Biological Psychiatry: CNNI

Commentary

Identifying the Long-term Brain Changes Associated With Childhood Trauma Exposure Using Data-Driven Machine Learning Techniques

Yann Quidé

Exposure to childhood trauma, often reported as repeated emotional, physical, and/or sexual abuse, is a form of chronic stress that is deleterious to neurodevelopment. It is a well-established risk factor for the development of mental disorders (e.g., anxiety, mood, psychotic, or posttraumatic stress disorders) (1), is reported in more than 50% of individuals seeking mental health assistance in adulthood (2), and is a significant contributor to the phenotypic heterogeneity observed within and between many psychiatric diagnoses. Many studies have sought to identify the neural correlates of childhood trauma exposure in psychiatric and nonpsychiatric populations (3), but findings have been inconsistent. These discrepancies may reflect a variety of confounding factors, including the type of analyses (e.g., whole brain vs. regions of interest; group differences vs. symptom severity), clinical status, medication intake, type of trauma, or time elapsed since trauma exposure. Therefore, large, cross-disorder studies accounting for some of these factors are needed to better characterize the long-term neural signature(s) of childhood trauma exposure.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Clausen *et al.* (4) aimed to identify the changes in gray matter volume of brain regions that could predict the severity of childhood trauma exposure. Using elastic net regularization, a data-driven machine learning approach at the whole-brain level (including all cortical and subcortical regions of interest from FreeSurfer segmentation), Clausen *et al.* (4) built predictive models of childhood trauma severity for individuals with and without current psychopathology. Within a relatively large community-based cohort of 577 participants, the overall severity of childhood trauma exposure was higher in individuals with varying levels of psychopathology (n = 301), compared with those who did not have any psychopathology (n = 276). In this context, Clausen *et al.* (4) were able to predict the severity of childhood trauma reported by participants according to patterns of gray matter volume in brain networks critical for emotional processing and integration of self-related information (the cingulate cortex, superior and inferior frontal gyri, and insula) or involved in processing reward values and in decision making (the orbital gyrus, caudate, and pallidum), after accounting for current psychopathology and other critical confounding factors.

These findings represent an important step in the identification of the neurobiological correlates of childhood trauma exposure that are common to both clinical cases and healthy (resilient) individuals. Morphological changes in networks of brain regions involved in emotion processing/regulation, interoception, and decision-making/reward processing have been previously reported in the context of trauma research (independently of clinical status) (3) and in the context of studies of diagnostic categories when trauma history (5) was not accounted for. Clausen *et al.* (4) provide evidence for a wider impact of childhood trauma exposure on brain development than previous findings from theory-driven analyses of specific regions of interest (e.g., the amygdala, hippocampus, and prefrontal cortex). Morphological changes in these regions have been associated with a range of other factors and may therefore represent the accumulation of several environmental factors over time that are related to trauma (trauma exposure, time elapsed since exposure) or not (socioeconomic status), as well as clinical factors including the diagnosis of a psychiatric disorder, the length of the illness, or medication intake. As alterations in these stress-sensitive regions did not predict the severity of childhood trauma in the study by Clausen *et al.* (4), they may represent a combination of these confounding factors rather than being specific to trauma exposure alone. To confirm this, future studies accounting for these factors are needed.

Consistent with previous reports of aberrant insula function in anxiety disorders with reported aberrant interoception (6), especially posttraumatic stress disorder (7), the severity of childhood trauma exposure was predicted by changes in insula volume. Similarly, decreased gray matter volume of the cerebellum also predicted the severity of childhood trauma exposure. The last decade of research has provided strong evidence for the involvement of the cerebellum in higher cognitive, social cognitive, and emotional processes (8). Consistent with recent evidence for early cerebellar dysfunctions during emotional processing associated with posttraumatic stress symptoms in survivors of sexual assaults (9), it is possible that changes in cerebellar structure/function may originate early after trauma exposure and persist and/or worsen during brain development. Although Clausen *et al.* (4) have helped unravel transdiagnostic neural correlates of childhood trauma exposure, future large multimodal studies (including structural and functional brain imaging) are required to confirm these hypotheses.

These results also have critical consequences for existing clinical practices by supporting the use of cost-effective approaches centered on unresolved childhood trauma (e.g., eye movement desensitization and reprocessing or trauma-focused cognitive and behavioral therapies) to

SEE CORRESPONDING ARTICLE ON PAGE 734

  https://doi.org/10.1016/j.bpsc.2019.06.005
Biological Psychiatry: Cognitive Neuroscience and Neuroimaging August 2019; 4:686–687 www.sobp.org/BPCNNI ISSN: 2451-9022

complement the usual treatments. These therapeutic approaches are particularly relevant because they have been associated with a normalization of symptoms and morphology/function of the brain regions identified in this study (10). This may be critical to assist reducing the social and economic burdens associated with unresolved childhood trauma.

