The Age-by-Disease Interaction Hypothesis of Late-Life Depression

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The phenomenologic diagnosis of depression is successful in increasing diagnostic reliability, but it is a classification scheme without biologic bases. One subtype of depression for which evidence suggests a unique biologic basis is late-life depression (LLD), with first onset of symptoms after the age of 65. LLD is common and poses a significant burden on affected individuals, caretakers, and society. The pathophysiology of LLD includes disruptions of the neural network underlying mood, which can be conceptualized as the result of dysfunction in multiple underlying biologic processes. Here, we briefly review current LLD hypotheses and then describe the characteristics of molecular brain aging and their overlap with disease processes. Furthermore, we propose a new hypothesis for LLD, the age-by-disease interaction hypothesis, which posits that the clinical presentation of LLD is the integrated output of specific biologic processes that are pushed in LLD-promoting directions by changes in gene expression naturally occurring in the brain during aging. Hence, the brain is led to a physiological state that is more susceptible to LLD, because additional pushes by genetic, environmental, and biochemical factors may now be sufficient to generate dysfunctional states that produce depressive symptoms. We put our propositions together into a decanalization model to aid in illustrating how age-related biologic changes of the brain can shift the repertoire of available functional states in a pro-depression direction, and how additional factors can readily lead the system into distinct and stable maladaptive phenotypes, including LLD. This model brings together basic research on neuropsychiatric and neurodegenerative diseases more closely with the investigation of normal aging. Specifically, identifying biologic processes affected during normal aging may inform the development of new interventions for the prevention and treatment of LLD. (Am J Geriatr Psychiatry 2013; 21:418–432)

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DEPRESSION, A COMPLEX BIOLOGIC DISEASE

A Common and Debilitating Disease

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), a diagnosis of major depressive disorder (MDD) requires an individual to experience low mood or anhedonia plus five symptoms from a list that includes change in sleep, feelings of guilt or worthlessness, anergia, poor concentration, change in appetite, psychomotor retardation, and thoughts of death or suicide.[1] MDD is a common mental illness that occurs across the lifespan; it is estimated to affect 10%–15% of the general population in their lifetime[2] and is responsible for significant disability worldwide.[3] "Depression" is a more general term used to refer to depressive symptoms that cause distress and functional impairment, irrespective of whether the symptoms meet the DSM-IV-TR criteria for MDD; this is how we will use the term in this article. Given that depression is a common cause of disability, the etiology of depression is a major focus of research.

A Neural Network Model of Depression

Convergent results from disparate areas of inquiry point to a model in which the signs and symptoms of depression result from disruption of the neural network underlying mood. Multiple network models of depression have been proposed on the basis of structural and functional data from individuals with depression.[4–6] Although the models differ with respect to specifics, they all generally implicate a similar subset of brain areas in the cortical and limbic systems. The prefrontal cortex, cingulate cortex, amygdala, hippocampus, and hypothalamus are some of the areas thought to be of critical importance. Evidence suggests that each of these brain areas can serve as functional nodes,[7] are necessary to the processing of emotions, and can be impaired in depression; hence, these are referred to here as a "neural network underlying mood" or "mood network." Specifically, the prefrontal and cingulate cortices are implicated in the control and regulation of subcortical limbic brain regions, including the amygdala, hippocampus, and hypothalamus,[8] and together are associated with emotional expression and experience.[9] In a simplified model, it is thought that, in individuals with depression, the normal top-down inhibitory control and regulation that is exerted by these cortical areas upon the limbic areas may break down as a result of cortical hypofunction, limbic hyperactivity, or a combination of both.

Multiple Biologic Processes Contribute to Depression

Neural network disruptions reflect the dysfunction of neurons and glial cells within respective areas that compose the mood network, which, in turn, are supported by various molecular dysfunctions. At the molecular level, there is compelling evidence for the involvement of various biologic processes including, but not limited to, altered monoaminergic neurotransmission, altered stress hormone homeostasis, reduced neurotrophic support,metabolic dysregulation, inflammation, oxidative stress responses, mitochondrial function, as well as other aspects of brain plasticity, synaptic function, and calcium regulation.[10] These biologic processes interact at the molecular level, are modulated by genetic variants, and impacted by environmental conditions, together leading to neuronal and glial dysfunction, mood network disruption, and depressive symptoms. Hence, the biologic underpinnings of depression may be varied and heterogeneous. Later in this article, we will propose that depressive symptoms may often arise for the first time in late life because of how these multiple biologic processes are selectively affected, or "pushed" in a disease direction, by the complex phenomenon of aging.

LATE-LIFE DEPRESSION: DEFINITION, EXTENT, BURDEN, AND HOPE

Among individuals 65 years or older, approximately 1% meet criteria of MDD, a prevalence much lower than that found in younger individuals.[11] However, approximately 15%–25% of individuals older than 65 experience depressive symptoms that, while not meeting criteria for MDD, do cause significant distress and interfere with daily functioning.[12] This discrepancy between formal diagnosis of MDD and clinically significant depressive symptoms likely reflects the tendency of older individuals

to underreport psychiatric symptoms such as those required for the DSM-IV-TR diagnosis of MDD, such as the predominance of vegetative and somatic symptoms as part of the clinical presentation of depression in older individuals, the inability of some older individuals to express depressive symptoms secondary to cognitive impairment,[13] and the possibility that depression in older individuals represents its own disease entity with unique clinical presentation and pathophysiology. For the remainder of this article, the term late-life depression (LLD) will be used to refer to individuals older than 65 who for the first time in their lives meet criteria for MDD or experience clinically significant depressive symptoms.

