Early-Life Adversity, Suicide Risk and Epigenetics of Trauma

César A. Alfonso and Thomas G. Schulze

1 Introduction

Suicide results from an interaction of biological and environmental factors. This chapter summarizes five decades of research dedicated to understanding the neurobiology of suicide, including distinct neurochemical and neuroendocrine pathways, genetics, epigenetics, and the relationship between trauma, specifically early life adverse events and adult retraumatization, and suicidality. Understanding the neurobiology of suicide, in particular gene-environment interactions, could be relevant in the clinical assessment of suicide risk and prevention. The authors are aware that there are no studies examining the neurobiology of suicide by self-immolation. However, general findings from suicide research may prove relevant in the care of persons at risk for self-immolation, in particular persons in low-and-middle income countries who experienced adverse early life events and women experiencing the intergenerational transmission of trauma.

C. A. Alfonso (✉)
World Psychiatric Association Psychotherapy Section, Geneva, Switzerland

Columbia University Medical Center, New York, NY, USA

Universitas Indonesia, Jakarta, Indonesia

National University of Malaysia, Kuala Lumpur, Malaysia
e-mail: cesaralfonso@mac.com, caa2105@cumc.columbia.edu

T. G. Schulze
World Psychiatric Association Secretary for Scientific Sections, Geneva, Switzerland

Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU, Munich, Germany

Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA
e-mail: thomas.schulze@med.uni-muenchen.de

C. A. Alfonso et al. (eds.), *Suicide by Self-Immolation*,
https://doi.org/10.1007/978-3-030-62613-6_12

Since one-third to one-half of suicides are genetically mediated [1] and about 50% of the risk for suicide attempts is heritable [2], understanding the neurobiology and pathophysiology of suicide is of essence to clinical practitioners caring for individuals with depressive and trauma and stressor-related disorders at risk for self-immolation.

2 Neurobiology of Suicide

This chapter section will first review correlates of neurochemistry and neurotransmission with heightened suicide. We will summarize study findings of neuropathological changes in brains of those who died by suicide, including MRI and functional imaging studies of persons with suicidal behavior. We will then examine the correlation of inflammatory biomarkers and lipid levels with suicide, and lastly, review the association of neuroendocrine changes in the hypothalamic-pituitary-adrenal (HPA) axis with impulsivity, aggression and suicide.

2.1 Neurotransmitters and Suicide

Studies looking at the association between serotonin neurotransmission and suicide date back to the 1970s. Low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (HIAA) in the cerebrospinal (CSF) fluid correlates with suicidal behavior [3], and also with extreme violence and fire setting [4]. Furthermore, low CSF 5-HIAA levels are predictive of future death by suicide [5].

Decreased activity in the brainstem serotonin pathways correlates with suicide, a finding that seems to be transdiagnostic [6]. The prefrontal cortex in persons who suicide shows a decrease in pre-synaptic serotonin transporter binding on nerve terminals and increases in post-synaptic serotonin$_{1A}$ and serotonin$_{2A}$ receptors [7, 8]. Using quantitative autoradiography to study post-mortem brains of over 200 patients, Underwood [9] and colleagues found that childhood trauma affects the serotonin system and contributes to a higher suicide risk in persons who experienced adverse childhood events who later develop major depression and alcoholism.

While the role of the serotonin system positively relates to suicidal behaviors, studies of other neurotransmitter pathways such as the dopaminergic system yield inconclusive findings. Studies of the noradrenergic system, similarly, show conflicting results while searching with specific biomarkers or correlates of suicide [10]. Low 3-methoxy-4-hydroxy-phenylglycol (MHPG) levels in the CSF of persons with major depression seem to correlate with lethality of suicidal behavior [2].

