European Neuropsychopharmacology

Systemic Neuro-Dysregulation in Depression: Evidence from Genome-wide Association

--Manuscript Draft--

Manuscript Number:	
Article Type:	Review article
Keywords:	Depression; GWAS; Genetics; Neuroscience; Psychiatry; Mood Disorders
Corresponding Author:	Justin Tubbs HONG KONG
First Author:	Justin Tubbs
Order of Authors:	Justin Tubbs
	Jiahong Ding
	Larry Baum
	Pak C. Sham
Abstract:	Depression is the world's leading cause of disability. Greater understanding of the neurobiological basis of depression is necessary for developing novel treatments with improved efficacy and acceptance. Recently, major advances have been made in the search for genetic variants associated with depression which may help to elucidate etiological mechanisms. The present review has two major objectives. First, we offer a brief review of two major biological systems with strong evidence for involvement in depression pathology: neurotransmitter systems and the stress response. Secondly, we provide a synthesis of the functions of the 269 genes implicated by the most recent genome-wide meta-analysis, supporting the importance of these systems in depression and providing insights into other possible mechanisms involving neurodevelopment, neurogenesis, and neurodegeneration. Our goal is to undertake a broad, preliminary stock-taking of the most recent hypothesis-free findings and examine the weight of the evidence supporting existing theories and novel directions. This qualitative review and accompanying gene function table provides a valuable resource and guide for basic and translational researchers, with suggestions for future mechanistic research, leveraging genetics to prioritize studies aimed at understanding the neurobiological processes involved in depression etiology and treatment.
Suggested Reviewers:	Cathryn Lewis cathryn.lewis@kcl.ac.uk depression genetics expert
	Carmine Pariante Carmine.pariante@kcl.ac.uk Depression expert
	Tao Li scutaoli1981@scu.edu.cn psychiatric genetics expert

April 9, 2020

A. Meyer-Lindenberg, MD, PhD
European Neuropsychopharmacology
Re: Manuscript Submission

Dear Dr. Meyer-Lindenberg

This letter accompanies the manuscript "Systemic Neuro-Dysregulation in Depression: Evidence from Genome-wide Association" to be considered for publication in *European Neuropsychopharmacology*.

Depression is currently the leading cause of worldwide disability, but available treatments show marginal efficacy and are often accompanied by side-effects and present practical limitations. Genome-wide association studies (GWAS) provide a hypothesis-free method for prioritizing biological pathways which may be relevant to complex disorders and can inform the development of novel treatments and research towards a mechanistic understanding of depression etiology.

We provide an overview of major biological systems which have consistently shown dysregulation in depression: neurotransmitters and the stress response, followed by a detailed qualitative analysis of the genes identified by the most recent GWAS meta-analysis of depression by Howard and colleagues (2019), presented in the context of known functions of these genes which may be relevant to depression, lending support to previously studied systems and implicating more novel research directions.

The goal of our paper as providing a broad overview of the most recent hypothesis-free genome-wide evidence, while also providing a synthesis of these genes with their known functions, which implicate both existing neurobiological theories and novel directions. This allows researchers across many sub-disciplines to take a bird's eye view of the current evidence and provides a platform for identifying targets relevant to their area of expertise. We hope that such a synthesis will be especially useful in hypothesis generation and prioritization for the basic and translational scientists who read *European Neuropsychopharmacology*.

This manuscript has not been previously published, nor is it being considered for publication elsewhere. All authors have approved the final version of the manuscript. This manuscript was not directly supported by any institutional funding or grants. The authors declare no conflicts of interest.

Thank you for your consideration. We look forward to hearing from you.

Pak-Chung Sham BM BCh MA MSc PhD MRCPsych
Suen Chi-Sun Professor in Clinical Science
Chair Professor of Psychiatric Genomics
Academic Lead in Research and Training, Centre for PanorOmic Sciences
Co-director, State Key Laboratory of Brain and Cognitive Sciences
Department of Psychiatry
Li Ka Shing Faculty of Medicine
The University of Hong Kong
pcsham@hku.hk

Systemic Neuro-Dysregulation in Depression: Evidence from Genome-wide Association

Justin D. Tubbs[1], Jiahong Ding[1], Larry Baum[1,2], Pak C. Sham*[1,2,3]

1. Department of Psychiatry, The University of Hong Kong, Hong Kong
2. State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong
3. Centre of PanorOmic Sciences, The University of Hong Kong, Hong Kong
*Corresponding Author: pcsham@hku.hk 1/F, 5 Sassoon Road, Pokfulam, Hong Kong

Abstract

Depression is the world's leading cause of disability. Greater understanding of the neurobiological basis of depression is necessary for developing novel treatments with improved efficacy and acceptance. Recently, major advances have been made in the search for genetic variants associated with depression which may help to elucidate etiological mechanisms. The present review has two major objectives. First, we offer a brief review of two major biological systems with strong evidence for involvement in depression pathology: neurotransmitter systems and the stress response. Secondly, we provide a synthesis of the functions of the 269 genes implicated by the most recent genome-wide meta-analysis, supporting the importance of these systems in depression and providing insights into other possible mechanisms involving neurodevelopment, neurogenesis, and neurodegeneration. Our goal is to undertake a broad, preliminary stock-taking of the most recent hypothesis-free findings and examine the weight of the evidence supporting existing theories and novel directions. This qualitative review and accompanying gene function table provides a valuable resource and guide for basic and translational researchers, with suggestions for future mechanistic research, leveraging genetics to prioritize studies aimed at understanding the neurobiological processes involved in depression etiology and treatment.

Keywords: Depression; GWAS; Genetics; Neuroscience; Psychiatry; Mood Disorders

Outline

1. Introduction
2. Depression is Associated with Systemic Neuro-Dysregulation
    - 2.1. Neurotransmitter Systems
        - 2.1.1. Monoamines
        - 2.1.2. Amino Acid Neurotransmitters
        - 2.1.3. Sex Differences
    - 2.2. Stress Response System
        - 2.2.1. Theoretical Considerations and Epidemiological Evidence
        - 2.2.2. Typical Neurobiological Stress Response
        - 2.2.3. Neurobiological Evidence for Dysregulation in Depression
        - 2.2.4. Sex Differences
    - 2.3. Systemic Dysfunction Shared with Anxiety
3. Depression Genetics
    - 3.1. An Overview of Depression Genetics
    - 3.2. Qualitative Analysis of Gene-Based Meta-Analysis Results
        - 3.2.1. Neurotransmitter-Related Genes
        - 3.2.2. Stress Response-Related Genes
        - 3.2.3. Remaining Genes
        - 3.2.4. Overlap with Anxiety Genes
4. Discussion

Abbreviations: World Health Organization (WHO), monoamine oxidase (MAO), norepinephrine (NE), electroconvulsive therapy (ECT), N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), selective serotonin reuptake inhibitors (SSRIs), positron emission tomography (PET), brain-derived neurotrophic factor (BDNF), fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF), hypothalamic-pituitary-adrenocortical (HPA), prefrontal cortex (PFC), anterior cingulate cortex (ACC), autonomic nervous system (ANS), corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), human herpesvirus (HHV), interferon-α (IFN-α), Institute for Health Metrics and Evaluation (IHME), disability adjusted life-years lost (DALYs), interleukin(IL), prostaglandin E2 (PGE2), mitogen-activated protein kinase (MAPK), cyclooxygenase (COX), central nervous system (CNS), indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO), genome-wide association studies (GWAS), single nucleotide polymorphisms (SNPs), Psychiatric Genomics Consortium (PGC), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), metabotropic glutamate receptors (mGluR)

1. Introduction

Depression is the leading cause of global disability according to the World Health Organization (WHO; 2017). As a complex multifactorial disorder, clinical depression is identified by core symptoms of low mood and/or anhedonia which may be accompanied by cognitive, behavioral, or neurovegetative deficits (American Psychiatric Association, 2013; WHO, 2018). Clinical depression is a severe disorder which causes suffering, impairs daily functioning, and may tragically lead to suicide. Alarmingly, depression appears to be on the rise in the United States and globally, especially among young people and women (Twenge et al., 2019; WHO, 2017).

A broader conceptualization of depression can encompass a set of adaptive cognitive, mood, behavioral, and biological responses that may have evolved to facilitate reevaluation of goals and conservation of energy following the perceived loss of a valuable resource or investment, or recuperation from injury (Beck and Bredemeier, 2016; Bergstrom and Meacham, 2016; Nesse, 2000). While this response pattern might have been adaptive in the harsh environments of our ancestors, it may be maladaptive in the current modern environment, where an overactivation of the system can lead to severe and persistent depression, a pathological state that causes substantial disability and mortality, including suicide. Beck and Bredemeier (2016) stress the importance of individual differences, ascribed partially to inherited genetic factors that influence exposure and resilience to stressors.

Compared to placebo, common pharmacological treatments for depression and anxiety demonstrate only modest effect sizes and can be accompanied by undesirable side effects (Locher et al., 2017; Sugarman et al., 2014), creating an urgent need for novel treatment options. Although psychiatry has a history of serendipitous drug discovery, an understanding of the

underlying psychobiological etiology of depression may lead to more targeted and effective treatments. Encouragingly, genome-wide approaches employing high-throughput genotyping technologies on large samples have demonstrated remarkable success in identifying specific genetic variants associated with depression (Howard et al., 2018; Hyde et al., 2016; Wray et al., 2018). Most recently, a meta-analysis of these studies identified 269 genes implicated in depression (Howard et al., 2019). These findings provide a hypothesis-free method for prioritizing future research towards a mechanistic understanding of depression and potential targets for intervention. Nevertheless, consideration of existing theories of depression may be valuable in the interpretation of new genetic findings.

Here, we conduct a qualitative review and synthesis of these gene-based findings in terms of the known gene functions, with the goal of performing a preliminary stock-taking of this most recent evidence in light of the most common neurobiological systems known to be involved in depression. Such a review should lay a foundation for researchers across sub-specialties to weigh the current evidence and make informed decisions when designing future research studies. We first provide a review of major biological systems historically of major research focus which have been consistently shown to be dysregulated in depressed patients: neurotransmitter systems and the stress response system. Figure 1 provides a simplified schematic model of major neurobiological systems which are likely involved in depression predisposition, etiology, and maintenance. Evidence suggests a higher prevalence of depression in women (Kessler et al., 2012), but while twin studies support the presence of sex-specific genetic effects (Kendler et al., 2006, 2001), recent genome-wide association studies (GWAS) have yet to identify any specific replicable loci (Dunn et al., 2018; Hall et al., 2018; Trzaskowski et al., 2019). Therefore, we briefly discuss evidence for sex differences in these systems which may be relevant to

depression. Additionally, given the high comorbidity between depression and anxiety (Kessler et al., 2007; Lamers et al., 2011), we identify possible overlapping biological disruption in these disorders. Following this abbreviated review of systemic dysregulation, we present a qualitative analysis of recent genetic findings in terms of neurotransmitter and stress systems and the overlap with genes implicated in anxiety, accompanied by a discussion of potentially novel insights from those implicated genes that do not have known functions in these systems. In light of these findings, we suggest strategies for future research into the psychobiological mechanisms underlying depression and the search for effective treatments.

2. Depression is Associated with Systemic Dysregulation

2.1. Neurotransmitter Systems

A rich literature exploring the role of neurotransmitter dysregulation in depression has grown from the serendipitous discovery of monoamine oxidase (MAO) inhibitors and tricyclic antidepressants as effective pharmacological treatments for mood disorders in the 1950s (Hirschfeld, 2000; Nutt, 2008). In an attempt to avoid the side-effects associated with these drugs which non-specifically increase the levels of brain monoamines, pharmaceuticals were later developed to selectively block the reuptake of specific monoamines including serotonin, norepinephrine (NE), and dopamine, increasing their availability in synapses and producing a delayed reduction in depression symptoms for some patients. Additionally, electroconvulsive therapy (ECT) has been shown to increase serotonin, NE, and dopamine function, which may lead to the rapid reduction in depressive and neurovegetative symptoms often observed following ECT. Recently, clinical trials of ketamine, an N-methyl-D-aspartate (NMDA)-type glutamatergic receptor antagonist, have further supported a role for glutamate and gamma-aminobutyric acid (GABA) in depression symptomatology (Lener et al., 2017). Such clinical evidence provides

primary support for the role of neurotransmitter dysregulation in depression, which has spurred further research to uncover the underlying biological mechanisms. However, it is likely that no single neurotransmitter dysfunction is the immediate cause of depression; multiple neurotransmitter systems, including serotonin, NE, dopamine, glutamate, and GABA are likely to interact with each other and with additional complex biological processes to explain the neurobiological basis of depression. In the following subsections, we discuss extant research linking dysfunction in monoamine and amino acid neurotransmitter systems to depression, concluding with a brief discussion of evidence for potential sex-specific effects.

2.1.1. Monoamines

Serotonin has wide-ranging effects on behavior, many of which align with common symptoms of depression. Through neuronal projections emanating from the brainstem raphe nuclei, serotonin plays a role in sleep through connections within the brainstem, appetite through the hypothalamus, as well as mood regulation, behavioral inhibition, impulsivity, aggression, and the stress response through projections to limbic regions (Ressler and Nemeroff, 2000). Further evidence points to a role for serotonin in memory, cognition, motor function, sexual behavior, and control of neuronal growth and differentiation (Ressler and Nemeroff, 2000). A number of unique characteristics may account for the diversity in biological and behavioral effects of serotonin, including distinct subdivisions of the raphe nucleus with projections to diverse brain regions, the wide array of serotonin receptor classes, and variation in the postsynaptic response to different serotonergic neuron firing patterns (Andrews et al., 2015; Ressler and Nemeroff, 2000). In addition to its importance in behavioral modulation, evidence shows that serotonin also has diverse effects on the immune system, e.g. the release of immune signaling molecules and the activation of T-cells (Herr et al., 2017). A large body of preclinical and clinical evidence has

linked reduced serotonin production, availability, and receptor binding to depression, which can be resolved in some patients through treatment with selective serotonin reuptake inhibitors (SSRIs; Ressler and Nemeroff, 2000).

Although early propositions that depression may ultimately be attributable to low levels of serotonin are oversimplified, a recent synthesis has attempted to construct a more nuanced picture of the complex role serotonin plays in depression symptomatology (Andrews et al., 2015). They review evidence from human and animal studies that serotonin transmission may actually be elevated in depression. Further, they suggest that the major evolved function of serotonin is in state-dependent energy regulation, as evidenced by its role in the storage and metabolism of energy molecules along with regulatory control over neuronal, organ system, and behavioral processes which are energy-intensive, including depression. Andrews et al. argue that this hypothesis accounts for the initial worsening and delayed reduction in depression symptoms in patients using SSRIs, where a perturbation of the energy equilibrium function of serotonin is followed by symptom improvement from compensatory mechanisms to restore homeostasis. However, potentially contradictory results come from recently renewed interest in psilocybin, a naturally-occurring serotonin receptor agonist, which produces a rapid and sustained reduction in symptoms in patients with treatment-resistant depression (Carhart-Harris et al., 2018, 2017, 2016). Although our mechanistic understanding of the role serotonergic neurons play in depression is far from complete, it is clear that dysregulated serotonin transmission plays a role in the manifestation of classic depression symptoms and that treatments which target these systems can be successful.

NE, being recognized early on as a monoamine modulated by first-generation antidepressants, has also been widely studied in its relation to depression and anxiety. A majority

of NE neurons originate in the locus coeruleus and project to multiple brain regions including the cortex, where they modulate attention, and the amygdala and hippocampus, where they are involved in the stress response and stress-related memory processes, as well as the thalamus, where they modulate levels of arousal (Moret and Briley, 2011). Disturbances in these behavioral and psychological processes align with common depression symptoms including deficits in attention, memory, and fatigue (Moret and Briley, 2011; Nutt, 2008). These behavioral consequences are context-dependent and mediated by complex processes which depend on NE availability, electrochemical signal properties, and transduction through the three major NE receptor classes. Although some studies support increased NE availability and/or receptor activity in depressed patients, contradictory results from others make conclusions about specific mechanisms difficult (Moret and Briley, 2011; Ressler and Nemeroff, 2000). Nonetheless, drugs which specifically target NE transmission are effective in treating some depressed patients, suggesting a role for dysregulated NE signaling in the manifestation of common depression symptoms (Moret and Briley, 2011; Nutt, 2008).

Dopamine's role in depression and other neuropsychiatric disorders like schizophrenia and Parkinson's disease has also been extensively studied. Positron emission tomography (PET) imaging and postmortem brain studies have provided conflicting results as to whether dopamine availability or receptor binding is elevated or decreased in depressed patients (Belujon and Grace, 2017; Felger and Treadway, 2017). Despite this contradictory evidence for the role of dopamine in depression, dopaminergic neurons projecting from the substantia nigra and ventral tegmental area towards the striatum, ventral striatum, and prefrontal cortex are known to be involved in motor function, reward-related processes, motivation and attention (Belujon and Grace, 2017; Nutt, 2008). These processes are often impaired in patients with depression,

suggesting that dysregulation of the dopamine system may play a role in symptoms of anhedonia and psychomotor retardation often seen in severe cases. Further, the occasional use of norepinephrine-dopamine reuptake inhibitors and/or antipsychotics in treatment-resistant depression suggests the involvement of dopamine in depression pathology (Nutt, 2008). Interestingly, there is evidence that dopaminergic signaling may be impaired by inflammation (Felger and Treadway, 2017). Despite some inconsistent findings concerning the direction of dysregulation, the functions of the dopamine system and the effectiveness of pharmaceutical treatments which target their reuptake support a role for dopamine signaling in depression psychopathology.

The delayed effects of monoamine antidepressants on patient symptoms suggest that their ultimate resolution may depend on longer-term structural and functional changes in neuronal organization. One potential mediator is neurogenesis, which is controlled by a number of growth factors including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and fibroblast growth factor 2 (FGF2). Studies in humans and animals have shown that neurogenesis, particularly in the hippocampus, and expression levels of neurogenic factors like BDNF and VEGF, are diminished in depression (Duman and Monteggia, 2006; Krishnan and Nestler, 2008). Furthermore, monoamine antidepressants, NMDA antagonists, transcranial magnetic stimulation, exercise, and ECT have been shown to increase neurotrophic gene expression in depressed patients (Duman and Monteggia, 2006; Krishnan and Nestler, 2008). However, knockdown mouse experiments have indicated that BDNF reductions are not sufficient to produce depression-like behavior, and that the consequences of BDNF expression are region- and antidepressant-specific. Therefore, while BDNF may play a role in successful antidepressant treatment, it may not represent a causal factor in depression etiology. Recently, serotonin has

been shown to regulate gene expression through modification of histone proteins (Farrelly et al., 2019), which provides another potential explanation for the delayed effects of serotonin-targeting pharmacological treatments.

2.1.2. Amino Acid Neurotransmitters

Recently, promising clinical trials have shown fast-acting antidepressant effects of ketamine, especially for patients with treatment-resistant depression (Fond et al., 2014; Xu et al., 2016), which implicates both glutamate and GABA, the major excitatory and inhibitory amino acid neurotransmitter systems ultimately mediating the effects of monoamine transmission. Evidence from depressed patients and animal models of depression support changes in glutamate and GABA transmission and associated alterations in the functional connectivity of brain networks for cognition and emotion regulation (Lener et al., 2017; Sanacora et al., 2012). Additionally, animal studies have shown that stress may lead to changes in glutamate release, synaptic clearing, and synaptic plasticity, which can be modulated by antidepressants (Sanacora et al., 2012). The success of ketamine as a potential treatment for depression further supports the role of inhibitory and excitatory dysregulation in depressed patients. Ketamine acts on NMDA receptors to disinhibit excitatory glutamatergic neurons in the cortex, and increases synthesis of BDNF to promote neuroplasticity and synaptogenesis. Lerner et al. (2016) suggest that there may be a subset of patients with glutamate and GABA deficits who respond especially well to ketamine.

2.1.3. Sex Differences

In line with sex differences in depression prevalence and genetic factors, it is postulated that males and females may respond differently to dysregulated neurotransmitter levels. Some studies report better SSRI treatment response in women compared to men, but other studies have

found no such difference (Gorman, 2006; Khan et al., 2005). In a meta-analysis of monoamine depletion studies, healthy women, especially those with a family history of depression, exhibited a larger decrease in mood than men following acute depletion of tryptophan, the precursor of serotonin (Ruhé et al., 2007). The few studies which have examined sex differences in ketamine treatment are contradictory, with one meta-analysis showing some support for a greater response in men (Coyle and Laws, 2015) and a recent relatively large clinical trial finding no such difference (Freeman et al., 2019).

