

Biological Alterations in Depression

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1. Introduction

According to the World Health Organization, depression is among the leading cause of disability worldwide with approximately 121 million people affected (<http://www.who.int>). It is estimated that 5% of men and 9% of women will experience depression in a given year (Kessler et al., 2005). Major Depressive Disorder (MDD) is characterized by persistent depressed mood or loss of interest or pleasure from daily activities. Additionally, patients may experience feelings of guilt or worthlessness, as well as psychomotor, physiological, and cognitive disturbances (DSM IV). Given that the etiology of depression is unclear, current antidepressant treatments are ineffective for most patients. Presently, less than 30% of patients achieve response or remission (Trivedi et al., 2006). Depression is a clinically and genetically heterogeneous disorder, which complicates efforts to identify causative factors of disease and replicate findings. In addition, diagnosis and therapeutic assessment are primarily based on subjective measures, making patient selection and outcome measures amenable to inconsistencies and irreproducibility.

Biomarkers that objectively establish diagnosis, prognosis, and antidepressant response can facilitate research and clinical management of patients with depression. Many analytes, including brain-derived neurotrophic factor (BDNF), serotonin transporter, and monoamines, have been linked with depressive symptoms and response to antidepressant therapy (Manji et al., 2001; Nestler et al., 2002; Thase, 2007). Although much progress has been made in identifying neurobiological correlates of depression, it is unclear whether these alterations are causally linked or are due to disease and/or treatment. With the goal of facilitating the search for depression biomarkers, this chapter will discuss several key molecular and neurochemical alterations that have been linked with depressive disorder.

2. Genetic studies

The role of genetics in the development of MDD is supported by findings from family, twin, and adoption studies. Studies that compared the prevalence of depression in monozygotic versus dizygotic twins indicate a heritability estimate of 35-50% (Bierut et al., 1999; Kendler et al., 1993; Sullivan et al., 2000). There is a two-to-threefold increased risk of developing MDD among first degree relatives of depressed individuals (Kelsoe, 2004; Sullivan et al., 2000), indicating that genetic variants can be used as prognostic and diagnostic markers. There are two widely used approaches to determine genetic markers of depression. Candidate gene analysis examines the frequency of genetic alleles between cases and

controls. Hypotheses are generated *a priori* based on the likelihood that the gene affects the risk of depression. Alternatively, advances in genotyping capabilities and more recently, gene sequencing, have enabled scientists to look for unbiased genome-wide associations between common single nucleotide polymorphisms (SNPs) and behavior. Genes that confer risk to depression have been primarily identified using candidate gene analysis approaches, while recent efforts to uncover genetic markers of antidepressant response include the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial and Genome-Based Therapeutic Drugs for Depression (GENDEP) study, which looked at genome-wide associations of common variants with antidepressant response. Genetic studies of depression (Levinson, 2006; Lohoff, 2010; Shyn & Hamilton, 2010) and antidepressant response (Crisafulli et al., 2011; Kato & Serretti, 2010; Porcelli et al., 2010) are reviewed in this chapter with a focus on several genes.

2.1 Genetic predictors of depression and antidepressant response

Antidepressant medications primarily work on altering neurotransmitters in the brain, thus much attention has been given to genes within the monoaminergic pathway (Kato & Serretti, 2010). An insertion/deletion polymorphism on the 5' promoter region of the serotonin transporter gene (*5-HTTLPR*) produces a long (*L*) allele or a short (*S*) lower-expressing allele. The *5-HTTLPR* variant alters expression of the serotonin transporter *in vitro* (Lesch et al., 1996) and has been linked with MDD (Caspi et al., 2010; Goldman et al., 2010; Uher & McGuffin, 2010), neuroticism (Lesch et al., 1996), affective disorder (Collier et al., 1996; Lasky-Su et al., 2005), suicidality (Anguelova et al., 2003; P. Y. Lin & Tsai, 2004), and anxiety related personality traits (Schinka et al., 2004; Sen et al., 2004). Patients with the low expressing allele exhibited increased amygdala activation in response to sad faces (Hariri et al., 2002), reduced gray matter volume in amygdala and perigenual cingulate cortex (Pezawas et al., 2005), as well as altered functional coupling in both regions (Pezawas et al., 2005), thus supporting the role of the serotonin transporter in the development of the amygdala-cingulate feedback circuitry. Carriers of the *S* allele who experienced stressful life events in the past were more vulnerable to depression and suicidality (Caspi et al., 2003; Kendler et al., 2005). However, several groups did not find an association between depression and *5-HTTLPR* alone (Middeldorp et al., 2010; Munafò & Flint, 2009; Risch et al., 2009) or in interaction with stressful life events (Risch et al., 2009). Homozygous carriers of the *L* allele showed higher response and remission rates (Serretti et al., 2005) and more favorable side effect profiles (Kato & Serretti, 2010; Kraft et al., 2007; Murphy et al., 2004), which did not replicate to a recent large clinical trial that did not find a link between *5-HTTLPR* and treatment response (Kraft et al., 2007). Altogether, these findings indicate that environment must be taken into account when evaluating the potential use of *5-HTTLPR* as a genetic marker of depression.

Other genes in the monoamine pathway have been studied for their link with depressive behavior. The serotonin-1A receptor (*HTR1A*) is located in the serotonergic neurons and on their post-synaptic targets. In the pre-synaptic neuron, 5HT1A auto-inhibits raphe firing and 5-HT synthesis. The -1019C/G variant (rs6295) found in the promoter region of *HTR1A* results in higher expression of serotonin-1A auto-receptor (5-HT1A), which leads to reduction in serotonergic neurotransmission (Stahl, 1994). The -1019C/G mutation is correlated with anxiety and depression (Gross et al., 2002; Lemonde et al., 2004; Strobel et al., 2003). In Asians, the G allele is associated with improved treatment outcomes (Hong et

al., 2006; Kato et al., 2009). However, this finding was not observed in Caucasians (Lemondé et al., 2004; Serretti et al., 2004), suggesting a confounding effect of race. The relationship between *HTR2A* and antidepressant response is unclear due to conflicting results (reviewed in Kato 2010). A recent meta-analysis did not find any association between *HTR1A* and *HTR2A* and treatment response; however, a polymorphism within *HTR2A* was correlated with tolerability (Kato & Serretti, 2010). No association has been established between *HTR2A* and MDD (Anguelova et al., 2003).

The tryptophan hydroxylases 1 and 2 (TPH1 and TPH2) catalyze the rate-limiting step in 5-HT biosynthesis. A functional variant in *TPH2* (Arg441His) results in 80% reduction of 5-HT in the brain (X. Zhang et al., 2004) and was found to be more frequent in patients with MDD (X. Zhang et al., 2005). However, other studies failed to replicate this finding (Delorme et al., 2006). Furthermore, the *TPH* 218A allele is associated with poor antidepressant response (Serretti et al., 2001a; Serretti et al., 2001b), a finding that was supported by a meta-analysis study (Kato & Serretti, 2010). Patients with the 218 C/C genotype were more likely to respond to antidepressant therapy (Kato & Serretti, 2010). Interestingly, the significant pooled odds ratio score (OR) was primarily influenced by the sum of the three studies that looked at the association between remission rates and the 218 genotype, suggesting that the *TPH* gene may be important in regulating long-term antidepressant response. Of interest is the recent correlation between *TPH2* haplotype markers and suicidality (De Luca et al., 2004; Lopez et al., 2007), suggesting that *TPH2* may mediate a subset of depressive symptoms like suicidal thoughts and feelings of guilt and worthlessness.