Increased glutamate signaling between cells in the brain is associated with suicide, with decreased expression of glutamate transporters by astrocytes in the locus

Table 1 Brain structural changes of suicidal patients documented by MRI studies[a]

Affected area of the brain	Clinical disorder
Subcortical grey matter hyperintensities	Major depression [12]
Periventricular white matter hyperintensities	Major depression [13]
Lower volume of bilateral orbitofrontal cortex	Major depression [14]
Lower volume of right amygdala	Major depression [14]
Smaller putamen	Major depression [15]
Smaller posterior third of corpus callosum	Major depression [16]
Smaller bilateral globus pallidus	Adjustment disorder [17]
Smaller right caudate	Adjustment disorder [17]

[a]Adapted from van Heeringen and Mann [2]

coeruleus and upregulated expression of N-methyl-D-aspartate (NMDA) receptors. Suicidal persons have measurably increased levels of quinolinic acid in the CSF, suggesting a connection between inflammation and glutamatergic pathways [11].

2.2 *Structural and Functional Changes in the Brain and Suicide*

Imaging studies are able to measure brain structural and functional changes in suicidal persons. Table 1 summarizes study findings of brain structural changes seen in magnetic resonance imaging (MRI) of suicidal persons.

Functional Positron Emission Tomography (PET) neuroimaging study findings show that prefrontal localized hypofunction is proportional to the lethality of suicide attempts [18]. Also, there is decreased connectivity between the anterior cingulate and posterior insula, and increased connectivity in the striatal motor-sensory network [2]. Brain areas generally involved in depressive disorders and suicide include the brainstem monoaminergic system, prefrontal cortex, anterior cingulate cortex, amygdala and hippocampus [11].

2.3 *Inflammatory Biomarkers and Suicide*

There is a well-established relationship between inflammation and depression, and emerging research findings suggest the same with suicidal behavior. Reduction in the density and soma size of astrocytes and oligodendrocytes in the subgenual anterior cingulate cortex and amygdala seem to correlate with suicidal behavior [19]. Astrocytes, as other glial cells, have a key role in modulating immunity and inflammatory processes. Low level inflammation altering glial cell functioning occurs in depressed and suicidal persons in the white matter of the prefrontal cortex and dorsal anterior cingulate cortex.

Pro-inflammatory cytokines, such as tumor necrosis factor, interleukin-6 (IL-6), IL-2, IL-8 and IL-1β, are inflammatory markers associated with depressive disorders. Higher levels of IL-6 and lower levels of IL-2 seem to correlate with suicidality. Other potential biomarkers for suicide include increased CSF levels of quinolinic acid and kynurenic acid [11].

2.4 Lipids and Suicidal Behavior

While some studies show an association between hypocholesterolemia and suicide [20], other investigators found no correlation [21, 22]. It could be that total serum cholesterol is not a precise or consistent biomarker for suicidal behavior, while CSF and brain measurements are more reliable. Moreover, there is some evidence that cholesterol may influence neurotransmitter signaling and that polyunsaturated fatty acids impact DNA methylation, therefore mediating gene-environment interactions that could result in suicidal behavior [11].

2.5 HPA Axis Dysregulation in Suicide, Impulsivity and Aggression

The hypothalamic-pituitary-adrenal (HPA) axis is the neuroendocrine system that intermediates our reactions to environmental stress. A blunted cortisol response in the dexamethasone suppression test significantly correlates with major depression but equivocally with suicidal behavior. Suicidal persons have elevated levels of cortisol in the urine and CSF, and these measurements are predictive of death by suicide [23]. As will be clarified later, life adversity may trigger DNA methylation and other epigenetic mechanisms causing HPA axis abnormalities as a possible pathway in the pathophysiology of suicide. Additionally, the HPA axis plays a role in impulsivity and aggression, and investigators that used a standardized laboratory social stress paradigm showed that stress responsivity differs in subtypes of suicidal individuals. Those who are highly impulsive and aggressive show a consistent hyperactive cortisol response [24].

3 Familial History of Suicide and Heightened Risk

An important risk factor for suicide is a family history of suicide, and all clinicians should ask patients at risk pertinent questions about family members who died by suicide or had known psychiatric illness with comorbid suicidal behavior. Those

with a family history of suicide have twice the risk of suicide after controlling for family psychiatric history [1].

