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Mini-Review

Sex Differences Modulating Serotonergic Polymorphisms Implicated in the Mechanistic Pathways of Risk for Depression and Related Disorders:

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Despite consistent observations of sex differences in depression and related emotional disorders, we do not yet know how these sex differences modulate the effects of genetic polymorphisms implicated in risk for these disorders. This Mini-Review focuses on genetic polymorphisms of the serotonergic system to illustrate how sex differences might modulate the neurobiological pathways involved in the development of depression. We consider the interacting role of environmental factors such as early-life stress. Given limited current knowledge about this topic, we highlight methodological considerations, challenges, and guidelines for future research. © 2016 Wiley Periodicals, Inc.

Key words: early-life stress; amygdala; anxiety; suicide; conduct disorder; personality

Major depressive disorder is an issue of global concern. With a 12-month prevalence of 6.7% and a lifetime risk of 17% in American adults, depression is a leading cause of disability worldwide (Center for Behavioral Health Statistics and Quality, 2015; Ustün et al., 2004). Depressed individuals have a 3.4% suicide risk compared with 0.017% in the general population (Blair-West et al., 1999). Depression frequently co-occurs with other medical and psychiatric conditions, including 51.2% comorbidity with anxiety, which is associated with slower recovery, higher rates of recurrence, and increased disability (Hirschfeld, 2001).

Despite the impact of depression, the development of preventive and remedial interventions is limited by our understanding of the multiple interacting biobehavioral pathways that contribute to the pathogenesis and expression of depression. To address these substantial gaps in knowledge, we might draw on findings with regard to sex and genetic polymorphisms as risk factors for depression and related conditions. These findings are relatively consistent, especially compared with the work on biobehavioral factors, and also provide an important foundation for ultimately understanding individual differences in biobehavior.

Heritability data highlight the role of genetic factors in risk for depression and related conditions. Twin studies show that heritability of depression, anxiety, and suicide are estimated to be 37% (Sullivan et al., 2000), 45% (Stein

SIGNIFICANCE

Depression and related disorders, such as anxiety, conduct disorder, and suicidality, exhibit sex differences. These differences stem from underlying biological differences in men and women, including response to early-life stress, sex chromosome expression, and hormonal control. This Mini-Review considers how these known differences might alter the effects of genetic polymorphisms of the serotonergic system and highlights the importance of considering gene–sex and gene–sex–environment interactions in the study of depression and related conditions.

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and Gorman, 2001), and 43% (McGuffin et al., 2010), respectively. Single gene variations involved in serotonergic metabolism in particular have been extensively studied for their role in depression. However, these single gene variations may confer depression risk through interactions with environmental factors rather than via their own discrete effects, and these gene–environment interactions may themselves be mediated by sexually dimorphic pathways.

Epidemiological studies have long highlighted sex differences in depression and its related phenomenology. Women have a 21.3% lifetime rate of depression compared with 12.7% for men (Kessler et al., 1993). Similarly, women have a higher lifetime rate of generalized anxiety disorder of 7.7% compared with 4.1% for men as well as higher comorbidity with depression, 38.3% for women compared with 30% for men (McLean et al., 2011). However, the suicide rate for depressed men is 7% compared with 1% for depressed women (Blair-West et al., 1999). Heritability of major depression is higher in women (42%) than in men (29%), which suggests modulation of genetic risk by sex (Kendler et al., 2006). Sex differences have also been observed in environmental risk factors, such as early-life stress (Bale and Epperson, 2015), and in biobehavioral factors implicated in the mechanisms by which risk for depression is conferred, including personality traits such as neuroticism (Goodwin and Gotlib, 2004) and brain measures such as amygdala reactivity (Williams et al., 2005). This Mini-Review focuses on the current state of knowledge with regard to sex differences in genetic variation implicated in risk for depression and related phenomena.

SCOPE OF THIS MINI-REVIEW

Our intention is to provide a focused review and personal view highlighting the potential mechanisms for how sex differences might modulate the effect of genetic polymorphisms in depression and its related conditions (i.e., gene–sex interactions) rather than a systematic review of gene–sex interactions. We hope to show the importance of considering sex differences, even when studying the brain at the genetic level.

This Mini-Review focuses on major depressive disorder, also including evidence with regard to anxiety and externalizing disorders that are highly comorbid with depression (Hirschfeld, 2001) and with regard to suicidality, given its association with depression (Blair-West et al., 1999). Although we focus on the serotonergic system, we do not intend to imply that it is the only system for which gene–sex interactions are relevant to depression and related phenomena. Rather, we hope this focused Mini-Review will serve as a template for considering sex differences in other biological genetic pathways implicated in depression.

We propose three potential pathways through which polymorphisms in genes involved in serotonin synthesis, transport, and breakdown may differentially impact behavior as a function of sex. First, we consider sex differences in response to early-life stress and the effects of stress on gene–sex interactions involving the serotonin transporter-linked polymorphic region (5-HTTLPR) in the serotonin transporter gene (*SLC6A4*), which codes for the protein that transports serotonin from the synaptic cleft to the presynaptic neuron. Next, we consider the effects of X-linkage, using as an example the monoamine oxidase-A-linked polymorphic region (MAOA-LPR), which alters the degradation serotonin and other amine neurotransmitters. Third, we consider how sex hormones interact with gene products, focusing on polymorphisms in two tryptophan hydroxylase (TPH) isozymes, TPH1 and TPH2, the rate-limiting enzymes in serotonin biosynthesis in the periphery and central nervous system (Zhang et al., 2004). We do not intend to suggest that these are the only pathways through which gene–sex interactions exert their effect within the serotonergic system or that genetic polymorphisms are modulated only by these pathways. Rather, our intention is to illustrate the central role of sex in the biobehavioral effects of polymorphisms involved in the serotonergic system.

For each polymorphism, we summarize findings of association with depression, its related disorders (anxiety disorders, conduct disorder, and suicide), trait risk factors (neuroticism, harm avoidance, aggression, and impulsiveness), and neurobiological endophenotypes, including amygdala hyperactivation, limbic structure and function, and affective processing (see Tables I–III). For all polymorphisms, we include studies with significant gene main effects or significant gene–environment interactions in one or both sexes. We classified a finding as showing a sex difference when 1) an allele conferred opposite risk in men and women, 2) significant main effects emerged only for one sex, or 3) differing interaction effects emerged. We classified a finding as having no sex difference only when the investigators explicitly tested for and ruled out a sex interaction. Studies were classified as having unclear gene–sex interactions when 1) only one sex was studied, 2) sex interactions were not tested in a mixed group, 3) marginally significant sex differences were found, or 4) sex differences were found in measures not included in the table. Because of space constraints, we limit the listing of the studies performed on the association between 5-HTTLPR and depression to those focusing solely on sex differences. A more complete listing may be found in Karg et al. (2011) and Sharpley et al. (2014). We chose to include studies performed on only one sex because the risk directionality of some of the alleles may be sex dependent. For example, although the preponderance of studies indicate that MAOA-L confers risk for conduct disorder in boys, the female-only study performed by Sjöberg et al. (2007) supports the hypothesis that the other allele, MAOA-H, confers risk in girls. However, additional studies performed with both sexes are essential to confirm these associations. Studies that show gene–sex interactions are listed in Table IV along with sample and effect sizes. The Mini-Review concludes by highlighting the conceptual and methodological difficulties of studying gene–sex interactions and suggesting directions for future research

TABLE I. Sex Modulation of 5-HTTLPR in Depression, Related Disorders, Risk Factors, and Endophenotypes[1]

