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REVIEW

Epigenetic mechanisms underlying the role of brain-derived neurotrophic factor in depression and response to antidepressants

Florian Duclot and Mohamed Kabbaj*

ABSTRACT

Major depressive disorder (MDD) is a devastating neuropsychiatric disorder encompassing a wide range of cognitive and emotional dysfunctions. The prevalence of MDD is expected to continue its growth to become the second leading cause of disease burden (after HIV) by 2030. Despite an extensive research effort, the exact etiology of MDD remains elusive and the diagnostics uncertain. Moreover, a marked inter-individual variability is observed in the vulnerability to develop depression, as well as in response to antidepressant treatment, for nearly 50% of patients. Although a genetic component accounts for some cases of MDD, it is now clearly established that MDD results from strong gene and environment interactions. Such interactions could be mediated by epigenetic mechanisms, defined as chromatin and DNA modifications that alter gene expression without changing the DNA structure itself. Some epigenetic mechanisms have recently emerged as particularly relevant molecular substrates, promoting vulnerability or resilience to the development of depressive-like symptoms. Although the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of MDD remains unclear, its modulation of the efficacy of antidepressants is clearly established. Therefore, in this review, we focus on the epigenetic mechanisms regulating the expression of BDNF in humans and in animal models of depression, and discuss their role in individual differences in vulnerability to depression and response to antidepressant drugs.

KEY WORDS: BDNF, Epigenetics, Individual differences

Introduction

Major depressive disorder (MDD) is a common debilitating disorder (Bromet et al., 2011) affecting many aspects of the patient's life and family. In addition to its high comorbidity with other neuropsychiatric conditions and increased rate of suicide, depression has a variety of socioeconomic consequences, including low education, unstable employment, reduced work performance and marital dysfunction (Kessler and Bromet, 2013). In 2000, the economic costs of depression in the United States alone were estimated at $83.1 billion, encompassing direct medical costs, suicide-related mortality costs, as well as indirect workplace costs (Greenberg et al., 2003). Moreover, the prevalence of depressive disorders is expected to continue its growth and become by the year 2030 the second leading cause of disease burden among the World Health Organization member states (Mathers and Loncar, 2006). Despite extensive research efforts in past decades, the etiology of depression remains elusive, its diagnosis uncertain and the pharmacotherapy inefficient. Indeed, the antidepressants currently used, which target the monoaminergic pathways, require weeks to months of treatment and exhibit very poor or no response in nearly 50% of patients (Magni et al., 2013; Trivedi et al., 2006; Warden et al., 2007). In addition to highlighting the critical need for new therapeutic strategies, such variability in response rates between patients reveals the importance of considering individual differences when examining prevention and therapeutic design.

This inter-individual variability certainly arises from the very complex nature of depressive disorders. Large efforts were made to investigate the importance of genetics in the etiology of depressive disorders, and as a result, MDD is recognized as a heritable disease (Kendler et al., 2005; Saveanu and Nemeroff, 2012; Sullivan et al., 2000). Nevertheless, genome-wide association studies failed to identify any genes clearly implicated in MDD (Bosker et al., 2011; Uher et al., 2013; Wray et al., 2012). Moreover, only one-third of the risk for developing MDD is inherited, while the remaining two thirds are of environmental influence (Saveanu and Nemeroff, 2012; Sullivan et al., 2000). Stress, early-life experiences, physical abuse and parental violence are all powerful environmental factors that can dramatically alter resilience against future adverse events and thus influence the vulnerability to develop depression, which may or may not be dependent on a genetic predisposition (Mill and Petronis, 2007; Saveanu and Nemeroff, 2012; Seok et al., 2012; Southwick and Charney, 2012). Accordingly, a multitude of studies have identified a variety of genetic polymorphisms as risk factors, therefore placing MDD as a prototypical case of gene × environment interactions (Mandelli and Serretti, 2013).

