Approches transcriptionelles dans des modèles animaux de stress et de dépression majeure

Thèse

Mena Fatma

Doctorat en médecine moléculaire
Philosophiæ doctor (Ph. D.)

Québec, Canada

Approches transcriptionelles dans des modèles animaux de stress et de dépression majeure

Thèse

Mena Fatma

Sous la direction de :

Dr. Benoit Labonté, directeur ou directrice de recherche

Résumé

La dépression majeure (DM) est la principale cause d'invalidité depuis trois décennies, avec plus de 300 millions de personnes touchées dans le monde. En effet, elle contribue largement à la charge économique mondiale globale des maladies. Malgré son impact sociétal important, les mécanismes biologiques de la dépression restent mal compris. Malheureusement, seuls 30 % environ des patients traités pour la dépression présentent une amélioration complète de leurs symptômes. Étant donné le taux d'échec élevé des essais cliniques d'antidépresseurs, récemment, un examen plus minutieux de leur utilisation a eu lieu, notamment pour investiguer la neurobiologie de la dépression et dans le design de potentiels traitements. Étant donné que la plupart de nos connaissances dans ce domaine proviennent de modèles animaux, ces modèles reproduisent en effet certains aspects de la DM humaine, mais on ne sait pas dans quelle mesure. Ce travail a pour but d'élucider dans quelle mesure ils récapitulent la pathologie moléculaire du trouble humain.

Dans cette thèse, nous nous sommes appuyés sur des analyses de réseaux d'expression différentielle et de co-expression pour cataloguer le chevauchement entre la DM humaine et 3 modèles murins de stress, à savoir le stress variable chronique, l'isolement social et le stress par défaite sociale chronique, et avons évalué leur capacité à reproduire les profils transcriptionnels associés à la DM humaine dans deux régions du cerveau, le mPFC et le NAc, largement impliquées dans la dépression. Nos résultats montrent que chaque modèle reproduit efficacement les caractéristiques transcriptionnelles communes mais aussi uniques du syndrome humain.

Dans l'ensemble, en identifiant des groupes de gènes fortement co-exprimés, partagés entre l'homme et la souris, nos résultats suggèrent que ces signatures transcriptionnelles sont impliquées de manière similaire dans le contrôle des voies fonctionnelles chez les deux espèces et confèrent un fort soutien à l'utilisation de ces modèles de souris pour l'étude des altérations moléculaires observées dans la DM tout en fournissant des implications importantes pour la recherche future et les applications cliniques.

Abstract

Major depressive disorder (MDD) is the leading cause of disability for three decades with over 300 million affected worldwide. Indeed, it is a major contributor to the overall global economic burden of disease. Despite its significant societal impact, the biological mechanisms of depression remain poorly understood. Unfortunately, only around 30% of patients treated for depression show complete improvement in their symptoms. Given, the high failure rate of antidepressant clinical trials, there has been increased scrutiny recently regarding their use for deciphering the neurobiology of depression and to design potential treatment interventions. Given the fact that most of our knowledge of the field comes from animal models, indeed, these models reproduce some aspects of human MDD but to what degree remains unknown. This work elucidates the extent to which they recapitulate the molecular pathology of the human disorder.

In this thesis, we leveraged differential expression and co-expression network analyses to catalogue the overlap between human MDD and 3 mouse model of stress, namely chronic variable stress, social isolation and chronic social defeat stress, and evaluated their capacity of reproducing the transcriptional profiles associated with human MDD in two brain regions, mPFC and NAc, widely implicated in depression. Our results show that each model efficiently reproduces common but also unique transcriptional features of the human syndrome.

Overall, by identifying strongly co-expressed groups of genes shared between humans and mice, our results suggest that these transcriptional signatures are similarly involved in the control of functional pathways in both species and confer strong support for the use of these mouse models for the study of the molecular alterations seen in MDD while providing important implications for future research and clinical applications.

Table des matières

Liste des figures, tableaux, illustrations

FIGURES

Introduction

Chapter-1

TABLES

Introduction

Chapter-1

BOX

Introduction

Liste des abréviations, sigles, acronymes

ABBREVIATIONS:

MDD, Major depressive Disorder

CSDS, chronic social defeat stress;

CVS, chronic variable Stess

SI, Adult Social Isolation

FET, Fisher's exact test;

mPFC, medial prefrontal cortex;

NAc, accumbens;

RRHO, rank–rank hypergeometric overlap; SI, isolation;

Susc, susceptible.

n.s.: non-significant

BA, Brodmann area;

DEG, differentially expressed gene;

Non-memb., non-membrane;

funct., function;

H, human;

Intracell., intracellular;

localiz., localization;

OR, odds ratio;

proc., process;

rc, receptor;

Res, resilient;

Memb., membrane;

Reg., regulation;

NA, no available information;

RIN, RNA integrity number;

PVN Paraventricular nucleus,

CRH, Corticotropin-releasing hormone,

AVP, Arginine-vasopressin,

OXT, oxytocin,

FKBP5, FK506 binding protein 51,

GR1, glucocorticoid receptor 1,

CRH-R, Corticotropin-releasing hormone receptor,

AVP-R, Arginine-vasopressin receptor

POMC, pro-opiomelanocortin,

ACTH, adrenocorticotropic hormone,

MC2R, Melanocortin-2,

ACTHR adrenocorticotropic hormone receptor.

In the memory of my younger brother, Zaid.

Remerciements

This thesis would not have been possible without the support of many people to whom I am eternally grateful. First and foremost, I would like to thank my supervisor, Dr. Benoit Labonté, for his support and guidance over the past three years. It was not possible without your mentorship. I am grateful for all the encouragement, criticism and feedback you have given me. Its just not professionally but you help shape me personally too. Thank you for everything.

I am very grateful to my committee members. I am very grateful for the insightful conversations and discussions we had over the course of my PhD. Caroline your support was inevitable. Jasna thanks for your guidance and for the great conversations at lunch. A special thanks to Prof. Etienne Sibille for taking the time to evaluate my thesis and for his valuable comments.

I would also like to make a special mention of our collaborator Eric J. Nestler and his lab members who were involved in this project, J. Scarpa and Eddie Loh. Thank you for providing everything that made this team effort a great success.

I would like to thank my lab mates, Thibault Bittar, stupid Francis Quessy, Andrée-Anne Lavigne, Eric Arsenault, Samaneh Mansouri, Daniel Gomis, Theo Stefan and Said Romaric. You guys make a wonderful team and working with you was more fun than I ever expected. Thank you all.

I would love to mention my strongest support, my friends, esp. Katarzyna Dudek, Mari Carmen Pelaez, Fernanda Kaufmann, Noopur Singh, Ashfia, Insiya, Banshi Nath among the others. I would also like to thank Manon Lebel for her utmost love and guidance. It was not at all possible without you all. I could not have asked for better friends to share this journey of mine with.

I would also like to thank my masters' mentor. He has guided and inspired me to pursue science.

I would be thoughtless if I didn't mention my family, who have been an essential part of my journey all through. My parents, Nafees and Takallum, and siblings, Mahar, Sidra, Zaid and Kaleem, provided endless love, support, and encouragement these years. My parents instilled in me the dedication and work ethic that allowed me to persevere throughout my academic career. They always encouraged and supported me to pursue PhD. Mummy and Abbu this is for you and because of you. My sister, Mahar, has been an awesome role model both professionally and personally. During this PhD I lost my brother, a special friend, Zaid Ahsan, he in his own way pushed me to do better in academia. I miss you so much, I wish you were here with me. I am also very thankful for my in-laws, who have always been incredibly supportive and encouraging. My cousin cum friend, Neda Jafri, has always been there for me, I am very grateful for being the best listener and absorbing all my negativity.

Lastly, I would like to thank my husband Faiz and daughter Nyrah. Faiz has always encouraged me in all my endeavours and supported me with all his might when I said I wanted to pursue Ph.D. in Quebec, although it was very hard. All these years living away from him was the hardest part of this PhD. I cannot thank him enough for all the love, support, and tolerance he has given me. Long distance relationship was a challenge but he made sure I didn't feel alone. I am particularly thankful for how he can always get me to smile no matter how challenging and stressful the day was. Nyrah, has reminded me to enjoy and appreciate the little things. She has made me much happier than I ever thought possible especially after Zaid. She has pushed me to work even harder. She has provided me with a renewed sense of purpose, commitment and motivation. Her smile and her laughter made me give up worries and stress and charges me with all the positive energies.

Avant-propos

This thesis is a part of the final step of the doctoral program in Molecular Medicine at Université Laval. All the work presented here was done under the supervision of my thesis director, Dr. Benoit Labonté, in the CERVO Brain Research Center. During my PhD, I published two articles, one as first author and the other as fifth author in a collaboration. I also published a first author review with my supervisor.

The thesis organised into the following main sections-

Introduction: giving an overview of Major Depressive Disorder (MDD) with clinical perspectives and a summary of the brain regions, animal models and tools used for transcriptomic analysis is provided, along with a literature review of the transcriptional dysregulation in human MDD and animal models of stress highlighting the need for a more comprehensive comparison of molecular interactions involved in depression. It includes some sections from my first author review along with Benoit Labonte, "Molecular programs underlying differences in the expression of mood disorders in males and females" published in 'Brain Research' in 2019. The introduction contains a table and a box whose content has been taken from chapter 6 on 'Depressive Illness' in the book 'Oxford Handbook of Psychiatry'. The introduction ends with the hypothesis.

Chapter 1: includes my 1st author article, published in 'Biological Psychiatry' in 2020 titled, 'Shared Transcriptional Signatures in Major Depressive Disorder and Mouse Chronic Stress Models'. In this article, we systematically compared transcriptional signatures, in two brain regions, of human MDD and of 3 chronic stress models in mice, CVS, CSDS and SI using advanced bioinformatics tools and assessed how each stress paradigm recapitulate the molecular organization of human MDD. In this article, I am one of the first authors. besides Scarpa JR, Loh YHE. Other authors include Thraore SR, Stefan T, Chen TH, Nestler EJ and Labonté B. I along with Scarpa JR, Loh YHE, Nestler EJ and Labonté B conceived the project, designed the experiments, and wrote the manuscript. I, Scarpa JR, Loh YHE, Thraore SR, Stefan T, Chen TH, Nestler EJ and Labonté B, generated and analyzed all the data and prepared the manuscript. I, Scarpa JR and Loh YHE contributed equally to the preparation of the article.

Conclusion: The article is followed by a conclusion.

General discussion: This thesis ends with a detailed general discussion.

Introduction

Major depressive disorder (MDD) is one of the most prevalent conditions and the leading cause of disability affecting 300 million people worldwide. This alone imposes a major socio-economic burden on the societies (WHO, 2017). Despite its profound societal impact, our capacity to treat the disease is still unsatisfyingly limited. In fact, roughly 30% of the patients respond, 32% show variable levels of improvements and 38% of the patients do not respond to available therapeutic options at all (Knoth, Bolge, Kim, & Tran, 2010; Thase & Schwartz, 2015). These concerning facts underscore the need for a better understanding of the molecular and functional mechanisms of the disease (Mena & Benoit, 2019b).

The clinical manifestations of MDD can be roughly defined by depressed mood, loss of interest and enjoyment (anhedonia) and reduced drive that lead to decreased social activity. There are two main diagnostic classification guides for MDD - the International Classification of Diseases (ICD-10) and the Fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The ICD-10 is the World Health Organization (WHO) classification and is the internationally used diagnostic classification for all classify all health disorders. The DSM-V (Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders) is a classifier for psychiatric disorders, mostly used in the United States, published by American Psychiatric Association (APA). Their diagnostic criteria of MDD are similar with slight differences. Other screening tools include Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD7) and Beck Depression Inventory-II (BDI-II). Table 1 represents the diagnostic criteria of DSM-V and ICD-10. Refer to box-1 for diagnostic symptoms adapted from (David Semple & Smyth, 2019).

Classification	ICD-10	DSM-5
MILD	2 typical symptoms + 2 other core symptoms	5 core symptoms + manageable distress + minor social/occupational impairment.
MODERATE	2 typical symptoms + 3+ other core symptoms	5+ core symptoms + variable degree of social/occupational impairment
SEVERE	3 typical symptoms + 4+ other core symptoms	5+ core symptoms + significant social/occupational impairment

Table1: Showing the MDD diagnostic criteria *used by the International Classification of Diseases (ICD-10) and the Fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) In the new ICD-11, severity is more qualitative, for example, 'MILD' is when none of the symptoms of a depressive episode are intense, there is some, but not considerable, difficulty in continuing normal activities, and no delusions or hallucinations. 'MODERATE' is when several symptoms of a depressive episode are present to a marked degree or a large number of depressive symptoms of lesser severity are present overall and there is considerable difficulty in continuing with normal activities, but the individual is still able to function in at least some areas. 'SEVERE' is when many or most symptoms of a depressive episode are present to a marked degree or a smaller number of symptoms are present and manifest to an intense degree and the individual is unable to function, except to a very limited degree [adapted from (David Semple & Smyth, 2019)].*

BOX-1- Diagnostic symptoms

MDD DIAGNOSIS

For MDD diagnosis, symptoms should be present for at least 2 weeks and present a change from normal, should not be secondary to the effects of drugs/alcohol misuse, medication, a medical disorder or bereavement and may cause significant distress and/ or impairment of social, occupational, or general functioning.

CORE SYMPTOMS

- Depressed mood
- Anhedonia
- Weight change: loss of weight when not dieting or gain of weight, associated with ↑ or↓ in appetite
- Disturbed sleep: insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Reduced libido
- Feeling of worthlessness or excessive or inappropriate guilt (which may be delusional)
- Diminished ability to think or concentrate or indecisiveness.
- Recurrent thoughts of death and suicide

SOMATIC SYMPTOMS

- Loss of emotional reactivity
- Diurnal mood variation
- Anhedonia
- EMV
- Psychomotor agitation or retardation
- Loss of appetite and weight
- Loss of libido

PSYCHOTIC SYMPTOMS

- Mood congruent: Delusions
- Hallucinations

- Mood incongruent:
- Persecutory delusions
- Thoughts insertion/withdrawal
- Delusions of control

OTHERS SYMPTOMS

- Significant anxious distress
- Catatonic symptoms
- Marked psychomotor retardation (depressive stupor)

Sex differences in depression

Importantly, MDD has been estimated to be 2-3 times more prevalent in females compared to males(Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Clinically speaking, studies report females to exhibit higher scores of depression, younger age of onset, higher number of depressive episode and relapse rate(Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Kornstein, Schatzberg, Thase, Yonkers, McCullough, Keitner, Gelenberg, Ryan, et al., 2000). Females have also been shown to exhibit higher rates of comorbid anxiety, non-lethal suicidal attempts, atypical symptoms and feelings of sadness, worthlessness, and excessive guilt(Altemus, Sarvaiya, & Neill Epperson, 2014; McCarter, 2008; Unick, Snowden, & Hastings, 2009), while males more often exhibit comorbid substance abuse including alcohol and drugs, fatigue, mood irritability, loss of interest in once-pleasurable activities, sleeping difficulties and lethal suicidal attempts and completion (Marcus et al., 2008; McCarter, 2008). This sexual dimorphism is also observed at the treatment level for which, males tend to respond better to tricyclic antidepressant drugs (TCA) and females to selective serotonin reuptake inhibitors (SSRI)(Khan, Brodhead, Schwartz, Kolts, & Brown, 2005; Kornstein, Schatzberg, Thase, Yonkers, McCullough, Keitner, Gelenberg, Davis, et al., 2000; LeGates, Kvarta, & Thompson, 2019), although these findings have been contested before (Keers & Aitchison, 2010; Quitkin et al., 2002; Stewart, McGrath, & Quitkin, 2002; Terranova et al., 2016) (Mena & Benoit, 2019a).

Sex differences in MDD is expressed at various biological parameters. For instance, free triiodothyronine (T3) hormone is higher in depressed men than depressed women(Berent, Zboralski, Orzechowska, & Galecki, 2014). Leptin is reported to be higher and adiponectin levels to be lower in depressed females whereas no differences

were found in males (Birur, Amrock, Shelton, & Li, 2017). Men with hypogonadism and men treated with androgen-depleting drugs (for prostate cancer), show a higher risk of developing MDD. C-reactive protein (CRP) levels are correlated with the severity of symptoms in woman (Labaka, Goni-Balentziaga, Lebena, & Perez-Tejada, 2018). Also, higher levels of interleukin (IL)-8, IL-6 and interferon-γ and lower levels of IL-5 were observed in depressed women whereas no differences in any inflammation markers were found in males (Labaka et al., 2018). Sexual dimorphism in MDD is also seen in adult neurogenesis (Lyons et al., 2010);(Schoenfeld & Gould, 2012), gut microbiome-brain axis (Jasarevic, Morrison, & Bale, 2016), sleep (Mallampalli & Carter, 2014), circadian rhythms (Yan & Silver, 2016), metabolic and cardiovascular health (Murphy & Loria, 2017), etc. It is beyond the scope of this manuscript to discuss these findings in length (Mena & Benoit, 2019a).

While the sexual dimorphism defining the phenotypic and clinical features of MDD is well accepted, the molecular mechanisms underlying these differences remain much less understood. Until recently, most of the studies investigating the molecular mechanisms of depression and stress were mainly conducted in males avoiding the consideration of sex as a factor of variability. This being said, recent studies are now reporting major sex differences in the molecular and functional alterations associated with MDD and stress in different animal models of depression (Hodes et al., 2015; C. Jiang et al., 2018; Labonte et al., 2017a; Seney et al., 2018). These studies are reporting sex-specific genome-wide and gene-specific epigenetic alterations impacting gene expression and downstream intracellular molecular cascades, ultimately interfering with the activity of several systems involved in stress and emotional regulations (Mena & Benoit, 2019a).

Brain regions associated with depression

Functional and brain imaging studies in MDD have identified alterations in several intertwined brain regions including prefrontal cortex (PFC), insula, dorsal striatum, nucleus accumbens (NAc), hippocampus, amygdala, ventral tegmental area (VTA), raphe nucleus, bed nucleus of the stria terminalis (BNST), locus coeruleus (LC), hypothalmus, lateral habenula (LHb) and periaqueductal gray (PAG) (Ming-HuHan, J.Russo, & J.Nestler, 2019; Muir, Lopez, & Bagot, 2018; Pandya, Altinay, Malone, & Anand, 2012; Russo & Nestler, 2013; Savitz & Drevets, 2009). Figure 1. represents different neuronal circuits implicated in depression. For instance, reduction in the activity of different regions of the PFC(Kimbrell et al., 2002; Koenigs & Grafman, 2009; Rigucci, Serafini, Pompili, Kotzalidis, & Tatarelli, 2010), anterior cingulate cortex(Drevets et al., 1997; Heshmati & Russo, 2015; Mayberg et al., 1999), LC(J. M. Weiss et al., 1994), raphe nucleus(Gos et al., 2008; Teissier et al., 2015), dorsal striatum and NAc(Gabbay et al., 2013; Heshmati & Russo, 2015) and hyperactivity in hypothalamus (F. Chen, Zhou, Bai, Zhou, & Chen, 2015), hippocampus(Campbell & Macqueen, 2004; MacQueen & Frodl, 2011), amygdala(A. Anand et al., 2005; Sheline et al., 2001), LHb(Yang, Wang, Hu, & Hu, 2018), VTA (Heshmati & Russo, 2015;

Polter & Kauer, 2014), insula and BNST(Alvarez et al., 2015) has been repeatedly cited in depression. Additionally, robust optogenetic evidences are supporting the contribution of specific neuronal circuits in mediating the expression of depressive-like behaviors in several animal models (Krishnan & Nestler, 2008). Brain regions and neuronal circuitries implicated in depression and depressive-like behaviors are depicted in Figure 1 (Mena & Benoit, 2019a).

Contrary to structural evidences, functional magnetic resonance imaging (fMRI) and positron-emission tomography (PET) studies show that transient dysphoria strongly associates with the neuronal activity of amygdala and subgenual cingulate cortex (Cg25, a subregion of prefrontal cortex). Chronic increase in the activity within these region has been observed in depressed individuals, which return back to normal levels with successful treatment (Krishnan & Nestler, 2008). Interestingly, treatment resistant-depression have shown sustained remission through deep brain stimulation of mPFC. Similar results were obtained with deep brain stimulation of NAc.(Schlaepfer et al., 2008). NAc plays a critical role in reward circuitry and has been extensively studied in animal models of chronic stress and depression (Nestler, 2015). Indeed, mPFC and NAc are very well intertwined with NAc being a major target of mPFC efferent projections (Krishnan & Nestler, 2008). In fact, NAc is reported to be involved in goal-directed and reward seeking behaviors, integrating information from limbic and cortical structures and projecting to basal ganglia nuclei (Knowland & Lim, 2018). On the other hand, mPFC acts as a central hub, receiving input from cortical, thalamic, and limbic regions and sends outputs to structures that directly regulate stress responses (Hare & Duman, 2020).

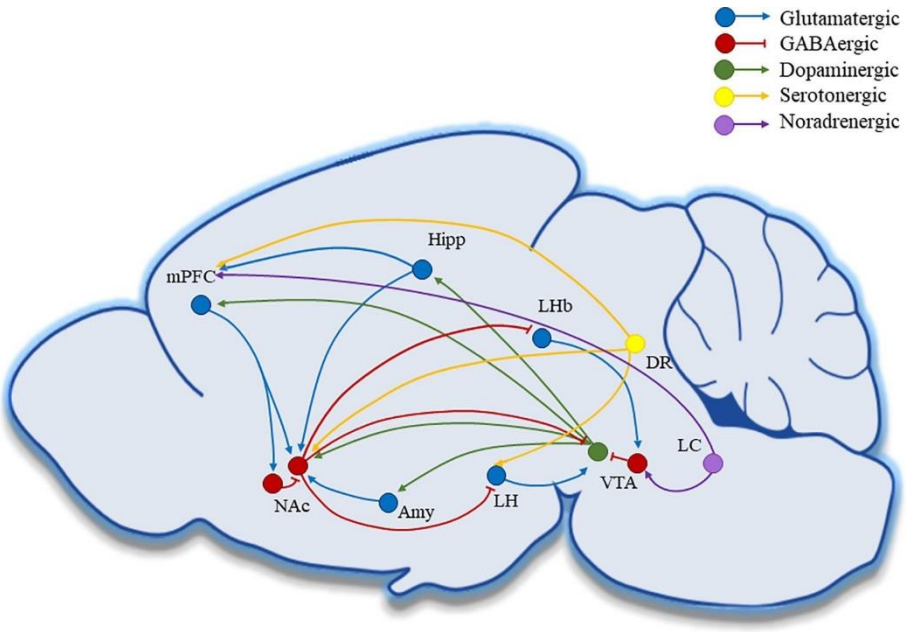


Fig. 1. Schematic representation of different neuronal circuits implicated in depression showing nucleus

accumbens (NAc), medial prefrontal cortex (mPFC), hippocampus (Hipp), amygdala (Amy), ventral tegmental area (VTA), lateral habenula (LHb), lateral hypothalamus (LH), dorsal raphe (DR) and locus-coeruleus (LC)

Animal models

Modelling mood disorders in animals is a challenging task. The subjective nature of the disorders, heterogeneity of etiopathophysiology and lack of insights into the driving mechanisms limits design of a perfect model of depression. Evaluation of animal models is generally based on criteria- face validity (phenotypic similarity or symptoms/behavior/anatomical/biochemical similarity to human patients), construct validity (how well the mechanism, being modelled, depicts the human pathology) and predictive or pharmacological validity (predict the potential of the pharmacological and non-pharmacological treatments in humans) (Belzung & Lemoine, 2011; McKinney, 2001; Nestler & Hyman, 2010; Willner, 1984, 1997). No animal model has yet been developed which can perfectly recapitulate the depression-like phenotype. Nonetheless, stress is a strong precipitating factor of major depressive disorder (MDD). In fact, most of studies in the field relied on stress based models of depression as there is a lack of a true MDD genetic model. The reason being the lack of highly penetrant genetic variants in MDD (Menard, Hodes, & Russo, 2016). Some of the major symptoms of depression like helplessness, anhedonia, behavioral despair as well as alterations in sleep and appetite patterns are recapitulated by certain animal models of depression (Demin et al., 2019; Mena & Benoit, 2019a). The next sections will describe some of the established rodent models used in the field.

Early-life stress (ELS)

Early life stress has been shown to alter individual's ability to react and cope with subsequent stressful events in later life (Krishnan & Nestler, 2011). Familial dysfunction, including consistent parental neglect, family conflict, inappropriate conditioning, physical or sexual abuse and compromised parent-child relationships, in early years, can have adverse effects on cognitive and emotional processing and can potentially increase the risk for depression and anxiety disorders (Anacker, O'Donnell, & Meaney, 2014). In fact, there is a strong body of evidence indicating early life as a critical developmental period where the risk for susceptibility or resilience to psychiatric later in life is shaped (Afifi et al., 2008; ANGELA CATHERINE BUSTAMANTE, 2017; Espejo et al., 2007; Kendler, Kuhn, & Prescott, 2004). In fact, early stress could establish the groundwork for later depression. This is an important aspect of depression modelled as ELS in animals.

Early life stress, classically enforced as maternal separation during early postnatal developmental periods, Separated pups are more submissive and generally seek a more passive coping strategy in response to stress throughout life (Menard et al., 2016). Indeed, separation from the mother, a powerful stressor for the developing rodent. Therefore, it's use as an acute or recurrent stressor is considered more plausible by some groups(Rice,

Sandman, Lenjavi, & Baram, 2008) than chronic paradigms because of the resultant compromise in the health of the pups. Variants of this model entail fragmented/impaired maternal care, by maternal distress through reduction of the amount of nesting material available to the dam (Brunson et al., 2005; Rice et al., 2008) hence, broadening the scope of the human conditioning. Extreme version of this model has also been employed, in which the dams are housed in a wire mesh floored cage with no bedding, while variations involve just limiting nesting material (Murthy & Gould, 2018; Walker et al., 2017), which results in an increase in maternal anxiety and fractured care where behavior toward the pups might be interpreted as abuse (Murthy & Gould, 2018; Rice et al., 2008). Furthermore, the "two-hit" models are also used in which maternal separation is followed by additional stress, either shortly thereafter or in adulthood (Pena et al., 2017; Pena et al., 2019). The first stressful strike creates an internal vulnerability that alone might be insufficient to create behavioral manifestation by itself, but when aggravated by subsequent stress, produces detectable behavioral changes (Murthy & Gould, 2018). Although, the association between early life stress and depressive behavior in adulthood is complex. Specific early developmental time window has been shown to be important for susceptibility to stress (Pena et al., 2017; Pena et al., 2019).

The MS model directly damages the responsiveness of the HPA axis (Ellenbroek, van den Kroonenberg, & Cools, 1998; Enthoven, Oitzl, Koning, van der Mark, & de Kloet, 2008; Levine, 2005; Lyons, Kim, Schatzberg, & Levine, 1998; Nishi, Horii-Hayashi, Sasagawa, & Matsunaga, 2013; Pryce et al., 2005). In fact, the HPA axis and stress responsiveness is relatively low during early postnatal life however, it is much more pronounced in later life (Levine, 2005; Walker, Scribner, Cascio, & Dallman, 1991). Interestingly, short time early-life stress, e.g. mimicking the situation where mother leaves her pups to find foods, is perceived as beneficial adaptations to stress (Levine, 2005; Nishi, Horii-Hayashi, & Sasagawa, 2014; Plotsky et al., 2005). Early life stress alters transcriptomic landscapes across reward circuitry in male and female mice, but recruits sex-specific transcriptional regulatory pathways (Pena et al., 2019). Importantly, in models of separation, deprivation, handling, and bedding manipulation, females may experience a greater intensity of abuse while males receive higher levels of maternal contact (Bath, 2020). However, the specific type, duration and timing of experiences may be critical for increasing the risk of developing specific subsets of symptoms within the broader classification of a given pathology, as well as sex differences in symptom development or presentation (Bath, 2020).

Chronic social defeat stress

One of the most widely used mouse models of depression is the chronic social defeat paradigm (Golden, Covington, Berton, & Russo, 2011; Krishnan & Nestler, 2011). It mimics an important aspect of human depression taking into account the context of bullying and excessive competitive behaviors in a social environment. Victims of bullying show significant mood dysfunction and are more than twice as likely to attempt

suicide later in life. On the other hand, excessive competitive behaviors in a social setting increase overall vulnerability to stress leading to depression-like symptoms (Menard et al., 2016).

In this model, mice are subjected to repeated bouts of social and physical subordination followed by separation of the mice by a perforated divider which allows for continued sensory, but not physical, contact resulting in the expression of stress susceptible or resilience (resistant) phenotype (Golden et al., 2011; Krishnan & Nestler, 2011; Russo & Nestler, 2013). As a matter of fact, humans exhibit profound individual differences in the response to stress. In some people, a variety of behavioral alterations are induced as a result of stress, while for most people, the same stressor doesn't cause any obvious effect. Therefore, only a subset of those exposed to chronic stress will exhibit clinical symptoms (susceptible) and most individuals will not develop behavioral abnormalities despite exposure to severe stress (resilient) (Feder, Nestler, & Charney, 2009; Russo, Murrough, Han, Charney, & Nestler, 2012). This variability comes from a complex blend of multiple interrelated elements including underlying genetic makeup (consortium, 2015; Hyde et al., 2016) altered signaling in the hypothalamic-pituitary-adrenal (HPA) stress axis (Herman & Cullinan, 1997; Reul et al., 2015), variable immune reactivity (Hodes et al., 2014; Menard et al., 2017) and psychobiological factors (Charney, 2004; Feder et al., 2009; Zachary Spencer Lorsch, 2018). As stress in life is unavoidable, understanding what makes an individual susceptible and the other stress resilient is very important. In fact, CSDS is the only model that exhibit both these phenotypes. This makes this model very attractive to understand and treat MDD better.

Susceptible animals show depressive-like traits (social withdrawal and anhedonia), anxiety-like behaviors and certain features of a metabolic syndrome (weight gain, insulin and leptin resistance), many of which are reversed by chronic but not acute antidepressant administration (Golden et al., 2011), while resilient mice show anxiety but no depressive-like behaviors (Becker et al., 2008; Berton, Hahn, & Thase, 2012; Golden et al., 2011; Krishnan & Nestler, 2011; Rygula et al., 2005). While this paradigm has been mainly used in males, recent findings show that it can also be used to reproduce depressive–like behaviors in females as well (Harris et al., 2018; Mena & Benoit, 2019a; Takahashi et al., 2017). Like human MDD, CSDS has been utilized to successfully induce wide-ranging transcriptional changes in the brain (Berton et al., 2006; Krishnan et al., 2007; Vialou et al., 2010) some of which correspond to those observed in human MDD patients (Dias et al., 2014; Krishnan et al., 2007);

Chronic mild stress (CMS) / chronic unpredictable stress (CUS) / chronic unpredictable mild stress (CUMS or UCMS) / chronic variable stress (CVS)

Chronic unpredictable mild (CUMS) and variable (CVS) stress models are also widely used to study depressive-like behaviors (Hodes et al., 2015; Katz, 1982; Labonte et al., 2017a; LaPlant et al., 2009; Willner, Muscat, & Papp, 1992). It is based on the idea that low level chronic and unpredictable stressors, similar to the stress

experienced in everyday life in humans, induce depressive behavior in susceptible individuals (Menard et al., 2016).

UCMS/CMS involves continuous (6-8 weeks) unpredictable exposure of stressful stimulus including restraint, tail suspension, disruption of the light/dark cycle, cage tilt, food or water restriction, changing of cage mates, temperature reductions, and foot-shocks (Russo & Nestler, 2013), whereas CVS involves daily exposure to physical stressors such as mild foot shocks, tail suspension and restraint for 3 weeks (Monteiro et al., 2015; Willner, 2017). These stress paradigms **induce anxiety, despair and anhedonia-like phenotypes** (Golden et al., 2011; Menard et al., 2016) **along with reduced sex drive, increased aggression and altered sleep patterns** (Menard et al., 2016). Most of the behavioral alterations are reversed by chronic, but not acute, treatments with antidepressants. It is also able to mimic neuroendocrine aspect of stress (Menard et al., 2016). Interestingly, both males and females are susceptible to CVS. Additionally, the subchronic version of CVS, (sCVS), consisting in exposing mice to six days of stress rather than 21 days is sufficient to induce a depressive-like phenotype in females but not males, mimicking variations in stress susceptibility between males and females (Hodes et al., 2015; Mena & Benoit, 2019a).

Social Isolation

Owing to its relevance to human depression and anxiety disorders, social isolation (SI) has been modelled in animals too (A.M.Hatch et al., 2009; Costello & Kendrick, 2000; Heinrich & Gullone, 2006; Wallace et al., 2009). Indeed, grief and partner loss in later life is relevant to depression especially in the elderly (Costello & Kendrick, 2000) along with significant association between social skills, levels of self-esteem and depression in adolescent substance abusers (Ammerman, Hersen, van Hasselt, Lubetsky, & Sieck, 1994; Menard et al., 2016). The association of loneliness with depression remains stable across the lifespan, although its prevalence differs with age (Matthews et al., 2016). In fact, rodents are also social animals by nature with various studies conducted with social isolation used to mimic loneliness in them. In a socially monogamous rodent model, prairie voles, partner loss or chronic social isolation induces depression-like behaviors, notably anhedonia, with females being more sensitive to isolation (Grippo et al., 2007; Menard et al., 2016). Moreover, anxiety- and anhedonia-like symptoms of social isolation in adults can be reversed by chronic, but not acute, antidepressant treatment (Wallace et al., 2009) underscoring the significance of this model to study depression and antidepressant responses (Menard et al., 2016).

SI could have a variety of molecular and behavioral consequences depending on the age of implementation(Hall, 1998). SI paradigms include isolation interventions of 2-10 weeks at either pre-weaning/neonatal or post-weaning/adolescent or adult stage (Lander, Linder-Shacham, & Gaisler-Salomon, 2017; Y. Liu, Lv, Wang, & Zhong, 2018; Makinodan, Rosen, Ito, & Corfas, 2012; Wallace et al., 2009; I. C. Weiss, Pryce, Jongen-Relo,

Nanz-Bahr, & Feldon, 2004; K. H. Wong, Jin, & Moqtaderi, 2013). It has been shown to induce anxiety-like behavior(Barrot et al., 2005; Lander et al., 2017), perturbation of HPA axis (Barrot et al., 2005; Butler, Ariwodola, & Weiner, 2014; Deroche, Piazza, Le Moal, & Simon, 1994; I. C. Weiss, Domeney, Heidbreder, Moreau, & Feldon, 2001) and reward responses (Ahmed, Stinus, Le Moal, & Cador, 1995; Barrot et al., 2005; Deroche et al., 1994) in the isolated rodents. Male and female animals exhibit different biological responses to SI (Abramov et al., 2004; Guo, Wu, Liu, Yang, & Chen, 2004; Pietropaolo, Singer, Feldon, & Yee, 2008; I. C. Weiss et al., 2001; I. C. Weiss et al., 2004).

Genetic models of depression

Some genetic models have also been used in the field, though they are not true genetic models of depression(Menard et al., 2016). For example, the Flinders Sensitive Line (FSL) rat genetic model of depression, shows abnormality in serotonergic, cholinergic and melatonin systems, displaying some similarities with depressed human like elevated rapid eye movement (REM) sleep, inhibitory behavior following stress, increased immobility in the forced swim test, etc. but it lacks one of the major symptoms of depression anhedonia(Overstreet & Wegener, 2013). Another genetic model Wistar Kyoto (WKY) rat is a control rat bred in parallel to the spontaneously hypertensive rat which exhibits both anxiety-like and depression-like behavior and elevated REM sleep (Overstreet & Wegener, 2013).

Statistical tools used in RNA-seq

RNA-Seq has emerged as a revolutionary new technology that allows RNA profiling using next-generation sequencing to provide a sensitive, quantitative measurement of gene expression. NGS provides higher resolution as well as higher precision in measuring the levels of transcripts for studying gene expression as compared with microarray technologies (T. Wang, Li, Nelson, & Nabavi, 2019). The data generated with this molecular tool is highly rich in information and potent enough to help uncover many aspects of the biological system of interest. Concurrently, as the dimensionality of available data increases, its scope become increasingly complex and require tailored statistical approaches to effectively address the question asked. There are different approaches used in the field. Some of them are discussed below:

Differential Expression Analysis

Standard differential expression analysis (differential variability), examines variance in different conditions, to determine whether a gene is upregulated or downregulated in one condition compared to another condition (Ho, Stefani, dos Remedios, & Charleston, 2008). There are a variety of tools are available for differential expression analysis. The two basic approaches of all DEGs tools are: to find differential expression between the different

conditions based on read counts from replicates, which involves calculation of the fold change of read counts while considering variations in sequencing depth and other variables and to assess the significance of the difference and apply multiple testing corrections (Sun, 2019).

Indeed, a variety of tools are available for differential expression analysis like limma- voom, edgeR, DESeq, baySeq, EBSeq, maSigPro, etc. The choice of tool depends on the experimental design. They work on statistically different algorithms. For instance, edgeR and DESeq are based on negative binomial (NB) distributions (Ren & Kuan, 2020) on other the hand baySeq and EBSeq are Bayesian approaches based on a negative binomial model (Li., 2019 Nov 21.). The choice of tool depends on the experimental design. For example, for pair-wise comparisons - EBSeq (Wesolowski, Birtwistle, & Rempala, 2013), baySeq (Hardcastle & Kelly, 2010), etc. are used, on the other hand for multiple comparisons edgeR, limma-voom, DESeq, maSigPro are used (Conesa et al., 2016). Tools like limma-voom (Ritchie et al., 2015) edgeR (Robinson & Oshlack, 2010) and DESeq/DESeq2 (Anders & Huber, 2010; Love, Huber, & Anders, 2014) use regression models that work on every single gene (Friederike Du¨ndar, Luce Skrabanek, & Zumbo, 2015; Oh et al., 2019). Linear regression models typically used to assess the strength of the relationship between gene expression and conditions like case or control, i.e., how much does gene expression really depend on the condition in question? It takes into account the error and the variation between the samples of different conditions (Cai et al., 2017).