5-HTTLPR		Depression	Anxiety	Conduct Disorder	Suicide
Independent effects within sexes					
Significant effects in males	S/LG Risk	**Steffens 2002**†, **Ancelin 2010**, **Uddin 2010**★, **Li 2013**★, **Starr 2013**†★	Lesch 1996, Sen 2004, Furmark 2004, **Mizuno 2006**, Greenberg 2000, **Zhang 2015**	Hallikainen 1999, **Cadoret 2003**, Reif 2007★	Bellivier 2000, Bondy 2000, Gorwood 2000, Courtet 2001, **Limosin 2005**, Caspi 2003★, **Li 2013**★
	LA Risk	**Li 2013**, **Starr 2013**†, **Sjoberg 2006**‡★, **Brummett 2008a**‡★, Carli 2011★, **Priess-Groben 2013**‡★	**Flory 1999**, **Cerasa 2013**, Ming 2015★	**Aslund 2013**★	Du 1999, **Hung 2011** **Baca-Garcia 2002**, Bellivier 2000, Bondy 2000, Gorwood 2000, Courtet 2001, Caspi 2003★
Significant effects in females	S/LG Risk	**Steffens 2002**, Gonda 2005, Zalsman 2006, **Uddin 2010**, **Eley 2004**†, Jacobs 2006★, **Sjoberg 2006**‡★, Zalsman 2006★, **Brummett 2008a**‡★, **Aslund 2009**†★, **Rucci 2009**★, **Hammen 2010**†★, **Van Strien 2010**★, **Beaver 2012**†★, Brown 2012★, **Ming 2013**†★, **Priess-Groben 2013**‡★, **Lee 2014**†★	Lesch 1996, Melke 2001, Furmark 2004, Sen 2004, **Cerasa 2013**, Greenberg 2000	**Sakai 2010**, **Douglas 2011**★, **Aslund 2013**★	
	LA Risk	**Baune 2008**†	**Maron 2004**, **Mizuno 2006**, Ming 2015★	**Cadoret 2003**	Du 1999, **Gaysina 2006**
Gene-sex interactions		★★★			
No sex difference			Greenberg 2000, Sen 2004		Bondy 2000
Sex difference			Cerasa 2013‡, Flory 1999†, Maron 2004†, Mizuno 2006‡, Zhang 2015†	Aslund 2013‡, Cadoret 2003‡, Douglas 2011, Sakai 2010†	Baca-Garcia 2002†, Gaysina 2006†, Hung 2011†, Li 2013†, Limosin 2005†
Did not examine/unclear			Furmark 2004, Lesch 1996, Melke 2001, Ming 2015	Hallikainen 1999, Reif 2007	Bellivier 2000, Courtet 2001, Gorwood 2000

5-HTTLPR		Neuroticism	Harm Avoidance	Aggression	Impulsiveness
Independent effects within sexes					
Significant effects in males	S/LG Risk	Lesch 1996, **Du 2000**, Greenberg 2000, Sen 2004|, Schinka 2004|, **Vormfelde 2006**	Mazzanti 1998, Munafò 2004, Katsuragi 1999, Greenberg 2000, **Gelernter 1998**	Hallikainen 1999, **Cadoret 2003**, Beitchman 2006, Haberstick 2006, **Verona 2006**	**Cadoret 2003**, Sakado 2003, **Paaver 2008**, **Walderhaug 2010**
	LA Risk	**Brummett 2003**			
Significant effects in females	S/LG Risk	Lesch 1996, Greenberg 2000, Sen 2004|, Schinka 2004	Mazzanti 1998, Munafò 2004, Katsuragi 1999, Greenberg 2000	Beitchman 2006, Haberstick 2006, **Li 2010**★	**Paaver 2008**★
	LA Risk		**Gelernter 1998**	**Cadoret 2003**	**Cadoret 2003**
Gene-sex interactions					
No sex difference		Greenberg 2000, Schinka 2004	Greenberg 2000	Haberstick 2006	
Sex difference		Du 2000†, Brummett 2003†, Vormfelde 2006†	Gelernter 1998‡	Cadoret 2003‡, Li 2010, Verona 2006	Cadoret 2003‡, Paaver 2008, Walderhaug 2010†
Did not examine/unclear		Lesch 1996, Sen 2004	Katsuragi 1999, Mazzanti 1998	Beitchman 2006	Sakado 2003

TABLE I. *Continued*

5-HTTLPR		Amygdala Hyperactivation	Limbic Structure	Limbic Function	Affective Processing
Independent effects within sexes					
Significant effects in males	S/LG Risk	Hariri 2002, Furmark 2004, Heinz 2005, Bertolino 2005, Canli 2005a, Canli 2005b, Canli 2008, Hariri 2005, Heinz 2007, Dannlowski 2007, Dannlowski 2008, Munafò 2008|, Furmark 2009, Gillihan 2011, Kobiella 2011, Klucken 2013a⋆, Klucken 2013b, Klucken 2015, Lemogne 2011⋆, Alexander 2012⋆	Canli 2005a, Pezawas 2005, Frodl 2008, Scherk 2009, Eker 2011, Kobiella 2011, Selvaraj 2011, **Price 2013**, Little 2014, Liu 2015, Jaworska 2016, Frodl 2010⋆, **Everaerd 2012⋆,** Rabl 2014⋆	Heinz 2005, Pezawas 2005, Canli 2008, Fortier 2010, Surguladze 2008, Holmes 2010, Kobiella 2011, Hermann 2012, El-Hage 2013, Klucken 2013b, Klucken 2015, **Zhang 2015**, Alexander 2012⋆, Klucken 2013a⋆	Brocke 2006, Herrmann 2007, Stein 2009, Beevers 2010a, Beevers 2010b, **Nikolova 2011⋆**
	LA Risk				**Brummett 2008b**
Significant effects in females	S/LG Risk	Hariri 2002, Furmark 2004, Hariri 2005, Bertolino 2005, Canli 2005a, Canli 2005b, Canli 2008, Dannlowski 2007, Dannlowski 2008, Munafò 2008|, Furmark 2009, Furman 2011, Gillihan 2011, Kobiella 2011, Drabant 2012, Klucken 2013b, Klucken 2015, Lemogne 2011⋆	Canli 2005a, Pezawas 2005, Frodl 2008, Scherk 2009, Eker 2011, Kobiella 2011, Selvaraj 2011, **Everaerd 2012, Price 2013**, **Cerasa 2014**, Little 2014, Liu 2015, Jaworska 2016, Frodl 2010⋆, Rabl 2014⋆	Heinz 2005, Pezawas 2005, Canli 2008, Fortier 2010, Surguladze 2008, Holmes 2010, Kobiella 2011, Drabant 2012, Hermann 2012, El-Hage 2013, Klucken 2013b, Klucken 2015	Neumeister 2002, **McCaffery 2003⋆**, **Grabe 2005⋆**, Brocke 2006, **Jabbi 2007⋆**, Herrmann 2007, **Brummett 2008b**, Stein 2009, Beevers 2010a, Beevers 2010b, **Jabbi 2007**, **Walderhaug 2007**§, **Antypa 2011,** Markus 2011
	LA Risk	Lee 2008b			
Gene-sex interactions					
No sex difference		Hariri 2002, Hariri 2005, Klucken 2013b, Klucken 2015, Kobiella 2011	Canli 2005a, Kobiella 2011, Little 2014, Rabl 2014, Scherk 2009	Klucken 2013b, Klucken 2015	Beevers 2010a, Beevers 2010b, Brocke 2006, Stein 2009
Sex difference			Cerasa 2014‡, Everaerd 2012, Price 2013‡		Antypa 2011, Brummett 2008b‡, Grabe 2005†, McCaffery 2003, Nikolova 2011†, Walderhaug 2007§†
Did not examine/unclear		Alexander 2012, Bertolino 2005, Canli 2005a, Canli 2005b, Canli 2008, Dannlowski 2005, Dannlowski 2008, Drabant 2012, Furman 2011, Furmark 2004, Furmark 2009, Gillihan 2011, Heinz 2004, Heinz 2007, Klucken 2013a, Kobiella 2011, Lemogne 2011, Munafò 2008	Eker 2011, Frodl 2008, Frodl 2010, Jaworska 2016, Liu 2015, Pezawas 2005, Selvaraj 2011	Alexander 2012, Canli 2008, Drabant 2012, Fortier 2010, Hermann 2012, Holmes 2010, Klucken 2013a, Kobiella 2011, Pezawas 2005, Surguladze 2008	Neumeister 2002

No sex difference: Denotes studies in which gene-sex interactions were not found
Sex difference: Denotes studies in which (†) significant effects emerged for only one sex, (‡) significant effects emerged in opposite directions by sex, or interaction effects were different.
Did not examine/Unclear: Denotes studies in which (1) only one sex was studied, (2) sex interactions were not ruled out, (3) marginally significant sex differences were found, or (4) sex differences were found in measures not included in the table.
Conduct disorder: Includes measures of delinquency and other externalizing symptoms when applicable
Limbic structure: Includes volumetric and other anatomical measures of limbic components. Because the directionality of risk assignment in these measures is not always clear, the alleles have been merged.
Limbic function: Includes functional connectivity, steady-state effects, and measures of limbic activity excluding amygdala hyperactivation. Because the directionality of risk assignment in these measures is not always clear, the alleles have been merged.
[1]This table only reflects studies with positive findings in one or both sexes.
⋆⋆⋆Due to space constraints, a listing of all studies on the main effect of 5-HTTLPR have been omitted. Refer to Karg et al., 2011 and Sharpley et al., 2014 for more complete meta-analyses.
⋆Denotes significant effects arising in the context of stress or early life adversity.
§Denotes specifically the SL genotype.
|Denotes meta-analyses.
Bold Underlining denotes studies that observed sex differences.

to advance our understanding of gene–sex interactions, particularly with regard to mechanistic pathways and their translational relevance for developing a neurobehavioral taxonomy for depression and related phenotypes.