Consensual validation among clinicians and researchers suggest that when there is a positive family history of suicide heightened risk results from a combination of factors, including modeling and imitation, contagion, the transmission of an impulsive aggression phenotype, early child rearing styles and concomitant environmental stressors, and a shared genetic makeup and biological predisposition [25, 26].

Although close to 50% of the familial transmission of suicide could be attributed to genes, predisposing factors for suicide include the familial transmission of impulsivity, aggression and the intergenerational transmission of trauma [26]. Epigenetic changes triggered by life stressors during critical and sensitive periods of development may alter gene expression, at least partially explaining how familial suicides heighten risk in future generations.

4 Early Life Trauma and Health Outcomes

Research studies of large population samples during the late 1990s found a definitive association between negative life experiences in childhood and poor health outcomes in adulthood [27]. The original ACE (adverse childhood experiences) studies in the United States coded *emotional, physical, and sexual abuse, witnessing domestic violence, and witnessing drug use* as traumatic life experiences. As expected, ACE correlate with adult mental health disturbances such as depressive disorders, anxiety disorders, and drug dependence. A surprising finding from the earlier studies was the additional association with obesity, hypersexuality and sleep disturbance. Later studies found that ACE correlate with PTSD, and increase prevalence of stroke, heart disease, HIV infection and other sexually transmitted diseases, and suicide. [27–30].

Data from 2015–2017 from 27/50 states in the United States based on clinical interviews of close to 150,000 subjects, and follow up systematic reviews and meta-analysis [28–30] found that:

- 2/3 Adults experienced at least one type of ACE traumatic event.
- 1/6 Adults experienced four or more types of trauma.
- Adults with the highest level of ACE exposure have higher prevalence of chronic health conditions and die younger.
- ACE increases the risk of harmful use of alcohol by a factor of 1.9
- ACE increases the risk of anxiety disorders by a factor of 2.5
- ACE increases the risk of major depression by a factor of 2.7
- ACE increases the risk of harmful use of illicit drugs by a factor of 3.5
- ACE increases the risk of PTSD by a factor of 4.4
- ACE correlates with poverty, lower educational attainment, lack of health insurance, and unemployment.
- ACE increases the risk of suicide and violence.

Although these study findings are clinically intuitive, an important contribution to the way mental health workers and caregivers conceptualize trauma is that the cumulative effect of trauma seems to be more important than the qualitative effect. Another important finding that informed research in epigenetics is that there is a sensitive period of development and traumatic experiences during this period may have a lasting impact on the brain, affecting the pathogenesis of illness.

Katz and colleagues [31] propose that psychodynamic and biopsychosocial formulations should incorporate the concept of allostasis as a way to understand the link between traumatic life events and negative health outcomes. Allostasis is defined as maintaining homeostasis through changes in the environment over time. Dysregulation of allostasis, referred to as *allostatic overload*, represents the physiological erosion caused by stressors on the brain circuitry involved in the stress response, or the multisystem response to stress. *Allostatic overload* could be mediated by epigenetic, inflammatory and neuroendocrine changes triggered by environmental factors that include traumatic life experiences. [31, 32].

Physiological alterations and structural changes caused by chronic stressors include neuronal loss in the hippocampus, development of atherosclerotic plaques, left ventricular hypertrophy, increased oxidative stress, and a prolonged inflammatory response. Currently, biomarkers such as cortisol, dehydroepiandrosterone, aldosterone, interleukin-6, tumor necrosis factor-alpha, c-reactive protein, insulin-like growth factor-1, high density lipoprotein, low density lipoprotein, total cholesterol, glycosylated hemoglobin, creatinine, variations in blood pressure and heart rate measurements, waist to hip ratio and body mass index are being assessed to create algorithms in order to quantify *allostatic overload* and an allostatic composite score. The allostatic composite score may provide an assessment of inflammatory, neuroendocrine and immune function when faced with adversity to be able to objectively measure the health protective effects of psychosocial interventions. [31, 32].

