EDITORIAL

The Double-Hit Effect of Childhood Maltreatment on Drug Relapse

Sonia J. Lupien, PhD

Three individuals with a substance use disorder enter an inpatient 12-step program in a community mental health center and for the first month of the program, all 3 individuals are abstinent. They are then discharged from inpatient treatment and return for face-to-face follow-up interviews at 14, 30, and 90 days postdischarge. At the latest postdischarge measure, it is observed that 1 individual did not relapse, while the other 2 relapsed at day 35. The first relapsing individual took drug of choice from day 35 to day 42 (7-day relapse), while the second individual took drug of choice from day 35 to day 90 (55-day relapse), thus showing greater severity of drug relapse than the first individual. In this issue of *JAMA Psychiatry*, Van Dam and colleagues[1] showed that what predicted relapse in the 2 individuals was exposure to childhood maltreatment, while what predicted the severity of drug relapse in these individuals were childhood maltreatment-related reductions in specific limbic regions of the brain.

Related article

To my knowledge, the study by Van Dam and colleagues[1] is the first to assess the unique and shared influence of childhood maltreatment and substance use disorder on gray matter volume (GMV) of the brain as assessed by voxel-based morphometry. In this study, they found that childhood maltreatment was specifically associated with lower GMV in the left hippocampus, parahippocampus, and anterior fusiform gyrus, while substance use disorder was uniquely associated with lower GMV in the thalamus, midcingulate gyrus, motor area, and cingulate gyrus. Interestingly, childhood maltreatment and substance use disorder did not interact to predict significant clusters in GMV, showing distinct effects of childhood maltreatment and substance use disorder on brain morphology. More importantly, it was shown that while childhood maltreatment prospectively predicted a shorter time of relapse to any drug, GMV reductions associated with childhood maltreatment predicted the severity of drug relapse.

This study showed that the first hit of childhood maltreatment is on brain morphology so that exposure to maltreatment in early life leads to lower GMV in the hippocampal regions and fusiform gyrus when measured during adulthood. This finding confirms previous results on the effects of childhood maltreatment on adult brain regions, particularly the hippocampal regions,[2] an effect that has been referred to as *limbic scars* by the group of Dannlowski and colleagues.[3] Thus, exposure to childhood maltreatment may set into motion a series of events that lead to a reorganization of synaptic development in the brain. However, the timing of these effects remains largely unknown. In the present study, decreased GMV in limbic regions was observed in adults who retrospectively reported greater childhood maltreatment as measured by the Childhood Trauma Questionnaire. In this regard, it is important to note that different effects of exposure to childhood maltreatment have been reported on the volume of the hippocampus in children and adults. Hence, smaller hippocampal volumes have been reported in adults retrospectively reporting childhood abuse (as in the present study),[4,5] while no differences in hippocampal volumes were observed in children exposed to maltreatment.[6-8] The contrasting effects of early adversity on hippocampal volumes in children and adults suggest that the effects of adversity on the hippocampus may not be readily apparent until adolescence or adulthood,[9] reflecting the presence of an incubation period for the effects of childhood maltreatment on hippocampal/limbic regions in humans. Interestingly, it is during adolescence that initiation of drug use/abuse occurs. Thus, it could be possible that the limbic regions shown to be responsive to childhood maltreatment also confer greater vulnerability to initiation of drug use/abuse during adolescence. Further studies assessing these brain regions in adolescents who initiate drug use/abuse or not should provide important data on this issue.

The results of this study also showed that the second hit of childhood maltreatment is on drug relapse severity through childhood maltreatment changes in brain morphology. Here, the authors have shown that the brain regions associated with childhood maltreatment are a significant predictor of relapse severity as assessed by days of use during the relapse period. The temporality of these effects is very interesting. In a first phase, exposure to childhood maltreatment could lead to changes in brain morphology across development. In a second phase, these changes in brain morphology could confer greater vulnerability to drug relapse severity later in adulthood.