Enzymes that mediate clearance of catecholamines including, monoamine oxidase A (MAO-A) and catechol-O-methyl transferase (COMT) have been linked to antidepressant response. Higher transcription efficiency is observed with the variable number tandem repeat (VNTR) sequence located 1.2kb upstream of the *MAO-A* gene (Sabol et al., 1998). Alternatively, the Val to Met substitution at codon 158 for membrane-bound COMT protein (codon 108 for soluble COMT) has been linked to lower enzymatic activity (Mannisto & Kaakkola, 1999) and improved response to citalopram (Arias et al., 2006) and mirtazapine (Szegedi et al., 2005) but not paroxetine (Arias et al., 2006; Szegedi et al., 2005).

A locus on Chr. 12 has been linked with MDD (Abkevich et al., 2003; McGuffin et al., 2005) and anxiety (Erhardt et al., 2007). Within this putative region lies the purinergic ATP-binding calcium channel gene (*P2X7*). A non-synonymous coding SNP within *P2X7* (Gln460Arg) is associated with MDD risk (Lucae et al., 2006). *P2X7* protein is required for IL-1 (interleukin-1) processing and secretion (Ferrari et al., 2006), highlighting the potential role of immune function in depressive behavior. Moreover, the FK506 binding protein 5 (*FKBP5*) in complex with Hsp90 regulates glucocorticoid receptor sensitivity. A functional variant within *FKBP5* that results in increased intracellular concentration of FKBP5 has been linked with recurrence of depressive episodes (Binder et al., 2004) and antidepressant response (Binder et al., 2004; Lekman et al., 2008b). FKBP5 activates glucocorticoid receptors and the hypothalamic-pituitary-adrenal axis, which regulate response to stress (Binder et al., 2004). Additionally, the corticotropin releasing hormone 1 (*CRH1*) variant is correlated with early onset of depressive symptoms (Papiol et al., 2007). CRH activates the HPA axis, thus supporting the role of the HPA axis in mediating depressive behavior.

Small low-powered studies were combined in a meta-analysis to clarify the associations of several genes with depression, which were unclear due to inconsistent or non-replicated findings. Lopez-Leon et al. found a protective effect for the *APOE* ϵ 2 allele (combined OR, 0.51; CI, 0.27-0.97) with no evidence of between-study heterogeneity (Lopez-Leon et al.,

2008). Alternatively, an increased risk were found for the methylenetetrahydrofolate reductase *MTHFR* C677T polymorphism (pooled OR, 1.36), the guanine nucleotide binding protein 3 *GNB3* C825T variant (pooled OR, 1.38; CI, 1.13-1.69), and the dopamine transporter *SLC6A3* 40 bp VNTR (pooled OR, 2.06; CI, 1.25-3.40) (Lopez-Leon et al., 2008).

Pharmacogenetic studies of antidepressants in the STAR*D trial have identified genes associated with treatment response (Hu et al., 2007; Lekman et al., 2008a; McMahon et al., 2006; Paddock, 2008), treatment resistance (Perlis et al., 2008), and treatment-emergent suicidal ideation (Laje et al., 2009; Laje et al., 2007; Perlis et al., 2007). In addition, polymorphisms in genes that encode drug-metabolizing enzymes and transporters have been tested for correlation with treatment response (Peters et al., 2008). Genes that were significantly associated with response to citalopram include *FKBP5* (Lekman et al., 2008a), glutamate receptor, ionotropic kainite 1 (*GRIK1*), N-methyl d-aspartate 2A (*GRIN2A*), 5-hydroxytryptamine receptor 2A (*HTR2A*), potassium channel, subfamily K, member 2 (*KCNK2*), phosphodiesterase (PDE), and solute carrier family 6 member 4 (*SLC6A4*) (E. Lin & Chen, 2008).

A link between genes and depression exists, however, putative genes identified to date do not significantly account for the phenotypic variance observed (Mann & Currier, 2006). Although these initial results may seem disappointing, they indicate that the genetics of depression is far from simple. It is likely that multiple genes with minor effect sizes interact with environmental factors to affect mood, making identification of genetic biomarkers challenging. Efforts to investigate gene by environmental effects can further delineate the contribution of each gene on disease and treatment outcomes (Lesch, 2004; Wermter et al., 2010).

3. Biochemical alterations

Several mechanisms are altered in depression and these include neurotransmission, neuroendocrine signaling, and neuroimmune functions. It is unclear whether these biochemical alterations are products or causative factors of depression. This section will discuss common biological alterations that have been observed in depression, facilitating identification of candidate biochemical markers for depression and antidepressant response.

3.1 Monoamines

The monoamine theory of depression developed following the observation that iproniazid, a drug that inhibits the metabolism of monoamines by blocking MAO, improved the mood of patients who are taking the drug (Delay et al., 1952). In addition, depletion of monoamines by agents like reserpine was found to induce depression (Goodwin & Bunney, 1971). This theory led to the development of antidepressant drugs that elevate monoamine levels at the synapse by blocking uptake transporters, catabolic enzymes or inhibitory pre-synaptic auto- or hetero-receptors. The monoamines provided a biochemical basis for depression, whereby depression is thought to result from a 'chemical imbalance' of monoamines in the brain (Schildkraut, 1965). However, several observations have cast doubt on the major role of monoamines in MDD. In addition to the untimely manner in which elevation of monoamines occur with respect to symptom resolution (Baldessarini, 1989), treatments that do not elevate monoamine levels like electroconvulsive therapy (ECT) have been effectively shown to treat depression (Pagnin et al., 2004). The monoamine theory of depression was then modified to indicate that elevation of monoamines is the first step in a cascade of molecular events that

ultimately leads to symptom improvement (Pineyro & Blier, 1999). Research focus began to shift towards evaluating the long-term adaptive changes that result from increased monoamines in the synapse. It was hypothesized that elevation in monoamines leads to reduction in the sensitivity and/or number of monoamine receptors. Although desensitization and internalization of monoamine receptors have been observed in several animal and post-mortem studies, results were often inconsistent and conflicting (Elhwuegi, 2004). Effective antidepressant agents that do not act by inhibiting monoamine reuptake proteins or metabolizing enzymes can still facilitate receptor internalization despite the absence of pre-synaptic input (Fishman & Finberg, 1987; Kientsch et al., 2001). More recently, it has been shown that monoamine elevation may lead to cellular genesis. Various antidepressant agents including, specific serotonin reuptake inhibitor (fluoxetine), monoamine oxidase inhibitor (tranylcypromine), specific norepinephrine reuptake inhibitor (reboxetine), and serotonin/norepinephrine uptake inhibitor (tricyclic antidepressants) have been shown to induce cell proliferation and neurogenesis (Santarelli et al., 2003), which suggests that monoamine elevation leads to other downstream molecular effects that can alter behavior. Despite decades of research aimed to evaluate the relationship between depression and monoamine alteration, direct evidence supporting the causative role of monoamines in MDD is lacking (Nestler, 1998), thus prompting efforts to study other pathways that may underlie depressive behavior.