The burden of LLD on the individual with the disease is significant. Individuals with LLD experience greater functional disability[14] and cognitive decline[15] than those without. Furthermore, they are at an increased risk of morbidity and mortality from medical illness,[16] a phenomenon most likely attributable to a combination of both maladaptive health risk behaviors and physiologic effects of LLD. Interestingly, emerging evidence suggests that the association between medical illness and depression is bidirectional, that is, not only does depression magnify the negative consequences of medical illness but medical illness also negatively affects the course of depression;[17,18] accordingly, depression has been proposed as a disease of accelerated aging.[19] In addition to amplifying the rates of morbidity and mortality from medical illness, LLD appears to lead to increased rates of suicide among older individuals.[20] Among individuals 75 years or older, 60%–75% of individuals committing suicide had diagnosable depression.[12]

LLD can be effectively treated using pharmacotherapy, psychotherapy, or both,[21] and response and remission rates are comparable with those in individuals with mid-life depression.[22] Successful diagnosis and treatment of LLD improves depressive symptoms and decreases suicide rates.[23] Despite the demonstrated effectiveness of treatment, many obstacles remain. For example, only 40%–50% of older adults respond to the first prescribed antidepressant medication.[24,25] In those that do respond, response is often slow, sometimes taking up to 4 months[26] and once response is achieved, relapse and recurrence are common. Approximately 60% of community-dwelling older adults with MDD who initially responded to antidepressant treatment became depressed again within 2 years, unless they were maintained on antidepressant pharmacotherapy. Multiple factors including coexisting anxiety, low self-esteem, poor sleep, and coexisting medical burden have been identified that predict more difficult-to-treat depression.[27]

With the hope that a better understanding of the biology underlying LLD would facilitate the development of improved treatments and outcomes for those with LLD, the biologic substrates of LLD are beginning to be characterized. Hence, several hypotheses for the etiology and pathophysiology of LLD have now been proposed.

CURRENT HYPOTHESES FOR BIOLOGIC MECHANISMS PROMOTING LLD

Three influential hypotheses for mechanisms recruited in LLD are the vascular hypothesis,[28] inflammation hypothesis,[29] and dementia prodrome hypothesis.[30] These hypotheses are not mutually exclusive and data exist to support aspects of all three. Moreover, all three hypotheses are consistent with a neural network model of depression described earlier, as well as the idea of multiprocess biologic vulnerability, which we will elaborate on later in this article.

The *vascular depression hypothesis* is based on the observation of an unexpectedly high degree of comorbidity between vascular disease, vascular disease risk factors, and ischemic brain lesions with depressive symptoms.[28] Despite this observation being over a century old,[31] the nature of the relationship remains unclear. That is, does vascular disease cause depression, depression cause vascular disease, or do both vascular disease and depression share a common etiology? Although there is some evidence for each of these scenarios, the vascular depression hypothesis assumes the former and posits that vascular disease may predispose, precipitate, or perpetuate LLD.[28] One way vascular disease might lead an individual to develop LLD is by causing brain lesions that directly disrupt the neural network underlying mood and, thus, the capacity to regulate mood and, subsequently, depressive symptoms. Although data supporting a causal link between vascular disease and LLD are difficult to obtain and

thus lacking, correlative data supporting the vascular depression hypothesis include magnetic resonance imaging studies of the brain of individuals with LLD showing higher rates of white-matter hyperintensities than nondepressed age-matched controls[32,33] and the finding that these white-matter hyperintensities correlate with functional changes in the mood neural network.[34]

The *inflammatory hypothesis* proposes that aging and disease-related processes result in a proinflammatory state that contributes to the etiology of LLD in a subset of individuals. It proposes that the proinflammatory state leads to changes in brain areas included in the neural network underlying mood, thus predisposing aging individuals to developing LLD.[29] The inflammatory hypothesis is supported by a number of experimental observations. For example, aging leads to an exaggerated and prolonged inflammatory response in the brain, and such dysregulation of inflammatory responses leads to emotional and cognitive changes reminiscent of LLD.[35–37] Furthermore, antidepressants have been shown to reduce inflammatory markers[38–40] and some anti-inflammatory agents appear to have antidepressant properties.[41–43]

The *dementia prodrome hypothesis*[30] is based on the observation that older adults with depressive symptoms have a much greater risk of developing dementia upon follow-up than those without depressive symptoms.[44,45] Multiple, nonmutually exclusive etiologic causes have been proposed to explain this association between depression and dementia[46] and, generally, they all propose that the processes that play an etiologic role in disrupting the neural circuitry underlying cognitive function and, thus, lead to dementia also disrupt the neural network underlying mood. One brain area that overlaps between the mood and cognitive neural networks that may have special importance for this hypothesis is the hippocampus. There is evidence that hippocampal atrophy, in addition to being a classic feature of many dementias and aging itself, confers vulnerability to depression.[47,48] Some of the processes with presumed etiologic roles could be subsumed under the *vascular* or *inflammatory* hypotheses, but others such as amyloid plaque formation[49,50] are unique to this hypothesis. Interestingly, hippocampal regions have been found to be especially vulnerable to ischemia[51] and to activation of the hypothalamic–pituitary–adrenal axis, resulting from stress and chronic medical illness.[52] The latter observation may be of particular relevance to the etiology of LLD relative to early-onset depression, given the well-known role of stress and hypothalamic–pituitary–adrenal axis dysfunction (i.e., glucocorticoid hypersecretion) on neurotoxicity of the hippocampus and the increased length and probability of exposure to stress with advancing age.[53,54] Therefore, extended disease- and/or age related exposure to elevated glucocorticoid levels could contribute to a series of physiologic changes akin to an accelerated aging process.[55] Interestingly, the hippocampus is not the only node in the mood network that undergoes structural remodeling as a result of stress-related hypothalamic–pituitary–adrenal axis dysfunction. The prefrontal cortex atrophies and the amygdala increases in size during acute stress and atrophies during extended periods of stress, thus suggesting multiple routes by which stress can disrupt the mood network.[56] One interpretation of the dementia prodrome hypothesis is that the neural networks underlying mood partially overlaps with areas subserving cognition, which are susceptible to subtle and/or cumulative disruption.[46]