Limma-voom, edgeR and DESeq/DESeq2 could be seen as the best performing tools (Schurch et al., 2016). DESeq and limma-voom tend to be more conservative than edgeR which seems to be “oversensitive”, but for with less than 12 replicates experiments edgeR is recommended (Schurch et al., 2016). Limma-voom differs from edgeR and DESeq majorly in that it takes into account transformed count values, log-cpm and instead of negative binomial it uses linear models (on the log-cpm normalised with precision weights). Factually speaking, unequal library sizes are often observed in RNA-seq experiments for various reasons. For instance, when DNA samples are multiplexed onto a sequencing lane in unequal quantities, differences in sequencing depth resulting from differences in time/stages of experiment or when technical replicates are combined for a subset of samples. In conditions like these, some of the NB-based analysis methods become very conservative and showed very poor FDR control, on the contrary, voom shows consistent performance when the library sizes were unequal (Ritchie et al., 2015).

Principal Components Analysis (PCA)

Apart from mainstream, RNA-seq analysis are often supplemented by PCA, to evaluate variability between experimental conditions and between replicates of the same treatment (Meng et al., 2016). It is a typical dimensionality reduction approach to shrink multidimensional datasets for analysis. This analysis yields principal components (PCs) that represent the directions along which the variation is maximal (Meng et al., 2016). It uses

linear combinations of the original data (e.g. gene expression values) to define new components (PCs), which brings out the latent information from the data (Misra et al., 2002). Mostly two principal components, explaining the majority of the variability, are taken (Friederike Du¨ndar et al., 2015). Importantly, it is useful to identify unexpected patterns and to visualize the overall effect of experimental covariates, such as sex, RIN, etc., and batch effects.

PCA is devised for multi-normal distributed data analysis. Interestingly, if expression data is strongly skewed or have extreme outliers, the first few axes might only separate those values instead of displaying the main axes of variation. On the other hand, if data are unimodal or display nonlinear trends, distortions in the resulting plots may be observed, where the second axis is an arched function of the first axis (Friederike Du¨ndar et al., 2015; Meng et al., 2016).

Rank Rank Hypergeometric Overlap

Rank Rank Hypergeometric Overlap (RRHO) probe the similarities as well as differences in transcriptional signatures across different experimental conditions. Gene expression comparison tools to evaluate alterations typically choose a fixed differential expression confidence threshold to conclude results. This approach is extremely useful but could potentially reduce the detection of small but concordant changes. On the contrary, RRHO is a threshold-free approach that can be applied to determine the extent and significance of overlap between two differential expression analyses (Plaisier, Taschereau, Wong, & Graeber, 2010). It is a useful tool as it considers both directionality and magnitude of gene alterations and has been analogously used to identify similarities in transcriptional signatures across different brain regions in a single experiment (Bagot et al., 2016). The algorithm used in this tool steps through two gene lists ranked by the degree of differential expression observed in two expression profiles, successively measuring the statistical significance of the number of overlapping genes. The result is a graphical map that shows the strength, pattern and bounds of correlation between two expression profiling experiments (Plaisier et al., 2010).

Gene Ontology and Pathway Analysis

Gene ontology (GO) and pathway analysis are the most widely used downstream analysis tools, aimed at elucidating the functions of the DE genes and identifying possible patterns among them.

GO assessing tools perform enrichment analysis on gene sets encompassing the three classes of GO terms: biological processes, cell components and molecular functions. There a variety of tools that perform GO analysis eg. DAVID, GOseq, AmiGO, etc. On the other hand, pathway analysis identifies relevant proteins within a pathway or building pathway de novo from the proteins of interest. Tools for pathway enrichments analysis are

MSigDB (Liberzon et al., 2015), STRING (Szklarczyk et al., 2017), or KEGG (Kanehisa et al., 2017). Additionally, identification of specific “master regulators” or transcription factors could also be carried out using tools like Ingenuity pathway analysis (IPA).

These enrichments are typically assessed by either one of two approaches: (i) over-representation analysis (ORA) or (ii) gene set enrichment analyses (GSEA). Over-representation analyses depend on a filtered list of genes of interest, e.g. genes that pass the DE threshold. which is then compared to the genes that are known to be part of a specific pathway or a generic gene set of interest, e.g. “Neurotransmission”. After comparison, a statistical test is used to determine the significance of the overlap between the gene list of interest and the known term. Although, this is a relatively straight-forward approach, there are major caveats including the fact that both magnitude and direction of the change of individual genes are not taken into account. It only relies on the presence or absence of a given gene within the lists that are being compared. Addressing this limitation of the ORA approach, GSEA employs functional scoring algorithms that typically do not require a pre-selected list of genes. Alternatively, these algorithms rely on a legit exhaustive list of genes. Moreover, for the purpose of sorting out, these genes should have some measure of change. The basic assumption employed here is that although massive alterations in individual genes can significantly affect related pathways, small but concordant changes in sets of functionally related genes (i.e., pathways) can also have significant effects. Therefore, the gene-level statistics for all genes in a pathway are grouped into a single pathway-level statistic (e.g. the sum of all log-fold changes), which will then be evaluated. Although, GSEA take into account the magnitude and direction of change, it considers pathways as independent units despite the fact that many pathways share individual genes (Alhamdoosh et al., 2017; Friederike Du¨ndar et al., 2015; Khatri, Sirota, & Butte, 2012; Langfelder & Horvath, 2008).

Weighted gene co-expression network analysis

Weighted gene co-expression network analysis (WGCNA) is a powerful tool that defines correlation patterns among genes across gene expression data (Langfelder & Horvath, 2008). A gene co-expression network is an undirected graph consisting of nodes and edges, where each node corresponds to a gene and each edge connects a pair of genes that are significantly correlated (J. Li et al., 2018). Weighted correlation network analysis (WGCNA) can be used for finding clusters (modules) of highly correlated genes, for summarizing such clusters using the module eigengene (an intramodular hub gene), for relating modules to one another and to external sample traits (using eigengene network methodology)(Foroushani et al., 2017; Horvath & Dong, 2008), and for calculating module membership measures**.** It has been efficaciously used in various biological contexts, e.g. autism, alzheimer’s disease, cancer, mouse genetics, yeast genetics, etc. (Langfelder & Horvath, 2008; Liang et al., 2018; Oron et al., 2019). In fact, it is a very useful tool to study complex heterogeneous disorders like

MDD, where a single gene couldn't be accounted for the pathology but involves multiple genes interacting with each other. Gene–gene interaction network approaches may enrich the variable space to better predict or characterize the genomic architecture of more complex phenotypes (Le et al., 2018). This greatly alleviates the multiple testing problem (Fuller et al., 2007)

Its workflow includes: 1. Build a mathematical representation of a gene co-expression network by an adjacency matrix, the values of which indicate co-expression (correlation) similarity between a pair of genes. 2. Detect modules: WGCNA identifies modules by using hierarchical clustering. WGCNA uses a topological overlap to measure the dissimilarity between clusters, which can result in biologically important modules in real data analysis. 3. Link modules to phenotypes: several methods can be used to measure the association of a module to a phenotypic trait (J. Li et al., 2018). For example, one can either take module eigengene (ME) or module significance (MS) to test the association with the phenotypic trait. ME of a module is defined as the first principal component of the module whereas MS is the average gene significance (GS) of all genes in the module (Foroushani et al., 2017; Horvath & Dong, 2008). The GS of a gene is the correlation between the gene and the phenotypic trait. 4. Evaluate inter-module relationships: ME is regarded as the representative profile of a module and WGCNA quantifies module similarity by eigengene correlation, which gives information about the modules that are related. 5. Find key drivers in interesting modules: highest connecting genes are very important as it could affect all connected genes. Instead of using unweighted assignment of connected = 1 and unconnected = 0, WGCNA uses a 'soft' threshold determining the weights of the edges connecting pairs of genes. This weighted approach has been proven to yield more robust results than unweighted networks (B. Zhang & Horvath, 2005a) and renders the network closer to a scale-free network (J. Li et al., 2018).

Molecular mechanisms of MDD

The underlying molecular mechanisms of MDD are largely unknown. It is long known that genetics play an important role in the pathogenesis of MDD, but its contribution still remains blurred. The heritability of MDD in twin studies has been estimated to be around 40% (Kendler, Gatz, Gardner, & Pedersen, 2006). Initially, genome wide association studies (GWAS) were unable to identify a single genomic locus significantly associated with the risk of MDD across populations ((Major Depressive Disorder Working Group of the Psychiatric et al., 2013)). Recently, two studies have identified single nucleotide polymorphisms (SNPs) that survive statistical thresholds in two separate populations of Han Chinese women (consortium, 2015) and Europeans (Hyde et al., 2016). Nevertheless, the genetic sponsors of MDD across populations still remain uncertain.

In order to obtain a better understanding of mechanism underlying MDD, researchers have examined molecular alterations in the post-mortem brains of MDD patients and animal models of stress. Much of this research has focused on studying gene expression dynamics.

Transcriptional regulation of MDD

Past studies have revealed a significant number of molecular alterations associated with MDD and stress using different approaches. On one hand, several groups used genome-wide approaches to identify functional pathways enriched for genes differentially expressed and epigenetically regulated. These studies revealed the extent of transcriptional and its regulation in MDD (Figure 2) and animal models of stress-induced depressive-like behaviors (Figure 3) showing disease-specific reprogramming of molecular programs in different brain regions. Other groups concentrated their efforts on promising genes and pathways including the hypothalamic-pituitary-adrenal (HPA) axis, neurotrophic factors, and neurotransmitter systems.

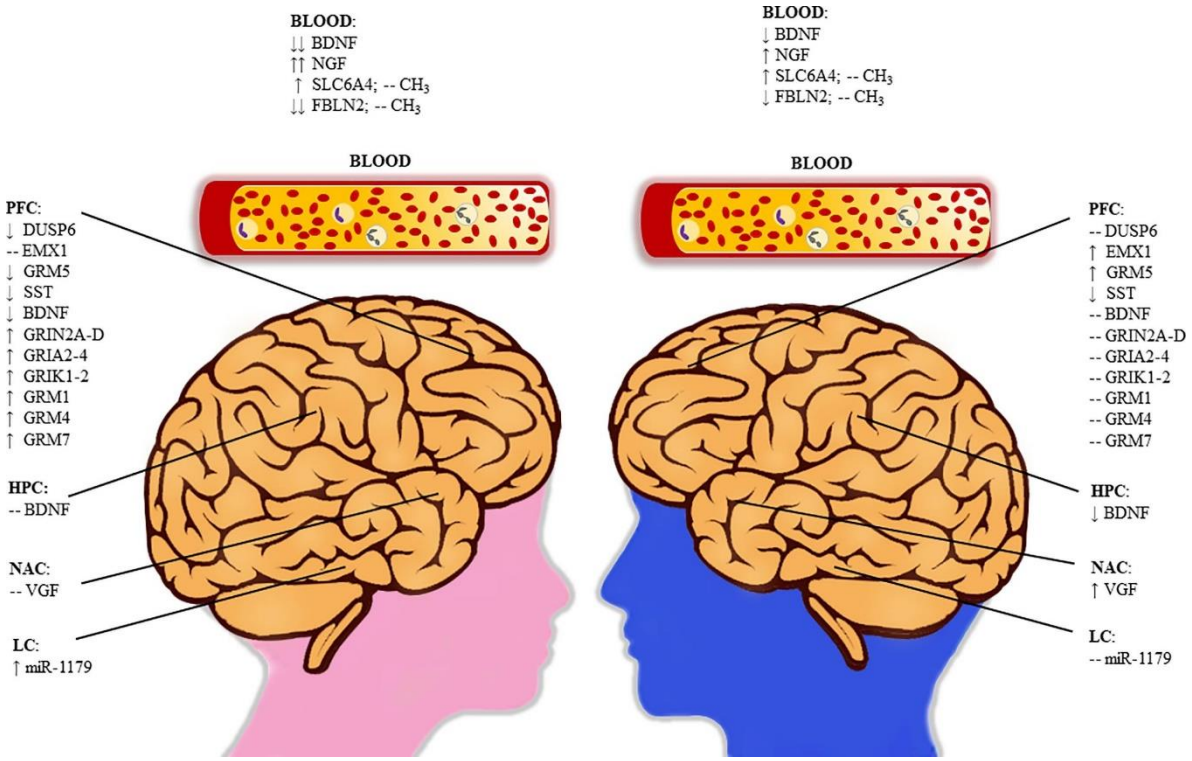


Fig. 2. Tissue-specific transcriptional regulation alterations in human MDD in males and females. - - indicates no change, upward and downward arrows indicating an increase or decrease expression and/or DNA methylation (CH_3).

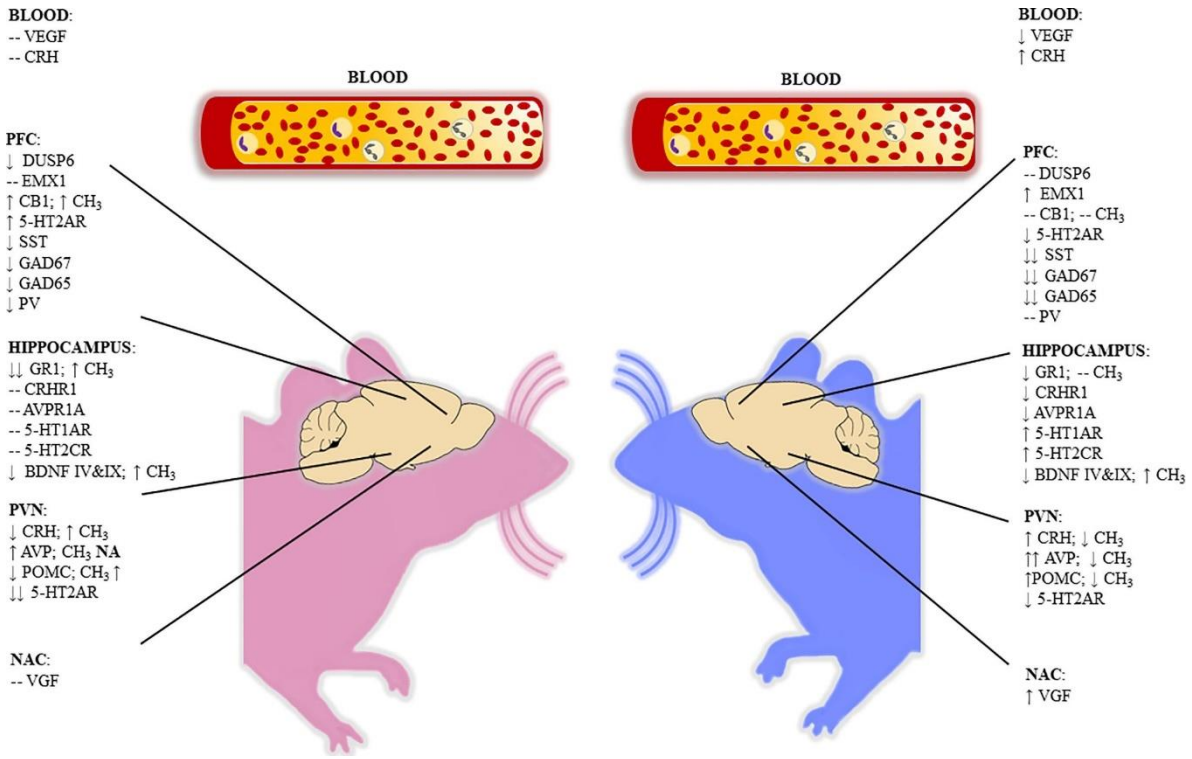


Fig. 3. Tissue-specific transcriptional regulation alterations in males and females in animal models of depression. - - indicates no change, NA indicates not reported, upward and downward arrows indicating an increase or decrease expression and/or DNA methylation (CH_3).

Hypothalamic-pituitary-adrenal (HPA) axis

As a hallmark functional alteration associated with MDD and stress, the HPA axis is one of the functional pathway that has received most attention (Turecki & Meaney, 2016). In response to stress, the PVN of the hypothalamus secretes corticotropin releasing hormone (CRH) and arginine vasopressin (AVP), which activates the production of proopiomelanocortin (POMC) in the pituitary gland, which eventually is cleaved to produce ACTH, β-lipotropin and β-endorphin. ACTH, in turn, stimulates the adrenal glands to secrete the final effectors, glucocorticoids (in humans-mainly cortisol) which brings necessary metabolic and behavioral changes in response to stress. The activity of HPA axis is regulated by negative feedback of cortisol. Cortisol binds to the glucocorticoid receptor (GR) and inhibits the CRH, AVP and ACTH release. FK506 Binding Protein 5 (FKBP5) diminishes the sensitivity of GR to cortisol, hence weakens the negative feedback loop. The activity of HPA axis is also inhibited by oxytocin (Ahmed et al., 1995; Barrot et al., 2005; Deroche et al., 1994; Nestler et al., 2002; Todkar et al., 2015; Tsigos & Chrousos, 2002). **Figure 4** represents an overview of the HPA. Abnormal HPA activity is associated with manifestations of MDD. Investigating the impact of variations in maternal care on offspring behavior during adulthood, Weaver and colleagues showed that pups raised by low licking and grooming mothers exhibit hypermethylation and lower H3K9me levels in the promoter of a variant ($GR1_7$) of the glucocorticoid receptor

gene (Weaver et al., 2004). They showed that this hypermethylation was associated with lower expression of $GR1_7$ and with the expression of depressive like-behaviors during adulthood. These initial findings found translational values in human populations. Indeed, McGowan *et al* (2009) showed that suicide victims of child abuse exhibit a similar hypermethylation of $GR1_F$, the human equivalent of $GR1_7$ in mice, associated with a significant decrease in GR expression in the hippocampus of male abused suicide completers compared to non-abused and healthy controls (McGowan et al., 2009). These effects were then extended to larger regions of the GR promoter, affecting the expression of other variants of the gene in abused suicide completers (Labonte et al., 2012) and patients with PTSD (Labonte, Azoulay, Yerko, Turecki, & Brunet, 2014). Since then, a large number of studies reported similar alterations associated with other psychiatric and stress conditions, suggesting that this region of the genome might be poised as a marker of early-life stress in humans (Turecki & Meaney, 2016).

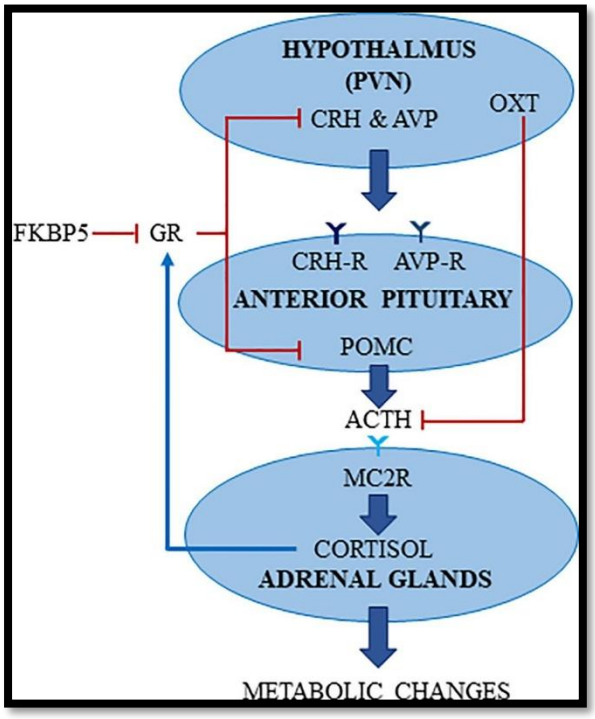


Fig. *4. Overview of the activity of the hypothalamic–pituitaryadrenal (HPA) axis in stress. Abbreviations: Paraventricular nucleus (PVN), corticotropin-releasing hormone (CRH), arginine-vasopressin (AVP), oxytocin (OXT), FK506 binding protein 51 (FKBP5), glucocorticoid receptor 1 (GR1), corticotropin-releasing hormone receptor (CRH-R), arginine-vasopressin receptor (AVP-R), pro-opiomelanocortin (POMC), adrenocorticotropic hormone (ACTH), Melanocortin-2 receptor (MC2R), also known as ACTH receptor (ACTHR).*

Besides the GR gene, molecular alterations of other key regulators of the HPA axis have also been studied in the MDD and rodent models of stress. For instance, chronic stress was shown to increase its expression in the paraventricular nucleus (PVN) of stressed male mice (Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010) and decrease DNA methylation in the CRH gene promoter (J. Chen et al., 2012; Elliott et al., 2010). Studies in suicide brains reporting changes in CRH binding sites (Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988), altered CRH receptor type ratios (Hiroi et al., 2001) and elevated CRH immunoreactivity and mRNA levels (Austin, Janosky, & Murphy, 2003; Merali et al., 2006).

Variations in other key players of the HPA axis, arginine vasopressin (*Avp*) and proopiomelanocortin (*Pomc*), have been reported across several brain regions in suicide completers(Lopez et al., 1992; Merali et al., 2006). The expression of these peptides has also been associated with stress-coping alterations in adult offspring separated from their mothers (Murgatroyd et al., 2009). Randesi et al (2018) found downregulation of *Crfr1* and *Avp* receptor 1 *a* (*Avpr1a*) in the hippocampus of male rats, but not female, after chronic immobilisation stress (Randesi et al., 2018).

Neurotrophic Factors

Several studies in humans and animal models have associated the activity of neurotrophic factors with the expression of MDD and stress-induced depressive like behaviors. For instance, decreased mRNA and protein expression of the brain-derived neurotrophic factor (BDNF) has been reported in the hippocampus and prefrontal cortex (PFC) depressed suicide completers (Banerjee, Ghosh, Ghosh, Bhattacharyya, & Mondal, 2013; Dwivedi et al., 2003). Interestingly, Hayley and colleagues found a female-specific downregulation of BDNF levels within the frontopolar prefrontal cortex among depressed suicides compared to their non-psychiatric controls (Hayley et al., 2015). On the other hand, male depressed suicide subjects, but not female, displayed significant reductions of BDNF protein levels in the hippocampus compared to non-suicide control (Hayley et al., 2015). These transcriptional variations have been associated with hypermethylation in BDNF regulatory region, namely promoter/exon IV in post-mortem brains (Keller et al., 2010). Similarly, CSD and traumatic stress in rats, were also shown to decrease the expression of *Bdnf* transcripts III and IV in male hippocampus (Roth, Zoladz, Sweatt, & Diamond, 2011; Tsankova et al., 2006) and not in PFC(Roth et al., 2011), respectively. Although similar, these regional transcriptional alterations are induced by different epigenetic mechanisms. In fact, while CSDS in mice increases hippocampal H3K27 dimethylation levels at the *Bdnf* promoter and compacts chromatin (Tsankova et al., 2006), traumatic stress in rats was shown to alter DNA methylation patterns in distinct regions of the hippocampus (Roth et al., 2011). Women with MDD have low serum BDNF levels associated with higher severity scores than men (Karege et al., 2002) though age could be a potential confounder (Bus et al., 2012).

The main receptor of BDNF, the tyrosine receptor kinase B (TrkB), has also shown to be dysregulated in MDD and rodent models of stress. For instance, BDNF deficient males (BDNF+/−) mice show higher TrkB phosphorylation than female mice in the frontal cortex and striatum, along with enhanced ERK signaling in the male BDNF+/− brain (Hill & van den Buuse, 2011). Lower TrkB expression has also been strongly associated with mood disorders, including depression (Aston, Jiang, & Sokolov, 2005; Dwivedi et al., 2003; Nakatani et al., 2006). Antidepressant treatment has been shown to increase its expression in cultured rat astrocytes (Mercier et al., 2004). Antidepressant effects of TrkB ligands on inflammation-induced depression has also been demonstrated in mice. Zhang et al (2015), reported pharmacological manipulation with a TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF) showing antidepressant effects on lipopolysaccharide (LPS)-induced depression-like behaviors, and pretreatment with ANA-12, a TrkB antagonist, blocked its antidepressant effects (J. C. Zhang et al., 2014). Interestingly, 7,8-DHF administration rescued LPS-triggered decrease of BDNF and spine density in the CA3 and dentate gyrus (DG) of the hippocampus and prefrontal cortex (PFC), whereas ANA-12 attenuated LPS-induced changes in BDNF and spine density in the nucleus accumbens (NAc) of male mice (J. C. Zhang et al., 2014). This indicates TrkB might be potentiating these region-specific expression and morphological changes. Fibrous astrocytes have also been reported to be hypertrophied, having significantly larger cell bodies and longer yet more ramified processes in ACC/BA24 of depressed suicide patients (Torres-Platas et al., 2011). This finding was consistent with ACC white matter alterations reported in post-mortem brain from depressed individuals (Torres-Platas et al., 2011). Decreased expression of the astrocytic variant of TrkB (TrkB.T1) in the brain of suicide completers (majorly males), have been associated with site specific promoter hypermethylation and enrichment of the repressive mark, H3K27me3 (Ernst, Chen, & Turecki, 2009). More recent studies also suggested an important regulatory role of a micro-RNA, mir-185, on this astrocytic variant in the suicide brain (Maussion et al., 2014; Maussion et al., 2012).

Finally, many studies have associated the single nucleotide polymorphism Val66Met in BDNF gene with heightened risk for psychiatric traits and suicidal behavior mainly via interaction with early-life adversity (Perroud et al., 2008; Sarchiapone et al., 2008). Interestingly, meta analyses of these findings suggested that this SNP may be more important for the development of depressive traits in men than women. For example, male mice with BDNF+/Met mutation, exhibited decreased BDNF levels and apical dendritic spine density in the PFC along with depression-like behavior after restrain stress (Yu et al., 2012). While these findings should be considered carefully, the few evidences of sex-specific variations in BDNF transcriptional alterations in MDD suggest that the molecular mechanisms underlying neurotrophins expression and activity may be sexually dimorphic.

Neurotransmitter Systems

The Norepinephrine System

The locus-coeruleus (LC) is the sole source of norepinephrine (NE) to the neocortex, hippocampus, cerebellum, and most of the thalamus (Alfinito, Chen, Mastroeni, Pawlyk, & Deecher, 2009; Aston-Jones & Cohen, 2005) and has been shown to be a sexually dimorphic brain region (Bangasser, Wiersielis, & Khantsis, 2016; Mulvey et al., 2018). Estrogen is an important regulator of NE in LC. Estrogen reduces the α2-andrenoceptor expression, which has been linked with genetic models of depression. In fact, α2-adrenoreceptor agonist treatment reduces anxiety-like behavior in female rats more significantly than male rats (Jang, Jung, Kim, & Noh, 2019). Interactions with function of the HPA axis have also been reported in the LC. For instance, females but not males with deleted GR expression in NE neurons exhibit reduced social interaction compared to controls. The authors also suggested that this reduction could explain the prevalence of atypical symptoms in depressed females, as low GR has been linked with atypical depression (Jacobson, 2018). To better understand the role of LC as a contributor to depressive pathology, more work is required to see how transcription and its regulation are altered following chronic stress in mouse models.

The Serotonergic System

The serotonergic system has been extensively investigated in mood disorders, especially in MDD and interesting lines of evidence suggest that some of its receptors may be regulated differently in males and females with MDD and in animal models of stress (Du, Faludi, Palkovits, Bakish, & Hrdina, 2001; Turecki et al., 1999)·(Joeyen-Waldorf, Edgar, & Sibille, 2009). For instance, acute restrain stressed females exhibit lower serotonin receptor, 5-hydroxytryptamine receptor 2A (5-HT2AR) mRNA expression than males in the PVN (Goel, Innala, & Viau, 2014). On the contrary, chronic mild stress (CMS) in rats reduces 5-HT2AR expression in the orbitofrontal cortex (OFC) males while it increases its expression in females. Interestingly, treatment with the tricyclic antidepressant clomipramine rescues these effects in female but not male rats (Pitychoutis, Dalla, Sideris, Tsonis, & Papadopoulou-Daifoti, 2012). Similarly, 5-HT1A receptor (5-HT1AR) basal expression was reported to be higher in women compared to men(Parsey et al., 2002), an effect that has been suggested to be mediated by estrogen (Goel & Bale, 2010). Interestingly, these patterns seem to be reversed by stress. For instance, CMS in rats increases 5-HT1AR levels in the CA1 region of male hippocampus but not females (Pitychoutis et al., 2012). Finally, 5-HT receptor 2C (5-HT2CR) has been reported to be significantly upregulated in the CA3 of hippocampus of male but not female rats exposed to CMS (Pitychoutis et al., 2012). Another serotonergic gene that received considerable attention in the context of early life adversity (ELA)-induced epigenetic regulation is the 5-HT transporter (5-HTT; SLC6A4) gene (Caspi et al., 2003). Interestingly, expression of 5-HTT was also decreased in rhesus macaques with ELA (Kinnally, Lyons, Abel, Mendoza, & Capitanio, 2008; Kinnally et al., 2010). 5-HTT KO mice show increased anxiety and depression-related behavior (Carroll et al., 2007). High

methylation levels within the solute carrier family 6 member 4 (SLC6A4) were found in response to childhood adversity in both sexes although some studies suggested that these levels may be higher in females (Dukal et al., 2015; Kang et al., 2013; Palma-Gudiel, Peralta, Deuschle, Navarro, & Fananas, 2019). On the other hand, results from the Iowa Adoptee Cohort (Lutz, Almeida, Fiori, & Turecki, 2015) suggest that male victims of child abuse exhibit global DNA hypermethylation within the SLC6A4 gene whereas females display site-specific hypermethylation as compared to non-abused (Lutz et al., 2015). Although these studies suggest different type of stress could affect different players of the same system in a sex specific manner, more information on human MDD subjects is still awaited.

The GABAergic and Glutamatergic Systems

Alterations of the GABAergic system has been consistently reported in mood disorders, including depression (Klempan et al., 2009; Merali et al., 2004; Torrey et al., 2005)·(Akbarian et al., 1995; Guidotti et al., 2000; Heckers et al., 2002; Volk, Austin, Pierri, Sampson, & Lewis, 2000)·(Ghosal, Hare, & Duman, 2017). Poulter and colleagues(Poulter et al., 2008) showed higher expression of DNMTs and lower expression of the GABA receptor α1 subunit in the brain of both males and females suicide completers. However, DNA methyltransferase 3 beta, (DNMT3B) expression was greater in female than in male suicide brains (Poulter et al., 2008), as consistently observed in schizophrenia and bipolar patients (Kundakovic, Chen, Costa, & Grayson, 2007; Veldic et al., 2004). Hypermethylation in α1 subunit promoter was negatively correlated with DNMT3B protein expression in the PFC of suicide completers. Additionally, expression levels of the somatostatin (SST), glutamic acid decarboxylase 65 (GAD65) and glutamic acid decarboxylase 67 (GAD67) genes were shown to be lower in males compared to females MDD, a finding consistent with results in unpredictable chronic mild stressed mice (Seney et al., 2013). Sex-specific expression patterns of the parvalbumin (PV) gene have also been shown in response to chronic stress. For instance, Shepard *et al* (2016) showed that female mice exhibit increased expression of PV following unpredictable chronic mild stress (UCMS). Interestingly, this female-specific increase was correlated with severe behavioral deficits along with prefrontal hypoactivity and altered amygdalar activity with no change in males(Shepard, Page, & Coutellier, 2016). Finally, Gray *et al* in 2015, investigated glutamatergic genes expression profile in the dorsolateral prefrontal cortex (DLPFC) of human MDD patients. They found an upregulation of several glutamate-related genes including GRIN2A-D, GRIA2-4, GRIK1-2, GRM1, GRM4, GRM5 and GRM7 in females MDD but not males although male MDD displayed downregulation of GRM5 (Gray, Hyde, Deep-Soboslay, Kleinman, & Sodhi, 2015).

Genome-Wide Approaches

There is a vast literature investigating transcriptional signatures in the brain of humans with MDD. For instance, genome-wide post-mortem brain studies in males revealed alterations in genes related to the glutamatergic,

GABAergic, serotonergic and polyaminergic systems across several cortical and subcortical brain regions (Klempan et al., 2009; Sequeira et al., 2007; Sequeira et al., 2009). Additional transcriptional alterations in lipid metabolism, immune response, ATP synthesis, regulation of transcription and translation, fibroblast growth factor signaling, and cell proliferation (Evans et al., 2004; Iwamoto, Kakiuchi, Bundo, Ikeda, & Kato, 2004; Kang et al., 2007; Klempan et al., 2009; Lalovic, Klempan, Sequeira, Luheshi, & Turecki, 2010; Tochigi et al., 2008) have been identified in cortical regions. More studies showed changes in genes regulating activity of the HPA axis in hypothalamus(S. S. Wang, Kamphuis, Huitinga, Zhou, & Swaab, 2008) and controlling circadian rhythms in cortical and subcortical regions (J. Z. Li et al., 2013). Similar findings have been reproduced in animal models of stress (Bagot et al., 2016; Carboni et al., 2018; Duman, Sanacora, & Krystal, 2019; Labonte et al., 2017a). Indeed, Hodes and colleagues showed that the overexpression of the DNA methyltransferase 3 alpha (Dnmt3a) in the NAc increases stress susceptibility in both sexes. NAc of human MDD shows a similar increase in its expression (Hodes et al., 2015). However, the downregulation of Dnmt3a in the same brain structure made female mice resilient to 6 days of variable stress with no effect in males. Moreover, network-based approaches also identified transcriptional signatures associated with the expression of stress susceptibility and resilience in a model of chronic social defeat stress (CSDS) (Bagot et al., 2016), antidepressant response following CSDS (Bagot et al., 2017) and with the expression of phenotypic features (sleep architecture) in a genetic model of stress susceptibility (P. Jiang et al., 2015)

But very few genome-wide studies have compared directly mice models of stress and MDD transcriptional profiles across different brain regions. Indeed, Labonté *et al*., found an overlap of differentially expressed genes of males and females between depressed humans and CVS stressed mice in the vmPFC and NAc (Labonte et al., 2017a). They also found gene ontology overlap identifying several pathways commonly associated with MDD in humans and CVS in mice. Additionally, the authors used network-based approaches to identify network hub genes, namely- the cytoplasmic dual specific phosphatase 6 (DUSP6) and the transcription factor empty spiracles homeobox 1 (EMX1) as drivers of MDD susceptibility in females and males, respectively. They showed that the viral downregulation of DUSP6 in the mPFC of mice increases stress susceptibility, while its overexpression rescued the stress-induced phenotype in female but not in male mice. These effects were associated with changes in extracellular signal-regulated kinase (ERK) phosphorylation and frequency of spontaneous excitatory post-synaptic current (EPSC) in a subpopulation of pyramidal cells in female mice. Alternatively, the viral overexpression of EMX1 in the mPFC increased stress susceptibility in male but not female mice with consistent physiological effects in a sex-specific fashion. Hence, validating the shared alterations between human MDD and CVS (Labonte et al., 2017a). Moreover, using the clustering approach, an overlap of hippocampal transcriptional signatures between MDD and learned helplessness model of stress and flinders sensitive line (FSL) rats was observed (Carboni et al., 2018). Interestingly, Lorsch *et al.* showed out of 30 CSDS-related gene network modules, across several brain regions, 56.6% are preserved in the human brain.

Intriguingly, greater module preservation in control conditions than in MDD with regard to resilience. They found Zfp189 as the key driver of a resilience specific gene network module of CSDS mice is also downregulated in PFC of MDD subjects (Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Salery, et al., 2019).

Hypothesis

Most of our knowledge in the field of MDD comes from works on animal models of depression. With the frequent failure of antidepressant candidate drug at clinical trial, there has been increased scrutiny into the animal models of depression. In fact, there is a growing concern about the degree of confidence we hold on these preclinical animal models and their behavioral endpoints (Bale et al., 2019). Therefore, it is of critical importance to validate these models with the best tools available. As a matter of fact, gene expression is a strong measure that can provide informative insights into the molecular pathophysiology of the disorder. However, applying such a measure encompasses an important conflict between the reductionist and "big data" frameworks. In fact, most studies have employed a reductionist agenda on differential expression, focusing on individual genes. This has an edge in that individual genes can be targeted therapeutically based on specific information on their dysregulation from this approach. Although, it is limited in that it ignores the totality of the transcriptional response to stress (Zachary Spencer Lorsch, 2018; Vella, Zoppis, Mauri, Mauri, & Di Silvestre, 2017). On the other hand, characterizing gene networks, which is more of a bird-eye approach, reveals the potential of individual genes to exert their effect on a broader gene expression network. Nonetheless, this requires a thorough understanding of the hierarchical regulation of gene expression changes (Zachary Spencer Lorsch, 2018). Altogether, a fusion of the individual-gene based, differential expression approach, network approach with a systems biology framework would give a more complete view of the molecular pathophysiology of MDD.

As described earlier, various studies describe transcriptional changes in MDD and animal models of depression. But very few studies compared directly the genome-wide transcriptional alterations between the two species in specific brain regions (Carboni et al., 2018; Labonte et al., 2017a; Lin, Lewis, & Sibille, 2011; Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Salery, et al., 2019). Although these studies provide some answers while raising other important questions. For instance, are these different mice models of chronic stress potent enough to model human depression? Which mice model of stress produces the closest molecular pathology to human MDD and how well the different mice models of chronic stress reproduce the molecular pathology of the human MDD? Although, different mouse models of chronic stress produce similar phenotypes, we don't know to what extent different chronic stress models produce the molecular pathology of human MDD. More specifically, how are genes differentially expressed in human MDD overlap with that in different mice models of chronic stress? What happens at the gene network level? How much are the gene networks of human MDD conserved in different mice models of chronic stress? What happens if we combine DEG and network approaches to compare the different animal models of depression and human MDD? And what are the network driver or hub genes relevant to human MDD? Despite the importance of such comparisons in understanding the human disorder and devising its treatments, no study extensively explored the overlap between human MDD and other models of

chronic stress in mice. This thesis aims to provide answers to these important questions with the ultimate goal of validating the molecular face validity of the animal models useful for the study of depression.

This thesis provides a comprehensive comparison of transcriptional signatures of human MDD and 3 different mice models of stress. Each of the three models employed, uses different paradigms that represent strong causal relation to MDD and are the most-widely used models to study MDD. As brain gene expression data shows significant regional variation (Pavlidis & Noble, 2001), we employed region-specific approach. Consequently, we used publically available RNA-seq datasets of the two most widely implicated brain regions in MDD which are also associated with treatment resistant depression, mPFC and NAc. These datasets were assessed using a combinatory approach involving differential expression analysis and network analysis. These analyses were complemented by other state of art bioinformatics analyses, such as GO analysis, RRHO analysis, conservation analysis, phenotype analysis and hub calling, to assess the capacity of each chronic stress paradigm to reproduce molecular pathology of the human disorder.