DEPRESSION AND RELATED CONDITIONS

Existing diagnostic categories of clinical depression and related disorders, currently defined by symptom criteria, may in fact comprise an ensemble of multiple underlying dysfunctions that are more cohesive when defined by neurobiobehavioral measures (Williams, 2016). These underlying neurobiobehavioral dysfunctions may not map to symptom-based boundaries, but they define consistent subtypes that are present across different diagnoses. Sex differences may be an important consideration for anchoring a neurobiobehavioral understanding of depression. For example, women have been reported to have a tendency to internalize distress, whereas men have been reported to have a tendency to externalize distress (Eaton et al., 2012). Internalizing might reflect the action of particular biobehavioral mechanisms for depressed or anxious outcomes in women, and externalizing might reflect the action of different mechanisms for antisocial or aggressive outcomes in men; investigation of sex differences could help to disentangle the pathways of genetic risk for clinical expressions of depression and emotional dysregulation. This Mini-Review considers these clinical expressions as including depression, anxiety, conduct disorders, and suicidality.

Another collection of depression-related phenomena may be considered "latent expressions" of risk for overt clinical states; these include personality traits as well as alterations in brain anatomy and functional activity. The personality trait of neuroticism in the Revised NEO Personality Inventory, reflecting a dispositional bias toward negative information, is higher in women than in men across 26 cultures, with U.S. women scoring 0.51 SD higher than their male counterparts (Costa et al., 2001). These higher levels of neuroticism are thought to be a latent trait that moderates the expression of a greater prevalence of depression in females (Goodwin and Gotlib, 2004). Similarly, trait harm avoidance is associated with panic disorder and general anxiety (Starcevic et al., 1996), and trait impulsiveness, which is thought to be reflective of low serotonin turnover, is associated with suicide (Fawcett et al., 1997). Likewise, structural and functional alterations of the brain are subject to sex differences that exist on the spectrum of subclinical to healthy brains. Dysfunctional activity in the amygdala and other limbic structures correlates with depression severity, probability of relapse, and dysregulated processing of emotionally valenced stimuli, which may reflect a trait risk for depression (for review see Drevets, 2000). Healthy women exhibit more persistent amygdala activity in response to fear signals than men (Williams et al., 2005). With regard to neuroanatomy, decreased hippocampal volume, which is thought to reflect the effects of chronic stress, has been observed in both male and female depressed patients (Videbech and Ravnkilde, 2004), although hippocampal size and microstructure are altered in men but not women with subclinical depression (Spalletta et al., 2014).

THE SEROTONIN SYSTEM IN MEN AND WOMEN

This Mini-Review focuses on the serotonergic system because it 1) plays an important role in mood and mood disorders, 2) is widely accepted to be sexually dimorphic, 3) encompasses polymorphisms that have been extensively studied with respect to mood disorders, and 4) is directly relevant to the efficacy of selective serotonin reuptake inhibitors (SSRIs), the most commonly used treatments for depression and anxiety, making it an important aspect of individualized treatment and precision medicine. Apart from its role as a neurotransmitter, serotonin also plays a role in brain development by regulating neurite outgrowth, synaptogenesis, and cell survival (Gaspar et al., 2003), all of which have important consequences for neurobiological function.

Sexual dimorphisms within the serotonin system have been known for the past 4 decades. Males and females exhibit different rates of serotonin synthesis (Nishizawa et al., 1997), different levels of serotonin metabolites (Gottfries et al., 1974), different receptor and transporter binding potentials (Jovanovic et al., 2008), and different SSRI response and tolerance (Kornstein et al., 2000). Furthermore, acute tryptophan depletion, which induces lower mood in recovered depressed patients by temporarily decreasing serotonin levels, leads to larger mood-lowering effects in women than in men (Booji et al., 2002).

Sex differences within the serotonergic system might, on their own, account for some of the sex differences in genetic risk for depression and related clinically expressed phenomena. In addition, sex differences multiply when serotonergic gene products interact with, regulate, and are modulated by other sexually dimorphic biological pathways. This Mini-Review discusses the interface of serotonergic genetic polymorphisms with three such pathways, the effects of early-life stress, the effects of sex chromosome differences, and the effects of sex hormones.

POTENTIAL PATHWAYS OF SEX MODULATION OF GENETIC POLYMORPHISMS

Mechanism: Early-Life Stress

Exposure to early-life stress is a risk factor for developing mood and anxiety disorders, partially because of long-term stress response dysregulation, cognitive coping strategies, and neurobiological anatomy (Heim and Nemeroff, 2001). Many genes that have been implicated in depression, including brain-derived neurotrophic factor (BDNF), catechol-O-methyltransferase, and corticotropin-releasing hormone receptor 1, have more pronounced effects in the context of early-life stress (Heim and Binder, 2012).

TABLE II. Sex Modulation of MAOA LPR in Depression, Related Disorders, Risk Factors, and Endophenotypes[1]

MAOA LPR		Depression	Anxiety	Conduct Disorder	Suicide
Independent effects within sexes					
Significant effects in males	L Risk	Cicchetti 2007★	**Voltas 2015**	Kim-Cohen 2006, Reif 2007, **Guo 2008**, Stetler 2014, Tiihonen 2015, Caspi 2002★, Foley 2004★, Nilsson 2006★, Widom 2006★, **Frazzetto 2007★**, Nilsson 2007★, Edwards 2010★, **Wakschlag 2010★**, **Aslund 2011★**, Derringer 2010★, **Nilsson 2011★**	
	H Risk	**Yu 2005a**, **Lung 2011**, **Adkins 2012**	Liu 2013, Reif 2014		**Du 2002**
Significant effects in females	L Risk	**Huang 2009**, Cicchetti 2007★, **Melas 2013★**	**Maron 2004**	Tiihonen 2015, Caspi 2002★, Widom 2006★, Ducci 2008★, **Prom-Wormley 2009**, Derringer 2010★	
	H Risk	**Schulze 2000**, **Yu 2005a**, **Rivera 2009**, **Nikulina 2012★**	**Deckert 1999**, **Samochowiec 2004**, **Maron 2005**, **Reif 2012**, Liu 2013, Reif 2014, **Voltas 2015**	Sjoberg 2007★, Nilsson 2008★, **Wakschlag 2010★**, **Aslund 2011★**, **Nilsson 2011★**	
Gene-sex interactions					
No sex difference				Tiihonen 2015, Widom 2006	
Sex difference		Adkins 2012, Huang 2009, Lung 2011†, Melas 2013†, Nikulina 2012†, Rivera 2009†, Schulze 2000†, Yu 2005a	Deckert 1999†, Maron 2004†, Maron 2005†, Reif 2012†, Samochowiec 2004†, Voltas 2015‡	Aslund 2011‡, Frazzetto 2007, Guo 2008†, Nilsson 2011‡, Prom-Wormley 2006†, Wakschlag 2010‡	Du 2002†
Did not examine/unclear		Cicchetti 2007	Liu 2013, Reif 2014	Caspi 2002, Derringer 2010, Ducci 2008, Edwards 2010, Foley 2004, Kim-Cohen 2006, Nilsson 2006, Nilsson 2007, Nilsson 2008, Reif 2007, Sjoberg 2007, Stetler 2014	