The Neural Network Model of Depression and LLD

Central to all three of the above hypotheses and consistent with the putative mechanisms of each is the concept that LLD, as discussed earlier with regard to depression generally, is also a disorder of mood network disruption. The clinical presentation of depression can differ dramatically among individuals and early-onset depression and LLD consistently present differently. Using the DSM-IV-TR criteria alone, there are 227 possible symptom constellations that would warrant a diagnosis of MDD,[1] but only a small percentage of LLD meets these diagnostic criteria. Such heterogeneity in the presentation of depression may be explained by the nature and location of the disruption in the neural network underlying mood, as these factors would determine how the mood network may engage adaptive mechanisms and process stimuli. And, though all disruptions would conceivably disrupt the neural networks underlying mood, the unique effects of each disruption could lead to a distinct clinical picture, thus providing a biologic explanation for the clinical heterogeneity of depression, including

variable symptomatic presentations and treatment response. Given what we know about the differences between early-onset depression and LLD (e.g., family history, and neurologic comorbidity), somewhat different processes would be expected to converge and give rise to mood network dysfunction and thus clinical depression. That is, the observation that LLD frequently presents clinically in a very different way from early-onset depression may be related to the fact that processes that disrupt the circuitry in older adults have a particular mechanism or anatomical propensity that is different from those that disrupt the circuitry in early-life depression, for example, the subcortical predominance of vascular lesions in older individuals or the particular vulnerability of the hippocampus in older individuals to ischemic damage and structural remodeling associated with stress.

MOLECULAR BRAIN AGING: AN ETIOLOGIC ROLE IN LLD?

At the gene level, a subset of genes is observed to have age-related and lifelong progressive changes in expression (at least from a cross-sectional point of view), which is selective to specific cellular functions. This observation is consistent with the idea that aging per se, like depression, reflects the integrated output of multiple and specific biologic processes (described later). Therefore, the presentation of depression on the backdrop of biologic aging raises the question "How does biologic aging contribute to LLD and other age-gated diseases?" Our group has begun to address this question by systematically identifying and quantifying molecular changes in the brain during aging and by investigating the extent of overlap between age- and disease-related processes. As described later, results from these studies demonstrate that age-related gene changes are selective and greatly overlap with biologic processes investigated in the context of multiple neurodegenerative and neuropsychiatric disorders. Moreover, age-related changes are overwhelmingly observed in prodisease directions (Table 1). These observations have led us to propose that biologic aging of the brain may in fact promote age-gated diseases, including LLD, by contributing to selective disruptions of specific neuronal and glial processes, each with putative etiologic roles in disease-related biologic processes, including mood network disruption.[57,58]

"Molecular Aging" of the Human Brain

It has been known for some time that robust changes in gene expression occur with aging.[59] The fact that age-related changes in gene expression extend to the brain may not be surprising given the body of knowledge about changes in structure and function of the brain with age. In light of the many changes seen with aging, one might hypothesize that age-related changes in gene expression reflect a general deterioration of the brain and, thus, a preponderance of genes would be affected. However, what is emerging from recent genome-wide studies is that the changes in gene expression with aging affect a relatively smaller number of genes than one might have expected. Studies in rodent, monkey, and human brains estimate the number of genes exhibiting age-related changes to represent less than 10%, and commonly less than 5%, of the entire genome.[60–66] In a study from our group, the age related changes of a large number of genes using microarray technology were profiled in prefrontal cortex samples from human subjects age 13–79 years.[66] The data from this study identified life-long progressive changes in expression with age of up to 7.5% of the genes tested. This restricted scope of transcript changes suggests that specific cellular populations and biologic processes are selectively vulnerable during aging. Interestingly, the set of age-dependent genes in our group's study was very similar to those observed in other studies,[57,60–62,64,66–68] and in fact displayed high degree of conservation across cohorts and cortical brain regions.[58] Expression of genes playing a role in glial-mediated inflammation, oxidative stress responses, mitochondrial function, synaptic function and plasticity, and calcium regulation has now consistently been shown across multiple studies to be affected by aging, despite differences in sample size, selection of tissue type or brain region, expression analysis platforms, and analytical methods.[57,60–62,64,66–68] Of note, not only is the identity of the genes and gene classes that are affected with aging consistent among studies but so are the directions of change. Overall, age-upregulated genes are mostly of glial origin and related to inflammation and cellular defenses,