Our analysis indicates significant overlap between MDD and the three mouse model of stress in mPFC as well as NAc. No one model is better than the other. Each of the chronic stress paradigms captures a distinct aspect of the human syndrome.

Chapitre 1 Shared Transcriptional Signatures in Major Depressive Disorder and Mouse Chronic Stress Models

1.1 Résumé

CONTEXTE : La plupart de nos connaissances sur les bases biologiques du trouble dépressif majeur (TDM) proviennent des études de modèles de stress chronique chez les rongeurs. Bien que ces modèles saisissent certains aspects des caractéristiques comportementales et neuroendocriniennes du TDM, la mesure dans laquelle elles reproduisent la pathologie moléculaire du syndrome humain reste inconnu.

MÉTHODES : Nous avons systématiquement comparé les signatures transcriptionnelles dans deux régions du cerveau impliquées dans la dépression - le cortex préfrontal médian et le noyau accumbens - chez les humains atteints de TDM et dans trois modèles de stress chronique chez la souris : les modèles de stress chronique variable, d'isolement social chez l'adulte et de défaite sociale chronique. Nous avons utilisé l'expression différentielle combinée à l'analyse de réseaux de co-expression pondérée de gènes pour créer des réseaux de gènes inter-espèces et évaluer la capacité de chaque paradigme de stress à récapituler l'organisation transcriptionnelle des réseaux de gènes dans le TDM humain.

RÉSULTATS : Nos résultats montrent un chevauchement important entre les altérations transcriptionnelles du cortex préfrontal médian et nucleus accumbens dans le TDM humain et dans les 3 modèles de stress chronique de la souris, avec chacun des paradigmes de stress chronique saisissant des aspects distincts des anomalies du TDM. Le stress variable chronique et l'isolement social chez l'adulte reproduisent mieux l'expression différentielle des gènes, tandis que la défaite sociale chronique et l'isolement social chez l'adulte reproduisent mieux les réseaux de gènes caractéristiques du TDM humain. Nous avons également identifié plusieurs réseaux de gènes et leurs gènes les constituant qui sont le plus significativement associés au TDM humain ainsi qu'aux modèles de stress chez la souris.

CONCLUSIONS : Cette étude démontre la capacité de trois modèles de stress chronique chez la souris à récapituler des aspects distincts de la vaste pathologie moléculaire du TDM humain, aucun modèle de souris n'étant apparemment meilleur qu'un autre.

1.2 Abstract

CONTEXTE : La plupart de nos connaissances sur les bases biologiques du trouble dépressif majeur (TDM) proviennent des études de modèles de stress chronique chez les rongeurs. Bien que ces modèles saisissent certains aspects des caractéristiques comportementales et neuroendocriniennes du TDM, la mesure dans laquelle elles reproduisent la pathologie moléculaire du syndrome humain reste inconnu.

MÉTHODES : Nous avons systématiquement comparé les signatures transcriptionnelles dans deux régions du cerveau impliquées dans la dépression - le cortex préfrontal médian et le noyau accumbens - chez les humains atteints de TDM et dans trois modèles de stress chronique chez la souris : les modèles de stress chronique variable, d'isolement social chez l'adulte et de défaite sociale chronique. Nous avons utilisé l'expression différentielle combinée à l'analyse de réseaux de co-expression pondérée de gènes pour créer des réseaux de gènes inter-espèces et évaluer la capacité de chaque paradigme de stress à récapituler l'organisation transcriptionnelle des réseaux de gènes dans le TDM humain.

RÉSULTATS : Nos résultats montrent un chevauchement important entre les altérations transcriptionnelles du cortex préfrontal médian et nucleus accumbens dans le TDM humain et dans les 3 modèles de stress chronique de la souris, avec chacun des paradigmes de stress chronique saisissant des aspects distincts des anomalies du TDM. Le stress variable chronique et l'isolement social chez l'adulte reproduisent mieux l'expression différentielle des gènes, tandis que la défaite sociale chronique et l'isolement social chez l'adulte reproduisent mieux les réseaux de gènes caractéristiques du TDM humain. Nous avons également identifié plusieurs réseaux de gènes et leurs gènes les constituant qui sont le plus significativement associés au TDM humain ainsi qu'aux modèles de stress chez la souris.

CONCLUSIONS : Cette étude démontre la capacité de trois modèles de stress chronique chez la souris à récapituler des aspects distincts de la vaste pathologie moléculaire du TDM humain, aucun modèle de souris n'étant apparemment meilleur qu'un autre.

Introduction

Major depressive disorder (MDD) is one of the most important causes of disability and loss of productivity in the world ("Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2017). Past research efforts have highlighted several underlying mechanisms potentially driving the expression of MDD, but little of this research has revealed new therapeutic targets. Restricted access to high quality brain tissue has limited the ability to study the human syndrome directly, with subsequent reliance on animal models driving the field. While several mouse and rat models have been used to study the behavioral impact of stress(Bale et al., 2019; Menard et al., 2016; Nestler & Hyman, 2010), their capacity to reliably reproduce the molecular alterations associated with human MDD remains unknown.

Chronic social defeat stress (CSDS)(Berton et al., 2006; Golden et al., 2011), chronic variable stress (CVS)(Hodes et al., 2015; Labonte et al., 2017b; LaPlant et al., 2009) and adult social isolation (SI) (J. Liu et al., 2012; Wallace et al., 2009) represent three chronic stress models in mice that have been shown to reproduce certain phenotypes associated with MDD. All three induce anhedonia and reduce exploratory behavior (interpreted as anxiety-like responses), with CSDS also inducing social avoidance. CSDS has the additional feature of differentiating a subpopulation of mice that are resistant (resilient) to the anhedonia and social deficits seen in susceptible mice.

Global transcriptional analyses in MDD have revealed region-specific alterations in numerous classes of genes in brain(Labonte et al., 2017b; J. Z. Li et al., 2013; Seney et al., 2018; Sequeira et al., 2007; Sequeira et al., 2009; Sequeira et al., 2012; S. S. Wang et al., 2008). While similar approaches have demonstrated that CSDS, CVS and SI also induce genome-wide changes in gene expression (Bagot et al., 2016; Bagot et al., 2017; Hodes et al., 2015; Krishnan et al., 2007; Labonte et al., 2017b; Lisowski et al., 2011; Malki et al., 2015), it is not known how these transcriptional profiles in stressed mice overlap with the ones associated with MDD. Indeed, with few exceptions (Labonte et al., 2017b; Lin et al., 2011; Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Wright, et al., 2019), direct comparative studies of human MDD and chronic stress models in rodents are not available.

Recent advances in statistical modelling of large scale genomic, transcriptional and epigenetic data are now providing unbiased data-driven alternative approaches to study the molecular changes underlying the expression of complex diseases in humans, mouse models and cell lines (Bagot et al., 2016; P. Jiang et al., 2015; Labonte et al., 2017b; Parikshak et al., 2013; B. Zhang et al., 2013). These approaches have revealed novel targets and functional pathways underlying stress susceptibility and resilience, and sex-specific features of MDD. In this study, we integrated gene-level and network-level analyses to evaluate how well CSDS, CVS and SI reproduce the transcriptional alterations in brain associated with human MDD.

Materials and Methods

Detailed methods are provided in the following section of *Supplemental Methods*. Briefly, FastQ and metadata files from human MDD (GSE102556), mouse chronic variable stress (GSE102556) and chronic social defeat stress (GSE72343) were obtained from Gene Expression Omnibus. New data for social isolation (J. Liu et al., 2012; Wallace et al., 2009) were generated. Reads were aligned to the GENCODE release 29 (GRCh38.p12) and M21 (GRCm38.p6) for human and mouse, respectively, using STAR and TopHat. Reads for each dataset were counted using HTSeq.

Bioinformatics analyses were performed on human-mouse orthologous genes. Gene expression was transformed and normalized using voom limma (Smyth, 2005). Differentially expressed genes (DEGs) were assessed through generalized linear models implemented in limma using phenotype as main factor, with $p<0.05$. Rank-rank hypergeometric overlap (RRHO) (Plaisier et al., 2010; Stein et al., 2014) was used to evaluate overlap in gene signatures between human MDD and the mouse models. Enrichment for functional terms in DEGs in human MDD and mouse models was performed using DAVID (Huang da, Sherman, & Lempicki, 2009).

We constructed brain region-specific gene networks in each cohort using weighted gene co-expression network analysis (WGCNA)(Horvath, 2011; B. Zhang & Horvath, 2005b). We tested conservation of brain region-specific human modules with each mouse model by analyzing overlap of module membership through Fisher's exact tests. We examined network phenotypic associations by relating module eigengene expression with phenotype status and calculating module overrepresentation for DEGs in the respective cohort. Finally, we used gene network correlation matrices to identify key regulators for each gene network and compared their interspecies preservation.

Supplemental Methods

Data acquisition and collection

FastQ and metadata files from the human MDD, mouse chronic variable stress (CVS) and chronic social defeat stress (CSDS) cohorts were downloaded from the Gene Expression Omnibus website (https://www.ncbi.nlm.nih.gov/gds) under the following accession numbers: human MDD (GEO GSE102556, CVS (GEO GSE102556) and CSDS (GSE72343). A full description of the cohorts, tissue preparation and RNAseq methods are described in the original manuscripts, but a summary is provided here.

Human cohort

We utilized gene expression data obtained by means of RNAseq on human postmortem sample published before in Labonté et al., 2017(Labonte et al., 2017b). Gene expression data from the cingulate gyrus 25 (Brodmann Area (BA) 25; mPFC) and nucleus accumbens (NAc) was gathered from 48 subjects including 26 MDD and 22 healthy controls. Briefly, all subjects were of European ancestry and French-Canadian descent with a well-identified founder effect(Labuda et al., 1996). Sociodemographic and clinical information are listed in **Table 1**. There was no age, pH and postmortem intervals (PMI) significant difference between MDD and controls. Other sociodemographic and clinical information included presence of comorbid disorders, treatment history, smoking history and presence of drug and/or alcohol abuse (**Table 1**). Information concerning psychiatric history and socio-demographics was obtained through psychological autopsies performed by trained clinicians with the informants best acquainted with the deceased as described elsewhere, which has been shown to yield highly valid information(Dumais et al., 2005; McGirr et al., 2006). Both cases and controls were characterized by the same psychological autopsy methods, therefore avoiding the occurrence of systematic biases. Diagnoses were obtained using DSM-IV(Association, 1994) criteria by means of SCID-I interviews(Spitzer, Williams, Gibbon, & First, 1992) adapted for psychological autopsies. Details on the original data generation and library processing can be found in Labonté et al., 2017(Labonte et al., 2017b).

Chronic Variable Stress (CVS) cohort

The CVS model gene expression data have been published before in Labonté et al., 2017(Labonte et al., 2017b). We used gene expression data from the medial PFC (mPFC) and NAc from a total of 40 samples including 20 stressed (10 males and 10 females) and 20 control (10 males and 10 females) mice. These data have been previously shown to be associated with a strong behavioral phenotype characterized by anxiety, anhedonia and despair-like behaviors(Labonte et al., 2017b). **Table 1** lists RIN values and sex as potential covariates. Details on the original data generation and library processing can be found in Labonté et al., 2017(Labonte et al., 2017b).

Prolonged Social Isolation (SI) cohort

The SI stress paradigm was modified from Liu et al., 2012(J. Liu et al., 2012) and Wallace et al., 2009(Wallace et al., 2009). Briefly, it consists in isolating single mice one per cage over a period of 12 weeks. Social isolation was initiated at 8 weeks of age on a group of 30 mice (only males). Unstressed controls (only males) consisted in group-housed (5 per cage) mice (n=15) maintained together for the same amount of time (12 weeks). The mPFC and NAc tissue was collected for RNA-seq using 12- and 14-gauge punches, respectively. RNA from socially isolated and control brain samples was extracted using an RNeasy micro kit using Trizol, followed by DNase 1 treatment, as described by the manufacturer (Qiagen). RNA integrity number (RIN) and concentration were assessed using a Bioanalyzer (Agilent). **Table1** lists RIN values as potential covariates. Libraries were constructed using the ScriptSeq Complete Gold Kit (Epicentre, Illumina) preceded by ribosomal RNA depletion

starting with 300 ng of mPFC RNA and NAc RNA. Samples were barcoded for multiplexing and sequenced at 50 bp paired-end on Illumina HiSeq2500. Samples were pooled eight per lane and sequenced twice at a depth of 50 million reads per sample.

Chronic Social Defeat Stress Cohort

The CSDS model gene expression data have been published before in Bagot et al., 2016(Bagot et al., 2016). We used data from the mPFC and NAc from a total of 33 samples including 11 control, 11 susceptible and 11 resilient mice. The behavioral output associated with this dataset can be found in Bagot et al., 2016(Bagot et al., 2016). **Table1** lists RIN values as potential covariates. Details on the original data generation and library processing can be found in and Bagot et al., 2016 (Bagot et al., 2016).

Power analysis

Although subtle in number, sample size varies across every cohort (**Supplemental Table 1**) which could impact our capacity to detect genes differentially expressed (DEG) in every cohort. In order to insure similar capacity to detect DEG across every cohort, we performed a power analysis using the data obtained in our analyses (number of DEG by cohort from the 9888 gene orthologues) to determine whether our power to detect DEGs is sufficient across cohorts with varying sample size. Using the mPFC, we have a power of 80% to detect DEGs ($p<0.05$) with a fold change > than 2 in the SI cohort with a sample size of 15 controls and 30 cases. This power increases to 81% for the human (22 controls and 26 cases) and 82% in CSDS (11 controls, 11 susceptibles and 11 resilients) cohorts, respectively. Finally, we have a power of 87% to detect DEGs in the CVS (20 controls and 20 cases) cohort. Thus, we have sufficient and similar power to detect DEGs even with variations in sample size across our cohorts.

Bioinformatics Analyses

Data processing

Human and mouse cohorts were processed the same way. Reads for the human data were aligned to the GENCODE release 29 (GRCh38.p12) of the human genome while the mouse (CVS, SI and CSDS) data were mapped to the GENCODE release M21 (GRCm38.p6) annotation using STAR and TopHat. Data sets from every cohort were mapped using the comprehensive gene annotation on the reference chromosome only. We first removed samples from each cohort with excessively low total mapping rates and high ribosomal RNA contents. In humans, all samples passed quality control thresholds with the exception of 1 control and 1 MDD in BA25 and 1 control in the NAc. In the mouse cohorts, 4 samples (3 CVS in the mPFC, 1 CVS mouse in the NAc) were removed in CVS, while 6 samples (4 SI in the mPFC, 1 control and 1 SI in the NAc) were taken off in SI, and 1

sample (1 susceptible in the NAc) was excluded in the CSDS cohort. Reads for each dataset were counted using HTSeq. A gene was considered the union of all its exons in any known isoforms, based on GENCODE annotations. Any reads that fell in multiple genes were excluded from the analysis. Threshold for filtering out genes expressed at low level was set to >5 reads in at least 80% of the samples as previously described(Akula et al., 2014).

Gene orthology

All bioinformatics analyses, including differential expression and gene network analyses, have been performed on human-mouse orthologous genes. Gene orthologues were identified using BioMart implemented in R. We restricted our gene orthologue selection to genes with a one to one interspecies conservation for maximal interspecies orthology, leaving a total of 9888 common genes in both species.

In order to determine the proportion of genes differentially expressed in each of the four cohorts captured by gene orthologues, we performed differential expression analysis on each cohort and compared DEGs identified from the whole transcriptome and orthologues only analyses. Overall, our results show that the orthologues only analysis captures between 42% to 75% of the transcriptional changes identified using the whole transcriptome in human and mouse (**Supplemental Table 5**). This suggests that a significant proportion of genes differentially expressed in MDD are also differentially expressed in stress while showing that stress alters the activity of transcriptional programs specific to human and mouse independently which is one limitation of our study. On the other hand, our analysis also shows that 93% to 99% of DEGs identified using the orthologues only are also differentially expressed in the analysis using the whole transcriptome confirming the validity of our approach in identifying genes differentially expressed in both species (**Supplemental Table 5**).

Supplemental Table 5. Whole transcriptome to orthologues only transcriptional overlap

		DEG All Genome	DEG Orthologues	DEG Overlap	DEG Unique All genome	DEG Unique Orthologues	% over all genome	% over orthologues
	Human	779	344	323	456	21	41.5	93.9
	CVS	2376	1806	1769	607	37	74.5	98.0
mPFC	SI	2699	1979	1949	750	30	72.2	98.5
	CSDS sus	556	383	368	188	15	66.2	96.1
	CSDS res	1346	1005	964	382	41	71.6	95.9
	Human	2018	1280	1195	823	85	59.2	93.4
	CVS	2603	1909	1882	721	27	72.3	98.6
Nac	SI	3190	2423	2398	792	25	75.2	99.0
	CSDS sus	560	347	335	225	12	59.8	96.5
	CSDS res	1276	939	913	363	26	71.6	97.2

Differential gene expression analysis.

Differentially expressed genes (DEGs) between groups of samples were determined in several stages to ensure both statistical significance and biological relevance. In the first stage, linear models implemented in the limma package(Smyth, 2005) of Bioconductor were used to compute the variance of gene expression across all groups. Gene expression was transformed and normalized using voom in the limma package. DEGs in all four cohorts were assessed through generalized linear models implemented in limma using phenotype (human: MDD and control, CVS and SI: stressed and control; CSDS: susceptible, resilient and control) as main factor. An individual gene was called differentially expressed if the *P*-value of its *t*-statistic was at most 0.05. DEGs in every brain region were assessed through different GLMs. Our statistical models were adjusted to control for the impact of different covariates in every brain regions as listed in **Table 1**. These variables were selected for adjustment based on a combination of domain knowledge and variance analysis of the RNA-seq data. Eigen-R2(L. S. Chen & Storey, 2008) was used to estimate the amount of variance in RNA-seq data explained by each covariable in

every cohort. The estimate for each variable is similar to taking the average of the correlations between the variable and the expression values for each gene. Correlation averages are vulnerable to technical artifacts such as stochastic noise for genes with little or no expression; Eigen-R2 uses principal component analysis to reduce the contributions of these and other problematic genes. In the human cohort, our statistical approach allowed us to generate a comprehensive evaluation of gene expression changes in MDD cases relative to controls, while controlling for the effects of major covariates. While covariates in the mouse cohorts were much less defined, the same approach allowed us to control for the effect of sex in CVS and RNA integrity in every cohort.

Rank-rank hypergeometric overlap (RRHO) analysis

The rank-rank hypergeometric overlap (RRHO) test(Plaisier et al., 2010; Stein et al., 2014) was used to evaluate degree of overlap in gene signatures between human MDD and each of the mouse models for both brain regions. RRHO difference maps were produced by calculating for each pixel the normal approximation of difference in log odds ratio and standard error of overlap with expression data in the gene orthologues list (*z* score). This *z* score was then converted to a *P*-value and corrected for multiple comparisons across pixels. For display, the *P*-value was multiplied by the sign of the effect to show both stronger and weaker matching between gene lists.

Gene ontology (GO) and ontological overlap analysis

Enrichment for functional terms in DEGs in human MDD and stressed mice from each of the mouse cohorts was performed using DAVID(Huang da et al., 2009). We restricted our analysis to the genes differentially expressed at $p<0.05$ using biological process, cellular component and molecular function of the GOTERM seed terms with orthologous genes as background list. Interspecies conservation of GO terms was performed by comparing GO terms from both species. First, GO categories enriched for genes differentially expressed ($P<0.05$) were identified in every brain region. Next, enriched GO categories were compared across species, and only terms being significantly enriched for DEG in both species were considered overlapping.

Cell type-specific gene enrichment

The assessment of module enrichment for genes expressed in specific cell types was performed using a published RNAseq dataset(Y. Zhang et al., 2014). We focused our analysis on neuronal, astrocytic, myelinating oligodendrocytes, microglial and endothelial cell types. We first excluded all genes with no human orthologues and filtered out genes expressed at values below 1 FPKM. We then created sublists for genes expressed at least 5 times more in one cell type vs the average of the other cells type and used two-sided Fisher's exact tests to quantify the significance of the enrichment with significance fixed at $p_{adj}<0.05$ and $OR>2.0$.

Weighted gene co-expression network analysis

We calculated gene networks in each cohort using weighted gene coexpression network analysis (WGCNA)(Horvath, 2011; B. Zhang & Horvath, 2005b) to identify coexpressed gene modules using RNA-seq expression data that were first normalized by conditional quantile normalization and corrected for the same variables applied in the differential expression analysis. We constructed brain region-specific coexpression networks that simultaneously captured the intra- and inter-tissue gene–gene interactions between the MDD and healthy controls in humans and stressed and control mice in every mouse models. The weighted network analysis began with a matrix of the Pearson correlations between all gene pairs; we then converted the correlation matrix into an unsigned adjacency matrix using a power function, so that the resulting adjacency matrix—i.e., the weighted coexpression network—is approximately scale-free. To explore the modular structures of the coexpression network, the adjacency matrix was further transformed into a topological overlap matrix(B. Zhang & Horvath, 2005b). To identify modules of highly co-regulated genes, we used average linkage hierarchical clustering to group genes based on the topological overlap of their connectivity, followed by a dynamic cut-tree algorithm to separate clustering dendrogram branches into gene modules. Each module was assigned a unique (and arbitrary) color identifier. We used DAVID(Huang da et al., 2009) to assess the functional annotation (GO) for each module, and we report *P*-values as provided by DAVID.

Interspecies gene network conservation

We tested conservation of brain region-specific human modules with every mouse models by analyzing overlap of module membership. Fisher's exact tests (two-sided) were used to quantify significant (P_{adj}<0.05) overlap and enrichment (odd ratio>1.0, >2.0, >3.0 and >5.0). All analyses have been performed on the gene networks showing significant enrichment at p_{adj}<0.05 with a OR>3.0. The human modules that show significant overlap with a module in each mouse models were considered conserved, while the others were considered species-specific.

Interspecies gene networks phenotypic association

We evaluated modules relevant to phenotypes by performing two different analyses. The first was a network-level analysis for which we started by calculating eigengene values for each module in human and each of the mouse cohorts. The module eigengene of a given module is defined as the first principal component of its standardized expression profile and, as such, is considered the best summary of a module expression(Foroushani et al., 2017; Horvath & Dong, 2008). We associated module eigengene expression with phenotype status. In the human, CVS and SI cohorts, the statistical significance of the modular eigengene values was computed through independent sample t-test to compare eigengene expression in cases (MDD in humans and stress in mouse) with its expression in controls. Given the three phenotypes design of the CSDS mouse models, module association with phenotype was tested using one-way ANOVA, with phenotype (control,

susceptible and resilient) as main factor, followed by Fisher LSD post-hoc tests. In a separate set of analyses, we used two-way ANOVA to assess the impact of sex on module association with phenotype in MDD and CVS, with sex (male and female) and phenotype (MDD and control in humans; stress and control in CVS) as main factors, followed by Fisher LSD post-hoc tests. In our initial assessment phase, significance was fixed at $p<0.05$. However, given our results from the mPFC show that the strongest gene network associations with MDD are sexually dimorphic and our SI and CSDS cohorts are composed of male mice uniquely, we decided to compare interspecies networks by investigating networks associated with the disease state at a more permissive p-value ($p<0.2$). Our second strategy was to assess module relevance to phenotypes, by calculating module overrepresentation for DEG calculated in the respective cohort. Module enrichment for DEG was calculated using Fisher's exact test. Modular enrichment and subsequent relevance to phenotype was considered significant at $P_{adj}<0.05$ with an odd ratio>2.

Key driver analysis

We called hub genes for every gene networks using connectivity measures generated from the WGCNA analysis. Hub genes were defined as the top 5% most connected genes based on K.In values generated from the WGCNA correlation matrices. Interspecies hub gene conservation was determined by recalculating connectivity measures (K.In) for each mouse models using only genes found in respective human gene networks. Connectivity values (k.in) were then ranked and compared to human connectivity values.

Statistical approach strengths and weaknesses

By combining all analytical approaches described above, our strategy provides a more complete view of the transcriptional overlaps between human MDD and all three mouse models. Indeed, differential expression, gene ontology overlap, RRHO and WGCNA analyses each capture partly overlapping modes of transcriptional regulation. On one hand, differential expression analysis uses variance in gene expression to identify directionality of genes differentially expressed in one condition over another (i.e. MDD vs CTRL). However, this approach, by itself, is prone to type 1 and 2 errors and is restricted by stringent statistical cutoffs. RRHO analysis ranks genes by their differential expression patterns to test the transcriptional overlaps between two conditions (i.e. MDD vs CTRL). This method is not restricted to stringent statistic thresholds but is more informative on global transcriptional patterns than identifying single gene targets. Similarly, gene ontology analysis has the advantage to identify gene ontology terms enriched for genes differentially expressed between two conditions (MDD vs CTRL) and compare these terms across different datasets (i.e. human vs mouse). Thus, common ontological terms can come up in different conditions even if the same genes are not differentially expressed. However, this approach relies on differential expression and ontological terms are defined from curated public datasets as opposed to data driven approaches such as gene network analyses. WGCNA is a data driven

approach to create biological gene networks based on pairwise correlations between genes. Applied in our context, it allows to define gene modules and intra-modular hub genes. It has the advantage to be well suited for the integration of different levels of analysis such as differential expression data. All together, the combination of every levels of analysis used in our study provides a more compete view of the complex transcriptional overlaps taking place between human MDD gene expression profiles and those from three mouse models of chronic stress in the brain.

Statistical analyses. Sample size calculation was not performed. However, we justified every experiment sample size based on several previously published reports using similar or even smaller sample sizes and showing the power to detect significant statistical differences. RNA-seq gene expression data for differential expression was normalized. The human RNAseq cohort was originally composed of 48 subjects (26 MDD; 22 controls (CTRLs)). The CVS cohort was composed of 40 mice (20 stressed, 20 control). RNAseq from SI was generated from a total of 45 mice (30 SI and 15 CTRL) and the CSDS cohort was originally composed of 33 samples (11 susceptible, 11 resilient and 11 control). RNA-seq and RRHO statistical methods are described above. Differential expression was not corrected for multiple testing. RRHO analysis was corrected using the Benjamini-Hochberg method. Bonferroni correction was used to correct for multiple testing when several Fisher's exact tests were performed simultaneously. The same samples used for differential expression analysis were included in the network analysis, the statistical methods for which are described above. Network analyses, including network construction, module conservation and module differential expression enrichment were adjusted for multiple testing while modular eigengene calculation and GO enrichment were not.

Code availability. Major network analysis tools are available as R packages at CRAN (http://cran.r-project.org/).

Data availability. Sequencing data and source files are available on NCBI GEO website.

Results

To identify converging MDD-relevant transcriptional pathways in mPFC and NAc in three mouse chronic stress models, we used publicly available human MDD (Labonte et al., 2017b) and mouse CVS(Labonte et al., 2017b) and CSDS(Bagot et al., 2016) datasets, and generated RNAseq profiles for these brain regions in mice after prolonged SI in adulthood (J. Liu et al., 2012; Wallace et al., 2009). We then systematically compared transcriptional profiles associated with each mouse model to human MDD (**Figure 1**). Details of the human and mouse cohorts are listed in **Table 1**.

Table 1. *Human and mouse cohorts' demographics*

Human	**MDD (n=26)**	**Control (n=22)**	
Age	45.2 ± 17.0	48.1 ± 17.0	
pH	6.66 ± 0.25	6.56 ± 0.29	
PMI	27.2 ± 16.5	27.0 ± 22.7	
Sex (M/F)	13/13	13/9	
RIN BA25	6.42 ± 0.90	6.7 ± 0.94	
RIN NAc	7.83 ± 0.75	7.35 ± 1.03	
Smoking (NA/No/Moderate/Heavy)	8/6/1/11	6/8/0/8	
Alcohol	4	1	
Drug of abuse	0	1	
Antidepressant	14	2*	
Mouse CVS	**CVS (n=20)**	**Control (n=20)**	
Sex (M/F)	10/10	10/10	
RIN mPFC	8.76 ± 0.40	8.91 ± 0.36	
RIN NAc	9.14 ± 0.24	9.15 ± 0.32	
Mouse SI	SI (n=30)	Control (n=15)	
Sex (M/F)	30/0	15/0	
RIN mPFC	8.87 ± 0.19	9.0 ± 0.18	
RIN NAc	9.29 ± 0.21	9.39 ± 0.13	
Mouse CSDS	Susceptible (n=11)	Resilient (n=11)	Control (n=11)
Sex (M/F)	11/0	11/0	11/0
RIN mPFC	8.46 ± 0.30	8.39 ± 0.34	8.56 ± 0.26
RIN NAc	8.62 ± 0.23	8.55 ± 0.17	8.90 ± 0.28

*Values are mean 6 SD except where indicated, *Prescribed for sleep disorders. BA, Brodmann area; CSDS, chronic social defeat stress; CVS, chronic variable stress; MDD, major depressive disorder; mPFC, medial*

prefrontal cortex; NA, no available information; NAc, nucleus accumbens; RIN, RNA integrity number; SI, social isolation.

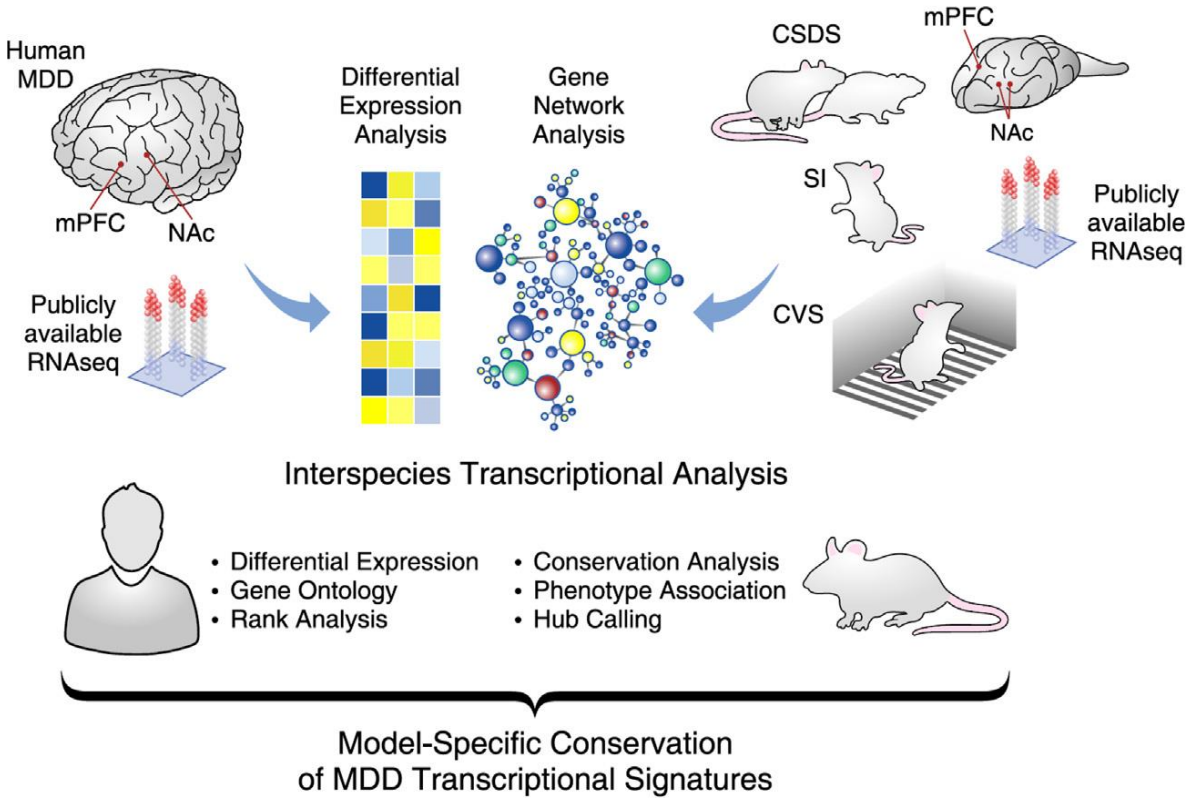


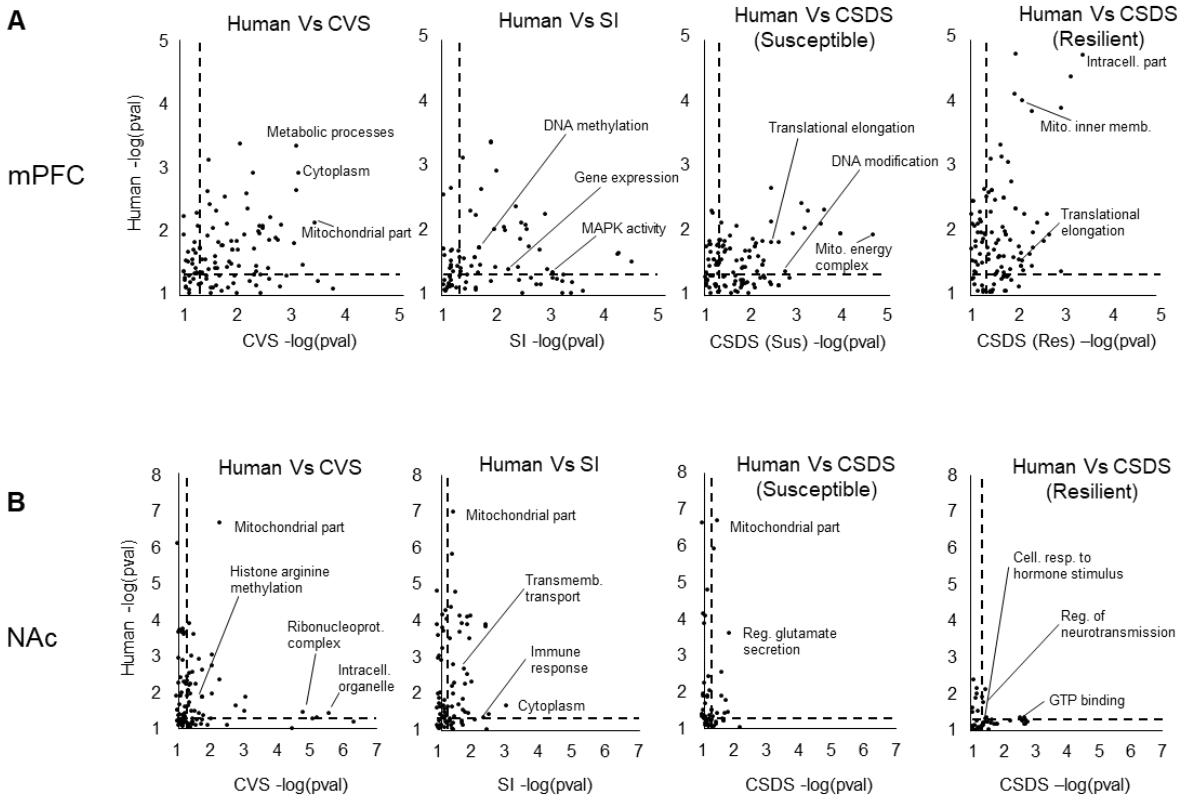
Figure 1. Interspecies assessment of transcriptional signatures in MDD and CSV, SI and CSDS in mice. *Publically available RNAseq data were obtained from cohorts of human major depressive disorder (MDD) and three mouse models of depressive-like behavior. These mouse models included the chronic variable stress (CVS), prolonged social isolation (SI) and chronic social defeat stress (CSDS) paradigms. Differential expression and weighted gene coexpression network analyses (WGCNA) were performed on each cohort by brain regions, including the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). Results from these analyses were combined and consistently compared across species. With these dataset, additional analyses including gene ontology overlap, hypergeometric rank, interspecies network conservation, phenotype association and hub calling analyses were performed. The final results allowed to catalogue the capacity of each mouse models to reproduce the transcriptional signatures relevant to MDD across different regions of the human brain.*

Shared transcriptional regulation revealed by differential expression analysis

We first identified 9,888 interspecies gene orthologues that are expressed in mPFC or NAc of both humans and mice. All subsequent analyses were performed on this gene set. Our analysis identified transcriptional changes

shared between human MDD and mouse CVS, SI or CSDS ($p<0.05$) in both brain regions (**Supplemental Tables 1**,**2**), among which are numerous shared alterations demonstrated previously, such as *Dusp4-6*, *Egr1-2* and *Nr4a3*(Labonte et al., 2017b) (**Figures 2A**,**D**). We also identified transcriptional changes in GABAergic markers (*Sst*, *Gabra4*, others) and transcription factors (*Crem*, *Creb*, c*Fos*). **Figures 2A**,**D** exhibit the degree and directionality of differential expression of these genes in mPFC and NAc in CVS, SI and mice susceptible to CSDS.

We compared gene ontology (GO) categories enriched for DEGs across species (**Supplemental Table 3**,**4**) and found that alterations of *mitochondrial functions* are common between human MDD and every mouse model in both mPFC and NAc (**Supplemental Figure 1A,B**). MDD-relevant mPFC alterations of *metabolic processes*, *DNA methylation* and *translational elongation* were uniquely reproduced in CVS, SI and susceptible CSDS mice, respectively (**Supplemental Figure 1A**). In NAc, alterations of *histone arginine methylation*, *immune responses* and *regulation of glutamate secretion* were common between human MDD and CVS, SI and susceptible CSDS mice, respectively (**Supplemental Figure 1B**). Interestingly, GO terms enriched for DEGs in mPFC and NAc of mice resilient to CSDS showed better similarity with human MDD than the susceptible mice, with important differences observed between the susceptible vs resilient phenotypes in both brain regions (**Supplemental Figure 1A**,**B**).



