REVIEW ARTICLE

Gene-environment Interactions in Late Life: Linking Psychosocial Stress with Brain Aging

Anthony S. Zannas*

Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Abstract: Gene-environment interactions (GxE) can have lasting consequences on brain structure and function, potentially contributing to diverse neuropsychiatric phenotypes. This has been extensively demonstrated by studies examining GxE in childhood and early adulthood, whereas much fewer studies have addressed this question in late life. The relative paucity of studies examining GxE in late life may stem from the working hypothesis that brains become less malleable to environmental inputs as life progresses. However, while some components of brain plasticity decline with increasing age, others are retained and may even become more pronounced in old ages. Moreover, the micro- and macro-structural brain changes that accrue as a result of aging-related morbidities are likely to accentuate the susceptibility of neural circuits to environmental stressors as life advances. Supporting this hypothesis, psychosocial stress can increase the risk for late-life neuropsychiatric syndromes, especially when afflicting genetically predisposed individuals. This article reviews evidence showing how gene-stress interactions can impact the aging brain and related phenotypes in late life, and it discusses the potential mechanisms underlying such GxE and their implications for the prevention and treatment of late-life neuropsychiatric syndromes.

1. INTRODUCTION

With populations aging worldwide, late-life neuropsychiatric disorders have become among the leading causes of morbidity and mortality [1], having enormous impact on individuals and societies. For example, it is estimated that 44 million individuals live with Alzheimer disease worldwide, and this number is expected to triple by the year 2050 [2]. Likewise, the global cost for dementia has reached $818 billion and is projected to increase to $2 trillion by 2030 [3]. To prepare for these challenges, it is imperative to gain deeper insights into factors and biological processes that influence brain aging in health and disease.

While aging is associated with a decline in several brain functions, the rate of this decline and the aging-related risk for neuropsychiatric syndromes vary substantially across individuals. The mechanisms underlying this inter-individual variability are the subject of intensive research efforts, with studies to date suggesting that aging-related phenotypes can be influenced by a complex interplay among genetic and environmental factors [4-6]. In certain cases, the impact of

genetic factors may be further accentuated in old ages [7, 8], indicating that gene-environment interactions (GxE) could exert cumulative effects on brain function as life advances.

Among GxE determinants of aging-related phenotypes, this article discusses how psychosocial stress may interact with genetic factors to influence brain aging and confer risk for late-life neuropsychiatric sequelae. The article first highlights evidence showing that the brain maintains substantial plasticity and vulnerability to environmental influences, including psychosocial stressors, in late life. As reviewed subsequently, the effects of stress on the aging brain can be magnified or attenuated by a number of genetic variants, and such gene-stress interactions can confer risk for neuropsychiatric syndromes in the elderly. Lastly, the article proposes potential mechanisms and implications of GxE for the prevention and treatment of late-life neuropsychiatric disorders.

2. PLASTICITY AND STRESS VULNERABILITY OF THE AGING BRAIN

2.1. Plasticity of the Aging Brain

It has been long hypothesized that brain plasticity –a term that denotes the capability of the human brain to change in response to environmental demands– declines as life advances. A number of studies addressed this hypothesis by directly comparing old and young adults, showing indeed

*Address correspondence to this author at the Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, Munich, 80804, Germany; Tel: +498930622567; E-mail: aszannas@gmail.com

that aging is associated with a decline in certain components of experience-dependent brain plasticity [9-11] and a concomitant downregulation of molecular mediators of plasticity [12]. Nonetheless, the aging-related decline in brain plasticity is neither linear nor universal. For example, the capability of the aged brain to undergo environment-dependent changes shows substantial inter-individual variability and may in some paradigms be comparable or even more pronounced than the young brain [13, 14]. Furthermore, there is growing evidence that the brain maintains high levels of plasticity in response to environmental exposures, including psychosocial stressors, even in very advanced ages. For example, the white matter microstructure of the aged brain undergoes experience-induced remodeling in response to changes in social activities and learning, and this capability is retained beyond 80 years of age [14, 15]. The aged brain can further undergo regional remodeling in response to environmental encounters; for instance, elderly individuals show lasting changes in hippocampal and amygdalar volumes following exposure to stressful life events (SLEs) in late life [16, 17]. Likewise, lasting changes in functional connectivity and strength of neural responsivity can occur in old individuals undergoing cognitive training [18, 19], and such adaptations parallel improvements in cognitive functioning [18, 20].