3.2 Hypothalamic Pituitary Adrenal (HPA) axis

Dysregulation in the HPA axis, which is characterized by elevated plasma cortisol and CRH is a common finding in depressed patients (Holsboer, 2000; Raison & Miller, 2003). In response to stress, the parvocellular neurons in the hypothalamus secrete CRH, stimulating the release of adrenocorticotropin releasing hormone (ACTH) from the anterior pituitary. ACTH, in turn, activates the synthesis and release of glucocorticoids (cortisol from humans and corticosterone in rodents) from the adrenal cortex. Glucocorticoids negatively regulate the HPA axis by inhibiting the synthesis and release of CRH from the hypothalamus.

Activation of the HPA axis mediates physiologic adaptation to stress, however, persistent stimulation can lead to glucocorticoid receptor (GR) desensitization (de Kloet et al., 2005). Patients with depression typically exhibit high levels of cortisol in plasma, saliva, and urine, as well as an increase in the size and activity of the pituitary and adrenal glands (Nemeroff & Vale, 2005). Impairment of the HPA axis, which is primarily characterized by the inability to suppress cortisol levels following pharmacologic stimulation of GR by dexamethasone, has been observed in depressed patients (Ising et al., 2005; Kunzel et al., 2003; Sher, 2006). HPA alterations normalize with antidepressant therapy (Holsboer, 2000) and this is associated with less relapse (Ising et al., 2007). Glucocorticoids not only exhibit immune and metabolic functions but it also regulates neurogenesis, neuronal survival, hippocampal size and structure, and acquisition of new memories (Herbert et al., 2006). Reduced maternal handling increases CRH signaling (Ladd et al., 1996) and sustains HPA hyperactivity, inducing depressive-like behavior in the pups (Francis et al., 1999; Meaney, 2001). In humans, early stressful life event is associated with dysregulated HPA axis (Heim et al., 2002) and development of depressive symptoms (Chapman et al., 2004; McCauley et al., 1997). One of the mechanisms by which antidepressants induce hippocampal neurogenesis is by activating GR (Anacker et al., 2011), thus implicating a direct relationship between HPA axis and neural brain signaling.

3.3 Other neuroendocrine markers

It was discovered that hypothyroidism elicits depressive behavior and that these symptoms can be reversed by thyroxine therapy (Asher, 1949). Similar symptoms are observed in depression and hypothyroidism, which include dysphoric mood, fatigue, anhedonia, and alteration in weight (Jackson, 1998). Low levels of thyroid hormones (T_3 and T_4) stimulate the release of thyrotropin releasing hormone (TRH) from the hypothalamus to the anterior pituitary. The pituitary, in turn, releases thyrotropin-stimulating hormone (TSH), which leads to the release of triiodothyronine (T_3) and thyroxine (T_4) from the thyroid. Thyroid hormones primarily regulate metabolism but may also be involved in neurotransmission (Dratman & Gordon, 1996). Although not all depressed patients display abnormalities in thyroid function, alterations have been observed including, elevation in T_4 (Baumgartner et al., 1988; Kirkegaard & Faber, 1991), lower TSH levels (Maes et al., 1989), as well as blunted response of TSH to TRH (Hein & Jackson, 1990; Maes et al., 1989). Type-II deiodinase (D-II) catalyzes deiodination of T_4 to T_3 . Psychotropic medications like lithium (Baumgartner et al., 1994b), desipramine (Campos-Barros et al., 1994), carbamazepine (Baumgartner et al., 1994a), and fluoxetine (Baumgartner et al., 1994c) stimulate the activity of D-II, indicating that mood regulatory agents indirectly regulate T_3 levels. Others, however, did not find any effects of antidepressant on thyroid function (Brambilla et al., 1982). Interestingly, one study found that morning and nocturnal changes in TSH may predict antidepressant response (Duval et al., 1996).

There is increasing evidence implicating the involvement of stress-responsive neuropeptide systems in depression and anxiety. The involvement of various neuropeptides has been reviewed (Allredge, 2010; Holmes et al., 2003) and a number of them will be described here. Administration of neuropeptide antagonists/agonists results in altered responses in rodent models of anxiety and depression (Rotzinger et al., 2010). Stress stimulates the release of vasopressin, which in turn enhances the effects of CRH on ACTH (G. Aguilera et al., 2003; Engelmann et al., 2004; J. N. Zhou et al., 2001). Depressed patients display altered levels of vasopressin in the suprachiasmatic nucleus (SCN) (J. N. Zhou et al., 2001), paraventricular nucleus (Purba et al., 1996), and supraoptic nucleus (Meynen et al., 2006). A polymorphism in the vasopressin receptor (V_{1B}) may be protective against MDD (Overstreet & Griebel, 2005; Salome et al., 2006). Antagonism of the V_{1B} receptor reduced depressive-like behavior (Griebel et al., 2002), which was comparable to treatment with antidepressant agents (Salome et al., 2006). This effect was mainly due to inhibition of the V_{1B} receptors in the lateral septum and amygdala (Stremmelin 2005). Similar to vasopressin, neuropeptide Y (NPY) is released under stress. NPY is abundantly expressed in the brain and is co-localized with noradrenaline, somatostatin, and GABA (γ -aminobutyric acid) (Kask et al., 2002). Reduction in NPY is associated with increased sensitivity to depression and stress, indicating that NPY agonists may exhibit antidepressive effects (Redrobe et al., 2002). A variant in the promoter region of *Npy* alters the expression of NPY *in vivo* and is linked with anxiety behavior and neural responses to stress (Z. Zhou et al., 2008). Substance P (SP), a known modulator of pain signaling, has been shown to interact with serotonergic signaling (Schwarz et al., 1999). Substance P binds to neurokinin-1 (NK_1) receptors found in the brain and in the periphery. Genetic ablation or pharmacologic antagonism of NK_1 receptors promotes monoaminergic activity (Froger et al., 2001; Maubach et al., 2002; Santarelli et al., 2001) and reduces anxiety-like behavior (Santarelli et al., 2001). Depressed patients have higher SP levels in the serum (Bondy et al., 2003). Interestingly, NK_1 antagonists activate the

serotonergic system similarly to serotonin reuptake inhibitor (escitalopram) (Guiard et al., 2004), indicating that NK1 antagonists may have antidepressive effects. Galanin is a 29-30 amino acid peptide that regulates various physiological responses like metabolism and food intake. Galanin binds to several galanin receptors (GALR), which in turn interacts with different G proteins, activating various signal transduction pathways (K. E. Smith et al., 1998; Wang et al., 1998). Galanin administration in rodents produces a variety of effects including, nerve regeneration, nociception, and alteration in sexual and feeding behavior (Wrenn & Crawley, 2001; Yoshitake et al., 2003). Galanin mediates 5-HT and norepinephrine levels (Ogren et al., 2006) and antagonism of GALR can enhance or reduce depressive-like behavior depending on which GALR subtype is being inhibited (Barr et al., 2006; X. Lu et al., 2005).