2.2. Stress Response

2.2.1. Theoretical Considerations and Epidemiological Evidence

The broad, complex and multidimensional nature of stress is evident by its definition from Beck and Bredemeier (2016, p. 611) as "...any significant change that an individual must adjust to" which "includes life situations as well as biological insults". Stress is probably the most extensively studied risk factor for mood and anxiety disorders, with the diathesis-stress model being one of the most influential theories of psychopathological etiology in the late 20th century (Hammen, 2005; Liu and Alloy, 2010). Critically, the currently high levels of perceived stress in the general population (Wiegner et al., 2015), especially among young people (American Psychological Association, 2018; Yang et al., 2012), highlight the importance of stress as a focus of research and a target for intervention to prevent or treat depression. Here, we review the conceptual framework for stress, discuss recent evidence for its role in depression, review the biological stress response in the body and brain, and conclude with a focus on genetic studies examining stress and depression.

The above definition of stress highlights the individual differences inherent in stress perception and response. Likely due to differences in stress-reactivity and reward circuitry, a

stressor which may deal a major blow to the psychological well-being for one person may fail entirely to be seen as threatening by another. Likewise, an individual's resilience and coping styles can modulate the effects of a perceived stressor on one's psychological well-being (Southwick and Charney, 2012). Finally, in addition to being a consequence of stress, depression itself is associated with the subsequent occurrence of stressful life events, potentially leading to a chronic cyclical maintenance of depression (Liu and Alloy, 2010).

Notably, the types of stress experienced today are very different qualitatively and temporally than those which shaped the evolution of the stress response in our ancestors (Nesse et al., 2016). Modern stressors are increasingly psychosocial rather than physical. Acute stressors, such as the threat of physical injury or an encounter with a predator, produce a relatively short-term stress response and can be resolved quickly. However, chronic stressors like interpersonal difficulties or high self-imposed goals are often prolonged and induce a repeated or sustained activation of the stress response, leading to long-term and often maladaptive alterations in physiology. Additionally, interpersonal and dependent stressful events, i.e. those influenced by an individual's own behavior, are more common in society today and are more predictive of depression than random, uncontrollable stressors (Kendler et al., 1999).

Strong epidemiological and observational evidence supports the association between stress and depression (for a review, see Liu & Alloy, 2010). Beck and Bredemeier (2016) build on this long history of previous research, formulating an integrative theory highlighting the contribution of stress, especially early in life, interacting with genetic predisposition, to the etiology of depressive behavior and cognition. The relationship between stress, genes and depression has been supported by twin studies and addressed in the controversial candidate-gene literature (Flint and Kendler, 2014; Smoller, 2016). More recently, genome-wide evidence has

also supported a gene-environment interaction involving stress, indicating potentially divergent effects by sex (Arnau-Soler et al., 2019; Colodro-Conde et al., 2018). Additionally, there is evidence that coping strategies (Dunn and Conley, 2015), chronic stress perception (Federenko et al., 2006) and stressful life events are themselves heritable (Power et al., 2013), partly due to common genetic variation overlapping between depression and neuroticism (Clarke et al., 2019). A more thorough discussion of the genetic factors contributing specifically to depression follows in the subsequent section on *Depression Genetics*.

The recently proposed unified model of depression (Beck and Bredemeier, 2016) emphasizes the effects of dysregulated biological stress processes on depression development, persistence, and recurrence. Indeed, a large body of evidence supports dysfunction of the hypothalamic-pituitary-adrenocortical (HPA) axis and chronically elevated levels of the stress hormone cortisol in response to stress among depressed patients (Gold, 2015; Pariante and Lightman, 2008). In order to understand how stress may lead to the neurobiological and behavioral changes associated with depression, it is necessary to consider the typical brain and biological mechanisms through which the human body responds to stress.

2.2.2. Typical Neurobiological Stress Response

Physical stressors like injuries or immune challenges which result in a change in bodily homeostasis first transmit signals to the brainstem, whereas psychogenic stressors like social rejection or novel environments initially activate the limbic forebrain, namely the amygdala, hippocampus, and prefrontal cortex (PFC; Ulrich-Lai & Herman, 2009). The initial perception of a stressor as threatening may be mediated by areas of the PFC and the anterior cingulate cortex (ACC), which are involved in higher-order integrative and judgmental processes (Dedovic et al.,

2009). Regardless of the type of stress, two major response pathways are activated by stress signals received by the brainstem or limbic regions.

The immediate response to stress exposure, often called the "fight or flight" response, is coordinated by the autonomic nervous system (ANS). Through the release of epinephrine from the adrenal medulla and norepinephrine through sympathetic nerves, the sympathetic division of the ANS provokes rapid changes in global and system-specific functions, e.g. increased inflammation, increased heart and respiratory rates, and suppressed feeding and digestion. This response is relatively short-lived, as the parasympathetic division, largely mediated through efferents of the vagus nerve, quickly initiates a return to homeostasis.

Output from the brainstem or limbic regions also activates the HPA axis, which produces a slower, but longer-lasting response to stressors (Ulrich-Lai and Herman, 2009). This begins when the hypothalamus secretes hormones, such as corticotropin-releasing factor (CRF) and vasopressin. This in turn triggers a cascade of responses including the release of adrenocorticotropic hormone (ACTH) from the pituitary gland and culminates with the production of glucocorticoids (e.g., cortisol in humans) and mineralocorticoids from the adrenal cortex. These steroid hormones have wide-ranging consequences, from the elevation of blood glucose and suppression of inflammation to neural changes which increase arousal and enhance emotional memory encoding. Chronic activation of the HPA axis by repeated or sustained stress may result in long-term changes in brain structure and function, leading to a heightened excitability of the stress-response system.

2.2.3. Evidence for Dysregulation in Depression

Research has consistently found the HPA axis to be hyperactive in patients with depression, possibly due to an impaired negative feedback mechanism, disrupting a normal

resolution to homeostasis following the stress response (Gold, 2015; Pariante and Lightman, 2008). Additionally, successful treatment of depression with antidepressants has been associated with a return of the normal negative feedback mechanism in the HPA axis. One hypothesis is that traumatic stressors early in life may precipitate a long-term sensitization of the HPA axis, resulting in an increased vulnerability to developing mood disorders in adulthood along with alterations in the immune system. However, although repeated uncontrollable and overwhelming stress in childhood causes long-term disruptions in the HPA axis that can lead to depression, healthy levels of mild, controlled, and manageable stress can lead to a well-regulated HPA axis along with enhanced resilience against the negative effects of future stressors and a decreased risk of depression (Southwick and Charney, 2012).

In contrast to typical or melancholic depression, patients with atypical depression usually display normal cortisol levels and less HPA activity, along with weight gain, hypersomnia, fatigue, and lower blood pressure (Gold and Chrousos, 2013). In one study, introducing an exogenous source of CRF led to high cortisol levels in melancholic depression, but low ACTH and cortisol levels in atypical depression (Gold and Chrousos, 2013). Such clinical heterogeneity in depression suggests that there is no single direction of HPA dysregulation, with different clinical presentations partially reflecting different patterns of dysregulation.

Neuroimaging studies have supported the role of HPA axis dysregulation with evidence of morphological and functional changes in the brains of depressed patients and their relatives. Studies have revealed volumetric reductions in the ACC, hippocampus, amygdala, medial PFC, and subgenual PFC (Price and Drevets, 2010; Schmaal et al., 2016b, 2016a), brain areas linked to the HPA stress response and regulated by cortisol (Romeo, 2013). Additionally, enlarged pituitary and adrenal glands are associated with depression, suggesting potential overstimulation

by CRF and ACTH (Price and Drevets, 2010). Further functional studies indicate higher metabolism and cerebral blood flow to the ACC in depressed patients as well as healthy controls administered with experimental sadness induction paradigms. Likewise, depressed patients exhibit exaggerated hemodynamic responses in the hippocampus and amygdala in response to sad stimuli. Finally, experiments in animal models have demonstrated that stress can lead to morphological changes in regions associated with depression including the hippocampus, medial PFC, and amygdala (Sanacora et al., 2012) and that treatment with antidepressants induces neurogenesis in the hippocampus, which is sufficient to resolve depression and anxiety-like behaviors in a chronic stress paradigm (Hill et al., 2015).

Post-mortem studies in humans have corroborated these neuroimaging findings in depression, demonstrating that while there is no change in the cell number, neuronal cell body size is diminished in the PFC, hippocampus, and amygdala, with a possible reduction in neuronal cell processes and impaired synaptic connections (Price and Drevets, 2010). Additionally, CRF and CRF receptor concentrations are elevated in the hypothalamus of depressed patients (Wang et al., 2008). Likewise, reductions in dendrite complexity and synaptic connections were also observed in depressed patients, with decreased grey-matter volume of the PFC and hippocampus (Duman, 2014). These findings suggest that altered synaptic plasticity might bring about functional disconnection, which may explain the impaired executive control of emotion in depression.

Furthermore, extensive rodent literature utilizing behavioral paradigms, neuroimaging, and lesion studies have supported similar HPA dysfunction in preclinical models of depression (Price and Drevets, 2010). Encouragingly, multiple modalities of depression treatment have been associated with the resolution of many of these observed neurophysiological changes (Price and

Drevets, 2010). Finally, animal models of depression have shown that both acute and chronic stressors lead to decreased expression of BDNF and other neuronal growth factors, along with decreased adult neurogenesis, and that these changes are partially reversed by antidepressants (Duman and Monteggia, 2006; Krishnan and Nestler, 2008).

2.2.4. Sex Differences

Because of an increased prevalence of depression among women, many studies have examined sex differences in HPA axis functioning (for a review, see Bangasser & Valentino, 2014). Although inconsistent among healthy participants, evidence suggests higher levels of HPA axis dysregulation among depressed women compared to men, which may be driven by differences in CRF sensitivity. Further, evidence points to a heightened activation of corticolimbic regions in women compared to men in response to negative emotional stimuli. Rodent research has also further characterized sex differences in stress-related brain regions (Bangasser and Valentino, 2014). In healthy rats, females show increased dendritic spines in the hippocampus compared to males, while males exhibit greater dendrite branching in the prefrontal cortex and amygdala. Stress has been found to elicit significant reductions in the prefrontal and hippocampal dendrites of male rats, yet the same effect is not seen in females.

Taken together, it is evident that HPA dysregulation is a major component of depression pathology. However, neuroimaging evidence so far has merely served to pinpoint the neuronal substrates of depression which are likely pertinent to HPA dysfunction. Causal inferences from structural brain alterations to depressive symptoms cannot be drawn based on such correlational findings. Therefore, novel methodology and integration at multiple biological and symptom levels, with potential multi-dimensional stratification, are necessary for moving towards a more complete understanding of the etiology of depression and the specific role of stress.

2.3 Systemic Dysfunction Shared with Anxiety

Substantial comorbidity is observed between depression and other psychiatric disorders, but most often with anxiety disorders (Kessler et al., 2007; Lamers et al., 2011) Whereas depression generally encompasses negative mood and cognition in response to a perceived loss, anxiety is a negative emotional and cognitive state resulting from the perception of a potential loss in the future, both of which may manifest in response to traumatic or stressful life events. However, both disorders share similar associations across personality dimensions, such as increased neuroticism and decreased conscientiousness (Kotov et al., 2010). The high comorbidity and symptom overlap between depression and anxiety may indicate the presence of shared biological mechanisms in the etiology and maintenance of the disorders. Depression and anxiety have been suggested as belonging to a broad category of internalizing disorders which share similar genetic predispositions to "anxious-misery" (Kendler et al., 2003). In fact, many twin studies suggest that depression and anxiety share most, if not all, of the same additive genetic factors and a negligible influence of shared or familial environment (Hettema, 2008; Kendler et al., 1992, 1987). What distinguishes these two disorders etiologically may be mostly due to individual-specific environmental factors. Because of the strong evidence for genetic overlap, we highlight evidence for potentially relevant shared biological mechanisms.

Similarly to depression, anxiety has been strongly linked to dysregulation across multiple neurotransmitter systems. Pharmacological antidepressant treatments which increase serotonin and norepinephrine are often successful in reducing anxiety symptoms (Goddard et al., 2010; Montoya et al., 2016; Ressler and Nemeroff, 2000). Relatively few studies have examined the role of dopamine in anxiety disorders, but one retrospective analysis indicated a reduction of striatal dopamine D2 receptors across anxiety disorders (Nikolaus et al., 2010). Neurogenic

factors, which have been suggested to mediate the anxiolytic effects of antidepressants, are reduced among anxiety patients (Suliman et al., 2013). Similarly, animal studies have shown that inhibiting hippocampal neurogenesis leads to anxiety-like behaviors (Revest et al., 2009), while inducing it is able to reduce anxiety-like behaviors (Hill et al., 2015). Further, preclinical models have shown a potential role for genetic variants in neurogenic factors to predispose anxiety susceptibility and mediate antidepressant medication effects (Chen et al., 2006). Amino acid neurotransmitters are also likely to play a role in anxiety disorders, with benzodiazepines, commonly prescribed for their anxiolytic effects, increasing the effects of GABA binding to $GABA_A$ receptors (Ravindran and Stein, 2010). Additionally, evidence from animal and clinical studies suggest a role for dysregulated glutamatergic signaling in anxiety disorders, with glutamate receptor antagonists exhibiting anxiolytic properties (for a review, see Riaza Bermudo-Soriano, Perez-Rodriguez, Vaquero-Lorenzo, & Baca-Garcia, 2012).

In addition to its well-characterized relation to depression risk, epidemiological evidence has also linked chronic stressors, especially in childhood, to risk of anxiety disorders (for a review, see Faravelli et al., 2012). As discussed in section 2.2.2, the biological response to stress is an adaptive mechanism for preparing the body and mind for response to a present or imminent threat. However, inappropriate chronic activation of the HPA axis towards stressors or potential threats may lead to systemic dysregulation which aligns with some of the hallmark symptoms of depression and anxiety. Indeed, like depression, anxiety has also been consistently linked to hyperactivation of the HPA-axis as measured by cortisol and ACTH concentrations, which can be attributed in some to severe stressors in early life (Faravelli et al., 2012). Volumetric changes observed in patients with anxiety disorders vary across subtype, but generally show differences in stress response and emotional processing-related brain regions including the amygdala, insula,

hippocampus, and medial PFC (Duval et al., 2015). Similarly, increased activation of the amygdala, insula, and ACC have been consistently observed across patients with anxiety disorders and among healthy controls administered anxiety-inducing paradigms (Duval et al., 2015; Holzschneider and Mulert, 2011).

Anxiety and depression share many similar features of biological dysregulation across neurotransmitter systems and the stress response, which may partially account for many of their shared symptoms and high comorbidity. It is important to recognize that these systems are highly interdependent and constantly interacting. The complex, heterogeneous behavioral and psychological manifestations of depression and anxiety are the result of intricate processes involving these and many other biological systems in interaction with the environment. With this acknowledgement and a brief introduction to the most studied biological systems associated with depression and evidence for their overlap with anxiety, we focus the remainder of this review on recent progress in depression genetics and how it may inform future research in depression etiology.

3. Depression Genetics

Genetic findings for major depression have recently been reviewed extensively (Flint and Kendler, 2014; Shadrina et al., 2018). Nevertheless, genetic studies have progressed rapidly, even in the time since the most recent comprehensive review in 2018, with increasingly large GWAS and meta-analyses providing new evidence for specific genetic variants implicated in depression (Howard et al., 2019). Further quantitative analyses will be necessary to interrogate these recent results completely, with recommendations recently provided by McIntosh, Sullivan, and Lewis (2019). However, a detailed qualitative "stock-taking" is helpful to prioritize future quantitative and experimental research targets. Thus, we present an abbreviated review of

previous genetic studies in depression, followed by an in-depth qualitative review of the most recent gene-based meta-analytic findings from Howard et al. (2019) in the context of the three previously discussed depression-related biological systems. Although GWAS results should be interpreted with caution due to the ease with which false positives can be rationalized (Biedrzycki et al., 2019), our synthesis provides a resource for basic and translational researchers to carefully weigh the existing evidence when identifying loci of interest for more in-depth follow-up studies. While acknowledging the highly polygenic architecture of depression, we believe that deeper examination of individual genes in cellular and animal models is still warranted given the current state of the field and will provide a deeper understanding of depression pathology and potential targets for drug development. Whenever possible, epistatic and gene x environment interactions should also be examined in future studies.

3.1. An Overview of Depression Genetics

The heritability of major depressive disorder is estimated by meta-analysis of twin studies to be 31-42% (Sullivan, Neale, & Kendler, 2000), with the remaining phenotypic variance accounted for mostly by individual-specific environmental factors. Further studies have revealed sex differences such that depression is more heritable in women (by 10% compared to men) and that some genetic factors have a sex-specific effect (Flint and Kendler, 2014). Naturally, since heritability estimates indicate a significant role for genetic factors, researchers have attempted to identify specific genetic loci which contribute to depression and may be targeted in treatment or prevention. Early linkage studies identified a few consistent genetic loci of interest, some of which may have sex-specific effects (Flint and Kendler, 2014). However, traditional linkage analyses, plagued by limitations in statistical power for variants with small effect size (Risch and

Merikangas, 1996; Sham et al., 2000), soon fell out of favor to candidate gene studies and later, GWAS.

Initially, candidate gene studies saw explosive growth in the field of psychiatric genetics, with a major focus on the monoamine system. These studies examine genetic variants which are hypothesized to be involved in the disorder of interest based on their biological function or previous association with the disease. The two most recent comprehensive reviews (Flint and Kendler, 2014; Shadrina et al., 2018) provide thorough discussions of the history, findings, and controversy of candidate gene studies for major depression. However, of note is a recent genome-wide analysis examining 18 commonly studied candidate genes for depression which found no support for main effects or gene-by-environment interactions for any of the genes studied, apart from limited support for *DRD2* (Border et al., 2019). This suggests that the large effect sizes reported in the early candidate gene literature may be false positives subject to publication bias and effect size inflation due to winner's curse. Dick and colleagues (2015) provide recommendations for future candidate gene research to avoid the pitfalls of these early studies. Candidate gene studies were a natural first step in the search for genes associated with psychiatric traits, which were eventually overtaken in popularity by hypothesis-free GWAS. However, together with new evidence from GWAS, these studies may be revisited and provide additional insights in the future.

GWAS, which test associations between a phenotype and hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome, have achieved remarkable success since their introduction in 2008 (Visscher et al., 2017). However, the quest for genome-wide significant signals in depression was initially disheartening. The first GWAS of depression (Sullivan et al., 2009), involving ~3,500 individuals of European ancestry, reported no genome-

wide significant SNPs. Additional GWAS were unsuccessful in identifying variants reaching the stringent threshold of genome-wide significance, until Kohli et al. (2011) found one genome-wide significant SNP around the gene *SLC6A15* (solute carrier family 6 protein). Further studies in depressed patients have shown associations between this risk allele and differences in resting state neural activity patterns (Wang et al., 2017), white matter structural integrity (Choi et al., 2016), along with cortisol response and deficits in memory and attention (Schuhmacher et al., 2013). Additionally, experiments in animals have shown that this gene regulates glutamate transport in the hippocampus (Santarelli et al., 2015), that the GWAS risk allele was correlated with reduced expression of *SLC6A15* in hippocampal regions, and that knockout of the gene induced depressive and anxiety-like behaviors (Santarelli et al., 2016). Nevertheless, this particular polymorphism was not confirmed nor successfully replicated in subsequent GWAS. It is widely acknowledged that the effects of most common SNPs across complex traits are modest at best, particularly so for depression (Zhang et al., 2018). With this in mind, the psychiatric genetics research community recognized that the best way to improve power for detecting more risk variants was to increase sample sizes dramatically (Flint and Kendler, 2014).

With collaborative international efforts, the Psychiatric Genomics Consortium (PGC) and other large-scale genotyping projects were able to increase sample sizes effectively (Cai et al., 2015; Sullivan et al., 2013). They eventually identified increased numbers of associated loci reaching genome wide significance, with 15 (Hyde et al., 2016), 44 (Wray et al., 2018), and 17 independent loci (Howard et al., 2018), where many of the loci overlapped across studies. A recent meta-analysis of these three successful GWAS with a combined sample size of over 800,000 individuals of European ancestry has achieved the remarkable feat of identifying 102 independent loci and 269 genes associated with depression (Howard et al., 2019). With no

dramatic increases in sample size expected on the near horizon, it is now necessary to take stock of these most recent genetic findings and set a path forward towards a more complete understanding of depression biology.

