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Epigenetic impact of the social and physical environment on brain and body

Bruce S. McEwen*, Karen Bulloch

Laboratory of Neuroendocrinology and Neuroimmunology and Inflammation Program The Rockefeller University, 1230 York Ave, New York, N.Y. 10065, United States of America

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ABSTRACT

Modern biomedical scientists are often trapped in silos of knowledge and practice, such as those who study brain structure, function and behavior, on the one hand, and body systems and disorders, on the other. Scientists and physicians in each of those silos have not often paid attention to the brain-body communication that leads to multi-morbidity of systemic and brain-related disorders [eg. depression with diabetes or cardiovascular disease]. Outside of biomedicine, social scientists have long recognized the impact of the social and physical environment on individuals and populations but have not usually connected these effects with changes in underlying biology. However, with the rise of epigenetics, science and the public understanding of science is leaving an era in which the DNA sequence was thought to be "destiny" and entering an era where the environment shapes the biology and behavior of individuals and groups through its interactive effects on brain and body. It does so, at least in part, by shaping epigenetically the structure and function of brain and body systems that show a considerable amount of adaptive plasticity throughout development and adult life. This results in substantial individual differences even between identical twins. These individual differences are produced epigenetically by the two-way interaction between the brain and hormones, immune system mediators and the autonomic nervous system. Disorders, then, are often multimorbid involving both brain and body, such as depression with diabetes and cardiovascular disease. It is therefore imperative to incorporate into "precision medicine" a better understanding of how these differences affect the efficacy of pharmacological, behavioral and psychosocial interventions. This article presents an overview of this new synthesis, using as an example emerging evidence about the linkages between systemic inflammation, insulin resistance and mental health and neurodegenerative diseases.

1. Introduction

Modern biomedical science is divided into silos of knowledge and practice, not only due to the growing amount of information in each siloed domain but also to the conceptual frameworks through which we each look at the world. Brain and body disorders are often considered separately without recognizing their frequent comorbidity. Moreover, the avalanche of new information within each silo requires periodic, if not continuous, updating as new knowledge emerges and makes us too busy to explore outside our silo. Furthermore, social scientists have long recognized the impact of psychosocial factors on individuals and populations but have not usually connected these effects with changes in underlying biology. This may happen because of the misunderstanding that "biology is destiny" and determined primarily by our genes. However, with the rise of epigenetics, we are leaving an era in which the DNA sequence that was supposed to "tell us all" about who we are and our vulnerabilities and strengths. Rather than a conflict we now know that there is a seamless process of genes interacting with environment (G x E, aka "epigenetics"). Indeed, the social as well as physical environment have a huge epigenetic impact on our brains and bodies.

The concept of "embodiment" [1] in sociology first recognized this, while the rise of "precision medicine" has largely overlooked the importance of psychosocial factors by using, instead, a highly reductionistic focus on understanding how genetic factors influence the response to pharmacological agents that are then supposed to more precisely and individually treat human illness [2]. This has been detrimental to individualized patient care and now is a good time to factor in psychocial factors and personal history to more effectively treat diseases.

Now that we know that the brain is capable of a considerable amount of adaptive plasticity throughout development and adult life that it shaped by experiences, the notion of embodiment begins to connect to the epigenetic view of biology that involves continuous G x E interactions, as will be elaborated below. Moreover, there is increasing recognition of the two-way interaction between the brain regulating and responding to circulating metabolic and steroid hormones, immune system mediators and the autonomic nervous system. And,

*Corresponding author.
E-mail address: mcewen@rockefeller.edu (B.S. McEwen).

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with the emergence of epigenetics, the psychosocial perspective of embodiment [1], which occurs in large part through the brain, takes "center stage" in thinking how daily experiences "get under the skin" over the life course and affect physical as well as mental health.

This is even more important now with recognition of the impact of preconception modifications of germ cells, as well as prenatal and early postnatal life experiences leading to an epigenetic life course development model [3]. This model makes us aware of the continuous influence of factors and experiences that determine the trajectory of the life course. This includes the critical importance of the formation of a positive and secure attachment between mother and child and the devastating effects of early life abuse and neglect as well as the impact of poverty [4,5]. Furthermore, experientially-regulated gene expression is a "one way street" and we cannot "turn back the clock" and truly reverse changes as the life course proceeds; rather, we can change the trajectory in a better or worse direction [6]. Moreover, because of the continuous reciprocal influences between the brain and body, we are also aware of "multimorbidity" of disorders in which mental and physical health problems co-exist [7].