Many years of research implicate the role of the neuroendocrine system in depression. Most neuroendocrine regulatory mechanisms occur through the bidirectional communication between the hypothalamus and pituitary. These findings indicate that the neural circuitry, neuronal signaling, and structural plasticity within this region are likely to be critical in behavioral responses.

4. Metabolic alterations

Metabolic syndrome is comprised of several features including, central obesity and insulin resistance, which, in concert, increases risk for developing cardiovascular disease and diabetes. Compared to healthy controls, depressed individuals are more likely to develop obesity, diabetes, and hypertension (Lindley et al., 2009), indicating potential overlap between depressive symptoms and metabolic syndrome. Independent of the criteria used to define metabolic syndrome (Raikkonen et al., 2007), a strong bidirectional association between depression and metabolic syndrome exists in women (Gil et al., 2006; Kinder et al., 2004; Raikkonen et al., 2007). The correlation between depressive symptoms and metabolic syndrome is slightly higher in monozygotic twins than dizygotic twins, suggesting that genetics play a critical role in both disorders (McCaffery et al., 2003). Resistance to insulin, which is a risk factor for developing metabolic syndrome, is a common occurrence in depressed patients (Koslow et al., 1982; Okamura et al., 2000; Winokur et al., 1988), which suggests that insulin links depression with metabolic syndrome. Insulin exerts dose-dependent effects on food intake and energy regulation. Ablation of insulin receptors on neuronal cells leads to an increased in body fat disposition, suggesting that insulin negatively regulates adiposity (Bruning et al., 2000). Additionally, insulin regulates monoamine uptake and metabolism, phosphoinositol turnover, as well as norepinephrine and dopamine transporter mRNA levels (Craft & Watson, 2004). It has been shown that insulin can recruit GABA receptors (Wan et al., 1997) and promote internalization of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, which suggests that insulin plays a critical role in neuronal signaling and synaptic plasticity (Huang et al., 1998). Interestingly, brain volume abnormalities and neurocognitive deficits commonly found in MDD patients have been observed in individuals with diabetes mellitus (DM), suggesting overlapping pathophysiology between MDD and DM (McIntyre et al., 2010). Insensitivity to insulin likely develops due to HPA axis hyperactivity (Rizza et al., 1982), impaired immune system (Fernandez-Real et al., 2001; Maes, 1995; Moller, 2000), and altered central serotonergic signaling (Goodnick et al., 1995; Horacek et al., 1999), all of which are common findings in depressed patients (Belmaker, 2008; Krishnan & Nestler, 2008).

Association between depression and obesity has been identified in several cross sectional studies (de Wit et al., 2010; Faith et al., 2002; Scott et al., 2008). A recent meta-analysis looked at the association between obesity and depression in a community-based setting and found that obese patients have an 18% increased risk of developing depressive symptoms (overall OR, 1.18) (de Wit et al., 2010). Subsequent sub-group analyses showed that the association with obesity holds true for depressed women but not for men, which suggests that comorbidity is likely to be affected by sex (de Wit et al., 2010). Similarly, a meta-analysis of longitudinal studies showed that baseline obesity increased the risk of depression (pooled OR, 1.57) and that depression increased the odds for developing obesity (pooled OR, 1.40). Prospective analysis of the cause-effect relationship between obesity and depression indicate reciprocal findings, whereby obesity was found to be a predictor of depression in eight out of the ten studies reviewed, while 53% of the studies found that depression predicts obesity (Faith et al., 2011). Interestingly, the positive association between depression and obesity is only detected in studies conducted in the United States but not in other European countries, indicating a strong contributory effect of environment (Atlantis & Baker, 2008). It is increasingly recognized that similar neural circuitry that regulate memory, reward, mood, and emotion also controls appetite, body weight, and energy homeostasis (Dallman, 2009; Zheng et al., 2009). Food induces olfactory and visual sensory inputs, which stimulate the orbitofrontal cortex, where acquisition, storage, and processing of memory and experiences associated with food is thought to occur (Verhagen, 2007). Stimulation of the mu-opioid receptor in the nucleus accumbens and ventral pallidum results in further intake of pleasurable foods (Will et al., 2003; M. Zhang & Kelley, 2000). The ventral tegmental area and the nucleus accumbens are part of the mesolimbic dopaminergic system, which regulates behavioral response (motivation) towards favorable stimuli (Berridge, 1996, 2007; Pecina et al., 2006), indicating that food intake and motivation are, at least partly, co-regulated by similar circuitry. The hypothalamus regulates homeostatic responses to altered nutrient levels and adiposity levels (Berthoud, 2002; Xue & Kahn, 2006) through various endocrine hormones including leptin (Farooqi et al., 2002; Friedman, 1999; O'Rahilly, 2002) and NPY (Luquet et al., 2005). Although leptin is primarily known for its role in appetite suppression and energy expenditure, leptin also mediates reproduction and cognition (Chehab, 2000; Farr et al., 2006). Independent of body mass, depressed patients show lower plasma levels of leptin (Jow et al., 2006; Kraus et al., 2001) although other studies did not find similar results (Antonijevic et al., 1998; Deuschle et al., 1996; Rubin et al., 2002). Rodents exposed to chronic unpredictable stress showed reduction in sucrose preference and higher depressive-like behavior, which was reversed by leptin administration, indicating that leptin exhibits antidepressive effects likely through innervations of the limbic brain circuitry (X. Y. Lu et al., 2006). In response to stressful events, leptin suppresses CRH, ACTH, and corticosterone secretion, suggesting a direct impact of leptin on the HPA axis (Ahima et al., 1996; Heiman et al., 1997; Huang et al., 1998). In addition, leptin-deficient *ob/ob* mice display altered *Slc6a4* expression (Collin et al., 2000), decreased neuronal and glial cells, and reduced brain weight and cortical volume (Ahima 1999, Stepan 1999), further supporting the role of leptin in MDD.

A common thread between MDD, DM, and heart disease exists. The co-occurrence and pathophysiologic overlap between metabolic syndrome, obesity, and depression may explain the significant association between depression, diabetes, and cardiovascular disease (Frasure-Smith et al., 1993; Goldney et al., 2004; Paile-Hyvarinen et al., 2007).

5. Neuroimmune

An interaction between behavior and the immune system was first recognized in 200 AD, when Galen observed that melancholic women were more susceptible to cancer (Leonard, 1988). Depressed patients exhibit reduced neutrophil phagocytosis, natural killer cell activity, and mitogen stimulated lymphocyte proliferation (Irwin et al., 1990). Furthermore, patients with MDD show increased cytokine secretion from activated macrophages and elevated acute phase proteins in the liver (Sluzewska et al., 1996), indicating dysregulation in immune response. Antidepressants inhibit the ability of lipopolysaccharide (LPS) to induce the synthesis and the release of pro-inflammatory cytokines, likely through elevation of cyclic adenosine monophosphate (cAMP) levels (Xia et al., 1996). It has been hypothesized that abnormal secretion of macrophage monokines leads to depressive behavior (R. S. Smith, 1991). Macrophages secrete neuroendocrine and immune modulators, including, interleukins (IL), tumor necrosis factors (TNF), ACTH, and endorphins (Nathan, 1987), thus indicating a regulatory role for macrophages in mediating the neuro-endocrine-immune interface.