TABLE 1. Age-Related Changes Observed in Prodisease Directions

		Disease							Age		
Disease-Associated Gene		**AD**	**PD**	**HD**	**ALS**	**SCZ**	**MD**	**BPD**	**ACC**	**BA9**	**BA47**
NF-kappa B	*NF-KB/RELA*	■	■						■	■	■
GABA transaminase	*ABAT/GABA-T*	■			■	■			■	■	
Clusterin/apolipoprotein-J	*CLU/APOJ*	■							■	■	■
Monoamine oxidase B	*MAOB*	■	■		■		■			■	■
Amyloid precursor-like protein 2	*APLP2*	■							■	■	■
Parkinson disease-7	*DJ-1*		■						■		
Parkinson disease-5	*UCHL1*		■						■	■	
Parkinson disease-13	*HTRA2*		■						■	■	■
Parkin	*PARKIN*		■						■	■	■
Reelin	*RELN*	■				■		■	■		■
Huntingtin	*HD*			■						■	
Manganese superoxide dismutase	*SOD2*	■			■	■				■	
Cannabanoid receptor-1	*CNR1*					■				■	■
Cholecystokinin	*CCK*					■			■	■	
Neuropeptide-Y	*NPY*			■		■	■	■	■	■	
Parkinson disease-6	*Pink1*		■						■	■	■
Serotonin 2A receptor	*HTR2A*					■	■		■	■	■
Regulator of G-protein signaling-4	*RGS4*					■		■	■	■	■
Somatostatin	*SST*	■	■	■		■	■	■	■	■	■
Brain-derived neurotrophic factor	*BDNF*	■	■	■		■	■	■	■	■	■
Dopamine receptor D1	*DRD1*					■			■	■	■
Parvalbumin	*PVALB*					■		■	■		■
Glutamate decarboxylase 1	*GAD67*					■	■	■		■	■

Notes: A number of genes display similar changes in expression levels between aging and multiple neurodegenerative and neuropsychiatric disorders, including depression. Red: increased expression; blue: decreased expression; AD: Alzheimer disease; PD: Parkinson disease; HD: Huntington disease; ALS: amyotrophic lateral sclerosis; SCZ: schizophrenia; MD: major depression; BPD: bipolar depression. Adapted from Glorioso et al.[57]

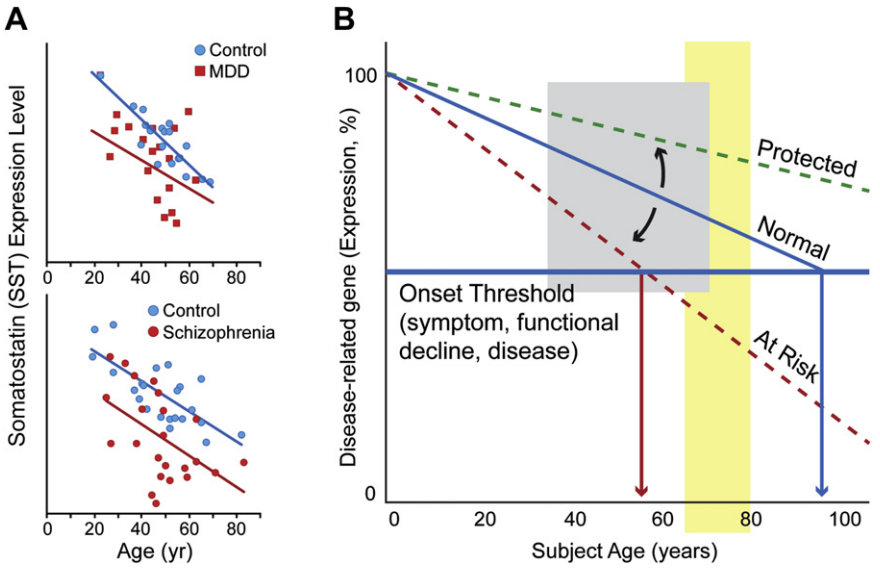
whereas downregulated genes display mostly neuron-enriched transcripts relating to cellular communication and signaling.[66] This consistency and specificity of age-related changes in fact fulfills criteria for biomarkers. Indeed, we have shown that the predicted age for a particular individual, based on regression analysis of expected age related trajectories for those age biomarkers (denoted as "molecular age"), is highly correlated with the chronologic age of that individual.[57,66]

Molecular Aging of the Brain Interacts With Neuropsychiatric and Neurodegenerative Disease Pathways

Studies of the molecular basis of neurodegenerative and neuropsychiatric disorders often describe age-related changes in genes of interest. For instance, we have reported that the variance in depression related decrease in the neuropeptide somatostatin (SST) can be mostly explained by superimposed age related changes[58,69] (Figure 1[A]). Indeed, consistent with prior findings,[66] normal subjects between the age of 20 and 70 years lose approximately 40%–50% of SST expression, whereas subjects affected with depression appear to be on an early trajectory of age related decline [69] (Figure 1[A], top panel), and similar findings have been reported in schizophrenia[70] (Figure 1[A], bottom panel). Central to our proposed model for age-by-disease interaction, it is not known whether these anticipated changes reflect a disease effect or an early age decline, which would have placed the system at increased vulnerability for depression.