Together these findings support the following conclusions: 1) aging is associated with variable and complex changes in brain plasticity that may be individual-, stimulus-, and context-specific; and 2) despite the aging-related decline in some components of brain plasticity, brain structure and function remain malleable to environmental encounters even in very advanced ages.

2.2. Psychosocial Stress and Neuropsychiatric Sequelae in Late Life

The capability of the aging brain to undergo lasting changes in response to environmental demands implies that psychosocial stressors could induce changes –for better or for worse– in brain structure and function. At the same time, the aging-related decline in some components of brain plasticity is thought to hinder the ability of certain brain regions to recover from stress exposure [21]. Consequently, old individuals may be susceptible to the negative influence of excessive or persistent stress occurring throughout the lifespan, potentially exhibiting stress-related increase in their risk for neuropsychiatric sequelae.

Several studies have addressed this hypothesis by examining the impact of stress on late-life neuropsychiatric sequelae, most notably depressive phenotypes and cognitive outcomes. Work examining depressive phenotypes shows that both SLEs and perceived stress are associated with heightened risk for developing late-life depression (LLD) and with poorer LLD prognosis [22-28]. Studies examining cognitive outcomes similarly show that cumulative numbers of SLEs, chronic stress exposure, and higher levels of perceived stress are linked with lower cognitive performance, as well as with increased risk for cognitive decline and dementia in both healthy adults and subjects with mild cognitive impairment (MCI) [29-35]. Some of these effects, however, may only concern specific stressors and selective domains of symp-

toms; for example, spousal loss was only shown to negatively influence executive function but not risk for dementia or other cognitive outcomes in elderly women [36].

Thus stress may negatively influence mood and cognition in the elderly, an observation with important implications for the prevention and treatment of late-life neuropsychiatric disorders. However, stress-related outcomes also exhibit striking variability across individuals [37, 38], and predicting which individuals may be vulnerable or resilient to stress will be a crucial step towards developing individualized prevention and treatment strategies. As discussed in the following section, this inter-individual variability could be conferred by a number of genetic variants that interact with stressors in complex ways, potentially magnifying or attenuating stress-related outcomes.

3. GENE-STRESS INTERACTIONS AND LATE-LIFE NEUROPSYCHIATRIC SYNDROMES

A vast number of studies have shown that neuropsychiatric disorders, like other complex phenotypes, may be shaped through a complex interplay between genetic and environmental factors [39, 40]. This interplay has been in most cases demonstrated through a candidate gene approach, showing that polymorphisms at several genetic loci, such as the genes encoding the serotonin transporter (*SLC6A4*), a protein that transports serotonin from the synaptic cleft back to the presynaptic neuron (for a meta-analysis see [41]), the FK506-binding protein 51 (*FKBP5*) (for a review see [42]), and the corticotropin-releasing hormone receptor 1 (*CRHR1*) [43], may moderate the effects of psychosocial stress on diverse phenotypes. While some of these findings have been accompanied with controversy [44-46], GxE have generally yielded more consistent associations –as compared to genome-wide association studies– with stress-related psychiatric disorders. More recently, gene-environment genome-wide interaction studies have begun to emerge [47, 48], with the potential to discover novel GxE in a less biased manner.

Notably, the majority of GxE studies to date have examined stress exposure and psychiatric phenotypes in childhood and young adulthood, whereas much fewer studies have addressed this question in late life. Given as discussed above that the aging brain remains susceptible to psychosocial stress, examining GxE in the elderly may provide novel insights into the pathogenesis of late-life neuropsychiatric disorders. While a comprehensive review of all such studies is beyond the scope of this article, the following paragraphs highlight evidence and key principles of how gene-stress interactions may influence late-life neuropsychiatric syndromes.