A bidirectional relationship between the brain, neuroendocrine, and immune systems exists, particularly in response to stress. Overactivity of the HPA axis, which is a common finding in depressed individuals (Holsboer, 2000; Raison & Miller, 2003), results in hypercortisolemia and suppression of the immune system. Conversely, persistent stress can result in fewer B cells, T cells, and lymphocytes (Olf, 1999), which can confer susceptibility to infections and cancer (Garssen & Goodkin, 1999; Kiecolt-Glaser et al., 1995; Reiche et al., 2005). Stressful events like separation or divorce are correlated with increased cancer risk, low proportions of NK and T cells, impairment of DNA repair, and abnormal immune response (Kiecolt-Glaser et al., 1987). The presence of reactive oxygen species has been detected in depressed patients (Irie et al., 2005). Levels of 8-hydroxydeoxyguanosine (8-OH-dG), a biomarker of cancer-related oxidative DNA damage, is positively correlated with depressive symptoms (Irie et al., 2005), which suggests that depression may be associated with cancer.

In 1987, Wagner-Jauregg demonstrated that activation of the immune system can affect various mental states (Raju, 1998). Cytokines regulate growth, differentiation, and function of many cells (Turnbull & Rivier, 1999). They can be broadly classified as pro-inflammatory or anti-inflammatory cytokines. Pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF- α stimulate immune cell production, activation, and proliferation. On the other hand, anti-inflammatory cytokines including, interleukin-4 (IL-4), interleukin-10 (IL-10), and interleukin-13 (IL-13) dampen the immune response. The role of cytokines in depression was identified following observation that interferon treatment induces 'sickness behavior,' which mimics depressive symptoms such as dysphoric mood, fatigue, anorexia, weight loss, and altered sleep patterns (Papanicolaou et al., 1998; Yirmiya, 2000). Depression is characterized by elevation of pro-inflammatory markers IL-6, c-reactive protein (CRP) (Maes, 1995), IL-1, and IL-2 (Dunn et al., 2005; Song et al., 1994). Treatment with LPS stimulated depressive-like behavior and cytokine secretion, which were reversed by antidepressants or cytokine antagonists (Yirmiya, 2000). Administration of IL-6 and IL-1 results in elevation of vasopressin, cortisol, CRH, and ACTH (Brebner et al., 2000; Harbuz et al., 1992; Xu et al., 1999), which suggests a pivotal role of cytokines in HPA axis activation (Dentino et al., 1999). In rodents, treatment with IL-1 resulted in increased DA, NE, and 5-HT activity in the brain (Dunn & Swiergiel, 1999; Merali et al., 1997; Song et al., 1999).

Cytokines acutely stimulate 5-HT neurotransmission and reduce its production by stimulating indoleamine 2,3-dioxygenase (IDO), an enzyme that converts the precursor of 5-HT (tryptophan) into kynurenine (Wichers & Maes, 2002). Pro-inflammatory cytokines have been shown to up-regulate serotonin transporter (Morikawa et al., 1998; Mossner & Lesch, 1998; Wichers & Maes, 2002), while anti-inflammatory cytokines like IL-4 reduces 5-HT uptake (Mossner et al., 2001). Together, these findings suggest that cytokines affect depressive behavior likely through regulation of monoamines and the HPA axis.

The symptom heterogeneity observed in depressed patients suggests that biological abnormalities are likely to be patient-dependent and disease-specific. Collectively, these results indicate that biochemical mechanisms likely interact to mediate a complex behavior like mood and anhedonia. It is therefore unlikely that a single biological marker will characterize a heterogeneous disorder like depression. Significant benefits can be rendered in evaluating the behavioral effects of a panel of biological markers or biochemical signatures, particularly since reciprocal communication between nervous, endocrine, and immune systems have been noted (Cserr & Knopf, 1992; Felten, 1991; Reichlin, 1993). For most cases, when associations between biochemical alterations and depression are detected, the causal relationship is often poorly understood.

6. Brain and molecular correlates

Direct and indirect evidence from neurostructural, neurofunctional, and molecular studies indicate impairments in neural circuitry, structural plasticity, and cellular resilience. These abnormalities reflect the molecular neurobiological underpinnings of depression as discussed below.

6.1 Neurostructural and neurofunctional studies

The cortical-limbic circuitry is implicated to mediate emotional processing in depressed patients (Davidson et al., 2002; Dougherty & Rauch, 1997; Mayberg, 1997). Results from positron emission tomography (PET) studies indicate that unmedicated patients with MDD exhibit increased activity and cerebral blood flow (CBF) to the amygdala, orbital cortex, and medial thalamus, as well as decreased CBF to the pre-frontal cortex (PFC) and anterior cingulate cortex (ACC) (Drevets, 2000a; Drevets et al., 1999). Meta-analyses of structural neuroimaging studies indicate that MDD is characterized by reduction of gray matter volumes in the ACC (Koolschijn et al., 2009), subgenual cingulate cortex (Hajek et al., 2008), and hippocampus (McKinnon et al., 2009). Post-mortem neuropathological studies have shown that patients with MDD show reduced cortex volume, decreased number of glial cells, and/or reduced neuron sizes (Ongur et al., 1998; Rajkowska, 2000; Rajkowska et al., 1999). Given the functional roles of specific brain regions in emotional processing, neuropathological abnormalities observed in depression suggest that areas that mediate autonomic and neuroendocrine responses (amygdala) is associated with increased activity and cerebral blood flow, while reduction in activity is observed in brain regions that control emotional processing (cortex) (Manji et al., 2001). Antidepressant treatment reduces CBF and metabolism in the amygdala (Drevets, 2000b; Drevets et al., 1999), attenuating hyperresponsiveness to stress (Rosenkranz et al., 2010). Similarly, larger hippocampal volume (Frodl et al., 2008; Kronmuller et al., 2008; MacQueen et al., 2008) and gray matter density in the ACC (Costafreda et al., 2009) were positively correlated with antidepressant response.

Inferences regarding the structural integrity of neural tracts can be made through diffusion tensor imaging (DTI), which measures the diffusion properties of water through brain tissues, *in vivo*. Patients that did not respond to 12 weeks of escitalopram (Alexopoulos et al., 2008) or citalopram (Alexopoulos et al., 2002) treatment showed microstructural abnormalities in white matter pathways connecting the cortex with the limbic and paralimbic areas, which indicates that poor therapeutic outcome is related to impaired cortical-limbic connectivity (Mayberg, 2003). Patients with prior exposure to parental verbal abuse (Choi et al., 2009) or have genetic polymorphisms (5-HTTLPR) (Alexopoulos et al., 2009) exhibit microstructural white matter abnormalities, suggesting that neural brain structure is subject to genetic and environmental control. Of note, impairment in brain morphology, neural circuitry, and brain function have been linked with monoaminergic and non-monoaminergic genetic variants (Scharinger et al., 2010). In addition to evaluating the structural integrity of neural brain circuits, functional activity within the limbic-cortical circuitry has been investigated. Brain activity can be evaluated by measuring blood oxygen level-dependent (BOLD) signals while patients are resting (intrinsic activity) or when performing a task (task-related activity). BOLD signaling is associated with changes in blood flow and tissue oxygen concentration, which are markers of brain activity. Depressed individuals have reduced activity in the limbic and cortical regions (Anand et al., 2005), which normalizes as symptoms resolve (Anand et al., 2005). Patients with MDD show hyperactivity in the amygdala (Surguladze et al., 2005) and reduced co-activation of the dorsal ACC (Matthews et al., 2008) when viewing negative facial expressions. These changes in brain activity are ameliorated with chronic antidepressant treatment (Chen et al., 2008; Fu et al., 2004; Sheline et al., 2001).