Expanding these observations to genome-wide investigations, we have reported that up to one-third of age-regulated genes (>800–1000 genes) in the human brain have been otherwise associated with neurodegenerative (Alzheimer, Parkinson and

FIGURE 1. Many genes, such as somatostatin, show similar age- and disease-related changes in gene expression, leading to our model of how age-related changes in the expression of disease-related genes could influence age of onset of disease. [A] Somatostatin expression decreases with age and individuals with major depression (top panel) and schizophrenia (bottom panel) display lower levels of expression than control subjects. We hypothesize that decreased expression of somatostatin in psychiatric disorders may represent an early brain- and age-related molecular phenotype in these individuals, which render these subjects vulnerable to developing psychiatric diseases. [B] In a model derived from the proposed age-by-disease interaction hypothesis, change in the expression of disease-related genes (a decrease is shown here) across a threshold (horizontal blue line) marks the onset of disease symptoms. Changes in the trajectory of age-related changes in the expression of disease-related genes (y-axis) determine the age (x-axis), or even if an individual develops disease symptoms (vertical red arrows). According to this model, modulators (black arrows), genetic or environmental, place subjects on an "at-risk" or protected trajectory for developing mood symptoms and LLD. Adapted from Morris et al.,[70] Tripp et al.,[69] and Glorioso et al.[57,58]



Huntington diseases, and amyotrophic lateral sclerosis) and neuropsychiatric disorders (bipolar depression, major depression, and schizophrenia).[58] Not only do the genes relevant to these brain diseases show age-related changes but the direction of the changes that occur with age is almost always in the direction thought to cause or promote diseases[58] (Table 1), as exemplified by SST age- and disease-related changes shown here (Figure 1[A]). Note that such normal age effects can go unnoticed in age-matched paired sample design, which may incorrectly suggest that changes in gene expression in depression, Alzheimer disease, or other age-gated diseases are separate from what would be seen in normal aging. Conversely, very few (<5%) of the larger pool of genes that do not display age-dependent changes are otherwise associated with neurodegenerative and neuropsychiatric diseases.[58] Together, these data suggest that, at the single gene level, aging may promote selective changes in gene expression in ways that promote diseases. Collectively, the large number of disease-related genes affected during aging in prodisease directions also suggests that system-level adaptations occur with age, such an age-by-disease interaction leads toward physiologic states that are in fact closer to disease states than at younger ages (see Douillard-Guilloux et al.[71]).

Genetic Determinants of the Age-by-Disease Interaction May Modulate the Vulnerability to Develop Age-Related Diseases: A Correlative Proof of Concept

The nature of external and internal events driving age-related transcript changes are mostly unknown and the underlying "molecular clock" is somewhat of a holy grail in aging research. Interestingly, genes forming the "molecular aging" profile include numerous transcriptional regulators,[57] and an individual's molecular age can deviate from its predicted

trajectory, together suggesting that modulating factors may contribute not only to age-related changes but also to their intrinsic variability. Hence, we have proposed that individuals with older predicted molecular ages compared with their chronologic age may not only display greater biologic brain aging but may also be at a greater risk of age-gated brain diseases, because gene expression of disease-related genes would have proceeded further in disease-promoting directions. In contrast, subjects with younger gene trajectories or predicted molecular ages would be at lower risk and may, in fact, display resiliency against LLD and other late-life disorders (Figure 1[B]).

Environmental and genetic factors represent obvious candidate modulators of the trajectory of biologic aging. In recent years, the identification of single-gene mutations affecting aging and longevity in nematodes, insects, and rodents has clearly demonstrated the presence of a genetic program underlying aging.[72] In the mammalian brain, the course of aging parallels that of peripheral tissues and additional mechanisms may reflect the specificities of postmitotic differentiated neurons,[73] but one might expect a certain level of conservation in basic molecular mechanisms relating to aging, including their regulation. In fact, using the above-described "molecular age" assay and focusing on a family of genes with phylogenetically conserved age-modulatory roles (i.e., sirtuins[74]), we have reported that subjects carrying a low-expressing polymorphism of the sirtuin 5 gene had molecular ages that were older than the actual chronologic age, as measured in the cingulate cortex of human postmortem samples.[57] We further showed that this effect was accompanied by expression changes for a set of genes whose products are localized to the mitochondria, including PINK-1 and DJ-1, two Parkinson disease–associated genes, in ways that would promote-mitochondrial dysfunction–related diseases, including the age-gated Parkinson disease. Confirmation of this putative mechanism will require large scale assessment of live subjects with Parkinson disease and normal controls to assess whether either disease onset and severity or age-related functional declines in the domains of mood, cognition, or motor function are differentially associated with this or other sirtuin 5 gene polymorphisms. Together, this (correlative) proof-of-principle study suggests that factors that affect biologic aging of the brain (genetic or environmental) can potentially place an individual at higher risk for disease, through a mechanism by which it accelerates brain molecular aging and, thus, promotes changes in expression of disease-relevant genes in disease-causing directions. With respect to Figure 1[B], the low-expressing polymorphism of the sirtuin 5 gene can be thought of as a modulator that puts one on the "at-risk" trajectory. The converse of this model is that, based on population frequencies, the "risk" allele may in fact be the major allele and, thus, considered normal, with the other allele conferring protection or resiliency. Hence, the assessment of risk and resiliency may, in fact, be built in the same model.[58] Here, the prediction would be that factors delaying age trajectories of gene changes may lead to younger brain molecular aging and potential resiliency toward developing functional declines and age-related disorders, including LLD (Figure 1[B]).