Most gene-stress interaction studies in late life have employed a cross-sectional design, examining LLD as the outcome of interest. The best-studied gene variant in this context is the functional polymorphism located in the promoter of the *SLC6A4* gene (*5-HTTLPR*), which can give rise to either a long (L) or a short (S) allele. This polymorphism was initially shown to interact with the number of SLEs occurring over the last year to predict LLD in Korean elders, with S allele carriers exhibiting higher LLD risk when exposed to greater numbers of SLEs [49]. Nonetheless, subse-

quent reports examining LLD symptomatology in other ethnicities found no significant interactions between *5-HTTLPR* and SLEs occurring within the last one or two years [50-52]. When examining the longitudinal course of LLD, the *5-HTTLPR* polymorphism was shown to moderate the impact of SLEs occurring within the last year, with S allele carriers demonstrating higher probability to remit when having higher baseline number of SLEs and greater SLE reduction over time [28]. Notably, a significant *5-HTTLPR*-stress interaction has been shown when examining lifetime trauma exposure [50], whereby S allele carriers exhibit higher levels of depressive symptoms when exposed to greater trauma burden along the lifespan. *5-HTTLPR* has been further found to interact with childhood trauma [53], with L allele elderly carriers showing more depressive symptoms when exposed to poverty or parental stressors during childhood. Lastly, studies examining the interaction of *5-HTTLPR* with medical stressors have reported both positive and negative findings; specifically, the S allele was found to strengthen the relationship between asthma and depressive symptoms in late life [54], whereas it did not influence the effect of hip fracture on depression [55]. Taken together, these studies indicate that *5-HTTLPR*-stress interactions may have variable effects on LLD, depending on the population and outcomes studied, as well as the type, timing, and duration of stress exposure.

Another notable gene variant examined by GxE studies in LLD is the valine (Val) to methionine (Met) polymorphism of the gene encoding the brain-derived neurotrophic factor (*BDNF* Val66Met). The *BDNF* Met allele was shown to strengthen the relationship between SLEs and LLD, whereas it also enhanced, through epistatic effects, the *5-HTTLPR*-SLE interaction [49]. Likewise, epistatic effects were found between the *BDNF* and *5-HTTLPR* polymorphisms on the levels of depressive symptomatology following hip fracture [55]. These studies highlight the potential of multiple genetic loci with important roles in brain function to influence depressive phenotypes through complex interactions with stress exposure in late life.

GxE studies in late life have also examined a number of other phenotypes. In a study examining negative affect in very old adults and centenarians, carriers of the ε4 allele of the apolipoprotein E gene (*APOE*) were found to have higher levels of negative affect when experiencing greater numbers of lifetime SLEs [56]. In a report examining memory performance as the phenotype of interest, *APOE* ε4 allele carriers with higher levels of life stress over the last year demonstrated lower performance in immediate and delayed recall [34]. Lastly, a study examining suicidality in Korean elders showed that the S allele of *5-HTTLPR* is associated with higher prevalence of suicidal ideation when combined with higher numbers of SLEs and lower levels of social support [57]. These findings demonstrate the potential pleiotropic effects of gene-stress interactions in late life, whereby the same gene variants can contribute to divergent phenotypes depending on the specific environmental context.

4. MECHANISTIC CONSIDERATIONS

The impact of gene-stress interactions on late-life neuropsychiatric syndromes could be mediated through their lasting effects on critical regions and circuits of the aging brain.

In line with this hypothesis, GxE can influence structure and function of brain regions involved in emotional and cognitive regulation. For example, SLEs interact with gene variants, such as the *5-HTTLPR* and stress-related genes, to influence cortical and subcortical brain volumes [58, 59]. The S allele of *5-HTTLPR* can further contribute to enhanced amygdala activation either through a main genotype effect [60] or through interactions with SLEs [61]. At the molecular level, gene-stress interactions may influence the expression of key regulators of brain activity and plasticity in a region-specific manner; for instance, early life stress was shown to interact with the serotonin transporter gene to differentially modulate *Bdnf* expression levels across corticolimbic regions in rats [62]. Such GxE-induced alterations in brain plasticity could confer region-specific vulnerability, likely by reducing the capability of the aging brain to recover from stressors or other insults.