3.2. Qualitative Analysis of Gene-Based Meta-Analysis Results

Here we synthesize the gene-based results of the most recent depression meta-analysis in the context of two major biological mechanisms known to be associated with depression: neurotransmitter systems and the stress-response. Further, we identify genes with an immune-related function, as immune system dysregulation is also strongly associated with depression symptomology (Miller and Raison, 2016). However, a detailed discussion of these immune-related results is beyond the scope of our current review. We also speculate on the importance of genes that do not have a known function within these categories.

For each of the 269 genes identified by Howard et al. (2019), we compiled information about known gene function and differential brain expression from the NCBI Gene database (National Library of Medicine (US) National Center for Biotechnology Information) and searched for related articles in PubMed which provided functional information or evidence for a hypothesis-driven association with depression or other psychiatric phenotypes. Gene functions were manually sorted into five non-mutually exclusive categories: Neurotransmitter-Related Function, Stress Response-Related Function, Immune-Related Function, Other CNS-Related Function, and Other Function. Neurotransmitter-related functions included any gene which impacts neurotransmitter production, availability, release, receptor binding, reuptake, or degradation. Stress response-related functions included genes implicated in the production or release of stress hormones, altered transcription or epigenetic changes in response to stress, or interaction with stress to predict neural changes or depression-like behaviors. The immune-

related function category included any gene with a known role in the development, production, trafficking, or function of lymphocytes or cytokines. The Other CNS-related category included any function within the central nervous system not directly implicating neurotransmitters or stress-related processes. Other functions included any known biological role not falling within any of the other categories. The functions of some genes identified by Howard et al. (2019) appear to be currently uncharacterized.

The results of this qualitative analysis are discussed below, with a complete function summary and categorization available in Supplementary Table S1. Figure 2 shows the number of total and unique genes exhibiting a function in each category. Of the 269 significant genes identified through meta-analysis by Howard et al. (2019), 18 have evidence for a function related to neurotransmitter systems, 13 for the stress response, and 34 for an immune-related function. Figure 3 is a Venn diagram visualizing the overlap between genes manually categorized in each of the functional categories, excluding those without a known function.

3.2.1. Neurotransmitter-Related Genes

With decades of research linking neurotransmitter system dysregulation to depression, it is no surprise that hypothesis-free genome-wide methods also implicate these systems. However, despite what the popular monoamine theory would predict, most of the neurotransmitter-related genes are not directly related to serotonin, NE, or dopamine systems. In fact, half have been shown to participate in glutamate signaling, suggesting a significant role in depression pathology and supporting results from recent studies which demonstrate the rapid-acting antidepressant effects of the NMDA receptor antagonist ketamine.

NMDA-, kainate-, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type ionotropic glutamate receptors all participate directly in excitatory electrochemical signal transduction. Animal studies have shown that disruptions in *SHISA9,* a subunit of AMPA

receptors, may lead to changes in short-term synaptic plasticity (von Engelhardt et al., 2010), synaptic transmission, and network activity in the hippocampi of mice (Karataeva et al., 2014). Likewise, *GPC6* has been shown to increase NMDA receptor availability in neurons induced from human stem cells (Sato et al., 2016), whilst *ANKS1B* may be involved in the trafficking of NMDA receptor subunits (Tindi et al., 2015). Knockdown of *ANKS1B* appears to impair glutamate signaling and synaptic plasticity in the mouse hippocampus (Tindi et al., 2015) and alters behavioral response to ketamine (Enga et al., 2017). Likewise, two studies in mice have demonstrated that overexpression of *EPHB2*, which modulates NMDA-dependent synaptic function, reverses cognitive deficits and depression- and anxiety-like behavior in an Alzheimer's disease model (Cissé et al., 2011; Hu et al., 2017). Another recent study has shown that knockdown of *EPHB2* results in depression-like behavior and reduced hippocampal neurogenesis (Zhen et al., 2018). However, these studies differ in their observed effect on NMDA receptor availability, with the Alzheimer's model results pointing to an upregulation of NMDA receptors by *EPHB2* (Cissé et al., 2011; Hu et al., 2017), while Zhen and colleagues (2018) demonstrate a downregulation. *KYNU* encodes kynureninase, an enzyme involved in the kynurenine pathway which leads to the production of quinolinic acid, an NMDA receptor agonist and glutamate reuptake inhibitor (Miller & Raison, 2016) which is upregulated in the ACC of depressed patients who die from suicide (Steiner et al., 2011). Finally, the *GRIK5* gene encodes a protein subunit of kainate receptors, which function pre- and post-synaptically to modulate glutamate and GABA signalling, and which are involved in excitotoxicity of neurons and oligodendrocytes (Matute, 2011). Studies in rodents have shown that blockade of this subunit produces an anxiolytic-like effect in a preclinical model of anxiety (Alt et al., 2007).

GRM5 and *GRM8,* which encode metabotropic glutamate receptors (mGluR) 5 and 8, were also significant in the gene-based meta-analysis of Howard and colleagues (2019). mGluR participates indirectly in glutamate transmission by regulating the excitability of glutamatergic neurons through second messenger systems. Although animal models of depression have shown that antagonism of mGluR5 induces an antidepressant-like effect, the few clinical trials which have examined mGluR5 antagonists in humans were unsuccessful in treating depression symptoms (Barnes et al., 2018). However, recent evidence shows that ketamine reduces mGluR5 availability in both depressed patients and healthy volunteers, and that this change is associated with symptom reduction in patients (Esterlis et al., 2018), providing another potential mechanism for ketamine action. mGluR5 activity has also been associated with other neuropsychiatric disorders. In patients with alcohol use disorder, higher mGluR5 binding in the amygdala was linked with the temptation to drink (Akkus et al., 2018), suggesting a potential relationship between this receptor and reward system-related behavior. Additionally, methylation of the *GRM5* promoter region has been associated with a decreased risk of schizophrenia (Kordi-Tamandani et al., 2013), while variants in the gene itself have been associated with impaired cognition and reduced right hippocampal volume in schizophrenia (Matosin et al., 2018). *GRM5* expression is increased in the postmortem noradrenergic neurons of the locus coeruleus of depressed patients (Chandley et al., 2014). *GRM8* expression is greater in the hippocampus of rats treated with SSRIs compared to their control counterparts (O'Connor et al., 2013). Candidate gene studies have also found evidence for an association between variants in *GRM8* and depression in Han Chinese (Li et al., 2016), autism in Han Chinese (Li et al., 2008), alcohol dependence (Chen et al., 2009; Long et al., 2015), and schizophrenia across multiple ethnic groups (Li et al., 2016; Takaki et al., 2004; Tavakkoly-Bazzaz et al., 2018; Lili Zhang et al.,

2014). Finally, the protein product of *CELF4* is involved in mRNA regulation specifically for excitatory neurotransmission (Wagnon et al., 2012), representing a general glutamatergic control mechanism. Therefore, accumulating genetic evidence seems to support the importance of glutamatergic signaling in the neurobiology of depression.

Gene-based results also implicate the major inhibitory GABAergic neurotransmitter system. *ERBB4* encodes the receptor for neuregulin 1 (encoded by *NRG1*), which together, among other neurodevelopmental functions, specifically control the development of GABAergic cortical neurocircuitry (Fazzari et al., 2010). This is bolstered by observed associations between common variants in *ERBB4* and GABA levels in the human brain, as measured by PET imaging and cerebrospinal fluid concentration (Luykx et al., 2012; Marenco et al., 2011). Multiple candidate gene studies and GWAS across many populations have confirmed an association between variants in the *ERBB4* and *NRG1* genes and schizophrenia (Feng et al., 2017; Mostaid et al., 2016). Recently, functional splice variants of *ERBB4* have been associated with deficiencies in parvalbumin interneurons of the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression (Chung et al., 2018), possibly implicating a shared genetic and biological risk pathway. An animal model study has proposed that one mechanism for the antidepressant effects of ketamine may be to downregulate *ERBB4/NRG1* signaling in parvalbumin interneurons (Wang et al., 2014). The protein encoded by *PLCL1* also plays an important role in GABAergic signaling through its ability to bind directly to the $GABA_A$ receptor and to proteins which are involved in GABA receptor trafficking (Terunuma et al., 2004). Mice with *PLCL1* knockdown exhibit an epileptic phenotype and a reduced tonic current in GABAergic neurons (Zhu et al., 2012).

The remaining neurotransmitter-related genes implicate monoamine system function. *DRD2* encodes the dopamine D2 receptor, which has been widely examined across neuropsychiatric disorders (Gatt et al., 2015), but most studied in its relation to schizophrenia, where it has been supported by candidate gene meta-analyses and GWAS (He et al., 2016; Luykx et al., 2017; Ripke et al., 2014). Nonetheless, meta-analyses of candidate gene studies have also supported an association between *DRD2* variants and depression (LuShun Zhang et al., 2014; Zou et al., 2012). Some studies have also revealed a role for *DRD2* variants in response time to SSRI treatment (Wang et al., 2012), rumination in depressed patients (Whitmer and Gotlib, 2012), and through its interaction with maternal parenting, in adolescent depression trajectories (Cao et al., 2018). Additionally, a variant in *ANKK1,* originally presumed to be located within the *DRD2* gene, has been associated with multiple psychiatric phenotypes (Ponce et al., 2009). This variant has also been found to associate with dopamine D2 receptor availability and binding in depressed patients and healthy controls (Pohjalainen et al., 1998; Savitz et al., 2013; Thompson et al., 1997). Although *BAG5* belongs to a family of genes which play a general role in regulating apoptosis, it has also been shown to specifically regulate dopaminergic neurodegeneration in a mouse model of Parkinson's disease (Kalia et al., 2004). Likewise, *OTX2* is thought to play a major role in neurodevelopment, but studies in mice also demonstrate a more specific role in dopaminergic neurogenesis in the adult brain (Di Giovannantonio et al., 2013). *PAX6,* which codes for a transcription factor known to be involved in general neurodevelopment, also likely has a role in the differentiation and maintenance of dopaminergic neurons, specifically (Thomas et al., 2016; White and Thomas, 2016).

Finally, *PCLO* encodes a protein that has been found to regulate both dopamine and serotonin reuptake (Uno et al., 2015) in addition to its role in presynaptic vesicle organization

(Parthier et al., 2018). Since its initial implication by GWAS as a potential risk factor for depression (Sullivan et al., 2009), a number of candidate gene studies have reported its association with neuroticism (Kuehner et al., 2011), bipolar disorder (Choi et al., 2011), depression (Hek et al., 2010; Minelli et al., 2012), and grey matter reductions in depressed patients (Igata et al., 2017).

3.2.2. Stress Response-Related Genes

Neurotransmitters are vital for orchestrating the stress response throughout the brain and body. Thus, not unexpectedly, eight genes which implicated neurotransmitter systems, *PCLO, OTX2, EPHB2, GRM5, ERBB4, NRG1, PAX6,* and *KYNU* also exhibit stress-related functions. Along with its role in monoamine reuptake, *PCLO* may also be involved in the stress response. A risk variant in the *PCLO* gene was associated with alterations in cortisol and ACTH levels in depressed patients following antidepressant treatment (Schuhmacher et al., 2011). The same risk variant was also associated with reduced cortisol awakening response in healthy participants, which may signify some deficit in HPA functioning (Kuehner et al., 2011). Similarly, evidence supports an additional stress-linked function for the *OTX2* gene. Peña and colleagues (2017) have demonstrated that early-life stress leads to long term changes in *OTX2* transcription in the reward-related ventral tegmental area of mice. These stress-induced changes increase risk for depressive-like behaviors after exposure to an additional stressor in adulthood. Following this study, Kaufman et al. (2018) reported that both early-life stress and *OTX2* methylation were predictive of depression scores in children, corroborating the previous preclinical findings. Similarly, animal models showed that *EPHB2* expression in the medial prefrontal cortex regulates stress vulnerability and depression-like behaviors (Zhang et al., 2016), while expression in the amygdala mediated stress-induced anxiety-like behaviors (Attwood et al., 2011). Across multiple chronic and acute stress paradigms in rodents, *GRM5* or its protein

product have been associated with changes in behavior, susceptibility or resilience to stress, hippocampal *GRM5* expression levels, and synaptic plasticity (Peterlik et al., 2017; Shin et al., 2015; Sun et al., 2017; Wagner et al., 2015; Wang et al., 2015; Wierońska et al., n.d.; Yim et al., 2012), with one study supporting a potentially sex-specific role (Wang et al., 2015). Rodent studies have demonstrated stress-induced changes in *ERBB4/NRG1* expression and signaling accompanied by depression-like behaviors (Brydges et al., 2014; Dang et al., 2016b, 2016a). Additional studies have reported an interaction between stress and experimentally disrupted *ERBB4/NRG1* signaling, which is associated with altered glutamate transmission, HPA axis function, cognition, and anxiety-like behavior (Chesworth et al., 2012; Chohan et al., 2014b, 2014a; Clarke et al., 2017; Taylor et al., 2013). *PAX6* expression was shown to be downregulated in the hippocampi of rats exposed to chronic unpredictable mild stress (Tayyab et al., 2019). Finally, *KYNU* expression was found to be increased in the amygdala and decreased in the medial prefrontal cortex of male rats exposed to an acute psychological stressor (Vecchiarelli et al., 2016).

DCC, ZKSCAN4, ZDHHC21, ESR2 and *PPID* exhibit functions related to the stress response, but were not implicated in neurotransmitter systems. *DCC*, which encodes the netrin-1 receptor responsible for mediating axon guidance, has been suggested to play a role in the stress response. *DCC* expression levels in the prefrontal cortex are linked to increased behavioral responses to stress in mice, and are upregulated in postmortem brains of depression patients (Torres-Berrío et al., 2017). Some evidence indicates that *ZKSCAN4* interacts with glucocorticoid receptors and may facilitate chromatin changes which repress glucocorticoid-induced transcription (Ecker et al., 2009), suggesting a potential regulatory mechanism for downstream effects of the HPA stress response. *ZDHHC21* has been shown to modulate α1-

adrenergic receptor function in the vasculature (Marin et al., 2016), which may indicate the involvement of global epinephrine signaling during the stress response. *ESR2,* which encodes estrogen receptor beta, has been shown to interact with negative life events to predict depression in menopausal Han Chinese women (Zhang et al., 2017). Finally, following a chronic stressor during adolescence, *PPID* was found to be upregulated along with increased glucocorticoid sensitivity in the hippocampus of female, but not male rats (Bourke et al., 2013). In another study, amygdala expression of *PPID* was also shown to regulate fear extinction in mice (Gunduz-Cinar et al., 2019).

3.2.4 Remaining Genes

Although we have shown that some genes identified by Howard et al. (2019) play a role in neurotransmitter systems, the stress response, or immune functioning, the vast majority have no known function in these specific systems. An in-depth discussion of the functions of these genes is beyond the scope of this review, but summary information for those genes with a known function are listed in the full Supplementary Table 1 along with relevant references. We briefly discuss general patterns which can be observed in the functions of these genes.

Of the remaining genes yet to be categorized, a large proportion have some evidence for a role in the CNS apart from neurotransmitter signaling or the stress response. Notably, many show involvement in either neurodevelopment, neurogenesis, or neurodegeneration. In fact, the top three genes identified by Howard et al (2019) all have a known function in one or more of these three processes (see supplementary table for details). Although more research is necessary to uncover their ultimate function in depression, genes involved in neurodevelopment may be responsible for dysfunction in reward- and stress-related brain circuitry which could predispose depression. Additionally, neurogenic genes suggest potential dysregulation in the dynamic

context-dependent process of neuroplasticity. Finally, genes involved in neurodegeneration may account for hippocampal atrophy as well as motor, cognitive, and memory deficits commonly associated with depression. Further research will be necessary to reveal the specific biological mechanisms linking genetic factors to common neuroimaging observations in depression, such as increased activation of the default mode network and volumetric reductions in stress-related brain regions.

Finally, the majority of genes were associated with functions unrelated to the central nervous or immune systems. Of course, it is possible that these represent false positive gene-based associations with depression. However, a more likely explanation is that these genes code for proteins whose functions are pleiotropic, performing different functions or eliciting different consequences across cell types and tissues. Another likely explanation is that the genes exert effects somewhere within causal pathways for depression which we simply have yet to discover. With further research, we expect the depression-related effects of these seemingly inexplicable genes to eventually be revealed.

3.2.4 Overlap with Anxiety Genes

Twin studies suggest very strong, if not complete, overlap in the genetic factors which contribute to depression and anxiety (Hettema, 2008; Kendler et al., 1987; Kendler et al., 1992), corroborated by recent evidence for a strong genetic correlation between common variants associated with both disorders (Brainstorm Consortium et al., 2018). Genetic studies of anxiety disorders are still in early stages, with a number of candidate gene studies across anxiety disorders showing conflicting results (Smoller, 2016). To our knowledge, only one of these examined candidate genes associated with anxiety, *DRD2*, overlaps with those identified in the most recent gene-based meta-analysis of depression (Howard et al., 2019; Sipilä et al., 2010).

Additionally, two overlapping genes were identified as having strong potential as candidate genes for anxiety by a functional genomics screening study in mice, with *DRD2* and *MEF2C* showing elevated expression levels in the prefrontal cortex and hippocampus, respectively, of mice administered the anxiogenic drug yohimbine (Le-Niculescu et al., 2011). Until recently, published GWAS of relatively small sample size have been unable to identify replicable loci associated with anxiety, with the exception of a small GWAS of twins which found association with SNPs in *RBFOX1*, also implicated in depression by Howard et al. (2019). However, marginal progress has been afforded by increases in sample size. One recent GWAS performed as part of the iPSYCH study identified one independent SNP in the PDE4B gene to be associated with anxiety (Meier et al., 2019). Additionally, a recent study, benefiting from a significant increase in sample size afforded by the UK Biobank, reported five independent SNPs associated with anxiety disorders (Purves et al., 2019) One of these independent signals, from SNPs in *TMEM106B*, overlaps with the gene-based results for depression (Howard et al., 2019). Although current genome-wide evidence for anxiety disorders is still lacking, increasing sample sizes will eventually help uncover common variants predisposing anxiety disorders, which twin studies suggest will have strong overlap with those for depression. Further research is necessary to identify individual-specific environmental factors which distinguish anxiety and depression, as well as the biological pathways which contribute to their shared diathesis.

4. Discussion

The results from this qualitative analysis demonstrate the power of hypothesis-free, genome-wide approaches in the search for key variants associated with complex disorders. Significant genes demonstrate functions across systems known to be involved in depression pathology. A number of genes lend support for decades of research examining neurotransmitter

imbalances and the effects of antidepressant medications. Other genes demonstrate interactions with life stressors and provide plausible biological mechanisms to explain the well-documented relationship between stress and depression. Still other genes implicate immune function, which observational and experimental evidence has shown to play an important role in depression symptoms and etiology. Together, these gene-based results support a role for dysregulation of these systems in depression and provide an evidence-based starting point for prioritizing genes and designing experiments to elucidate the causal biological pathways which lead to depression.

Perhaps more importantly than lending support to known system dysfunction, these results also suggest novel research directions. Only one significant gene was found for which a known function in the serotonin system existed. Although treatments which target the serotonin system are effective for some depressed patients, it may be that serotonin dysregulation is not in fact a direct causal factor in depression, but rather an intermediary in the true causal pathway of depression etiology and treatment effects. Another possibility is that epigenetics may play a role in the dysregulation of serotonin systems during depression independent of underlying serotonin-related genotypes (Pfeiffer et al., 2018). Interestingly, the gene-based results seem to support a relatively major role for glutamatergic signaling in depression, in line with the encouraging results from trials of ketamine treatment for depressed patients discussed above in *Neurotransmitter Systems*.

Importantly, although some genes support these three traditional lines of research focus, the vast majority indicated no known function in the neurotransmitter, stress, or immune system categories chosen *a priori*. Genes with a suggested function in the CNS represent the most promising novel directions for further interrogation in preclinical models, highlighting the potential role of neural development, plasticity, and degeneration to shape and reshape brain

structures and connections which may be involved in predisposition or maintenance of depression. Although neurotransmitter, stress, and immune systems have received the vast majority of attention from researchers over the past half century, recent hypothesis-free genomic methods point to these additional biological systems and processes which deserve further attention. However, when possible, future research should be integrative - simultaneously examining multiple systems and their interaction.