5 Trauma and Suicide

ACE and a chaotic early family environment increase suicide risk. It is important for clinicians when working with suicidal patients to identify the following early life adverse events as risk factors for suicide [33], especially when in combination with psychiatric symptoms, recent stressors and retraumatization:

- History of death of a parent
- Emotional abuse
- Physical abuse
- Sexual abuse
- Witnessing family violence
- Witnessing use of substances in the household
- Relocation and changing homes
- Separation from caregivers

A functional imaging study of suicidal individuals [34] found hypoconnectivity in the frontoparietal network of the brain in persons with major depressive disorder with a history of childhood trauma. The study investigators proposed that the scar of trauma is reflected in functional dysconnectivity decades after the occurrence of trauma. [34].

It is important to realize that early life adversity and adult retraumatization may or may not cause posttraumatic stress disorder (PTSD). Nevertheless, traumatic life experiences during the vulnerable period of development in early childhood cause long-lasting biological changes that affect coping skills when faced with stressors later in life. ACE increase suicide risk, even if diagnostic criteria for PTSD are not met. Subsyndromal or subthreshold PTSD carries significant morbidity, which includes heightened risk for suicide [35].

6 Gene-Environment Interactions and Epigenetics of Suicide

The relationship between early trauma and the pathogenesis of suicide is multifactorial, including allostatic overload, inflammatory changes, the body's response to stress mediated by HPA axis shifts, and epigenetic changes.

Epigenetic changes result in the alteration of gene activity without changes in DNA nucleotide sequence or structure. These changes can be triggered by the environment, hence the proposed paradigm of gene-by-environment interactions as a new way to reframe the biopsychosocial model of health and illness [36]. Epigenetic changes are triggered by toxins, pollutants, bacteria, viruses, radiation exposure, nutritional changes, hormonal exposure, changes *in utero,* and psychosocial stressors. Trauma, in particular during the sensitive period of brain development, may trigger enduring epigenetic changes.

Studies show that epigenetics may be an important underlying mechanism for all neuroscience and behavior [37]. Epigenetic processes occur through different means, including *DNA methylation*, *histone modifications* and non-coding *RNA interference* and silencing [38]. Of these, DNA methylation—the addition of methyl groups to cytosines in the DNA sequence—is the most widely studied epigenetic mechanism. DNA methylation can alter gene expression, a process by which gene by environment interactions could affect biological responses. Epigenetic changes may be permanent, reversible, and are heritable by offspring, perhaps explaining the intergenerational transmission of trauma. Additionally, study findings suggest that epigenetics plays an important role in the neurobiology and pathogenesis of suicide. [9, 10, 23].

While the heritability of suicide remains unclear, epigenetic mechanisms may regulate gene expression in suicidal behavior [39]. Table 2 summarizes study findings of epigenetic mechanisms associated with suicide.

The interactions between acute trauma, enduring stressors, emotions, hormonal and peptide surges, up and down regulation of receptors and neurotransmission cause epigenetic changes in the brain with associated changes in endocrine and

Table 2 Epigenetic mechanisms in suicide

DNA methylation
Ribosomal RNA promoter hypermethylation in the hippocampus [40]
Hypermethylation in the HTR2A promoter region in the frontal lobe [41]
Hypermethylation of the BDNF promoter (exon IV) in the Wernicke area [42]
Hypermethylation in the promoter region of GABAA receptor subunit alpha 1 in the frontal cortex [43]
Histone modification
H3K27 (Histone 3 Lysine 27) hypermethylation and decreased TrkB.T1 (Tropomyosin- related kinase B) expression in the orbitofrontal cortex [44]
Increased levels of H3K4me3 (transcriptional active chromatin biomarker) in the promoter region upregulating the activity of OAZ1 (ornithine decarboxylase antizyme 1) [45]
RNA interference
Increase in Hsa-miR-185 expression in the frontal cortex [46]

immune systems and inflammatory response. It is clinically important to recognize that although epigenetic changes may remain stable through life, they may be altered and reversible trough psychotherapy, psychosocial and environmental interventions.

