Published in final edited form as:
Psychiatr Clin North Am. 2011 June ; 34(2): 357–376. doi:10.1016/j.psc.2011.02.003.

Gene-environment interactions in geriatric depression

Francis E. Lotrich, M.D., Ph.D.
Assistant Professor of Psychiatry, Western Psychiatric Institute and Clinics, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Abstract

Risk for the development of major depressive disorder (MDD) is likely influenced by an interacting set of genes and environments. Many elderly are exposed to a variety of potential MDD precipitants. Medical co-morbidities, high inflammatory states, care-giver stress, and cerebrovascular changes are often observed proximal to the development of an episode. Additionally, some adults have histories of exposure to environmental stressors such as early life traumas that may result in a life-long predisposition to MDD. Despite these exposures, many people do not develop MDD; and genetic influences are hypothesized to be one influence on vulnerability and resilience. Over the last seven years, several studies have examined a variety of genes for this gene × environment (G×E) interaction. Most have examined a length polymorphism in the promoter region for the serotonin transporter gene, but some have examined brain derived neurotrophic factor, various genes encoding for key players in the hypothalamic-pituitary-adrenal axis, as well as other genes involved in the monoaminergic, neuroendocrine, and inflammatory systems. There is marked variation in the design of these studies, as well as in the measures of environment, MDD, and genotyping. Interpreting the sometimes inconsistent findings among studies is complicated by this heterogeneity. However, some tentative trends have emerged. An overview is provided of both the methodologies and results of these studies, noting consistent trends as well as confounds. The progress made to date will hopefully inform the next generation of studies.

Keywords

polymorphism; stress; elderly; geriatric; depression

Major Depressive Disorder (MDD) can be complicated to study -- it has a heterogeneous manifestation and course. Even with respect to environmental precipitants, the onset of depressive episodes have been variously associated with the post-partum period,[1] the post-menopausal period,[2] thyroid disease,[3] circadian changes,[4] sleep impairment,[5] stimulant withdrawal,[6] cerebro-vascular disease, [7-9] chronic illness, [10] inflammatory cytokines,[11] as well as psychosocial stresses[12] including interpersonal losses,[13, 14] threats to safety, physical impairments,[15] pain,[16] etc. Because old age can be associated with deteriorating health, vascular disease, changing sleep patterns, bereavement, etc., many of these potential precipitants accumulate later in life.[17] However, only a minority of people exposed to a

Francis Lotrich, WPIC 3811 Ohara Street, Pittsburgh, PA 15213, (412) 246-6276 (phone), (412) 246-6260 (fax), lotrichfe@upmc.edu.

The author has nothing to disclose.

combination of these events actually develops depression. Stress does appear to have a causal influence on development of MDD in some people, some times;[18] but simple exposure to accumulating environmental stress is not enough to fully explain MDD.

Genetic influences on vulnerability and resilience to these precipitants likely play a role. But the heritability for MDD is estimated to only be about 37%.[19] Consistent with this, meta-analyses of case-control association studies suggest potential roles for polymorphisms in several genes,[20] with effect sizes that are typically very small. No single gene, acting alone, appears to play a major role. However, case-control genetic association studies generally face the limitation of not accounting for differences in exposure to the multitude of potential environmental influences. Thus, there remains the intriguing possibility that particular genes interact with particular environments to influence MDD. In examining this possibility, there are significant challenges to successfully completing gene × environment interaction (G×E) studies, although there recently has been encouraging progress. The field is nascent, but there are now multiple G×E studies examining the serotonin transporter (SERT), brain-derived neurotropic factor (BDNF), the hypothalamic-pituitary-adrenal (HPA) axis, inflammatory cytokines, and other monoaminergic genes.

Methodological considerations

Before reviewing these recent results, important methodological concerns should be noted.