This article presents an overview of this new synthesis, using as an example emerging evidence about the linkages between systemic and brain inflammation, insulin resistance and diabetes, and mental health and neurodegenerative disease.

2. Epigenetics: old and new meaning

Catalyzing this new outlook, the emerging science of G x E interactions, referred to now as "epigenetics", helps us understand the mechanisms of brain-body interactions and the plasticity and vulnerability of the brain. This means not only the influence of physical factors such as heat and cold and pollution but also the powerful effect of psychosocial interactions throughout the life course [3]. "Epigenetics" originally meant the emergence of developmentally-programmed characteristics as a fertilized egg develops into a living organism characteristic of that species [8]. But the characteristics of each individual are influenced by experiences, and that is where the modern use of "epigenetics" comes from. An example of this is a pair of identical twins with genes that predispose them to schizophrenia or bipolar illness; yet, the probability of both twins getting the disease is only in the range of 40–60%. This leaves plenty of room for experiences and other environmental factors to either prevent of precipitate the disorder. As an indicator of this, the methylation patterns of DNA diverge as identical twins grow older [9]. Thus, "epigenetics" now means "above the genome", that is, not changing the genetic code; it replaces and makes unnecessary the old question: "which is more important, genes or environment?"

There are multiple "epigenetic" mechanisms that are beyond the scope of this article. For example, the CpG methylation of DNA is now a well-known form of epigenetic modification [10]. And there are other mechanisms that include histone modifications that repress or activate chromatin unfolding [11] and the actions of non-coding RNA's [12], as well as transposons and retrotransposons involving rearrangement of genes within a chromosome [13] and the process of RNA editing [14,15].

3. Brain as repository of lived experiences that embed memories and change architecture

We now know that the brain is the repository of "lived experiences" over the life course. Our capacity for recording experiences begins prenatally and continues over the life course, with a cumulative impact on physical and mental health [1,16]. Our demonstration of stress-induced remodeling of dendrites in hippocampal CA3 neurons was one of many prior and subsequent discoveries that provided a neuroanatomical mechanism that helped to explain behavioral effects of stress on memory and related processes [17]. The resulting cascade of investigations in stress neurobiology have had increasing relevance to human mental and physical health [18–20]. Adaptive plasticity is the capacity of the adult as well as developing brain for remodeling of dendrites, turnover of synapses and limited adult neurogenesis that was first suggested by the enriched environment studies on brain cortex thickness [21,22] based on the work of Donald Hebb [23]. For stress-induced remodeling, glucocorticoids, excitatory amino acids and other cellular mediators are involved [24,25]. Yet, from the work of Robert Sapolsky we also know that permanent damage to the hippocampus and other brain structures is also mediated by glucocorticoids together with excitatory amino acids [26–28]. Thus there is an inverted U shaped dose-response curve in which physiological levels of glucocorticoids and excitatory amino acids operate synergistically and beneficially to alter neuronal connectivity; but higher levels and prolonged activity of these same mediators, such as that occurring in stroke, seizures and head trauma, cause permanent damage and neuron loss via a pathophysiological synergy between glutamate and glucocorticoids [27,29,30]. Severe and prolonged stress can cause structural and functional brain changes that, while not permanent damage, nevertheless require external intervention with pharmacological or behavioral therapies to get the brain "unstuck".

4. Brain-body interactions

Furthermore, long regarded as separate from the body except for autonomic regulation and neuroendocrine function, the brain is now recognized as having many reciprocal interactions with systemic physiology [31]. Through hormones and other circulating mediators, systemic physiology can affect many aspects of normal cognitive and neurological function by modifying neural structure and function; By directly affecting the brain, systemic physiology contributes to the co-morbidity of brain-based and systemic disorders, such as depression with cardiovascular disease and diabetes. Moreover, the affected brain regions, in turn, influence the activity of those same mediators. Exosomes [32] that are released by brain and other organs are emerging and potential hormone-like signaling mediators between body and brain,

The concepts embodied in "allostasis" and "allostatic load" and overload emphasize that the same systems that help the body and brain adapt to experiences also contribute to pathophysiology when the same mediators are overused or dysregulated among themselves [33]. Moreover, health promoting and health damaging behaviors that often accompany stressful experiences and, more generally, living in stressful social and physical environments all contribute to allostatic load and overload [34].

