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EDITORIAL

Understanding gene × early adversity interactions: possibilities for insight in the biology of psychiatric disorders

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Adverse events occurring early in life have consistently been shown to strongly increase the risk for psychiatric disorders, including mood and anxiety disorders but also psychoses and personality disorders. The more severe forms of early adverse life events, such as childhood maltreatment, sexual or emotional abuse or physical and emotional neglect in childhood, have been associated with the highest rates of increased risk. However, other forms of early adverse experiences, such as parental loss, bullying, or low socioeconomic status in childhood, were also shown to increase risk for a number of psychiatric disorders [1].

Next to genetic predisposition, and for many disorders even to a greater extent, adverse life events are the strongest predisposing factors for psychiatric diseases. Understanding how such environmental factors moderate risk is, therefore, an important step in better understanding psychiatric pathology. A series of studies have shown that exposure to adverse life events, especially when occurring in childhood, can lead to lasting biological changes that impact the function of several key systems. Brain imaging studies have reported lasting structural changes in adults exposed to childhood trauma in a number of brain regions [2]. These changes appear to be more or less specific to the type of experienced adversity. Structural changes in areas relevant for emotion processing, such as the hippocampus, are seen with maltreatment but not neglect. Thinning of the visual cortex has been reported with witnessing domestic violence and thinning of the sensory cortical area for genitalia with sexual abuse [2]. These structural changes, especially the ones specific to a certain type of adversity, may be adaptive in the face of expected future adversity and seem to extend to all individuals exposed to adversity and not dependent on the development of psychopathology per se. In addition to changes in brain structure and function, lasting changes in the endocrine stress axis as well as the immune response have been reported following exposure to early adversity. These changes may not only be linked to an increased risk for psychiatric disorders but also for metabolic and cardiovascular disease [3]. To which extent specific types of adversity are linked to differential effects on the endocrine or immune system are less well studied.

While a large body of evidence shows the association of early adversity with an increased risk for psychopathology in general, the differential effects of the types of exposure on their neurobiological consequences described above suggest that there could also be differential effects on risk for specific diagnostic categories, comorbidity or other clinical features. Ferrer et al. [4], for example, report that physical abuse in childhood is associated with the persistence of attention deficit hyperactivity disorder (ADHD) into adulthood, while emotional or sexual abuse tracks with the later development of borderline personality disorder (BPD) or comorbid BPD-ADHD. The authors note that this lends "supports to the possibility that a specific type of traumatic event could increase the risk for the consolidation of a concrete psychiatric disorder in the trajectory from childhood to adulthood of vulnerable subjects." Exposure to early adversity has also been linked to developing more severe, chronic, and treatment resistant psychiatric disease. Here again, specific kinds of adversity may have more or less impact on these different trajectories. In a

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large longitudinal study, Angst et al. [5] reported that while sexual trauma was unrelated to developing chronicity of unipolar depression or bipolar disorder, experiencing childhood family problems increased the risk of chronicity by a factor of 1.7.

In addition to different types of adversity, timing of exposure during different developmental periods may also be an important factor for differential disease risk. This could be mediated by differential vulnerability of certain systems during developmental periods [6]. The increasing availability of large longitudinal cohorts with prospective assessment of adversity will allow a better understanding of the impact of these time windows.

A series of epidemiological but also molecular genetic studies indicate that risk conveyed by early adversity is likely moderated by genetic factors. Interestingly, the same gene × environment interactions (G×E) are often associated with increased risk for a number of psychiatric diagnoses. For examples, an interaction between a functional polymorphism in a gene encoding a co-chaperone of the glucocorticoid receptor, *FKBP5*, has been shown to interact with exposure to child abuse to predict mood disorders, post-traumatic stress disorder, aggression as well as psychoses [7–9]. This would suggest that some genetic variants modify overall risk for psychiatric disorders conveyed by exposure to early adversity independent of the diagnosis.