Supplemental Figure 1. ***A-B****, GO ontology overlap between terms enriched for genes differentially expressed (p<0.05) in humans with MDD and those enriched with differentially expressed genes (p<0.05) in CVS, SI and susceptible or resilient mice to CSDS in the (**A**) mPFC and (**B**) NAc. Each models are enriched with similar but also distinct terms relevant to MDD in humans*

Next, we compared DEGs in human MDD with those induced by CVS, SI or CSDS. **Figure 2B** shows that 16.9% of DEGs in mPFC of human MDD are also differentially expressed in mouse mPFC after CVS (58/344; 24 common, 34 opposite), 18.6% following SI (64/344; 39 common, 25 opposite) and 5.2% in CSDS susceptible mice (18/344; 16 common, 2 opposite). Similarly, in NAc, 20.0% of DEGs in human MDD are also differentially expressed in mouse NAc after CVS (257/1280; 150 common, 107 opposite), 26.7% following SI (342/1280; 210 common, 132 opposite) and only 2.7% in CSDS susceptible mice (34/1280; 14 common, 20 opposite; **Figure 1E**). Globally, our analysis identified 3 genes differentially expressed in NAc of human MDD and all three mouse models (*Zranb1* [H: logFC: -0.054; p=0.045, CVS: logFC:0.09; p=0.015, SI: logFC:-0.08; p=3.23E-5, CSDS susceptible: logFC:0.13; p=0.040)], *Copg2* [H: logFC: -0.13; p=0.001, CVS: logFC: 0.08; p=0.002, SI: logFC=-0.071; p=0.0037, CSDS susceptible: logFC:-0.13; p=0.025], *2410131k1Rik* [H: logFC: -0.14; p=6.7E-4, CVS:

logFC=0.07; p=0.03, SI: logFC=0.07; p=0.037, CSDS susceptible: logFC: -0.13; p=0.038]). No genes were commonly differentially expressed across all three models in mPFC. Our analysis also revealed overlap with human MDD and CSDS resilient mice in mPFC (15.7%; 54/344; 52 common, 2 opposite; **Supplemental Figure 2A**) and NAc (9.2%; 118/1280; 67 common, 51 opposite; **Supplemental Figure 2B**).

Because DEG analysis depends upon significance cut-offs and the statistical test used—with widely divergent DEGs identified by different approaches, we extended our interspecies analysis using an unbiased, threshold-free rank-rank hypergeometric overlap (RRHO) procedure(Stein et al., 2014). In mPFC, dramatic shared regulation of genes was observed between human MDD and CSDS susceptible mice, with much weaker shared regulation observed for SI and CVS (maximum Fisher's Exact Test [FET] p_{adj}<1.0E-742, **Figure 2C**). A weaker, but significant signal was found in NAc where coordinated up and downregulation of transcriptional signatures was found between human MDD and all three mouse models (maximum FET p_{adj}<1.0E-742, **Figure 2F**). Comparison of human MDD and CSDS resilient mice revealed strong overlap for genes commonly up and downregulated in mPFC (maximum FET p_{adj}<1.0E-742, **Supplemental Figure 2C),** with weaker concordance in NAc (**Supplemental Figure 2D)**.

Overall, results from DEG and RRHO analyses show that each chronic stress model recapitulates a significant subset of gene expression changes seen in mPFC and NAc of human MDD, with DEG analysis showing stronger effects for SI and CVS and RRHO analysis showing stronger effects for CSDS. Explanations for this difference are considered in the Discussion. Another important observation is that the specific genes that comprise the overlap with human MDD are largely different for each mouse stress model.

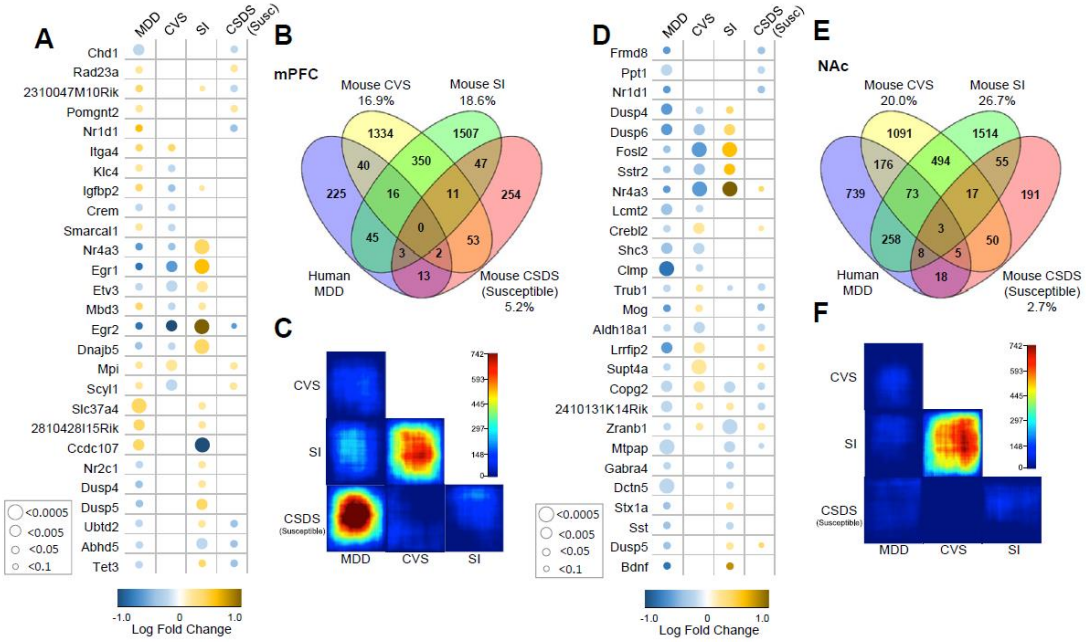
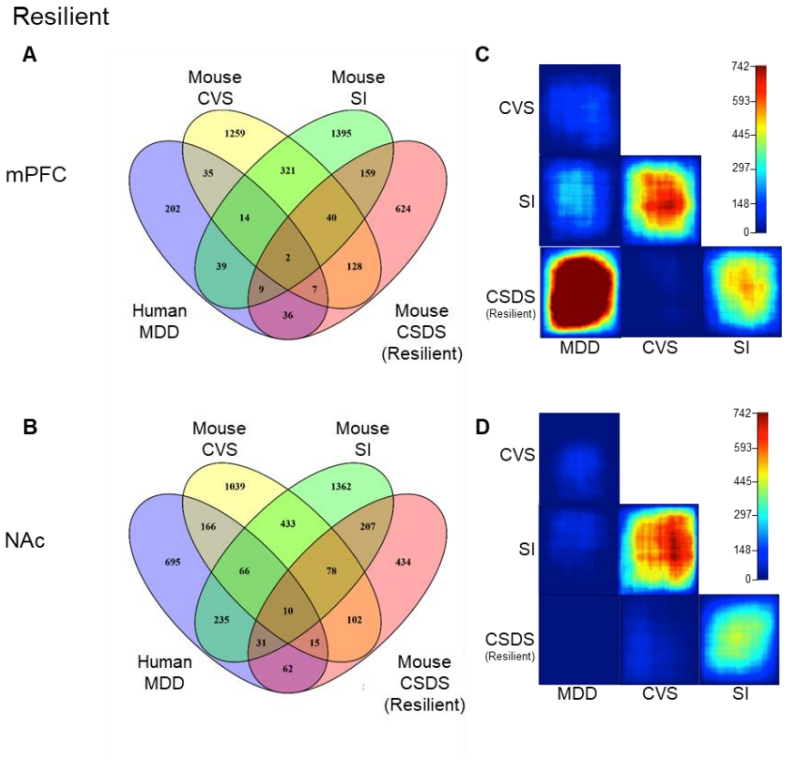


Figure 2. **Differential expression analysis reveals gene signatures associated with MDD in humans and CVS, SI and CSDS in mice**. *A, Representative list of genes differentially expressed in the mPFC of human MDD and mouse models. Colors represent fold changes values with bleu showing genes downregulated and yellow showing gene upregulated in MDD or stressed conditions compared to controls. The radius of the circles represents the statistical significance of the differential expression. Blank compartments represent genes being non significantly differentially expressed (p>0.1). B, CVS (yellow), SI (green) and susceptible mice to CSDS (red) each reproduce specific transcriptional changes found in the mPFC of human with MDD (blue). Values in the different portions of the Venn diagram represent the number of genes differentially expressed in common between humans and each of the mouse models of depressive-like behaviors. C, Unbiased rank-rank hypergeometric overlap (RRHO) analysis reveals shared transcriptional changes in the mPFC between human MDD and all three mouse models of depressive-like behaviors. The bar on the right of the plots show levels of significance for the rank overlap between humans and each of the mouse models with maximum Fisher's Exact Test [FET] p<1.0E-742. D, Representative list of genes differentially expressed in the NAc of human MDD and mouse models. Colors represent fold changes values with bleu showing genes downregulated and yellow showing gene upregulated in MDD or stressed conditions compared to controls. The radius of the circles represents the statistical significance of the differential expression. Blank compartments represent genes being non significantly differentially expressed (p>0.1). E, CVS (yellow), SI (green) and susceptible mice to CSDS (red) each reproduce specific transcriptional changes found in the NAc of human with MDD (blue). Values in the different portions of the Venn diagram represent the number of genes differentially expressed in common between humans and each of the mouse models of depressive-like behaviors. F, Unbiased rank-rank hypergeometric overlap (RRHO) analysis reveals shared transcriptional changes in the NAc between human*

MDD and all three mouse models of depressive-like behaviors. Similar transcriptional overlap is also observed across mouse models. The bar on the right of the plots show levels of significance for the rank overlap between humans and each of the mouse models with maximum Fisher's Exact Test [FET] p<1.0E-742.

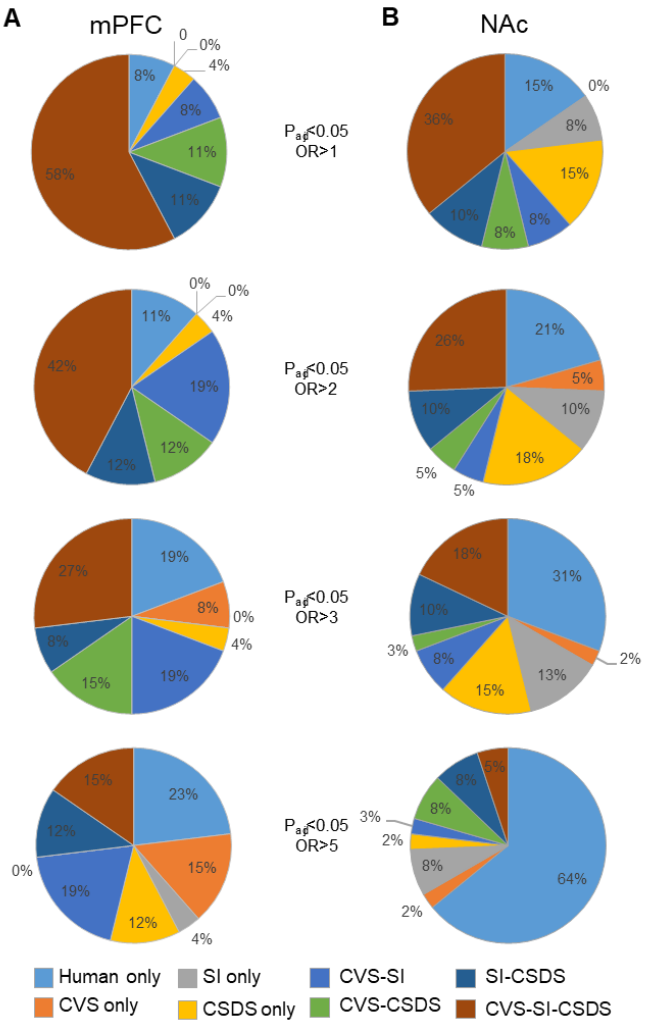


Supplemental Figure 2. ***A-B****, CVS (yellow), SI (green) and resilient mice to CSDS (red) mouse models each reproduce specific transcriptional changes found in the (****A****) mPFC and (****B****) NAc of humans with MDD (blue). Values in the different portions of the Venn diagram represent the number of genes differentially expressed in common between humans and each of the mouse models of depressive-like behaviors.* ***C-D****, Unbiased rank-rank hypergeometric overlap (RRHO) analysis reveals shared transcriptional changes in the (****C****) mPFC and (****D****) between human MDD and all three mouse models of depressive-like behaviors. The bar on the right of the plots show levels of significance for the rank overlap between humans and each of the mouse models with maximum Fisher's Exact Test [FET] p<1.0E-742.*

Shared transcriptional regulation revealed by gene network analyses

Recent work in mouse and human has revealed the value of going beyond differential expression analysis to characterizing gene networks, which reveal distinct but equally important transcriptional insight(Bagot et al., 2016; Horvath, 2011; Labonte et al., 2017b; B. Zhang & Horvath, 2005b). To determine the conservation of gene networks in human MDD and mouse stress models, we constructed brain region-specific co-expression gene networks for human MDD and mouse CVS, SI and CSDS. We identified 26, 58, 46 and 25 mPFC gene networks, and 39, 29, 31 and 42 NAc gene networks, in MDD, CVS, SI and CSDS, respectively. Each of these gene networks was given an arbitrary color name and was attributed a functional term based on their constituent genes.

Next, we calculated module conservation between the human and mouse cohorts by directly comparing the genes contained within each module. To avoid artifactual overlap due to module size, we first tested different odds ratio thresholds (OR>1.0, >2.0, >3.0 and >5.0) on gene networks showing significant interspecies enrichment (p_{adj}<0.05; **Supplemental Figure 3**). In mPFC, we found that the proportion of overlap between human and each of the mouse models does not vary much with increasing OR thresholds: the proportion of human modules being conserved in one, two or every mouse model varied from 92% at OR>1 to 77% with OR>5.0. In contrast, in NAc, this proportion went from 85% at OR>1.0 down to 36% at OR>5.0. This suggests that, while a significant number of human gene networks in mPFC and NAc are conserved in mice, those from mPFC are better conserved.



Supplemental Figure 3. *Human-mouse interspecies module conservation in the mPFC (**A**) and in the NAc (**B**). Enrichment was performed on module membership by brain region with p_{adj}<0.05 at increasing odd ratios (OR<1; OR<2; OR>3; OR>5). Pie plots are depicting the % of human modules conserved in each of the mouse models. Color legend is shown at the bottom of the figure. CVS: chronic variable stress, SI: social isolation, CSDS chronic social defeat stress.*

Based on this analysis, we used an OR>3.0 for further analyses. At this threshold, 81% of human gene networks in mPFC are conserved in at least one of the mouse models (FET p_{adj}< 0.05; OR>3.0), with 27% of the human networks conserved in all three mouse models (**Figure 3A**). More specifically, 69% of human networks are conserved in CVS and 54% in both SI and CSDS (**Figure 3A**). In NAc, 69% of human networks are conserved

in at least one of the three mouse models (FET p_{adj}< 0.05; OR>3.0), and 18% are conserved in all three mouse models, with 31% of human networks conserved in CVS and 49% and 46% preserved in SI and CSDS, respectively (**Figure 3B**). GO terms associated with these shared modules in mPFC and NAc are shown in **Figure 3**. Together, these results show that CVS, SI and CSDS each reproduces common but also unique transcriptional features of gene networks in human MDD.

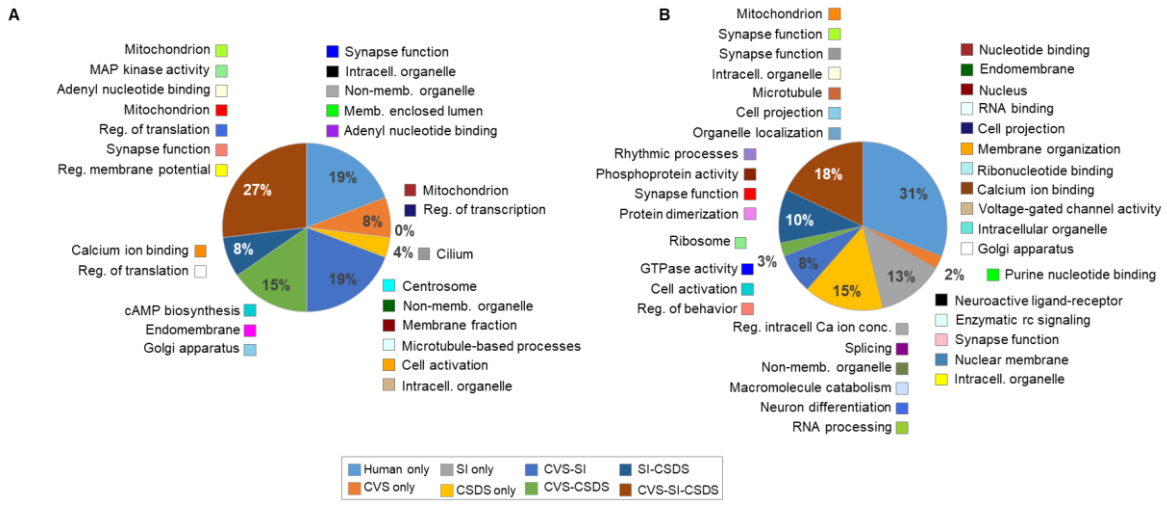
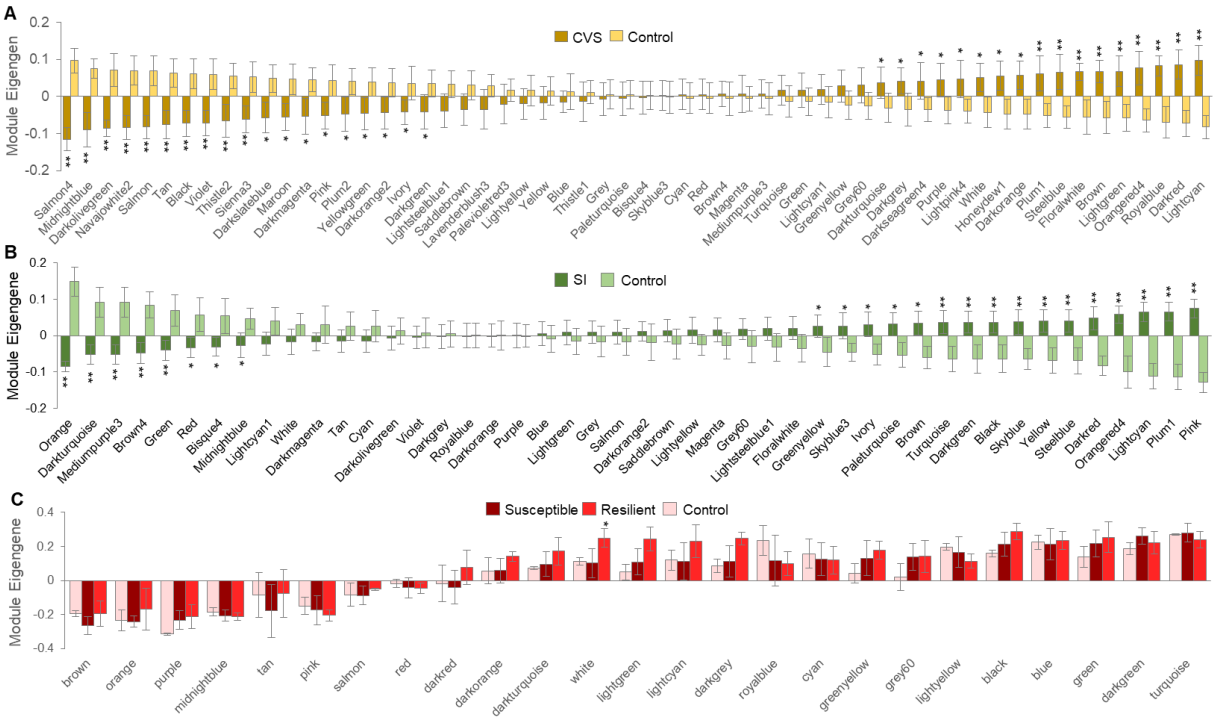


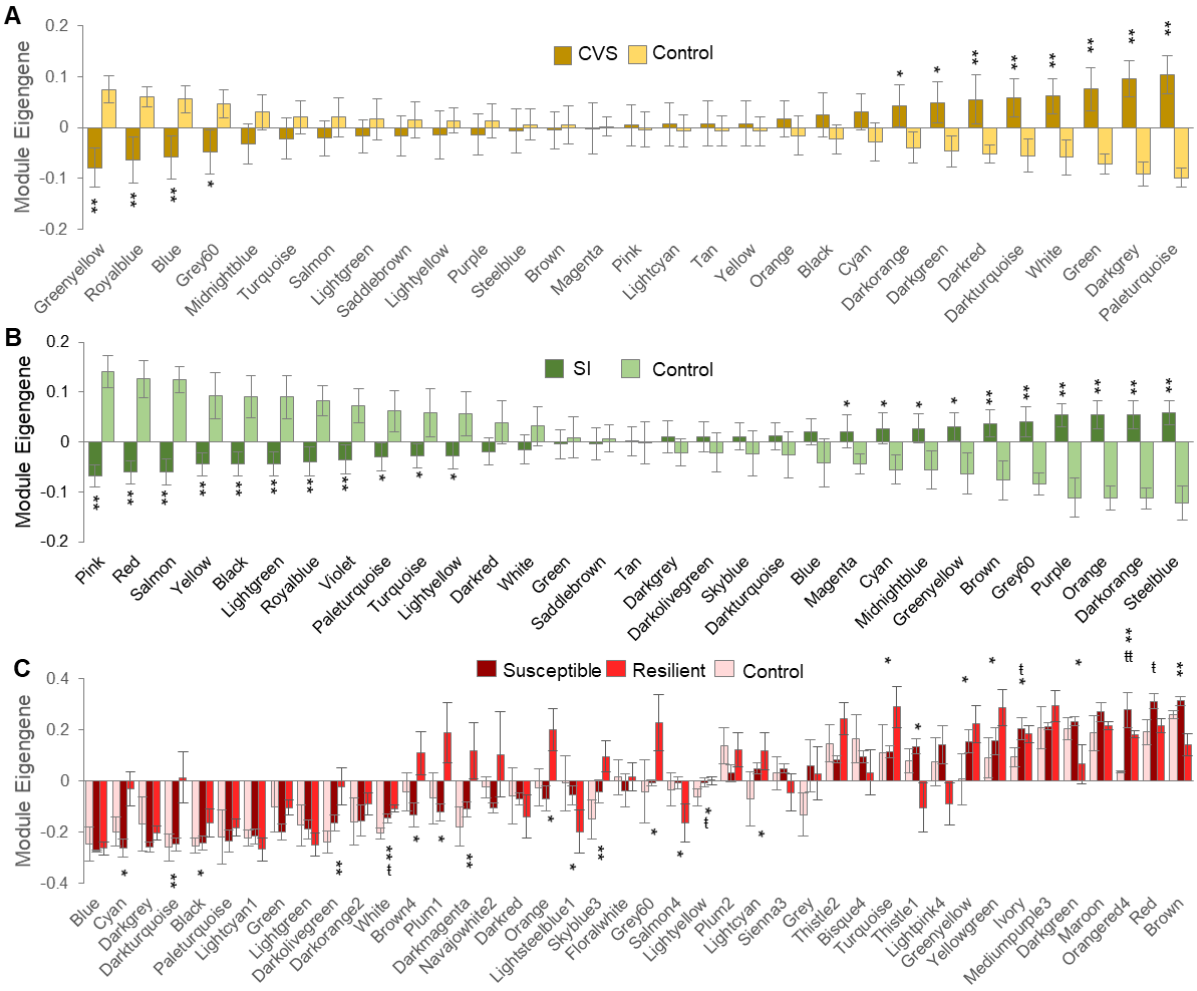
Figure 3. **CVS, SI and CSDS reproduce the transcriptional structure of gene network in human brain.** *Human-mouse interspecies module conservation in the mPFC (A) and in the NAc (B). Enrichment was performed on module membership by brain region with padj<0.05 at odd ratio (OR)>3. Pie charts are depicting the % of human modules conserved in each of the mouse models. Color legend is shown at the bottom of the figure. Besides each section of the pie appear the human modules (colored square) along with their ontological term. CVS: chronic variable stress, SI: social isolation, CSDS chronic social defeat stress.*

Transcriptional organization of gene networks associated with human MDD and mouse chronic stress

In the previous section, we determined which human gene networks were conserved in each mouse model. We then extended these analyses by testing whether the preserved genes networks were associated with "phenotype": namely, with MDD in humans and with stress exposure in the three mouse models. To determine which gene networks are most strongly associated with these phenotypes, we integrated our network and DEG analyses. We started by correlating the first principal component of each gene network ("module eigengene") with phenotype status to determine which networks are most strongly associated with DEGs in both species. Our analyses revealed that seven (4 upregulation; 3 downregulation; **Figure 4A**) gene networks in mPFC and 20 (5 upregulation; 15 downregulation; **Figure 4C**) in NAc are associated with MDD, while several gene networks in both brain regions of each mouse model associated with chronic stress (**Supplemental Figures 4, 5** and **6**).



Supplemental Figure 4. *Gene networks in the mPFC associate with the expression of stress in CVS, SI and CSDS. Bar graphs show significant differences in the module eigengene values between unstressed control and (**A**) CVS, (**B**) SI and (**C**) CSDS in the mPFC. Bars represent mean eigengene values with error bars showing standard error on mean. **A,B**, * p<0.2, ** p<0.05 for stress vs control. **C**, ŧ p<0.2, ŧŧ p<0.05 susceptible vs control and* p<0.2, ** p<0.05 resilient vs control.*



Supplemental Figure 5. *Gene networks in the NAc associate with the expression of stress in CVS, SI and CSDS. Bar graphs show significant differences in the module eigengene values between unstressed control and (**A**) CVS, (**B**) SI and (**C**) CSDS in the NAc. Bars represent mean eigengene values with error bars showing standard error on mean. **A,B**, * p<0.2, ** p<0.05 for stress vs control. C, ŧ p<0.2, ŧŧ p<0.05 susceptible vs control and* p<0.2, ** p<0.05 resilient vs control.*

We next directly compared the capacity of each mouse model to reproduce the associations found in human MDD. In mPFC, we identified two gene networks associated with human MDD that are also associated with CVS, while one with SI, two with CVS and SI but none with CSDS susceptible mice (**Figure 4A**). In NAc, we identified seven gene networks commonly associated with MDD and SI, one with CSDS susceptibility, and two with both SI and CSDS susceptibility (**Figure 4C**). GO terms associated with these shared networks are shown in **Figure 4A**,**C**. Similar associations with CSDS resilience are provided in **Supplemental Figure 6**.

We also assessed the capacity of each mouse model to reproduce the overrepresentation of DEGs in human gene networks. Our analyses in mPFC show that CVS has a limited capacity to reproduce the enrichment patterns for DEGs: when combining genes significantly up- and downregulated, CVS reproduced only 15% of the human enrichment patterns, while 58% were reproduced by SI and 65% by CSDS susceptible mice (**Figure 4B**). These patterns did not change when considering genes up- or downregulated uniquely in mPFC, but increased to 62% for CVS, 77% for SI and 85% for CSDS susceptible mice when considering only significantly downregulated genes (**Figure 4B**). In contrast, our results in NAc suggest that all three chronic stress models similarly reproduced human DEG enrichment patterns in gene networks: 56% for CVS and 64% for both SI and CSDS susceptible mice (**Figure 4D**).

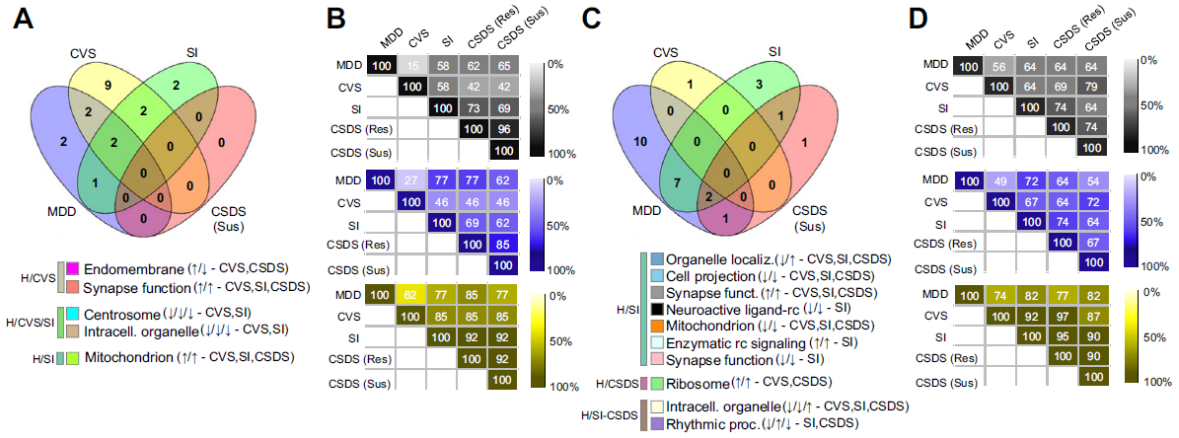
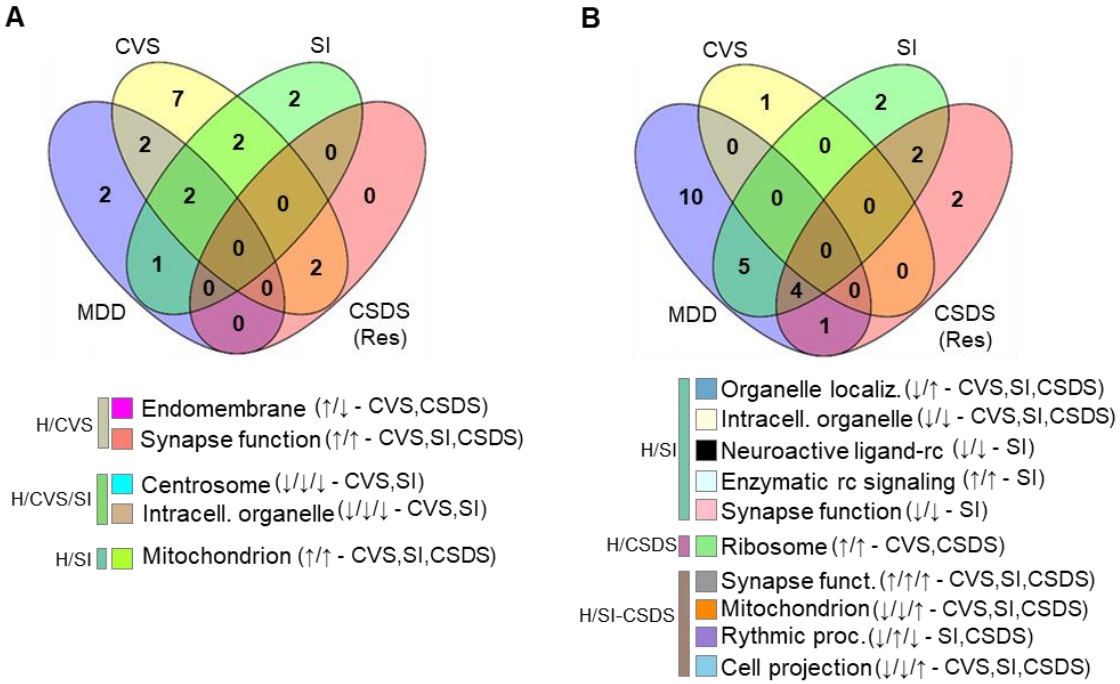


Figure 4. The transcriptional organization of gene networks associates with MDD in human and stress phenotypes in CVS, SI and CSDS. *A, C The proportion of interspecies preserved gene networks associated with MDD in human and stress in CVS, SI and CSDS susceptible differs by stress paradigms in the (A) mPFC and (C) NAc. Values in the Venn diagrams represent the number of gene networks preserved in human and mouse (padj<0.05; OR>3.0) and associated with MDD and stress (p<0.2) in human (blue) and CVS (yellow), SI (green) and CSDS susceptible (red). The legends below Venn diagrams in A and C represent the gene network (colored square) associated with their ontological terms commonly associated with the phenotype in human and mice. The arrows in the legend indicate directionality of the association in human MDD (up: increased in MDD*

compared to control, down: decreased in MDD vs control) followed by directionality of the association in respective mouse models. Human, CVS, SI and CSDS susceptible indications at the end of each network line represent whether each networks are conserved (based on module membership) in CVS, SI or CSDS or not (human only). B,D Heat maps showing the capacity of each mouse model to reproduce patterns of enrichment of genes differentially expressed in the human gene networks in the (B) mPFC and (D) NAc. Numbers in the maps show the percentage of human gene networks showing the same enrichment patterns (black: up and downregulated genes combined, blue: downregulated genes only and yellow upregulated genes only) for genes differentially expressed in each of the mouse models.



Supplemental Figure 6. *The proportion of interspecies preserved gene networks associated with MDD in human and stress in CVS, SI and CSDS resilient differs by stress paradigms in the (**A**) mPFC and (**B**) NAc. Values in the Venn diagrams represent the number of gene networks preserved in human and mouse (p_{adj}<0.05; OR>3.0) and associated with MDD and stress (p<0.2) in human (blue) and CVS (yellow), SI (green) and CSDS resilient (red). The legends below Venn diagrams in **A** and **B** represent the gene network (colored square) associated with their ontological terms commonly associated with the phenotype in human and mice. The arrows in the legend indicate directionality of the association in human MDD (up: increased in MDD compared to control, down: decreased in MDD vs control) followed by directionality of the association in respective mouse models. Human, CVS, SI and CSDS resilient indications at the end of each network line represent whether each networks are conserved (based on module membership) in CVS, SI or CSDS or not (human only).*

Identification of mouse model-specific hub genes relevant to human MDD

We integrated these analyses to rank each human gene network by their "relevance" based on: a) association with MDD or stress exposure and b) enrichment of DEGs in human MDD and in each of the three mouse models for mPFC (**Figure 5A**) and NAc (**Figure 5C**). GO terms associated with these shared networks are shown in these figures.

Next, we calculated and compared hub genes in all human and mouse networks. Hub genes are highly connected with neighboring genes within a given module and have been shown to be significantly associated with disease traits in other experimental systems (Bagot et al., 2016; Horvath, 2011; Labonte et al., 2017b; Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Wright, et al., 2019; B. Zhang & Horvath, 2005b). In mPFC, we concentrated our interest on the h*Yellow* gene network (**Figure 5B**), which is composed of 675 genes out of which 34 (top 5% most connected genes) are hub genes. This module is involved in the regulation of membrane potential. ~6% of genes in this module are enriched in oligodendrocytes (p_{adj}<2.2E-14; OR>6.0; **Supplemental Figure 7A**). h*Yellow* is conserved in every mouse model and is significantly associated with stress in SI, an observation consistent with previous findings showing significant alterations of oligodendrocyte structure and function induced by SI in mice(J. Liu et al., 2012) and with recent postmortem observations in suicide completers with a history of child abuse(Lutz et al., 2017b; Tanti et al., 2018). h*Yellow* is also enriched for genes significantly downregulated in human MDD (p_{adj}<4.0E-4, OR>1.3), SI (p_{adj}<2.4E-12, OR> 1.8) and both CSDS susceptible (p_{adj}<5.4E-30, OR>2.6) and CSDS resilient (p_{adj}<4.1E-29, OR> 2.5) mice, with no association seen for CVS (**Figure 5A**). Our analysis shows that the mouse equivalent of h*Yellow* in CVS shares 172 genes, while SI and CSDS equivalent networks share 148 and 39 genes, respectively, with their human counterpart. Our analysis also shows that human hub genes in *hYellow* are well conserved in all three mouse models (**Figure 5B**). For instance, restricting our analysis to the 5% most highly connected (hub) genes, we found that, out of the 34 human hub genes within the h*Yellow* network, 8 conserved their hub status in CVS, 7 in SI and 6 in CSDS (**Figure 5C,D**). **Figure 5E** lists conserved hub genes between all human and mouse models. Our analysis shows that the GRB2-associated-binding protein 1 (*Gab1*) gene serves as a hub in human and every mouse model suggesting that it may have similar control over this network activity in both species.

In NAc, we focused our investigation on the h*Salmon* network (**Figure 5F**), which is composed of 196 genes (10 hub genes) involved in control of behavior. h*Salmon* is significantly associated with human MDD and is enriched for genes significantly downregulated in human MDD (p_{adj}<0.005, OR>1.8), CVS (p_{adj}<0.05, OR>1.5) and CSDS susceptible mice (p_{adj}<0.05, OR>1.4; **Figure 5F**). The mouse equivalent of h*Salmon* in CVS shares 12 genes, while SI and CSDS mouse equivalent networks share 8 and 26 genes, respectively, with their human

counterpart. Additionally, out of the 10 hub genes within the h*Salmon* network, 3 conserved their hub status in CVS, 2 in SI and 3 in CSDS susceptible mice (**Figure 5G-I**). We found *Lrrc7*, encoding leucine rich repeat containing 7 protein, as a common hub between humans and all three mouse models (**Figure 5J**).