There seems to be a sensitive period of development where epigenetic changes occur and "adversity leaves behind biological memories that persistently alter genome function and increase susceptibility to illnesses". [47] The effect of adversity on DNA methylation depends primarily on the developmental timing of exposure to traumatic events. Exposure in very early childhood is associated with widespread epigenetic changes. If exposure to adverse events occurs in middle childhood changes in DNA methylation can be detected when there is severe sexual or physical abuse, but not consistently for other types of trauma [47].

A systematic review by Jiménez and colleagues from the Universidad de Chile and Luyten and colleagues from the University College of London [48] found that a variety of psychosocial interventions reverse epigenetic changes that correlate with psychopathology and suicide risk. These include brief manualized interventions such as prolonged exposure therapy for PTSD, cognitive behavioral therapy for anxiety disorders, cognitive behavioral therapy in combination with medication for depressive disorders, and dialectical behavioral therapy for borderline personality disorder. Psychotherapies serve to recalibrate the individual's sensitivity to the social environment. Further studies are needed to clarify if the biological changes achieved with these brief interventions endure through time and to compare study results with psychotherapeutic interventions of longer duration.

7 Conclusion

The neurobiology and pathogenesis of suicide is complex and involves multiple neurotransmitter systems (serotonergic, noradrenergic, dopaminergic, glutamatergic) and different regions of the brain (brainstem, prefrontal cortex, anterior

cingulate cortex, amygdala and hippocampus). Although there are no clinically practical biomarkers of suicide that could be presently used for screening patients at risk, research is underway testing the sensitivity and specificity of levels of pro-inflammatory cytokines, quinolinic acid and kynurenic acid, among others, to assess their potential use in suicide screening and prevention.

Gene-environment interactions and epigenetic processes may mediate heightened risk of suicide in vulnerable populations. Even though there are no studies to date looking at the neurobiology of suicide by self-immolation, it is plausible that factors such as the intergenerational transmission of trauma, early life adversity and violent retraumatization during young adulthood could cause epigenetic changes that place individuals at suicide risk. Nevertheless, research on epigenetics and suicide, although seemingly promising, is in its infancy. Sample sizes for the studies reviewed in this chapter are quite small, and while the combination of study results clearly show a pattern, they still do not constitute hard evidence and findings need to be replicated in larger cohorts and diverse settings before asserting correlation and causality.

There is some data showing that psychosocial interventions, including brief psychotherapy interventions, could reverse epigenetic changes associated major depression, PTSD and stressor related disorders, decreasing suicide risk. Since these disorders are present in most persons who self-immolate, brief psychotherapies, an integral part of suicide prevention strategies, could have long lasting benefits.

References

1. Joiner TE, Brown JS, Wingate LR. The psychology and neurobiology of suicidal behavior. Annu Rev Psychol. 2005;56:287–314.
2. Van Heeringen K, Mann JJ. The neurobiology of suicide. Lancet Psychiatry. 2014;1(1):63–72. https://doi.org/10.1016/S2215-0366(14)70220-2.
3. Asberg M, Traskman L, Thoren P. 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch Gen Psychiatry. 1976;33:1193–7.
4. Virkkunen M, Rawlings R, Tokola R, Poland RE. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Arch Gen Psychiatry. 1994;51:20–7.
5. Mann JJ, Malone KM, Sweeney JA, et al. Attempted suicide characteristics and cerebrospinal fluid amine metabolites in depressed inpatient. Neuropsychopharmacology. 1996;15:576–86.
6. Mann JJ, Arango V, Marzuk PM, et al. Evidence for the 5-HT hypothesis of suicide: a review of post-mortem studies. Br J Psychiatry. 1989;155:7–14.
7. Arango V, Underwood M, Mann JJ. Biological alterations in the brainstem of suicides. In: Mann JJ, editor. Suicide, psychiatric clinics of North America. Philadelphia: WB Saunders; 1997.
8. Underwood MD, Mann JJ, Arango V. Serotonergic and noradrenergic neurobiology of alcoholic suicide. Alcohol Clin Exp Res. 2004;28:57s–69s.
9. Underwood MD, Kassir SA, Bakalian MJ, Galfalvy H, Dwork AJ, Mann JJ, Arango V. Serotonin receptors and suicide, major depression, alcohol use disorder and reported early life adversity. Transl Psychiatry. 2018;8:279.
10. Currier M, Mann JJ. Stress, genes and the biology of suicidal behavior. Psychiatr Clin North Am. 2008;31(2):247–69. https://doi.org/10.1016/j.psc.2008.01.005.