I. How environment (E) is categorized likely matters

E can be **(i)** an acute precipitating trigger for the onset of an MDD episode, **(ii)** an element of predispositional vulnerability to MDD, **(iii)** a perpetuating factor once an MDD episode has occurred and preventing its remission, **(iv)** or simply a secondary epiphenomenon statistically correlated with already having MDD. The question of whether MDD co-morbidities (one type of E) are predispositions, precipitants, perpetuating factors, and/or epiphenomena can be a very complex question without a simple answer.[21] An example of a precipitating event that triggers the onset of an MDD episode could be a myocardial infarction.[22] A predisposition for MDD vulnerability could be lower childhood social class resulting in decreased glucocorticoid and increased proinflammatory signaling later in life.[23] Perpetuating factors after MDD has developed could be social isolation and resultant inability to cope with stress.[24, 25] Finally, having MDD may increase the likelihood of smoking, with secondary effects on pulmonary health.[26] It is conceivable that one set of genes interacts with environmentally-influenced predisposition, another set interacts with environmental precipitants, and a third with perpetuating environments. Therefore, in determining the interaction of vulnerability genes with E, a longitudinal perspective is often necessary. Also, because environmental variables can obviously fluctuate over time, using a single period of time to assess E can sometimes be a misleading proxy for E.[27] Choosing what E to include in G×E studies should be guided by known science,[28] carefully defining the nature, extent, and timing of E.

II. Genetic correlations with E likely matters

Because each individual can shape the interpersonal interactions and environment around them, one's own genetic make-up appears to indirectly influence exposure to psychosocial stressors, social supports, and vascular disease. Statistically, this means that there are often G-E correlations, situations in which G appears to ‘affect’ E. Simply put, people can select and modify their own environments; and genetically similar people end up in similar environments. Examples of this abound. To illustrate, a Taq1A polymorphism in the dopamine receptor 2 gene has been associated with multiple illnesses that involve impulse dyscontrol, and children with the A1 allele are more likely to discontinue school. But this

genetic risk can be mitigated by having a mentor, indicating an interaction between genetic vulnerability and mentorship.[29] However, children with A1 were also less likely to have a mentor in the first place, indicating the gene also adversely influenced access to this beneficial environment.[29] Thus, there is also a G-E correlation in addition to a G×E interaction.

In a similar fashion, genetic variability may be associated with almost two-thirds of the likelihood of experiencing personal stressful life events (i.e., not all is simply bad luck).[30] Likewise, heritability may explain as much as 75% of differences in social support among people,[31] something that remains true later in life.[32] In fact, studies of older adult twins indicate that many environment stressors (e.g., divorce, spouse in nursing home, change in residence, etc.) are under genetic influence, with as much as 43% heritability.[33] Thus in interpreting the results of G×E studies, one should recognize that the exposure to 'E' itself can be partially 'influenced' by G.

III. How 'MDD,' 'E,' and 'G' are each measured likely matters[34]

Diagnoses of MDD by structured interview or by cut-off criteria on a self-report scale can be partially correlated -- but these methods can also differ.[35] As just one example, brain injury, stroke, or Parkinson's disease can affect the relationship between a self-reported score-based diagnosis and a diagnosis based on a structured interview.[36-38] Even in healthy old-old adults, self-reports may have limited correlation with interview based diagnoses.[39] Taking a lesson from mice, different chromosomal areas are associated with different anxiety measures, depending on what behavioral test is used.[40] The differences could be associated with potentially different evolutionary constructs.[41] In humans, there are similarly unique heritabilities for specific depression symptoms,[42, 43] and it is conceivable for some genes to better associate with MDD diagnosed using one methodology as compared to another.

Moreover, there may be etiologically different categories of MDD later in life,[44] depending on the concurrent development of cerebrovascular disease, recurrent life time history of episodes, new onset following the occurrence of a psychosocial stressor, prodromal symptoms of Alzheimer's disease, etc. In confirming or replicating results across studies, the potential for non-replication because of measurement 'artifact' could be mitigated by studies using a variety of methods and instruments for assessing E and MDD.

In addition, both depression and environmental measures can also obviously be confounded by recall bias,[45] with this problem likely worsening with age.[46, 47] It is possible that depressed mood as well as genes that affect memory could influence recall.[48] Thus, studies that rely on retrospective recall of either E and/or MDD diagnosis face this limitation. For psychosocial 'stressors', how E is perceived may be important. That is, the emotional valence or the controllability of major life events may both conceivably affect the relationship with depression. For examine, a divorce could be a negative or a positive occasion, depending on the circumstances. Similarly, the extent to which one has control over the impact of the divorce may influence its impact on depression. Simply adding major life events together has the potential to be misleading. And there is vast heterogeneity among studies with respect to how life events are quantified, measured, and defined.