ALTERED BIOLOGIC LANDSCAPE AND PHYSIOLOGIC HOMEOSTASIS IN DEPRESSION AND AGING: AN AGE-BY-DISEASE INTERACTION HYPOTHESIS FOR LLD

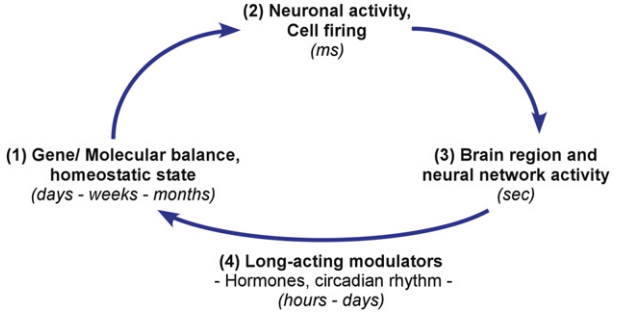
The above observations of 1) parallel age and disease trajectories in gene changes, 2) anticipated and greater extent of changes in neurodegenerative and neuropsychiatric diseases, 3) relative paucity of disease association for age-independent genes, and 4) putative genetic modulation of age-mediated risk together provide a compelling rationale for investigating aging and brain disorders simultaneously. Indeed, these observations suggest that age-related changes in gene function may, in fact, promote vulnerability to develop a set of diseases that are otherwise described as age-gated or age-dependent, through progressive changes in gene expression for disease-related genes in directions predicted to promote those diseases. This model departs from the current framework for neurodegenerative and neuropsychiatric disorders in that it places the aging process and age-related changes in gene expression as a putative driving force in the etiology and onset of multiple brain disorders, rather than a mere clinical confounding parameter. How could such a model work?

A Gene–Cell–Neural Network Feedback Loop Maintaining Physiologic Homeostasis Is Affected in Depression and Aging

The physiologic and functional output of any biologic system or subsystem represents the vertical integration of events occurring at the levels of molecule, cell, cellular connectivity and communication, and endocrine control, among others. Constant feedback among biologic scales contributes to maintaining the physiologic output of the system in homeostasis, as illustrated in a simplified interactive feedback loop that incorporates genes, cells, and cell assemblies (Figure 2). Modulators of this feedback loop include hormone-like factors that follow constitutive, activity-dependent, or cyclic pattern and most frequently regulate patterns of gene expression in target cells through the activation of signal transduction pathways or by direct activation of nuclear receptors. These long-acting modulators are responsible for inducing and maintaining long-term adaptive shifts in molecular balances and associated changes in biologic landscapes.

An example of modulator of neural network activity that contributes to such feedback loops is brain-derived neurotrophic factor (BDNF). BDNF is essential for maintaining multiple aspects of neuron structure and function, a role that is mediated by membrane receptors and signal transduction pathways that affect the expression of specific sets of genes. Expression of the BDNF gene and release of BDNF protein are triggered by neuronal activity, but are also under constant constitutive release that follows a circadian pattern.[75] It is thought that the variable kinetics of BDNF release are critical to the continuous neuronal adaptations that are required to face an energetic and functional environment that is under constant flux.[76] For instance, using human postmortem samples and genetic studies in mice, we recently showed that BDNF levels are reduced in the amygdala of women affected with major depression and that this reduction correlated with (and likely induced, based on mouse genetic studies) molecular adaptations in specific subsets of γ-aminobutyric acid–containing inhibitory neurons that target the dendrites of pyramidal neurons, a cellular compartment critical for integrating incoming information-rich signals.[77] We have speculated that a state of BDNF-dependent reduced dendritic inhibition may represent a novel stable state over time, although it is

FIGURE 2. **Integration of multiple biologic scales and maintenance of neural network homeostasis: a simplified interactive *gene → cell → neural network → gene* feedback loop. The molecular composition (1) of particular neurons, in terms of receptors, signal transduction pathways, channel composition, etc., determines the firing properties of those cells (2). The firing patterns and local connectivity of those individual neurons determine the characteristic activity of a particular brain region (3), which, in concert with related brain areas, contributes to neural network–based functional output. The critical component of the feedback loop is the constant internal molecular and cellular adaptation that occurs in response to cellular and neural network activities (4). Notably, molecular adaptations are mediated and modulated by long-acting factors such as metabolic-, stress-, and sex-related hormones and neurotrophic factors (4). The corresponding changes in gene expression and associated protein–mediated functions, in turn, allow for the long-term cellular adaptations necessary for fine-tuning short-term neuronal firing properties and for adapting neural activity in response to an ever-changing molecular and cellular environment, thus closing the *gene → cell → neural network → gene* integrative feedback loop. Over time, stable states of dynamic equilibrium are reached, which can, however, be set at various levels. In turn, these different stable or homeostatic biologic states can be conceptualized as "regional attractor states" within the broader biologic landscape (see Figure 3).**



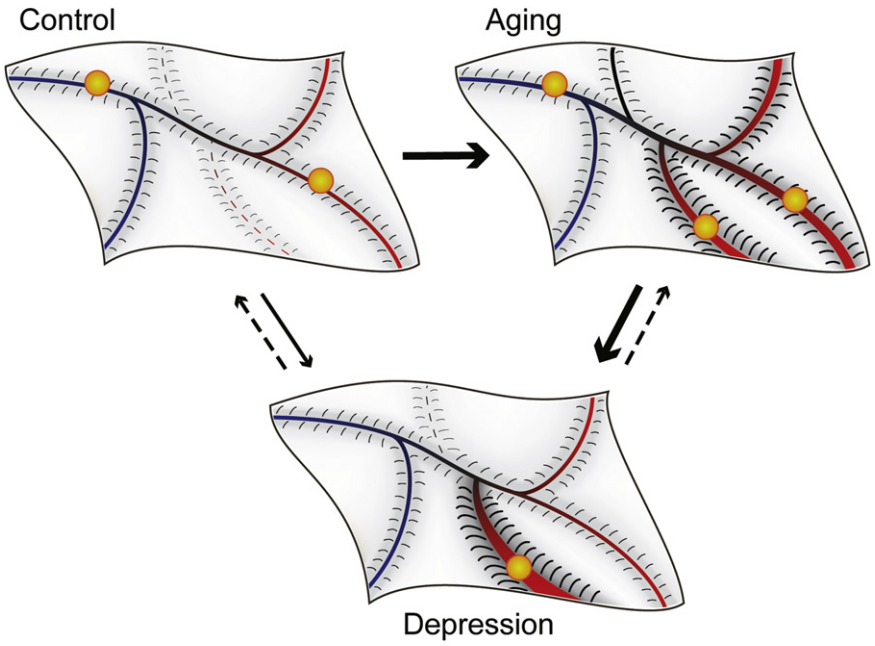
maladaptive in that it may mediate increased amygdala reactivity, a neural network endophenotype frequently observed in MDD and thought to underlie the rumination or bias for negative emotions in depressed subjects.[78] Supporting our age-by-disease interaction model, BDNF is also robustly downregulated with increasing age, suggesting that similar downstream changes may occur in older subjects (see Douillard-Guilloux et al.[71]).