It is necessary to acknowledge three potential limitations of our qualitative review. First, although gene-based methods are a powerful tool for identifying risk loci in genome-wide studies (Neale and Sham, 2004), they have been limited by the inability to distinguish true causal genes from those which are indirectly associated with a phenotype due to linkage disequilibrium. Thus, a proportion of the 269 genes may represent indirect association rather than being causally involved in depression. Recently, a conditional gene-based association test to eliminate indirectly associated genes has been developed to address this issue (Li et al., 2019). Secondly, our purpose was to perform a qualitative review where evidence in relation to each gene was gathered by manual searches of the literature, such that some relevant papers may have been missed. Nevertheless, such a qualitative review is useful to synthesize the recent genome-wide advances in the context of existing theories of depression, setting the scene for more sophisticated and comprehensive quantitative approaches. Finally, our review relies on results from the most recent GWAS meta-analysis (Howard et al., 2019), which over-represents individuals of high socioeconomic status and tests genetic associations exclusively in participants of European ancestry. A focus on representative cross-population data collection and analysis techniques is not only helpful in identifying and validating loci, but may be necessary for future clinical

applicability of genetic research. The analysis by Howard et al. also did not examine sex-chromosome loci, which may help to identify the source of noted sex differences in depression.

In light of these recent successes in genome-wide methods, we suggest that the three major interdependent goals in the field of psychiatric genomics: gene discovery, biological mechanisms, and clinical translation, are now within our reach. The proliferation of national biobanks and international consortia will undoubtedly result in continued growth in sample size, accompanied by increased power to detect associations. However, simply increasing sample size is not enough if an understanding of biological mechanism is the ultimate goal. Significant emphasis must simultaneously be placed on deep cross-disorder phenotyping including the collection of detailed symptom information, brain imaging measures, and biomarkers for HPA axis functioning, immune system activity, and gut bacteria. Along with novel methods development, this will lead to a better understanding of shared and unique contributions of genes and gene networks to specific deficits.

The major challenge once variants are identified is in moving from GWAS results to biological mechanisms. This will depend on cellular and animal studies of the most promising genetic results, with a focus on integration of multi-omic data. These can be complemented and informed by *in-silico* approaches like Mendelian randomization. Our current understanding of depression also points to the need to interrogate these genetic results in terms of sex-specific effects, development, and interaction with environmental stressors.

Finally, with patients in mind, translation must also be a major goal for researchers. Successful examples of drug targets identified through GWAS exist (Visscher et al., 2017); GWAS-supported drug targets are over two times more likely to be approved for clinical use (King et al., 2019), and drug repositioning represents a powerful tool for psychiatry (Gaspar et

al., 2019; So et al., 2017). Although current utility is limited, polygenic risk and treatment response prediction may become useful for physicians and patients in managing psychiatric symptoms and risk in the future.

Although it is likely that the field has only scratched the surface of all potential variants associated with depression, the effect sizes of additional common variants will almost certainly be smaller than those we see currently. In the meantime, these genes represent the best candidates for preclinical research studies to elucidate psychobiological mechanisms of depression and potential avenues for successful intervention.

References

Akkus, F., Mihov, Y., Treyer, V., Ametamey, S.M., Johayem, A., Senn, S., Rösner, S., Buck, A., Hasler, G., 2018. Metabotropic glutamate receptor 5 binding in male patients with alcohol use disorder. Transl. Psychiatry 8, 17. https://doi.org/10.1038/s41398-017-0066-6

Alt, A., Weiss, B., Ornstein, P.L., Gleason, S.D., Bleakman, D., Stratford, R.E., Witkin, J.M., 2007. Anxiolytic-like effects through a GLUK5 kainate receptor mechanism. Neuropharmacology 52, 1482–1487. https://doi.org/10.1016/j.neuropharm.2007.02.005

American Psychiatric Association, 2013. Depressive Disorders, in: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596.dsm04

American Psychological Association, 2018. STRESS IN AMERICA ™ GENERATION Z.

Andrews, P.W., Bharwani, A., Lee, K.R., Fox, M., Thomson, J.A., 2015. Is serotonin an upper or a downer? The evolution of the serotonergic system and its role in depression and the antidepressant response. Neurosci. Biobehav. Rev. 51, 164–188. https://doi.org/10.1016/j.neubiorev.2015.01.018

Arnau-Soler, A., Adams, M.J., Clarke, T.K., MacIntyre, D.J., Milburn, K., Navrady, L., Hayward, C., McIntosh, A., Thomson, P.A., 2019. A validation of the diathesis-stress model for depression in Generation Scotland. Transl. Psychiatry 9, 25. https://doi.org/10.1038/s41398-018-0356-7

Attwood, B.K., Bourgognon, J.M., Patel, S., Mucha, M., Schiavon, E., Skrzypiec, A.E., Young, K.W., Shiosaka, S., Korostynski, M., Piechota, M., Przewlocki, R., Pawlak, R., 2011. Neuropsin cleaves EphB2 in the amygdala to control anxiety. Nature 473, 372–377. https://doi.org/10.1038/nature09938

Bangasser, D.A., Valentino, R.J., 2014. Sex differences in stress-related psychiatric disorders: Neurobiological perspectives. Front. Neuroendocrinol. 35, 303–319. https://doi.org/10.1016/j.yfrne.2014.03.008

Barnes, S.A., Sheffler, D.J., Semenova, S., Cosford, N.D.P., Bespalov, A., 2018. Metabotropic Glutamate Receptor 5 as a Target for the Treatment of Depression and Smoking: Robust Preclinical Data but Inconclusive Clinical Efficacy. Biol. Psychiatry 83, 955–962. https://doi.org/10.1016/j.biopsych.2018.03.001

Beck, A.T., Bredemeier, K., 2016. A unified model of depression: Integrating clinical, cognitive, biological, and evolutionary perspectives. Clin. Psychol. Sci. 4, 596–619. https://doi.org/10.1177/2167702616628523

Belujon, P., Grace, A.A., 2017. Dopamine system dysregulation in major depressive disorders. Int. J. Neuropsychopharmacol. 20, 1036–1046. https://doi.org/10.1093/ijnp/pyx056

Bergstrom, C.T., Meacham, F., 2016. Depression and anxiety: Maladaptive byproducts of adaptive mechanisms. Evol. Med. Public Heal. 2016, 214–218. https://doi.org/10.1093/EMPH/EOW019

Biedrzycki, R.J., Sier, A.E., Liu, D., Dreikorn, E.N., Weeks, D.E., 2019. Spinning convincing stories for both true and false association signals. Genet. Epidemiol. https://doi.org/10.1002/gepi.22189

Border, R., Johnson, E.C., Evans, L.M., Smolen, A., Berley, N., Sullivan, P.F., Keller, M.C., 2019. No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. Am. J. Psychiatry 176, 376–387. https://doi.org/10.1176/appi.ajp.2018.18070881

Bourke, C.H., Raees, M.Q., Malviya, S., Bradburn, C.A., Binder, E.B., Neigh, G.N., 2013. Glucocorticoid sensitizers Bag1 and Ppid are regulated by adolescent stress in a sex-dependent manner. Psychoneuroendocrinology 38, 84–93. https://doi.org/10.1016/j.psyneuen.2012.05.001

Brainstorm Consortium, T.B., Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G.J., Gormley, P., Malik, R., Patsopoulos, N.A., Ripke, S., Wei, Z., Yu, D., Lee, P.H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., Berr, C., Letenneur, L., Hannequin, D., Amouyel, P., Boland, A., Deleuze, J.-F., Duron, E., Vardarajan, B.N., Reitz, C., Goate, A.M., Huentelman, M.J., Kamboh, M.I., Larson, E.B., Rogaeva, E., St George-Hyslop, P., Hakonarson, H., Kukull, W.A., Farrer, L.A., Barnes, L.L., Beach, T.G., Demirci, F.Y., Head, E., Hulette, C.M., Jicha, G.A., Kauwe, J.S.K., Kaye, J.A., Leverenz, J.B., Levey, A.I., Lieberman, A.P., Pankratz, V.S., Poon, W.W., Quinn, J.F., Saykin, A.J., Schneider, L.S., Smith, A.G., Sonnen, J.A., Stern, R.A., Van Deerlin, V.M., Van Eldik, L.J., Harold, D., Russo, G., Rubinsztein, D.C., Bayer, A., Tsolaki, M., Proitsi, P., Fox, N.C., Hampel, H., Owen, M.J., Mead, S., Passmore, P., Morgan, K., Nöthen, M.M., Rossor, M., Lupton, M.K., Hoffmann, P., Kornhuber, J., Lawlor, B., McQuillin, A., Al-Chalabi, A., Bis, J.C., Ruiz, A., Boada, M., Seshadri, S., Beiser, A., Rice, K., van der Lee, S.J., De Jager, P.L., Geschwind, D.H., Riemenschneider, M., Riedel-Heller, S., Rotter, J.I., Ransmayr, G., Hyman, B.T., Cruchaga, C., Alegret, M., Winsvold, B., Palta, P., Farh, K.-H., Cuenca-Leon, E., Furlotte, N., Kurth, T., Ligthart, L., Terwindt, G.M., Freilinger, T., Ran, C., Gordon, S.D., Borck, G., Adams, H.H.H., Lehtimäki, T., Wedenoja, J., Buring, J.E., Schürks, M., Hrafnsdottir, M., Hottenga, J.-J., Penninx, B., Artto, V., Kaunisto, M., Vepsäläinen, S., Martin, N.G., Montgomery, G.W., Kurki, M.I., Hämäläinen, E., Huang, H., Huang, J., Sandor, C., Webber, C., Muller-Myhsok, B., Schreiber, S., Salomaa, V., Loehrer, E., Göbel, H., Macaya, A., Pozo-Rosich, P., Hansen, T., Werge, T., Kaprio, J., Metspalu, A., Kubisch, C., Ferrari, M.D., Belin, A.C., van den Maagdenberg, A.M.J.M., Zwart, J.-A., Boomsma, D., Eriksson, N., Olesen, J., Chasman, D.I., Nyholt, D.R., Avbersek, A., Baum, L., Berkovic, S., Bradfield, J., Buono, R., Catarino, C.B., Cossette, P., De Jonghe, P., Depondt, C., Dlugos, D., Ferraro, T.N., French, J., Hjalgrim, H., Jamnadas-Khoda, J., Kälviäinen, R., Kunz, W.S., Lerche, H., Leu, C., Lindhout, D., Lo, W., Lowenstein, D., McCormack, M., Møller, R.S., Molloy, A., Ng, P.-W., Oliver, K., Privitera, M., Radtke, R., Ruppert, A.-K., Sander, T., Schachter, S., Schankin, C., Scheffer, I., Schoch, S., Sisodiya, S.M., Smith, P., Sperling, M., Striano, P., Surges, R., Thomas, G.N., Visscher, F., Whelan, C.D., Zara, F., Heinzen, E.L., Marson, A., Becker, F., Stroink, H., Zimprich, F., Gasser, T., Gibbs, R., Heutink, P., Martinez, M., Morris, H.R., Sharma, M., Ryten, M., Mok, K.Y., Pulit, S., Bevan, S., Holliday, E., Attia, J., Battey, T., Boncoraglio, G., Thijs, V., Chen, W.-M., Mitchell, B., Rothwell, P., Sharma, P., Sudlow, C., Vicente, A., Markus, H., Kourkoulis, C., Pera, J., Raffeld, M., Silliman, S., Boraska Perica, V., Thornton, L.M., Huckins, L.M., William Rayner, N., Lewis, C.M., Gratacos, M., Rybakowski, F., Keski-Rahkonen, A., Raevuori, A., Hudson, J.I., Reichborn-Kjennerud, T., Monteleone, P., Karwautz, A., Mannik, K., Baker, J.H., O'Toole, J.K., Trace, S.E., Davis, O.S.P., Helder, S.G., Ehrlich, S., Herpertz-Dahlmann, B., Danner, U.N., van Elburg, A.A., Clementi, M., Forzan, M., Docampo, E., Lissowska, J., Hauser, J., Tortorella, A., Maj, M., Gonidakis, F., Tziouvas, K., Papezova, H., Yilmaz, Z., Wagner, G., Cohen-Woods, S., Herms, S., Julià, A., Rabionet, R., Dick, D.M., Ripatti, S., Andreassen, O.A., Espeseth, T., Lundervold, A.J., Steen, V.M., Pinto, D., Scherer, S.W., Aschauer, H.,

Schosser, A., Alfredsson, L., Padyukov, L., Halmi, K.A., Mitchell, J., Strober, M., Bergen, A.W., Kaye, W., Szatkiewicz, J.P., Cormand, B., Ramos-Quiroga, J.A., Sánchez-Mora, C., Ribasés, M., Casas, M., Hervas, A., Arranz, M.J., Haavik, J., Zayats, T., Johansson, S., Williams, N., Dempfle, A., Rothenberger, A., Kuntsi, J., Oades, R.D., Banaschewski, T., Franke, B., Buitelaar, J.K., Arias Vasquez, A., Doyle, A.E., Reif, A., Lesch, K.-P., Freitag, C., Rivero, O., Palmason, H., Romanos, M., Langley, K., Rietschel, M., Witt, S.H., Dalsgaard, S., Børglum, A.D., Waldman, I., Wilmot, B., Molly, N., Bau, C.H.D., Crosbie, J., Schachar, R., Loo, S.K., McGough, J.J., Grevet, E.H., Medland, S.E., Robinson, E., Weiss, L.A., Bacchelli, E., Bailey, A., Bal, V., Battaglia, A., Betancur, C., Bolton, P., Cantor, R., Celestino-Soper, P., Dawson, G., De Rubeis, S., Duque, F., Green, A., Klauck, S.M., Leboyer, M., Levitt, P., Maestrini, E., Mane, S., De-Luca, D.M.-, Parr, J., Regan, R., Reichenberg, A., Sandin, S., Vorstman, J., Wassink, T., Wijsman, E., Cook, E., Santangelo, S., Delorme, R., Rogé, B., Magalhaes, T., Arking, D., Schulze, T.G., Thompson, R.C., Strohmaier, J., Matthews, K., Melle, I., Morris, D., Blackwood, D., McIntosh, A., Bergen, S.E., Schalling, M., Jamain, S., Maaser, A., Fischer, S.B., Reinbold, C.S., Fullerton, J.M., Guzman-Parra, J., Mayoral, F., Schofield, P.R., Cichon, S., Mühleisen, T.W., Degenhardt, F., Schumacher, J., Bauer, M., Mitchell, P.B., Gershon, E.S., Rice, J., Potash, J.B., Zandi, P.P., Craddock, N., Ferrier, I.N., Alda, M., Rouleau, G.A., Turecki, G., Ophoff, R., Pato, C., Anjorin, A., Stahl, E., Leber, M., Czerski, P.M., Cruceanu, C., Jones, I.R., Posthuma, D., Andlauer, T.F.M., Forstner, A.J., Streit, F., Baune, B.T., Air, T., Sinnamon, G., Wray, N.R., MacIntyre, D.J., Porteous, D., Homuth, G., Rivera, M., Grove, J., Middeldorp, C.M., Hickie, I., Pergadia, M., Mehta, D., Smit, J.H., Jansen, R., de Geus, E., Dunn, E., Li, Q.S., Nauck, M., Schoevers, R.A., Beekman, A.T., Knowles, J.A., Viktorin, A., Arnold, P., Barr, C.L., Bedoya-Berrio, G., Bienvenu, O.J., Brentani, H., Burton, C., Camarena, B., Cappi, C., Cath, D., Cavallini, M., Cusi, D., Darrow, S., Denys, D., Derks, E.M., Dietrich, A., Fernandez, T., Figee, M., Freimer, N., Gerber, G., Grados, M., Greenberg, E., Hanna, G.L., Hartmann, A., Hirschtritt, M.E., Hoekstra, P.J., Huang, A., Huyser, C., Illmann, C., Jenike, M., Kuperman, S., Leventhal, B., Lochner, C., Lyon, G.J., Macciardi, F., Madruga-Garrido, M., Malaty, I.A., Maras, A., McGrath, L., Miguel, E.C., Mir, P., Nestadt, G., Nicolini, H., Okun, M.S., Pakstis, A., Paschou, P., Piacentini, J., Pittenger, C., Plessen, K., Ramensky, V., Ramos, E.M., Reus, V., Richter, M.A., Riddle, M.A., Robertson, M.M., Roessner, V., Rosário, M., Samuels, J.F., Sandor, P., Stein, D.J., Tsetsos, F., Van Nieuwerburgh, F., Weatherall, S., Wendland, J.R., Wolanczyk, T., Worbe, Y., Zai, G., Goes, F.S., McLaughlin, N., Nestadt, P.S., Grabe, H.-J., Depienne, C., Konkashbaev, A., Lanzagorta, N., Valencia-Duarte, A., Bramon, E., Buccola, N., Cahn, W., Cairns, M., Chong, S.A., Cohen, D., Crespo-Facorro, B., Crowley, J., Davidson, M., DeLisi, L., Dinan, T., Donohoe, G., Drapeau, E., Duan, J., Haan, L., Hougaard, D., Karachanak-Yankova, S., Khrunin, A., Klovins, J., Kučinskas, V., Lee Chee Keong, J., Limborska, S., Loughland, C., Lönnqvist, J., Maher, B., Mattheisen, M., McDonald, C., Murphy, K.C., Nenadic, I., van Os, J., Pantelis, C., Pato, M., Petryshen, T., Quested, D., Roussos, P., Sanders, A.R., Schall, U., Schwab, S.G., Sim, K., So, H.-C., Stögmann, E., Subramaniam, M., Toncheva, D., Waddington, J., Walters, J., Weiser, M., Cheng, W., Cloninger, R., Curtis, D., Gejman, P. V, Henskens, F., Mattingsdal, M., Oh, S.-Y., Scott, R., Webb, B., Breen, G., Churchhouse, C., Bulik, C.M., Daly, M., Dichgans, M., Faraone, S. V, Guerreiro, R., Holmans, P., Kendler, K.S., Koeleman, B., Mathews, C.A., Price, A., Scharf, J., Sklar, P., Williams, J., Wood, N.W., Cotsapas, C., Palotie, A., Smoller, J.W., Sullivan, P., Rosand, J., Corvin, A.,

Neale, B.M., Schott, J.M., Anney, R., Elia, J., Grigoroiu-Serbanescu, M., Edenberg, H.J., Murray, R., 2018. Analysis of shared heritability in common disorders of the brain. Science 360. https://doi.org/10.1126/science.aap8757

Brydges, N.M., Seckl, J., Torrance, H.S., Holmes, M.C., Evans, K.L., Hall, J., 2014. Juvenile stress produces long-lasting changes in hippocampal DISC1, GSK3β and NRG1 expression. Mol. Psychiatry 19, 854–855. https://doi.org/10.1038/mp.2013.193

Cai, N., Bigdeli, T.B., Kretzschmar, W., Lei, Y., Liang, J., Song, L., Hu, Jingchu, Li, Q., Jin, W., Hu, Z., Wang, Guangbiao, Wang, Linmao, Qian, P., Liu, Yuan, Jiang, T., Lu, Y., Zhang, X., Yin, Y., Lie, Y., Xu, X., Gao, J., Reimers, M., Webb, T., Riley, B., Bacanu, S., Peterson, R.E., Chen, Yiping, Zhong, H., Liu, Z., Wang, Gang, Sun, J., Sang, H., Jiang, G., Zhou, X., Li, Yi, Zhang, W., Wang, Xueyi, Fang, X., Pan, R., Miao, G., Zhang, Q., Hu, Jian, Yu, F., Du, B., Sang, W., Li, Keqing, Chen, G., Cai, M., Yang, L., Yang, D., Ha, B., Hong, X., Deng, H., Li, G., Li, Kan, Song, Y., Gao, S., Zhang, J., Gan, Z., Meng, H., Pan, J., Gao, C., Zhang, K., Sun, N., Li, Youhui, Niu, Q., Zhang, Y., Liu, Tieqiao, Hu, C., Zhang, Z., Lv, L., Dong, J., Wang, Xiaoping, Tao, M., Wang, Xumei, Xia, J., Rong, H., He, Q., Liu, Tiebang, Huang, G., Mei, Q., Shen, Z., Liu, Ying, Shen, J., Tian, T., Liu, X., Wu, W., Gu, D., Fu, G., Shi, J., Chen, Yunchun, Gan, X., Liu, L., Wang, Lina, Yang, F., Cong, E., Marchini, J., Yang, H., Wang, Jian, Shi, S., Mott, R., Xu, Q., Wang, Jun, Kendler, K.S., Flint, J., 2015. Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 523, 588–591. https://doi.org/10.1038/nature14659