Similar to the electrocardiogram (ECG), unfiltered electrical activity generated by the brain can be measured by an electroencephalogram (EEG). EEG signals can be converted to show a topographical representation of the distribution of the EEG waveforms across the cortex known as the quantitative electroencephalograph (QEEG) brain map. The QEEG image is used to assess brain activity and metabolism in real-time, providing a global assessment of brain activity. Brain electrical activity can be measured using cordance, low-resolution brain electromagnetic tomography (LORETA), and antidepressant treatment (ATR) index. Cordance, which uses QEEG measurements conducted from a full scalp electrode array, assesses perfusion of cerebral cortex and brain activity on cortical convexities like PFC (Cook et al., 1998; Leuchter et al., 1999). Several groups have demonstrated the usefulness of cordance in characterizing antidepressant response (Bares et al., 2008; Cook et al., 2002). Responders and non-responders differ in QEEG measurements at rest and during task-oriented activities (Bruder et al., 2008). LORETA, which assesses activity of deeper cortical regions like ACC and orbitofrontal cortex (Pizzagalli et al., 2001), identifies cortical alterations in relation to depression and antidepressant response (Anderer et al., 2002; Saletu et al., 2010). Both cordance and LORETA require whole-head electrode montages for data collection, which entails up to 75 minutes of QEEG recording, limiting its clinical utility. On the other hand, the ATR only uses a five-electrode montage placed on the frontal brain regions, which limits QEEG recording to 10 minutes (Leuchter et al., 2009a; Leuchter et al., 2009b). The largest study that evaluated the use of ATR in predicting antidepressant response is the Biomarkers for Rapid Identification of Treatment Effectiveness trial in Major Depression (BRITE-MD) trial. In this study, positive ATR predicted response and remission to escitalopram. Patients with negative ATR values were either switched to bupropion or continued to be treated with escitalopram. In comparison to patients who stayed on

escitalopram, patients who switched to bupropion were 1.9 times more likely to respond to treatment (Leuchter et al., 2009a; Leuchter et al., 2009b). These results support the use of ATR as a biomarker for monitoring treatment response and clinical progression.

6.2 Cellular and molecular markers

Lower hippocampal volume (Videbech & Ravnkilde, 2004), which is commonly found in post-mortem brain tissues of depressed individuals (MacQueen et al., 2003), results in reduced hippocampal plasticity. Reduction in neurogenesis, brain volume, and thickness is likely due to decreased neurotrophins and/or changes in neuroplasticity (Geuze et al., 2005). Neurotrophins, including brain-derived neurotrophic factor (BDNF), have been repeatedly implicated in the pathogenesis and treatment of MDD (Duman & Monteggia, 2006). Administration of BDNF induces cell proliferation and neurogenesis (Pencea et al., 2001; Zigova et al., 1998), and leads to lower depressive-like behavior (Shirayama et al., 2002; Siuciak et al., 1997). Neurogenesis, resulting from either antidepressant treatment or cell implantation, attenuates depressive behavior (Tfilin et al., 2009). Depressed patients show reduced BDNF levels (Sen et al., 2008), which can result in lower number of dendrites in the synapse (Manji et al., 2003; Nestler et al., 2002). Antidepressants stimulate BDNF synthesis (Duman, 2004) and normalizes reduced BDNF levels in depressed patients (Brunoni et al., 2008; Sen et al., 2008). A functional variant at codon 66, resulting in a valanine to methionine change (Val66Met), is reported to correspond with drug response. Carriers of the Met allele were reported to have better treatment outcomes (Gratacos et al., 2008; Kato & Serretti, 2010), however, others did not find any correlation between the Val66Met variant and treatment response (Kato & Serretti, 2010; Tsai et al., 2003; Wilkie et al., 2007). Furthermore, genetic susceptibility to depression was not associated with the *BDNF* Val166Met variant (Gratacos et al., 2007; Lopez-Leon et al., 2008). The Met allele is associated with impaired intra-cellular packaging and activity dependent secretion of BDNF, which disrupts hippocampal function (Egan et al., 2003). Impaired suppression of the HPA axis following dexamethasone treatment was also observed in the *BDNF* Met carriers (Schule et al., 2006). Of note, mouse lines that did not express *Bdnf* during fetal development or post-natal development were hyperactive, hyperaggressive, and showed higher depressive-like behavior compared to transgenic mice that were conditioned to express *Bdnf* during post-natal development (Chan et al., 2006), suggesting that the behavioral effects of BDNF are region and time-dependent. Interestingly, an interaction between the *BDNF* G196A variant, the serotonin transporter gene, and stressful life events has been observed (M. Aguilera et al., 2009; Pezawas et al., 2008).

BDNF is activated by cyclic-AMP response element-binding protein (CREB). The cAMP-CREB cascade has been extensively studied for its involvement in cell survival and neural plasticity (D'Sa & Duman, 2002; Duman et al., 1997). The cAMP-CREB pathway is upregulated following chronic antidepressant treatment (Duman et al., 1999). Activation of the CREB pathway is thought to result in neurogenesis. Activated or phosphorylated CREB is found in actively dividing neural progenitor cells in the hippocampal subgranular zone (SGZ) (Nakagawa et al., 2002a). Mice lacking *Creb* show markedly reduced cell proliferation (Nakagawa et al., 2002b) and administration of a phosphodiesterase inhibitor, which activates the cAMP cascade, increases neurogenesis and improve depressive behavior (Takahashi et al., 1999). Although CREB plays a critical role in neurogenesis, CREB is not necessary to elicit antidepressant effects. After antidepressant treatment, no difference in

depressive-like responses was observed between *Creb* deficient mice and wild-type controls, indicating that the behavioral effects of antidepressant drugs may occur through other CREB-independent mechanisms.

Given that depressed patients exhibit reduced neuronal and glial cells, molecular mechanisms that stimulate neurogenesis (activation of CREB and BDNF synthesis) are likely to be critical in MDD. Presently, the clinical significance of cellular genesis in depression is largely unknown. It is likely that cellular proliferative and survival processes interact to facilitate remodeling of synaptic connections that can lead to altered mood. It is noteworthy to consider, however, that in the absence of stress, the neural circuitry underlying depression may be different (Krishnan & Nestler, 2008). There is a possibility that reversal of stress-induced neural plasticity changes is not required for antidepressive effects (Nestler et al., 2002).