The rs6265 polymorphism located in the pro-domain of the brain-derived neurotrophic factor (BDNF) substitutes a Val with a Met residue (Val66Met) and results in impairments of activity-dependent BDNF release (Egan et al., 2003). Notably, Met carriers exhibit a higher risk of suicide attempts (Sarchiapone et al., 2008) and higher vulnerability to stressful life events than Val individuals (Brown et al., 2014; Hosang et al., 2014). Interestingly, this polymorphism interacts with antidepressant efficacy because Met carriers appear to exhibit a better response to classical antidepressants (Choi et al., 2006; Niitsu et al., 2013). Nevertheless, such observations are highly dependent on the type of antidepressant, gender, ethnicity and the presence of other polymorphisms (Brunoni et al., 2013; Liu et al., 2012; Tsai et al., 2010; Wang et al., 2014), suggesting only a weak association between rs6265 and antidepressant response.

BDNF is a critical pro-survival factor for the developing and adult central nervous system, through modulation of activity-induced neuronal plasticity (Park and Poo, 2013), and has been repeatedly implicated in the etiology of depression. Moreover, its antidepressant properties are now clearly demonstrated and led to

Department of Biomedical Sciences, Neuroscience Program, Florida State University, Tallahassee, FL 32306, USA.

*Author for correspondence (mohamed.kabbaj@med.fsu.edu)

The Journal of Experimental Biology (2015) doi:10.1242/jeb.107086

the elaboration of the neurotrophic hypothesis of depression. It proposes that a deficiency in neurotrophic signaling (and particularly BDNF) underlies depressive states through impairments in neuronal plasticity, and that antidepressant treatments restore neurotrophin expression and signaling in brain areas such as the hippocampus (Duman et al., 1997; Duman and Monteggia, 2006). However, further preclinical studies demonstrated that an impairment in BDNF expression and signaling per se does not lead to depressive-like behaviors, but does affect the efficacy of antidepressant treatments (Adachi et al., 2008; Castrén and Rantamäki, 2010; Chourbaji et al., 2011; Chourbaji et al., 2004; Duman and Monteggia, 2006; Saarelainen et al., 2003). It is therefore clearly established that hippocampal BDNF signaling plays a critical role in the therapeutic effects of antidepressant treatments, whereas its role in the etiology of depression remains unclear. Interestingly, accounting for the complex *Bdnf* gene structure can help clarifying this uncertainty. The human *BDNF* and rodent *Bdnf* gene structures share substantial similarities, with several 5′ non-coding exons, and one 3′ coding exon. Importantly, each exon has its own promoter, which gives rise to several transcripts, but all leading to the same protein (Aid et al., 2007; Pruunsild et al., 2007). This structure allows for a very complex regulation of the *Bdnf* gene transcription in a time-, tissue- and stimulus-specific manner, which are all critical parameters for BDNF regulation of neuronal plasticity (Park and Poo, 2013). Notably, mice lacking promoter-4-driven *Bdnf* transcription show depression-like behaviors under stressful conditions (Sakata et al., 2010), suggesting a promoter-specific involvement of *Bdnf* in the response to stress.

In humans, however, numerous studies report reduced serum BDNF levels in depressed patients, which are then normalized to the levels of healthy controls by antidepressant treatment (Bocchio-Chiavetto et al., 2006; Brunoni et al., 2008; Hoyer et al., 2012; Pallavi et al., 2013; Sen et al., 2008). However, serum BDNF levels do not systematically correlate with the severity of depressive symptoms, which questions its use as an accurate biomarker for depression (Molendijk et al., 2011; Molendijk et al., 2014). Nonetheless, a meta-analysis revealed a significant correlation between changes in serum BDNF levels and depression scores following antidepressant treatment (Brunoni et al., 2008), which suggests that serum BDNF levels relate to therapeutic efficacy. Indeed, serum BDNF levels are differentially regulated in ‘good’ versus ‘poor’ responders to antidepressant treatments in MDD, following classical (venlafaxine) or atypical antidepressant treatments such as ketamine, exercise or cognitive behavioral therapy (Dreimüller et al., 2012; Haile et al., 2014; Kobayashi et al., 2005; Rojas et al., 2011; Toups et al., 2011). Furthermore, clinical evidence suggests that high serum BDNF levels prior to or early after treatment predict a subsequent positive response to a classical antidepressant (Dreimüller et al., 2012; Mikoteit et al., 2014; Tadić et al., 2011; Wolkowitz et al., 2011). Therefore, although the link between serum and central BDNF remains difficult to establish, it is clear that BDNF plays a critical role in the pathophysiology of depression and represents a particularly interesting candidate in shaping the individual differences observed in vulnerability to depression and antidepressant response.