Finally, the information provided by genotyping can be affected by population stratification (particularly when cases and controls in association studies arise from different subpopulations); differing linkage between measured single nucleotide polymorphisms (SNPs) and potentially causal polymorphisms in populations of differing ancestry; effects on statistical power when testing multiple polymorphisms (particularly whole genome-wide studies); and laboratory reliability of different genotyping methods.[49, 50]

IV. Study design likely matters

A basic design is to examine two environments (e.g., “stressed” and “not stressed”) and to examine whether genotype interacts with E in predicting the presence of depression. A related design is to include quantitative gradations in level of E – and to assess for G×E interaction. A third design is to assume that E is probably influential, select only those subjects exposed to E, and test for a direct main effect of G. This latter design does not examine interaction per se, but is a powerful method for detecting G in the setting of known environmental ‘stressors’. Each of these designs can be employed in prospective, cross-sectional, or retrospective fashion – with varying degrees of attention to measurement, feasibility, assumptions, and statistical power.

V. Finally the age of the population examined likely matters

The extent of potential predisposing factors (e.g., prior history of MDD episodes, poor sleep, chronic inflammation, frailty, pain, cognitive impairment, lack of social supports, etc.) and potential precipitating factors (e.g., major illness, sudden disability, loss of loved one, increased care-giver requirements, etc.) differ in the elderly. This could conceivably either mitigate or vitiate the effect size of G×E interactions.

These five general elements tremendously vary across the studies that have been done to date. Thus comparing results across studies is very difficult. Nonetheless, despite the inter-study variability, some tentative conclusions are possible.

Polymorphisms in the serotonin (5-HT) transporter (SERT)

It has now been seven years since the first report of an interaction between stress and an insertion/deletion polymorphism in the promoter region of the SERT gene (5-HTTLPR; with short (S) and long (L) alleles) in the development of depression in young adults.[51] This initial prospective study longitudinally assessed E as the cumulative number of stressful life events, including childhood maltreatment over a five year period.[51] Those with the S/S genotype were more sensitive to the adverse effects of stress on depression risk. This finding was soon ‘replicated’ by another prospective study that assessed E as various threat levels within one month prior to depression assessment. In this second study, the difference between 5-HTTLPR genotypes was greatest at moderate threat levels,[52] suggesting a left-shift in the “stress-depression” curve and greater sensitivity in the short term to moderate threats among those with the S/S genotype. This finding predicts minimal difference between genotypes when no stress exists or at very high levels of precipitating stress. There have now been almost sixty additional studies examining 5-HTTLPR for a potential G×E interaction, with mixed results.[53-55] A complete review of all these studies is not our intent, but rather we will attempt to highlight both inconsistencies and consistent findings.

Like the prospective studies above, several G×E studies are longitudinal. Most of these have replicated an interaction. In female twins, stressful life events in the three months prior to a diagnostic interview was more depressogenic in those with the S/S genotype,[56] an effect also seen in twins who reported childhood adversity,[57] and also 125 orphans with prior institutional deprivation.[58] A recent study specifically assessed bullying in 2017 children, and again reported evidence for the S/S subjects subsequently developing more depression.[59] Complicating this trend, some longitudinal studies have only replicated a G×E interaction for maltreatment and adolescent depression for females, but not males;[60] or the replication of G×E was evident later in life only when cumulative life events were tallied over five years and not just one year.[61] Conversely, another prospective study reported that S/S genotype increased risk for adult MDD in those with only one traumatic event, essentially shifting the stress-depression curve leftward.[62] In all of these studies, the S/S

genotype was more prone to MDD than the L/L genotype; but whether there is an additive, recessive, or dominant effect for the S allele was not consistent between these studies.

Critically, there are some important longitudinal studies that did not find a G×E interaction. A very large study of over four-thousand seven year olds found no evidence for G×E, strongly arguing against a role for 5-HTTLPR as a risk factor for MDD in children at this very young age.[63] In another large study of subjects of various ages including older adults twins (total n=3243), no role for 5-HTTLPR was again found.[64] In this study, depression symptoms in a telephone survey were assessed 1-10 years after a prior survey queried about stressful events that initial year.