MAOA LPR		Neuroticism	Harm Avoidance	Aggression	Impulsiveness
Independent effects within sexes					
Significant effects in males	L Risk			Eisenberger 2007, Kuepper 2013, Weder 2009★, Beaver 2013, Gorodetsky 2014★	Stetler 2014, **Huang 2004★**, Enoch 2010★
	H Risk	**Eley 2003**		Manuck 2000, Beitchman 2004, Gorodetsky 2014	Manuck 2000
Significant effects in females	L Risk			Eisenberger 2007, Kuepper 2013, Weder 2009★	Kinnally 2009 Kinnally 2009★, Enoch 2010★
	H Risk		Yu 2005b	**Verhoeven 2012**	
Gene-sex interactions					
No sex difference				Eisenberger 2007, Kuepper 2013, Weder 2009	
Sex difference		Eley 2003†		Verhoeven 2012†	Huang 2004
Did not examine/unclear			Yu 2005b	Beaver 2013, Beitchman 2004, Gorodetsky 2014, Manuck 2000	Enoch 2010, Kinnally 2009, Manuck 2000, Stetler 2014

TABLE II. *Continued*

MAOA LPR		Amygdala Hyperactivation	Limbic Structure	Limbic Function	Affective Processing
Independent effects within sexes					
Significant effects in males	L Risk	**Meyer-Lindenberg 2006**, Buckholtz 2008, Denson 2014, **Holz 2016**⋆	**Meyer-Lindenberg 2006**	Fan 2003, **Meyer-Lindenberg 2006**, Passamonti 2006, Eisenberger 2007, Buckholtz 2008, Passamonti 2008, Alia-Klein 2009, Dannlowski 2009, **Williams 2009**, Denson 2014, Lei 2014, Reif 2014, Clemens 2015, **Holz 2016**⋆	Brummett 2008c, Alia-Klein 2009, Bouma 2012
	H Risk	**Holz 2016**			Buckholtz 2008, Reif 2014
Significant effects in females	L Risk	Lee 2008a, **Holz 2016**	**Meyer-Lindenberg 2006**	Fan 2003, Eisenberger 2007, Lee 2008a, Dannlowski 2009, **Williams 2009**, Reif 2014, Clemens 2015, **Holz 2016**⋆	Bouma 2012
Gene-sex interactions					
No sex difference	H Risk	**Holz 2016**⋆		Eisenberger 2007, Fan 2003	**Jabbi 2007**, **Chen 2013, Wakschlag 2010**⋆, Reif 2014
Sex difference		Holz 2016‡, Meyer-Lindenberg 2006†	Meyer-Lindenberg 2006†	Holz 2016‡, Meyer-Lindenberg 2006†, Williams 2009	Chen 2013†, Jabbi 2007, Wakschlag 2010†
Did not examine/unclear		Buckholtz 2008, Denson 2014, Lee 2008		Alia-Klein 2009, Buckholtz 2008, Clemens 2015, Dannlowski 2009, Denson 2014, Lee 2008, Lei 2014, Passamonti 2006, Passamonti 2008, Reif 2014	Alia-Klein 2009, Bouma 2012, Brummett 2008, Buckholtz 2008, Reif 2014

No sex difference: Denotes studies in which gene-sex interactions were not found
Sex difference: Denotes studies in which (†) significant effects emerged for only one sex, (‡) significant effects emerged in opposite directions by sex, or interaction effects were different.
Did not examine/Unclear: Denotes studies in which (1) only one sex was studied, (2) sex interactions were not ruled out, (3) marginally significant sex differences were found, or (4) sex differences were found in measures not included in the table.
Conduct disorder: Includes measures of delinquency and other externalizing symptoms when applicable
Limbic structure: Includes volumetric and other anatomical measures of limbic components. Because the directionality of risk assignment in these measures is not always clear, the alleles have been merged.
Limbic function: Includes functional connectivity, steady-state effects, and measures of limbic activity excluding amygdala hyperactivation. Because the directionality of risk assignment in these measures is not always clear, the alleles have been merged.
[1]This table only reflects studies with positive findings in one or both sexes.
⋆Denotes significant effects arising in the context of stress or early life adversity.
|Denotes meta-analyses.
Bold Underlining denotes studies that observed sex differences.

TABLE III. Sex Modulation of TPH1 and TPH2 in Depression, Related Disorders, Risk Factors, and Endophenotypes[1]

Parameter	Depression		Anxiety		Conduct Disorder		Suicide	
Independent effects within sexes by gene	TPH1	TPH2	TPH1	TPH2	TPH1	TPH2	TPH1	TPH2
Significant effects in males	**Serretti 2001**, Eley 2004, Gizatullin 2006, Jokela 2007★, Viikki 2010	Zill 2004b, Zhang 2005, Zhou 2005, Van Den Bogaert 2006, Anttila 2009, Tsai 2009, Gao 2012, Nobile 2009★, Ma 2015★		Zhou 2005, Campos 2011			Nielsen 1994, Nielsen 1998, Rujescu 2003, Bellivier 2004|, Galfalvy 2009, Gizatullin 2006, Li 2006, Gonzalez-Castro 2014	Mann 1997, Zill 2004a, Zhou 2005, Ke 2006, Lopez de Lara 2007, Yoon 2009, Grohmann 2010, Perez-Rodiguez 2010, Zhang 2010
Significant effects in females	Eley 2004, Sun 2004, Gizatullin 2006, Jokela 2007★, Viikki 2010	Zill 2004b, Zhang 2005, Zhou 2005, Van Den Bogaert 2006, Anttila 2009, Lin 2009, Tsai 2009, **Utge 2010**, **Shen 2011**, Fasching 2012, Gao 2012, Nobile 2009★, Mandelli 2012★, Ma 2015★	Sun 2004	Zhou 2005, **Maron 2007**, **Kim 2009**, Lin 2009, Campos 2010			Rujescu 2003, Bellivier 2004|, Galfalvy 2009, Gizatullin 2006, Li 2006, Zaboli 2006, Gonzalez-Castro 2014	Mann 1997, Zill 2004a, Zhou 2005, Ke 2006, Lopez de Lara 2007, Yoon 2009, Grohmann 2010, Perez-Rodiguez 2010, Zhang 2010
Gene-sex interactions								
No sex difference	Eley 2004, Viikki 2010							Lopez de Lara 2007
Sex difference	Serretti 2001†	Shen 2011†, Utge 2010		Kim 2009†, Maron 2007†				
Did not examine/unclear	Gizatullin 2006, Jokela 2007, Sun 2004	Anttila 2009, Fasching 2012, Gao 2012, Lin 2009, Ma 2015, Mandelli 2012, Nobile 2009, Tsai 2009, Van Den Bogaert 2006, Zhang 2005, Zhou 2005, Zill 2004b	Sun 2004	Campos 2010, Lin 2009, Zhou 2005			Bellivier 2004|, Galfalvy 2009, Gizatullin 2006, González-Castro 2014, Li 2006, Nielsen 1994, Nielsen 1998, Rujescu 2003, Zaboli 2006	Grohmann 2010, Ke 2006, Mann 1997, Perez-Rodriguez 2010, Zhang 2010, Zhou 2005, Zill 2004a, Yoon 2009

Parameter	Neuroticism		Harm Avoidance		Aggression		Impulsiveness	
Independent effects within sexes by gene	TPH1	TPH2	TPH1	TPH2	TPH1	TPH2	TPH1	TPH2
Significant effects in males		Lehto 2015	Andre 2013	Reuter 2007, Gutknecht 2007	New 1998, Manuck 1999, Rujescu 2002, Staner 2002, Koh 2012	Perez-Rodiguez 2010	New 1998, Staner 2002, Galfalvy 2009	**Stoltenberg 2012**
Significant effects in females		Lehto 2015	**Keltikangas-Järvinen 2007**, Andre 2013	Reuter 2007, Gutknecht 2007	Manuck 1999, Rujescu 2002, Staner 2002, Koh 2012	Perez-Rodiguez 2010, Yang 2010	Staner 2002, Galfalvy 2009	
Gene-sex interactions								
No sex difference					Koh 2012, Rujescu 2001, Staner 2002		Staner 2002	
Sex difference			Keltikangas-Järvinen 2007†					Stoltenberg 2012†