Cao, C., Rijlaarsdam, J., van der Voort, A., Ji, L., Zhang, W., Bakermans-Kranenburg, M.J., 2018. Associations Between Dopamine D2 Receptor (DRD2) Gene, Maternal Positive Parenting and Trajectories of Depressive Symptoms from Early to Mid-Adolescence. J. Abnorm. Child Psychol. 46, 365–379. https://doi.org/10.1007/s10802-017-0294-5

Carhart-Harris, R.L., Bolstridge, M., Day, C.M.J., Rucker, J., Watts, R., Erritzoe, D.E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J.A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., Nutt, D.J., 2018. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl). 235, 399–408. https://doi.org/10.1007/s00213-017-4771-x

Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M.J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J.A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V.H., Nutt, D.J., 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The Lancet Psychiatry 3, 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Carhart-Harris, R.L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J.N., Wall, M.B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H.V., Nutt, D.J., 2017. Psilocybin for treatment-resistant depression: FMRI-measured brain mechanisms. Sci. Rep. 7, 13187. https://doi.org/10.1038/s41598-017-13282-7

Chandley, M.J., Szebeni, A., Szebeni, K., Crawford, J.D., Stockmeier, C.A., Turecki, G., Kostrzewa, R.M., Ordway, G.A., 2014. Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. Int. J. Neuropsychopharmacol. 17, 1569–1578. https://doi.org/10.1017/S1461145714000662

Chen, A.C.H., Tang, Y., Rangaswamy, M., Wang, J.C., Almasy, L., Foroud, T., Edenberg, H.J., Hesselbrock, V., Nurnberger, J., Kuperman, S., O'Connor, S.J., Schuckit, M.A., Bauer, L.O., Tischfield, J., Rice, J.P., Bierut, L., Goate, A., Porjesz, B., 2009. Association of single nucleotide polymorphisms in a glutamate receptor gene (GRM8) with theta power of event-

related oscillations and alcohol dependence. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 150, 359–368. https://doi.org/10.1002/ajmg.b.30818
Chen, Z.Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science (80-.). 314, 140–143. https://doi.org/10.1126/science.1129663
Chesworth, R., Yulyaningsih, E., Cappas, E., Arnold, J., Sainsbury, A., Karl, T., 2012. The response of neuregulin 1 mutant mice to acute restraint stress. Neurosci. Lett. 515, 82–86. https://doi.org/10.1016/j.neulet.2012.03.024
Chohan, T.W., Boucher, A.A., Spencer, J.R., Kassem, M.S., Hamdi, A.A., Karl, T., Fok, S.Y., Bennett, M.R., Arnold, J.C., 2014a. Partial genetic deletion of neuregulin 1 modulates the effects of stress on sensorimotor gating, dendritic morphology, and HPA axis activity in adolescent mice. Schizophr. Bull. 40, 1272–1284. https://doi.org/10.1093/schbul/sbt193
Chohan, T.W., Nguyen, A., Todd, S.M., Bennett, M.R., Callaghan, P., Arnold, J.C., 2014b. Partial genetic deletion of neuregulin 1 and adolescent stress interact to alter NMDA receptor binding in the medial prefrontal cortex. Front. Behav. Neurosci. 8, 298. https://doi.org/10.3389/fnbeh.2014.00298
Choi, K.H., Higgs, B.W., Wendland, J.R., Song, J., McMahon, F.J., Webster, M.J., 2011. Gene expression and genetic variation data implicate PCLO in bipolar disorder. Biol. Psychiatry 69, 353–359. https://doi.org/10.1016/j.biopsych.2010.09.042
Choi, S., Han, K.M., Kang, J., Won, E., Chang, H.S., Tae, W.S., Son, K.R., Kim, S.J., Lee, M.S., Ham, B.J., 2016. Effects of a polymorphism of the neuronal amino acid transporter SLC6A15 gene on structural integrity of white matter tracts in major depressive disorder. PLoS One 11, e0164301. https://doi.org/10.1371/journal.pone.0164301
Chung, D.W., Chung, Y., Bazmi, H.H., Lewis, D.A., 2018. Altered ErbB4 splicing and cortical parvalbumin interneuron dysfunction in schizophrenia and mood disorders. Neuropsychopharmacology 43, 2478–2486. https://doi.org/10.1038/s41386-018-0169-7
Cissé, M., Halabisky, B., Harris, J., Devidze, N., Dubal, D.B., Sun, B., Orr, A., Lotz, G., Kim, D.H., Hamto, P., Ho, K., Yu, G.Q., Mucke, L., 2011. Reversing EphB2 depletion rescues cognitive functions in Alzheimer model. Nature 469, 47–52. https://doi.org/10.1038/nature09635
Clarke, D.J., Stuart, J., McGregor, I.S., Arnold, J.C., 2017. Endocannabinoid dysregulation in cognitive and stress-related brain regions in the Nrg1 mouse model of schizophrenia. Prog. Neuro-Psychopharmacology Biol. Psychiatry 72, 9–15. https://doi.org/10.1016/j.pnpbp.2016.08.006
Clarke, T.K., Zeng, Y., Navrady, L., Xia, C., Haley, C., Campbell, A., Navarro, P., Amador, C., Adams, M.J., Howard, D.M., Soler, A., Hayward, C., Thomson, P.A., Smith, B.H., Padmanabhan, S., Hocking, L.J., Hall, L.S., Porteous, D.J., Deary, I.J., McIntosh, A.M., 2019. Genetic and environmental determinants of stressful life events and their overlap with depression and neuroticism [version 2; referees: 1 approved, 2 approved with reservations]. Wellcome Open Res. 3, 11. https://doi.org/10.12688/wellcomeopenres.13893.2
Colodro-Conde, L., Couvy-Duchesne, B., Zhu, G., Coventry, W.L., Byrne, E.M., Gordon, S., Wright, M.J., Montgomery, G.W., Madden, P.A.F., Ripke, S., Eaves, L.J., Heath, A.C., Wray, N.R., Medland, S.E., Martin, N.G., 2018. A direct test of the diathesis–stress model for depression. Mol. Psychiatry 23, 1590–1596. https://doi.org/10.1038/mp.2017.130
Coyle, C.M., Laws, K.R., 2015. The use of ketamine as an antidepressant: A systematic review

and meta-analysis. Hum. Psychopharmacol. 30, 152–163. https://doi.org/10.1002/hup.2475
Dang, R., Cai, H., Zhang, L., Liang, D., Lv, C., Guo, Y., Yang, R., Zhu, Y., Jiang, P., 2016a. Dysregulation of Neuregulin-1/ErbB signaling in the prefrontal cortex and hippocampus of rats exposed to chronic unpredictable mild stress. Physiol. Behav. 154, 145–150. https://doi.org/10.1016/j.physbeh.2015.11.023
Dang, R., Guo, Y., Zhang, L., Chen, L., Yang, R., Jiang, P., 2016b. Chronic stress and excessive glucocorticoid exposure both lead to altered Neuregulin-1/ERBB signaling in rat myocardium. Steroids 112, 47–53. https://doi.org/10.1016/j.steroids.2016.04.011
Dedovic, K., Duchesne, A., Andrews, J., Engert, V., Pruessner, J.C., 2009. The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. Neuroimage 47, 864–871. https://doi.org/10.1016/j.neuroimage.2009.05.074
Di Giovannantonio, L.G., Di Salvio, M., Acampora, D., Prakash, N., Wurst, W., Simeone, A., 2013. Otx2 selectively controls the neurogenesis of specific neuronal subtypes of the ventral tegmental area and compensates En1-dependent neuronal loss and MPTP vulnerability. Dev. Biol. 373, 176–183. https://doi.org/10.1016/J.YDBIO.2012.10.022
Dick, D.M., Agrawal, A., Keller, M.C., Adkins, A., Aliev, F., Monroe, S., Hewitt, J.K., Kendler, K.S., Sher, K.J., 2015. Candidate Gene–Environment Interaction Research: Reflections and Recommendations. Perspect. Psychol. Sci. 10, 37–59. https://doi.org/10.1177/1745691614556682
Duman, R.S., 2014. Neurobiology of stress, depression, and rapid acting antidepressants: Remodeling synaptic connections. Depress. Anxiety 31, 291–296. https://doi.org/10.1002/da.22227
Duman, R.S., Monteggia, L.M., 2006. A Neurotrophic Model for Stress-Related Mood Disorders. Biol. Psychiatry 59, 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013
Dunn, E.C., Sofer, T., Wang, M.J., Soare, T.W., Gallo, L.C., Gogarten, S.M., Kerr, K.F., Chen, C.Y., Stein, M.B., Ursano, R.J., Guo, X., Jia, Y., Yao, J., Rotter, J.I., Argos, M., Cai, J., Perreira, K., Wassertheil-Smoller, S., Smoller, J.W., 2018. Genome-wide association study of depressive symptoms in the Hispanic Community Health Study/Study of Latinos. J. Psychiatr. Res. 99, 167–176. https://doi.org/10.1016/j.jpsychires.2017.12.010
Dunn, S.H., Conley, Y.P., 2015. A systematic review of genetic influences on coping. Biol. Res. Nurs. 17, 87–93. https://doi.org/10.1177/1099800414527340
Duval, E.R., Javanbakht, A., Liberzon, I., 2015. Neural circuits in anxiety and stress disorders: A focused review. Ther. Clin. Risk Manag. 11, 115–126. https://doi.org/10.2147/TCRM.S48528
Ecker, K., Lorenz, A., Wolf, F., Ploner, C., Böck, G., Duncan, T., Geley, S., Helmberg, A., 2009. A RAS recruitment screen identifies ZKSCAN4 as a glucocorticoid receptor-interacting protein. J. Mol. Endocrinol. 42, 105–117. https://doi.org/10.1677/JME-08-0087
Enga, R.M., Rice, A.C., Weller, P., Subler, M.A., Lee, D., Hall, C.P., Windle, J.J., Beardsley, P.M., van den Oord, E.J., McClay, J.L., 2017. Initial characterization of behavior and ketamine response in a mouse knockout of the post-synaptic effector gene Anks1b. Neurosci. Lett. 641, 26–32. https://doi.org/10.1016/J.NEULET.2017.01.044
Esterlis, I., DellaGioia, N., Pietrzak, R.H., Matuskey, D., Nabulsi, N., Abdallah, C.G., Yang, J., Pittenger, C., Sanacora, G., Krystal, J.H., Parsey, R. V, Carson, R.E., DeLorenzo, C., 2018. Ketamine-induced reduction in mGluR5 availability is associated with an antidepressant response: an [11C]ABP688 and PET imaging study in depression. Mol. Psychiatry 23, 824–832. https://doi.org/10.1038/mp.2017.58

Faravelli, C., Lo Sauro, C., Lelli, L., Pietrini, F., Lazzeretti, L., Godini, L., Benni, L., Fioravanti, G., Alina Talamba, G., Castellini, G., Ricca, V., 2012. The Role of Life Events and HPA Axis in Anxiety Disorders: A Review. Curr. Pharm. Des. 18, 5663–5674. https://doi.org/10.2174/138161212803530907

Farrelly, L.A., Thompson, R.E., Zhao, S., Lepack, A.E., Lyu, Y., Bhanu, N. V., Zhang, B., Loh, Y.H.E., Ramakrishnan, A., Vadodaria, K.C., Heard, K.J., Erikson, G., Nakadai, T., Bastle, R.M., Lukasak, B.J., Zebroski, H., Alenina, N., Bader, M., Berton, O., Roeder, R.G., Molina, H., Gage, F.H., Shen, L., Garcia, B.A., Li, H., Muir, T.W., Maze, I., 2019. Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. Nature 567, 535–539. https://doi.org/10.1038/s41586-019-1024-7

Fazzari, P., Paternain, A. V., Valiente, M., Pla, R., Luján, R., Lloyd, K., Lerma, J., Marín, O., Rico, B., 2010. Control of cortical GABA circuitry development by Nrg1 and ErbB4 signalling. Nature 464, 1376–1380. https://doi.org/10.1038/nature08928

Federenko, I.S., Schlotz, W., Kirschbaum, C., Bartels, M., Hellhammer, D.H., Wüst, S., 2006. The heritability of perceived stress. Psychol. Med. 36, 375–385. https://doi.org/10.1017/S0033291705006616

Felger, J.C., Treadway, M.T., 2017. Inflammation Effects on Motivation and Motor Activity: Role of Dopamine. Neuropsychopharmacology 42, 216–241. https://doi.org/10.1038/npp.2016.143

Feng, Y., Cheng, D., Zhang, C., Li, Y., Zhang, Z., Wang, J., Feng, X., 2017. Association between ErbB4 single nucleotide polymorphisms and susceptibility to schizophrenia: A meta-analysis of case-control studies. Medicine (Baltimore). 96, e5920. https://doi.org/10.1097/MD.0000000000005920

Flint, J., Kendler, K.S., 2014. The Genetics of Major Depression. Neuron 81, 484–503. https://doi.org/10.1016/j.neuron.2014.01.027

Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lançon, C., Brittner, M., Micoulaud-Franchi, J.A., Richieri, R., Courtet, P., Abbar, M., Roger, M., Leboyer, M., Boyer, L., 2014. Ketamine administration in depressive disorders: A systematic review and meta-analysis. Psychopharmacology (Berl). 231, 3663–3676. https://doi.org/10.1007/s00213-014-3664-5

Freeman, M.P., Papakostas, G.I., Hoeppner, B., Mazzone, E., Judge, H., Cusin, C., Mathew, S., Sanacora, G., Iosifescu, D., DeBattista, C., Trivedi, M.H., Fava, M., 2019. Sex differences in response to ketamine as a rapidly acting intervention for treatment resistant depression. J. Psychiatr. Res. 110, 166–171. https://doi.org/10.1016/j.jpsychires.2019.01.010

Gaspar, H.A., Gerring, Z., Hübel, C., Middeldorp, C.M., Derks, E.M., Breen, G., 2019. Using genetic drug-target networks to develop new drug hypotheses for major depressive disorder. Transl. Psychiatry 2019 91 9, 1–9. https://doi.org/10.1038/s41398-019-0451-4

Gatt, J.M., Burton, K.L.O., Williams, L.M., Schofield, P.R., 2015. Specific and common genes implicated across major mental disorders: A review of meta-analysis studies. J. Psychiatr. Res. 60, 1–13. https://doi.org/10.1016/j.jpsychires.2014.09.014

Goddard, A.W., Ball, S.G., Martinez, J., Robinson, M.J., Yang, C.R., Russell, J.M., Shekhar, A., 2010. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depress. Anxiety 27, 339–350. https://doi.org/10.1002/da.20642

Gold, P.W., 2015. The organization of the stress system and its dysregulation in depressive illness. Mol. Psychiatry 20, 32–47. https://doi.org/10.1038/mp.2014.163

Gold, P.W., Chrousos, G.P., 2013. Melancholic and atypical subtypes of depression represent distinct pathophysiological entities: CRH, neural circuits, and the diathesis for anxiety and

depression. Mol. Psychiatry 18, 632–634. https://doi.org/10.1038/mp.2013.5
Gorman, J.M., 2006. Gender differences in depression and response to psychotropic medication. Gend. Med. 3, 93–109. https://doi.org/10.1016/S1550-8579(06)80199-3
Gunduz-Cinar, O., Brockway, E., Lederle, L., Wilcox, T., Halladay, L.R., Ding, Y., Oh, H., Busch, E.F., Kaugars, K., Flynn, S., Limoges, A., Bukalo, O., MacPherson, K.P., Masneuf, S., Pinard, C., Sibille, E., Chesler, E.J., Holmes, A., 2019. Identification of a novel gene regulating amygdala-mediated fear extinction. Mol. Psychiatry 24, 601–612. https://doi.org/10.1038/s41380-017-0003-3
Hall, L.S., Adams, M.J., Arnau-Soler, A., Clarke, T.K., Howard, D.M., Zeng, Y., Davies, G., Hagenaars, S.P., Fernandez-Pujals, A.M., Gibson, J., Wigmore, E.M., Boutin, T.S., Hayward, C., Scotland, G., Porteous, D.J., Deary, I.J., Thomson, P.A., Haley, C.S., McIntosh, A.M., 2018. Genome-wide meta-analyses of stratified depression in Generation Scotland and UK Biobank. Transl. Psychiatry 8. https://doi.org/10.1038/s41398-017-0034-1
Hammen, C., 2005. Stress and Depression. Annu. Rev. Clin. Psychol. 1, 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938
He, H., Wu, H., Yang, L., Gao, F., Fan, Y., Feng, J., Ma, X., 2016. Associations between dopamine D2 receptor gene polymorphisms and schizophrenia risk: a PRISMA compliant meta-analysis. Neuropsychiatr. Dis. Treat. 12, 3129–3144. https://doi.org/10.2147/NDT.S118614
Hek, K., Mulder, C.L., Luijendijk, H.J., van Duijn, C.M., Hofman, A., Uitterlinden, A.G., Tiemeier, H., 2010. The PCLO gene and depressive disorders: replication in a population-based study. Hum. Mol. Genet. 19, 731–734. https://doi.org/10.1093/hmg/ddp529
Herr, N., Bode, C., Duerschmied, D., 2017. The Effects of Serotonin in Immune Cells. Front. Cardiovasc. Med. 4, 48. https://doi.org/10.3389/fcvm.2017.00048
Hettema, J.M., 2008. What is the genetic relationship between anxiety and depression? Am. J. Med. Genet. Part C Semin. Med. Genet. 148C, 140–146. https://doi.org/10.1002/ajmg.c.30171
Hill, A.S., Sahay, A., Hen, R., 2015. Increasing Adult Hippocampal Neurogenesis is Sufficient to Reduce Anxiety and Depression-Like Behaviors. Neuropsychopharmacology 40, 2368–2378. https://doi.org/10.1038/npp.2015.85
Hirschfeld, R.M.A., 2000. History and evolution of the monoamine hypothesis of depression. J. Clin. Psychiatry 61, 4–6.
Holzschneider, K., Mulert, C., 2011. Neuroimaging in anxiety disorders. Dialogues Clin. Neurosci. 13, 453–461.
Howard, D.M., Adams, M.J., Clarke, T.K., Hafferty, J.D., Gibson, J., Shirali, M., Coleman, J.R.I., Hagenaars, S.P., Ward, J., Wigmore, E.M., Alloza, C., Shen, X., Barbu, M.C., Xu, E.Y., Whalley, H.C., Marioni, R.E., Porteous, D.J., Davies, G., Deary, I.J., Hemani, G., Berger, K., Teismann, H., Rawal, R., Arolt, V., Baune, B.T., Dannlowski, U., Domschke, K., Tian, C., Hinds, D.A., Trzaskowski, M., Byrne, E.M., Ripke, S., Smith, D.J., Sullivan, P.F., Wray, N.R., Breen, G., Lewis, C.M., McIntosh, A.M., 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat. Neurosci. 22, 343–352. https://doi.org/10.1038/s41593-018-0326-7
Howard, D.M., Adams, M.J., Shirali, M., Clarke, T.-K., Marioni, R.E., Davies, G., Coleman, J.R.I., Alloza, C., Shen, X., Barbu, M.C., Wigmore, E.M., Gibson, J., Hagenaars, S.P., Lewis, C.M., Ward, J., Smith, D.J., Sullivan, P.F., Haley, C.S., Breen, G., Deary, I.J.,