Also, one prospective study has found that the risk allele is actually the L allele.[65] Because of several negative and contradictory results, a recent meta-analysis examined a subset of these studies, along with several other cross-sectional studies, and concluded that there may be no G×E interaction for 5-HTTLPR.[55] Regardless, the clear conclusion is that the G×E interaction is definitely not universal. But, what accounts for the differences between studies other than chance?[66]

One question is: does 5-HTTLPR interact with predispositional stress (e.g., trauma in childhood influencing MDD risk in adulthood) or with adverse life events that are precipitants of depression (i.e. stress immediately preceding an MDD episode)? Studies that assess childhood maltreatment or early trauma of some type and then MDD years later are often studies where stress may result in some enduring change in predispositional vulnerability. Of these “predispositional” studies, most replicate the original finding of Caspi et al.[60, 67-69] Some other studies depend on how E was defined. For example, an interaction for 5-HTTLPR was found in adults only when stressful traumatic events were assessed across three levels of diversity, but not when they were dichotimezed.[70] In another, the G×E interaction was found only with childhood sexual trauma but not maltreatment more generally.[71] The few exceptions include a predispositional study where no G×E was found in older adults when E was measured as father's education (a potential surrogate for childhood adversity).[72] Also, only a non-significant trend for greater depression symptoms in S/S carriers was noted in a study where child adversity was measured as a continuous measure (with explicit items regarding sexual and physical abuse purposefully not asked).[57] Thus, most evidence implicates a role for the S/S genotype in augmenting the predisposition for MDD that results from severe childhood trauma, in particular sexual abuse. But the severity of the traumatic childhood experiences and how it is assessed and measured may be an important variable, and possibly account for the limited number of negative findings.

G×E studies examining cumulative stress as a potential precipitating event in the months or year preceding a depressive episode have been variable. Here, it is possible that the nature (e.g. level of threat) and timing (e.g., a few months preceding MDD) are crucial variables in determining whether G×E occurs. In a similar manner, 5-HTTLPR may affect the potency but not the efficacy of a selective serotonin reuptake inhibitor.[73] That is, 5-HTTLPR may shift the concentration-response curve – and thus at high or at very low concentrations there is no difference in antidepressant response. In the pharmacology case, E is readily quantified as a medication concentration in the blood. If G similarly shifts the “stress-response curve” (i.e. it takes less stress to trigger an MDD episode in an S/S carrier), then a 5-HTTLPR influence on depression would only be evident at moderate levels of stress. Thus, assessing the magnitude, the duration, and the timing of stress becomes important for ‘precipitation studies’, albeit more difficult than simply measuring a blood level. Whether this possibility may account for ‘negative’ studies' ([e.g.,64]) is purely speculative at this point.

In older adults, medical illness is one specific type of precipitating environmental "stressor." Here, the results are fairly consistent. In 521 elderly subjects prospectively studied over 2 years, the S/S genotype increased the risk for MDD in those with four or more chronic medical disorders, supporting a G×E interaction.[74] Interestingly, another study also reported that the S allele was associated with a left shift in the disease-burden and depression relationship; however in this case, those with two or three chronic medical illness were more at risk for depression symptoms if they had the S allele.[75] Examining more specific medical conditions, the S/S genotype has been associated with increased risk for depression in those with Parkinsons,[76] those with severe coronary disease,[22] following a myocardial infarction,[77, 78] following a hip fracture,[15] and following a stroke.[79, 80] The only two published exceptions to this trend that we found to date include a large study of patients with existing cardiac illness where no role of 5-HTTLPR was found,[81] and a prospective examination of patients undergoing bypass graft surgery.[82] Interestingly this latter study found potential evidence for a complicating G-E correlation such that the L allele was associated with additional cardiac events following surgery. Thus studies examining cardiovascular disease may be confounded by the possibility that L allele increases the likelihood of being exposed to a cardiac event (potentially reversing its beneficial effect). This is consistent with studies that find that the L allele is associated with increased platelet reactivity in depressed elderly.[83] Notable, the relationship between MDD and vascular disease is likely bidirectional.[84] Also, many of the potential genetic influences on depression may also influence coronary artery disease.[85] Thus with the potential exception of cardiac illness where studies may be confounded by potential G-E correlation, there is fairly well-replicated support for the S/S genotype augmenting the detrimental effect of 'medical illness burden' on depression risk

There have also recently been a few prospective studies of patients who are treated with interferon-alpha, an inflammatory cytokine that can trigger MDD in about one-quarter of patients. Here, two studies have found that evidence for the S/S genotype increasing incidence for MDD during interferon-alpha therapy,[86, 87] although there are two others (one in a Chinese population; and one measuring depression symptoms using a questionnaire) that did not.[88, 89] This raises the possibility that in older adults, the S/S genotype may sometimes be interacting with increased exposure to inflammatory cytokines (something associated with increasing medical burden). Elevated inflammatory cytokines may be important biomarkers for the development of geriatric depression during medical illnesses.[90] Interestingly, cytokines can affect expression of the serotonin transporter,[91] and this affect may be influenced by the 5-HTTLPR polymorphism.[92] As only a subset of patients with elevated cytokines develop MDD, this is an area of genetic vulnerability and resilience still awaiting further work.