Large studies with detailed measures of type and timing of adversity as well as outcomes will be needed to dissect how different genetic factors contribute to altering risk for psychopathology overall or for a specific disorder or symptom domain. These studies could also aid in identifying which molecular pathways contribute to common or distinct risk.

So far, the vast majority of gene × early adversity studies have been focusing on selected candidate genes, often fraught with methological problems including insufficient power. It is, however, clear that risk for psychopathology will be moderated by a large number of genetic factors, each with small individual effects [10]. Aggregating this risk using polygenic risk scores in gene × environment interaction studies is one possible approach to better reflect the likely genetic structure of such interactions.

The use of such polygenic risk scores in G×E will allow to address a number of interesting questions. These include whether a global polygenic risk for a certain psychiatric disorder would interact similarly or differentially with specific environmental risk factors. Polygenic scores can also be used to address more focused questions by investigating scores related to certain molecular pathways. The possibilities of functional sub-setting of these risk scores are increasing with the ever-growing functional annotation of the genome and genetic polymorphisms in specific tissues and under specific challenge conditions. Large projects, such as PsychENCODE (https://www.nimhgenetics.org/available_data/psychencode/), will be instrumental for this endeavor.

In addition to a fine-tuned genetic analysis, a more detailed characterization of the environment is needed. Both negative as well as positive environments need to be considered and recorded. Especially, positive environmental factors are often not assessed. However, for many genetic risk factors, a differential susceptibility hypothesis has been postulated, so that the alleles conferring risk in negative environment are those with increased benefit in positive environments. In addition, individual-level as well as group-level environments need to be considered. For the latter, new tools using big data analysis will allow more objective assessments, such as geo-coding of the neighborhood.

Setting up longitudinal cohorts with both detailed genetic as well as environmental data over time will be critical for a better understanding of the pathogenesis of psychiatric disorders. Adding measures of intermediate phenotypes will further increase the possibilities of biological insight and allow to better formulate causal hypotheses that can then be tested. Wearable devices are increasingly robust at not only providing actigraphy data but also information on sleep quality, heart rate variability, and other autonomic nervous systems measures. Devices that would allow to measure parameters in blood using non-invasive photo-absorption technologies are being developed for medical use. In the future, recordings that can now only be obtained in face-to-face visits at a research laboratory may then be possible in the field, even without the need of research personnel. Finally, such devices also allow to record online measures of symptoms during different times of the day in the home environment as well to perform neuropsychological assessments in different situations.

Paired with our increasing knowledge about the function of genetic variants in specific tissues or cells on transcriptional but also epigenetic read-outs, these approaches offer unprecedented possibilities in the dissection of gene × early adversity interaction in psychiatry and for uncovering the pathomechanisms underlying these disorders.

References

1. Kessler RC et al (2010) Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br J Psychiatry 197(5):378–385
2. Teicher MH, Samson JA (2016) Annual research review: enduring neurobiological effects of childhood abuse and neglect. J Child Psychol Psychiatry 57(3):241–266
3. Danese A et al (2007) Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA 104(4):1319–1324

4. Danese A, McEwen BS (2012) Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav 106(1):29–39
5. Nanni V, Uher R, Danese A (2012) Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry 169(2):141–151
6. Angst J et al (2011) Childhood adversity and chronicity of mood disorders. Eur Arch Psychiatry Clin Neurosci 261(1):21–27
7. Zannas AS, Binder EB (2014) Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. Genes Brain Behav 13(1):25–37
8. Mihaljevic M et al (2016) The emerging role of the FKBP5 gene polymorphisms in vulnerability-stress model of schizophrenia: further evidence from a Serbian population. Eur Arch Psychiatry Clin Neurosci. doi:10.1007/s00406-016-0720-7
9. Martin-Blanco A et al (2016) The role of hypothalamus-pituitary-adrenal genes and childhood trauma in borderline personality disorder. Eur Arch Psychiatry Clin Neurosci 266(4):307–316
10. Halldorsdottir T, Binder EB (2017) Gene × environment interactions: from molecular mechanisms to behavior. Annu Rev Psychol 68:215–241