11. Lutz PE, Mechawar N, Turecki G. Neuropathology of suicide: recent findings and future directions. Mol Psychiatry. 2017;22:1395–412.
12. Ehrlich S, Breeze JL, Hesdorff er DC, et al. White matter hyperintensities and their association with suicidality in depressed young adults. J Affect Disord. 2005;86:281–7.
13. Pompili M, Innamorati M, Mann JJ, et al. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2008;32:1501–7.
14. Monkul ES, Hatch JP, Nicoletti MA, et al. Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. Mol Psychiatry. 2007;12:360–6.
15. Dombrovski AY, Siegle GJ, Szanto K, Clark L, Reynolds CF, Aizenstein H. The temptation of suicide: striatal gray matter, discounting of delayed rewards, and suicide attempts in late-life depression. Psychol Med. 2012;42:1203–15.
16. Cyprien F, Courtet P, Malafosse A, et al. Suicidal behavior is associated with reduced corpus callosum area. Biol Psychiatry. 2011;70:320–6.
17. Vang FJ, Ryding E, Trskman-Bendz L, van Westen D, Lindstrom MB. Size of basal ganglia in suicide attempters, and its association with temperament and serotonin transporter density. Psychiatry Res. 2010;183:177–9.
18. Oquendo MA, Placidi GP, Malone KM, et al. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. Arch Gen Psychiatry. 2003;60:14–22.
19. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res. 2008;42:151–7.
20. Wu S, Ding Y, Wu F, Xie G, Hou J, Mao P. Serum lipid levels and suicidality: a meta-analysis of 65 epidemiological studies. J Psychiatry Neurosci. 2016;41:56–69.
21. Deisenhammer EA, Kramer-Reinstadler K, Liensberger D, Kemmler G, Hinterhuber H, Fleischhacker WW. No evidence for an association between serum cholesterol and the course of depression and suicidality. Psychiatry Res. 2004;121:253–61.
22. Roy A, Roy M. No relationship between serum cholesterol and suicidal ideation and depression in African American diabetics. Arch Suicide Res. 2006;10:11–4.
23. Mann JJ. Neurobiology of suicidal behavior. Nat Rev Neurosci. 2003;4:819–28.
24. Stanley B, Michel CA, Galfalvy HC, Kelp JG, Rizk MM, Richardson-Vejlgaard R, Oquendo MA, Mann JJ. Suicidal subtypes, stress responsivity and impulsive aggression. Psychiatry Res. 2019;280:112486. https://doi.org/10.1016/j.psychres.2019.112486.
25. Mann JJ. A current perspective of suicide and attempted suicide. Ann Intern Med. 2002;136:302–11.
26. Brent DA, Melhem N. Familial Transmission of Suicidal Behavior. Psychiatr Clin North Am. 2008;31(2):157–77.
27. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ACE) study. Am J Prev Med. 1998;14:245–58.
28. Merrick MT, Ford DC, Ports KA, et al. Vital signs: estimated Proportion of Adult Health Problems Attributable to Adverse Childhood Experiences and Implications for Prevention—25 States, 2015–2017. MMWR Morb Mortal Wkly Rep. 2019;68:999–1005.
29. Slopen N, Koenen KC, Kubzansky LD. Cumulative adversity in childhood and emergent risk factors for long-term health. J Pediatr. 2014;164:631–8.
30. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017;2:e356–66.
31. Katz DA, Sprang G, Cooke C. The cost of chronic stress in childhood: understanding and applying the concept of allostatic load. Psychodyn Psychiatry. 2012;40(3):469–80.
32. Alfonso CA, Friedman RC, Downey JI. Advances in psychodynamic psychiatry. New York: Guilford Press; 2018.