In the absence of a clear genetic etiology, the regulation of BDNF expression has been the focus of extensive research, which brought substantial insight into its regulation in the pathophysiology of MDD and the therapeutic effects of antidepressants (for a review, see Castrén and Rantamäki, 2010; Masi and Brovedani, 2011). Recently, studies of the epigenome have shed additional light on the molecular correlates for the individual variability observed in MDD. Indeed, under direct control of environmental stimuli such as stress or antidepressant treatment, DNA methylation and histone post-translational modifications exert a dynamic and stimulus-specific regulation of gene transcription. Notably, at the translational level, microRNAs also modulate the vulnerability to depression and antidepressant response. MicroRNA levels are altered in the prefrontal cortex of suicidal subjects (Lopez et al., 2014; Smalheiser et al., 2012) and serum of depressed patients, where higher levels of the BDNF-related miR-132 are correlated to higher depression scores (Li et al., 2013). Moreover, the BDNF-targeting microRNA miR-16 and miR-124 are both upregulated by stress in the rat hippocampus and associated with subsequent induction of depressive-like symptoms (Bahi et al., 2014; Bai et al., 2012). Finally, the BDNF-targeting miR-30a-5p and miR-206 modulate the upregulation of BDNF following treatment with the antidepressant paroxetine and ketamine (Angelucci et al., 2011; Yang et al., 2014), denoting a regulation of BDNF by microRNAs in the pathophysiology of depression, response to stress and antidepressant efficacy. Nevertheless, we here review how epigenetic mechanisms at the *Bdnf* gene (histone modifications and DNA methylation) provide a molecular substrate for the individual differences in the vulnerability to depression and antidepressant response in humans and in animal models.

Individual differences in the epigenetic regulation of the *BDNF* gene in humans

Depressed patients have reduced BDNF levels in the serum, which are normalized after a positive response to antidepressant treatment (Brunoni et al., 2008). Although the source of serum BDNF relevant to depressive symptoms appears to be concentrated in the platelets (Karege et al., 2005a; Lee and Kim, 2009), its functional significance with regard to central BDNF levels remains unclear. In rats, a positive correlation between serum and central BDNF levels is generally observed at baseline, particularly in young animals (Karege et al., 2002; Klein et al., 2011; Sartorius et al., 2009). Following stress or antidepressant treatment, however, such correlation is inconsistent, probably because of conflicting factors such as age or strain of the animals, or the time of analysis (Béjot et al., 2011; Elfving et al., 2010; Kyerematenteng et al., 2012; Luo et al., 2010). Nevertheless, lower BDNF levels are found in the hippocampus and prefrontal cortex (PFC) of subjects who committed suicide compared with non-suicide controls, whereas higher BDNF levels are observed in individuals treated with antidepressants compared with drug-free controls (Chen et al., 2001; Dwivedi et al., 2003; Karege et al., 2005b). This suggests that serum BDNF levels have the potential to appropriately reflect central levels of the neurotrophin (Table 1).

This question is of particular importance in epigenetic studies, because epigenetic mechanisms are highly dynamic and tissue-specific. As an example, a recent study of the human methylome uncovered highly variable patterns of DNA methylation between tissues within an individual that greatly exceed the inter-individual differences in any given tissue observed (Davies et al., 2012). These tissue-specific differences in DNA methylation are mainly located at intragenic CG methylation sites, whereas promoters appear more conserved across tissues. Notably, despite such tissue specificity, differences in DNA methylation between two individuals are significantly correlated between the blood and the cortex, as well as between the blood and the cerebellum (Davies et al., 2012). Furthermore, another recent study of the stress-responsive gene *Fkbp5* in mice reveals that DNA methylation in the blood correlates with both the methylation and expression levels in the hippocampus

The Journal of Experimental Biology (2015) doi:10.1242/jeb.107086

Table 1. Epigenetic regulation of *BDNF* in depressive disorders and antidepressant response in humans