7. Depression signatures

7.1 Gene expression signatures

Gene expression profiling studies provide an unbiased look at the relationship between gene expression and depressive disorder, which is useful in identifying novel targets for antidepressant therapy (for a detailed review see Sequeira & Turecki, 2006). Bernard and colleagues collected gene expression data from the locus coeruleus of healthy, depressed, and bipolar patients. In this study, they found significant alterations in patients with MDD but not bipolar subjects. Gene expression alterations were detected in the glutamate signaling genes (*SLC1A2*, *SLC1A3* and *GLUL*), growth factor genes (*FGFR3* and *TrkB*), and several astroglial genes (Bernard et al., 2010). Similarly, dysregulation of fibroblast growth factor genes (*FGF1*, *FGF2*, *FGFR2*, and *FGF3*) were detected in cortical regions of depressed patients, irrespective of previous antidepressant treatment (Evans et al., 2004). Consistent with previous findings, expression of genes involved in signal transmission of glutamate and GABA were found to be dysregulated in depressed patients (Choudary et al., 2005) and in suicide victims with and without depression (Sequeira et al., 2009). Alteration in genes regulating oligodendrocyte function (Sequeira & Turecki, 2006) and cell-cell communication (Sequeira et al., 2009) were altered in MDD, suggesting impairment in brain circuitry. Notably, reduced oligodendrocyte expression and neuronal changes in amygdala were detected in both depressed individuals and in rodents exposed to unpredictable chronic mild stress (Sibille et al., 2009), indicating a connection between stress response and neural circuitry.

For biomarkers to be clinically useful, putative analytes must be detected in easily accessible samples like plasma or serum. Using LPS-stimulated blood samples, Spijker et al. compared gene expression profiles between healthy and unmedicated patients with MDD. A significant difference in gene expression pattern was observed in a subset of genes, all of which have not been previously associated with depression (Spijker et al., 2010). Transcriptome changes in the leukocyte mRNA is correlated with response to antidepressant agents or lithium therapy (Iga et al., 2008). The authors found that normalization in gene expression pattern correlates with antidepressant response (Iga et al., 2008). In addition to analyzing global changes in the brain or plasma transcriptome, genetic regulatory elements of depression or antidepressant response can be identified using quantitative trait loci (QTL) mapping analysis. In this approach, DNA variants that regulate gene expression locally or distally (*cis* or *trans*-regulatory elements) are analyzed for

correlation with depressive behavior, thereby facilitating analysis for regulatory genes underlying depressive behavior. This approach has been used to detect regulatory genetic elements for several behaviors (Bryant et al., 2009; Radcliffe et al., 2006).

7.2 Protein signatures

Other efforts to identify depression signatures include protein expression profiling. Plasma samples from control, depressed, and schizophrenic patients were analyzed for 79 plasma protein biomarkers including, cytokines, neurotrophins, and chemokines (Domenici et al., 2010). Interestingly, insulin and matrix metalloproteinase 9 (MMP-9) displayed the biggest difference between control and depressed patients (Domenici et al., 2010). Efforts to expand the panel of protein markers to include peripheral and neuropsychological markers are currently underway (Tadic et al., 2011). The global analysis of protein expression is still in its infancy although several groups have performed proteomic analysis in the cerebrospinal fluid (CSF) (Raedler & Wiedemann, 2006) and in discrete brain regions collected post-mortem (Beasley et al., 2006). In order to characterize the cause-effect relationship between biological alterations, treatment, and behavior, protein profiling studies in human samples should be complemented with proteomic studies in animals, which are more amenable for determination of disease and treatment effects.

8. Other mechanisms

8.1 Epigenetics

Discordance of depression between monozygotic twins suggests other non-genetic factors are involved (Mill & Petronis, 2007). Alteration in gene expression can occur without changes in the DNA sequence through epigenetic mechanisms like histone modification and methylation of DNA CpG islands. Deacetylation of histones results in DNA coiling, which prevents binding of transcription factors to the DNA, suppressing gene transcription. Alternatively, methylation alters DNA chemistry, which blocks gene transcription. Epigenetic mechanisms can explain how genetically weak signals of risk combined with environmental factors predispose patients to depression (Caspi & Moffitt, 2006).

Adverse childhood experiences confer risk to depressive behavior (Heim & Nemeroff, 2001) likely through epigenetic alteration. Offspring who received minimal maternal care had higher DNA methylation at the glucocorticoid receptor (GR) promoter region and were more responsive to stress compared to control animals (Liu et al., 1997; Weaver et al., 2004). Methylation in the GR promoter region leads to reduced binding of the nerve growth factor induced protein-A (NGF-1A), affecting GR regulation (Weaver et al., 2004; Weaver et al., 2007). Notably, low levels of maternal care led to epigenetic repression of the estrogen-alpha receptor that resulted in transmission of maternal behavior to offspring (Champagne et al., 2006; Champagne et al., 2003), thus indicating transgenerational phenotypic transfer through epigenetic alterations.

Mice that are deficient in *Hdac5* display enhanced vulnerability to stress, suggesting that stress reduces histone deacetylase activity leading to down-regulation of gene expression (Renthal et al., 2007). The adverse effect of stress on *Hdac5* activity is reversed by chronic antidepressant treatment (Renthal et al., 2007). Antidepressant treatment increases histone acetylation at the *Bdnf* promoter region, activating *Bdnf* expression (Tsankova et al., 2006). BDNF mediates formation and differentiation of new neurons, facilitating long-term potentiation and memory development.

RNA-mediated modifications through non-coding RNAs (ncRNA) and microRNAs (miRNA) can activate or silence gene transcription. The role of miRNA in regulating serotonergic transmission has been reviewed (Millan, 2011). MicroRNAs are short RNAs (22-24 nucleotides) that bind to complementary sequences on target mRNAs, typically leading to gene silencing (Bartel, 2009; Carthew & Sontheimer, 2009; Winter et al., 2009). A recent study by Baudry et al. shows that miR-16 negatively regulates the expression of serotonin transporter (SERT). Fluoxetine treatment stimulates the release of S100 calcium binding protein B (S100 β) in the raphe, leading to elevation of miR-16 and reduction in SERT (Baudry et al., 2010). MiR-16 also represses the expression of anti-apoptotic protein (B-cell lymphoma 2) Bcl-2 (Cimmino et al., 2005), indicating a critical role of miR-16 in neurotransmission as well as cell proliferation. In addition, genetic studies using seahare (*Aplysia*) identified miR-124 as a translational repressor of CREB, which suggests that microRNAs indirectly regulate secondary messenger pathways by modulating CREB expression (Rajasethupathy et al., 2009). Overexpression of ncRNA was found in Alzheimer's patients (Faghihi et al., 2010), however, an association between ncRNA and depression is yet to be established.

Consistent with the notion that genes are interconnected within a network, it is conceivable that an epigenetic regulatory network exists. Efforts to identify epigenomic signatures are underway (Akbarian & Huang, 2009) and this data should be integrated with other data sets like the brain transcriptome and behavior to identify causative pathways in depression. Of great interest is the assessment of epigenetic transgenerational transmission of a trait and genomic imprinting (epigenetic alteration on gene expression is based on whether the gene is inherited from the father or the mother). These epigenetic phenomena facilitate our understanding of how environment and genetics interact to mediate behavior, ultimately providing a comprehensive picture of the molecular mechanisms underlying depression.