5. The impact of the social environment

The increase in perceived "stress" in modern life provides examples that manifest themselves in different ways depending on income and education, as summarized in two publications by the MacArthur Research Network on Socioeconomic Status [http://www.macses.ucsf.edu]. Health damaging behaviors occurring within an impoverished and stressful environment contribute heavily to the allostatic load that develops, along with multiple negative environmental factors such as noise, pollution, lack of green space, crowding, neighborhood crime and violence, food deserts, lack of transportation, and poor schools [3]. Steeper income gradients in a city, state or nation have a negative influence epigenetically on health and lifespan [35,36]. Positive influences include community groups that facilitate social support, promote healthy behaviors and encourage participation for positive change, along with safe and attractive neighborhoods, access to health, affordable food and public transportation.

6. Early life experiences and transgenerational Influences

Early life abuse and neglect as well as growing up in and living in poverty have numerous epigenetic effects, as has become evident in

both animal models and studies on human development. Based on the pioneering work of Levine and Denenberg on "neonatal handling" of infant rats [37], Michael Meaney has led the way in demonstrating the important role of postnatal maternal care in emotional and cognitive development. That is, infant rats raised with a nurturing mother are less fearful and explore novelty. In contrast, pups raised with an anxious mother providing inconsistent care shows the opposite outcome [38]. This is called "epigenetic transgenerational behavioral transmission" [39–41]. Indeed, chaos in the nest has negative effects on the offspring development as does chaos in the home [42,43].

Yet, even before conception as well as during life in the womb, paternal and maternal obesity can affect the child, possibly involving "epigenetic" changes of the DNA of the sperm and egg that do not alter the genetic code per se, but, rather, how it is read [44,45].. Prenatally and before conception, bariatric surgery is reported to alter epigenetic "signatures" in germ cells and also improve the in utero environment to reduce the propensity for metabolic disorders in post-natal life [44,45]. This would also likely reduce other comorbid disorders of mental, behavioral and physical health.

Adverse early life experience in infancy and childhood involving poverty, abuse and neglect, affect how genes are expressed and determine how well brain and body develop and function during childhood into young adulthood. Indeed, the brain is continually changing with experiences, creating memories and alerting brain architecture via mechanisms that are facilitated in part by circulating sex, stress and metabolic hormones and chemicals produced by the immune system, with effects on the rest of the body along with the nervous system [25]. While it is impossible to "roll back the clock" and truly "reverse" the effects of experiences, positive or negative, the epigenetic life course perspective points to opportunities for changing by psychosocial interventions the trajectory of the life course during windows of opportunity such as adolescence and other life transitions [3] [6]. There are no "magic bullets" like penicillin that revolutionized treatment of infectious disease for treating the complex, multi-morbid psychosocially influenced disorders of modern life [46]. Indeed, "magic bullets" do not in any way describe the imperfect effects of antidepressants or drugs, like statins, that may help but do not "cure" those diseases [3].

7. Neuroimmune mechanisms over the life course

Systemic and brain inflammation are features of most diseases such as diabetes, cardiovascular disease, arthritis, cancer and Alzheimer's disease. The mechanisms that underlie this involve diverse immune-related cells that generate pro- and anti-inflammatory cytokines. In the brain, microglia are primarily responsible for inflammation that increases with aging [47]. The microglia show many of the properties ascribed to dendritic cells, including antigen presentation [48], and can be aroused to express these characteristics following interferon gamma administration [49] and viral infection [50]. Modulation of normal microglial function involves the action of the RNA editing enzyme APOBEC1 [51], whereby the genetic deletion of this enzyme leads microglia to develop an inflammatory tone that over the lifespan of the animal results in progressive age-related signs of neurodegeneration, characterized by clustering of activated MG, aberrant myelination, increased inflammation, and lysosomal anomalies that culminate in behavioral and motor deficiencies [52]. Thus genetic dysregulation of inflammation in the brain takes a toll on neurological and behavioral functions, and the determinants of diabetes, depression and dementia are a good example of the interplay between inflammation and the progression of a disorder that affects both body and brain.