33. Lagomasino IT, Stern TA. The suicidal patient. In: MGH guide to primary care psychiatry. New York: McGraw-Hill; 2004.
34. Yu M, Linna KA, Shinohara RT, Oathes DJ, Cook PA, Duprata R, Mooree TM, Oquendo MA, Phillips ML, McInnis M, Fava M, Trivedi MH, McGrath P, Parseyk R, Weissman MM, Sheline YI. Childhood trauma history is linked to abnormal brain connectivity in major depression. PNAS. 2019;116(17):8582–90.
35. Marshall RD, Olfson M, Hellman F, Blanco C, Guardiano M, Struering EL. Comorbidity, impairment, and suicidality in subthreshold PTSD. Am J Psychiatry. 2001;158:1467–73.
36. Plakun EM. What psychotherapists should understand about DNA methylation. J Psychiatr Pract. 2019;25(3):212–4.
37. Chambers J. The neurobiology of attachment: from infancy to clinical outcomes. Psychodyn Psychiatr. 2017;45(4):542–63.
38. Labonte B, Turecki G. The epigenetics of suicide: explaining the biological effects of early life environmental adversity. Archiv Suicide Res. 2010;14:291–310.
39. Bani-Fatemi A, Howe S, De Luca V. Epigenetic studies of suicidal behavior. Neurocase. 2015;21(2):134–43. https://doi.org/10.1080/13554794.2013.826679.
40. McGowan PO, Sasaki A, Huang TC, Unterberger A, Suderman M, Ernst C, Szyf M. Promoter wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. PLoS One. 2008;3(5):e2085.
41. Abdolmaleky HM, Yaqubi S, Papageorgis P, Lambert AW, Ozturk S, Sivaraman V, Thiagalingam S. Epigenetic dysregulation of 5-HTR2A in the brain of patients with schizophrenia and bipolar disorder. Schizophr Res. 2011;129(2–3):183–90.
42. Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V, Chiariotti L. Increased BDNF promoter methylation in the Wernicke area of suicide subjects. Archiv Gen Psychiatr. 2010;67(3):258–67.
43. Poulter MO, et al. GABAA receptor promoter hypermethylation in suicide brain: implications for the involvement of epigenetic processes. Biol Psychiatry. 2008;64(8):645–52.
44. Ernst C, Chen ES, Turecki G. Histone methylation and decreased expression of TrkB.T1 in orbital frontal cortex of suicide completers. Molecul Psychiatr. 2009;14(9):830–2.
45. Fiori LM, Turecki G. Genetic and epigenetic influences on expression of spermine synthase and spermine oxidase in suicide completers. Int J Neuropsychopharmacol. 2010;13(6):725–36.
46. Maussion G, Yang J, Yerko V, Barker P, Mechawar N, Ernst C, Turecki G. Regulation of a truncated form of tropomyosin-related kinase B (TrkB) by Hsa-miR-185* in frontal cortex of suicide completers. PLoS One. 2012;7(6):e39301.
47. Dunn EC, et al. Sensitive periods for the effect of childhood adversity on DNA methylation: results from a prospective, longitudinal study. Biol Psychiatry. 2019;85:838–49.
48. Jiménez JP, Botto A, Herrera L, Leighton C, Rossi JL, Quevedo Y, Luyten P. Psychotherapy and genetic neuroscience: an emerging dialog. Front Genet. 2018;9(257):1–19.