TABLE III. *Continued*

Parameter	Neuroticism	Harm Avoidance	Aggression	Impulsiveness
Did not examine/unclear	Lehto 2015 Andre 2013	Gutknecht 2007, Reuter 2007	Manuck 1999, New 1998 Perez-Rodiguez 2010, Yang 2010	Galfalvy 2009, New 1998

Parameter	Amygdala Hyperactivation		Limbic Structure		Limbic Function		Affective Processing	
Independent effects within sexes by gene	TPH1	TPH2	TPH1	TPH2	TPH1	TPH2	TPH1	TPH2
Significant effects in males		Brown 2005, Canli 2005c, Canli 2008, Furmark 2009		Inoue 2010, Yoon 2012		Canli 2008, Hermann 2012⋆		Herrmann 2007, **Armbruster 2010,** Perez-Rodiguez 2010, Yoon 2012
Significant effects in females	Lee 2009	Brown 2005, Canli 2005b, Canli 2008, Lee 2008b, Furmark 2009		Inoue 2010, Yoon 2012		Canli 2008, Hermann 2012⋆		Herrmann 2007, **Armbruster 2010**, Perez-Rodiguez 2010, Yoon 2012
Gene-sex interactions								
No sex difference				Inoue 2010				
Sex difference								Armbruster 2010‡
Did not examine/unclear	Lee 2009	Brown 2005, Canli 2005c, Canli 2008, Furmark 2009, Lee 2008b		Yoon 2012		Canli 2008, Hermann 2012		Herrmann 2007, Perez-Rodriguez 2010, Yoon 2012

No sex difference: Denotes studies in which gene-sex interactions were not found
Sex difference: Denotes studies in which (†) significant effects emerged for only one sex, (‡) significant effects emerged in opposite directions by sex, or interaction effects were different.
Did not examine/Unclear: Denotes studies in which (1) only one sex was studied, (2) sex interactions were not ruled out, (3) marginally significant sex differences were found, or (4) sex differences were found in measures not included in the table.
Conduct disorder: Includes measures of delinquency and other externalizing symptoms when applicable
Limbic structure: Includes volumetric and other anatomical measures of limbic components. Because the directionality of risk assignment in these measures is not always clear, the alleles have been merged.
Limbic function: Includes functional connectivity, steady-state effects, and measures of limbic activity excluding amygdala hyperactivation. Because the directionality of risk assignment in these measures is not always clear, the alleles have been merged.
[1]This table only reflects studies with positive findings in one or both sexes.
⋆Denotes significant effects arising in the context of stress or early life adversity.
[|]Denotes meta-analyses.
Bold Underlining denotes studies that observed sex differences.

TABLE IV. Studies Reporting Gene–Sex Interactions in Depression, Related Disorders, Risk Factors, and Endophenotypes

Sources	F/M*	Parameter	Finding	Effect (*P*)†
5-HTTLPR				
Ancelin et al., 2010	1,040/752	Depression	S interacts with lipid levels in males	0.02
Antypa et al., 2011	186/59	Facial emotion recognition	SS females recognize negative emotions at lower intensity	<0.05
Aslund et al., 2009	717/765	Depression	SS interacts with maltreatment in females	0.034
Aslund et al., 2013	714/753	Delinquency	Interacts with high SES in L males, S females; with low SES in LL males, SS females	0.022
Baca-Garcia et al., 2002	214/178	Suicide attempts	S associated in females	0.02
Baune et al., 2008	194/146	Depression	L associated with melancholic depression in females	0.05
Beaver et al., 2012	924/778	Depressive symptoms	SS interacts with stress in females	<0.05
Brummett et al., 2003	129/73	Neuroticism	S protective in males	<0.01
Brummett et al., 2008a	160/55	Depression	S interacts with stress in females; L interacts with stress in males	<0.003
Brummett et al., 2008b	31/41	Negative affect (tryptophan infusion)	LL associated in males; SS associated in females	0.013
Cadoret et al., 2003	59/39	Conduct disorder; aggression	L associated in males; S associated in females	<0.05
Cerasa et al., 2014	76/62	Anxiety; Amygdala volume	SS associated with anxiety and increased volume in females, protective in males	0.01; 0.002
Douglas et al., 2011	567/814	Antisocial personality disorder	S interacts with life events in females	<0.001
Du et al., 2000	109/77	Neuroticism	S associated in males	0.018
Eley et al., 2004	220/157	Depression	S associated in females	0.03
El-Hage et al., 2013	42/39	Resting cerebral blood flow in amygdala	Higher in S males	<0.03
Everaerd et al., 2012	221/136	Hippocampal volume	S associated with decrease in women; S interacts with childhood adversity in males	0.023; 0.007
Flory et al., 1999	135/135	Anxiety	L associated in males	0.03
Gaysina et al., 2006	219/175	Suicide attempts	L associated in females	0.002
Gelernter et al., 1998	132/190	Harm Avoidance	S associated in males; S protective in females	0.04
Grabe et al., 2005	676/300	Mental/physical distress	S interacts with unemployment and chronic disease in females	<0.001
Hammen et al., 2010	214/132	Depression	S interacts with stress in females	0.01
Hung et al., 2011	63/105	Suicide attempts	L associated in males	0.012
Jabbi et al., 2007	31/33	Cortisol stress response	SS associated with larger response in females	<0.006
Lee et al., 2014	960/258	Depression	S associated in females	0.015
Li et al., 2010	1,144/1,054	Antisocial behavior	SS interacts with maltreatment in females	<0.01
Li et al., 2013	453/577	Suicide attempts; depression	S associated in males with low family support; S protective in males with high family support	<0.05
Limosin et al., 2005	52/48	Suicide attempts	S associated in males	0.05
Maron et al., 2004	18/11	CCK-4-induced panic attacks	Lower rate in S females	0.03
McCaffery et al., 2003	191/191	Cardiovascular response	Greater response in SS women	<0.05

TABLE IV. *Continued*

Sources	F/M*	Parameter	Finding	Effect (*P*)†
Ming et al., 2013	131/121	Depressive symptoms	S interacts with stress in females	<0.0001
Mizuno et al., 2006	59/45	Anxiety	SL associated in females; SS associated in males	<0.05
Nikolova et al., 2011	27/33	Reward response	S associated with stress-related reduction in males	0.002
Paaver et al., 2008	261/222	Impulsivity	S interacts with family relations in females	0.036
Price et al., 2013	25/26	Hippocampal volume	S increases volume in females, decreases volume in males	<0.03
Priess-Groben et al., 2013	129/180	Depressive symptoms	Life stress and MAOA-L interacts with S in females and L in males	0.009
Rucci et al., 2009	147/75	Depression	L decreases manic/hypomanic component in females	0.012
Sakai et al., 2010	254/213	Conduct problems	S associated in females	<0.05
Sjoberg et al., 2006	119/81	Depression	S confers risk in females and protection in males	0.018; 0.032
Starr et al., 2013	217/137	Depression	S interacts with security in males	0.05
Steffens et al., 2002	194/95	Depression	SS associated in males	0.02
Uddin et al., 2010	560/524	Depressive symptoms	SL protective in females; SL protective in males only with deprivation	0.03; 0.04
Van Strien et al., 2010	153/133	Emotional eating	S moderates depression and emotional eating in females	<0.01
Verona et al., 2006	56/55	Aggression	SS interacts with acute stress in males	<0.05
Volf et al., 2015	109/101	Resting EEG	SL associated with more power in women	0.041
Vormfelde et al., 2006	98/97	Neuroticism	L protective in males	0.049
Walderhaug et al., 2007	44/39	Mood (tryptophan depletion)	SL protective in females	0.019
Walderhaug et al., 2010	14/38	Impulsivity	S associated in males	0.033
Zhang et al., 2015	158/104	Anxiety; Functional connectivity	SS associated in males	0.006; < 0.005
MAOA-LPR				
Adkins et al., 2012	987/922	Depression	H males experience increased distress in late adolescence	<0.05
Aslund et al., 2011	882/943	Delinquency	L interacts with maltreatment in males; H interacts with maltreatment in females	<0.001
Buckholtz et al., 2008	63/60	Amygdala activity; Functional connectivity	S associated with dysregulated amygdala activity, increased vmPFC connectivity in males	<0.01; < 0.008
Chen et al., 2013	193/152	Happiness	L associated in females	0.002
Deckert et al., 1999	254/145	Panic disorder	H associated in females	0.001
Du et al., 2002	39/97	Depressed suicide	H associated in males	0.012
Eley et al., 2003	76/41	Neuroticism	H associated in males	<0.01
Frazetto et al., 2007	153/82	Physical aggression	L interacts with life events in males	0.009
Guo et al., 2008	1,324/1,200	Delinquency	L associated in males	0.008
Holz et al., 2016	53/72	Activity in amygdala and hippocampus	Increased with life events in male L, decreasing in male H; reversed in females	0.008; 0.005
Huang S et al., 2009	281/309	Depression	L associated with severe depression in females	0.041
Huang Y et al., 2004	424/342	Impulsivity	L interacts with abuse in males	0.038
Jabbi et al., 2007	31/33	Baseline cortisol	H associated with higher cortisol in females	<0.009