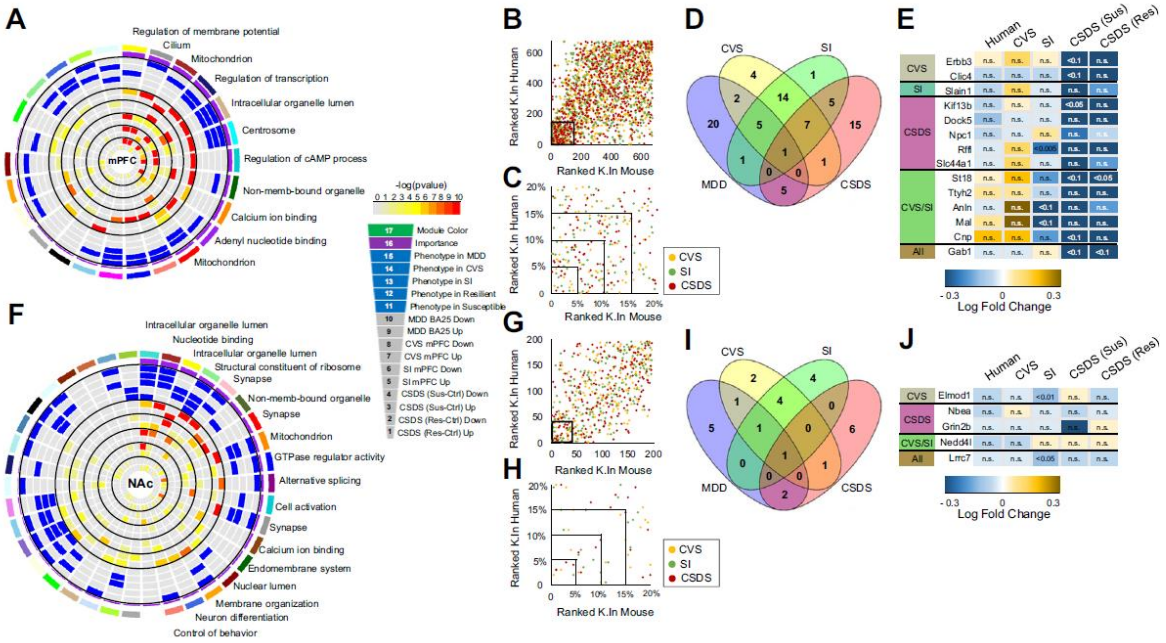
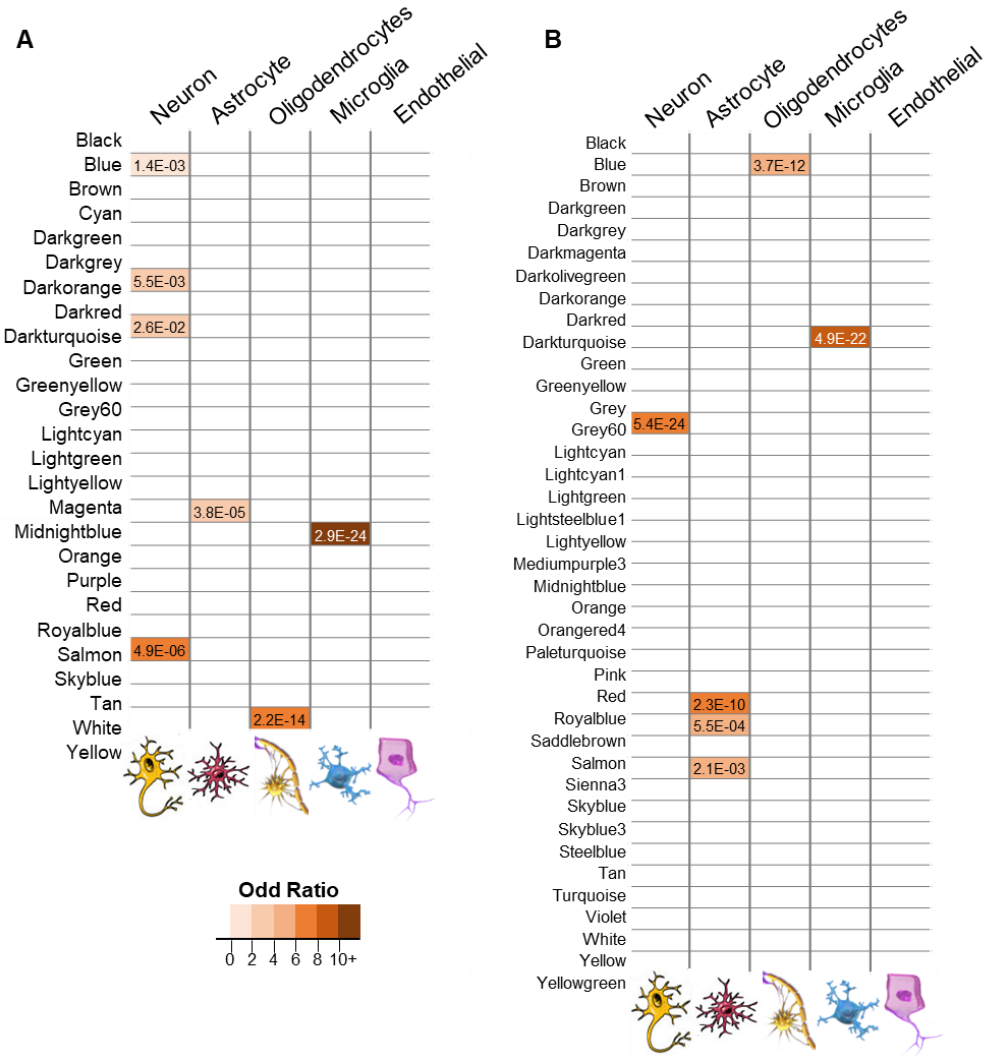


Figure 5. CVS, SI and CSDS recapitulate the transcriptional organization of gene networks associated with MDD in human mPFC and NAc. *A Circos plots displaying the degree of enrichment for DEGs (p<0.05) in human gene networks in mPFC. Each slice of the chart represents a gene network. The key for the concentric circles is shown on the right of the graph. The outermost rectangle is an arbitrary color as the network name, followed by module "importance" (a composite measure considering the degree of enrichment for DEGs and association with phenotype in human, CVS, SI and CSDS susceptible or resilient). The innermost concentric circles represent the degree to which DEGs in humans and each of the mouse models are contained within a given module from the mPFC (colors reflect corrected FET pval with key provided to the right of the plot). B Scatter plot comparing hYellow network gene ranking (connectivity K.In) in humans and each mouse model (yellow: CVS, green: SI and red: CSDS). The inner square represents the 20% most connected genes. C Scatter plot showing the proportion of most highly connected genes in human and each mouse stress model (enlargement of inner square in B) with the top 5% representing interspecies conserved hub genes in the hYellow gene network. D Venn diagram depicting the number of hub genes within hYellow preserved in each mouse model (blue: human, yellow: CVS, green: SI and red: CSDS). E Table listing hYellow hub genes preserved in human and each of the mouse models with colors in the table indicating fold change in the expression of each gene over respective control conditions (scale presented below the table). n.s.: non-significant transcriptional change. F Circos plots displaying the degree of enrichment for DEGs (p<0.05) in human gene networks in NAc.*

The innermost concentric circles represent the degree to which DEGs in humans and each mouse model are contained within a given module from the NAc (colors reflect corrected FET pval with key provided to the right of the plot). G Scatter plot comparing hSalmon network gene ranking (connectivity K.In) in humans and each mouse model (yellow: CVS, green: SI and red: CSDS). The inner square represents the 20% most connected genes. H Scatter plot showing the proportion of most highly connected genes in human and each mouse model of chronic stress (enlargement of inner square in G) with the top 5% representing interspecies conserved hub genes in the hSalmon gene network. I Venn diagram depicting the number of hub genes within hSalmon preserved in each mouse model (blue: human, yellow: CVS, green: SI and red: CSDS). J Table listing hSalmon hub genes preserved in human and each of the mouse model with colors in the table indicating fold change in the expression of each gene over respective control conditions (scale presented below the table). n.s.: non-significant transcriptional change.



Supplemental Figure 7. *Gene networks in human mPFC and NAc are enriched with genes expressed in specific cell types. A subset of human gene network in (**A**) the mPFC and (**B**) NAc are enriched with genes highly expressed in neuronal, astrocytic, oligodendrocytic, microglial and endothelial cell types. Heatmaps plot the adjusted p values of the enrichments with colors representing variations in odd ratio in (**A**) the human mPFC and (**B**) the human NAc.*

Discussion

Dissecting the molecular underpinnings of MDD has relied heavily on the use of rodent stress models, the validation of which is based on construct, face and predictive validity (Nestler & Hyman, 2010; Willner, 1984). However, there has recently been increased scrutiny of mouse chronic stress models given the inherent difficulty of achieving face validity by relating behavioral abnormalities in mice vs. humans (Bale et al., 2019). A major goal of the present study was to ascertain face validity of mouse chronic stress models at the molecular level through genome-wide transcriptional analysis which is inherently far more objective than behavioral comparisons.

Leveraging DEGs and WGCNA, we evaluated the capacity of CVS, SI and CSDS, three of the most widely used mouse chronic stress models, to reproduce the transcriptional profiles associated with human MDD in two brain regions—mPFC and NAc—widely implicated in depression. Our results show that each model efficiently reproduces common but also unique transcriptional features of the human syndrome. A striking finding is that each of several bioinformatics approaches identified distinct overlaps between human MDD and the three mouse stress models in mPFC and NAc. These differences reflect the knowledge that DEGs, RRHO and WGCNA each captures only partly overlapping modes of transcriptional regulation. Overall, the results of this comprehensive analytical pipeline suggest that no one mouse model is better than another, consistent with the interpretation that each model captures a significant portion of the molecular pathology associated with the broad and heterogeneous human syndrome.

Our analyses culminated with the identification of network hub genes as performed previously for human MDD (Labonte et al., 2017b) and mouse CSDS and CVS(Bagot et al., 2016; Labonte et al., 2017b; Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Wright, et al., 2019). This multilevel integrative analysis allowed us to identify hub genes for each gene network and evaluate whether these hubs are preserved in each mouse model. We used this approach to rank gene networks integrating simultaneously their association with human MDD or stress exposure in mice with DEG patterns across species. In mPFC, we identified h*Yellow* as being involved in the regulation of membrane potential, including numerous genes enriched in oligodendrocytes. Disruption of white matter integrity has been associated with MDD(L. Wang, Leonards, Sterzer, & Ebinger, 2014). Recent findings in human postmortem brain showed impaired myelin-related gene expression and reduced myelin thickness in the anterior cingulate of suicide completers with childhood abuse(Lutz et al., 2017b). Elevated numbers of mature oligodendrocytes along with decreased expression of myelin basic protein has also been reported in mPFC of abused suicide completers(Tanti et al., 2018). Our results show that h*Yellow* is conserved in all three mouse models and enriched for DEGs in human MDD and SI and CSDS but not CVS in mice. Interestingly, SI(J. Liu et al., 2012) and CSDS(H. Zhang et al., 2016) have been associated with consistent changes in

oligodendrocytic genes along with loss of myelin integrity in mPFC. Overall, our results are in accordance with previous findings linking altered oligodendrocytic functions with MDD and provide a transcriptional substrate through which these alterations in MDD could be reproduced by these mouse stress model.

We successfully identified a series of hub genes consistently preserved in human MDD and each of the three mouse models. Of particular interest, *GAB1* was the only human hub gene in the h*Yellow* network conserved in all mouse models. *Gab1* is known to enhance PI3K/AKT activation and to extend the duration of Ras/MAPK signalling (Kiyatkin et al., 2006); it is also downregulated by glucocorticoids (Juszczak & Stankiewicz, 2018). Additionally, PKA activates ERBB2 and its effector GAB1 to elevate *Oct6* and *Egr2* expression and trigger myelination(Ghidinelli et al., 2017).

Similarly, in NAc we identified h*Salmon* as a gene network enriched with genes associated with the GO term "control of behavior". We found the *Lrrc7* hub gene, which encodes Densin-180, conserved in all mouse models. Densin-180 is found in postsynaptic densities (PSDs) where it interacts with key synaptic signaling proteins including α-actinin, CamKIIα, shank, maguin-1 and β- and δ-catenin(Thalhammer, Trinidad, Burlingame, & Schoepfer, 2009). Densin-180 controls positioning of CamKIIα at the PSD (Strack, Robison, Bass, & Colbran, 2000), and its deletion impairs glutamate receptor-dependent forms of long-term depression and modifies spine morphology (Carlisle et al., 2011). Thus, by playing central roles in crucial intracellular pathways, *Gab1* and *Llrc7* likely modulate the expression of adaptive responses to chronic stress, although more work is required to elucidate their specific contributions in CVS, SI and CSDS.

Another interesting finding emerging from our study refers to the degree of overlap that SI shares with CSDS and, to a lower extent, with CVS, while CVS and CSDS share very few similarities in terms of network association with human MDD. This may refer to the type of chronic stressors constituting these different paradigms. CVS uses physical stressors (e.g., foot shocks, tail suspension and tube restraint)(Hodes et al., 2015; Labonte et al., 2017b), whereas SI and CSDS rely on psychosocial stressors either social exclusion(J. Liu et al., 2012; Wallace et al., 2009) or social defeat(Berton et al., 2006; Golden et al., 2011). The molecular similarity between SI and CSDS may therefore reflect the involvement of common coping strategies triggered by psychosocial stress. Our results raise the possibility that each of three chronic stress models might capture a distinct subtype or aspect of the heterogeneous MDD syndrome. Analysis of much larger human cohorts will be needed to test whether a given mouse model is associated with a given symptom cluster or historical feature (e.g., early life stress) of MDD.

Interestingly, our results highlighted a significant level of overlap between human MDD and CSDS resilience. This overlap could reflect the fact that all organisms mount resilient-related adaptations in an attempt to cope with stress. Indeed, numerous molecular adaptations induced by chronic stress in mouse have been linked

causally to behavioral resilience(Bagot et al., 2016; Bagot et al., 2017). Another possibility is that prior antidepressant medication, although clinically ineffective, may have triggered the activation of resilient-like molecular programs, as shown before in mice following CSDS(Bagot et al., 2017). While we controlled for the effect of medication in our human cohort, we cannot exclude the possibility that such treatment may have induced long-term transcriptional changes. Future work with larger human cohorts is also needed to address this question.

mPFC and NAc differ considerably at the molecular, cellular, and circuit levels between mouse and human, and such divergence represents an obvious limitation intrinsic to interspecies comparative studies. This being said, significant degrees of conservation have also been demonstrated for both brain regions(Defelipe, 2011; Duzel et al., 2009; Geschwind & Rakic, 2013; Hodge et al., 2019; McCutcheon, Abi-Dargham, & Howes, 2019; Strand et al., 2007), with significant preservation in processing of rewarding and motivational cues and in the top-down control of emotions. The high levels of interspecies transcriptional convergence observed in the present study presumably reflects this conservation.

The transcriptional signatures of MDD exhibit strong sexual dimorphism (Fatma & Labonte, 2019; Labonte et al., 2017b; Seney et al., 2018). Despite this important fact, we performed our study by controlling statistically for the effects of sex. Only our human and CVS cohorts included females. This may, unfortunately, limit our interpretation of the data and may have potentially masked some effects, as we (Labonte et al., 2017b) and others (Seney et al., 2018) have shown dramatic transcriptional sex differences with several examples of opposite changes in gene expression seen in males vs. females. The statistical approach we used, controlling for the main effect of sex in humans and CVS accounted for this effect. SI and CSDS (Harris et al., 2017) can be performed in females, and it will be interesting in future studies to assess our predictions in the two sexes.

To conclude, by identifying the transcriptional signatures shared between human MDD and CVS, SI and CSDS in mice, our analyses provide a framework supporting the use of mouse models for the study of MDD and guide their selection for studying specific aspects of the syndrome. Clearly none of the mouse models fully recapitulates MDD nor would they be expected to(Nestler & Hyman, 2010). Rather, they replicate aspects of the syndrome. This is not an impediment, but instead an opportunity to use these three and presumably other mouse models to more fully integrate molecular mechanisms of MDD. The approaches used in this study are highly reliable when associating specific molecular signatures with precise clinical and behavioral assessments in humans(B. Zhang et al., 2013) and mice(P. Jiang et al., 2015). This enterprise is certainly ambitious, especially considering the intrinsic limitations associated with postmortem tissue, although studies using peripheral tissue (e.g., blood) would be worth exploring. Nevertheless, by knowing that transcriptionally speaking CVS, SI and

CSDS each reproduces certain details of the transcriptional signatures of MDD, future studies can more precisely associate these transcriptional signatures with specific symptomatic and historical profiles of the syndrome.

Author contributions

Y.H.E.L., M.F, J.R. S., E.J.N. and B.L. conceived the project, designed the experiments, and wrote the manuscript. Y.H.E. L., J.R.S., R.S.T., T.S., M.F., T.H.C. and B.L. also generated and analyzed all the data. All authors contributed to the preparation of the manuscript.

Acknowledgement

BL holds a Sentinelle Nord Research Chair, is supported by a NARSAD young investigator award, a CIHR (SVB397205) and Natural Science and Engineering Research Council (NSERC; RGPIN-2019-06496) grants and receives FRQS Junior-1 salary support. EJN is supported by the National Institute of Mental Health (P50MH096890 and R01MH051399) and by the Hope for Depression Research Foundation (HDRF).

Financial disclosures

Authors report ii biomedical financial interests or potential conflicts of interest.

Conclusion

Around three hundred million people worldwide suffer from depression. The burden of this dreadful disorder is ever increasing (Mena & Benoit, 2019a). In fact, only around 30% of patients who are treated for depression show complete improvement in their symptoms (Blackburn, 2019; Mena & Benoit, 2019a). Sadly, we are still stagnant in improving the therapeutic options for this disorder (Bale et al., 2019). Factually speaking, newly designed drugs display very low success rate and are very prone to failure in clinical trials (Blackburn, 2019). Consequently, there has been increased questioning recently on the use of animal models in depression as they display low face validity at the behavioral level as compared to humans (Bale et al., 2019; Planchez, Surget, & Belzung, 2019). This thesis aims to ascertain face validity of mouse chronic stress models at the molecular level through genome-wide transcriptional analysis, which is intrinsically far more powerful than subjective behavioral comparisons. Here, three most commonly used chronic stress mouse models - namely CVS, CSDS and SI- were used to evaluate transcriptional overlap with human MDD in two brain regions, mPFC and NAc, repeatedly cited in MDD. Different bioinformatics tools, i.e DEGs, RRHO, WGCNA, GO, conservation analysis, phenotype association and hub calling, were applied on self generated and publically available RNA-seq datasets of human MDD and all mouse models of stress. Our results catalogued the capacity of each chronic stress mouse model to replicate the transcriptional signature of MDD across the two brain regions. We showed that each mouse model not only recapitulates shared but also exclusive transcriptional landscapes of MDD efficiently. We presented a large, rigorous and comprehensive analysis of the brain regions of human MDD and mouse models of stress. Interestingly, all bioinformatics tools, DEGs, RRHO, and WGCNA, yielded unique overlaps between MDD and the three mouse models of stress. The statistical approach that DEGs (threshold-dependent), RRHO (threshold-free), and WGCNA (correlated network) use are different. Hence, they capture only a distinct portion of the transcriptional overlap between MDD and mouse model of stress. Conclusively, no model is better than the other and each and each mouse models model specific molecular aspects of the human disorder.

Our results show that hYellow module as being conserved in mPFC of all 3 mouse models. Our GO analysis shows the involvement of this module in the regulation of membrane potential. Also, hYellow was enriched with numerous oligodendrocytic genes. In this thesis, we efficiently identified a series of hub genes that are consistently conserved in human MDD and each of the 3 mouse models of stress. We found GAB1 (GRB2-associated-binding protein 1) of human Yellow network as the only hub gene conserved in all mouse models of stress in mPFC. Similarly, in NAc we concentrated on hSalmon module, associated with the GO term control of behavior. We found the Lrrc7 hub gene, which encodes densin-180, conserved in all mouse models.

An important outcome of this thesis is the degree of overlap that SI shares with CSDS and, to a lower extent, with CVS, while CVS and CSDS share very few similarities in terms of network association with human MDD.

Differences in the type of stress used in these paradigms might explain these results. This may be related to the type of chronic stressors constituting these different paradigms. Surprisingly, we also found a significant overlap between human MDD and CSDS resilience.

In conclusion, none of the three mouse models of stress examined, completely reproduce the transcriptional alterations seen in human MDD, nor would they be expected to do so (Nestler & Hyman, 2010). Indeed, the associated different types of stress in these paradigms mimic different human pathological stressors. These mouse model of stress, rather, reproduce different subtype and aspects of the human disorder. As a matter of fact. this is not an impediment but instead an opportunity to appropriately use these 3 mouse models, and presumably other ones, to more fully integrate molecular mechanisms of MDD. The approaches used in this study are robust and highly reliable when associating specific molecular signatures with precise clinical and behavioral assessments in humans (P. Jiang et al., 2015) and mice (P. Jiang et al., 2015).

General Discussion

MDD is a debilitating condition, which affects a major chunk of our society. Epidemiological statistics of MDD indicates that we still lack proper therapeutic interventions. One of the important factors responsible for this gap is the failure of candidate anti-depressants drugs at clinical trials. Consequently, there are doubts in the field that if these animals model are a reliable tool to study depression. Factually speaking, modeling complete depression pathology in animals is nearly impossible, primarily due to its heterogeneous etiology and complex inheritance. Indeed, MDD lacks true genetic models but stress based animal models have been extensively used to study depression. Although chronic stress is known to induce depressive-like behaviour in animals, it is extremely important to determine if it induces molecular pathology of human MDD as well. This thesis provides a critical proof-of-principle necessary to ascertain the face validity of chronic stress animal models at the molecular level. We ran a deep dig into the transcriptomes of the two species, human and mouse, employing statistical approaches of different resolutions which provides detailed information starting from single-gene level to its gene network dynamics. These approaches include differential expression and network analysis which complement each other and together bring out better transcriptional insights than these do alone. In other words, a combination of these two tools paints a more complete picture of the complex transcriptional response to stress. Eventually, this blend gave us a higher degree of freedom to navigate and compare the transcriptome of the two species.

In this thesis, we used several different bioinformatics approaches to inspect overlaps between human MDD and the three mouse stress models. We used both threshold-dependent (DEGs) and threshold-free (RRHO) approaches to compare gene expression of MDD and mouse models of stress. The network approach (WGCNA) added more rigor to the structure of analysis, by allowing integration of gene significance data (e.g. correlation between gene expression and MDD or mouse model of stress) and module membership data for identification of biologically and statistically interesting genes (B. Zhang & Horvath, 2005a). These different analyses capture different dimensions of big and highly complex datasets. DEGs and RRHO reflect single-dimensional changes-comparison of expression of 'a gene' between different conditions-, while network differential connectivity presented changes in two-dimensional setting where it captures changes in the correlations between sets of genes. Differential expression and differential connectivity are very different and are fundamentally independent metrics but could co-exist (Bagot et al., 2016). We integrated these analyses to rank each human gene network by its relevance/importance based on phenotype association (MDD or stress exposure) and enrichment of DEGs in MDD and in each of the 3 mouse models for both brain regions. We related the resultant modules to gene ontology information to evaluate their biological plausibility. As it is known the modules may correspond to biological pathways (Langfelder & Horvath, 2007), we focused the analysis on intramodular hub genes (or the module eigengenes) which are genes highly connected with neighboring genes within a given module. This is

an excellent biologically driven data reduction strategy for huge and complex datasets like ours (Fuller et al., 2007). Hub genes have been reported to be significantly linked with the other clinical outcomes in different studies (Fu, Zhou, Zhang, Wang, & Wang, 2019; Mosca et al., 2017; B. Zhang et al., 2013). Identification of network hub genes has been performed previously for human MDD (Bagot et al., 2016) and mouse CSDS and CVS (Bagot et al., 2016; Labonte et al., 2017a; Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Salery, et al., 2019). In our study, we performed a very sophisticated multilevel integrative analysis which allowed us to identify hub genes for each gene network related to human MDD and evaluate whether these hub genes are preserved in each mouse model.

Our results show that hYellow module is conserved in mPFC of all 3 mouse models. Our GO analysis shows the involvement of this module in the regulation of membrane potential. Also, hYellow was enriched with numerous oligodendrocytic genes. Interestingly, MDD has been linked with altered white matter integrity (Boda, 2019; L. Wang et al., 2014). In fact, oligodendrocyte involvement in mood regulatory mechanisms has been long-anticipated (Edgar & Sibille, 2012). For instance, GRs are expressed in mature oligodendrocytes as well as their progenitors and are involved in the promotion of myelination (Cheng & de Vellis, 2000; Matsusue, Horii-Hayashi, Kirita, & Nishi, 2014). Also, GRs on activation affects oligodendrocytes and their progenitors morphology and proliferation rates via downstream intracellular pathways (Alonso, 2000; Miyata et al., 2011; Wennstrom, Hellsten, Ekstrand, Lindgren, & Tingstrom, 2006; B. Zhou, Zhu, Ransom, & Tong, 2021). Talking of neurotrophic theory of depression, BDNF plays vitally important roles in myelination. Also, it is known that BDNF mimetic agents promote oligodendrocyte-mediated myelination in vitro (A. W. Wong et al., 2014). Among the many assorted neurotransmitter receptors present in OL lineage cells, glutamate receptors seem to be a little exclusive as they are sundry and differentially expressed by progenitors and mature OLs. Recently, a study reported that nerve-glia antigen 2 (NG2) cleavage by an enzyme in OPCs impairs N-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP) in pyramidal neurons of the somatosensory cortex (Sakry et al., 2014). Moreover, higher glutamate levels in depression could be at least partially explained by alterations in NMDA and AMPA/kainite receptors of OL which can cause glutamate receptor-induced excitotoxicity and glutamate overload in OLs. It's worth mentioning that OPC activation-derived GABA release might shape GABAergic synapses and impact hippocampal excitatory–inhibitory balance in CSDS mice model, although yet to be confirmed (B. Zhou et al., 2021). Even though the role of purinoceptors in depression is yet to be clearly understood, there are sound evidence of ATP-gated purinergic receptors, P2X7 receptors (P2X7R), playing an important role in the pathology of depression. For instance, P2X7Rs in OL lineage cells regulate the release and uptake of various neurotransmitters such as 5-HT, glutamate, GABA, noradrenaline and nitric oxide in stress animals as well as in MDD (Verkhratsky, Krishtal, & Burnstock, 2009). Also, over activation of P2X7Rs is associated with demyelination and cell death of OLs (Matute, 2008; B. Zhou et al., 2021). Moreover, ablation of P2X7Rs significantly upregulates basal BDNF levels in the CNS which eventually rescues depressive-like

behavior in mice (Csolle et al., 2013). Interestingly, the two important 5-HT receptors, 5-HT1AR and 5-HT2AR, are expressed in OL lineage cells. Reports confirmed that myelin-related transcriptional factors are downregulated on exposure to 5-HT and eventually results in the myelination malformation and injury of OL lineage cells through 5-HT2AR (Fan et al., 2015; B. Zhou et al., 2021). To add, two DA receptors, D2 and D3, play an important part in myelin maintenance and are also predominantly expressed in mature OLs and OPCs during myelin formation (Bongarzone, Howard, Schonmann, & Campagnoni, 1998; Howard et al., 1998; B. Zhou et al., 2021). Interestingly**,** D2 receptor ablation (D2R-/-) results in augmented anxiety and depression-like behaviors in mice and a decrease in myelin levels as well when chronically stressed (Choi et al., 2017; B. Zhou et al., 2021). Exciting genome-wide findings in human postmortem brain indicate myelin-related gene expression dysregulation and reduced myelin thickness in the anterior cingulate of suicide completers with childhood abuse (Lutz et al., 2017a). Also, an increase in numbers of mature oligodendrocytes in conjunction with decreased myelin basic protein expression has been reported in mPFC of suicide completers with childhood abuse (Tanti et al., 2018). Most importantly, recently at a single-nucleus transcriptomics level analyses of dlPFC from postmortem brains of MDD patients, it has been reported that excitatory neurons and immature oligodendrocyte precursor cells (OPCs) sponsored almost half of all the DEGs found to be relevant to MDD (Nagy et al., 2020). Additionally, hYellow was also enriched for DEGs in human MDD and in SI and CSDS but not CVS in mice. Interestingly, SI (J. Liu et al., 2012) and CSDS (H. Zhang et al., 2016) have been linked with significant alterations in oligodendrocytic genes in conjunction with loss of myelin integrity in mPFC. Overall, our results are in agreement with previous and recent findings linking altered oligodendrocytic functions with MDD.

Interestingly, GAB1 (GRB2-associated-binding protein 1) was the only human hub gene in the hYellow network conserved in mPFC of all mouse models of stress. As a matter of fact, phosphorylation of TrkB leads to recruitment of adaptor proteins including Gab1 which in turn leads to subsequent activation of PI3K/AKT pathway and extension of the duration of Ras/MAPK signaling (Duman & Voleti, 2012; C. Jiang & Salton, 2013; Kiyatkin et al., 2006; Marshall et al., 2018). It is also downregulated by glucocorticoids (Juszczak & Stankiewicz, 2018). Moreover, PKA activates ERBB2 and its effector GAB1 to elevate Oct6 and Egr2 expression and trigger myelination (Ghidinelli et al., 2017). In addition, a recently published report confirms that Gab1 is crucial to CNS myelination and oligodendrocyte differentiation (L. Zhou et al., 2020).

Likewise, in NAc we focussed on human Salmon network module. This module is associated with the function ‘control of behavior’. One of its hub genes, Lrrc7 which encodes densin-180, was conserved in all mouse models. Densin-180 is found in postsynaptic densities, where it interacts with key synaptic signaling proteins, including a-actinin, CamKIIa, shank, maguin-1, and b- and d-catenin (Thalhammer et al., 2009). It controls the positioning of CamKIIa at the postsynaptic density (Strack et al., 2000), and its deletion impairs glutamate receptor–dependent forms of long-term depression and modifies spine morphology (Carlisle et al., 2011). Also, densin-

180 has been recently reported to control trafficking and signaling of L-type voltage-gated Ca2+ channels ($Ca_v1.2$), associated with MDD risk, at excitatory synapses (S. Wang et al., 2017). Thus, with central roles in crucial intracellular pathways and working around key MDD-risk-potential molecules, Gab1 and Llrc7 are likely to regulate the expression of adaptive responses to chronic stress, although more work is required to elucidate their specific contributions in CVS, SI, and CSDS.

All the other modules mentioned in mPFC and NAc are also important as they are also common between human and all mice models. They are fairly associated with the phenotypes and contain a significantly high degree of DEGs. For example, *'blue'* module which is associated with the GO term 'synapse', *'brown'* with 'mitochondrion', *'midnightblue'* with regulation of transcription, etc. in mPFC; and *'brown'* associated with 'nucleotide binding', '*pink'* with 'synapse', '*darkorange'* with 'mitochondrion', etc, in NAc. Unfortunately, this thesis could not cover them all but it would be something interesting to explore in the future. Also, in future designing therapeutic interventions to target these gene networks subsets rather than simply modulating DEGs may be critical to generate more effective treatments (Bagot et al., 2016; Schrattenholz, Groebe, & Soskic, 2010).

Mitochondria are known to be one of the first organelles to react to stressors (Klinedinst and Regenold 2014). They are involved in a variety of metabolic pathways- ATP production, calcium homeostasis, maintaining the levels of ROS, activation of some signalling cascades and regulation of apoptosis. Our results indicate mitochondrial dysfunction as a commonly associated term between human MDD and every mouse model in both mPFC and NAc. During a stressful event, as the energy demand surges up, an increased number of mitochondria are recruited and their volume increases. This demand is met by the utilization of stored energy substrates like glucose, fatty acids and amino acids. Also, mitochondria crosstalk with several signalling pathways, like mitogen-activated protein kinase (MAPK), to help meet energy demands in the advent of stress. Indeed, some of the vegetative symptoms of MDD associated with energy metabolism like weight changes, fatigue, psychomotor retardation, etc. might be related to mitochondrial dysfunction. Interestingly, GRs are expressed in mitochondria in several cell types including brain cells (Demonacos, Djordjevic-Markovic, Tsawdaroglou, & Sekeris, 1995; Hunter et al., 2016). In fact, prolonged exposure to GCs leads to mitochondrial structural and functional abnormalities. Additionally, mitochondrial dysfunction is thought to be associated with the impairment of neural network and cellular resilience. In fact, mitochondria dysfunction can alter the potential of neuronal plasticity at the axonal synapses and dendritic spines (Bansal & Kuhad, 2016). Inhibition of mitochondrial complexes I, III and IV were seen in the cerebral cortex and cerebellum of chronically stressed rats, which could be rescued by the administration of N-methyl-D-aspartate (NMDA) antagonist, ketamine. Moreover, MAOs are bound to the outer membrane of mitochondria and irreversible MAO inhibitor, L-deprenyl, inhibits state 3 respiration. Norepinephrine β2 receptor agonist, formoterol, showed upregulated FCCP-uncoupled oxygen consumption rate, mtDNA copy number and expression of peroxisome proliferator-activated

receptor γ coactivator 1α (PGC-1α) and multiple mitochondrial genes in mice (Bansal & Kuhad, 2016). In the same vein, establishment of mitochondrial biogenesis was observed with agonists for 5-HT receptors 5-HT1F and 5-HT2 (Bansal & Kuhad, 2016). Furthermore, mitochondria are finely associated with neuroplasticity and neurotrophic factors. For instance, one of the ways through which BDNF establishes its neuroprotective effects is significantly increasing the efficiency of respiratory coupling through (MEK) kinase pathway (Markham, Bains, Franklin, & Spedding, 2014). This effect is reversed by rotenone which is a mitochondrial complex I inhibitor. Finally, CREB, found in the mitochondrial matrix of neurons, binds directly to cyclic AMP response elements (CREs) found within the mitochondrial genome (Bansal & Kuhad, 2016).

Although, it is evident that we cannot fully model complex disorders like depression in animals, but they are certainly reflective of important phenotypes relevant to the disorder (Bale et al., 2019). Take behavior as an example, animal models of chronic stress present anhedonia – a key feature of human depression whereas human symptoms like feelings of excessive guilt are not apparent. Additionally, different chronic stress models present some uniqueness in parallel to the common features. For example, CVS, SI and CSDS, mouse models induce anxiety-like responses & anhedonia, but CSDS uniquely induces social avoidance. Not just behavior, these stress models also present distinctive physiological consequences like neuroendocrine and immunological outcomes of stress. This implies obvious molecular differences between these stress models. Consistent with this implication, our results revealed that every mouse model captures a subset of molecular changes relevant to human MDD. This also answers a very important question 'which model best represents the human syndrome'. According to our results, no one model is better than the other and each of the three mouse models reproduces a significant portion of the molecular alterations of human MDD. Every model of chronic stress employed, reflect unique human MDD relevant transcriptional landscapes along with the common signatures. This implies every model holds special importance as a tool to study specific aspects of the human syndrome. Furthermore, our results show SI shares significant overlap with CSDS and, with a lesser magnitude with CVS, while CVS and CSDS share very few similarities in terms of network association with human MDD. The difference in the type of stress paradigms employed in these models may explain these observations. As a matter of fact, CSDS and SI are psychosocial stress whereas CVS is a physical stressor. Consequently, same type of stress may ping similar coping strategies which might reflect molecularly (Sapolsky, 2015). As a matter of fact, neural correlates of stress processing is strongly dependent on stressor type. Physical stress is reported to trigger a more motoric-sensoric fight-or-flight response while psychosocial stress is shown to challenge more emotion regulation, goal-directed behavior and reward processing (Kogler et al., 2015; L. Liu et al., 2018). There are other studies that highlighted the difference between the two types of stress. For instance, Kavushansky et al. confirmed that the hormonal response profile and the expression of plasticity-related genes in the hippocampus differ in response to physical stress and psychosocial stress (Kavushansky, Ben-Shachar, Richter-Levin, & Klein, 2009). Also, changes in hippocampal concentrations of extracellular zinc, a signaling molecule

in synaptic neuro-transmission, vary between physical and psychological stress (Takeda, Sakurada, Kanno, Minami, & Oku, 2006). Moreover, metabolic profiling of hippocampus shows that physical stress is mainly associated with lipid metabolism and glutamate metabolism while psychosocial stress is linked with cell signaling, cellular proliferation, and neurodevelopment (Kogler et al., 2015; L. Liu et al., 2018). Altogether, different stressors can root diversified and even opposite stress responses. This being said that they do have common trajectories. For instance, an imaging study comparing physical and psychosocial reported these stressors do share activation patterns along with the functional heterogeneity (Kogler et al., 2015). For future, these findings can be further validated with other psychosocial stress paradigms like crowding, social instability, etc. and physical stress paradigms like CUMS, learned helplessness, etc.

Interestingly, we found a significant overlap between human MDD and CSDS resilience. It's important to revisit what is resilience in order to understand these results better. Resilience is not simply the absence of susceptibility, but an active homeostatic coping response to stress. The concept of resilience is difficult to define since it covers many divergent behavioral phenotypes. However, resilience refers to the ability of an individual to protect themselves from the negative social, psychological, and biological effects of stress conditions that would otherwise compromise their physical or psychological functioning. The resilience capacity comes not only from the mere absence of key molecular abnormalities of susceptible animals (passive resilience), but also from the presence of novel molecular adaptations which occur in resilient individuals to help promote normal behavioral function (active resilience) (Z. S. Lorsch, Hamilton, Ramakrishnan, Parise, Salery, et al., 2019). Similarly, in animal models, resilient animals are not totally devoid of symptoms and, in fact, exhibit some important behavioral adaptations that appear maladaptive, but they exhibit clear resistance to many other maladaptive sequelae of the chronic social stress. In fact, various molecular adaptations induced by chronic stress in mice have been causally linked to behavioral resilience (Bagot et al., 2016; Bagot et al., 2017). This might explain our results as all organisms undergo resilience-related adaptations in an attempt to cope with stress. Resilience is also linked with several important aspects of life like demographical, cultural and socio-economic factors. Socio-economic status is an interesting research topic and has been conceived as "a broad concept that refers to the placement of persons, families, households, and census tracts or other aggregates with respect to the capacity to consume goods that are valued in society" (Miech & Hauser, 2001; Stepleman L.M., 2009). In fact, low position in the social (and economic/resource) hierarchy has been suggested to be stressful across a wide range of species, eg non-human primates (Beery & Kaufer, 2015; Sapolsky, 2005, 2015; Sapolsky & Ray, 1989; Shively & Day, 2015; Virgin & Sapolsky, 1997), humans, etc. Interestingly, subjective perception of socioeconomic status appears to be an even more powerful stressor than objective socio-economic status itself (Beery & Kaufer, 2015; Siegrist & Marmot, 2004; Singh-Manoux, Marmot, & Adler, 2005). Excitingly, several studies have revealed that low status is not potentially always stressful. It is partly dependent on species-specific life-history traits. For instance, subordinate status is most stressful in species with dictatorial

or despotic hierarchies, and may not be a stressor in democratic or egalitarian hierarchies. Similarly, high status is more stressful in cultures where dominance has high competition and must be continuously defended than in stable social hierarchies (Sapolsky, 2005). In fact, a study on primates found that subordinates had higher basal CORT levels only when they are exposed to higher rates of stressors due to subordinate status, and when subordinate status gave them few opportunities for social contact (Abbott et al., 2003). In naked mole rats, a highly social rodent, except a few all animals of the colony are reproductively suppressed subordinates which are related to breeders but do not have CORT levels higher than the breeders (Beery & Kaufer, 2015). While it is not yet clear how stress relates to status in this species, social subordination must be considered in the context of how it affects the individuals involved. Another possible explanation for the overlap seen between CSDS resilience and MDD is that prior antidepressant medication, though clinically ineffective, may have triggered the activation of resilient-like molecular programs, as shown before in mice following CSDS (Bagot et al., 2017). Although, the effect of medication was controlled for in our human cohort, we cannot ignore the possibility that such treatment may have induced long-term transcriptional alterations. Though, this needs to be tested with much larger human cohorts.