Nonetheless, similar to findings in children and young adults, the interaction of 5-HTTLPR with psychosocial precipitating stressors later in life is less clear. In one study of adults aged 41 to 80, there was no G×E interaction with either total number of adverse life experiences recalled or with adverse events and long term difficulties in the previous five years.[93] However, a study of Korean elders found a G×E interaction,[94] and the S/S genotype was also associated with increased risk in caregivers under this type stress.[72] Another study of older adults found a G×E interaction only when the life event history was severe and traumatic, but not otherwise.[95] Again, differences in the severity stress among these studies may continue to play an important role.

In brief summary, there are some tentative conclusions that can be made. (i) A universal interaction between "stress" and 5-HTTLPR is not likely, as evidenced by negative findings in several large studies. (ii) Older adults with S/S genotypes have enhanced depression risk secondary to medical illness as a "precipitating" factor, and this appears to be mostly

replicated. (iii) Also, in younger adults with S/S genotypes, enhanced "predispositional" risk from severe childhood trauma appears to be mostly replicated. The implication of this for the elderly is that the relative risk for late-life MDD episodes is 90-fold for people with a prior history of past MDD episodes.[17] Thus, the 5-HTTLPR × early trauma interaction may affect recurrent MDD and extend into late-life. (iv) Whether S/S also increases risk for the effect of cumulative precipitating stressors in late life may depend on the severity of the stress. Findings among studies in this area are very variable - with notable heterogeneity in design, as well as variability in E, G, and MDD assessment. Thus at this point, this possibility is less conclusive.

The pathophysiology of how the S/S genotype could be influencing risk for MDD remains to be clarified but plausible possibilities include effects on cerebral white matter disease,[96, 97] effects on hippocampus volume,[98, 99] effects on amygdala function,[100] effects on amygdala and frontal cortical connectivity,[101, 102] effects on sleep quality,[86, 103] effects on the cortisol stress axis,[104, 105] etc.

Polymorphisms in the hypothalamic pituitary adrenal (HPA) axis

Abnormal axis (HPA) feedback and hyper-reactivity are often present in people with MDD.[106, 107108] This includes disrupted glucocorticoid receptor (GR) expression, translocation, and concomitant resistance to cortisol.[107] Chronic psychosocial stress may also impair appropriate regulation of the HPA axis.[109] One plausible hypothesis is that an imbalance between mineralocorticoid and glucocorticoid responses occur in MDD.[110] Thus, polymorphisms in genes for GR, in corticotrophin releasing hormone (CRH), in both CRH receptors (CRHR1 and CRHR2), and in a GR chaperone (FKBP5) may all play roles in response to stress.[111] Over the past several years, a few G×E studies examining HPA genes have occurred. For example, in a longitudinal study of 906 aging subjects, child adversity affected both depression risk and cortisol levels; and polymorphisms in the GR gene increased the risk for depression.[112] The polymorphisms of interest for GR appear to influence acute corticosteroid response as well as HPA axis reactivity.[110]

CRHR1 gene polymorphisms also interact with childhood abuse to predict sensitivity to a dexamethasone/CRH challenge.[113] Consistent with this, several polymorphisms and a haplotype spanning intron 1 interact with childhood abuse to predict MDD in adulthood.[114] This haplotype finding was replicated in one longitudinal cohort but not in another (although the other cohort measured abuse differently).[115] Also, there appears to be a G×G×E interaction in which 5-HTTLPR and CRHR1 may interact with child abuse history to predict adult MDD.[70] Of note, these studies have specifically examined childhood trauma, and not stressors more proximal to MDD episodes later in life. But they are consistent with findings that serotonin transporter function can be influenced by glucocorticoids, and that this influence is moderated by 5-HTTLPR in creating a long-lasting predisposition to MDD.[116]