		In patients (versus controls)	After AD treatment (versus untreated)	Details	References
Blood	Protein levels	↓	↑	BDNF levels after AD treatment positively correlate to therapeutic efficiency	Brunoni et al., 2008
	DNA methylation at P4	↑	↓	Predicts AD response in suicidal subjects	Kang et al., 2013
	H3K27 methylation at P4	n.d.	↓	Associated with higher BDNF levels following 8 weeks of citalopram treatment	Lopez et al., 2013
Brain	Protein levels	↓	↑	In hippocampus and PFC	Chen et al., 2001; Dwivedi et al., 2003; Karege et al., 2005b
	DNA methylation at P4	↑	n.d.	In Wernicke's area of suicide completers	Keller et al., 2010
	H3K27 methylation at P4	n.d.	↓	Associated with higher BDNF levels in PFC of patients with history of classical antidepressant use	Chen et al., 2011

AD, antidepressant; BDNF, brain-derived neurotrophic factor; n.d., not determined; P4, *BDNF* promoter 4; PFC, prefrontal cortex.

(Ewald et al., 2014). Measuring DNA methylation in the blood of patients therefore appears particularly appropriate in the context of inter-individual differences.

Of note, CpG islands have been proposed in the promoters of exons I, II, IV, V, VI and IXa in rodent *Bdnf*, whereas only three CpG islands can be detected in the promoters of exons I, II, and VI of the human *BDNF* gene (Boulle et al., 2012).

Epigenetic regulation of *BDNF* and depressive symptoms

Patients with life-time MDD exhibit a marked reprogramming of gene expression, reflected, in part, by an alteration of their methylome (Uddin et al., 2011). In line with the reduced serum BDNF levels observed in depressed individuals, several groups have reported a hypermethylation of the *BDNF* gene promoter in MDD patients. The first report originated from a post-mortem analysis of DNA methylation in the Wernicke's area of subjects who committed suicide, and revealed lower BDNF expression associated with increased DNA methylation of four CpG sites located at *BDNF* promoter 4 (Keller et al., 2010). Interestingly, hypermethylation of the same loci has also been reported in the blood of depressed patients with suicidal behaviors (Kang et al., 2013), suggesting that DNA methylation at *BDNF* promoters can reflect similar changes in the brain. Notably, global DNA methylation in Wernicke's area, as well as DNA methylation of gene coding for the BDNF receptor TrkB remained similar to control subjects (Keller et al., 2010; Keller et al., 2011). In the frontal cortex, however, the TrkB.T1 isoform is downregulated in suicide completers when compared with controls, and is associated with a coherent increase in DNA methylation and repressive methylation of histone H3 at the Lys27 residue (H3K27) (Ernst et al., 2009a; Ernst et al., 2009b). Changes in DNA methylation are thus gene- and structure-specific, and reflect the complex nature of depressive disorders. Nevertheless, these early studies do suggest that monitoring the epigenetic regulation of the *BDNF* gene in the blood can provide valuable diagnostic information. Supporting this idea, blood DNA methylation at *BDNF* P1, but not P4, was proposed as a diagnostic for MDD (Fuchikami et al., 2011).

Stress is considered one of the most powerful environmental stimuli and can induce depressive symptoms in some individuals – termed vulnerable – while others remain resilient, to some extent. Thus, monitoring the response of the epigenome following stress emerges as particularly relevant for investigating individual differences in vulnerability to MDD. *BDNF* P4 is hypermethylated in the blood of individuals developing post-stroke depression (Kim et al., 2013), supporting other findings described above. Although not associated with the severity of depressive symptoms at baseline, the DNA methylation of the *BDNF* gene was significantly associated with the worsening of the depressive symptoms over 1 year, revealing that *BDNF* DNA methylation could be an interesting biomarker for vulnerability to post-stroke depression (Kim et al., 2013). DNA methylation of *BDNF* P6 in the blood, however, does not appear to be significantly affected by acute psychosocial stress (Unternaehrer et al., 2012), a stressor associated with the development of depressive-like symptoms in humans and rodents (Berton et al., 2006; Björkqvist, 2001). Although the two studies investigated the consequences of two different types of stress on two different promoters of the *BDNF* gene, these observations denote a strong specificity for the stimulus in the regulation of *BDNF* through DNA methylation. However, it is important to note that our current knowledge of the epigenetic regulation of *BDNF* in the vulnerability to depression in humans originates from measurements following the development of symptoms. To investigate the vulnerability to develop symptoms, further studies monitoring such epigenetic modifications in the context of individual differences are required. For instance, although very challenging, longitudinal studies of DNA methylation of the *BDNF* gene in the blood of the same individual before and after development of depressive symptoms would provide valuable information.