ELS seems to be another attractive animal model for the extension of the work presented here. In humans, the phenomenon of resilience has been shown to be a common consequence of adversity in both children and adults (Masten, 2001; Russo et al., 2012). Remarkably, children display significant resilience across a range of negative environmental stressors (Masten, 2001). “Stress inoculation” has been shown to be beneficial in various animals (Russo et al., 2012). For instance, infant rats exposed to intermittent foot shocks subsequently respond more effectively when confronted with novel situations compared to their non–stressed counterparts (Levine, 1962). Subsequent work on brief intermittent mother–offspring separations in squirrel monkeys at 17 weeks of age has confirmed that after 10 separation sessions previously separated monkeys showed improved behavioral and hormonal response compared to non–separated monkeys (Parker, Buckmaster, Schatzberg, & Lyons, 2004). Separated monkeys also demonstrated reduced anhedonia, suggesting improved cognitive control of behavior (Parker, Buckmaster, Justus, Schatzberg, & Lyons, 2005). These and related findings highlight the importance of early critical window of stress exposure and suggest that early intermittent separations promote resilience (Russo et al., 2012). Therefore, adequate exposure to ELS could impart resilience in future life. The potential of conferring susceptibility or resilience makes ELS an interesting target for future extension of this thesis. It would be exciting to check if the ELS conferred susceptibility or resilience shares the same overlap with MDD and other models. Also, another stirring question would be, how much ELS conferred resilience and CSDS associated resilience overlap with each other.

Our results indicate the possibility that similar types of stress, might reproduce a distinct subtype of MDD. Segregating specific causal subtypes like partner loss, burnout, bullying in human patients might bring out very

useful insights. Assorting and comparing human patients with similar subtypes to a related mouse model of stress would probably bring out interesting latent information. Although a much larger human cohort will be needed to test whether a particular mouse model is associated with a given stressor (e.g., early life stress) of MDD. Although, this would be complex as very often human MDD is multifactorial. Also, checking for any association between specific human symptoms and specific mouse models of stress would be another interesting avenue to explore but, again, would require a huge sample size. Furthermore, in future it would be interesting to see how other psychiatric disorders with converging symptoms with MDD like bipolar disorder, anxiety disorder, etc. overlap with each other.

However, there are significant differences between mPFC and NAc at the molecular, cellular, and circuit levels between mice and humans. This discrepancy represents an obvious weakness of interspecies comparative studies. This being said, significant degrees of similarities have also been documented for both brain regions (Defelipe, 2011; Duzel et al., 2009; Geschwind & Rakic, 2013; Hodge et al., 2019; McCutcheon et al., 2019; Strand et al., 2007), with significant conservation in the processing of rewarding and motivational cues and in the top-down control of emotions. The high levels of interspecies transcriptional convergence observed in the current study presumably reflect this conservation. Importantly, our study suggests that, while a significant number of human gene network modules in both mPFC and NAc are conserved in mice, but in mPFC, they are better conserved. Although mPFC and NAc are two potent MDD-relevant pathological regions, extending our analysis to other MDD-relevant brain regions would be a great avenue to explore in future. For instance, hippocampus is an extremely stress-sensitive region and is a core component of the limbic-cortical circuitry (McEwen, Nasca, & Gray, 2016). It has important roles in memory and cognitive functions along with regulation of stress and emotions (McEwen et al., 2016). In fact, many studies reported abnormal activation of the hippocampus in MDD patients (Milne, MacQueen, & Hall, 2012). MDD patients may have cognitive impairment along with memory deficits which may be associated with hippocampus dysfunction. Hippocampus can be divided into three different components. These are: the cornu ammonis (CA), dentate gyrus (DG) and subiculum. CA is related to learning and memory functions, and is further divided into CA1, CA2, CA3, and CA4 sub regions. It mainly participates in short-term image contact, image formation and fear memory formation(K. S. Anand & Dhikav, 2012). In addition, it is involved in medium-term and short-term spatial memory. The DG, on the other hand, is the receptacle for incoming spatial information to the hippocampus. Additionally, it also processes and encodes spatial information and helps form spatial learning and memory (K. S. Anand & Dhikav, 2012). On the other hand, the subiculum is associated with information output, transmitting information processed from the DG to the other brain regions and is also the effector of the baroreceptor reflex (Hao et al., 2020). The hippocampus is a key regulator of prefrontal cortical function along with the nucleus accumbens and the ventral tegmental area (MacQueen & Frodl, 2011). Hence, it serves as one of the interesting targets for an extension of our study, with sub region specific investigation. The ventral tegmental area is another interesting region in MDD pathology,

which is an important source of dopamine in mesolimbic regions, involved in motivation and reward circuitry. It is well intertwined with mPFC, NAc as well as hippocampus and is widely implicated in MDD pathology (Fox & Lobo, 2019).

MDD features strong sexual dimorphism at different biological levels, including its transcriptional landscape (Labonte et al., 2017a; Mena & Benoit, 2019a; Seney et al., 2018). Nonetheless, in our study, we statistically controlled for the effects of sex as females were included only in our human and CVS cohorts. This is a major caveat of our study. Indeed, it might restrict our interpretation of the data and may have potentially masked some effects, given the fact that previous studies (Labonte et al., 2017a; Seney et al., 2018) have shown dramatic transcriptional sex differences. The statistical approach we used for controlling the main effect of sex in humans and CVS, accounts for this effect. Indeed, SI and CSDS (Harris et al., 2018) can be performed in females, and it will be interesting in future studies to know how our findings stand in the two sexes.

Transcriptome is significantly region-specific as well as cell-type specific (Itoh et al., 2018; LoVerso & Cui, 2016). Although our study was region specific, it lacked the cell-type specificity. This limitation could also potentially lead to masking of some effects and limit our understanding of the results. Our results, nevertheless, indicated the possible role of oligodendrocyte in the pathology of MDD, in future, it would be interesting to validate this finding in a cell-type specific setup and also to see the extent of overlap of other cell-types' transcriptome between human MDD and mouse models of stress. Importantly, the overlaps presented in this thesis don't include the whole transcriptome, instead, represent 9888 interspecies gene orthologues that are expressed in mPFC or NAc of both humans and mice. All analyses in our studies were performed on this gene set. Hence, the findings should be carefully interpreted

For better modelling of a subjective disorder like depression, understanding the ethology of the model animal is essential. Understanding the actions of our experimental animals would allow us to paint a better picture of what is actually happening and to establish a better correlation with the human syndrome. For instance, activities like jerking, freezing, rearing, grooming, mobility, scanning, sniffing, stretch attend, etc. (Z. S. Lorsch et al., 2020) are important behavior features of rodents that should be taken together into account while assessing depressive-like behaviors. It is more informative than just assessing a single parameter and can specifically delineating the behavioral domains abnormality associated with a specific animal model (Z. S. Lorsch et al., 2020). Unfortunately, as most of our datasets were already published, we couldn't test these behaviors in our study. But including these assessments in future research would definitely strengthen MDD research. Analysis as such could serve as a better tool to assess anti-depressant candidate drugs' effectiveness than the usual behavioral test batteries which is obviously, not effective enough.

Another smirched arena of MDD is the clinical criteria of its diagnosis. These criteria are rather subjective than objective. In other words, the tests are non-quantitative and the chances of human error are high. Moreover, these diagnostic criteria for MDD cannot be applied to animal models. Consequently, this directly affects the quests for causal mechanisms and treatment drugs for the disorder. From this perspective, having robust laboratory-based diagnostic tools would enrich MDD research more.

Furthermore, we should try to understand depressive behavior with a more holistic approach. Defining the etiology of a complex subjective disorder like depression is not easy. We should try to understand what happens in different brain regions that give rise to a depressive episode. Then, what are the environmental cues which influenced cells of these regions? Next, how and what hormones sensitized these regions days before the depressive episode? Then, how do experiences reshape our brain circuitry and its response to a trigger, weeks to months before? Also, how does that immature frontal cortex in adolescence shape our brain and eventually our personality as an adult? Next, how do early life experiences cause lifelong changes in brain function and gene expression? What combinations genes you inherited as a fertilized egg that define your stress response system? Followed by, how do ecological and cultural factors that shape the social environment contribute to stress resilience and susceptibility and does the evolution of these factors revert the stress resilience or susceptibility? Finally, how did the behavior, brain and eventually, genes evolve? All these aspects of research should be taken into account when we are trying to understand the disorder and we cannot devise its optimal treatment if just focus on just one aspect.

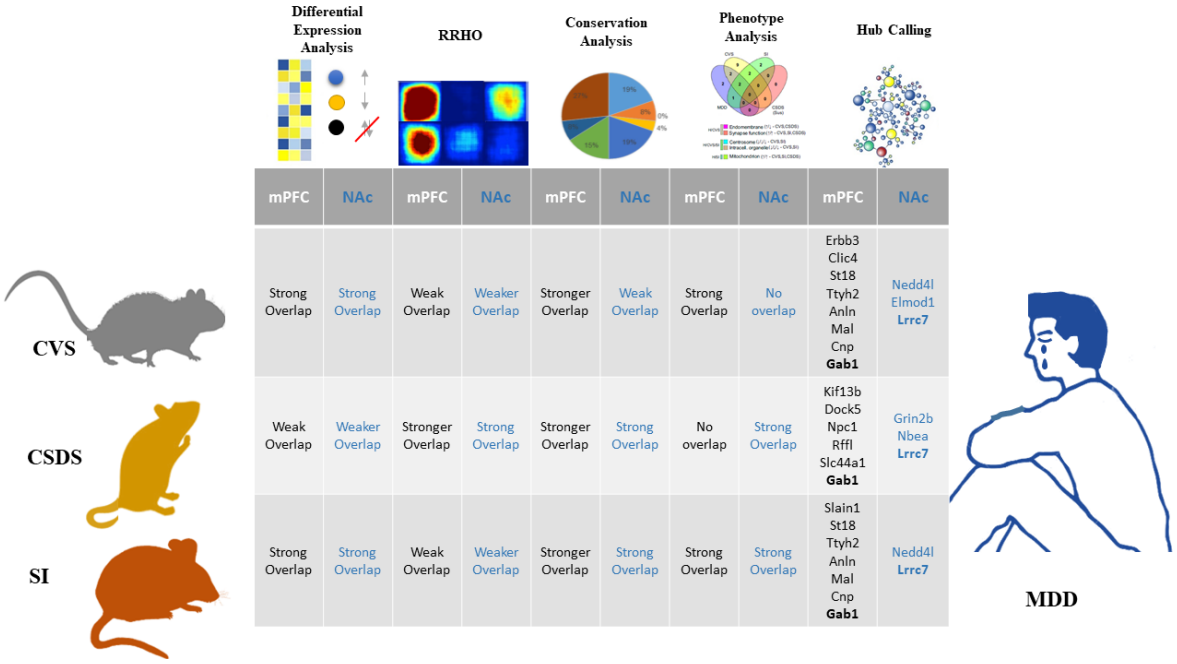
These questions cannot be answered using human tissues only as not only the access to human brain tissues is limited but also they are only available as post-mortem samples which restrict us to seek answers to some very important questions. Animal models are our only way out to seek solutions to these essential questions. Although, animal models should be chosen thoughtfully according to the question we ask and our data provides a molecular catalogue encompassing the transcriptional capacity of each mouse model to reproduce the molecular signatures relevant to MDD across different regions of the human brain.

The next logical question would be how are these transcriptional networks regulated in the two species and how do they differ? Epigenetics guide transcriptional alterations on the notes of environmental cues like stress. There are a variety of mechanisms that regulate gene expression. These include DNA methylation, post translational modification of histone tails which includes methylation, acetylation, sumoylation, ubiquitination, phosphorylation, etc. of residues in the N-terminal tails of histones, chromatin remodelling, histone variants, non-coding RNAs. With its sensitivity to stress and its ability to regulate subtle genome-wide transcriptional changes, short as well as long-term, epigenetic mechanisms are directly related to the pathogenesis of MDD. In fact, transcriptional changes associated with epigenetic alterations have been observed in the mouse brain as well

as human in the context of stress and MDD (Mena & Benoit, 2019a). As a matter of fact, DNA methylation is the most studied epigenetic mark in human MDD and in mice models of stress while the others remain minimally explored. Not only that, we also lack knowledge on how these epigenetic mechanisms affect transcriptional networks on a global scale. An interesting study, reconcile this relationship between epigenetic changes and gene networks in MDD by evaluating DNA methylation patterns in PFC of MDD patients through WGCNA (A. C. Bustamante, Armstrong, & Uddin, 2018). Although the no probes utilized in this analysis remained significant following multiple test correction, genome-wide network analysis revealed a module relevant to MDD, associated with transcription and DNA binding function. As it is evident that these mechanisms can also explain changes in transcriptional profiles in MDD, involving both single-gene and network level, these alterations are likely the product of a complex epigenetic code involving key regulatory genes (Zachary Spencer Lorsch, 2018). Delineating the relationship between these epigenetic changes and MDD transcriptional networks is an important step in understanding the mechanism of MDD and formulating its optimal treatment. Although similar overlap between MDD and mice models is anticipated, there would be some obvious shifts as well. For future, it would be a vital venture to explore to see if the overlap of each of the several epigenetic marks synchronise with the transcriptional overlap between human MDD and mouse model of stress and to see how these epigenetic marks regulate their transcriptional networks. To conclude, epigenetic mechanisms have the ability to be the medicine of the future, hence should be the subject of future research.

Mice are considered the most widely used laboratory animals in basic as well as translational research. This is mainly because mice can be easily genetically manipulated compared to other mammals and most paradigms translate well between the species. There is various evidence that suggests the conservation of brain across species, from mouse to human. This includes basic behaviors and underlying brain structure, circuitry, cellularity, and molecular functions and their mechanisms. For instance, the fear and fright circuits are highly conserved in its components and function across mammals (Bale et al., 2019). Evolutionarily talking, around 90 million years ago humans and mice had their last common ancestor (Springer & Murphy, 2007). Since then, the two species evolved in different aspects eg their body size, life span, ecological niche, behavior, and pathogenic challenges. Naturally, mouse models of human diseases do have limitations. They can show mild to strong divergence from human disease in terms of incidence, symptoms, pathology, severity, treatment effectiveness, recovery, etc. This presents a key hurdle in translational research. Consequently, interspecies comparative studies identifying cellular and molecular differences between human and mouse brains is so much more important than being realised. Importantly, the presence of such differences does not invalidate the mouse as an experimental model, but rather highlights the importance of the need to define interspecies difference to optimize their utilization and eventually improve their contribution to human disease/disorder research. Although utilization of human inducible pluripotent stem cells and organoids provide a decent complement to mouse models, it is far from the symptomology of human neuropsychiatric diseases (Bale et al., 2019). Indeed, there are several factors that

stresses the importance of animal models such as mice. One of such factors is the limited access to human tissue and many techniques routinely used in studies of models cannot be applied to human patients or human tissue samples. For instance, mouse models can be used for in-vivo manipulations in the brain to affirm causal effects on depression-like behaviors (Z. S. Lorsch et al., 2020). Moreover, we can seek answers to important biological questions through mouse as experiments can be performed relatively quick with adequate statistical power in contrast to human studies that are generally time consuming and is limited to smaller numbers. Furthermore, mouse models offer less variability, genetically as well as inter-individually through controlled experimental setups. Therefore, mouse models will continue to be an irreplaceable tool of choice for MDD research. The identification of human-mouse interspecies differences will accelerate translational research from mouse models to human patients (Li J, 2020; Z. S. Lorsch et al., 2020). Although, this should be kept clear that we are not modeling MDD per se, but instead only the specific aspects of the disorder.



	Differential Expression Analysis		RRHO		Conservation Analysis		Phenotype Analysis		Hub Calling	
	mPFC	NAc	mPFC	NAc	mPFC	NAc	mPFC	NAc	mPFC	NAc
CVS	Strong Overlap	Strong Overlap	Weak Overlap	Weaker Overlap	Stronger Overlap	Weak Overlap	Strong Overlap	No overlap	Erbb3 Clic4 St18 Ttyh2 Anln Mal Cnp **Gab1**	Nedd4l Elmod1 **Lrrc7**
CSDS	Weak Overlap	Weaker Overlap	Stronger Overlap	Strong Overlap	Stronger Overlap	Strong Overlap	No overlap	Strong Overlap	Kif13b Dock5 Npc1 Rffl Slc44a1 **Gab1**	Grin2b Nbea **Lrrc7**
SI	Strong Overlap	Strong Overlap	Weak Overlap	Weaker Overlap	Stronger Overlap	Strong Overlap	Strong Overlap	Strong Overlap	Slain1 St18 Ttyh2 Anln Mal Cnp **Gab1**	Nedd4l **Lrrc7**

Fig-1: Mice model of chronic stress captures significant overlap with human MDD.

The transcriptional overlap of the three mouse models, chronic variable stress (CVS), prolonged social isolation (SI) and chronic social defeat stress (CSDS) with human Major Depressive Disorder (MDD) across two different brain regions, including the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc), has been summarised here. A sophisticated bioinformatics analyses pipeline employing different analyses including differential expression analysis, rank rank hypergeometric overlap analysis (RRHO), interspecies network conservation analysis, phenotype association and hub calling analyses along with Gene ontology overlap (not shown here) was used. Here differential expression analysis, RRHO, interspecies network conservation

analysis, phenotype association show the degree of overlap found between the three mouse model and MDD across the two brain region while hub calling analysis shows the names of the hub genes, with common hub gene between human MDD and all the three mouse mode highlighted in bold.

Overall this thesis provides a strong molecular framework supporting the use of mouse models for the study of MDD by identifying the transcriptional signatures shared between human MDD and CVS, SI, and CSDS in mice. It is a helpful guide for the selection of the mouse models presented for studying specific aspects of the MDD.

Bibliographie

A.M.Hatch, G.S.Wiberg, Z.Zawidzka, M.Cann, J.M.Airth, & H.C.Grice. (2009). Isolation syndrome in the rat. *Toxicology and Applied Pharmacology, 7*(5), 737-745. Retrieved from https://www.sciencedirect.com/science/article/pii/0041008X65901328?via%3Dihub. doi:10.1016/0041-008X(65)90132-8

Abbott, D. H., Keverne, E. B., Bercovitch, F. B., Shively, C. A., Mendoza, S. P., Saltzman, W., . . . Sapolsky, R. M. (2003). Are subordinates always stressed? A comparative analysis of rank differences in cortisol levels among primates. *Horm Behav, 43*(1), 67-82. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12614636. doi:10.1016/s0018-506x(02)00037-5

Abramov, U., Raud, S., Koks, S., Innos, J., Kurrikoff, K., Matsui, T., & Vasar, E. (2004). Targeted mutation of CCK(2) receptor gene antagonises behavioural changes induced by social isolation in female, but not in male mice. *Behav Brain Res, 155*(1), 1-11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15325774. doi:10.1016/j.bbr.2004.03.027

Afifi, T. O., Enns, M. W., Cox, B. J., Asmundson, G. J., Stein, M. B., & Sareen, J. (2008). Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *Am J Public Health, 98*(5), 946-952. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18381992. doi:10.2105/AJPH.2007.120253

Ahmed, S. H., Stinus, L., Le Moal, M., & Cador, M. (1995). Social deprivation enhances the vulnerability of male Wistar rats to stressor- and amphetamine-induced behavioral sensitization. *Psychopharmacology (Berl), 117*(1), 116-124. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7724696.

Akbarian, S., Kim, J. J., Potkin, S. G., Hagman, J. O., Tafazzoli, A., Bunney, W. E., Jr., & Jones, E. G. (1995). Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Arch Gen Psychiatry, 52*(4), 258-266.

Akula, N., Barb, J., Jiang, X., Wendland, J. R., Choi, K. H., Sen, S. K., . . . McMahon, F. J. (2014). RNA-sequencing of the brain transcriptome implicates dysregulation of neuroplasticity, circadian rhythms and GTPase binding in bipolar disorder. *Mol Psychiatry, 19*(11), 1179-1185. doi:10.1038/mp.2013.170

Alfinito, P. D., Chen, X., Mastroeni, R., Pawlyk, A. C., & Deecher, D. C. (2009). Estradiol increases catecholamine levels in the hypothalamus of ovariectomized rats during the dark-phase. *Eur J Pharmacol, 616*(1-3), 334-339. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19576879. doi:10.1016/j.ejphar.2009.06.045

Alhamdoosh, M., Ng, M., Wilson, N. J., Sheridan, J. M., Huynh, H., Wilson, M. J., & Ritchie, M. E. (2017). Combining multiple tools outperforms individual methods in gene set enrichment analyses. *Bioinformatics, 33*(3), 414-424. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27694195. doi:10.1093/bioinformatics/btw623

Alonso, G. (2000). Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia, 31*(3), 219-231. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10941148. doi:10.1002/1098-1136(200009)31:3<219::aid-glia30>3.0.co;2-r

Altemus, M., Sarvaiya, N., & Neill Epperson, C. (2014). Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol, 35*(3), 320-330. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24887405. doi:10.1016/j.yfrne.2014.05.004

Alvarez, R. P., Kirlic, N., Misaki, M., Bodurka, J., Rhudy, J. L., Paulus, M. P., & Drevets, W. C. (2015). Increased anterior insula activity in anxious individuals is linked to diminished perceived control. *Transl Psychiatry, 5*, e591. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26125154. doi:10.1038/tp.2015.84

Ammerman, R. T., Hersen, M., van Hasselt, V. B., Lubetsky, M. J., & Sieck, W. R. (1994). Maltreatment in psychiatrically hospitalized children and adolescents with developmental disabilities: prevalence and correlates. *J Am Acad Child Adolesc Psychiatry, 33*(4), 567-576. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8005910. doi:10.1097/00004583-199405000-00015

Anacker, C., O'Donnell, K. J., & Meaney, M. J. (2014). Early life adversity and the epigenetic programming of hypothalamic-pituitary-adrenal function. *Dialogues Clin Neurosci, 16*(3), 321-333. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25364283.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., . . . Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry, 57*(10), 1079-1088. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15866546. doi:10.1016/j.biopsych.2005.02.021

Anand, K. S., & Dhikav, V. (2012). Hippocampus in health and disease: An overview. *Ann Indian Acad Neurol, 15*(4), 239-246. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23349586. doi:10.4103/0972-2327.104323

Anders, S., & Huber, W. (2010). Differential expression analysis for sequence count data. *Genome Biol, 11*(10), R106. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20979621. doi:10.1186/gb-2010-11-10-r106

Association, A. P. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC.

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci, 28*, 403-450. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16022602. doi:10.1146/annurev.neuro.28.061604.135709

Aston, C., Jiang, L., & Sokolov, B. P. (2005). Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Mol Psychiatry, 10*(3), 309-322. doi:10.1038/sj.mp.4001565 [doi]

4001565 [pii]

Austin, M. C., Janosky, J. E., & Murphy, H. A. (2003). Increased corticotropin-releasing hormone immunoreactivity in monoamine-containing pontine nuclei of depressed suicide men. *Mol Psychiatry, 8*(3), 324-332. doi:10.1038/sj.mp.4001250

Bagot, R. C., Cates, H. M., Purushothaman, I., Lorsch, Z. S., Walker, D. M., Wang, J., . . . Nestler, E. J. (2016). Circuit-wide Transcriptional Profiling Reveals Brain Region-Specific Gene Networks Regulating Depression Susceptibility. *Neuron, 90*(5), 969-983. doi:10.1016/j.neuron.2016.04.015

Bagot, R. C., Cates, H. M., Purushothaman, I., Vialou, V., Heller, E. A., Yieh, L., . . . Nestler, E. J. (2017). Ketamine and Imipramine Reverse Transcriptional Signatures of Susceptibility and Induce Resilience-Specific Gene Expression Profiles. *Biol Psychiatry, 81*(4), 285-295. doi:10.1016/j.biopsych.2016.06.012

Bale, T. L., Abel, T., Akil, H., Carlezon, W. A., Jr., Moghaddam, B., Nestler, E. J., . . . Thompson, S. M. (2019). The critical importance of basic animal research for neuropsychiatric disorders. *Neuropsychopharmacology, 44*(8), 1349-1353. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31048727. doi:10.1038/s41386-019-0405-9

Banerjee, R., Ghosh, A. K., Ghosh, B., Bhattacharyya, S., & Mondal, A. C. (2013). Decreased mRNA and Protein Expression of BDNF, NGF, and their Receptors in the Hippocampus from Suicide: An Analysis in Human Postmortem Brain. *Clin Med Insights Pathol, 6*, 1-11. doi:10.4137/CMPath.S12530

Bangasser, D. A., Wiersielis, K. R., & Khantsis, S. (2016). Sex differences in the locus coeruleus-norepinephrine system and its regulation by stress. *Brain Res, 1641*(Pt B), 177-188. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26607253. doi:10.1016/j.brainres.2015.11.021

Bansal, Y., & Kuhad, A. (2016). Mitochondrial Dysfunction in Depression. *Curr Neuropharmacol, 14*(6), 610-618. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26923778. doi:10.2174/1570159x14666160229114755

Barrot, M., Wallace, D. L., Bolanos, C. A., Graham, D. L., Perrotti, L. I., Neve, R. L., . . . Nestler, E. J. (2005). Regulation of anxiety and initiation of sexual behavior by CREB in the nucleus accumbens. *Proc Natl Acad Sci U S A, 102*(23), 8357-8362. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15923261. doi:10.1073/pnas.0500587102

Bath, K. G. (2020). Synthesizing Views to Understand Sex Differences in Response to Early Life Adversity. *Trends Neurosci, 43*(5), 300-310. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32353334. doi:10.1016/j.tins.2020.02.004

Becker, C., Zeau, B., Rivat, C., Blugeot, A., Hamon, M., & Benoliel, J. J. (2008). Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin. *Mol Psychiatry, 13*(12), 1079-1092. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17893702. doi:10.1038/sj.mp.4002097

Beery, A. K., & Kaufer, D. (2015). Stress, social behavior, and resilience: insights from rodents. *Neurobiol Stress, 1*, 116-127. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25562050. doi:10.1016/j.ynstr.2014.10.004

Belzung, C., & Lemoine, M. (2011). Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. *Biol Mood Anxiety Disord, 1*(1), 9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22738250. doi:10.1186/2045-5380-1-9

Berent, D., Zboralski, K., Orzechowska, A., & Galecki, P. (2014). Thyroid hormones association with depression severity and clinical outcome in patients with major depressive disorder. *Mol Biol Rep, 41*(4), 2419-2425. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24443228. doi:10.1007/s11033-014-3097-6

Berton, O., Hahn, C. G., & Thase, M. E. (2012). Are we getting closer to valid translational models for major depression? *Science, 338*(6103), 75-79. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23042886. doi:10.1126/science.1222940

Berton, O., McClung, C. A., Dileone, R. J., Krishnan, V., Renthal, W., Russo, S. J., . . . Nestler, E. J. (2006). Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science, 311*(5762), 864-868. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16469931. doi:10.1126/science.1120972

Birur, B., Amrock, E. M., Shelton, R. C., & Li, L. (2017). Sex Differences in the Peripheral Immune System in Patients with Depression. *Front Psychiatry, 8*, 108. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28670290. doi:10.3389/fpsyt.2017.00108

Blackburn, T. P. (2019). Depressive disorders: Treatment failures and poor prognosis over the last 50 years. *Pharmacol Res Perspect, 7*(3), e00472. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31065377. doi:10.1002/prp2.472

Boda, E. (2019). Myelin and oligodendrocyte lineage cell dysfunctions: New players in the etiology and treatment of depression and stress-related disorders. *Eur J Neurosci*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31736197. doi:10.1111/ejn.14621

Bongarzone, E. R., Howard, S. G., Schonmann, V., & Campagnoni, A. T. (1998). Identification of the dopamine D3 receptor in oligodendrocyte precursors: potential role in regulating differentiation and myelin formation. *J Neurosci, 18*(14), 5344-5353. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9651217.

Brunson, K. L., Kramar, E., Lin, B., Chen, Y., Colgin, L. L., Yanagihara, T. K., . . . Baram, T. Z. (2005). Mechanisms of late-onset cognitive decline after early-life stress. *J Neurosci, 25*(41), 9328-9338. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16221841. doi:10.1523/JNEUROSCI.2281-05.2005

Bus, B. A., Tendolkar, I., Franke, B., de Graaf, J., den Heijer, M., Buitelaar, J. K., & Oude Voshaar, R. C. (2012). Serum brain-derived neurotrophic factor: determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people. *World J Biol Psychiatry, 13*(1), 39-47. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21247257. doi:10.3109/15622975.2010.545187

BUSTAMANTE, A. C. (2017). *EPIGENETIC & TRANSCRIPTOMIC ALTERATIONS ASSOCIATED WITH CHILDHOOD MALTREATMENT, MAJOR DEPRESSIVE DISORDER, AND POST-TRAUMATIC STRESS DISORDER.* (Doctor of Philosophy in Neuroscience), Graduate College of the
University of Illinois at Urbana-Champaign, Urbana, Illinois.

Bustamante, A. C., Armstrong, D. L., & Uddin, M. (2018). Epigenetic profiles associated with major depression in the human brain. *Psychiatry Res, 260*, 439-442. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29272728. doi:10.1016/j.psychres.2017.12.010

Butler, T. R., Ariwodola, O. J., & Weiner, J. L. (2014). The impact of social isolation on HPA axis function, anxiety-like behaviors, and ethanol drinking. *Front Integr Neurosci, 7*, 102. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24427122. doi:10.3389/fnint.2013.00102

Cai, L., Li, Q., Du, Y., Yun, J., Xie, Y., DeBerardinis, R. J., & Xiao, G. (2017). Genomic regression analysis of coordinated expression. *Nat Commun, 8*(1), 2187. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29259170. doi:10.1038/s41467-017-02181-0

Campbell, S., & Macqueen, G. (2004). The role of the hippocampus in the pathophysiology of major depression. *J Psychiatry Neurosci, 29*(6), 417-426. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15644983.

Carboni, L., Marchetti, L., Lauria, M., Gass, P., Vollmayr, B., Redfern, A., . . . Mathe, A. A. (2018). Cross-species evidence from human and rat brain transcriptome for growth factor signaling pathway dysregulation in major depression. *Neuropsychopharmacology, 43*(10), 2134-2145. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29950584. doi:10.1038/s41386-018-0117-6

Carlisle, H. J., Luong, T. N., Medina-Marino, A., Schenker, L., Khorosheva, E., Indersmitten, T., . . . Kennedy, M. B. (2011). Deletion of densin-180 results in abnormal behaviors associated with mental illness and reduces mGluR5 and DISC1 in the postsynaptic density fraction. *J Neurosci, 31*(45), 16194-16207. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22072671. doi:10.1523/JNEUROSCI.5877-10.2011

Carroll, J. C., Boyce-Rustay, J. M., Millstein, R., Yang, R., Wiedholz, L. M., Murphy, D. L., & Holmes, A. (2007). Effects of mild early life stress on abnormal emotion-related behaviors in 5-HTT knockout mice. *Behav Genet, 37*(1), 214-222. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17177116. doi:10.1007/s10519-006-9129-9

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386-389. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12869766. doi:10.1126/science.1083968
301/5631/386 [pii]

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry, 161*(2), 195-216. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14754765. doi:10.1176/appi.ajp.161.2.195

Chen, F., Zhou, L., Bai, Y., Zhou, R., & Chen, L. (2015). Hypothalamic-pituitary-adrenal axis hyperactivity accounts for anxiety- and depression-like behaviors in rats perinatally exposed to bisphenol A. *J Biomed Res, 29*(3), 250-258. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26060449. doi:10.7555/JBR.29.20140058

Chen, J., Evans, A. N., Liu, Y., Honda, M., Saavedra, J. M., & Aguilera, G. (2012). Maternal Deprivation in Rats is Associated with Corticotrophin-Releasing Hormone (CRH) Promoter Hypomethylation and Enhances CRH Transcriptional Responses to Stress in Adulthood. *J Neuroendocrinol, 24*(7), 1055-1064. doi:10.1111/j.1365-2826.2012.02306.x

Chen, L. S., & Storey, J. D. (2008). Eigen-R2 for dissecting variation in high-dimensional studies. *Bioinformatics, 24*(19), 2260-2262. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18718946. doi:btn411 [pii]
10.1093/bioinformatics/btn411

Cheng, J. D., & de Vellis, J. (2000). Oligodendrocytes as glucocorticoids target cells: functional analysis of the glycerol phosphate dehydrogenase gene. *J Neurosci Res, 59*(3), 436-445. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10679781. doi:10.1002/(SICI)1097-4547(20000201)59:3<436::AID-JNR19>3.0.CO;2-Z

Choi, M. H., Na, J. E., Yoon, Y. R., Lee, H. J., Yoon, S., Rhyu, I. J., & Baik, J. H. (2017). Role of Dopamine D2 Receptor in Stress-Induced Myelin Loss. *Sci Rep, 7*(1), 11654. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28912499. doi:10.1038/s41598-017-10173-9

Conesa, A., Madrigal, P., Tarazona, S., Gomez-Cabrero, D., Cervera, A., McPherson, A., . . . Mortazavi, A. (2016). A survey of best practices for RNA-seq data analysis. *Genome Biol, 17*, 13. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26813401. doi:10.1186/s13059-016-0881-8

consortium, C. (2015). Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature, 523*(7562), 588-591. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26176920. doi:10.1038/nature14659

Costello, J., & Kendrick, K. (2000). Grief and older people: the making or breaking of emotional bonds following partner loss in later life. *J Adv Nurs, 32*(6), 1374-1382. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11136405.

Csolle, C., Baranyi, M., Zsilla, G., Kittel, A., Goloncser, F., Illes, P., . . . Sperlagh, B. (2013). Neurochemical Changes in the Mouse Hippocampus Underlying the Antidepressant Effect of Genetic Deletion of P2X7 Receptors. *PLoS One, 8*(6), e66547. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23805233. doi:10.1371/journal.pone.0066547

David Semple, & Smyth, R. (2019). *Oxford Handbook of Psychiatry* (new fourth edition ed.): Oxford University Press, 2019.

Defelipe, J. (2011). The evolution of the brain, the human nature of cortical circuits, and intellectual creativity. *Front Neuroanat, 5*, 29. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21647212. doi:10.3389/fnana.2011.00029

Demin, K. A., Sysoev, M., Chernysh, M. V., Savva, A. K., Koshiba, M., Wappler-Guzzetta, E. A., . . . Kalueff, A. V. (2019). Animal models of major depressive disorder and the implications for drug discovery and development. *Expert Opin Drug Discov, 14*(4), 365-378. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30793996. doi:10.1080/17460441.2019.1575360

Demonacos, C., Djordjevic-Markovic, R., Tsawdaroglou, N., & Sekeris, C. E. (1995). The mitochondrion as a primary site of action of glucocorticoids: the interaction of the glucocorticoid receptor with mitochondrial DNA sequences showing partial similarity to the nuclear glucocorticoid responsive elements. *J Steroid Biochem Mol Biol, 55*(1), 43-55. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7577720. doi:10.1016/0960-0760(95)00159-w

Deroche, V., Piazza, P. V., Le Moal, M., & Simon, H. (1994). Social isolation-induced enhancement of the psychomotor effects of morphine depends on corticosterone secretion. *Brain Res, 640*(1-2), 136-139. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8004442.

Dias, C., Feng, J., Sun, H., Shao, N. Y., Mazei-Robison, M. S., Damez-Werno, D., . . . Nestler, E. J. (2014). beta-catenin mediates stress resilience through Dicer1/microRNA regulation. *Nature, 516*(7529), 51-55. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25383518. doi:10.1038/nature13976

Drevets, W. C., Price, J. L., Simpson, J. R., Jr., Todd, R. D., Reich, T., Vannier, M., & Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature, 386*(6627), 824-827. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9126739. doi:10.1038/386824a0

Du, L., Faludi, G., Palkovits, M., Bakish, D., & Hrdina, P. D. (2001). Serotonergic genes and suicidality. *Crisis, 22*(2), 54-60.

Dukal, H., Frank, J., Lang, M., Treutlein, J., Gilles, M., Wolf, I. A., . . . Witt, S. H. (2015). New-born females show higher stress- and genotype-independent methylation of SLC6A4 than males. *Borderline Personal Disord Emot Dysregul, 2*, 8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26401310. doi:10.1186/s40479-015-0029-6

Dumais, A., Lesage, A. D., Alda, M., Rouleau, G., Dumont, M., Chawky, N., . . . Turecki, G. (2005). Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. *Am J Psychiatry, 162*(11), 2116-2124. doi:162/11/2116 [pii]
10.1176/appi.ajp.162.11.2116 [doi]

Duman, R. S., Sanacora, G., & Krystal, J. H. (2019). Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. *Neuron, 102*(1), 75-90. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30946828. doi:10.1016/j.neuron.2019.03.013

Duman, R. S., & Voleti, B. (2012). Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. *Trends Neurosci, 35*(1), 47-56. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22217452. doi:10.1016/j.tins.2011.11.004

Duzel, E., Bunzeck, N., Guitart-Masip, M., Wittmann, B., Schott, B. H., & Tobler, P. N. (2009). Functional imaging of the human dopaminergic midbrain. *Trends Neurosci, 32*(6), 321-328. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19446348. doi:10.1016/j.tins.2009.02.005

Dwivedi, Y., Rizavi, H. S., Conley, R. R., Roberts, R. C., Tamminga, C. A., & Pandey, G. N. (2003). Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry, 60*(8), 804-815. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12912764. doi:10.1001/archpsyc.60.8.804

Edgar, N., & Sibille, E. (2012). A putative functional role for oligodendrocytes in mood regulation. *Transl Psychiatry, 2*, e109. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22832953. doi:10.1038/tp.2012.34

Ellenbroek, B. A., van den Kroonenberg, P. T., & Cools, A. R. (1998). The effects of an early stressful life event on sensorimotor gating in adult rats. *Schizophr Res, 30*(3), 251-260. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9589519. doi:10.1016/s0920-9964(97)00149-7

Elliott, E., Ezra-Nevo, G., Regev, L., Neufeld-Cohen, A., & Chen, A. (2010). Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. *Nat Neurosci, 13*(11), 1351-1353. doi:10.1038/nn.2642

Enthoven, L., Oitzl, M. S., Koning, N., van der Mark, M., & de Kloet, E. R. (2008). Hypothalamic-pituitary-adrenal axis activity of newborn mice rapidly desensitizes to repeated maternal absence but becomes highly responsive to novelty. *Endocrinology, 149*(12), 6366-6377. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18635659. doi:10.1210/en.2008-0238

Ernst, C., Chen, E. S., & Turecki, G. (2009). Histone methylation and decreased expression of TrkB.T1 in orbital frontal cortex of suicide completers. *Mol Psychiatry, 14*(9), 830-832. doi:mp200935 [pii]
10.1038/mp.2009.35 [doi]

Espejo, E. P., Hammen, C. L., Connolly, N. P., Brennan, P. A., Najman, J. M., & Bor, W. (2007). Stress sensitization and adolescent depressive severity as a function of childhood adversity: a link to anxiety disorders. *J Abnorm Child Psychol, 35*(2), 287-299. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17195949. doi:10.1007/s10802-006-9090-3

Evans, S. J., Choudary, P. V., Neal, C. R., Li, J. Z., Vawter, M. P., Tomita, H., . . . Akil, H. (2004). Dysregulation of the fibroblast growth factor system in major depression. *Proc Natl Acad Sci U S A, 101*(43), 15506-15511. doi:10.1073/pnas.0406788101

Fan, L. W., Bhatt, A., Tien, L. T., Zheng, B., Simpson, K. L., Lin, R. C., . . . Pang, Y. (2015). Exposure to serotonin adversely affects oligodendrocyte development and myelination in vitro. *J Neurochem, 133*(4), 532-543. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25382136. doi:10.1111/jnc.12988

Fatma, M., & Labonte, B. (2019). Molecular programs underlying differences in the expression of mood disorders in males and females. *Brain Research*(1719), 89-103.