An immunophilin that is involved in translocation of GR from the cytosol to the nucleus, FKBP5, may likewise play an important role.[117, 118] Alleles associated with enhanced expression of FKBP5 lead to an increased GR resistance and decreased efficiency of the negative feedback of the HPA axis. Polymorphisms for the FKBP5 gene have been primarily been examined with respect to post-traumatic stress disorder, where they may be associated with prolonged HPA response to trauma, potentially resulting in long-lasting changes.[119] One hypothesis is that these HPA-related polymorphisms are primarily interactive with early-life trauma, leading to a life-long predisposition or vulnerability to the effects of other types of stresses later in life.[119] Whether this is true for geriatric depression remains to be examined. Finally, it is biologically plausible that other polymorphisms in

genes encoding for HPA-related proteins such as CRHR2 and CRH may also interact with stress.[120, 121]

Although it is plausible that HPA genes may both affect vascular disease and MDD risk (including a plausible G-E correlation), any potentially interacting role for CRH1, CRH2, or FKBP5 in late-life MDD remains awaits future study. Moreover, whether HA axis genes may interact with more proximal “precipitating” factors or medical-illness-related inflammatory changes is currently unknown.

Brain-Derived Neurotrophic Factor (BDNF)

Impairment in growth factors such as BDNF may lead to MDD, and BDNF Met/Val variants have been associated with MDD.[122] Interestingly, major traumas early in life can directly affect methylation and expression of BDNF.[123] Also, serotonin transporter function can be modulated by BDNF.[124] BDNF genetic variants may also influence GR sensitivity[125] and interact with stress to influence vulnerability.[68] Consequently, both the BDNF gene Val66Met polymorphism and polymorphisms in its receptor have been associated with late-life MDD,[126] along with increased suicidal ideation.[127]

Consistent with this, the BDNF Met/Val functional polymorphism has been found to interact with stress in a couple studies.[69, 128] It is possible that the effect of early life stress on brain arousal pathways is influenced by this polymorphism, resulting in a predisposition to depression later in life.[129] The BDNF Val/Met polymorphism may also interact with both 5-HTTLPR and caregiving stress (as measured in parents of psychotic patients) to influence depression.[130] This is consistent with two BDNF × SERT × stress interactions found in younger patients.[57, 68] There are a limited number of studies examining G×E for BDNF, and future work is clearly indicated. Nonetheless, the potential for G×G×E is enticing.

Other monoaminergic genes

A very limited number of studies have started to explore the potential for other monoaminergic genes and their interaction with E. There have not been enough published reports yet to make any inferences regarding trends or consistencies among studies. However, there are some suggestive findings. A potentially functional polymorphism in catecholamine-O-methyl transferase (COMT) may interact with 5-HTTLPR and stress to influence depression risk.[131] Interestingly, the COMT polymorphism was also associated with depressive symptoms post-partum, both alone and in G×G interaction with MAOA.[132] A polymorphism in the 5-HT1A gene interacted with recent stressful events in females aged either 20-24 or 60-64, associating with depression in select post-hoc analyses, though no G×E interaction was noted in general for this gene.[133] Polymorphisms in 5-HT1A have been linked to depression, and 5-HT1A binding is reduced in depressed people.[134] A polymorphism in 5-HT1A has also been found to predict depressive symptoms in patient receiving interferon-alpha.[88] Using urban/rural residency to define ‘E’, the 5-HT2A gene may interact with residency to influence depression symptoms;[135] and a polymorphism in the 5-HT3A receptor gene may interact with early-life stress, resulting in differences in hippocampus and frontal grey matter.[136] Again using rural residency as a surrogate marker for stress in a recent study of Chinese citizens, a norepinephrine transporter polymorphism interacted to influence MDD risk.[137] Notably, these are all single studies, with a variety of approaches, designs, and ways of defining E. Thus there are enticing leads, but further replication work is needed.

Two other monoaminergic genes of potential importance include tryptophan hydroxylases 1 and 2 (TPH1 and TPH2). In the peripheral systemic circulation, the relative action of TPH1 and indolamine deoxygenase can influence whether tryptophan is metabolized to serotonin

or to kynurenine and other glutamatergic compounds.[138] The kynurenine/tryptophan ratio is elevated in melancholic adolescents[139] and depressed subjects receiving interferon-alpha.[140] Elevated tryptophan may mitigate the effect of the S/S genotype on mood,[141] and 5-HTTLPR interacts with tryptophan depletion in acute studies of mood.[142, 143] In adults, TPH1 polymorphisms may moderate the effect of social support on depression.[144] There is also some evident that TPH1 polymorphisms interact with stressful childhood experiences in influence harm avoidance, which may increase risk for MDD.[145] Whether TPH1 polymorphisms interact with 5-HTTLPR in a G×G×E fashion remains to be determined. TPH2 also may interact with family structure to influence childhood depression symptoms.[146] Also, although indolamine deoxygenase gene has glucocorticoid response elements,[147] whether polymorphisms in this gene interact with stress in increasing MDD risk is not know to our knowledge. Regardless, further work is required with respect to G×E studies.