TABLE IV. *Continued*

Sources	F/M*	Parameter	Finding	Effect (P)†
Lung et al., 2011	567/410	Depression	H associated in males	0.041
Maron et al., 2004	18/11	CCK-4-induced panic attacks	Higher rate in L females	0.007
Maron et al., 2005	286/87	Panic disorder with agoraphobia	H associated in females	0.016
Melas et al., 2013	993/675	Depression	L interacts with childhood adversity in females	0.006
Meyer-Lindenberg et al., 2006	72/70	Limbic volume and activity	L associated with amygdalar, hippocampal, cingulate activity, orbitofrontal volume in males	<0.05
Nikulina et al., 2012	280/295	Dysthymia	H interacts with life stress in females	<0.05
Nilsson et al., 2011	735/851	Adolescent alcohol consumption	H associated in females; L associated in males	0.006; < 0.001
Prom-Wormley et al., 2009	721/578	Conduct disorder	H associated in females	0.05
Reif et al., 2012	1,636/739	Panic disorder	H associated in females	0.006
Rivera et al., 2009	884/344	Depression	H associated in females	<0.05
Samochowiec et al., 2004	225/78	Anxiety disorders	H associated with panic attacks and generalized anxiety disorder in females	<0.05
Schulze et al., 2000	170/77	Depression	H associated in females	0.029
Verhoeven et al., 2012	332/100	Aggression	H associated in females	0.03
Voltas et al., 2015	143/85	Anxiety	H associated in females; L in males	0.026; 0.031
Wakschlag et al., 2010	99/77	Conduct disorder; hostile attribution bias	L associated with conduct disorder in males; H associated with CD and bias in females	0.03; 0.002; 0.04
Williams et al., 2009	69/141	Emotion-processing event related potentials	Differing response localization between L males and females	<0.05
Yu et al., 2005a	236/205	Depression	H associated in females; smaller effect in males	0.008
TPH1 and TPH2				
Armbruster et al., 2010	228/219	Startle response	Higher in TPH2 −703 G/G females; higher in T males	0.043; 0.039
Keltikangas-Järvinen et al., 2007	186/155	Harm avoidance	TPH1 haplotype (A218C A and A779C A) interacts with childhood environment in females	0.002
Kim et al., 2009	272/183	Panic disorder	TPH2 rs4570625 T protective in females	0.041
Maron et al., 2007	375/141	Panic disorder	TPH2 rs1386494 G protective in females	0.01
Serretti et al., 2001	851/573	Depression	TPH1 A218C A protective in males	0.016
Shen et al., 2011	278/90	Depression	TPH2 haplotype (rs4290270 A and rs7305115 A) associated in females	0.001
Stoltenberg et al., 2012	309/168	Impulsivity	TPH2 rs1386483 A associated in males	0.018
Utge et al., 2010	967/687	Clinical manifestations of depression	TPH2 rs12229394 associated with depression accompanied by fatigue in females	0.005

*Numbers of female/male participants.
†Main effects in studies with positive findings only in one sex or gene–sex interaction effects when examined.

Graphical Abstract Text

The effects of polymorphisms in serotonin transporter, monoamine oxidase A (MAOA), and tyrosine hydroxylase genes on depression, clinical expressions, and latent risk factors are modulated by sex differences.

Psychological and biological responses to stress, particularly early-life stress, are sexually dimorphic (for review see Bale and Epperson, 2015). Men and women differ in the types of stressors that most impact depression risk (Chu et al., 2013). Although women are more likely to develop a depressive disorder, men may be more susceptible to the immediate neurobiological effects of stress, including stress-related c-fos expression, enhanced fear conditioning, and increased hypothalamic–pituitary–adrenal axis response (for review see Altemus, 2006). Work in animals has suggested neurobiological mechanisms for the observed sex difference in stress response. For example, male rats exposed to perinatal stress show a period in adolescence of increased neurogenesis, BDNF expression, and spatial learning that is reduced by adulthood, whereas female rats exhibit the opposite pattern of decreased neurogenesis in adolescence, followed by an increase in adulthood (Loi et al., 2014). When examining three-way interactions among stress, sex, and genotype, researchers must remember that observed differences in subclinical traits, neuroimaging, and neuroanatomy may represent either risk mechanisms or protective compensatory mechanisms.

5-HTTLPR

The 5-HTTLPR polymorphism is associated with the largest body of research with regard to sex differences; a recent review of sex differences in 5-HTTLPR included 78 studies (Gressier et al., 2016). The 5-HTTLPR polymorphism consists of a 16-repeat long variant and a 14-repeat short variant, which causes decreased SLC6A4 transcription (Lesch et al., 1996). The long variant is further modified by a single nucleotide polymorphism, A/G SNP rs25531, with L(A) variants expressing normally and L(G) variants expressing similarly to the S allele (Wendland et al., 2006). In this Mini-Review, we designate the S and L(G) alleles as low-expressing alleles.

Although 5-HTTLPR and gender may modulate depression risk, severity, and suicide risk independently of environmental stress (see Table I), the depressogenic effect of the low-expressing alleles may be potentiated by stressful life events, particularly in early childhood (Caspi et al., 2003). This finding has been supported by subsequent meta-analyses (Karg et al., 2011; Sharpley et al., 2014), although others have yielded negative results (Munafò et al., 2009; Risch et al., 2009). The gene–environment interaction becomes stronger when taking sex into account, with a majority of studies showing that low-expressing alleles interact with stress to confer risk more specifically in females (see Table I).

Neuroimaging evidence supports the hypothesis that the 5-HTTLPR polymorphism differently influences hippocampal, amygdalar, and cortical structure in men and women in the context of early-life stress (see Fig. 1). However, although several studies have established a relationship between low-expressing alleles and amygdala hyperreactivity, no sex differences have been found because few studies have explicitly examined gene–sex interactions (see Table I). Connections between genotype and personality traits provide a mechanism by which 5-HTTLPR may differentially interact with sex to alter preclinical risk factors independently of early-life stress exposure (Table I).

The mechanistic basis of how 5-HTTLPR variation leads to biobehavioral sex differences is still unclear, but multiple lines of evidence illustrate sex-specific effects on serotonin metabolism. 5-HTTLPR genotype interacts with sex to modulate resting-state cerebral blood flow in the amygdala (El-Hage et al., 2013) as well as resting-state electroencephalography activity (Volf et al., 2015). Depressed women but not men exhibit lower levels of serotonin transporter availability relative to their healthy counterparts (Staley et al., 2006). The low-expressing allele is associated with lower 5-hydroxyindolacetic (5-HIAA) in males and higher 5-HIAA in females, indicative of differing rates of CNS serotonin turnover (Williams et al., 2003). Women who are homozygous for low-expressing alleles exhibit altered 5-HT1A receptor binding, which may indicate either a higher 5-HT1A receptor density or a lower level of serotonin with respect to high-expressing allele carriers, a difference not observed in men (Lothe et al., 2009). Tryptophan depletion leads to increased impulsivity in men and increased caution and mood reduction in women and is particularly marked in women who are homozygous for either allele (Walderhaug et al., 2007). The effect of 5-HTTPLR genotype on women is further underscored by another study showing tryptophan depletion-induced mood reductions in women who are homozygous for the low-expressing alleles, no change in women who are homozygous for the high-expressing allele, and intermediate effects in heterozygote women, depending on the presence of a family history of depression (Neumeister et al., 2002).