McIntosh, A.M., 2018. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat. Commun. 9, 1–28. https://doi.org/10.1038/s41467-018-03819-3
Hu, R., Wei, P., Jin, L., Zheng, T., Chen, W.-Y., Liu, X.-Y., Shi, X.-D., Hao, J.-R., Sun, N., Gao, C., 2017. Overexpression of EphB2 in hippocampus rescues impaired NMDA receptors trafficking and cognitive dysfunction in Alzheimer model. Cell Death Dis. 8, e2717–e2717. https://doi.org/10.1038/cddis.2017.140
Hyde, C.L., Nagle, M.W., Tian, C., Chen, X., Paciga, S.A., Wendland, J.R., Tung, J.Y., Hinds, D.A., Perlis, R.H., Winslow, A.R., 2016. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat. Genet. 48, 1031–1036. https://doi.org/10.1038/ng.3623
Igata, R., Katsuki, A., Kakeda, S., Watanabe, K., Igata, N., Hori, H., Konishi, Y., Atake, K., Kawasaki, Y., Korogi, Y., Yoshimura, R., 2017. PCLO rs2522833-mediated gray matter volume reduction in patients with drug-naive, first-episode major depressive disorder. Transl. Psychiatry 7, e1140–e1140. https://doi.org/10.1038/tp.2017.100
Kalia, S.K., Lee, S., Smith, P.D., Liu, L., Crocker, S.J., Thorarinsdottir, T.E., Glover, J.R., Fon, E.A., Park, D.S., Lozano, A.M., 2004. BAG5 Inhibits Parkin and Enhances Dopaminergic Neuron Degeneration. Neuron 44, 931–945. https://doi.org/10.1016/j.neuron.2004.11.026
Karataeva, A.R., Klaassen, R. V., Ströder, J., Ruiperez-Alonso, M., Hjorth, J.J.J., van Nierop, P., Spijker, S., Mansvelder, H.D., Smit, A.B., 2014. C-Terminal Interactors of the AMPA Receptor Auxiliary Subunit Shisa9. PLoS One 9, e87360. https://doi.org/10.1371/journal.pone.0087360
Kaufman, J., Wymbs, N.F., Montalvo-Ortiz, J.L., Orr, C., Albaugh, M.D., Althoff, R., O'Loughlin, K., Holbrook, H., Garavan, H., Kearney, C., Yang, B.-Z., Zhao, H., Peña, C., Nestler, E.J., Lee, R.S., Mostofsky, S., Gelernter, J., Hudziak, J., 2018. Methylation in OTX2 and related genes, maltreatment, and depression in children. Neuropsychopharmacology 43, 2204–2211. https://doi.org/10.1038/s41386-018-0157-y
Kendler, K.S., Gardner, C.O., Neale, M.C., Prescott, C.A., 2001. Genetic risk factors for major depression in men and women: similar or different heritabilities and same or partly distinct genes? Psychol. Med. 31, 605–16.
Kendler, K.S., Gatz, M., Gardner, C.O., Pedersen, N.L., 2006. A Swedish national twin study of lifetime major depression. Am. J. Psychiatry 163, 109–114. https://doi.org/10.1176/appi.ajp.163.1.109
Kendler, K.S., Heath, A.C., Martin, N.G., Eaves, L.J., 1987. Symptoms of Anxiety and Symptoms of Depression. Arch. Gen. Psychiatry 44, 451. https://doi.org/10.1001/archpsyc.1987.01800170073010
Kendler, K.S., Karkowski, L.M., Prescott, C.A., 1999. Causal relationship between stressful life events and the onset of major depression. Am. J. Psychiatry 156, 837–841. https://doi.org/10.1176/ajp.156.6.837
Kendler, K.S., Neale, M.C., Kessler, R.C., Heath, A.C., Eaves, L.J., 1992. Major depression and generalized anxiety disorder: Same genes, (partly) different environments? Arch. Gen. Psychiatry 49, 716–722. https://doi.org/10.1001/archpsyc.1992.01820090044008
Kendler, K.S., Prescott, C.A., Myers, J., Neale, M.C., 2003. The Structure of Genetic and Environmental Risk Factors for Common Psychiatric and Substance Use Disorders in Men and Women. Arch. Gen. Psychiatry 60, 929–937. https://doi.org/10.1001/archpsyc.60.9.929
Kessler, R.C., Merikangas, K.R., Wang, P.S., 2007. Prevalence, Comorbidity, and Service

Utilization for Mood Disorders in the United States at the Beginning of the Twenty-first Century. Annu. Rev. Clin. Psychol. 3, 137–158. https://doi.org/10.1146/annurev.clinpsy.3.022806.091444

Kessler, R.C., Petukhova, M., Sampson, N.A., Zaslavsky, A.M., Wittchen, H.U., 2012. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int. J. Methods Psychiatr. Res. 21, 169–184. https://doi.org/10.1002/mpr.1359

Khan, A., Brodhead, A.E., Schwartz, K.A., Kolts, R.L., Brown, W.A., 2005. Sex Differences in Antidepressant Response in Recent Antidepressant Clinical Trials. J. Clin. Psychopharmacol. 25, 318–324. https://doi.org/10.1097/01.jcp.0000168879.03169.ce

King, E.A., Wade Davis, J., Degner, J.F., 2019. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet. 15. https://doi.org/10.1371/journal.pgen.1008489

Kohli, M.A., Lucae, S., Saemann, P.G., Schmidt, M. V, Demirkan, A., Hek, K., Czamara, D., Alexander, M., Salyakina, D., Ripke, S., Hoehn, D., Specht, M., Menke, A., Hennings, J., Heck, A., Wolf, C., Ising, M., Schreiber, S., Czisch, M., Müller, M.B., Uhr, M., Bettecken, T., Becker, A., Schramm, J., Rietschel, M., Maier, W., Bradley, B., Ressler, K.J., Nöthen, M.M., Cichon, S., Craig, I.W., Breen, G., Lewis, C.M., Hofman, A., Tiemeier, H., van Duijn, C.M., Holsboer, F., Müller-Myhsok, B., Binder, E.B., 2011. The neuronal transporter gene SLC6A15 confers risk to major depression. Neuron 70, 252–65. https://doi.org/10.1016/j.neuron.2011.04.005

Kordi-Tamandani, D.M., Dahmardeh, N., Torkamanzehi, A., 2013. Evaluation of hypermethylation and expression pattern of GMR2, GMR5, GMR8, and GRIA3 in patients with schizophrenia. Gene 515, 163–166. https://doi.org/10.1016/J.GENE.2012.10.075

Kotov, R., Gamez, W., Schmidt, F., Watson, D., 2010. Linking "big" personality traits to anxiety, depressive, and substance use disorders: A meta-analysis. Psychol. Bull. 136, 768–821. https://doi.org/10.1037/a0020327

Krishnan, V., Nestler, E.J., 2008. The molecular neurobiology of depression. Nature 455, 894–902. https://doi.org/10.1038/nature07455

Kuehner, C., Huffziger, S., Witt, S.H., Rietschel, M., 2011. PCLO rs2522833 impacts HPA system activity in healthy young adults. Transl. Psychiatry 1, e10–e10. https://doi.org/10.1038/tp.2011.11

Lamers, F., van Oppen, P., Comijs, H.C., Smit, J.H., Spinhoven, P., van Balkom, A.J.L.M., Nolen, W.A., Zitman, F.G., Beekman, A.T.F., Penninx, B.W.J.H., 2011. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the {Netherlands} {Study} of {Depression} and {Anxiety} ({NESDA}). J. Clin. Psychiatry 72, 341–348. https://doi.org/10.4088/JCP.10m06176blu

Le-Niculescu, H., Balaraman, Y., Patel, S.D., Ayalew, M., Gupta, J., Kuczenski, R., Shekhar, A., Schork, N., Geyer, M.A., Niculescu, A.B., 2011. Convergent functional genomics of anxiety disorders: translational identification of genes, biomarkers, pathways and mechanisms. Transl. Psychiatry 1, e9. https://doi.org/10.1038/tp.2011.9

Lener, M.S., Niciu, M.J., Ballard, E.D., Park, M., Park, L.T., Nugent, A.C., Zarate, C.A., 2017. Glutamate and Gamma-Aminobutyric Acid Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine. Biol. Psychiatry 81, 886–897. https://doi.org/10.1016/j.biopsych.2016.05.005

Li, H., Li, Y., Shao, J., Li, R., Qin, Y., Xie, C., Zhao, Z., 2008. The association analysis of RELN and GRM8 genes with autistic spectrum disorder in chinese han population. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 147B, 194–200. https://doi.org/10.1002/ajmg.b.30584

Li, M., Jiang, L., Mak, T.S.H., Kwan, J.S.H., Xue, C., Chen, P., Leung, H.C.-M., Cui, L., Li, T., Sham, P.C., 2019. A powerful conditional gene-based association approach implicated functionally important genes for schizophrenia. Bioinformatics 35, 628–635. https://doi.org/10.1093/bioinformatics/bty682

Li, W., Ju, K., Li, Z., He, K., Chen, J., Wang, Q., Yang, B., An, L., Feng, G., Sun, W., Zhou, J., Zhang, S., Song, P., Khan, R.A.W., Ji, W., Shi, Y., 2016. Significant association of GRM7 and GRM8 genes with schizophrenia and major depressive disorder in the Han Chinese population. Eur. Neuropsychopharmacol. 26, 136–146. https://doi.org/10.1016/j.euroneuro.2015.05.004

Liu, R.T., Alloy, L.B., 2010. Stress generation in depression: A systematic review of the empirical literature and recommendations for future study. Clin. Psychol. Rev. 30, 582–593. https://doi.org/10.1016/j.cpr.2010.04.010

Locher, C., Koechlin, H., Zion, S.R., Werner, C., Pine, D.S., Kirsch, I., Kessler, R.C., Kossowsky, J., 2017. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. JAMA psychiatry 74, 1011–1020. https://doi.org/10.1001/jamapsychiatry.2017.2432

Long, E.C., Aliev, F., Wang, J.-C., Edenberg, H.J., Nurnberger, J., Hesselbrock, V., Porjesz, B., Dick, D.M., 2015. Further Analyses of Genetic Association Between GRM8 and Alcohol Dependence Symptoms Among Young Adults. J. Stud. Alcohol Drugs 76, 414–8. https://doi.org/10.15288/jsad.2015.76.414

Luykx, J.J., Broersen, J.L., de Leeuw, M., 2017. The DRD2 rs1076560 polymorphism and schizophrenia-related intermediate phenotypes: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. 74, 214–224. https://doi.org/10.1016/j.neubiorev.2017.01.006

Luykx, J.J., Vinkers, C.H., Bakker, S.C., Visser, W.F., van Boxmeer, L., Strengman, E., van Eijk, K.R., Lens, J.A., Borgdorff, P., Keijzers, P., Kappen, T.H., van Dongen, E.P.A., Bruins, P., Verhoeven, N.M., de Koning, T.J., Kahn, R.S., Ophoff, R.A., 2012. A Common Variant in ERBB4 Regulates GABA Concentrations in Human Cerebrospinal Fluid. Neuropsychopharmacology 37, 2088–2092. https://doi.org/10.1038/npp.2012.57

Marenco, S., Geramita, M., van der Veen, J.W., Barnett, A.S., Kolachana, B., Shen, J., Weinberger, D.R., Law, A.J., 2011. Genetic Association of ErbB4 and Human Cortical GABA Levels In Vivo. J. Neurosci. 31, 11628–11632. https://doi.org/10.1523/JNEUROSCI.1529-11.2011

Marin, E.P., Jozsef, L., Di Lorenzo, A., Held, K.F., Luciano, A.K., Melendez, J., Milstone, L.M., Velazquez, H., Sessa, W.C., 2016. The Protein Acyl Transferase ZDHHC21 Modulates α1 Adrenergic Receptor Function and Regulates Hemodynamics. Arterioscler. Thromb. Vasc. Biol. 36, 370–379. https://doi.org/10.1161/ATVBAHA.115.306942

Matosin, N., Newell, K.A., Quidé, Y., Andrews, J.L., Teroganova, N., Green, M.J., Fernandez, F., 2018. Effects of common GRM5 genetic variants on cognition, hippocampal volume and mGluR5 protein levels in schizophrenia. Brain Imaging Behav. 12, 509–517. https://doi.org/10.1007/s11682-017-9712-0

Matute, C., 2011. Therapeutic potential of kainate receptors. CNS Neurosci. Ther. 17, 661–669.

https://doi.org/10.1111/j.1755-5949.2010.00204.x
McIntosh, A.M., Sullivan, P.F., Lewis, C.M., 2019. Uncovering the Genetic Architecture of Major Depression. Neuron 102, 91–103. https://doi.org/10.1016/j.neuron.2019.03.022
Meier, S.M., Trontti, K., Purves, K.L., Als, T.D., Grove, J., Laine, M., Pedersen, M.G., Bybjerg-Grauholm, J., Bækved-Hansen, M., Sokolowska, E., Mortensen, P.B., Hougaard, D.M., Werge, T., Nordentoft, M., Breen, G., Børglum, A.D., Eley, T.C., Hovatta, I., Mattheisen, M., Mors, O., 2019. Genetic Variants Associated With Anxiety and Stress-Related Disorders: A Genome-Wide Association Study and Mouse-Model Study. JAMA psychiatry. https://doi.org/10.1001/jamapsychiatry.2019.1119
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34. https://doi.org/10.1038/nri.2015.5
Minelli, A., Scassellati, C., Cloninger, C.R., Tessari, E., Bortolomasi, M., Bonvicini, C., Giacopuzzi, M., Frisoni, G.B., Gennarelli, M., 2012. PCLO gene: Its role in vulnerability to major depressive disorder. J. Affect. Disord. 139, 250–255. https://doi.org/10.1016/J.JAD.2012.01.028
Montoya, A., Bruins, R., Katzman, M.A., Blier, P., 2016. The noradrenergic paradox: implications in the management of depression and anxiety. Neuropsychiatr. Dis. Treat. 12, 541–557. https://doi.org/10.2147/NDT.S91311
Moret, C., Briley, M., 2011. The importance of norepinephrine in depression. Neuropsychiatr. Dis. Treat. 7, 9–13. https://doi.org/10.2147/NDT.S19619
Mostaid, M.S., Lloyd, D., Liberg, B., Sundram, S., Pereira, A., Pantelis, C., Karl, T., Weickert, C.S., Everall, I.P., Bousman, C.A., 2016. Neuregulin-1 and schizophrenia in the genome-wide association study era. Neurosci. Biobehav. Rev. 68, 387–409. https://doi.org/10.1016/J.NEUBIOREV.2016.06.001
National Library of Medicine (US) National Center for Biotechnology Information, n.d. Gene [WWW Document]. URL https://www.ncbi.nlm.nih.gov/gene (accessed 7.10.19).
Neale, B.M., Sham, P.C., 2004. The future of association studies: Gene-based analysis and replication. Am. J. Hum. Genet. 75, 353–362. https://doi.org/10.1086/423901
Nesse, R.M., 2000. Is depression an adaptation? Arch. Gen. Psychiatry 57, 14–20.
Nesse, R.M., Bhatnagar, S., Ellis, B., 2016. Evolutionary Origins and Functions of the Stress Response System, in: Stress: Concepts, Cognition, Emotion, and Behavior. Elsevier, pp. 95–101. https://doi.org/10.1016/B978-0-12-800951-2.00011-X
Nikolaus, S., Antke, C., Beu, M., Müller, H.-W., 2010. Cortical GABA, Striatal Dopamine and Midbrain Serotonin as the Key Players in Compulsive and Anxiety Disorders - Results from In Vivo Imaging Studies. Rev. Neurosci. 21, 119–140. https://doi.org/10.1515/REVNEURO.2010.21.2.119
Nutt, D.J., 2008. Relationship of Neurotransmitters to the Symptoms of Major Depressive Disorder, J Clin Psychiatry.
O'Connor, R.M., Pusceddu, M.M., Dinan, T.G., Cryan, J.F., 2013. Impact of early-life stress, on group III mGlu receptor levels in the rat hippocampus: Effects of ketamine, electroconvulsive shock therapy and fluoxetine treatment. Neuropharmacology 66, 236–241. https://doi.org/10.1016/j.neuropharm.2012.05.006
Pariante, C.M., Lightman, S.L., 2008. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 31, 464–468. https://doi.org/10.1016/j.tins.2008.06.006

Parthier, D., Kuner, T., Körber, C., 2018. The presynaptic scaffolding protein Piccolo organizes the readily releasable pool at the calyx of Held. J. Physiol. 596, 1485–1499. https://doi.org/10.1113/JP274885

Peña, C.J., Kronman, H.G., Walker, D.M., Cates, H.M., Bagot, R.C., Purushothaman, I., Issler, O., Loh, Y.-H.E., Leong, T., Kiraly, D.D., Goodman, E., Neve, R.L., Shen, L., Nestler, E.J., 2017. Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science 356, 1185–1188. https://doi.org/10.1126/science.aan4491

Peterlik, D., Stangl, C., Bauer, A., Bludau, A., Keller, J., Grabski, D., Killian, T., Schmidt, D., Zajicek, F., Jaeschke, G., Lindemann, L., Reber, S.O., Flor, P.J., Uschold-Schmidt, N., 2017. Blocking metabotropic glutamate receptor subtype 5 relieves maladaptive chronic stress consequences. Brain. Behav. Immun. 59, 79–92. https://doi.org/10.1016/j.bbi.2016.08.007

Pfeiffer, J.R., Mutesa, L., Uddin, M., 2018. Traumatic Stress Epigenetics. Curr. Behav. Neurosci. Reports 5, 81–93. https://doi.org/10.1007/s40473-018-0143-z

Pohjalainen, T., Rinne, J.O., Någren, K., Lehikoinen, P., Anttila, K., Syvälahti, E.K.G., Hietala, J., 1998. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol. Psychiatry 3, 256–260. https://doi.org/10.1038/sj.mp.4000350

Ponce, G., Pérez-González, R., Aragüés, M., Palomo, T., Rodríguez-Jiménez, R., Jiménez-Arriero, M.A., Hoenicka, J., 2009. The ANKK1 Kinase Gene and Psychiatric Disorders. Neurotox. Res. 16, 50–59. https://doi.org/10.1007/s12640-009-9046-9

Power, R.A., Wingenbach, T., Cohen-Woods, S., Uher, R., Ng, M.Y., Butler, A.W., Ising, M., Craddock, N., Owen, M.J., Korszun, A., Jones, L., Jones, I., Gill, M., Rice, J.P., Maier, W., Zobel, A., Mors, O., Placentino, A., Rietschel, M., Lucae, S., Holsboer, F., Binder, E.B., Keers, R., Tozzi, F., Muglia, P., Breen, G., Craig, I.W., Müller-Myhsok, B., Kennedy, J.L., Strauss, J., Vincent, J.B., Lewis, C.M., Farmer, A.E., McGuffin, P., 2013. Estimating the heritability of reporting stressful life events captured by common genetic variants. Psychol. Med. 43, 1965–1971. https://doi.org/10.1017/S0033291712002589

Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology 35, 192–216. https://doi.org/10.1038/npp.2009.104

Purves, K.L., Coleman, J.R.I., Meier, S.M., Rayner, C., Davis, K.A.S., Cheesman, R., Bækvad-Hansen, M., Børglum, A.D., Cho, S.W., Deckert, J., Gaspar, H.A., Bybjerg-Grauholm, J., Hettema, J.M., Hotopf, M., Hougaard, D., Hübel, C., Kan, C., McIntosh, A.M., Mors, O., Mortensen, P.B., Nordentoft, M., Werge, T., Nicodemus, K.K., Mattheisen, M., Breen, G., Eley, T.C., 2019. A Major Role for Common Genetic Variation in Anxiety Disorders. bioRxiv 203844. https://doi.org/10.1101/203844

Ravindran, L.N., Stein, M.B., 2010. The pharmacologic treatment of anxiety disorders: A review of progress. J. Clin. Psychiatry. https://doi.org/10.4088/JCP.10r06218blu

Ressler, K.J., Nemeroff, C.B., 2000. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress. Anxiety. https://doi.org/10.1002/1520-6394(2000)12:1+<2::AID-DA2>3.0.CO;2-4

Revest, J.-M., Dupret, D., Koehl, M., Funk-Reiter, C., Grosjean, N., Piazza, P.-V., Abrous, D.N., 2009. Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Mol. Psychiatry 14, 959–967. https://doi.org/10.1038/mp.2009.15

Riaza Bermudo-Soriano, C., Perez-Rodriguez, M.M., Vaquero-Lorenzo, C., Baca-Garcia, E., 2012. New perspectives in glutamate and anxiety. Pharmacol. Biochem. Behav. 100, 752–