Other genes

There is preliminary evidence for other candidate genes. Although few of these studies have been replicated, there is the possibility that specific genes may interact with specific “precipitants.” That is, there may be unique “subtypes” of depression in which different genes interact with different environmental precipitants; for examples, risk genes for menopausal, for inflammatory cytokines, for circadian shift, etc.. As noted in the introduction to this review, there are many seemingly different and varied plausible ‘environmental’ precipitants for MDD that have been described, and each may have its own unique genetic interactions.

As examples, a gene influencing metabolism of estrogen, coding for the enzyme CYP1A1, may double depression risk in peri-menopausal women.[148] Polymorphisms affecting interleukin-6 may influence depression risk in the setting of increased inflammation, potentially in interaction with 5-HTTLPR.[87, 149] In late life, MDD has been associated with both vascular disease as well as a prodromal condition to Alzheimer's disease. Here, APOE4 may increase risk non-vascular late-life MDD, but not MDD associated with cerebrovascular disease.[150] A polymorphism in NPY may protect against depression in the setting of stress;[151] and two studies have reported an interaction between the cannibinoid receptor gene polymorphism and stressful events in the risk for depression[81, 152] Thus ultimately, there may be the potential for several cumulative G×E interactions in late-life – depending on which combination of environmental precipitants are present. For the elderly, it is likely that future studies will need to increasingly attend multiple measures of “E” (in addition to childhood adversity or recent psychosocial stress).

Possible epigenetic mechanisms

Early life traumas appear to be the most studied and replicated risk for MDD in most of the G×E studies to date. So how does this affect risk later in life? Early life trauma can manifest many years later as increased proinflammatory signaling,[23] and genomic studies of MDD have identified roles for genes such as TBX21 and PSMB4, which are influential in inflammation.[153] Thus, changes in inflammatory and endocrine processes are implicated in the etiology of MDD. However, early life stress has many additional potential long lasting effects. Of particular note, epigenetic phenomena are increasingly being understood as mediating many of the life-long effects of early environmental events.[154]

That is, it is possible that environment can induce changes in the genome itself, either through modification of nucleotides or through packaging of the DNA in histones. In fact, chromatin remodeling may be one way in which early environmental conditions can have prolonged influences on vulnerability to MDD.[155] Alternatively, maternal effects on pups

can influence HPA reactivity later in life via effects on DNA methylation of the GR gene.[156] This is also possible in humans whereby early adversity may have prolonged influences on brain GR.[157] Thus, events in childhood could lead to enhanced sensitivity to 'stress' later in life, as well as enhanced sensitivity of the inflammatory pathways.[23] Also, just as BDNF variants may interact with stress to influence MDD vulnerability, increased methylation of BDNF has also been found in the brains of suicidal subjects.[158] And there appears to be a role for early traumas in increasing the level of BDNF methylation.[123]

Interestingly, in non-abused patients with MDD, no GR methylation differences from controls were found. [159] However in this study, production of NGFI-A, a transcription factor for GR, was decreased in the hippocampus of depressed subjects.[159] This is interesting because NGFI-A can mediate the effects of serotonergic signaling and BDNF. Thus, there may be alternative routes to MDD that converge on pathways such as this. That is, either GR methylation because of early-life trauma can occur or transcription factors changes in late-life can occur, and either of these paths could lead to decreased expression of GR.

To complicate the picture more, polymorphisms may affect epigenetic processes. For instance, 5-HT transporter levels are influenced by methylation of the SERT gene,[160] and this could interact with 5-HTTLPR in expression of the transporter.[161] One possibility is that both the 5-HTTLPR and increased methylation could additively be necessary for decreased SERT expression.[162] However, research in this area is preliminary.

Clearly there are many candidate pathways and interactions that require explication. Epigenetic effects are just one. Future studies will need to (i) better delineate genetic influences on vulnerability to early life trauma; (ii) define which epigenetic effects of trauma are important for subsequent predisposition to depression; (iii) assess how predisposition interacts with subsequent environmental precipitants; and (iv) determine which genes interact with which precipitants – in the presence of absence of these other sources of vulnerability.