Epigenetic regulation of *BDNF* and antidepressant response

Classical antidepressant treatments upregulate BDNF levels in the serum and brain, as observed in MDD patients with a history of antidepressant use (Chen et al., 2001; Duman and Monteggia, 2006), an effect directly associated with their therapeutic efficacy (Brunoni et al., 2008). Interestingly, a recent study in a small cohort of subjects uncovered higher post-mortem BDNF levels in the PFC of subjects with a history of classical antidepressant treatment, associated with lower histone H3K27 methylation at *BDNF* P4, compared with healthy controls and depressed subjects without a history of antidepressant use (Chen et al., 2011). Such increase in BDNF levels associated with a reduction of the repressive H3K27 methylation at *BDNF* P4 is also observed in blood samples following 8 weeks of citalopram treatment (Lopez et al., 2013), indicating, once more, that blood levels can reflect central neuroadaptations. Interestingly, H3K27 methylation at *BDNF* P4 is inversely correlated with serum BDNF levels and treatment efficacy, such that only subjects presenting with positive therapeutic responses to citalopram exhibited higher *BDNF* and lower H3K27 methylation (Lopez et al., 2013). However, H3K27 methylation did not differ between future responders and non-responders prior to the treatment period (Lopez et al., 2013). Therefore, although blood

levels of H3K27 methylation at *BDNF* P4 might be relevant markers for classical antidepressant efficacy, their use as predictors remains limited. DNA methylation at *BDNF* P4, however, might possess a predicting ability. Indeed, in depressed individuals suffering from suicidal behaviors, the classification of 'high-' and 'low-methylated' individuals predicted their response to classical antidepressant treatment, with individuals with low DNA methylation at *BDNF* P4 exhibiting an enhanced reduction in suicidal ideation (Kang et al., 2013).

The combined interests in BDNF and the epigenome have brought valuable insight into the pathophysiology of MDD, as well as new potential therapeutics. While the use of DNA and histone methylation events for diagnostic purposes is limited by the fact that similar BDNF alterations are observed in different neuropsychiatric disorders, their potential to predict subsequent therapeutic efficacy is very encouraging. It would thus be highly valuable and informative to take into account the inter-individual variability in these epigenetic marks at baseline for future investigations of therapeutic efficiency.

Epigenetic regulation of the *BDNF* gene and vulnerability to depression in animal models

Because of its high complexity and comorbidity with other neuropsychiatric disorders, modeling MDD in animals is a notable challenge. Nevertheless, a few experimental paradigms have been developed to accurately model distinct aspects of human depression, each with its own advantages and limitations (Hollis et al., 2013; Krishnan and Nestler, 2010; Krishnan and Nestler, 2011; Nestler and Hyman, 2010; Razafsha et al., 2013). Most animal models of depression are based on repeated exposure to stressors that differ in nature and intensity, and induce a series of long-lasting depressive-like behaviors (most commonly anhedonia and social withdrawal), associated with neuroendocrine, immune, vegetative and metabolic alterations, as well as perturbations of neuronal connectivity and neuronal plasticity. Notably, not all animals develop such depressive-like symptoms, which allows the discrimination of vulnerable and resilient subpopulations and thus the investigation of neurobiological correlates of vulnerability to depression (Franklin et al., 2012; Russo et al., 2012). The depressive-like symptoms induced in these animal models are associated with long-term changes in the expression of a variety of genes, including epigenetic factors, as well as local and global reorganization of the epigenome (Vialou et al., 2013; Zannas and West, 2014). Among such genes, *BDNF*, its regulators and its downstream effectors (referred to here as the BDNF system) are critical modulators of the depressive-like phenotype in a tissue-specific manner. In the following sections, we will therefore focus on the BDNF system and its epigenetic regulation in the nucleus accumbens and hippocampus, because these structures are the most studied to date.