774. https://doi.org/10.1016/j.pbb.2011.04.010
Ripke, S., Neale, B.M., Corvin, A., Walters, J.T.R., Farh, K.H., Holmans, P.A., Lee, P., Bulik-Sullivan, B., Collier, D.A., Huang, H., Pers, T.H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S.A., Begemann, M., Belliveau, R.A., Bene, J., Bergen, S.E., Bevilacqua, E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N.G., Buckner, R.L., Byerley, W., Cahn, W., Cai, G., Campion, D., Cantor, R.M., Carr, V.J., Carrera, N., Catts, S. V., Chambert, K.D., Chan, R.C.K., Chen, R.Y.L., Chen, E.Y.H., Cheng, W., Cheung, E.F.C., Chong, S.A., Cloninger, C.R., Cohen, D., Cohen, N., Cormican, P., Craddock, N., Crowley, J.J., Curtis, D., Davidson, M., Davis, K.L., Degenhardt, F., Del Favero, J., Demontis, D., Dikeos, D., Dinan, T., Djurovic, S., Donohoe, G., Drapeau, E., Duan, J., Dudbridge, F., Durmishi, N., Eichhammer, P., Eriksson, J., Escott-Price, V., Essioux, L., Fanous, A.H., Farrell, M.S., Frank, J., Franke, L., Freedman, R., Freimer, N.B., Friedl, M., Friedman, J.I., Fromer, M., Genovese, G., Georgieva, L., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., Golimbet, V., Gopal, S., Gratten, J., De Haan, L., Hammer, C., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V., Hartmann, A.M., Henskens, F.A., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A., Hollegaard, M. V., Hougaard, D.M., Ikeda, M., Joa, I., Julià, A., Kahn, R.S., Kalaydjieva, L., Karachanak-Yankova, S., Karjalainen, J., Kavanagh, D., Keller, M.C., Kennedy, J.L., Khrunin, A., Kim, Y., Klovins, J., Knowles, J.A., Konte, B., Kucinskas, V., Kucinskiene, Z.A., Kuzelova-Ptackova, H., Kähler, A.K., Laurent, C., Keong, J.L.C., Lee, S.H., Legge, S.E., Lerer, B., Li, M., Li, T., Liang, K.Y., Lieberman, J., Limborska, S., Loughland, C.M., Lubinski, J., Lönnqvist, J., Macek, M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J., Marsal, S., Mattheisen, M., Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier, S., Meijer, C.J., Melegh, B., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mokrab, Y., Morris, D.W., Mors, O., Murphy, K.C., Murray, R.M., Myin-Germeys, I., Müller-Myhsok, B., Nelis, M., Nenadic, I., Nertney, D.A., Nestadt, G., Nicodemus, K.K., Nikitina-Zake, L., Nisenbaum, L., Nordin, A., O'Callaghan, E., O'Dushlaine, C., O'Neill, F.A., Oh, S.Y., Olincy, A., Olsen, L., Van Os, J., Pantelis, C., Papadimitriou, G.N., Papiol, S., Parkhomenko, E., Pato, M.T., Paunio, T., Pejovic-Milovancevic, M., Perkins, D.O., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A., Pulver, A.E., Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M.A., Richards, A.L., Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R., Schall, U., Schubert, C.R., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman, L.J., Shi, J., Sigurdsson, E., Silagadze, T., Silverman, J.M., Sim, K., Slominsky, P., Smoller, J.W., So, H.C., Spencer, C.C.A., Stahl, E.A., Stefansson, H., Steinberg, S., Stogmann, E., Straub, R.E., Strengman, E., Strohmaier, J., Stroup, T.S., Subramaniam, M., Suvisaari, J., Svrakic, D.M., Szatkiewicz, J.P., Söderman, E., Thirumalai, S., Toncheva, D., Tosato, S., Veijola, J., Waddington, J., Walsh, D., Wang, D., Wang, Q., Webb, B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams, S., Witt, S.H., Wolen, A.R., Wong, E.H.M., Wormley, B.K., Xi, H.S., Zai, C.C., Zheng, X., Zimprich, F., Wray, N.R., Stefansson, K., Visscher, P.M., Adolfsson, R., Andreassen, O.A., Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Børglum, A.D., Cichon, S., Darvasi, A., Domenici, E., Ehrenreich, H., Esko, T., Gejman, P. V., Gill, M., Gurling, H., Hultman, C.M., Iwata, N., Jablensky, A. V., Jönsson, E.G., Kendler, K.S., Kirov, G., Knight, J., Lencz, T., Levinson, D.F., Li, Q.S., Liu, J., Malhotra, A.K., McCarroll, S.A., McQuillin, A., Moran, J.L., Mortensen, P.B., Mowry, B.J., Nöthen, M.M., Ophoff, R.A., Owen, M.J.,

Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D., Rietschel, M., Riley, B.P., Rujescu, D., Sham, P.C., Sklar, P., St Clair, D., Weinberger, D.R., Wendland, J.R., Werge, T., Daly, M.J., Sullivan, P.F., O'Donovan, M.C., 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427. https://doi.org/10.1038/nature13595

Risch, N., Merikangas, K., 1996. The Future of Genetic Studies of Complex Human Diseases. Science (80-.). 273, 1516–1517. https://doi.org/10.1126/science.273.5281.1516

Romeo, R.D., 2013. The Teenage Brain: The Stress Response and the Adolescent Brain. Curr. Dir. Psychol. Sci. 22, 140–145. https://doi.org/10.1177/0963721413475445

Ruhé, H.G., Mason, N.S., Schene, A.H., 2007. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: A meta-analysis of monoamine depletion studies. Mol. Psychiatry 12, 331–359. https://doi.org/10.1038/sj.mp.4001949

Sanacora, G., Treccani, G., Popoli, M., 2012. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology 62, 63–77. https://doi.org/10.1016/j.neuropharm.2011.07.036

Santarelli, S., Namendorf, C., Anderzhanova, E., Gerlach, T., Bedenk, B., Kaltwasser, S., Wagner, K., Labermaier, C., Reichel, J., Drgonova, J., Czisch, M., Uhr, M., Schmidt, M. V., 2015. The amino acid transporter SLC6A15 is a regulator of hippocampal neurochemistry and behavior. J. Psychiatr. Res. 68, 261–269. https://doi.org/10.1016/j.jpsychires.2015.07.012

Santarelli, S., Wagner, K. V., Labermaier, C., Uribe, A., Dournes, C., Balsevich, G., Hartmann, J., Masana, M., Holsboer, F., Chen, A., Müller, M.B., Schmidt, M. V., 2016. SLC6A15, a novel stress vulnerability candidate, modulates anxiety and depressive-like behavior: Involvement of the glutamatergic system. Stress 19, 83–90. https://doi.org/10.3109/10253890.2015.1105211

Sato, K., Takahashi, K., Shigemoto-Mogami, Y., Chujo, K., Sekino, Y., 2016. Glypican 6 Enhances N-Methyl-D-Aspartate Receptor Function in Human-Induced Pluripotent Stem Cell-Derived Neurons. Front. Cell. Neurosci. 10, 259. https://doi.org/10.3389/fncel.2016.00259

Savitz, J., Hodgkinson, C.A., Martin-Soelch, C., Shen, P.-H., Szczepanik, J., Nugent, A.C., Herscovitch, P., Grace, A.A., Goldman, D., Drevets, W.C., 2013. DRD2/ANKK1 Taq1A polymorphism (rs1800497) has opposing effects on D2/3 receptor binding in healthy controls and patients with major depressive disorder. Int. J. Neuropsychopharmacol. 16, 2095–101. https://doi.org/10.1017/S146114571300045X

Schmaal, L., Hibar, D.P., Sämann, P.G., Hall, G.B., Baune, B.T., Jahanshad, N., 2016a. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. R Goya-Maldonado 17, 57. https://doi.org/10.1038/mp.2016.60

Schmaal, L., Veltman, D.J., van Erp, T.G.M., Sämann, P.G., Frodl, T., Jahanshad, N., Loehrer, E., Tiemeier, H., Hofman, A., Niessen, W.J., Vernooij, M.W., Ikram, M.A., Wittfeld, K., Grabe, H.J., Block, A., Hegenscheid, K., Völzke, H., Hoehn, D., Czisch, M., Lagopoulos, J., Hatton, S.N., Hickie, I.B., Goya-Maldonado, R., Krämer, B., Gruber, O., Couvy-Duchesne, B., Rentería, M.E., Strike, L.T., Mills, N.T., de Zubicaray, G.I., McMahon, K.L., Medland, S.E., Martin, N.G., Gillespie, N.A., Wright, M.J., Hall, G.B., MacQueen, G.M., Frey, E.M., Carballedo, A., van Velzen, L.S., van Tol, M.J., van der Wee, N.J., Veer, I.M., Walter, H., Schnell, K., Schramm, E., Normann, C., Schoepf, D., Konrad, C., Zurowski, B., Nickson, T., McIntosh, A.M., Papmeyer, M., Whalley, H.C., Sussmann, J.E., Godlewska,

B.R., Cowen, P.J., Fischer, F.H., Rose, M., Penninx, B.W.J.H., Thompson, P.M., Hibar, D.P., 2016b. Subcortical brain alterations in major depressive disorder: findings from the {ENIGMA} {Major} {Depressive} {Disorder} working group. Mol. Psychiatry 21, 806–812. https://doi.org/10.1038/mp.2015.69

Schuhmacher, A., Lennertz, L., Wagner, M., Höfels, S., Pfeiffer, U., Guttenthaler, V., Maier, W., Zobel, A., Mössner, R., 2013. A variant of the neuronal amino acid transporter SLC6A15 is associated with ACTH and cortisol responses and cognitive performance in unipolar depression. Int. J. Neuropsychopharmacol. 16, 83–90. https://doi.org/10.1017/S1461145712000223

Schuhmacher, A., Mössner, R., Höfels, S., Pfeiffer, U., Guttenthaler, V., Wagner, M., Schwab, S.G., Maier, W., Zobel, A., 2011. PCLO rs2522833 modulates HPA system response to antidepressant treatment in major depressive disorder. Int. J. Neuropsychopharmacol. 14, 237–245. https://doi.org/10.1017/S1461145710000854

Shadrina, M., Bondarenko, E.A., Slominsky, P.A., 2018. Genetics factors in major depression disease. Front. Psychiatry 9, 334. https://doi.org/10.3389/fpsyt.2018.00334

Sham, P.C., Cherny, S.S., Purcell, S., Hewitt, J.K., 2000. Power of Linkage versus Association Analysis of Quantitative Traits, by Use of Variance-Components Models, for Sibship Data. Am. J. Hum. Genet. 66, 1616–1630. https://doi.org/10.1086/302891

Shin, S., Kwon, O., Kang, J.I., Kwon, S., Oh, S., Choi, J., Kim, C.H., Kim, D.G., 2015. mGluR5 in the nucleus accumbens is critical for promoting resilience to chronic stress. Nat. Neurosci. 18, 1017–1024. https://doi.org/10.1038/nn.4028

Sipilä, T., Kananen, L., Greco, D., Donner, J., Silander, K., Terwilliger, J.D., Auvinen, P., Peltonen, L., Lönnqvist, J., Pirkola, S., Partonen, T., Hovatta, I., 2010. An Association Analysis of Circadian Genes in Anxiety Disorders. Biol. Psychiatry 67, 1163–1170. https://doi.org/10.1016/J.BIOPSYCH.2009.12.011

Smoller, J.W., 2016. The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. Neuropsychopharmacology 41, 297–319. https://doi.org/10.1038/npp.2015.266

So, H.-C., Chau, C.K.-L., Chiu, W.-T., Ho, K.-S., Lo, C.-P., Yim, S.H.-Y., Sham, P.-C., 2017. Analysis of genome-wide association data highlights candidates for drug repositioning in psychiatry. Nat. Neurosci. 20, 1342–1349. https://doi.org/10.1038/nn.4618

Southwick, S.M., Charney, D.S., 2012. The Science of Resilience: Implications for the Prevention and Treatment of Depression. Science (80-.). 338, 79–82. https://doi.org/10.1126/science.1222942

Steiner, J., Walter, M., Gos, T., Guillemin, G.J., Bernstein, H.-G., Sarnyai, Z., Mawrin, C., Brisch, R., Bielau, H., Meyer zu Schwabedissen, L., Bogerts, B., Myint, A.-M., 2011. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J. Neuroinflammation 8, 94. https://doi.org/10.1186/1742-2094-8-94

Sugarman, M.A., Loree, A.M., Baltes, B.B., Grekin, E.R., Kirsch, I., 2014. The efficacy of paroxetine and placebo in treating anxiety and depression: a meta-analysis of change on the Hamilton Rating Scales. PLoS One 9, e106337. https://doi.org/10.1371/journal.pone.0106337

Suliman, S., Hemmings, S.M.J., Seedat, S., 2013. Brain-Derived Neurotrophic Factor (BDNF) protein levels in anxiety disorders: systematic review and meta-regression analysis. Front. Integr. Neurosci. 7, 55. https://doi.org/10.3389/fnint.2013.00055

Sullivan, P.F., Daly, M.J., Ripke, S., Lewis, C.M., Lin, D.Y., Wray, N.R., Neale, B., Levinson,

D.F., Breen, G., Byrne, E.M., Rietschel, M., Hoogendijk, W., Hamilton, S.P., Weissman, M.M., Breuer, R., Cichon, S., Degenhardt, F., Frank, J., Gross, M., Herms, S., Hoefels, S., Maier, W., Mattheisen, M., Nöethen, M.M., Schulze, T.G., Steffens, M., Treutlein, J., Boomsma, D.I., De Geus, E.J., Jan Hottenga, J., Jung-Ying, T., MMiddeldorp, C., Nolen, W.A., Penninx, B.P., Smit, J.H., van Grootheest, G., Willemsen, G., Zitman, F.G., Coryell, W.H., Knowles, J.A., Lawson, W.B., Potash, J.B., Scheftner, W.A., Shi, J., Holsboer, F., Muglia, P., Tozzi, F., Blackwood, D.H.R., MacIntyre, D.J., McIntosh, A., McLean, A., Middeldorp, C.M., van den Oord, E.J.C.G., Lucae, S., Binder, E., Müller-Myhsok, B., Czamara, D., Kohli, M.A., Ising, M., Uhr, M., Bettecken, T., Barnes, M.R., Craig, I.W., Farmer, A.E., McGuffin, P., Byrne, E., Gordon, S.D., Heath, A.C., Henders, A.K., Hickie, I.B., Madden, P.A.F., Martin, N.G., Montgomery, G.M., Nyholt, D.R., Pergadia, M.L., Hamilton, S.P., McGrath, P.J., Shyn, S.I., Slager, S.L., Oskarsson, H., Sigurdsson, E., Stefansson, H., Stefansson, K., Steinberg, S., Thorgeirsson, T., Guipponi, M., Lewis, G., O'Donovan, M., Tansey, K.E., Uher, R., Castro, V.M., Churchill, S.E., Fava, M., Gainer, V.S., Gallagher, P.J., Goryachev, S., Iosifescu, D. V., Kohane, I.S., Murphy, S.N., Perlis, R.H., Smoller, J.W., Weilburg, J.B., Kutalik, Z., Preisig, M., Grabe, H.J., Nauck, M., Schulz, A., Teumer, A., Völzke, H., Landen, M., Lichtenstein, P., Magnusson, P., Pedersen, N., Viktorin, A., 2013. A mega-Analysis of genome-wide association studies for major depressive disorder. Mol. Psychiatry 18, 497–511. https://doi.org/10.1038/mp.2012.21

Sullivan, P.F., de Geus, E.J.C., Willemsen, G., James, M.R., Smit, J.H., Zandbelt, T., Arolt, V., Baune, B.T., Blackwood, D., Cichon, S., Coventry, W.L., Domschke, K., Farmer, A., Fava, M., Gordon, S.D., He, Q., Heath, A.C., Heutink, P., Holsboer, F., Hoogendijk, W.J., Hottenga, J.J., Hu, Y., Kohli, M., Lin, D., Lucae, S., MacIntyre, D.J., Maier, W., McGhee, K.A., McGuffin, P., Montgomery, G.W., Muir, W.J., Nolen, W.A., Nöthen, M.M., Perlis, R.H., Pirlo, K., Posthuma, D., Rietschel, M., Rizzu, P., Schosser, A., Smit, A.B., Smoller, J.W., Tzeng, J.-Y., van Dyck, R., Verhage, M., Zitman, F.G., Martin, N.G., Wray, N.R., Boomsma, D.I., Penninx, B.W.J.H., 2009. Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. Mol. Psychiatry 14, 359–375. https://doi.org/10.1038/mp.2008.125

Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. Am. J. Psychiatry 157, 1552–1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Sun, H., Su, R., Zhang, X., Wen, J., Yao, D., Gao, X., Zhu, Z., Li, H., 2017. Hippocampal GR- and CB1-mediated mGluR5 differentially produces susceptibility and resilience to acute and chronic mild stress in rats. Neuroscience 357, 295–302. https://doi.org/10.1016/J.NEUROSCIENCE.2017.06.017

Takaki, H., Kikuta, R., Shibata, H., Ninomiya, H., Tashiro, N., Fukumaki, Y., 2004. Positive associations of polymorphisms in the metabotropic glutamate receptor type 8 gene (*GRM8*) with schizophrenia. Am. J. Med. Genet. 128B, 6–14. https://doi.org/10.1002/ajmg.b.20108

Tavakkoly-Bazzaz, J., Azarnezhad, A., Mousavi, N., Salehipour, P., Shahsavand Ananloo, E., Alizadeh, F., 2018. TCF4 and GRM8 gene polymorphisms and risk of schizophrenia in an Iranian population: a case-control study. Mol. Biol. Rep. 45, 2403–2409. https://doi.org/10.1007/s11033-018-4406-2

Taylor, S.B., Taylor, A.R., Koenig, J.I., 2013. The interaction of disrupted Type II Neuregulin 1 and chronic adolescent stress on adult anxiety- and fear-related behaviors. Neuroscience

249, 31–42. https://doi.org/10.1016/J.NEUROSCIENCE.2012.09.045
Tayyab, M., Farheen, S., M, M.M.P., Khanam, N., Mobarak Hossain, M., Shahi, M.H., 2019. Antidepressant and Neuroprotective Effects of Naringenin via Sonic Hedgehog-GLI1 Cell Signaling Pathway in a Rat Model of Chronic Unpredictable Mild Stress. NeuroMolecular Med. 21, 250–261. https://doi.org/10.1007/s12017-019-08538-6
Terunuma, M., Jang, I.-S., Ha, S.H., Kittler, J.T., Kanematsu, T., Jovanovic, J.N., Nakayama, K.I., Akaike, N., Ryu, S.H., Moss, S.J., Hirata, M., 2004. GABAA Receptor Phospho-Dependent Modulation Is Regulated by Phospholipase C-Related Inactive Protein Type 1, a Novel Protein Phosphatase 1 Anchoring Protein. J. Neurosci. 24, 7074–7084. https://doi.org/10.1523/JNEUROSCI.1323-04.2004
Thomas, M.G., Welch, C., Stone, L., Allan, P., Barker, R.A., White, R.B., 2016. PAX6 expression may be protective against dopaminergic cell loss in Parkinson's disease. CNS Neurol. Disord. Drug Targets 15, 73–9.
Thompson, J., Thomas, N., Singleton, A., Piggott, M., Lloyd, S., Perry, E.K., Morris, C.M., Perry, R.H., Ferrier, I.N., Court, J.A., 1997. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. Pharmacogenetics 7, 479–84.
Tindi, J.O., Chavez, A.E., Cvejic, S., Calvo-Ochoa, E., Castillo, P.E., Jordan, B.A., 2015. ANKS1B Gene Product AIDA-1 Controls Hippocampal Synaptic Transmission by Regulating GluN2B Subunit Localization. J. Neurosci. 35, 8986–8996. https://doi.org/10.1523/JNEUROSCI.4029-14.2015
Torres-Berrío, A., Lopez, J.P., Bagot, R.C., Nouel, D., Dal Bo, G., Cuesta, S., Zhu, L., Manitt, C., Eng, C., Cooper, H.M., Storch, K.-F., Turecki, G., Nestler, E.J., Flores, C., 2017. DCC Confers Susceptibility to Depression-like Behaviors in Humans and Mice and Is Regulated by miR-218. Biol. Psychiatry 81, 306–315. https://doi.org/10.1016/j.biopsych.2016.08.017
Trzaskowski, M., Mehta, D., Peyrot, W.J., Hawkes, D., Davies, D., Howard, D.M., Kemper, K.E., Sidorenko, J., Maier, R., Ripke, S., Mattheisen, M., Baune, B.T., Grabe, H.J., Heath, A.C., Jones, L., Jones, I., Madden, P.A.F., McIntosh, A.M., Breen, G., Lewis, C.M., Børglum, A.D., Sullivan, P.F., Martin, N.G., Kendler, K.S., Levinson, D.F., Wray, N.R., 2019. Quantifying between-cohort and between-sex genetic heterogeneity in major depressive disorder. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 180, 439–447. https://doi.org/10.1002/ajmg.b.32713
Twenge, J.M., Cooper, A.B., Joiner, T.E., Duffy, M.E., Binau, S.G., 2019. Age, Period, and Cohort Trends in Mood Disorder Indicators and Suicide-Related Outcomes in a Nationally Representative Dataset, 2005-2017. https://doi.org/10.1037/abn0000410.supp
Ulrich-Lai, Y.M., Herman, J.P., 2009. Neural regulation of endocrine and autonomic stress responses. Nat. Rev. Neurosci. 10, 397–409. https://doi.org/10.1038/nrn2647
Uno, K., Nishizawa, D., Seo, S., Takayama, K., Matsumura, S., Sakai, N., Ohi, K., Nabeshima, T., Hashimoto, R., Ozaki, N., Hasegawa, J., Sato, N., Tanioka, F., Sugimura, H., Fukuda, K.-I.-, Higuchi, S., Ujike, H., Inada, T., Iwata, N., Sora, I., Iyo, M., Kondo, N., Won, M.-J., Naruse, N., Uehara-Aoyama, K., Itokawa, M., Yamada, M., Ikeda, K., Miyamoto, Y., Nitta, A., 2015. The Piccolo Intronic Single Nucleotide Polymorphism rs13438494 Regulates Dopamine and Serotonin Uptake and Shows Associations with Dependence-Like Behavior in Genomic Association Study. Curr. Mol. Med. 15, 265–74.
Vecchiarelli, H.A., Gandhi, C.P., Hill, M.N., 2016. Acute Psychological Stress Modulates the Expression of Enzymes Involved in the Kynurenine Pathway throughout Corticolimbic