Summary

After seven years and almost 60 heterogeneous studies later, we can probably safely conclude that a 5-HTTLPR by 'stress' interaction is not universal. However, the pattern of results suggest that the nature of 'stress' that is measured, and how it is measured matters. Based on the results of these studies, several intriguing hypotheses present themselves: Does S/S increase the maximal effect of childhood trauma, leading to recurrent MDD that recurs through old age? Does the S/S allele interact with elevated inflammatory cytokines, shifting the inflammation-MDD curve leftward? Does S/S shift the precipitating stress-MDD curve leftward, for psychosocial precipitants?

Only very tentative conclusions are possible. For 5-HTTLPR, there is some evidence that the long-lasting effects of severe early life trauma is enhanced by the S/S genotype. Preliminary findings also support this for genes affecting the HPA axis and BDNF. In most of these studies, the interactive effects seem to be most evident at very severe stress, and often sexual trauma. This suggests that these genes may influence the maximal effect of early-life trauma (shifting the curve upward rather than leftward), a set of hypotheses that requires more definitive testing. In elderly adults, one would specifically predict that this type of G×E would result in an enhanced history of recurrent depression (i.e., early onset MDD) throughout the life.

Whether 5-HTTLPR influences the potency of precipitating psychosocial stressors is debatable. One possibility is the 'double-hit' hypothesis, whereby early trauma increases the risk for MDD by shifting the 'precipitating stress-MDD' relationship in subsequent years.[163]

In other words, traumatized children are more vulnerable to the effects of subsequent stresses as adults. Thus, 5-HTTLPR may influence the maximal effect of early trauma, and by this pathway indirectly influence the subsequent 'precipitating stress-MDD' relationship later in life. Alternatively, 5-HTTLPR may shift left-ward the 'precipitating stress-MDD' relationship regardless of childhood trauma. There is some evidence for this.[52] Regardless, testing and replication of this hypothesis will require careful attention to measurement of E, including its timing, intensity, and chronicity.

In adults, the influence of medical illness on co-morbid MDD does appear to be enhanced by the S/S genotype, with the preponderance of evidence suggesting that the 'potency' of illness is affected (shifting the curve leftward). However, this affect on potency may conceivably be mitigated by concurrent effects on platelet reactivity and vascular risk. Nonetheless, one critical question is: what aspect of medical illness is in interaction with genetics? Is it psychosocial stress, increased inflammation, or something else? If it is increased inflammation, then this proffers the opportunity to have a blood-based measure of 'environment.' One speculative but tempting hypothesis is that the S/S genotype affects the 'inflammation-MDD' relationship. To examine this, inflammatory cytokines such as interleukin-6 and interleukin-1b can be used as direct biomarkers of 'medical stress.' In other words, quantitatively measuring E using endocrine and inflammatory biomarkers may be one way of feasibly determining its interaction with 5-HTTLPR.

Polymorphisms in BDNF, the HPA axis, and other monoaminergic genes are also recently being examined as potential sources of vulnerability to adverse environments. This same set of questions will likely apply to them, but additional hypotheses arise. For example, do specific precipitants such as low-estrogen states interact with specific genes products such as CYP1A1? That is, should we be matching specific environments with specific polymorphisms? This question is particularly important for the elderly, where a variety of potential sources for depression can exist, sometimes simultaneously.

One might anticipate no progress for a complex, multi-factorial disorder such as geriatric MDD, which can have a complicated recurring presentation, a new onset late in life, and/or comorbidity with either vascular disease or prodromal dementia. Nonetheless, progress has been made. As we better understand the potential nature of G×E interactions, as well as the pathways that likely mediate these effects, we can anticipate further progress. With careful attention to robust measures of E, of G and of MDD, it is likely that this trend will accelerate.

Synopsis

In older adults, several environmental challenges can potentially trigger the onset of an episode of major depression. Vulnerability to these challenges can be influenced by genetics. There is accumulating evidence for an interaction between stress and a serotonin transporter polymorphism, though there is also heterogeneity among studies. Other relevant genes include those encoding for the neuroendocrine stress axis, growth factors, and other monoaminergic systems. Each of these may interact with either predisposing traumas in early childhood or precipitating events later in life.

Acknowledgments

This work was supported by NIMH grant MH074012

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