Although representing a new step forward in our understanding of the long-term neural consequences of childhood trauma, Clausen *et al.* (4) note several limitations. First, the cross-sectional design of the study could not determine if these effects were a direct consequence of childhood trauma exposure or if they were triggered by childhood trauma exposure and persist during development. This is especially critical for populations that are at genetic risk of developing various psychopathologies. Large longitudinal studies with initial data ascertainment conducted as soon as possible after trauma exposure will be able to characterize the gene by environment interactions and their associated neurobiological consequences. These will also unravel the specific developmental time windows during which the brain is particularly sensitive to the effects of trauma exposure.

Second, Clausen *et al.* (4) noted that contrary to prospective research, the use of retrospective reports of childhood trauma, although usually found to be reliable in adult psychiatric populations, may introduce biases, mostly owing to the time elapsed since trauma exposure. Within this time, populations exposed to early trauma are more likely to develop at-risk behaviors and to be exposed to additional severe adverse life events that would significantly contribute to the exacerbation of these trauma-related changes. In individuals who have developed severe psychiatric conditions, the length of illness and their exposure to medications (often represented by a cocktail of different agents, including antidepressants, antipsychotics, and/or mood stabilizers) may impair recall of the severity of these traumatic events over time.

Another limitation includes the use of a composite score to estimate the total severity of childhood trauma exposure. Although it helps to generalize the total severity of childhood trauma exposure experienced among individuals, especially when trauma subtypes are highly intercorrelated, it prevents the characterization of the effects of specific trauma subtypes (e.g., sexual abuse). The development of large-scale, transdiagnostic databases like the one built by the Laureate Institute for Brain Research is necessary and critical to identify individuals who are experiencing significant levels of specific trauma subtypes. Finally, while conferring increased statistical power, this large study was an aggregate of different cohorts from one single site. Although most assessments, including the assessment of childhood trauma exposure, were common across the cohorts, several potential moderators were different. This has limited the investigation of further interactions with other environmental factors known to impact brain development, such as socioeconomic status or levels of intelligence.

Despite these limitations, Clausen *et al.* (4) offer new perspectives on the use of data-driven techniques to determine the long-term neural alterations associated with childhood trauma. Additional therapeutic approaches for unresolved childhood trauma to treatment as usual may offer alternative approaches in normalizing trauma-related aberrant cognitive and emotional processes. Future large longitudinal and multimodal studies are necessary to confirm these findings and to unravel the mechanisms that facilitate interactions between childhood trauma exposure and genetic risk factors in the development of psychiatric disorders.

Acknowledgments and Disclosures

I thank Oliver J. Watkeys and Melissa J. Green for proofreading this commentary.

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

Article Information

From the School of Psychiatry, University of New South Wales (UNSW), Sydney, and Neuroscience Research Australia, Randwick, New South Wales, Australia.

Address correspondence to Yann Quidé, Ph.D., School of Psychiatry, University of New South Wales (UNSW), Sydney, NSW 2052, Australia; E-mail: y.quide@unsw.edu.au; yannquide@gmail.com.

Received Jun 13, 2019; accepted Jun 13, 2019.

References

1. Lewis SJ, Arseneault L, Caspi A, Fisher HL, Matthews T, Moffitt TE, *et al.* (2019): The epidemiology of trauma and post-traumatic stress disorder in a representative cohort of young people in England and Wales. Lancet Psychiatry 6:247–256.
2. Rossiter A, Byrne F, Wota AP, Nisar Z, Ofuafor T, Murray I, *et al.* (2015): Childhood trauma levels in individuals attending adult mental health services: An evaluation of clinical records and structured measurement of childhood trauma. Child Abuse Negl 44:36–45.
3. Teicher MH, Samson JA, Anderson CM, Ohashi K (2016): The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 17:652–666.
4. Clausen AN, Aupperle RL, Yeh H-W, Waller D, Payne J, Kuplicki R, *et al.* (2019): Machine learning analysis of the relationships between gray matter volume and childhood trauma in a transdiagnostic community-based sample. Biol Psychiatry Cogn Neurosci Neuroimaging 4:734–742.
5. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, *et al.* (2015): Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72:305–315.
6. Khalsa SS, Adolphs R, Cameron OG, Critchley HD, Davenport PW, Feinstein JS, *et al.* (2018): Interoception and mental health: A roadmap. Biol Psychiatry Cogn Neurosci Neuroimaging 3:501–513.
7. Wang T, Liu J, Zhang J, Zhan W, Li L, Wu M, *et al.* (2016): Altered resting-state functional activity in posttraumatic stress disorder: A quantitative meta-analysis. Sci Rep 6:27131.
8. Guell X, Gabrieli JDE, Schmahmann JD (2018): Triple representation of language, working memory, social and emotion processing in the cerebellum: Convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. Neuroimage 172:437–449.
9. Quidé Y, Cléry H, Andersson F, Descriaud C, Saint-Martin P, Barantin L, *et al.* (2018): Neurocognitive, emotional and neuroendocrine correlates of exposure to sexual assault in women. J Psychiatry Neurosci 43:318–326.
10. Quidé Y, Witteveen AB, El-Hage W, Veltman DJ, Olff M (2012): Differences between effects of psychological versus pharmacological treatments on functional and morphological brain alterations in anxiety disorders and major depressive disorder: A systematic review. Neurosci Biobehav Rev 36:626–644.