Other relevant hormone-type factors that follow similar complex patterns of programmed and activity-dependent release and that have often been associated with depression-related mechanisms include metabolic (e.g., insulin and thyroid) and sex and stress steroid hormones. These factors may originate in peripheral organs and/or brain, but notably exert their effects on neurons and other brain cells by controlling and coordinating transcriptional programs through binding and activating nuclear receptors, which directly act as transcription factors for various gene sets. Recently, we have investigated the coordination of gene transcript levels across brain areas (denoted "gene synchrony") and reported significant changes in gene synchrony between the amygdala and the anterior cingulate cortex in subjects with MDD, compared with psychiatric control subjects.[79] The interpretation of these findings was that the transcriptional regulation of those genes had changed between these two areas in the context of depression. Notably, investigating potential upstream mediators, we showed that this state of altered corticolimbic gene synchrony in depression could be explained by the combined dysregulation of several hormone-like factors previously implicated in depression, such as insulin, interleukin-1, thyroid hormone, estradiol, and glucocorticoids.[79] On the basis of these results, we have speculated on the presence of a distinct and integrated hormone-like-factor–mediated corticolimbic homeostatic, although maladaptive and pathologic, state in major depression.

A Decanalization Perspective on Changing Biologic Landscapes to Illustrate the Age-by-Disease Interaction Hypothesis of LLD

The "gene →cell →neural network →gene" loop is essential for biologic adaptation, so that each system or subsystem reaches an equilibrium state from which it is biologically allowed to wobble within a determined range to maintain physiologic homeostasis in the face of a fluctuating environment. A useful concept to visualize such homeostasis and associated disturbances is provided by the "canalization" framework (Figure 3). Waddington et al.[80,81] first used this conceptualization to model how genetic, environmental or other influences can interact to affect the course of development of normative phenotypes and how "decanalization" can lead to distinct and stable alternative phenotypes. In this model, the normal function of a biologic system or subsystem over time is represented by a ball in the canal of the model surface, with depth and slope of the canal banks representing the magnitude of the constraining forces on normal variability (Figure 3, top-left panel). "Canalizing" influences maintain progression toward the normative canal. Disruptive or "decanalizing" influences can be of two forms: temporary or structural. Temporary decanalizing effects lead the system away from the normative canal for a short duration, as the system will naturally come back to a stable state within the normative canal. Structural decanalizing effects, on the contrary, affect the shape of the model surface such that new canals representing alternative stable phenotypes may be formed and/or the slope of the banks of the canals representing barriers of entry into or exit from the canals may change. Indeed, a central feature of this concept is that the canalization landscape is not rigid. Development, disease processes, and aging (as we propose here) affect the topography of the landscape. Here, we define decanalizing influences as events that induce structural changes away from a normative, optimal, and adaptive landscape profile. For instance, we can conceptualize the function of the corticolimbic neural network underlying mood as the biologic system in question, where the "gene →cell →neural network →gene" loop just described allows the system to move in the canalization model within a delineated range of variable states (Figure 3, top-left panel), corresponding to the natural propensity to adapt and experience states of normal, high, or low mood. In other words, the canalization landscape provides a defined repertoire of physiologic/emotional states, and the depth of canals and slope of their banks represent the propensity of the individual to reside or experience the respective states.

FIGURE 3. **A canalization–decanalization representation of the age-by-disease interaction hypothesis of LLD and its putative effect on homeostatic states of a neural network underlying mood. This model allows for the visualization of how canalizing influences can interact to maintain normative biology, for example, mood network function, and how decanalizing influences can lead to stable alternative, but sometimes maladaptive functioning, as for mood network dysregulation in clinical depression. Here, the normal variability over time in the functional state of the neural network underlying mood is represented by a ball, which can circulate along the canals of a model surface (or biologic landscape), representing the repertoire of allowed physiologic states (top-left panel). Decanalizing influences lead the system away from the normative canal or affect the shape of the model surface such that canals representing alternative stable phenotypes are either made easier to enter into or formed de novo. In depression (bottom panel), decanalizing influences change the topography of the model surface such that it is easier for the "ball" to enter into existing or new canals representing alternative stable, but maladaptive, functioning of the neural network underlying mood and remain in those canals. Just as development and diseases can modify the topography or landscape of the model surface, so too does aging (top-right panel). Because the biologic processes disrupted in aging overlap to a significant degree with those recruited in a number of brain diseases including LLD, the areas of the model surface that change with aging are more likely to be those corresponding to disease states (red section of the landscape). The result is that aging changes the topography of the brain biologic landscape, leading to a shift in the repertoire of available physiologic states in a prodisease or LLD direction.**