Given the findings of gene–sex–environment interactions, another important mechanism may be the interaction of 5-HTTLPR genotype and stress. The low-expressing alleles correlated with greater cortisol reactivity to stress in both a mixed group (Way and Taylor, 2010) and a group of girls (Gotlib et al., 2008). Sex also interacts with the 5-HTTLPR polymorphism to predict cortisol awakening response, adrenocorticotropic hormone (ACTH) levels after dexamethasone administration (Wust et al., 2009), diurnal cortisol (Wankerl et al., 2010), and cortisol response to stress (Jabbi et al., 2007). A study of macaques showed a higher ACTH stress response only in females with a history of adversity (Barr et al., 2004). Altogether, these data provide evidence that 5-HTTLPR confers depression risk through differential susceptibility to stress, with the low-expressing alleles associated with sensitivity to the environment and the high-expressing allele associated with immunity to environmental effects (Paaver et al., 2008; Nilsson et al., 2015). The low-expressing allele predicts increased stress generation in both males and females with low relational security and decreased stress generation with high relational security (Starr et al., 2013). A similar differential susceptibility model has been shown to underlie the influence of other

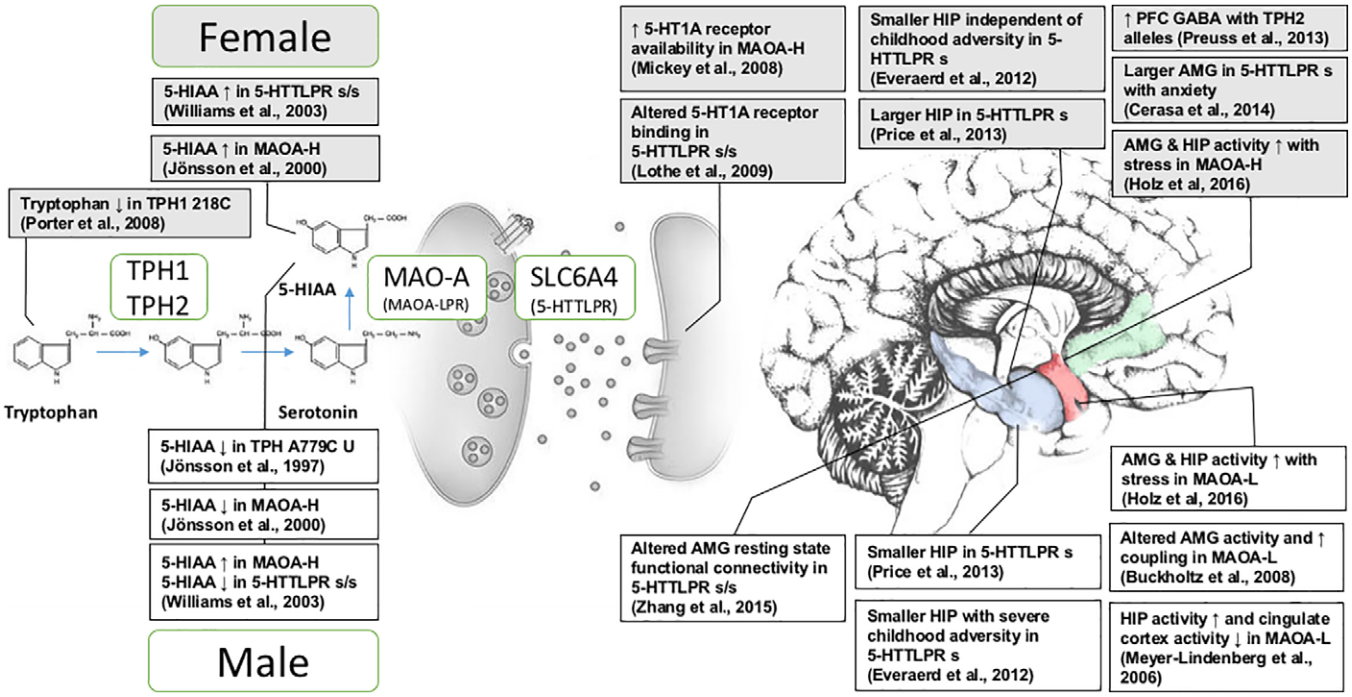

Fig. 1. Different effects of serotonergic genotype in the female (**top**) and male (**bottom**) brains. AMG, amygdala, HIP, hippocampus; PFC, prefrontal cortex.

serotonin system genes in an additive multilocus score (Vrshek-Schallhorn et al., 2015). These findings underscore the importance of additional research on the biological mechanisms of interactions among 5-HTTLPR genotype, sex, and environmental stress.

Mechanism: Sex Chromosomes

A systematic coverage of epigenetic sex differences is beyond the scope of this Mini-Review. In the current context, we highlight a special case of epigenetic modification, X-inactivation of the sex chromosome, the consequences of which are not currently well specified. The choice of which X-chromosome will be inactivated in a given cell is random, creating a mosaic of different cell populations (Migeon, 2007). Furthermore, approximately 15% of genes escape inactivation, and an additional 10% show heterogeneous inactivation, creating differences in gene expression levels between males and females and variability among females (Carrel and Willard, 2005). In addition, the sex-determining region Y (SRY), which is found only on the male Y-chromosome, plays a role in modulating autosomal gene expression (Wijchers et al., 2010). Given the complexity of gene–sex interactions, it is difficult to conclude with certainty when X-inactivation is a primary factor. However, inheritance patterns in family studies have raised the possibility that sex-linked genes play a role in depression; maternal grandfather longevity was associated with mental health in a male group, although maternal mental health was not associated, suggestive of an X-linked recessive genetic basis (Vaillant et al., 2005). Several X-linked genes have been associated with depression endophenotypes, including HTR2C, although its interactions with sex remain unclear (Avery and Vrshek-Schallhorn, 2016).

MAOA-LPR

MAOA is an X-linked gene that regulates monoamine neurotransmission by degrading serotonin, noradrenaline, and dopamine; *MAOA* knockout mice are characterized by higher levels of serotonin and noradrenaline and increased aggressive behavior (Cases et al., 1995). In humans, the polymorphic region located upstream of the coding sequence has been widely studied with regard to conduct disorder, which co-occurs with depression and other affective disorders in both children and adults (Puig-Antich, 1982; Marriage et al., 1986; Zoccolillo, 1992). The polymorphism consists of two, three, three and one-half, four, or five copies of a repeat sequence, with the rarer two, three, and five repeats exhibiting lower promoter activity (Sabol et al., 1998; Guo et al., 2008).

Males carrying low-activity alleles (MAOA-L) are more likely to develop a conduct disorder and exhibit increased aggression and impulsivity, particularly in the presence of childhood maltreatment (see Table II; for review see Byrd and Manuck, 2014), whereas the high-activity allele (MAOA-H) has been associated with increased ventrolateral prefrontal activity (Cerasa et al., 2008a) and gray matter loss (Cerasa et al., 2008b). In

females, however, conduct disorder and aggression have been linked to the high-activity alleles (MAOA-H; Wakschlag et al., 2010; Aslund et al., 2011). MAOA-H also confers risk for depression and anxiety disorders in women specifically (see Table II). Other polymorphisms in *MAOA*, including 1460T, MAOA-CA, and 941T, have also shown sex differences in conferring risk for depression and anxiety (Tadic et al., 2003; Slopien et al., 2012).

Studies on brain structure and activity have indicated subclinical sex differences that may explain the opposing findings in the clinical literature (Fig. 1). Amygdala activity during emotional face matching increases with childhood stress in male MAOA-L carriers and decreases with childhood stress in male MAOA-H carriers, with the reverse occurring in females (Holz et al., 2016). Amygdala volume, however, was not affected by MAOA genotype or an interaction effect between genotype and sex (Cerasa et al., 2011). Increased hippocampal activity (Meyer-Lindenberg et al., 2006) and dysregulated ventromedial prefrontal cortex (Buckholtz et al., 2008) were observed in MAOA-L males but not females (see Fig. 1). Studies on personality provide minimal evidence for sex differences (see Table II), with no sex differences seen in trait aggression, reactive aggression, or dorsal anterior cingulate cortex reactivity to social exclusion (Eisenberger et al., 2007; Kuepper et al., 2013).