Feder, A., Nestler, E. J., & Charney, D. S. (2009). Psychobiology and molecular genetics of resilience. *Nat Rev Neurosci, 10*(6), 446-457. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19455174. doi:10.1038/nrn2649

Foroushani, A., Agrahari, R., Docking, R., Chang, L., Duns, G., Hudoba, M., . . . Zare, H. (2017). Large-scale gene network analysis reveals the significance of extracellular matrix pathway and homeobox genes in acute myeloid leukemia: an introduction to the Pigengene package and its applications. *BMC Med Genomics, 10*(1), 16. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28298217. doi:10.1186/s12920-017-0253-6

Fox, M. E., & Lobo, M. K. (2019). The molecular and cellular mechanisms of depression: a focus on reward circuitry. *Mol Psychiatry, 24*(12), 1798-1815. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30967681. doi:10.1038/s41380-019-0415-3

Friederike Du¨ndar, Luce Skrabanek, & Zumbo, P. (2015). Introduction to differential gene expression analysis using RNA-seq. In © *2015-2019 Applied Bioinformatics Core* (2019 ed., pp. 63-78): Weill Cornell Medical College.

Fu, Y., Zhou, Q. Z., Zhang, X. L., Wang, Z. Z., & Wang, P. (2019). Identification of Hub Genes Using Co-Expression Network Analysis in Breast Cancer as a Tool to Predict Different Stages. *Med Sci Monit, 25*, 8873-8890. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31758680. doi:10.12659/MSM.919046

Fuller, T. F., Ghazalpour, A., Aten, J. E., Drake, T. A., Lusis, A. J., & Horvath, S. (2007). Weighted gene coexpression network analysis strategies applied to mouse weight. *Mamm Genome, 18*(6-7), 463-472. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17668265. doi:10.1007/s00335-007-9043-3

Gabbay, V., Ely, B. A., Li, Q., Bangaru, S. D., Panzer, A. M., Alonso, C. M., . . . Milham, M. P. (2013). Striatum-based circuitry of adolescent depression and anhedonia. *J Am Acad Child Adolesc Psychiatry, 52*(6), 628-641 e613. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23702452. doi:10.1016/j.jaac.2013.04.003

Geschwind, D. H., & Rakic, P. (2013). Cortical evolution: judge the brain by its cover. *Neuron, 80*(3), 633-647. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24183016. doi:10.1016/j.neuron.2013.10.045

Ghidinelli, M., Poitelon, Y., Shin, Y. K., Ameroso, D., Williamson, C., Ferri, C., . . . Feltri, M. L. (2017). Laminin 211 inhibits protein kinase A in Schwann cells to modulate neuregulin 1 type III-driven myelination. *PLoS Biol, 15*(6), e2001408. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28636612. doi:10.1371/journal.pbio.2001408

Ghosal, S., Hare, B., & Duman, R. S. (2017). Prefrontal Cortex GABAergic Deficits and Circuit Dysfunction in the Pathophysiology and Treatment of Chronic Stress and Depression. *Curr Opin Behav Sci, 14*, 1-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27812532. doi:10.1016/j.cobeha.2016.09.012

Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. (2017). *Lancet, 390*(10100), 1211-1259. doi:10.1016/s0140-6736(17)32154-2

Goel, N., & Bale, T. L. (2010). Sex differences in the serotonergic influence on the hypothalamic-pituitary-adrenal stress axis. *Endocrinology, 151*(4), 1784-1794. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20185764. doi:10.1210/en.2009-1180

Goel, N., Innala, L., & Viau, V. (2014). Sex differences in serotonin (5-HT) 1A receptor regulation of HPA axis and dorsal raphe responses to acute restraint. *Psychoneuroendocrinology, 40*, 232-241. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24485495. doi:10.1016/j.psyneuen.2013.11.020

Golden, S. A., Covington, H. E., 3rd, Berton, O., & Russo, S. J. (2011). A standardized protocol for repeated social defeat stress in mice. *Nat Protoc, 6*(8), 1183-1191. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21799487. doi:10.1038/nprot.2011.361

Gos, T., Krell, D., Brisch, R., Bielau, H., Trubner, K., Steiner, J., . . . Bogerts, B. (2008). Demonstration of decreased activity of dorsal raphe nucleus neurons in depressed suicidal patients by the AgNOR staining method. *J Affect Disord, 111*(2-3), 251-260. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18423885. doi:10.1016/j.jad.2008.03.002

Gray, A. L., Hyde, T. M., Deep-Soboslay, A., Kleinman, J. E., & Sodhi, M. S. (2015). Sex differences in glutamate receptor gene expression in major depression and suicide. *Mol Psychiatry, 20*(9), 1057-1068. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26169973. doi:10.1038/mp.2015.91

Grippo, A. J., Gerena, D., Huang, J., Kumar, N., Shah, M., Ughreja, R., & Carter, C. S. (2007). Social isolation induces behavioral and neuroendocrine disturbances relevant to depression in female and male prairie voles. *Psychoneuroendocrinology, 32*(8-10), 966-980. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17825994. doi:10.1016/j.psyneuen.2007.07.004

Guidotti, A., Auta, J., Davis, J. M., Di-Giorgi-Gerevini, V., Dwivedi, Y., Grayson, D. R., . . . Costa, E. (2000). Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry, 57*(11), 1061-1069. doi:yoa9104 [pii]

Guo, M., Wu, C. F., Liu, W., Yang, J. Y., & Chen, D. (2004). Sex difference in psychological behavior changes induced by long-term social isolation in mice. *Prog Neuropsychopharmacol Biol Psychiatry, 28*(1), 115-

121. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14687865. doi:10.1016/j.pnpbp.2003.09.027

Hall, F. S. (1998). Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. *Crit Rev Neurobiol, 12*(1-2), 129-162. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9444483.

Hao, Z. Y., Zhong, Y., Ma, Z. J., Xu, H. Z., Kong, J. Y., Wu, Z., . . . Wang, C. (2020). Abnormal resting-state functional connectivity of hippocampal subfields in patients with major depressive disorder. *BMC Psychiatry, 20*(1), 71. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32066415. doi:10.1186/s12888-020-02490-7

Hardcastle, T. J., & Kelly, K. A. (2010). baySeq: empirical Bayesian methods for identifying differential expression in sequence count data. *BMC Bioinformatics, 11*, 422. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20698981. doi:10.1186/1471-2105-11-422

Hare, B. D., & Duman, R. S. (2020). Prefrontal cortex circuits in depression and anxiety: contribution of discrete neuronal populations and target regions. *Mol Psychiatry, 25*(11), 2742-2758. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32086434. doi:10.1038/s41380-020-0685-9

Harris, A. Z., Atsak, P., Bretton, Z. H., Holt, E. S., Alam, R., Morton, M. P., . . . Gordon, J. A. (2017). A Novel Method for Chronic Social Defeat Stress in Female Mice. *Neuropsychopharmacology*. doi:10.1038/npp.2017.259

Harris, A. Z., Atsak, P., Bretton, Z. H., Holt, E. S., Alam, R., Morton, M. P., . . . Gordon, J. A. (2018). A Novel Method for Chronic Social Defeat Stress in Female Mice. *Neuropsychopharmacology, 43*(6), 1276-1283. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29090682. doi:10.1038/npp.2017.259

Hayley, S., Du, L., Litteljohn, D., Palkovits, M., Faludi, G., Merali, Z., . . . Anisman, H. (2015). Gender and brain regions specific differences in brain derived neurotrophic factor protein levels of depressed individuals who died through suicide. *Neurosci Lett, 600*, 12-16. doi:10.1016/j.neulet.2015.05.052

Heckers, S., Stone, D., Walsh, J., Shick, J., Koul, P., & Benes, F. M. (2002). Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messenger RNA in bipolar disorder and schizophrenia. *Arch Gen Psychiatry, 59*(6), 521-529.

Heinrich, L. M., & Gullone, E. (2006). The clinical significance of loneliness: a literature review. *Clin Psychol Rev, 26*(6), 695-718. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16952717. doi:10.1016/j.cpr.2006.04.002

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci, 20*(2), 78-84. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9023876. doi:10.1016/s0166-2236(96)10069-2

Heshmati, M., & Russo, S. J. (2015). Anhedonia and the brain reward circuitry in depression. *Curr Behav Neurosci Rep, 2*(3), 146-153. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26525751. doi:10.1007/s40473-015-0044-3

Hill, R. A., & van den Buuse, M. (2011). Sex-dependent and region-specific changes in TrkB signaling in BDNF heterozygous mice. *Brain Res, 1384*, 51-60. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21281620. doi:10.1016/j.brainres.2011.01.060

Hiroi, N., Wong, M. L., Licinio, J., Park, C., Young, M., Gold, P. W., . . . Bornstein, S. R. (2001). Expression of corticotropin releasing hormone receptors type I and type II mRNA in suicide victims and controls. *Mol Psychiatry, 6*(5), 540-546. doi:10.1038/sj.mp.4000908

Ho, J. W., Stefani, M., dos Remedios, C. G., & Charleston, M. A. (2008). Differential variability analysis of gene expression and its application to human diseases. *Bioinformatics, 24*(13), i390-398. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18586739. doi:10.1093/bioinformatics/btn142

Hodes, G. E., Pfau, M. L., Leboeuf, M., Golden, S. A., Christoffel, D. J., Bregman, D., . . . Russo, S. J. (2014). Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proc Natl Acad Sci U S A, 111*(45), 16136-16141. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25331895. doi:10.1073/pnas.1415191111

Hodes, G. E., Pfau, M. L., Purushothaman, I., Ahn, H. F., Golden, S. A., Christoffel, D. J., . . . Russo, S. J. (2015). Sex Differences in Nucleus Accumbens Transcriptome Profiles Associated with Susceptibility versus

Resilience to Subchronic Variable Stress. *J Neurosci, 35*(50), 16362-16376. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26674863. doi:10.1523/JNEUROSCI.1392-15.2015

Hodge, R. D., Bakken, T. E., Miller, J. A., Smith, K. A., Barkan, E. R., Graybuck, L. T., . . . Lein, E. S. (2019). Conserved cell types with divergent features in human versus mouse cortex. *Nature, 573*(7772), 61-68. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31435019. doi:10.1038/s41586-019-1506-7

Horvath, S. (2011). Weighted Network Analysis. In *Applications in Genomics and Systems Biology*: Springer.

Horvath, S., & Dong, J. (2008). Geometric interpretation of gene coexpression network analysis. *PLoS Comput Biol, 4*(8), e1000117. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18704157. doi:10.1371/journal.pcbi.1000117

Howard, S., Landry, C., Fisher, R., Bezouglaia, O., Handley, V., & Campagnoni, A. (1998). Postnatal localization and morphogenesis of cells expressing the dopaminergic D2 receptor gene in rat brain: expression in non-neuronal cells. *J Comp Neurol, 391*(1), 87-98. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9527544. doi:10.1002/(sici)1096-9861(19980202)391:1<87::aid-cne8>3.0.co;2-n

Huang da, W., Sherman, B. T., & Lempicki, R. A. (2009). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc, 4*(1), 44-57. doi:10.1038/nprot.2008.211

Hunter, R. G., Seligsohn, M., Rubin, T. G., Griffiths, B. B., Ozdemir, Y., Pfaff, D. W., . . . McEwen, B. S. (2016). Stress and corticosteroids regulate rat hippocampal mitochondrial DNA gene expression via the glucocorticoid receptor. *Proc Natl Acad Sci U S A, 113*(32), 9099-9104. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27457949. doi:10.1073/pnas.1602185113

Hyde, C. L., Nagle, M. W., Tian, C., Chen, X., Paciga, S. A., Wendland, J. R., . . . Winslow, A. R. (2016). Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nat Genet, 48*(9), 1031-1036. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27479909. doi:10.1038/ng.3623

Itoh, N., Itoh, Y., Tassoni, A., Ren, E., Kaito, M., Ohno, A., . . . Voskuhl, R. R. (2018). Cell-specific and region-specific transcriptomics in the multiple sclerosis model: Focus on astrocytes. *Proc Natl Acad Sci U S A, 115*(2), E302-E309. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29279367. doi:10.1073/pnas.1716032115

Iwamoto, K., Kakiuchi, C., Bundo, M., Ikeda, K., & Kato, T. (2004). Molecular characterization of bipolar disorder by comparing gene expression profiles of postmortem brains of major mental disorders. *Mol Psychiatry, 9*(4), 406-416. doi:10.1038/sj.mp.4001437

Jacobson, L. (2018). Glucocorticoid receptor deletion from locus coeruleus norepinephrine neurons promotes depression-like social withdrawal in female but not male mice. *Brain Res*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30576626. doi:10.1016/j.brainres.2018.12.026

Jang, M., Jung, T., Kim, S. H., & Noh, J. (2019). Sex differential effect of dexmedetomidine on fear memory extinction and anxiety behavior in adolescent rats. *Neurosci Res*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30685494. doi:10.1016/j.neures.2019.01.006

Jasarevic, E., Morrison, K. E., & Bale, T. L. (2016). Sex differences in the gut microbiome-brain axis across the lifespan. *Philos Trans R Soc Lond B Biol Sci, 371*(1688), 20150122. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26833840. doi:10.1098/rstb.2015.0122

Jiang, C., Lin, W. J., Labonte, B., Tamminga, C. A., Turecki, G., Nestler, E. J., . . . Salton, S. R. (2018). VGF and its C-terminal peptide TLQP-62 in ventromedial prefrontal cortex regulate depression-related behaviors and the response to ketamine. *Neuropsychopharmacology*. doi:10.1038/s41386-018-0277-4

Jiang, C., & Salton, S. R. (2013). The Role of Neurotrophins in Major Depressive Disorder. *Transl Neurosci, 4*(1), 46-58. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23691270. doi:10.2478/s13380-013-0103-8

Jiang, P., Scarpa, J. R., Fitzpatrick, K., Losic, B., Gao, V. D., Hao, K., . . . Kasarskis, A. (2015). A systems approach identifies networks and genes linking sleep and stress: implications for neuropsychiatric disorders. *Cell Rep, 11*(5), 835-848. doi:10.1016/j.celrep.2015.04.003

Joeyen-Waldorf, J., Edgar, N., & Sibille, E. (2009). The roles of sex and serotonin transporter levels in age- and stress-related emotionality in mice. *Brain Res, 1286*, 84-93. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19577546. doi:10.1016/j.brainres.2009.06.079

Juszczak, G. R., & Stankiewicz, A. M. (2018). Glucocorticoids, genes and brain function. *Prog Neuropsychopharmacol Biol Psychiatry, 82*, 136-168. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29180230. doi:10.1016/j.pnpbp.2017.11.020

Kang, H. J., Adams, D. H., Simen, A., Simen, B. B., Rajkowska, G., Stockmeier, C. A., . . . Duman, R. S. (2007). Gene expression profiling in postmortem prefrontal cortex of major depressive disorder. *J Neurosci, 27*(48), 13329-13340. doi:10.1523/jneurosci.4083-07.2007

Kang, H. J., Kim, J. M., Stewart, R., Kim, S. Y., Bae, K. Y., Kim, S. W., . . . Yoon, J. S. (2013). Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. *Prog Neuropsychopharmacol Biol Psychiatry, 44*, 23-28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23333376. doi:10.1016/j.pnpbp.2013.01.006

Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., & Aubry, J. M. (2002). Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res, 109*(2), 143-148. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11927139.

Katz, R. J. (1982). Animal model of depression: pharmacological sensitivity of a hedonic deficit. *Pharmacol Biochem Behav, 16*(6), 965-968. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7202217.

Kavushansky, A., Ben-Shachar, D., Richter-Levin, G., & Klein, E. (2009). Physical stress differs from psychosocial stress in the pattern and time-course of behavioral responses, serum corticosterone and expression of plasticity-related genes in the rat. *Stress, 12*(5), 412-425. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19929444. doi:10.1080/10253890802556081

Keers, R., & Aitchison, K. J. (2010). Gender differences in antidepressant drug response. *Int Rev Psychiatry, 22*(5), 485-500. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21047161. doi:10.3109/09540261.2010.496448

Keller, S., Sarchiapone, M., Zarrilli, F., Videtic, A., Ferraro, A., Carli, V., . . . Chiariotti, L. (2010). Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Arch Gen Psychiatry, 67*(3), 258-267. doi:10.1001/archgenpsychiatry.2010.9

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*(1), 109-114. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16390897. doi:10.1176/appi.ajp.163.1.109

Kendler, K. S., Kuhn, J. W., & Prescott, C. A. (2004). Childhood sexual abuse, stressful life events and risk for major depression in women. *Psychol Med, 34*(8), 1475-1482. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15724878. doi:10.1017/s003329170400265x

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry, 62*(6), 617-627. doi:10.1001/archpsyc.62.6.617

Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., & Nelson, C. B. (1993). Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord, 29*(2-3), 85-96.

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*(4), 318-324.

Khatri, P., Sirota, M., & Butte, A. J. (2012). Ten years of pathway analysis: current approaches and outstanding challenges. *PLoS Comput Biol, 8*(2), e1002375. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22383865. doi:10.1371/journal.pcbi.1002375

Kimbrell, T. A., Ketter, T. A., George, M. S., Little, J. T., Benson, B. E., Willis, M. W., . . . Post, R. M. (2002). Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biol Psychiatry, 51*(3), 237-252. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11839367.

Kinnally, E. L., Lyons, L. A., Abel, K., Mendoza, S., & Capitanio, J. P. (2008). Effects of early experience and genotype on serotonin transporter regulation in infant rhesus macaques. *Genes Brain Behav, 7*(4), 481-

486. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18081711. doi:10.1111/j.1601-183X.2007.00383.x

Kinnally, E. L., Tarara, E. R., Mason, W. A., Mendoza, S. P., Abel, K., Lyons, L. A., & Capitanio, J. P. (2010). Serotonin transporter expression is predicted by early life stress and is associated with disinhibited behavior in infant rhesus macaques. *Genes Brain Behav, 9*(1), 45-52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19817873. doi:10.1111/j.1601-183X.2009.00533.x

Kiyatkin, A., Aksamitiene, E., Markevich, N. I., Borisov, N. M., Hoek, J. B., & Kholodenko, B. N. (2006). Scaffolding protein Grb2-associated binder 1 sustains epidermal growth factor-induced mitogenic and survival signaling by multiple positive feedback loops. *J Biol Chem, 281*(29), 19925-19938. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16687399. doi:10.1074/jbc.M600482200

Klempan, T. A., Sequeira, A., Canetti, L., Lalovic, A., Ernst, C., ffrench-Mullen, J., & Turecki, G. (2009). Altered expression of genes involved in ATP biosynthesis and GABAergic neurotransmission in the ventral prefrontal cortex of suicides with and without major depression. *Mol Psychiatry, 14*(2), 175-189. doi:4002110 [pii]

10.1038/sj.mp.4002110 [doi]

Knoth, R. L., Bolge, S. C., Kim, E., & Tran, Q. V. (2010). Effect of inadequate response to treatment in patients with depression. *Am J Manag Care, 16*(8), e188-196. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20690785.

Knowland, D., & Lim, B. K. (2018). Circuit-based frameworks of depressive behaviors: The role of reward circuitry and beyond. *Pharmacol Biochem Behav, 174*, 42-52. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29309799. doi:10.1016/j.pbb.2017.12.010

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behav Brain Res, 201*(2), 239-243. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19428640. doi:10.1016/j.bbr.2009.03.004

Kogler, L., Muller, V. I., Chang, A., Eickhoff, S. B., Fox, P. T., Gur, R. C., & Derntl, B. (2015). Psychosocial versus physiological stress - Meta-analyses on deactivations and activations of the neural correlates of stress reactions. *Neuroimage, 119*, 235-251. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26123376. doi:10.1016/j.neuroimage.2015.06.059

Kornstein, S. G., Schatzberg, A. F., Thase, M. E., Yonkers, K. A., McCullough, J. P., Keitner, G. I., . . . Keller, M. B. (2000). Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry, 157*(9), 1445-1452. doi:10.1176/appi.ajp.157.9.1445

Kornstein, S. G., Schatzberg, A. F., Thase, M. E., Yonkers, K. A., McCullough, J. P., Keitner, G. I., . . . Keller, M. B. (2000). Gender differences in chronic major and double depression. *J Affect Disord, 60*(1), 1-11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10940442.

Krishnan, V., Han, M. H., Graham, D. L., Berton, O., Renthal, W., Russo, S. J., . . . Nestler, E. J. (2007). Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell, 131*(2), 391-404. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17956738. doi:10.1016/j.cell.2007.09.018

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature, 455*(7215), 894-902. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18923511. doi:10.1038/nature07455

Krishnan, V., & Nestler, E. J. (2011). Animal models of depression: molecular perspectives. *Curr Top Behav Neurosci, 7*, 121-147. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21225412. doi:10.1007/7854_2010_108

Kundakovic, M., Chen, Y., Costa, E., & Grayson, D. R. (2007). DNA methyltransferase inhibitors coordinately induce expression of the human reelin and glutamic acid decarboxylase 67 genes. *Mol Pharmacol, 71*(3), 644-653. doi:10.1124/mol.106.030635

Labaka, A., Goni-Balentziaga, O., Lebena, A., & Perez-Tejada, J. (2018). Biological Sex Differences in Depression: A Systematic Review. *Biol Res Nurs, 20*(4), 383-392. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29759000. doi:10.1177/1099800418776082

Labonte, B., Azoulay, N., Yerko, V., Turecki, G., & Brunet, A. (2014). Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. *Transl Psychiatry, 4*, e368. doi:10.1038/tp.2014.3

Labonte, B., Engmann, O., Purushothaman, I., Menard, C., Wang, J., Tan, C., . . . Nestler, E. J. (2017a). Sex-specific transcriptional signatures in human depression. *Nat Med, 23*(9), 1102-1111. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28825715. doi:10.1038/nm.4386

Labonte, B., Engmann, O., Purushothaman, I., Menard, C., Wang, J., Tan, C., . . . Nestler, E. J. (2017b). Sex-specific transcriptional signatures in human depression. *Nat Med*. doi:10.1038/nm.4386

Labonte, B., Yerko, V., Gross, J., Mechawar, N., Meaney, M. J., Szyf, M., & Turecki, G. (2012). Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. *Biol Psychiatry, 72*(1), 41-48. doi:10.1016/j.biopsych.2012.01.034

Labuda, M., Labuda, D., Korab-Laskowska, M., Cole, D. E., Zietkiewicz, E., Weissenbach, J., . . . Glorieux, F. H. (1996). Linkage disequilibrium analysis in young populations: pseudo-vitamin D-deficiency rickets and the founder effect in French Canadians. *Am J Hum Genet, 59*(3), 633-643.

Lalovic, A., Klempan, T., Sequeira, A., Luheshi, G., & Turecki, G. (2010). Altered expression of lipid metabolism and immune response genes in the frontal cortex of suicide completers. *J Affect Disord, 120*(1-3), 24-31. doi:10.1016/j.jad.2009.04.007

Lander, S. S., Linder-Shacham, D., & Gaisler-Salomon, I. (2017). Differential effects of social isolation in adolescent and adult mice on behavior and cortical gene expression. *Behav Brain Res, 316*, 245-254. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27618762. doi:10.1016/j.bbr.2016.09.005

Langfelder, P., & Horvath, S. (2007). Eigengene networks for studying the relationships between co-expression modules. *BMC Syst Biol, 1*, 54. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18031580. doi:10.1186/1752-0509-1-54

Langfelder, P., & Horvath, S. (2008). WGCNA: an R package for weighted correlation network analysis. *BMC Bioinformatics, 9*, 559. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19114008. doi:10.1186/1471-2105-9-559

LaPlant, Q., Chakravarty, S., Vialou, V., Mukherjee, S., Koo, J. W., Kalahasti, G., . . . Russo, S. J. (2009). Role of nuclear factor kappaB in ovarian hormone-mediated stress hypersensitivity in female mice. *Biol Psychiatry, 65*(10), 874-880. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19251249. doi:10.1016/j.biopsych.2009.01.024

Le, T. T., Savitz, J., Suzuki, H., Misaki, M., Teague, T. K., White, B. C., . . . Bodurka, J. (2018). Identification and replication of RNA-Seq gene network modules associated with depression severity. *Transl Psychiatry, 8*(1), 180. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30185774. doi:10.1038/s41398-018-0234-3

LeGates, T. A., Kvarta, M. D., & Thompson, S. M. (2019). Sex differences in antidepressant efficacy. *Neuropsychopharmacology, 44*(1), 140-154. doi:10.1038/s41386-018-0156-z

Levine, S. (1962). Plasma-free corticosteroid response to electric shock in rats stimulated in infancy. *Science, 135*(3506), 795-796. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14464660. doi:10.1126/science.135.3506.795-a

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology, 30*(10), 939-946. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15958281. doi:10.1016/j.psyneuen.2005.03.013

Li J, P. L., Godoy MI, Pembroke WG, Rexach JE, Condro MC, Alvarado AG, Harteni M, Chen Y, Stiles L, Chen AY, Wanner IB, Yang X, Goldman SA, Geschwind DH, Kornblum HI, Zhang Y. (2020). Conservation and divergence of vulnerability and responses to stressors between human and mouse astrocytes. doi:10.1101/2020.04.17.044222

Li, J., Zhou, D., Qiu, W., Shi, Y., Yang, J. J., Chen, S., . . . Pan, H. (2018). Application of Weighted Gene Co-expression Network Analysis for Data from Paired Design. *Sci Rep, 8*(1), 622. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29330528. doi:10.1038/s41598-017-18705-z

Li, J. Z., Bunney, B. G., Meng, F., Hagenauer, M. H., Walsh, D. M., Vawter, M. P., . . . Bunney, W. E. (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc Natl Acad Sci U S A, 110*(24), 9950-9955. doi:10.1073/pnas.1305814110

Li., D. (2019 Nov 21.). Computational Biology. In H. H (Ed.), *Computational Biology*. Brisbane (AU): Codon Publications;.

Liang, J. W., Fang, Z. Y., Huang, Y., Liuyang, Z. Y., Zhang, X. L., Wang, J. L., . . . Liu, R. (2018). Application of Weighted Gene Co-Expression Network Analysis to Explore the Key Genes in Alzheimer's Disease. *J Alzheimers Dis, 65*(4), 1353-1364. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30124448. doi:10.3233/JAD-180400

Lin, L. C., Lewis, D. A., & Sibille, E. (2011). A human-mouse conserved sex bias in amygdala gene expression related to circadian clock and energy metabolism. *Mol Brain, 4*, 18. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21542937. doi:10.1186/1756-6606-4-18

Lisowski, P., Juszczak, G. R., Goscik, J., Wieczorek, M., Zwierzchowski, L., & Swiergiel, A. H. (2011). Effect of chronic mild stress on hippocampal transcriptome in mice selected for high and low stress-induced analgesia and displaying different emotional behaviors. *Eur Neuropsychopharmacol, 21*(1), 45-62. doi:10.1016/j.euroneuro.2010.08.004

Liu, J., Dietz, K., DeLoyht, J. M., Pedre, X., Kelkar, D., Kaur, J., . . . Casaccia, P. (2012). Impaired adult myelination in the prefrontal cortex of socially isolated mice. *Nat Neurosci, 15*(12), 1621-1623. doi:10.1038/nn.3263

Liu, L., Zhou, X., Zhang, Y., Pu, J., Yang, L., Yuan, S., . . . Xie, P. (2018). Hippocampal metabolic differences implicate distinctions between physical and psychological stress in four rat models of depression. *Transl Psychiatry, 8*(1), 4. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29317595. doi:10.1038/s41398-017-0018-1

Liu, Y., Lv, L., Wang, L., & Zhong, Y. (2018). Social Isolation Induces Rac1-Dependent Forgetting of Social Memory. *Cell Rep, 25*(2), 288-295 e283. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30304669. doi:10.1016/j.celrep.2018.09.033

Lopez, J. F., Palkovits, M., Arato, M., Mansour, A., Akil, H., & Watson, S. J. (1992). Localization and quantification of pro-opiomelanocortin mRNA and glucocorticoid receptor mRNA in pituitaries of suicide victims. *Neuroendocrinology, 56*(4), 491-501.

Lorsch, Z. S. (2018). *TRANSCRIPTIONAL NETWORKS OF RESILIENCE IN A MOUSE MODEL OF DEPRESSION.* (Doctor of Philosophy), Icahn School of Medicine at Mount Sinai, New York.

Lorsch, Z. S., Ambesi-Impiombato, A., Zenowich, R., Morganstern, I., Leahy, E., Bansal, M., . . . Hanania, T. (2020). Computational Analysis of Multidimensional Behavioral Alterations After Chronic Social Defeat Stress. *Biol Psychiatry*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/33309017. doi:10.1016/j.biopsych.2020.10.010

Lorsch, Z. S., Hamilton, P. J., Ramakrishnan, A., Parise, E. M., Salery, M., Wright, W. J., . . . Nestler, E. J. (2019). Stress resilience is promoted by a Zfp189-driven transcriptional network in prefrontal cortex. *Nat Neurosci, 22*(9), 1413-1423. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31427770. doi:10.1038/s41593-019-0462-8

Lorsch, Z. S., Hamilton, P. J., Ramakrishnan, A., Parise, E. M., Wright, W. J., Salery, M., . . . Nestler, E. J. (2019). Zfp189 Mediates Stress Resilience Through a CREB-Regulated Transcriptional Network in Prefrontal Cortex. *Nature Neuroscience, In press*.

Love, M. I., Huber, W., & Anders, S. (2014). Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol, 15*(12), 550. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25516281. doi:10.1186/s13059-014-0550-8

LoVerso, P. R., & Cui, F. (2016). Cell type-specific transcriptome profiling in mammalian brains. *Front Biosci (Landmark Ed), 21*, 973-985. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27100485. doi:10.2741/4434

Lutz, P. E., Almeida, D., Fiori, L. M., & Turecki, G. (2015). Childhood maltreatment and stress-related psychopathology: the epigenetic memory hypothesis. *Curr Pharm Des, 21*(11), 1413-1417. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25564388.

Lutz, P. E., Tanti, A., Gasecka, A., Barnett-Burns, S., Kim, J. J., Zhou, Y., . . . Turecki, G. (2017a). Association of a History of Child Abuse With Impaired Myelination in the Anterior Cingulate Cortex: Convergent Epigenetic, Transcriptional, and Morphological Evidence. *Am J Psychiatry, 174*(12), 1185-1194. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28750583. doi:10.1176/appi.ajp.2017.16111286

Lutz, P. E., Tanti, A., Gasecka, A., Barnett-Burns, S., Kim, J. J., Zhou, Y., . . . Turecki, G. (2017b). Association of a History of Child Abuse With Impaired Myelination in the Anterior Cingulate Cortex: Convergent Epigenetic, Transcriptional, and Morphological Evidence. *Am J Psychiatry*, appiajp201716111286. doi:10.1176/appi.ajp.2017.16111286

Lyons, D. M., Buckmaster, P. S., Lee, A. G., Wu, C., Mitra, R., Duffey, L. M., . . . Schatzberg, A. F. (2010). Stress coping stimulates hippocampal neurogenesis in adult monkeys. *Proc Natl Acad Sci U S A, 107*(33), 14823-14827. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20675584. doi:10.1073/pnas.0914568107

Lyons, D. M., Kim, S., Schatzberg, A. F., & Levine, S. (1998). Postnatal foraging demands alter adrenocortical activity and psychosocial development. *Dev Psychobiol, 32*(4), 285-291. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9589217.

MacQueen, G., & Frodl, T. (2011). The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? *Mol Psychiatry, 16*(3), 252-264. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20661246. doi:10.1038/mp.2010.80

Major Depressive Disorder Working Group of the Psychiatric, G. C., Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., . . . Sullivan, P. F. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry, 18*(4), 497-511. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22472876. doi:10.1038/mp.2012.21

Makinodan, M., Rosen, K. M., Ito, S., & Corfas, G. (2012). A critical period for social experience-dependent oligodendrocyte maturation and myelination. *Science, 337*(6100), 1357-1360. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22984073. doi:10.1126/science.1220845

Malki, K., Mineur, Y. S., Tosto, M. G., Campbell, J., Karia, P., Jumabhoy, I., . . . Schalkwyk, L. C. (2015). Pervasive and opposing effects of Unpredictable Chronic Mild Stress (UCMS) on hippocampal gene expression in BALB/cJ and C57BL/6J mouse strains. *BMC Genomics, 16*, 262. doi:10.1186/s12864-015-1431-6

Mallampalli, M. P., & Carter, C. L. (2014). Exploring sex and gender differences in sleep health: a Society for Women's Health Research Report. *J Womens Health (Larchmt), 23*(7), 553-562. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24956068. doi:10.1089/jwh.2014.4816

Marcus, S. M., Kerber, K. B., Rush, A. J., Wisniewski, S. R., Nierenberg, A., Balasubramani, G. K., . . . Trivedi, M. H. (2008). Sex differences in depression symptoms in treatment-seeking adults: confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. *Compr Psychiatry, 49*(3), 238-246. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18396182. doi:10.1016/j.comppsych.2007.06.012

Markham, A., Bains, R., Franklin, P., & Spedding, M. (2014). Changes in mitochondrial function are pivotal in neurodegenerative and psychiatric disorders: how important is BDNF? *Br J Pharmacol, 171*(8), 2206-2229. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24720259. doi:10.1111/bph.12531

Marshall, J., Zhou, X. Z., Chen, G., Yang, S. Q., Li, Y., Wang, Y., . . . Cao, C. (2018). Antidepression action of BDNF requires and is mimicked by Galphai1/3 expression in the hippocampus. *Proc Natl Acad Sci U S A, 115*(15), E3549-E3558. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29507199. doi:10.1073/pnas.1722493115

Masten, A. S. (2001). Ordinary magic. Resilience processes in development. *Am Psychol, 56*(3), 227-238. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11315249. doi:10.1037//0003-066x.56.3.227

Matsusue, Y., Horii-Hayashi, N., Kirita, T., & Nishi, M. (2014). Distribution of corticosteroid receptors in mature oligodendrocytes and oligodendrocyte progenitors of the adult mouse brain. *J Histochem Cytochem, 62*(3), 211-226. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24309510. doi:10.1369/0022155413517700

Matthews, T., Danese, A., Wertz, J., Odgers, C. L., Ambler, A., Moffitt, T. E., & Arseneault, L. (2016). Social isolation, loneliness and depression in young adulthood: a behavioural genetic analysis. *Soc Psychiatry Psychiatr Epidemiol, 51*(3), 339-348. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26843197. doi:10.1007/s00127-016-1178-7

Matute, C. (2008). P2X7 receptors in oligodendrocytes: a novel target for neuroprotection. *Mol Neurobiol, 38*(2), 123-128. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18704769. doi:10.1007/s12035-008-8028-x

Maussion, G., Yang, J., Suderman, M., Diallo, A., Nagy, C., Arnovitz, M., . . . Turecki, G. (2014). Functional DNA methylation in a transcript specific 3'UTR region of TrkB associates with suicide. *Epigenetics, 9*(8), 1061-1070. doi:10.4161/epi.29068

Maussion, G., Yang, J., Yerko, V., Barker, P., Mechawar, N., Ernst, C., & Turecki, G. (2012). Regulation of a truncated form of tropomyosin-related kinase B (TrkB) by Hsa-miR-185* in frontal cortex of suicide completers. *PLoS One, 7*(6), e39301. doi:10.1371/journal.pone.0039301

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., . . . Fox, P. T. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry, 156*(5), 675-682. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10327898. doi:10.1176/ajp.156.5.675

McCarter, T. (2008). Depression overview. *Am Health Drug Benefits, 1*(3), 44-51. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25126224.