8. Inflammation, insulin resistance, depression and dementia

The growing frequency of obesity, Type 2 diabetes, major depression and dementia in our and other societies has led to an increasing understanding of causal linkages among these disorders as well as their linkages to the stressors of modern life [53]. There is growing evidence for a relationship between insulin resistance and risk for cognitive decline and dementia [54,55]. An oxidative stress and inflammatory cascade has been suggested as a pathway from insulin resistance to Alzheimer's pathology [56,57] representing an example of an allostatic overload.

Yet insulin receptors in the hippocampus are not only involved in regulation of glucose uptake [58] but also in signaling for memory and synaptic plasticity [59,60] and in mood regulation, including that related to insulin resistance [61,62]. The connection of the hippocampus to mood regulation also create an opportunity to investigate the actions of antidepressant drugs that are able to ameliorate depressive-like behavior and normalize altered hippocampal architecture, particularly in the ventral hippocampus [63].

There appears to be a common denominator between depression and insulin resistance, namely, acetyl-L-carnitine [LAC] that is able to rapidly ameliorating depressive-like behavior in animal models deficient in LAC because of genetic or stress-induced causes [64]. LAC actions are mediated in part via epigenetic up-regulation of mGlu2 in presynaptic terminals that slows overflow of glutamate and ameliorates the impairment of neural architecture by that excess glutamate produces [65–67]. This was further enhanced by the discovery that connected the LAC story to insulin resistance. The Flinders Sensitive Line [FSL] rat, where LAC deficiency is associated with depressive-like behavior, was found also to show elevated serum insulin, leptin and triglycerides; moreover, LAC supplementation not only reduced the depressive like behavior within 3–5 days, but it also treated the metabolic dysregulation [68]. Current work is exploring In ongoing studies on human MDD to determine whether there is a human counterpart of the FSL rat among people with MDD [69], Consistent with lower LAC in more severe forms of MDD, there is a suggestive association between low LAC levels and childhood trauma in patients with a treatment resistant course of illness [69]. Together with the association between reduced LAC and insulin resistance [IR] in animal models, LAC is potential a biomarker to delineate, diagnose and treat a novel biologically-defined MDD subtype that may associate LAC with insulin resistance.

9. Conclusion: incorporating psychosocial influences into medicine

For meaningful treatment of many disorders, it is urgent to incorporate into "precision medicine" the influence of psychosocial factors over the life course, while recognizing more fully the impact of brain-body interactions for both cause and prevention of multi-morbid disorders. This includes the ubiquitous role of inflammation and epigenetic mechanisms like RNA editing. Programs like the Nurse-Family Partnership [https://www.nursefamilypartnership.org/] promote better parenting; and schools as well as other organizations that provide sanctuary, safety, nutrition and focus foster better mental and physical health [70]. Based on what is known about the multi-morbidity from early life adversity, such interventions are bound to improve health brain and body development and reduce the incidence of systemic and brain-relate disorders, including metabolic disorders and cardiovascular disease.

Where prevention has not occurred, "top down" physiological and behavioral interventions allow the "wisdom of he body" to prevail and open "windows of plasticity" to redirect brain circuit changes. Regular physical activity can alter brain architecture and function and strengthen both prefrontal cortex and hippocampus control of the amygdala [71–74]. Mindfulness based stress reduction [MBSR] as well as meditation are gaining in popularity as a way of reducing anxiety and thus reducing perceived stress, with increasing evidence of changes in the brain [17,75,76]. Given the rapid rise of obesity and Type 2 diabetes already in adolescent youth [77], intervention is imperative to redirect the progression of the allostatic load towards a healthier path through diet and increased physical activity.

Finally, because of the multiple epigenetic psychosocial and physical influences on the individual genetic makeup, it is important to treat each person as an individual rather than assuming that all will respond similarly to a given treatment. The efficacy of pharmacological agents is altered by psychosocial stressors as well as by physical factors like air pollution that increases inflammatory tone in the body [78]. The motivation to engage in any behavioral or other therapy on a regular basis is dependent on the motivation of the individual and their commitment to a positive outcome. This may be impaired by a negative mood as well as by lack of access to facilities where the interventions can occur. Positive social interactions with peers can help overcome these obstacles along with policies of government that create safe environments and green space and reduce air pollution. We also need progressive policies of employers to facilitate involvement in interventions and pursue a healthy lifestyle. Only in this way can the true potential of *individualized precision medicine* be realized.