Interestingly, the limbic regions associated with relapse severity in the study by Van Dam and colleagues[1] are the same that are involved in the physiological stress response. Stress activates the hypothalamic-pituitary-adrenal axis, leading to secretion of glucocorticoids. Various studies performed in both animals and humans have shown that chronic exposure to stress hormones from the prenatal period to aging impacts limbic regions (and particularly the hippocampal regions) involved in cognition and mental health.[10] Specific effects on the brain, behavior, and cognition emerge as a function of the timing and the duration of exposure to stress, and some of these effects depend on interaction between genes and exposure to environmental adversity. Studies in human children exposed to severe deprivation (eg, orphanages and institutions), neglect, and abuse

(childhood maltreatment) report lower basal levels of glucocorticoids, a finding that is similar to what has been observed in primates (see article by Gunnar and Donzella[11]). One mechanism that has been invoked to explain the development of hypocortisolism is downregulation of the hypothalamic-pituitary-adrenal axis at the level of the pituitary in response to chronic corticotropin-releasing hormone drive from the hypothalamus,[12] while a second mechanism that has been invoked is target tissue supersensitivity to glucocorticoids.[13]

Importantly, this hypocortisolism in humans in response to childhood maltreatment may not be permanent: studies in infants in foster care have shown that training foster parents to provide sensitive and supportive care of foster care children results in normalization of basal glucocorticoid levels in the children after only 10 weeks of parent training.[14] This is important information along with the findings of a study showing that exposure to early abuse during childhood is significantly associated with epigenetic regulation of the glucocorticoid receptor in the postmortem brains of suicide victims.[15]

Consequently, there is good news coming out of the results reported by Van Dam and colleagues.[1] The fact that the brain may be highly responsive to environmental conditions during early development opens the door to new avenues of research assessing the impact of early interventions on the pattern of brain development during childhood. In children facing childhood maltreatment, forms of environmental enrichment, such as support from a family member, enriched daycare/school environment, or social support from members of the community, could induce a reorganization of synaptic development, programming of neurotrophic factors, or changes in gene expression that could lead to resilience later in life and to lower probability of drug initiation and/or abuse and/or relapse. If this is the case, then it may be that any type of intervention performed during the early years could have a tremendous effect in preventing the deleterious effects of drug abuse through changes in brain organization responsive to environmental factors.

ARTICLE INFORMATION

Author Affiliations: Centre de Recherche, Institut Universitaire en Santé Mentale de Montréal, Montréal, Quebec, Canada; Department of Psychiatry, University of Montréal, Montréal, Quebec, Canada.

Corresponding Author: Sonia J. Lupien, PhD, Centre de Recherche, Institut Universitaire en Santé Mentale de Montréal, 7401 rue Hochelaga, Montréal, Quebec H1N 3M5, Canada (sonia.lupien@umontreal.ca).

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REFERENCES

1. Van Dam NT, Rando K, Potenza MN, Tuit K, Sinha R. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume [published online June 11, 2014]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2014.680.

2. Teicher MH, Anderson CM, Polcari A. Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proc Natl Acad Sci U S A*. 2012;109(9):563-572.

3. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry*. 2012;71(4):286-293.

4. Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med*. 1997;27(4):951-959.

5. Vythilingam M, Heim C, Newport J, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry*. 2002;159(12):2072-2080.

6. De Bellis MD, Keshavan MS, Clark DB, et al. AE Bennett Research Award: developmental traumatology, part II: brain development. *Biol Psychiatry*. 1999;45(10):1271-1284.

7. De Bellis MD, Hall J, Boring AM, Frustaci K, Moritz G. A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry*. 2001;50(4):305-309.

8. Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus*. 2008;18(8):729-736.

9. Tottenham N, Sheridan MA. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci*. 2009;3:68.

10. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009;10(6):434-445.

11. Gunnar MR, Donzella B. Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology*. 2002;27(1-2):199-220.

12. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology*. 2005;30(10):1010-1016.

13. Yehuda R, Yang RK, Buchsbaum MS, Golier JA. Alterations in cortisol negative feedback inhibition as examined using the ACTH response to cortisol administration in PTSD. *Psychoneuroendocrinology*. 2006;31(4):447-451.

14. Gunnar MR, Quevedo KM. Early care experiences and HPA axis regulation in children: a mechanism for later trauma vulnerability. *Prog Brain Res*. 2008;167:137-149.

15. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci*. 2009;12(3):342-348.