McCutcheon, R. A., Abi-Dargham, A., & Howes, O. D. (2019). Schizophrenia, Dopamine and the Striatum: From Biology to Symptoms. *Trends Neurosci, 42*(3), 205-220. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30621912. doi:10.1016/j.tins.2018.12.004

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology, 41*(1), 3-23. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26076834. doi:10.1038/npp.2015.171

McGirr, A., Tousignant, M., Routhier, D., Pouliot, L., Chawky, N., Margolese, H. C., & Turecki, G. (2006). Risk factors for completed suicide in schizophrenia and other chronic psychotic disorders: a case-control study. *Schizophr Res, 84*(1), 132-143. doi:10.1016/j.schres.2006.02.025

McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., . . . Meaney, M. J. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci, 12*(3), 342-348. doi:nn.2270 [pii]

10.1038/nn.2270 [doi]

McKinney, W. T. (2001). Overview of the past contributions of animal models and their changing place in psychiatry. *Semin Clin Neuropsychiatry, 6*(1), 68-78. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11172533. doi:10.1053/scnp.2001.20292

Mena, F., & Benoit, L. (2019a). Molecular programs underlying differences in the expression of mood disorders in males and females. *Brain Res*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31129154. doi:10.1016/j.brainres.2019.05.016

Mena, F., & Benoit, L. (2019b). Molecular programs underlying differences in the expression of mood disorders in males and females. *Brain Res, 1719*, 89-103. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31129154. doi:10.1016/j.brainres.2019.05.016

Menard, C., Hodes, G. E., & Russo, S. J. (2016). Pathogenesis of depression: Insights from human and rodent studies. *Neuroscience, 321*, 138-162. doi:10.1016/j.neuroscience.2015.05.053

Menard, C., Pfau, M. L., Hodes, G. E., Kana, V., Wang, V. X., Bouchard, S., . . . Russo, S. J. (2017). Social stress induces neurovascular pathology promoting depression. *Nat Neurosci, 20*(12), 1752-1760. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29184215. doi:10.1038/s41593-017-0010-3

Meng, C., Zeleznik, O. A., Thallinger, G. G., Kuster, B., Gholami, A. M., & Culhane, A. C. (2016). Dimension reduction techniques for the integrative analysis of multi-omics data. *Brief Bioinform, 17*(4), 628-641. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26969681. doi:10.1093/bib/bbv108

Merali, Z., Du, L., Hrdina, P., Palkovits, M., Faludi, G., Poulter, M. O., & Anisman, H. (2004). Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. *J Neurosci, 24*(6), 1478-1485. doi:10.1523/JNEUROSCI.4734-03.2004 [doi]

24/6/1478 [pii]

Merali, Z., Kent, P., Du, L., Hrdina, P., Palkovits, M., Faludi, G., . . . Anisman, H. (2006). Corticotropin-releasing hormone, arginine vasopressin, gastrin-releasing peptide, and neuromedin B alterations in stress-relevant brain regions of suicides and control subjects. *Biol Psychiatry, 59*(7), 594-602. doi:10.1016/j.biopsych.2005.08.008

Mercier, G., Lennon, A. M., Renouf, B., Dessouroux, A., Ramauge, M., Courtin, F., & Pierre, M. (2004). MAP kinase activation by fluoxetine and its relation to gene expression in cultured rat astrocytes. *J Mol Neurosci, 24*(2), 207-216. doi:JMN:24:2:207 [pii]

10.1385/JMN:24:2:207 [doi]

Miech, R. A., & Hauser, R. M. (2001). Socioeconomic status and health at midlife. A comparison of educational attainment with occupation-based indicators. *Ann Epidemiol, 11*(2), 75-84. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11164123. doi:10.1016/s1047-2797(00)00079-x

Milne, A. M., MacQueen, G. M., & Hall, G. B. (2012). Abnormal hippocampal activation in patients with extensive history of major depression: an fMRI study. *J Psychiatry Neurosci, 37*(1), 28-36. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21745440. doi:10.1503/jpn.110004

Ming-HuHan, J.Russo, S., & J.Nestler, E. (2019). Chapter 12 - Molecular, Cellular, and Circuit Basis of Depression Susceptibility and Resilience. In *Neurobiology of Depression* (2019/02/08 ed.).

Misra, J., Schmitt, W., Hwang, D., Hsiao, L. L., Gullans, S., Stephanopoulos, G., & Stephanopoulos, G. (2002). Interactive exploration of microarray gene expression patterns in a reduced dimensional space. *Genome Res, 12*(7), 1112-1120. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12097349. doi:10.1101/gr.225302

Miyata, S., Koyama, Y., Takemoto, K., Yoshikawa, K., Ishikawa, T., Taniguchi, M., . . . Tohyama, M. (2011). Plasma corticosterone activates SGK1 and induces morphological changes in oligodendrocytes in corpus callosum. *PLoS One, 6*(5), e19859. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21655274. doi:10.1371/journal.pone.0019859

Monteiro, S., Roque, S., de Sa-Calcada, D., Sousa, N., Correia-Neves, M., & Cerqueira, J. J. (2015). An efficient chronic unpredictable stress protocol to induce stress-related responses in C57BL/6 mice. *Front Psychiatry, 6*, 6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25698978. doi:10.3389/fpsyt.2015.00006

Mosca, E., Bersanelli, M., Gnocchi, M., Moscatelli, M., Castellani, G., Milanesi, L., & Mezzelani, A. (2017). Network Diffusion-Based Prioritization of Autism Risk Genes Identifies Significantly Connected Gene Modules. *Front Genet, 8*, 129. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28993790. doi:10.3389/fgene.2017.00129

Muir, J., Lopez, J., & Bagot, R. C. (2018). Wiring the depressed brain: optogenetic and chemogenetic circuit interrogation in animal models of depression. *Neuropsychopharmacology*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30555161. doi:10.1038/s41386-018-0291-6

Mulvey, B., Bhatti, D. L., Gyawali, S., Lake, A. M., Kriaucionis, S., Ford, C. P., . . . Dougherty, J. D. (2018). Molecular and Functional Sex Differences of Noradrenergic Neurons in the Mouse Locus Coeruleus. *Cell Rep, 23*(8), 2225-2235. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29791834. doi:10.1016/j.celrep.2018.04.054

Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmuhl, Y., Fischer, D., . . . Spengler, D. (2009). Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci, 12*(12), 1559-1566. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19898468. doi:10.1038/nn.2436

Murphy, M. O., & Loria, A. S. (2017). Sex-specific effects of stress on metabolic and cardiovascular disease: are women at higher risk? *Am J Physiol Regul Integr Comp Physiol, 313*(1), R1-R9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28468942. doi:10.1152/ajpregu.00185.2016

Murthy, S., & Gould, E. (2018). Early Life Stress in Rodents: Animal Models of Illness or Resilience? *Front Behav Neurosci, 12*, 157. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30108490. doi:10.3389/fnbeh.2018.00157

Nagy, C., Maitra, M., Tanti, A., Suderman, M., Theroux, J. F., Davoli, M. A., . . . Turecki, G. (2020). Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte

precursor cells and excitatory neurons. *Nat Neurosci, 23*(6), 771-781. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32341540. doi:10.1038/s41593-020-0621-y

Nakatani, N., Hattori, E., Ohnishi, T., Dean, B., Iwayama, Y., Matsumoto, I., . . . Yoshikawa, T. (2006). Genome-wide expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation. *Hum Mol Genet, 15*(12), 1949-1962. doi:ddl118 [pii]
10.1093/hmg/ddl118 [doi]

Nemeroff, C. B., Owens, M. J., Bissette, G., Andorn, A. C., & Stanley, M. (1988). Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch Gen Psychiatry, 45*(6), 577-579.

Nestler, E. J., Barrot, M., DiLeone, R. J., Eisch, A. J., Gold, S. J., & Monteggia, L. M. (2002). Neurobiology of depression. *Neuron, 34*(1), 13-25. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11931738.

Nestler, E. J., & Hyman, S. E. (2010). Animal models of neuropsychiatric disorders. *Nat Neurosci, 13*(10), 1161-1169. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20877280. doi:10.1038/nn.2647

Nishi, M., Horii-Hayashi, N., & Sasagawa, T. (2014). Effects of early life adverse experiences on the brain: implications from maternal separation models in rodents. *Front Neurosci, 8*, 166. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24987328. doi:10.3389/fnins.2014.00166

Nishi, M., Horii-Hayashi, N., Sasagawa, T., & Matsunaga, W. (2013). Effects of early life stress on brain activity: implications from maternal separation model in rodents. *Gen Comp Endocrinol, 181*, 306-309. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23032077. doi:10.1016/j.ygcen.2012.09.024

Oh, S., Li, C., Baldwin, R. L., Song, S., Liu, F., & Li, R. W. (2019). Temporal dynamics in meta longitudinal RNA-Seq data. *Sci Rep, 9*(1), 763. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30679697. doi:10.1038/s41598-018-37397-7

Oron, O., Getselter, D., Shohat, S., Reuveni, E., Lukic, I., Shifman, S., & Elliott, E. (2019). Gene network analysis reveals a role for striatal glutamatergic receptors in dysregulated risk-assessment behavior of autism mouse models. *Transl Psychiatry, 9*(1), 257. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31624228. doi:10.1038/s41398-019-0584-5

Overstreet, D. H., & Wegener, G. (2013). The flinders sensitive line rat model of depression--25 years and still producing. *Pharmacol Rev, 65*(1), 143-155. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23319547. doi:10.1124/pr.111.005397

Palma-Gudiel, H., Peralta, V., Deuschle, M., Navarro, V., & Fananas, L. (2019). Epigenetics-by-sex interaction for somatization conferred by methylation at the promoter region of SLC6A4 gene. *Prog Neuropsychopharmacol Biol Psychiatry, 89*, 125-131. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30201454. doi:10.1016/j.pnpbp.2018.09.002

Pandya, M., Altinay, M., Malone, D. A., Jr., & Anand, A. (2012). Where in the brain is depression? *Curr Psychiatry Rep, 14*(6), 634-642. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23055003. doi:10.1007/s11920-012-0322-7

Parikshak, N. N., Luo, R., Zhang, A., Won, H., Lowe, J. K., Chandran, V., . . . Geschwind, D. H. (2013). Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. *Cell, 155*(5), 1008-1021. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24267887. doi:10.1016/j.cell.2013.10.031

Parker, K. J., Buckmaster, C. L., Justus, K. R., Schatzberg, A. F., & Lyons, D. M. (2005). Mild early life stress enhances prefrontal-dependent response inhibition in monkeys. *Biol Psychiatry, 57*(8), 848-855. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15820705. doi:10.1016/j.biopsych.2004.12.024

Parker, K. J., Buckmaster, C. L., Schatzberg, A. F., & Lyons, D. M. (2004). Prospective investigation of stress inoculation in young monkeys. *Arch Gen Psychiatry, 61*(9), 933-941. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15351772. doi:10.1001/archpsyc.61.9.933

Parsey, R. V., Oquendo, M. A., Simpson, N. R., Ogden, R. T., Van Heertum, R., Arango, V., & Mann, J. J. (2002). Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT1A receptor binding potential measured by PET using [C-11]WAY-100635. *Brain Res, 954*(2), 173-182. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12414100.

Pavlidis, P., & Noble, W. S. (2001). Analysis of strain and regional variation in gene expression in mouse brain. *Genome Biol, 2*(10), RESEARCH0042. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11597334. doi:10.1186/gb-2001-2-10-research0042

Pena, C. J., Kronman, H. G., Walker, D. M., Cates, H. M., Bagot, R. C., Purushothaman, I., . . . Nestler, E. J. (2017). Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. *Science, 356*(6343), 1185-1188. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28619944. doi:10.1126/science.aan4491

Pena, C. J., Smith, M., Ramakrishnan, A., Cates, H. M., Bagot, R. C., Kronman, H. G., . . . Nestler, E. J. (2019). Early life stress alters transcriptomic patterning across reward circuitry in male and female mice. *Nat Commun, 10*(1), 5098. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31704941. doi:10.1038/s41467-019-13085-6

Perroud, N., Courtet, P., Vincze, I., Jaussent, I., Jollant, F., Bellivier, F., . . . Malafosse, A. (2008). Interaction between BDNF Val66Met and childhood trauma on adult's violent suicide attempt. *Genes Brain Behav, 7*(3), 314-322. doi:10.1111/j.1601-183X.2007.00354.x

Pietropaolo, S., Singer, P., Feldon, J., & Yee, B. K. (2008). The postweaning social isolation in C57BL/6 mice: preferential vulnerability in the male sex. *Psychopharmacology (Berl), 197*(4), 613-628. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18317735. doi:10.1007/s00213-008-1081-3

Pitychoutis, P. M., Dalla, C., Sideris, A. C., Tsonis, P. A., & Papadopoulou-Daifoti, Z. (2012). 5-HT(1A), 5-HT(2A), and 5-HT(2C) receptor mRNA modulation by antidepressant treatment in the chronic mild stress model of depression: sex differences exposed. *Neuroscience, 210*, 152-167. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22441040. doi:10.1016/j.neuroscience.2012.03.003

Plaisier, S. B., Taschereau, R., Wong, J. A., & Graeber, T. G. (2010). Rank-rank hypergeometric overlap: identification of statistically significant overlap between gene-expression signatures. *Nucleic Acids Res, 38*(17), e169. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20660011. doi:10.1093/nar/gkq636

Planchez, B., Surget, A., & Belzung, C. (2019). Animal models of major depression: drawbacks and challenges. *J Neural Transm (Vienna), 126*(11), 1383-1408. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31584111. doi:10.1007/s00702-019-02084-y

Plotsky, P. M., Thrivikraman, K. V., Nemeroff, C. B., Caldji, C., Sharma, S., & Meaney, M. J. (2005). Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. *Neuropsychopharmacology, 30*(12), 2192-2204. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15920504. doi:10.1038/sj.npp.1300769

Polter, A. M., & Kauer, J. A. (2014). Stress and VTA synapses: implications for addiction and depression. *Eur J Neurosci, 39*(7), 1179-1188. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24712997. doi:10.1111/ejn.12490

Poulter, M. O., Du, L., Weaver, I. C., Palkovits, M., Faludi, G., Merali, Z., . . . Anisman, H. (2008). GABAA receptor promoter hypermethylation in suicide brain: implications for the involvement of epigenetic processes. *Biol Psychiatry, 64*(8), 645-652. doi:S0006-3223(08)00693-8 [pii]
10.1016/j.biopsych.2008.05.028 [doi]

Pryce, C. R., Ruedi-Bettschen, D., Dettling, A. C., Weston, A., Russig, H., Ferger, B., & Feldon, J. (2005). Long-term effects of early-life environmental manipulations in rodents and primates: Potential animal models in depression research. *Neurosci Biobehav Rev, 29*(4-5), 649-674. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15925698. doi:10.1016/j.neubiorev.2005.03.011

Quitkin, F. M., Stewart, J. W., McGrath, P. J., Taylor, B. P., Tisminetzky, M. S., Petkova, E., . . . Klein, D. F. (2002). Are there differences between women's and men's antidepressant responses? *Am J Psychiatry, 159*(11), 1848-1854. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12411218. doi:10.1176/appi.ajp.159.11.1848

Randesi, M., Zhou, Y., Mazid, S., Odell, S. C., Gray, J. D., Correa da Rosa, J., . . . Kreek, M. J. (2018). Sex differences after chronic stress in the expression of opioid-, stress- and neuroplasticity-related genes in the rat hippocampus. *Neurobiol Stress, 8*, 33-41. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29888302. doi:10.1016/j.ynstr.2018.01.001

Ren, X., & Kuan, P. F. (2020). Negative binomial additive model for RNA-Seq data analysis. *BMC Bioinformatics, 21*(1), 171. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32357831. doi:10.1186/s12859-020-3506-x

Reul, J. M., Collins, A., Saliba, R. S., Mifsud, K. R., Carter, S. D., Gutierrez-Mecinas, M., . . . Linthorst, A. C. (2015). Glucocorticoids, epigenetic control and stress resilience. *Neurobiol Stress, 1*, 44-59. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27589660. doi:10.1016/j.ynstr.2014.10.001

Rice, C. J., Sandman, C. A., Lenjavi, M. R., & Baram, T. Z. (2008). A novel mouse model for acute and long-lasting consequences of early life stress. *Endocrinology, 149*(10), 4892-4900. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18566122. doi:10.1210/en.2008-0633

Rigucci, S., Serafini, G., Pompili, M., Kotzalidis, G. D., & Tatarelli, R. (2010). Anatomical and functional correlates in major depressive disorder: the contribution of neuroimaging studies. *World J Biol Psychiatry, 11*(2 Pt 2), 165-180. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19670087. doi:10.1080/15622970903131571

Ritchie, M. E., Phipson, B., Wu, D., Hu, Y., Law, C. W., Shi, W., & Smyth, G. K. (2015). limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res, 43*(7), e47. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25605792. doi:10.1093/nar/gkv007

Robinson, M. D., & Oshlack, A. (2010). A scaling normalization method for differential expression analysis of RNA-seq data. *Genome Biol, 11*(3), R25. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20196867. doi:10.1186/gb-2010-11-3-r25

Roth, T. L., Zoladz, P. R., Sweatt, J. D., & Diamond, D. M. (2011). Epigenetic modification of hippocampal Bdnf DNA in adult rats in an animal model of post-traumatic stress disorder. *J Psychiatr Res*. doi:10.1016/j.jpsychires.2011.01.013

Russo, S. J., Murrough, J. W., Han, M. H., Charney, D. S., & Nestler, E. J. (2012). Neurobiology of resilience. *Nat Neurosci, 15*(11), 1475-1484. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23064380. doi:10.1038/nn.3234

Russo, S. J., & Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nat Rev Neurosci, 14*(9), 609-625. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23942470. doi:10.1038/nrn3381

Rygula, R., Abumaria, N., Flugge, G., Fuchs, E., Ruther, E., & Havemann-Reinecke, U. (2005). Anhedonia and motivational deficits in rats: impact of chronic social stress. *Behav Brain Res, 162*(1), 127-134. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15922073. doi:10.1016/j.bbr.2005.03.009

Sakry, D., Neitz, A., Singh, J., Frischknecht, R., Marongiu, D., Biname, F., . . . Mittmann, T. (2014). Oligodendrocyte precursor cells modulate the neuronal network by activity-dependent ectodomain cleavage of glial NG2. *PLoS Biol, 12*(11), e1001993. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25387269. doi:10.1371/journal.pbio.1001993

Sapolsky, R. M. (2005). The influence of social hierarchy on primate health. *Science, 308*(5722), 648-652. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15860617. doi:10.1126/science.1106477

Sapolsky, R. M. (2015). Stress and the brain: individual variability and the inverted-U. *Nat Neurosci, 18*(10), 1344-1346. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26404708. doi:10.1038/nn.4109

Sapolsky, R. M., & Ray, J. C. (1989). Styles of dominance and their endocrine correlates among wild olive baboons (Papio anubis). *Am J Primatol, 18*(1), 1-13. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31964045. doi:10.1002/ajp.1350180102

Sarchiapone, M., Carli, V., Roy, A., Iacoviello, L., Cuomo, C., Latella, M. C., . . . Janal, M. N. (2008). Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients. *Neuropsychobiology, 57*(3), 139-145. doi:10.1159/000142361

Savitz, J., & Drevets, W. C. (2009). Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. *Neurosci Biobehav Rev, 33*(5), 699-771. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19428491. doi:10.1016/j.neubiorev.2009.01.004

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., . . . Sturm, V. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology, 33*(2), 368-377. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17429407. doi:10.1038/sj.npp.1301408

Schoenfeld, T. J., & Gould, E. (2012). Stress, stress hormones, and adult neurogenesis. *Exp Neurol, 233*(1), 12-21. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21281629. doi:10.1016/j.expneurol.2011.01.008

Schrattenholz, A., Groebe, K., & Soskic, V. (2010). Systems biology approaches and tools for analysis of interactomes and multi-target drugs. *Methods Mol Biol, 662*, 29-58. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20824465. doi:10.1007/978-1-60761-800-3_2

Schurch, N. J., Schofield, P., Gierlinski, M., Cole, C., Sherstnev, A., Singh, V., . . . Barton, G. J. (2016). How many biological replicates are needed in an RNA-seq experiment and which differential expression tool should you use? *RNA, 22*(6), 839-851. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27022035. doi:10.1261/rna.053959.115

Seney, M. L., Chang, L. C., Oh, H., Wang, X., Tseng, G. C., Lewis, D. A., & Sibille, E. (2013). The Role of Genetic Sex in Affect Regulation and Expression of GABA-Related Genes Across Species. *Front Psychiatry, 4*, 104. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24062698. doi:10.3389/fpsyt.2013.00104

Seney, M. L., Huo, Z., Cahill, K., French, L., Puralewski, R., Zhang, J., . . . Sibille, E. (2018). Opposite Molecular Signatures of Depression in Men and Women. *Biol Psychiatry, 84*(1), 18-27. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29548746. doi:10.1016/j.biopsych.2018.01.017

Sequeira, A., Klempan, T., Canetti, L., ffrench-Mullen, J., Benkelfat, C., Rouleau, G. A., & Turecki, G. (2007). Patterns of gene expression in the limbic system of suicides with and without major depression. *Mol Psychiatry, 12*(7), 640-655. doi:4001969 [pii]
10.1038/sj.mp.4001969 [doi]

Sequeira, A., Mamdani, F., Ernst, C., Vawter, M. P., Bunney, W. E., Lebel, V., . . . Turecki, G. (2009). Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One, 4*(8), e6585. doi:10.1371/journal.pone.0006585 [doi]

Sequeira, A., Morgan, L., Walsh, D. M., Cartagena, P. M., Choudary, P., Li, J., . . . Vawter, M. P. (2012). Gene expression changes in the prefrontal cortex, anterior cingulate cortex and nucleus accumbens of mood disorders subjects that committed suicide. *PLoS One, 7*(4), e35367. doi:10.1371/journal.pone.0035367

Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry, 50*(9), 651-658. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11704071.

Shepard, R., Page, C. E., & Coutellier, L. (2016). Sensitivity of the prefrontal GABAergic system to chronic stress in male and female mice: Relevance for sex differences in stress-related disorders. *Neuroscience, 332*, 1-12. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27365172. doi:10.1016/j.neuroscience.2016.06.038

Shively, C. A., & Day, S. M. (2015). Social inequalities in health in nonhuman primates. *Neurobiol Stress, 1*, 156-163. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27589665. doi:10.1016/j.ynstr.2014.11.005

Siegrist, J., & Marmot, M. (2004). Health inequalities and the psychosocial environment-two scientific challenges. *Soc Sci Med, 58*(8), 1463-1473. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14759690. doi:10.1016/S0277-9536(03)00349-6

Singh-Manoux, A., Marmot, M. G., & Adler, N. E. (2005). Does subjective social status predict health and change in health status better than objective status? *Psychosom Med, 67*(6), 855-861. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16314589. doi:10.1097/01.psy.0000188434.52941.a0

Smyth, G. K. (2005). Limma: linear models for microarray data. In V. C. R. Gentleman, S. Dudoit, R. Irizarry, W. Huber (Ed.), *Bioinformatics and Computational Biology Solutions using R and Bioconductor* (Vol. 1, pp. 397-420). New York: Springer,.

Spitzer, R. L., Williams, J. B., Gibbon, M., & First, M. B. (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry, 49*(8), 624-629.

Springer, M. S., & Murphy, W. J. (2007). Mammalian evolution and biomedicine: new views from phylogeny. *Biol Rev Camb Philos Soc, 82*(3), 375-392. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17624960. doi:10.1111/j.1469-185X.2007.00016.x

Stein, J. L., de la Torre-Ubieta, L., Tian, Y., Parikshak, N. N., Hernandez, I. A., Marchetto, M. C., . . . Geschwind, D. H. (2014). A quantitative framework to evaluate modeling of cortical development by neural stem cells. *Neuron, 83*(1), 69-86. doi:10.1016/j.neuron.2014.05.035

Stepleman L.M., W. D. E., Bottonari K.A. . (2009). Socioeconomic Status: Risks and Resilience. . In S. M. e. In: Loue S. (Ed.), *Determinants of Minority Mental Health and Wellness.* . New York, NY. : Springer.

Stewart, J. W., McGrath, P. J., & Quitkin, F. M. (2002). Do age of onset and course of illness predict different treatment outcome among DSM IV depressive disorders with atypical features? *Neuropsychopharmacology, 26*(2), 237-245. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11790519. doi:10.1016/S0893-133X(01)00313-X

Strack, S., Robison, A. J., Bass, M. A., & Colbran, R. J. (2000). Association of calcium/calmodulin-dependent kinase II with developmentally regulated splice variants of the postsynaptic density protein densin-180. *J Biol Chem, 275*(33), 25061-25064. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10827168. doi:10.1074/jbc.C000319200

Strand, A. D., Aragaki, A. K., Baquet, Z. C., Hodges, A., Cunningham, P., Holmans, P., . . . Olson, J. M. (2007). Conservation of regional gene expression in mouse and human brain. *PLoS Genet, 3*(4), e59. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17447843. doi:10.1371/journal.pgen.0030059

Sun, X. (2019). *Compare RNA-Seq Diff A-Seq Differential Expr ential Expression Analysis Methods ession Analysis Methods* (Masters), Iowa State University, Ames, Iowa.

Takahashi, A., Chung, J. R., Zhang, S., Zhang, H., Grossman, Y., Aleyasin, H., . . . Russo, S. J. (2017). Establishment of a repeated social defeat stress model in female mice. *Sci Rep, 7*(1), 12838. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28993631. doi:10.1038/s41598-017-12811-8

Takeda, A., Sakurada, N., Kanno, S., Minami, A., & Oku, N. (2006). Response of extracellular zinc in the ventral hippocampus against novelty stress. *J Neurochem, 99*(2), 670-676. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16879707. doi:10.1111/j.1471-4159.2006.04092.x

Tanti, A., Kim, J. J., Wakid, M., Davoli, M. A., Turecki, G., & Mechawar, N. (2018). Child abuse associates with an imbalance of oligodendrocyte-lineage cells in ventromedial prefrontal white matter. *Mol Psychiatry, 23*(10), 2018-2028. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29158585. doi:10.1038/mp.2017.231

Teissier, A., Chemiakine, A., Inbar, B., Bagchi, S., Ray, R. S., Palmiter, R. D., . . . Ansorge, M. S. (2015). Activity of Raphe Serotonergic Neurons Controls Emotional Behaviors. *Cell Rep, 13*(9), 1965-1976. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26655908. doi:10.1016/j.celrep.2015.10.061

Terranova, J. I., Song, Z., Larkin, T. E., 2nd, Hardcastle, N., Norvelle, A., Riaz, A., & Albers, H. E. (2016). Serotonin and arginine-vasopressin mediate sex differences in the regulation of dominance and aggression by the social brain. *Proc Natl Acad Sci U S A, 113*(46), 13233-13238. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27807133. doi:10.1073/pnas.1610446113

Thalhammer, A., Trinidad, J. C., Burlingame, A. L., & Schoepfer, R. (2009). Densin-180: revised membrane topology, domain structure and phosphorylation status. *J Neurochem, 109*(2), 297-302. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19187442. doi:10.1111/j.1471-4159.2009.05951.x

Thase, M. E., & Schwartz, T. L. (2015). Choosing medications for treatment-resistant depression based on mechanism of action. *J Clin Psychiatry, 76*(6), 720-727; quiz 727. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26132673. doi:10.4088/JCP.14052ah2c

Tochigi, M., Iwamoto, K., Bundo, M., Sasaki, T., Kato, N., & Kato, T. (2008). Gene expression profiling of major depression and suicide in the prefrontal cortex of postmortem brains. *Neurosci Res, 60*(2), 184-191. doi:10.1016/j.neures.2007.10.010

Todkar, A., Granholm, L., Aljumah, M., Nilsson, K. W., Comasco, E., & Nylander, I. (2015). HPA Axis Gene Expression and DNA Methylation Profiles in Rats Exposed to Early Life Stress, Adult Voluntary Ethanol Drinking and Single Housing. *Front Mol Neurosci, 8*, 90. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26858597. doi:10.3389/fnmol.2015.00090

Torres-Platas, S. G., Hercher, C., Davoli, M. A., Maussion, G., Labonte, B., Turecki, G., & Mechawar, N. (2011). Astrocytic hypertrophy in anterior cingulate white matter of depressed suicides.

Neuropsychopharmacology, 36(13), 2650-2658. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21814185. doi:10.1038/npp.2011.154

Torrey, E. F., Barci, B. M., Webster, M. J., Bartko, J. J., Meador-Woodruff, J. H., & Knable, M. B. (2005). Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. *Biol Psychiatry, 57*(3), 252-260. doi:S0006-3223(04)01099-6 [pii]
10.1016/j.biopsych.2004.10.019 [doi]

Tsankova, N. M., Berton, O., Renthal, W., Kumar, A., Neve, R. L., & Nestler, E. J. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci, 9*(4), 519-525. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16501568. doi:10.1038/nn1659

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res, 53*(4), 865-871. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12377295.

Turecki, G., Briere, R., Dewar, K., Antonetti, T., Lesage, A. D., Seguin, M., . . . Rouleau, G. A. (1999). Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. *Am J Psychiatry, 156*(9), 1456-1458.

Turecki, G., & Meaney, M. J. (2016). Effects of the Social Environment and Stress on Glucocorticoid Receptor Gene Methylation: A Systematic Review. *Biol Psychiatry, 79*(2), 87-96. doi:10.1016/j.biopsych.2014.11.022

Unick, G. J., Snowden, L., & Hastings, J. (2009). Heterogeneity in comorbidity between major depressive disorder and generalized anxiety disorder and its clinical consequences. *J Nerv Ment Dis, 197*(4), 215-224. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19363376. doi:10.1097/NMD.0b013e31819d954f

Veldic, M., Caruncho, H. J., Liu, W. S., Davis, J., Satta, R., Grayson, D. R., . . . Costa, E. (2004). DNA-methyltransferase 1 mRNA is selectively overexpressed in telencephalic GABAergic interneurons of schizophrenia brains. *Proc Natl Acad Sci U S A, 101*(1), 348-353. doi:10.1073/pnas.2637013100 [doi]
2637013100 [pii]

Vella, D., Zoppis, I., Mauri, G., Mauri, P., & Di Silvestre, D. (2017). From protein-protein interactions to protein co-expression networks: a new perspective to evaluate large-scale proteomic data. *EURASIP J Bioinform Syst Biol, 2017*(1), 6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28477207. doi:10.1186/s13637-017-0059-z

Verkhratsky, A., Krishtal, O. A., & Burnstock, G. (2009). Purinoceptors on neuroglia. *Mol Neurobiol, 39*(3), 190-208. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19283516. doi:10.1007/s12035-009-8063-2

Vialou, V., Robison, A. J., Laplant, Q. C., Covington, H. E., 3rd, Dietz, D. M., Ohnishi, Y. N., . . . Nestler, E. J. (2010). DeltaFosB in brain reward circuits mediates resilience to stress and antidepressant responses. *Nat Neurosci, 13*(6), 745-752. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20473292. doi:10.1038/nn.2551

Virgin, C. E., Jr., & Sapolsky, R. M. (1997). Styles of male social behavior and their endocrine correlates among low-ranking baboons. *Am J Primatol, 42*(1), 25-39. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9108969. doi:10.1002/(SICI)1098-2345(1997)42:1<25::AID-AJP2>3.0.CO;2-0

Volk, D. W., Austin, M. C., Pierri, J. N., Sampson, A. R., & Lewis, D. A. (2000). Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. *Arch Gen Psychiatry, 57*(3), 237-245.

Walker, C. D., Bath, K. G., Joels, M., Korosi, A., Larauche, M., Lucassen, P. J., . . . Baram, T. Z. (2017). Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: critical considerations of methodology, outcomes and translational potential. *Stress, 20*(5), 421-448. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28617197. doi:10.1080/10253890.2017.1343296

Walker, C. D., Scribner, K. A., Cascio, C. S., & Dallman, M. F. (1991). The pituitary-adrenocortical system of neonatal rats is responsive to stress throughout development in a time-dependent and stressor-specific fashion. *Endocrinology, 128*(3), 1385-1395. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1847856. doi:10.1210/endo-128-3-1385

Wallace, D. L., Han, M. H., Graham, D. L., Green, T. A., Vialou, V., Iniguez, S. D., . . . Nestler, E. J. (2009). CREB regulation of nucleus accumbens excitability mediates social isolation-induced behavioral deficits. *Nat Neurosci, 12*(2), 200-209. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19151710. doi:10.1038/nn.2257

Wang, L., Leonards, C. O., Sterzer, P., & Ebinger, M. (2014). White matter lesions and depression: a systematic review and meta-analysis. *J Psychiatr Res, 56*, 56-64. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24948437. doi:10.1016/j.jpsychires.2014.05.005

Wang, S., Stanika, R. I., Wang, X., Hagen, J., Kennedy, M. B., Obermair, G. J., . . . Lee, A. (2017). Densin-180 Controls the Trafficking and Signaling of L-Type Voltage-Gated Cav1.2 Ca(2+) Channels at Excitatory Synapses. *J Neurosci, 37*(18), 4679-4691. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28363979. doi:10.1523/JNEUROSCI.2583-16.2017

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*(8), 786-799, 741. doi:10.1038/mp.2008.38

Wang, T., Li, B., Nelson, C. E., & Nabavi, S. (2019). Comparative analysis of differential gene expression analysis tools for single-cell RNA sequencing data. *BMC Bioinformatics, 20*(1), 40. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30658573. doi:10.1186/s12859-019-2599-6

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., . . . Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nat Neurosci, 7*(8), 847-854. doi:10.1038/nn1276 [doi]

nn1276 [pii]

Weiss, I. C., Domeney, A. M., Heidbreder, C. A., Moreau, J. L., & Feldon, J. (2001). Early social isolation, but not maternal separation, affects behavioral sensitization to amphetamine in male and female adult rats. *Pharmacol Biochem Behav, 70*(2-3), 397-409. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11701213.

Weiss, I. C., Pryce, C. R., Jongen-Relo, A. L., Nanz-Bahr, N. I., & Feldon, J. (2004). Effect of social isolation on stress-related behavioural and neuroendocrine state in the rat. *Behav Brain Res, 152*(2), 279-295. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15196796. doi:10.1016/j.bbr.2003.10.015

Weiss, J. M., Stout, J. C., Aaron, M. F., Quan, N., Owens, M. J., Butler, P. D., & Nemeroff, C. B. (1994). Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. *Brain Res Bull, 35*(5-6), 561-572. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7859114.

Wennstrom, M., Hellsten, J., Ekstrand, J., Lindgren, H., & Tingstrom, A. (2006). Corticosterone-induced inhibition of gliogenesis in rat hippocampus is counteracted by electroconvulsive seizures. *Biol Psychiatry, 59*(2), 178-186. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16431219. doi:10.1016/j.biopsych.2005.08.032

Wesolowski, S., Birtwistle, M. R., & Rempala, G. A. (2013). A Comparison of Methods for RNA-Seq Differential Expression Analysis and a New Empirical Bayes Approach. *Biosensors (Basel), 3*(3), 238-258. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25506422. doi:10.3390/bios3030238

WHO, W. H. O. (2017). The global burden of disease: 2017 update.

Willner, P. (1984). The validity of animal models of depression. *Psychopharmacology (Berl), 83*(1), 1-16. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/6429692. doi:10.1007/BF00427414

Willner, P. (1997). Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. *Psychopharmacology (Berl), 134*(4), 319-329. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9452163. doi:10.1007/s002130050456

Willner, P. (2017). The chronic mild stress (CMS) model of depression: History, evaluation and usage. *Neurobiol Stress, 6*, 78-93. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28229111. doi:10.1016/j.ynstr.2016.08.002

Willner, P., Muscat, R., & Papp, M. (1992). Chronic mild stress-induced anhedonia: a realistic animal model of depression. *Neurosci Biobehav Rev, 16*(4), 525-534. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1480349.

Wong, A. W., Giuffrida, L., Wood, R., Peckham, H., Gonsalvez, D., Murray, S. S., . . . Xiao, J. (2014). TDP6, a brain-derived neurotrophic factor-based trkB peptide mimetic, promotes oligodendrocyte myelination. *Mol Cell Neurosci, 63*, 132-140. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25461619. doi:10.1016/j.mcn.2014.10.002

Wong, K. H., Jin, Y., & Moqtaderi, Z. (2013). Multiplex Illumina sequencing using DNA barcoding. *Curr Protoc Mol Biol, Chapter 7*, Unit 7 11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23288465. doi:10.1002/0471142727.mb0711s101

Yan, L., & Silver, R. (2016). Neuroendocrine underpinnings of sex differences in circadian timing systems. *J Steroid Biochem Mol Biol, 160*, 118-126. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26472554. doi:10.1016/j.jsbmb.2015.10.007

Yang, Y., Wang, H., Hu, J., & Hu, H. (2018). Lateral habenula in the pathophysiology of depression. *Curr Opin Neurobiol, 48*, 90-96. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29175713. doi:10.1016/j.conb.2017.10.024

Yu, H., Wang, D. D., Wang, Y., Liu, T., Lee, F. S., & Chen, Z. Y. (2012). Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants. *J Neurosci, 32*(12), 4092-4101. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22442074. doi:10.1523/JNEUROSCI.5048-11.2012

Zhang, B., Gaiteri, C., Bodea, L. G., Wang, Z., McElwee, J., Podtelezhnikov, A. A., . . . Emilsson, V. (2013). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell, 153*(3), 707-720. doi:10.1016/j.cell.2013.03.030

Zhang, B., & Horvath, S. (2005a). A general framework for weighted gene co-expression network analysis. *Stat Appl Genet Mol Biol, 4*, Article17. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16646834. doi:10.2202/1544-6115.1128

Zhang, B., & Horvath, S. (2005b). General framework for weighted gene coexpression analysis. In *Statistical Applications in Genetics and Molecular Biology 4*.

Zhang, H., Yan, G., Xu, H., Fang, Z., Zhang, J., Zhang, J., . . . Huang, Q. (2016). The recovery trajectory of adolescent social defeat stress-induced behavioral, (1)H-MRS metabolites and myelin changes in Balb/c mice. *Sci Rep, 6*, 27906. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27283029. doi:10.1038/srep27906

Zhang, J. C., Wu, J., Fujita, Y., Yao, W., Ren, Q., Yang, C., . . . Hashimoto, K. (2014). Antidepressant effects of TrkB ligands on depression-like behavior and dendritic changes in mice after inflammation. *Int J Neuropsychopharmacol, 18*(4). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25628381. doi:10.1093/ijnp/pyu077

Zhang, Y., Chen, K., Sloan, S. A., Bennett, M. L., Scholze, A. R., O'Keeffe, S., . . . Wu, J. Q. (2014). An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J Neurosci, 34*(36), 11929-11947. doi:10.1523/jneurosci.1860-14.2014

Zhou, B., Zhu, Z., Ransom, B. R., & Tong, X. (2021). Oligodendrocyte lineage cells and depression. *Mol Psychiatry, 26*(1), 103-117. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/33144710. doi:10.1038/s41380-020-00930-0

Zhou, L., Shao, C. Y., Xie, Y. J., Wang, N., Xu, S. M., Luo, B. Y., . . . Shen, Y. (2020). Gab1 mediates PDGF signaling and is essential to oligodendrocyte differentiation and CNS myelination. *Elife, 9*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31944179. doi:10.7554/eLife.52056