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Declaration of Competing Interest

None.

References

[1] Krieger N. Embodiment: a conceptual glossary for epidemiology. J Epidemiol Community Health 2005;59:350–5.
[2] Kohane IS. HEALTH CARE POLICY. Ten things we have to do to achieve precision medicine. Science 2015;349:37–8.
[3] Halfon N, Larson K, Lu M, Tullis E, Russ S. Lifecourse health development: past, present and future. Matern Child Health J 2014;18:344–65.
[4] van Rosmalen L, van der Horst FC, van der Veer R. From secure dependency to attachment: Mary Ainsworth's integration of Blatz's security theory into Bowlby's attachment theory. Hist Psychol 2016;19:22–39.
[5] McEwen CA, McEwen B. S.: social structure, adversity, toxic stress, and intergenerational poverty: an early childhood model. Ann Rev Sociol 2017;43:445–72.
[6] Gray JD, Rubin TG, Hunter RG, McEwen BS. Hippocampal gene expression changes underlying stress sensitization and recovery. Mol Psychiatry 2014;19:1171–8.
[7] Tomasdottir MO, Sigurdsson JA, Petursson H, Kirkengen AL, Krokstad S, McEwen B, et al. Self reported childhood difficulties, Adult Multimorbidity and Allostatic Load A Cross-Sectional Analysis of the Norwegian HUNT Study. PLoS One 2015;10:e0130591.
[8] Waddington CH. The epigenotype. Endeavoour 1942;1:18–20.
[9] Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A 2005;102:10604–9.
[10] Szyf M, McGowan P, Meaney MJ. The social environment and the epigenome. Environ Mol Mutagen 2008;49:46–60.
[11] Allfrey VG. Changes in chromosomal proteins at times of gene activation. Fed Proc 1970;29:1447–60.
[12] Mehler MF. Epigenetic principles and mechanisms underlying nervous system functions in health and disease. Prog Neurobiol 2008;86:305–41.
[13] Griffiths BB, Hunter RG. Neuroepigenetics of stress. Neuroscience 2014;275:420–35.
[14] Mehler MF, Mattick JS. Noncoding RNAs and RNA editing in brain development, functional diversification, and neurological disease. Physiol Rev 2007;87:799–823.
[15] Papavasiliou FN, Chung YC, Gagnidze K, Hajdarovic KH, Cole DC, Bulloch K. Epigenetic modulators of Monocytic function: implication for steady state and disease in the CNS. Front Immunol 2015;6:661.
[16] Kirkengen AL. The lived experience of violation: How abused children become unhealthy adults Bucharest. Romania: Zeta Books; 2010.
[17] McEwen BS. Stress-induced remodeling of hippocampal CA3 pyramidal neurons. Brain Res 1645;2016:50–4.
[18] Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 2016;17:652–66.
[19] Chattarji S, Tomar A, Suvrathan A, Ghosh S, Rahman MM. Neighborhood matters: divergent patterns of stress-induced plasticity across the brain. Nat Neurosci 2015;18:1364–75.
[20] McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron 2013;79:16–29.
[21] Bennett E, Diamond M, Krech D, Rosenzweig M. Chemical and anatomical plasticity of brain. Science 1964;146:610–9.
[22] Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. Neurol 1973;41:371–8.
[23] Hebb DO. The organization of behavior; a neuropsychological theory. New York: Wiley; 1949.
[24] McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci 1999;22:105–22.
[25] McEwen BS. Stress, sex, and neural adaptation to a changing environment: mechanisms of neuronal remodeling. Ann N Y Acad Sci 2010;1204(Suppl):E38–59.
[26] Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid Cascade hypothesis. EndocrRev 1986;7:284–301.
[27] Sapolsky R. Stress, the aging brain and the mechanisms of neuron death. Cambridge MIT Press 1992;1:423.
[28] Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nat Rev Neurosci 2012;13:22–37.
[29] Conrad CD, Lupien SJ, McEwen BS. Support for a bimodal role for type II adrenal steroid receptors in spatial memory. Neurobiol of Learning & Memory 1999;72:39–46.
[30] Joels M. Corticosteroid effects in the brain: U-shape it. Trends Pharmacol Sci 2006;27:244–50.
[31] McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007;87:873–904.
[32] Eldh M, Ekstrom K, Valadi H, Sjostrand M, Olsson B, Jernas M, et al. Exosomes communicate protective messages during oxidative stress; possible role of exosomal shuttle RNA. PLoS One 2010;5:e15353.