Circuits in Adult Male Rats. Neural Plast. 2016, 1–12. https://doi.org/10.1155/2016/7215684

Visscher, P.M., Wray, N.R., Zhang, Q., Sklar, P., McCarthy, M.I., Brown, M.A., Yang, J., 2017. 10 Years of GWAS Discovery: Biology, Function, and Translation. Am. J. Hum. Genet. 101, 5–22. https://doi.org/10.1016/j.ajhg.2017.06.005

von Engelhardt, J., Mack, V., Sprengel, R., Kavenstock, N., Li, K.W., Stern-Bach, Y., Smit, A.B., Seeburg, P.H., Monyer, H., 2010. CKAMP44: A Brain-Specific Protein Attenuating Short-Term Synaptic Plasticity in the Dentate Gyrus. Science (80-.). 327, 1518–1522. https://doi.org/10.1126/science.1184178

Wagner, K. V, Hartmann, J., Labermaier, C., Häusl, A.S., Zhao, G., Harbich, D., Schmid, B., Wang, X.-D., Santarelli, S., Kohl, C., Gassen, N.C., Matosin, N., Schieven, M., Webhofer, C., Turck, C.W., Lindemann, L., Jaschke, G., Wettstein, J.G., Rein, T., Müller, M.B., Schmidt, M. V, 2015. Homer1/mGluR5 Activity Moderates Vulnerability to Chronic Social Stress. Neuropsychopharmacology 40, 1222–1233. https://doi.org/10.1038/npp.2014.308

Wagnon, J.L., Briese, M., Sun, W., Mahaffey, C.L., Curk, T., Rot, G., Ule, J., Frankel, W.N., 2012. CELF4 Regulates Translation and Local Abundance of a Vast Set of mRNAs, Including Genes Associated with Regulation of Synaptic Function. PLoS Genet. 8, e1003067. https://doi.org/10.1371/journal.pgen.1003067

Wang, N., Zhang, G.-F., Liu, X.-Y., Sun, H.-L., Wang, X.-M., Qiu, L.-L., Yang, C., Yang, J.-J., 2014. Downregulation of Neuregulin 1-ErbB4 Signaling in Parvalbumin Interneurons in the Rat Brain May Contribute to the Antidepressant Properties of Ketamine. J. Mol. Neurosci. 54, 211–218. https://doi.org/10.1007/s12031-014-0277-8

Wang, S.-S., Kamphuis, W., Huitinga, I., Zhou, J.-N., Swaab, D.F., 2008. Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: the presence of multiple receptor imbalances. Mol. Psychiatry 13, 786–799. https://doi.org/10.1038/mp.2008.38

Wang, Y., Liu, X., Yu, Y., Han, Y., Wei, J., Collier, D., Li, T., Ma, X., 2012. The role of single nucleotide polymorphism of D2 dopamine receptor gene on major depressive disorder and response to antidepressant treatment. Psychiatry Res. 200, 1047–1050. https://doi.org/10.1016/j.psychres.2012.06.024

Wang, Y., Ma, T., Zhu, Y.-S., Chu, X.-F., Yao, S., Wang, H.-F., Cai, J., Wang, X.-F., Jiang, X.-Y., 2017. The KSR2 -rs7973260 Polymorphism is Associated with Metabolic Phenotypes, but Not Psychological Phenotypes, in Chinese Elders . Genet. Test. Mol. Biomarkers 21, 416–421. https://doi.org/10.1089/gtmb.2016.0402

Wang, Y., Ma, Y., Hu, J., Cheng, W., Jiang, H., Zhang, X., Li, M., Ren, J., Li, X., 2015. Prenatal chronic mild stress induces depression-like behavior and sex-specific changes in regional glutamate receptor expression patterns in adult rats. Neuroscience 301, 363–374. https://doi.org/10.1016/J.NEUROSCIENCE.2015.06.008

White, R.B., Thomas, M.G., 2016. Developmental transcription factors in age-related CNS disease: a phoenix rising from the ashes? Neural Regen. Res. 11, 64–5. https://doi.org/10.4103/1673-5374.175044

Whitmer, A.J., Gotlib, I.H., 2012. Depressive rumination and the C957T polymorphism of the DRD2 gene. Cogn. Affect. Behav. Neurosci. 12, 741–747. https://doi.org/10.3758/s13415-012-0112-z

WHO, 2018. International statistical classification of diseases and related health problems (11th Revision) [WWW Document]. URL https://icd.who.int/browse11/l-m/en

WHO, 2017. Depression and other common mental disorders: global health estimates, World Health Organization. https://doi.org/CC BY-NC-SA 3.0 IGO

Wiegner, L., Hange, D., Björkelund, C., Ahlborg, G., 2015. Prevalence of perceived stress and associations to symptoms of exhaustion, depression and anxiety in a working age population seeking primary care - an observational study. BMC Fam. Pract. 16, 38. https://doi.org/10.1186/s12875-015-0252-7

Wierońska, J.M., Brański, P., Szewczyk, B., Pałucha, A., Papp, M., Gruca, P., Moryl, E., Pilc, A., n.d. Changes in the expression of metabotropic glutamate receptor 5 (mGluR5) in the rat hippocampus in an animal model of depression. Pol. J. Pharmacol. 53, 659–62.

Wray, N.R., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow, A.R., Lewis, C.M., Levinson, D.F., Breen, G., Borglum, A., Sullivan, P.F., 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat. Genet. 50, 668–681. https://doi.org/10.1101/167577

Xu, Y., Hackett, M., Carter, G., Loo, C., Gálvez, V., Glozier, N., Glue, P., Lapidus, K., McGirr, A., Somogyi, A.A., Mitchell, P.B., Rodgers, A., 2016. Effects of Low-Dose and Very Low-Dose Ketamine among Patients with Major Depression: a Systematic Review and Meta-Analysis. Int. J. Neuropsychopharmacol. 19, pyv124. https://doi.org/10.1093/ijnp/pyv124

Yang, T., Rockett, I.R.H., Lv, Q., Cottrell, R.R., 2012. Stress Status and Related Characteristics among Urban Residents: A Six-Province Capital Cities Study in China. PLoS One 7, e30521. https://doi.org/10.1371/journal.pone.0030521

Yim, Y.S., Lee, J., Kim, G.-T., Song, T., Kim, C.H., Kim, D.G., 2012. Hippocampal mGluR5 predicts an occurrence of helplessness behavior after repetitive exposure to uncontrollable stress. Neurosci. Lett. 519, 62–66. https://doi.org/10.1016/J.NEULET.2012.05.022

Zhang, J., Chen, L., Ma, J., Qiao, Z., Zhao, M., Qi, D., Zhao, Y., Ban, B., Zhu, X., He, J., Yang, Y., Pan, H., 2017. Interaction of estrogen receptor β and negative life events in susceptibility to major depressive disorder in a Chinese Han female population. J. Affect. Disord. 208, 628–633. https://doi.org/10.1016/J.JAD.2016.08.083

Zhang, LuShun, Hu, L., Li, X., Zhang, J., Chen, B., 2014. The DRD2 rs1800497 polymorphism increase the risk of mood disorder: Evidence from an update meta-analysis. J. Affect. Disord. 158, 71–77. https://doi.org/10.1016/J.JAD.2014.01.015

Zhang, Lili, Zhong, X., An, Z., Han, S., Luo, X., Shi, Y., Yi, Q., 2014. Association analysis of the *GRM8* gene with schizophrenia in the Uygur Chinese population. Hereditas 151, 140–144. https://doi.org/10.1111/hrd2.00045

Zhang, R.X., Han, Y., Chen, C., Xu, L.Z., Li, J.L., Chen, N., Sun, C.Y., Chen, W.H., Zhu, W.L., Shi, J., Lu, L., 2016. EphB2 in the Medial Prefrontal Cortex Regulates Vulnerability to Stress. Neuropsychopharmacology 41, 2541–2556. https://doi.org/10.1038/npp.2016.58

Zhang, Y., Qi, G., Park, J.-H., Chatterjee, N., 2018. Estimation of complex effect-size distributions using summary-level statistics from genome-wide association studies across 32 complex traits. Nat. Genet. 50, 1318–1326. https://doi.org/10.1038/s41588-018-0193-x

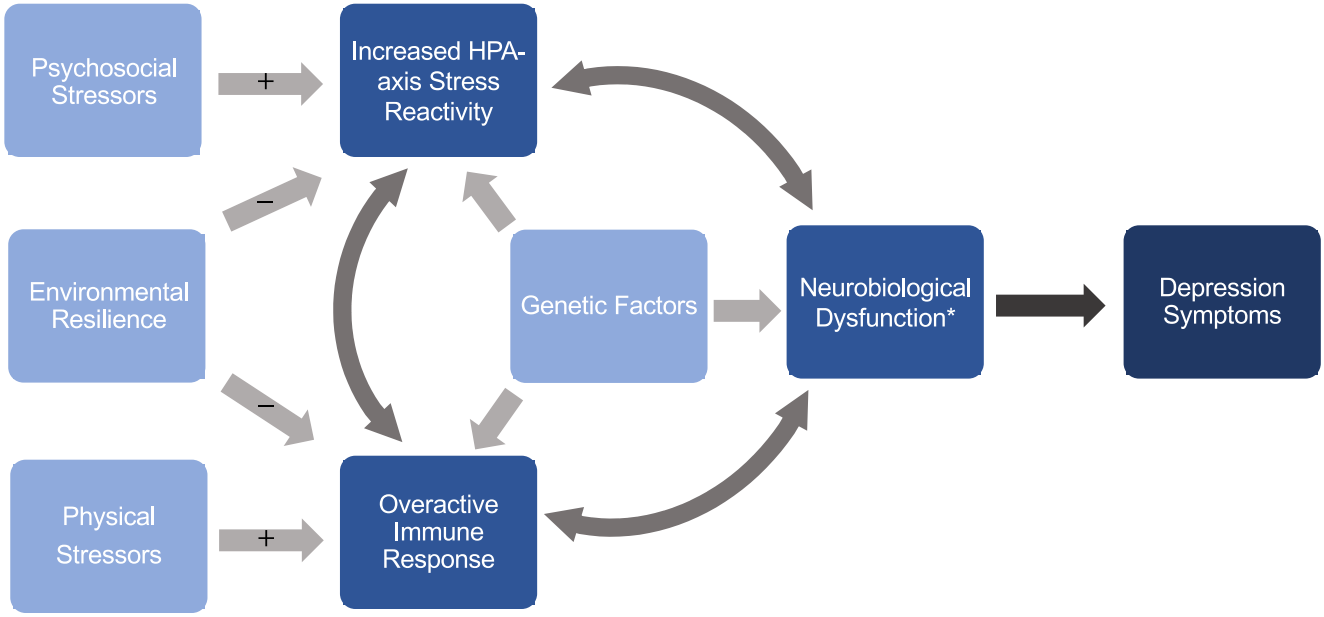
Zhen, L., Shao, T., Luria, V., Li, G., Li, Z., Xu, Y., Zhao, X., 2018. EphB2 Deficiency Induces Depression-Like Behaviors and Memory Impairment: Involvement of NMDA 2B Receptor Dependent Signaling. Front. Pharmacol. 9, 862. https://doi.org/10.3389/fphar.2018.00862

Zhu, G., Yoshida, S., Migita, K., Yamada, J., Mori, F., Tomiyama, M., Wakabayashi, K., Kanematsu, T., Hirata, M., Kaneko, S., Ueno, S., Okada, M., 2012. Dysfunction of Extrasynaptic GABAergic Transmission in Phospholipase C-Related, but Catalytically

Inactive Protein 1 Knockout Mice Is Associated with an Epilepsy Phenotype. J. Pharmacol. Exp. Ther. 340, 520–528. https://doi.org/10.1124/jpet.111.182386
Zou, Y.-F., Wang, F., Feng, X.-L., Li, W.-F., Tian, Y.-H., Tao, J.-H., Pan, F.-M., Huang, F., 2012. Association of DRD2 gene polymorphisms with mood disorders: A meta-analysis. J. Affect. Disord. 136, 229–237. https://doi.org/10.1016/J.JAD.2010.11.012

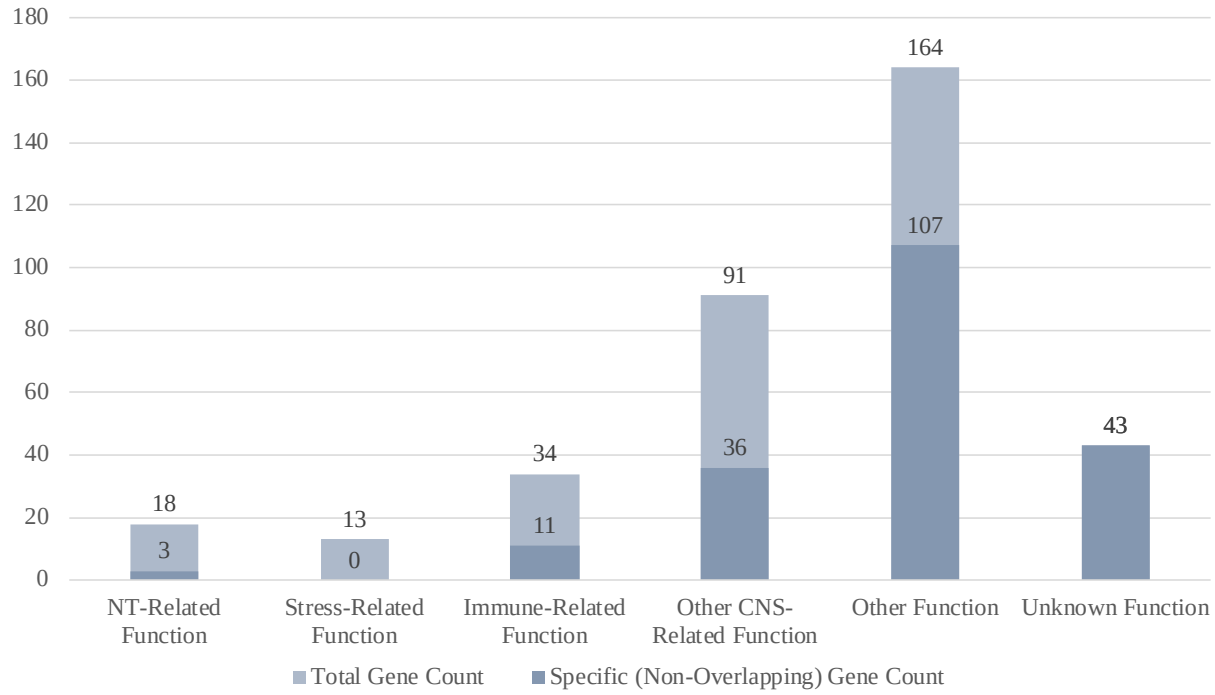
Figures

Figure 1. Simplified Flow Chart of Major Systems Contributing to Depression Etiology and Maintenance



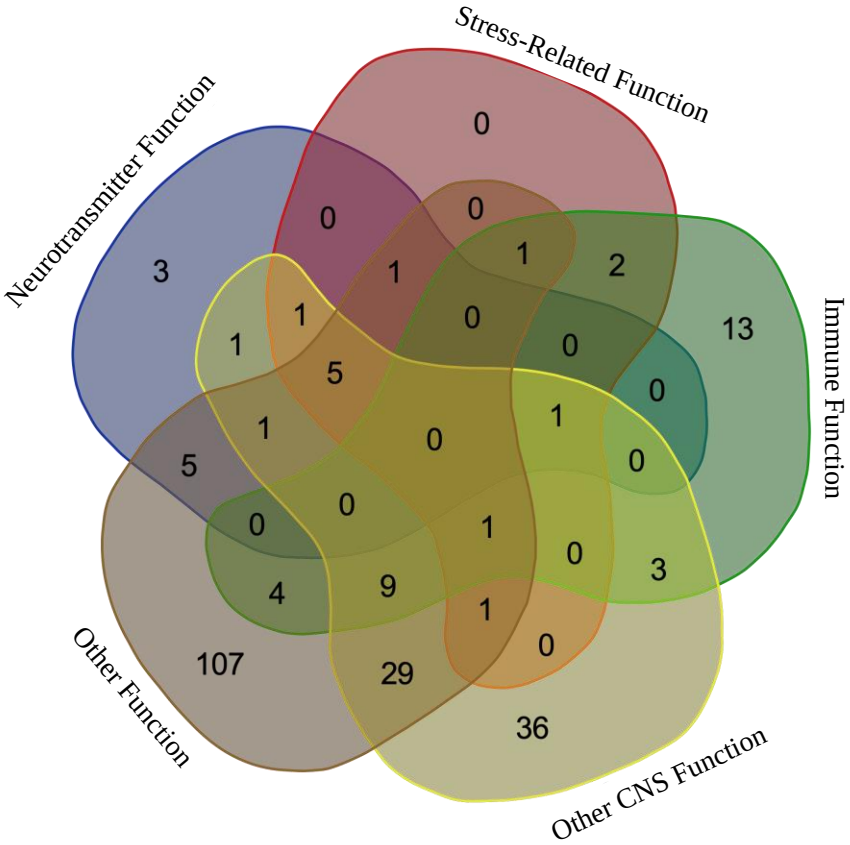
*Note. In this basic model, genetic factors predispose depression through dysfunction in the interactive neurobiological, immune, and stress-response systems. Psychosocial environmental stressors likely exert their major influence through HPA axis functioning, whereas physical stressors are largely mediated by the immune response. Resilience to environmental stressors are likely to decrease HPA and immune dysfunction. *Although neurobiological dysfunction has historically focused heavily on neurotransmitter systems, our qualitative analysis of the most recent genetic findings suggests that other mechanisms, particularly neurodevelopment, neurogenesis, and neurodegeneration may also play a significant role in depression pathology. Abbreviations: HPA, Hypothalamic–Pituitary–Adrenal.*

Figure 2. Gene Counts Within Manually-Curated Functional Categories



Note. For each gene associated with depression from the most recent meta-analysis (Howard et al., 2019), we searched for any known function and manually categorized them into the following non-exclusive categories: NT-Related, Stress-Related, Immune-Related, Other CNS-Related (excluding NT function), Other, and Unknown. This figure shows the number of genes falling within each category along with the number of genes with a function unique to that category with no known overlapping function with any other category. The Other Function category contained the greatest number of genes, followed by Other CNS, Unknown, Immune, NT, and Stress. Abbreviations: NT, Neurotransmitter; CNS, Central Nervous System.

Figure 3. Venn Diagram of Gene Counts Across Functional Categories



Note. This Venn diagram shows the number of unique and overlapping genes across five manually-curated categories, demonstrating that many genes exhibit functions across multiple categories. Created using (http://bioinformatics.psb.ugent.be/webtools/Venn/). Abbreviations: CNS, Central Nervous System.

Role of Funding Source:

This manuscript was not directly supported by any institutional funding or grants.

Contributors:

JDT was responsible for manuscript preparation and gene function classification/literature search. JD aided in manuscript preparation, gene function classification/literature search, and manuscript revision. LB assisted in literature review and provided revisions. PCS conceived of the review and provided feedback and revisions to the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest:

The authors declare no conflicts of interest.

Acknowledgements:

None.