8.2 Sleep and circadian rhythm

It was previously thought that insomnia is a risk factor for depression (Breslau et al., 1996; Ford & Kamerow, 1989; Hohagen et al., 1993) and years of research did not clarify the exact relationship between insomnia and depression (Riemann, 2007; Riemann et al., 2001). In an EEG, normal sleep can be partitioned into several stages. The first is progression from light sleep (N1 stage), followed by an "intermediate" level of sleep (stage N2) that leads to the "deep" sleep, which is characterized by slow delta waves on the EEG (stage N3). Stages N1-N3 are part of non-rapid eye movement sleep, which alternates with rapid eye movement (REM) sleep throughout the night (Benca & Peterson, 2008). Depression is characterized by abnormal sleep (difficulty falling asleep, nocturnal awakenings, early-morning awakenings), decreased slow-wave sleep, shortened rapid eye movement (REM) latency, and increased REM density (Thase et al., 1997; Tsuno et al., 2005). Interestingly, total sleep deprivation improves symptoms in 40-60% of depressed patients (Giedke & Schwarzler, 2002; Wirz-Justice & Van den Hoofdakker, 1999), which is thought to be due to activation of the limbic dopaminergic pathways (Ebert et al., 1994; Ebert et al., 1996). Additionally, the slow-wave sleep is marginally affected by antidepressant therapy (Sharpley & Cowen, 1995; Tsuno et al., 2005), indicating partial involvement of monoamines in sleep regulation.

In addition to disruption in sleep pattern, depressed patients also exhibit alteration in biological rhythms, including appetite and hormone levels. Patients with seasonal affective disorders (SAD) have depressive symptoms during the winter months when daylight is

shorter. The bright light therapy has been effectively used to treat SAD (Lam, 2006) and non-seasonal depression (Terman & Terman, 2005) and is thought to work by shifting the circadian clock (Wirz-Justice et al., 2005). Similar to 5-HT, melatonin is derived from tryptophan and is a critical regulator of circadian rhythm. Depressed patients display altered melatonin release and abnormal melatonin levels (Rubin et al., 1992; Wetterberg, 1999), particularly in the acute phase of depressive illness (Srinivasan et al., 2006). Antidepressant therapy increases melatonin (Srinivasan et al., 2006; Thompson et al., 1985). Of note, a pilot study that looked at the use of melatonin in addition to cortisol as a prognostic marker for depression found promising results (Buckley & Schatzberg, 2010). Genetic regulators of the molecular clock (*Clock*, *Bmal1*, *Npas2*, *GSK3 β* , and *Timeless*) have been linked with various mood disorders (McClung, 2007). Mutant mouse models exhibiting point mutations on the *Clock* gene display anxiety-like and depressive-like behavior (Roybal et al., 2007) and increased dopamine transmission in the ventral tegmental area (VTA) (McClung et al., 2005; Nestler & Carlezon, 2006), suggesting that the *Clock* gene regulates dopamine signaling. Interestingly, there is circadian rhythm with regards to concentration, release, and synthesis of 5-HT, norepinephrine, and dopamine (Barassin et al., 2002; Shieh et al., 1997; Weiner et al., 1992), as well as in the expression and activity of monoamine receptors (Kafka et al., 1983; Wesemann & Weiner, 1990; Witte & Lemmer, 1991), indicating a link between monoamine signaling and circadian rhythm.

9. Future directions: Moving towards a systems biology approach

Based on these findings, it is unlikely that a single biomarker can describe a multifactorial disorder like depression. Data from the last decades indicate that alterations in MDD are interconnected (Figure 1). This figure illustrates that there are neuroanatomical, neurobiochemical, neuroimmune, neuroendocrine, genetic, and metabolic mechanisms underlying MDD. Given the involvement of various biological systems, it is no surprise that depression is characterized by heterogeneous molecular and clinical manifestations, which complicate the search for depressive biomarkers. Therefore, uncovering the etiology and mechanism underlying depression necessitates modification of clinical and pre-clinical study designs and the use of combinatorial approaches to assess multiple phenotypic variances.

To obtain an in-depth clinical and biological assessment of depression, methodological aspects that should be considered when conducting clinical studies include obtaining a detailed family, medical, drug, and experiential history, performing longer patient follow-up (6 months to 1 year), assessing for metabolic, psychosomatic, and behavioral symptoms, and collecting blood samples for biological assessment of disease or changes in symptoms. This information can aid in identifying genetic, environmental, and biological factors that contribute to patient-specific depressive behavior, which can further delineate behavioral and biological alterations that differ or overlap between depressed patients.

Animal studies offer several advantages including lower cost, subject availability, and ease in brain and blood sample accessibility. In addition, the behavioral effects of drugs, genetics, and environment are more feasible to investigate in animal models of depression since the genome and the environment can be easily manipulated. Despite apparent advantages in using animals for depression studies, pre-clinical models of depression suffer from lack of face and construct validity (Nestler & Hyman, 2010). Depressive symptoms are challenging to model in animals given that diagnosis and prognosis are based on empirical clinical

Advancements in methodologies and information technology have facilitated identification of molecular and neurochemical correlates of MDD. Optogenetics helps elucidate the inter-relationship between neural circuitry, brain signaling, and biological response. Genomics, proteomics, epigenomics, and metabolomics provide an unbiased way to characterize biological alterations that underlie depressive behavior. In light of the many biological systems that are affected in depression, combinatorial approaches should be used to examine changes in various (cellular, molecular, biochemical, and behavioral) phenotypes, providing us with a comprehensive disease model.

Research studies conducted over the last forty years have not led to a detailed understanding of the mechanisms underlying MDD. Although this may seem disappointing at first, advances in technology and scientific approach indicate that the road to elucidating depression is one filled with hope and excitement.

10. References

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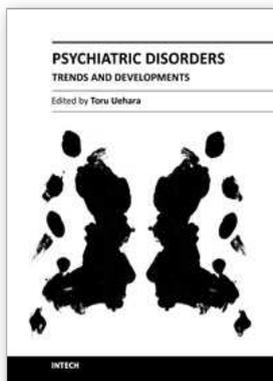
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Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, severe and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning is in some cases tragic. Aside from knowing the physical organic factors, such as infections, endocrinal illnesses or head injuries, the aetiology of psychiatric disorders has remained a mystery. However, recent advances in psychiatry and neuroscience have been successful in discovering subsequent pathophysiology and reaching associated bio-psycho-social factors. This book consists of recent trends and developments in psychiatry from all over the world, presented in the form of multifarious and comprehensive articles. The first two sections of the book are reserved for articles on schizophrenia and depression, two major illnesses present in this field. The third section of the book is reserved for addiction psychiatry, related not only to socio-cultural but also biological alterations. The last section of the book, titled Biological Neuropsychiatry, consists of three topics - updated molecular biology, fundamental neuroscience and clinical neuropsychiatric conditions. Doubtlessly, this book will be fruitful for future developments and collaboration in world psychiatry.

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