[33] McEwen BS. Protective and damaging effects of stress mediators. New England JMed 1998;338:171–9.
[34] McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. Dial in Clin Neurosci: Stress 2006;8:367–81.
[35] Marmot M. Social determinants of health inequalities. Lancet 2005;365:1099–104.
[36] Wilkinson RG, Pickett K. The spirit level: Why greater equality makes societies stronger. New York: Bloomsbury Press; 2010.
[37] Levine S, Haltmeyer GC, Karas GG, Denenberg VH. Physiological and behavioral effects of infantile stimulation. Physiology and Behavior 1967;2:55–9.
[38] Tang AC, Reeb-Sutherland BC, Romeo RD, McEwen BS. On the causes of early life experience effects: evaluating the role of mom. Front Neuroendocrinol 2014;35:245–51.
[39] Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science 1999;286:1155–8.
[40] Francis DD, Szegda K, Campbell G, Martin WD, Insel TR. Epigenetic sources of behavioral differences in mice. Nat Neurosci 2003;6:445–6.
[41] Priebe K, Romeo RD, Francis DD, Sisti HM, Mueller A, McEwen BS, et al. Maternal influences on adult stress and anxiety-like behavior in C57BL/6J and BALB/CJ mice: A cross-fostering study. Dev Psychobiol 2005;47:398–407 (Wiley Periodicals, Inc).
[42] Molet J, Maras PM, Avishai-Eliner S, Baram TZ. Naturalistic rodent models of chronic early-life stress. Dev Psychobiol 2014;56:1675–88.
[43] Evans GW, Wachs TD. Chaos and its influence on children's development: An ecological perspective. 1st ed. Washington, DC: American Psychological Association; 2010.
[44] Donkin I, Versteyhe S, Ingerslev LR, Qian K, Mechta M, Nordkap L, et al. Obesity and bariatric surgery drive epigenetic variation of spermatozoa in humans. Cell Metab 2016;23:369–78.
[45] Kral JG, Biron S, Simard S, Hould F-S, Lebel S, Marceau S, et al. Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. Pediatrics 2006;118:1644–9.
[46] Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129–36.
[47] Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K. Microglia derived from aging mice exhibit an altered inflammatory profile. Glia 2007;55:412–24.
[48] D'Agostino PM, Gottfried-Blackmore A, Anandasabapathy N, Bulloch K. Brain dendritic cells: biology and pathology. Acta Neuropathol 2012;124:599–614.
[49] Gottfried-Blackmore A, Kaunzner UW, Idoyaga J, Felger JC, McEwen BS, Bulloch K. Acute in vivo exposure to interferon-g enables resident brain dendritic cells to become effective antigen presenting cells. Proc Natl Acad Sci U S A 2009;106:20918–23.
[50] D'Agostino PM, Kwak C, Vecchiarelli HA, Toth JG, Miller JM, Masheeb Z, et al. Viral-induced encephalitis initiates distinct and functional CD103+ CD11b+ brain dendritic cell populations within the olfactory bulb. Proc Natl Acad Sci U S A 2012;109:6175–80.
[51] Rayon-Estrada V, Harjanto D, Hamilton CE, Berchiche YA, Gantman EC, Sakmar TP, et al. Epitranscriptomic profiling across cell types reveals associations between APOBEC1-mediated RNA editing, gene expression outcomes, and cellular function. Proc Natl Acad Sci U S A 2017;114:13296–301.
[52] Cole DC, Chung Y, Gagnidze K, Hajdarovic KH, Rayon-Estrada V, Harjanto D, et al. Loss of APOBEC1 RNA-editing function in microglia exacerbates age-related CNS pathophysiology. Proc Natl Acad Sci U S A 2017;114:13272–7.
[53] Rasgon NL, McEwen BS. Insulin resistance-a missing link no more. Mol Psychiatry 2016;21:1648–52.
[54] Gold SM, Dziobek I, Sweat V, Tirsi A, Rogers K, Bruehl H, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia 2007;50:711–9.
[55] Convit A. Links between cognitive impairment in insulin resistance: an explanatory model. Neurobiol Aging 2005;26S:S31–5.
[56] Gold PW, Licinio J, Pavlatou MG. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-gamma systems. Mol Psychiatry 2013;18:154–65.
[57] Manolopoulos KN, Klotz LO, Korsten P, Bornstein SR, Barthel A. Linking Alzheimer's disease to insulin resistance: the FoxO response to oxidative stress. Mol Psychiatry 2010;15:1046–52.