Effect of Depression on the Canalization Landscape

As described earlier, a multisystem deregulation is likely to occur in depression and variable sets of stable biologic disturbances may characterize individual subjects, despite similarities in clinical presentation. Intrinsic to the canalization model is the notion that the underlying architecture of the landscape is determined and maintained by the molecular and cellular composition of the system and that minute homeostatic changes in "gene →cell →neural network → gene" feedback loops cooperate to affect and mold the shape of the landscape, hence changing the biologic landscape and associated repertoire of allowed functional states. In other words, biologic changes occurring in the context of diseases (e.g., low BDNF and altered GABA inhibition, and altered corticolimbic gene synchrony) have long-term effects on the structure of the biologic landscape, leading to altered constraints on adaptive movements within that landscape. In disease, strong attractor states are, thus, created by increasing the slope of the banks of existing or new canals, resulting in higher propensity to enter into and remain in those states (Figure 3, bottom panel). For instance, the core symptoms of depression points to a critical deficit in mood regulation, specifically a high propensity for

entering low mood states and a reduced ability to experience positive emotions, supporting the presence of a novel attractor state in an area of the canalization landscape corresponding to a low mood state (i.e., deep landscape groove in the bottom panel of Figure 3). As depression is often characterized by life-long chronicity and increased severity, this modified landscape is thus not expected to easily revert back to a control topography, but rather to lead to increased delineation and reduced barrier to entry into grooves corresponding to low mood states.

Effect of Aging on the Canalization Landscape: Implications for LLD

Just as development and diseases can modify the canalization landscape, the numerous biologic changes occurring in the human brain during aging are adaptive in the way that they maintain brain functional homeostasis. This would translate in morphologic changes in the canalization landscape, that is, changes in the slopes of the banks of existing canals or emergence of new ones (Figure 3, right panel). As previously described, age-dependent changes in the function of multiple genes affect various, yet specific, cellular and molecular pathways in directions predicting increased vulnerability to disease states; so the modifications to the landscape are most likely to affect areas corresponding to disease states (red section of the landscape in Figure 3), with increased probability of residing in those states, through steepening of the banks of the canals or lowering barriers of entry into the canals. The result is a shift in the repertoire of available states in a prodisease direction. Like in the original conceptualization, genetic and environmental influences, via their effects on multiple biologic processes, could further push the trajectory of an individual toward a canal representing normative mood network function or toward other canals corresponding to mood network disruption, resulting, for instance, in more stable states of low mood associated with clinical depression (Figure 3, bottom panel). Therefore, as aging proceeds, the dynamics of changes between states are progressively affected, so that combinations of small environmental perturbations and milder genetic vulnerability could now become sufficient to lead to states of network dysfunction and depression, whereas a "younger" landscape may be "structurally" resilient to such influences. Together, we propose that the characteristics of biologic aging of the brain, and specifically their overlap with neurologic and neuropsychiatric disease processes, correspond to changes in the canalization and biologic landscape that places the system at elevated vulnerability for increased incidence and stability of disease states, including corticolimbic disruption and low mood associated with depression.

SUMMARY, CONCLUSIONS, AND FUTURE DIRECTIONS

Here, we hypothesize and provide data supporting a novel putative mechanism for the development of LLD. According to this proposed age-by-disease interaction hypothesis, LLD and associated symptoms may partly arise from normal changes in the expression of depression- and other disease-related genes, which occur in disease-causing directions with increasing age. This model does not preclude previously hypothesized mechanisms (e.g., vascular, inflammatory, and dementia prodrome hypotheses), but rather positions age-related changes in gene expression as the mechanism driving dysfunctions in biologic processes that in turn promote LLD, including vascular, inflammatory, neurotrophic, and dementia-related processes. Perhaps the most exciting implication of this model relates to how it might inform in several ways research and development of new interventions for the prevention and treatment of LLD. First, identifying the biologic changes that occur during normal aging may provide valuable information about the cellular and molecular processes that may contribute to age-related brain diseases such as LLD, hence providing mechanistic entry points and potential targets for early intervention. According to this model, one intervention would be to slow down the trajectory of molecular aging for critical genes, via targeting biologic modulators and transcriptional regulators for instance. Candidate interventions may include known interventions such as antidepressant medications, psychotherapy, and exercise, because investigating how these therapeutic approaches affect molecular aging trajectories may help in optimizing their implementation with respect to timing and duration of intervention for age-dependent diseases. Hence, understanding the "molecular clock" and

associated mechanisms underlying age-dependent changes in humans and model organisms would be critical for both disease and aging research. Mechanisms related to oxidative stress, cellular metabolism, and genome integrity, through either repair or maintenance of proper telomere length for instance, are current topics of research.[64,82–85] The brain and neuronal system specificities of these biologic processes represent unique areas of investigation for psychiatric and/or neurologic disorders. Another important topic of further investigation relates to the individual variability in age-related vulnerability to develop functional declines and associated disease symptoms, including LLD. Identifying genetic and environmental factors that place individuals on accelerated or slowed-down molecular trajectories for critical genes may lead to individualized strategies aimed at promoting resilience and successful aging. Finally, for the broader fields of aging and gerontology, the implication of this hypothesis is that it brings together research on normal aging more closely with the investigation of neuropsychiatric and neurodegenerative diseases. Indeed, our data firmly support the assertion that they may in fact be related facets of similar biologic processes, while also providing a putative mechanism of the age-by-disease interaction.

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