Just as with 5-HTTLPR, MAOA-LPR may exert its effects through sex-dependent differential susceptibility. Sex differences may be due to differential responses to stress or to sex-dependent methylation patterns, which are themselves also affected by stress. Sex interacts with MAOA genotype to influence both baseline cortisol and subjective stress (Jabbi et al., 2007). Depressed females, particularly those who have experienced early-life stress, exhibit lower methylation at the *MAOA* locus (Domschke et al., 2012; Melas et al., 2013). Another possible mechanism of sex difference is the *SRY* element found on the Y chromosome, which activates and regulates *MAOA* transcription (Wu et al., 2009). A more thorough understanding of how sex-dependent methylation and sex-based gene dose effects contribute to the impact of risk polymorphisms may yield additional insight into biological mechanisms.

Mechanism: Hormones

There is a strong case to be made for the role of estrogen and other sex steroids as factors in mood and depression. The highest rates of depression onset in women correspond with major hormonal changes, peaking in puberty, in the postpartum period, and at the age of menopause onset (Joffe and Cohen, 1998). Testosterone has been shown to have antidepressant and anxiolytic effects in both men and women (McHenry et al., 2014), and changes in salivary testosterone over the course of a day correlate with depression and anxiety measures (Granger et al., 2003). Hormones may also affect mood indirectly by altering gene expression, changing the rate of gene transcription, or regulating mRNA stability (Ing, 2005). The expression of both serotonin transporter (McQueen et al., 1997) and MAOA (Gundlah et al., 2002) is regulated by estrogen. Exogenous hormone administration has also been shown to alter the functioning of the serotonergic system; female-to-male transsexuals undergoing androgen treatment have increased serotonin transporter binding, whereas male-to-female transsexuals undergoing antiandrogen and estrogen treatments have decreased serotonin transporter binding (Kranz et al., 2015).

TPH

TPH is the rate-limiting enzyme in serotonin synthesis. The TPH2 isozyme is the predominant form in the brain, highly expressed in the serotonergic raphe nuclei (Bach-Mizrachi et al., 2005); however, the TPH1 isozyme is also highly expressed in the amygdala (Zill et al., 2007). Both forms are regulated by both estrogen (Hiroi et al., 2006; Hiroi and Honda, 2013; Gutknecht et al., 2015) and testosterone (Goldstein et al., 1992), and both have been linked to depression and related conditions in both men and women (see Table III). The TPH A218C polymorphism is associated with depression in males only (Serretti et al., 2001). Other alleles play a stronger role in conferring risk for depression and anxiety to women in the peripartum phase (Sun et al., 2004; Lin et al., 2009), suggestive of an intermediary role for hormones.

Variation in TPH2 has also been associated with depression and suicide in both men and women as well as with amygdala activity (see Table III). TPH2 variations also exhibit gene–sex interactions, predicting depression (Shen et al., 2011) and panic disorder (Maron et al., 2007) in women but not in men. Adult male T carriers of the TPH2 G-703T polymorphism have a stronger overall startle response, whereas the effect is reversed in adult females; this finding in females achieves significance only after accounting for menstrual cycle phase, and no sex interaction effects were seen in children or older adults, suggestive of a modulatory role for hormones (Armbruster et al., 2010).

Most studies have not addressed sex differences, but there is evidence from metabolic and animal studies to support the differences that have been found in both TPH1 and TPH2. The TPH1 218C (in depressed women, but not depressed men) allele is associated with decreased plasma tryptophan in women but not in men (Porter et al., 2008). TPH2 knockout mice exhibit anxiety- and depression-like behaviors, with males showing increased impulsivity and aggression and females showing increased reactivity to aversive conditions (Gutknecht et al., 2015).

CONCLUSIONS AND CONSIDERATIONS FOR FUTURE RESEARCH

By giving three examples of how sex modulates genotype to yield differing risk and expression of depression and related conditions, we hope to have made clear the importance of considering sex differences in the context

of genetic variation. We expect that there are still many undiscovered gene–sex interactions because many of the genetic polymorphisms that have previously been associated with depression have not been explicitly studied with regard to sex differences. More research is required to clarify the mechanisms through which genes contribute differentially to depression in men and women, and we conclude by raising methodological considerations and guidelines for future research.

This Mini-Review of sex differences suggests several methodological considerations for future research on sex differences. To address them, we must re-evaluate how we conceptualize genetic risk, diagnostic categories, and sex itself. As we have shown, the same genotype can lead to different conditions in men and women, and alleles that confer risk to one sex may confer protection to the other; risk, therefore, cannot be directly attributed to a particular allele outside of the context of its effects on biological pathways and its interactions with the environment. We have also seen how similar underlying biological dysfunctions may give rise to different behavioral outputs in men and women. This raises the issue of how to group participants for experimental studies of gene–sex interactions, given that they may be heterogeneous with respect both to diagnosis and to genetic risk profile. Another consideration is how to conceptualize sex. Some sex differences, such as those stemming from X-inactivation, arise from the most simplistic, chromosome-based formulation of sex, whereas others, such as hormones, arise from factors that vary with sex. Although this Mini-Review focuses on the interplay of biological sex and genes, genetic effects might also be modulated by gender, self-identity, and cultural expectations.

It is essential that future research in the genetics of depression explicitly check for interactions with sex and sex-related factors known to be relevant. For example, because some sex differences are dependent on levels of cycling hormones, it is vital to incorporate the hormonal status of female participants. Otherwise, the effect of sexually asymmetric alleles may be diluted to the point of statistical insignificance or even bidirectionally cancel out. In addition, it is important to check for three-way interactions among environment, sex, and genotype. The sex differences relevant to depression and related conditions may be obscured by compensatory mechanisms in healthy individuals, given that sexual dimorphisms in the brain may in fact exist to prevent rather than cause sexually dimorphic behavior in the healthy brain (De Vries 2004). It is possible that some sex differences emerge only in the context of pathology, such as in the case of early-life stress modulation of gene–sex interactions. Therefore, researchers must be careful in extrapolating sex differences or lack thereof in healthy individuals to patients.

Future studies of gene–sex differences may move beyond understanding the basis of genetic risk toward understanding the pathogenic mechanism of disease. Studies that consider multiple time points and longitudinal trajectories rather than cross-sectional grouping of participants are required to elucidate the role of sex differences and genetic risk in causal pathways for depression and emotional disorder. Such studies might incorporate intermediate measures such as subclinical manifestations of depression, stress response dysregulation, and personality traits to elucidate the mechanisms by which risk converts to overt psychopathology. Studies on groups of individuals who are biologically homogenous rather than symptomatically homogenous may help to isolate the distinct mechanisms of depression pathogenesis that create epidemiological differences between the sexes. Studies that cross traditional diagnostic boundaries may better capture the full range of behavioral output in men and women and better elucidate how sex differences in behavior and psychopathology emerge from similar underlying biology.

Finally, because the ultimate goal of research on depression is to treat individuals, it is vital to extend these considerations of gene–sex interactions to the domain of treatment. Given that men and women exhibit different pathways to pathology, it is reasonable to expect different pathways to recovery. Research has supported the existence of gender differences in the response to pharmacological treatment (Gorman, 2006). Understanding the different mechanisms that contribute to psychopathology in men and women is essential for developing and targeting personalized interventions.

Although it is premature to define generalizable rules about these interactions or even to draw strong conclusions about the examples discussed, we may in the interim outline some central considerations that emerge from reviewing our current state of knowledge. We note that 1) there is a paucity of information on the impact of sex and gene interactions; 2) evidence from limited studies do support the idea that there are sex and gene interactions with clinically relevant outcomes; 3) these differences might be potentiated by environmental stressors; 4) these gene–sex and gene–sex–environment interactions must be tested explicitly; 5) adopting more nuanced conceptions of genetic risk, diagnostic categories, and sex itself will help to clarify these interactions; and 6) additional research using these methodological recommendations is essential for understanding underlying mechanisms. Although by necessity this Mini-Review has focused on depression and sex differences on the serotonergic system, we hope that it will facilitate a broader consideration of the topic because there are likely many more differences between sexes that are relevant for understanding the trajectory of mental disorders.

CONFLICT OF INTEREST STATEMENT

LMW has received consultant fees from Humana for projects not related to this work. LMP and AG-P have no conflicts of interest to declare. None of the authors has a conflict of interest related to this work.

ROLE OF AUTHORS

LMP conceived the scope of this Mini-Review. ANG-P and LMW developed the intellectual content with LMP. All authors wrote the Mini-Review.

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