[58] Piroli GG, Grillo CA, Reznikov LR, Adams S, McEwen BS, Charron MJ, et al. Corticosterone impairs insulin-stimulated translocation of GLUT4 in the rat hippocampus. Neuroendocrinology 2007;85:71–80.
[59] Winocur G, Greenwood CE, Piroli GG, Grillo CA, Reznikov LR, Reagan LP, et al. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. Behav Neurosci 2005;119:1389–95.
[60] Grillo CA, Piroli GG, Lawrence RC, Wrighten SA, Green AJ, Wilson SP, et al. Hippocampal insulin resistance impairs spatial learning and synaptic plasticity. Diabetes 2015;64:3927–36.
[61] Rasgon N, Lin KW, Lin J, Epel E, Blackburn E. Telomere length as a predictor of response to pioglitazone in patients with unremitted depression: a preliminary study. Transl Psychiatry 2016;6:e709.
[62] Rasgon N, Jarvik L. Insulin resistance, affective disorders, and Alzheimer's disease: review and hypothesis. J Gerontology 2004;59A:178–83.
[63] Kheirbek MA, Hen R. Dorsal vs ventral hippocampal neurogenesis: implications for cognition and mood. Neuropsychopharmacology 2011;36:373–4.
[64] Nasca C, Xenos D, Barone Y, Caruso A, Scaccianoce S, Matrisciano F, et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. Proc Natl Acad Sci U S A 2013;110:4804–9.
[65] Nasca C, Bigio B, Zelli D, Nicoletti F, McEwen BS. Mind the gap: glucocorticoids modulate hippocampal glutamate tone underlying individual differences in stress susceptibility. Mol Psychiatry 2015;20:755–63.
[66] Lau T, Bigio B, Zelli D, McEwen BS, Nasca C. Stress-induced structural plasticity of medial amygdala stellate neurons and rapid prevention by a candidate antidepressant. Mol Psychiatry 2017;22:227–34.
[67] Nasca C, Zelli D, Bigio B, Piccinin S, Scaccianoce S, Nistico R, et al. Stress dynamically regulates behavior and glutamatergic gene expression in hippocampus by opening a window of epigenetic plasticity. Proc Natl Acad Sci U S A 2015;112:14960–5.
[68] Bigio B, Mathe AA, Sousa VC, Zelli D, Svenningsson P, McEwen BS, et al. Epigenetics and energetics in ventral hippocampus mediate rapid antidepressant action: implications for treatment resistance. Proc Natl Acad Sci U S A 2016;113:7906–11.
[69] Nasca C, Bigio B, Lee FS, Young SP, Kautz MM, Albright A, et al. Acetyl-l-carnitine deficiency in patients with major depressive disorder. Proc Natl Acad Sci U S A 2018;115:8627–32.
[70] Abramovitz R, Bloom SL. Creating sanctuary in residential treatment for youth: from the “well-ordered asylum” to a “living-learning environment.” Psychiatry Q 2003;74:119–35.
[71] Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 2011;108:3017–22.
[72] Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Ageing, fitness and neurocognitive function. Nature 1999;400:418–9.
[73] Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006;61:1166–70.
[74] Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A 2004;101:3316–21.
[75] Valk SL, Bernhardt BC, Trautwein FM, Bockler A, Kanske P, Guizard N, et al. Structural plasticity of the social brain: differential change after socio-affective and cognitive mental training. Sci Adv 2017;3:e1700489.
[76] Holzel BK, Carmody J, Evans KC, Hoge EA, Dusek JA, Morgan L, et al. Stress reduction correlates with structural changes in the amygdala. Soc Cogn Affect Neurosci 2010;5:11–7.
[77] Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics 2012;130:e856–64.
[78] Fonken LK, Xu X, Weil ZM, Chen G, Sun Q, Rajagopalan S, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. Mol Psychiatry 2011;16:987–95 [973].