, higher vmPFC activity following errors was associated with increased anxiety. Among treatment-seeking adolescents, there was no relation between error-related activity in the vmPFC and anxiety.

These data provide intriguing evidence that the neurodevelopmental trajectory that results in high levels of anxiety differs among adolescents who had low BI in early childhood, adolescents who had high BI during early childhood, and treatment-seeking adolescents. Although the evidence from

this study is compelling, certain limitations leave open the possibility for other explanations of the observed results. These limitations are inherent to longitudinal studies of modest sample size and underscore the need for larger, more comprehensive longitudinal studies. The most notable limitation was that the current levels of anxiety differed among the three groups, and the level was much higher in the treatment-seeking group. Moreover, the level of anxiety symptoms in the children who had been assessed for BI was in the normative range, with few children in the clinical range. It is not clear whether the findings related to early childhood BI trajectories would extend to adolescents with anxiety in the clinical range. Related to this issue, the comparison of the cohort that had been ascertained in early childhood to the treatment-seeking cohort is complicated by potential cohort effects such as local environment, recruitment strategies, and bias based on children signing up for a research study versus seeking clinical treatment. In part related to this issue, the age range of the children in the two different cohorts was not the same. Each of these issues could contribute to the observed differences in the relation between error processing and anxiety in the BI versus treatment-seeking cohorts.

Even in light of these modest limitations, however, this study is important because it is one of the first to indicate that different brain mechanisms may be involved in the expression of anxiety during adolescence based on prior history. More fundamentally, this study provides some of the first evidence for equifinality in anxiety symptoms in adolescents and is consistent with work supporting equifinality in other symptom domains.[2] The most important next steps are to devise longitudinal studies that are powered to track trajectories in a single cohort, rather than relying on comparing multiple cohorts. Because emerging evidence indicates that trajectories may start in infancy,[10] studies should start at the time of birth, or even during the mother's pregnancy. Sample sizes would need to be large enough (at least several hundred) so that a sufficient number of children have clinically significant anxiety in adolescence. Finally, such longitudinal studies must track as many cognitive, emotional, social, and brain-based measures as possible in order to understand the trajectories and interactions of relevant constructs.

Such early-starting, comprehensive, longitudinal studies would provide a better ability to predict risk for anxiety and to intervene in a person-centered manner. We could then test for deviations from the norm in multidimensional trajectories that are known to result in anxiety. Interventions could be tailored that specifically correct one or several abnormal trajectories into a normative trajectory. These interventions could include neurostimulation, brain training techniques such as attention bias modification, parent training, or psychotherapy. This research strategy could help to usher in real personalized medicine for psychiatry.

The current study by Smith *et al.*[3] provides some of the first and best evidence that there are multiple different trajectories that can result in the same symptoms of anxiety in adolescence. It is now time to design definitive studies to address this issue and to leverage these different trajectories to devise person-centered treatments.

Accepted September 5, 2019.

Dr. Sylvester is with Washington University School of Medicine, St. Louis, Missouri.

This research was supported by the National Institutes of Health (grant K23MH109983), the Parker Fund, and the Taylor Institute.

Disclosure: Dr. Sylvester has reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Chad M. Sylvester, MD, PhD, Washington University School of Medicine, 660 S Euclid Avenue, St. Louis, MO; e-mail: chad.sylvester@wustl.edu

https://doi.org/10.1016/j.jaac.2019.09.030

REFERENCES

1. Pine DS. Research review: a neuroscience framework for pediatric anxiety disorders. J Child Psychol Psychiatry Allied Discip. 2007;48:631-648.
2. Beauchaine TP, Constantino JN, Hayden EP. Psychiatry and developmental psychopathology: unifying themes and future directions. Compr Psychiatry. 2018;87:143-152.
3. Smith AR, White LK, Leibenluft E, *et al.* The heterogeneity of anxious phenotypes: neural responses to errors in treatment-seeking anxious and behaviorally inhibited youths. J Am Acad Adolesc Child Psychiatry. 2020;59:759-769.
4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593-602.
5. Kessler RC, Avenevoli S, McLaughlin KA, *et al.* Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). Psychol Med. 2012;42:1997-2010.
6. Glantz MD, Anthony JC, Berglund PA, *et al.* Mental disorders as risk factors for later substance dependence: estimates of optimal prevention and treatment benefits. Psychol Med. 2009;39:1365-1377.
7. Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM. Behavioral inhibition: linking biology and behavior within a developmental framework. Annu Rev Psychol. 2005;56:235-262.
8. Clauss JA, JU Blackford. Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. J Am Acad Child Adolesc Psychiatry. 2012;51:1066-1075.
9. Henderson HA, Pine DS, Fox NA. Behavioral inhibition and developmental risk: a dual-processing perspective. Neuropsychopharmacology. 2015;40:207-224.
10. Sylvester CM, Smyser CD, Smyser T, *et al.* Cortical functional connectivity evident after birth and behavioral inhibition at age two years. Am J Psychiatry. 2018;175:180-187.