While several of the mechanisms underlying gene-stress interactions in advanced ages may be similar with GxE occurring earlier in life, these effects could be accentuated by aging-related alterations in stress responsivity and brain sensitivity. Aging has been associated with increased basal glucocorticoid levels and altered feedback regulation of the hypothalamic-pituitary-adrenal axis [63]. Furthermore, the effects of late-life GxE on the brain may be accentuated by the micro- and macro-structural brain changes that accumulate as a result of programmed aging processes, environmental insults, and aging-related morbidities. Key aging-related brain processes thought to predispose to the development of neuropsychiatric syndromes include pro-inflammatory states and vascular pathologies [64, 65]. These processes may interact with stress exposure and GxE to promote susceptibility of distinct brain regions. Supporting this hypothesis, higher levels of perceived stress have been associated with more depressive symptoms in the presence of vascular risk factors [66]. Furthermore, increases in the number of recent SLE exposure over time are accompanied with progression of cerebral white matter hyperintensities [67], which are aging-related lesions linked with chronic ischemia [68]. Acceleration of aging-related brain changes also occurs with variation in genetic loci involved in vascular processes, such as genes of the renin-angiotensin system [69]. Gene variants likely influence neuropsychiatric phenotypes through interactions with multiple risk factors; for example, the ε4 allele of *APOE* has been shown by independent studies to increase risk for cognitive decline through interactions with both hypertension and low physical activity [70, 71]. The combined small effects of numerous GxE, which involve a multitude of gene variants, psychosocial stressors, and other environmental factors, can in turn shape vulnerability or resilience of the aging brain for the development of neuropsychiatric disorders.

Concerning the molecular cascade of events that could underlie the lasting effects of GxE, evidence supports the role of epigenetic mechanisms, a set of biochemical processes that regulate gene expression without altering the underlying DNA sequence. In both humans and rodent models, lasting epigenetic modifications, such as changes in DNA methylation, have been shown to occur in a variety of tissues following exposure to psychosocial stress at different time
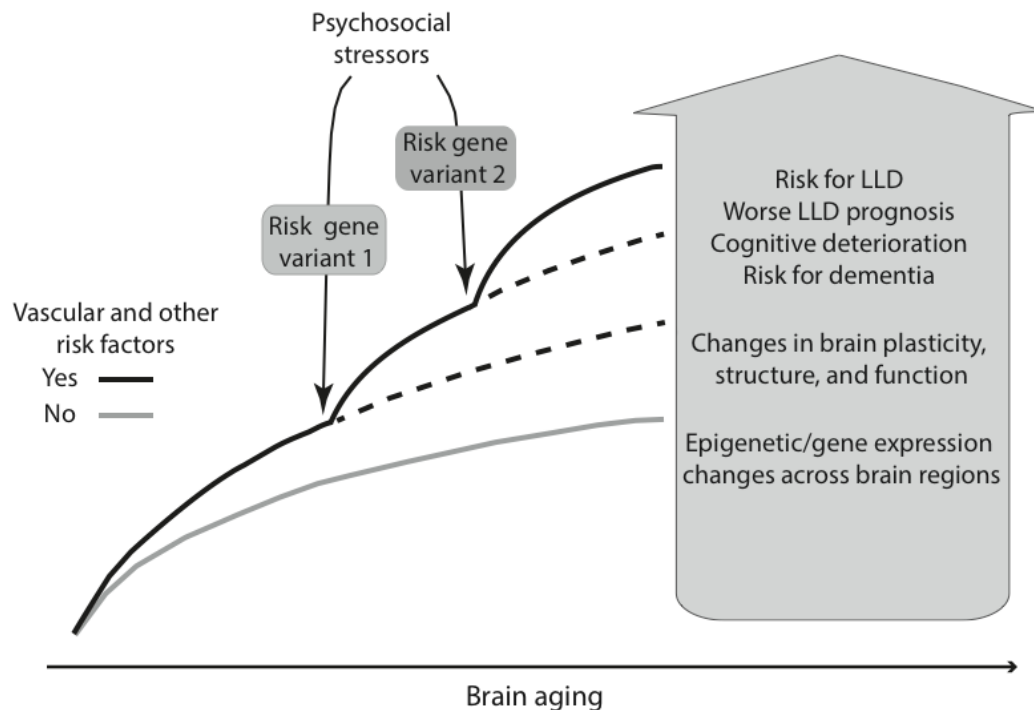
Fig. (1). Oversimplified scheme showing how gene-stress interactions can influence the trajectory of brain aging, potentially contributing to neuropsychiatric phenotypes with advancing age. Healthy aging is associated to an extent with molecular changes and alterations in brain plasticity, structure, and function. These aging-related brain changes can be accentuated by gene-stress interactions, and the altered aging trajectory can predispose to the development of late-life neuropsychiatric syndromes. For simplicity, gene-stress interactions only involving two gene variants are shown, though these syndromes in reality emerge through a complex interplay among numerous genetic and environmental factors. As demonstrated, vascular and other risk factors can influence the trajectory of brain aging independently and in conjunction with gene-environment interactions. The dotted line represents the projected trajectory without exposure to each stressor and risk gene variant.

points throughout life [72-74]. Although no longitudinal studies have systematically assessed the epigenetic impact of stress occurring specifically in late life, cross-sectional evidence suggests that epigenetic changes both within selective genomic loci and at the genome-wide level may accumulate upon repetitive exposure to lifetime stress, eventually becoming evident in advanced ages [74, 75]. Importantly, DNA methylation changes depend on the underlying genetic code [76] and can mediate gene-stress interactions in an allele-specific manner [73]. Consequently, genotype-specific epigenetic modifications induced by stress exposure may explain, at the molecular level, how gene-stress interactions are embedded and shape brain structure and function. Although there are inherent limitations in directly assessing epigenetic modifications in the living human brain, neuroimaging-based brain phenotypes have been shown, for example, to correlate with peripheral blood DNA methylation signatures in genes with important roles in emotion processing and stress regulation, such as the aforementioned *SLC6A4* and *FKBP5* genes [73, 77, 78]. The advent of neuroimaging modalities that assess epigenetic markers in the living brain [79] may further open new avenues into work examining how GxE are biologically embedded in the aging brain.

CONCLUSION AND FUTURE DIRECTIONS

The present article discusses how gene-stress interactions may influence the aging brain and contribute to neuropsy-

chiatric phenotypes in late life. As highlighted above and schematically simplified in Fig. (**1**), multiple gene-stress interactions may act concomitantly, along with other environmental factors and aging-related brain processes, to induce changes in gene expression patterns across distinct brain regions, structurally and functionally modulate circuits with critical roles in the regulation of mood and cognition, and confer vulnerability or resilience for the development of neuropsychiatric syndromes.

The evidence presented herein can inform future research examining GxE in late life in the following ways. First, GxE findings on specific gene variants can vary broadly when considering stressors of different type, timing, and duration. These characteristics should thus be precisely defined and carefully selected a priori. Second, stressors occurring at vastly different life stages -including trauma during childhood, but also SLEs at advanced ages- can significantly influence the trajectory of brain aging and neuropsychiatric phenotypes in late life. Some of these effects appear to be long-lasting and cumulative, whereas others may be more dynamic and reversible. Furthermore, various stressors occurring at different time points throughout life may interact in complex ways, eventually sensitizing or protecting genomic sites to subsequent stress exposure. For example, higher levels of early life stress have been shown to blunt the relationship between lifetime stress and epigenetic aging [74]. Employing, when possible, a life course perspective

that considers exposure to multiple stressors at different time points in life may provide deeper insights into the pathogenesis of late-life neuropsychiatric syndromes. Lastly, GxE studies in late life have so far focused on individual candidate genes. However, the majority of neuropsychiatric phenotypes are thought to result from the complex interplay among multiple genes and environmental factors. Approaches examining multiple gene variants, such as gene-environment genome-wide interaction studies, may better capture this complexity but require substantially larger sample sizes.

The observations that the aged brain retains both plasticity to environmental modifications and vulnerability to psychosocial stressors emphasize the importance of prevention strategies or stress-coping interventions that could ameliorate ongoing stress in the elderly, such as meditation and relaxation techniques, as well as strengthening of social support and promotion of resilience that have been shown to influence aging trajectories [80]. The GxE studies to date suggest that such interventions could have more profound impact when tailored to elders with "risky" genetic makeup. This hypothesis remains to be examined in future clinical studies.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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