Nucleus accumbens

Epidemiological studies have clearly shown that chronic psychological stressors are critical contributors to the development of depression in humans (Björkqvist, 2001; Meltzer et al., 2011; Roy and Campbell, 2013; Taylor et al., 2011). Such repeated exposure to a social stressor can be mimicked in rodents by using a modified version of the resident-intruder procedure called social defeat, which generates persistent emotional stress (Tidey and Miczek, 1997). Interestingly, when mice are subjected to 10 consecutive days of social defeat, some animals, termed susceptible, develop depressive-like symptoms (anhedonia, social avoidance, behavioral despair, alterations of circadian rhythms and weight loss), while others are resilient (Krishnan et al., 2007). In addition to phenotypic differences, susceptible and resilient mice exhibit distinct profiles of gene expression in the nucleus accumbens (NAc) and ventral tegmental area (VTA), highlighting an adaptive control of gene expression in the NAc and VTA of resilient mice (Krishnan et al., 2007; Wilkinson et al., 2009). Notably, high BDNF levels and subsequent activation of its downstream effectors Akt and extracellular-regulated mitogen-activated protein kinases (ERKs) were observed in the NAc of susceptible animals. Moreover, viral-mediated BDNF knockdown in the VTA, but not the NAc, promotes resiliency to social-defeat-induced anhedonia (Berton et al., 2006; Krishnan et al., 2007). However, knockdown of BDNF in the VTA induces pro-hedonic behaviors and also reduces behavioral despair in non-stressed animals (Taliaz et al., 2013), suggesting that the maintenance of physiological BDNF levels in the VTA is critical for a 'normal' hedonic state. Further analyses suggest that upon exposure to social defeat, the activation of BDNF-containing neurons in the VTA leads to release of BDNF in the NAc and activation of its downstream signaling pathway, which in turn promotes vulnerability to social defeat (Berton et al., 2006; Krishnan et al., 2007).

Despite its clear effect as a vulnerability factor in the NAc, the precise regulation of BDNF transcription in the originating VTA remains unclear. Nevertheless, several studies conducted in the NAc provide indirect evidence. In addition to a high comorbidity between depressive symptoms and substance abuse in humans (Ford et al., 2009), social defeat and repeated cocaine exposure share similarities in molecular alterations induced in the NAc. Indeed, both stimuli downregulate HDAC5, which in mice enhances social-defeat-induced social avoidance (Renthal et al., 2007), as well as the lysine methyltransferase G9a and H3K9 dimethylation in susceptible mice and depressed patients (Covington, III et al., 2011). Conversely, overexpression of G9a in the NAc reduces the social avoidance and activation of the TrkB signaling pathway induced by the combination of cocaine exposure and social defeat (Covington, III et al., 2011). Interestingly, both G9a, through control of H3K9 dimethylation, and HDAC5 have been linked to regulation of BDNF expression (Chase and Sharma, 2013; Duclot and Kabbaj, 2013; Gupta-Agarwal et al., 2012; Tian et al., 2009; Tsankova et al., 2006). Furthermore, previous exposure to cocaine enhances *BDNF* upregulation in the NAc following acute stress through histone H3 acetylation at its promoter 1 (Cleck et al., 2008). Altogether, these studies suggest that repeated cocaine exposure alters the epigenome toward a permissive state, enhancing *BDNF* upregulation and promoting vulnerability to subsequent stress. Notably, chronic social defeat also increases the permissive H3K4 methylation of the DNA N-methyl-transferase 3a (DNMT3a) gene promoter, leading to its upregulation in the NAc (LaPlant et al., 2010). Interestingly, viral-mediated overexpression of DNMT3a in the mouse NAc enhances the social avoidance induced by a submaximal exposure to social defeat (LaPlant et al., 2010), which thus highlights DNMT3a and DNA methylation in the NAc as important vulnerability factors.

In addition to the BDNF system, a variety of epigenetic-related factors are also differentially regulated between vulnerable and resilient mice in the NAc: the histone methyl-transferases Mll1, SUV39H1 and GLP (Covington, III et al., 2011), and HDAC2 (Covington et al., 2009; Krishnan et al., 2007). Of note, while HDAC5 is downregulated in the NAc of susceptible mice (Renthal et al., 2007), HDAC2, which is known to bind *Bdnf* P1, P2 and P4 (Gräff et al., 2012; Guan et al., 2009), is upregulated, suggesting that the two enzymes target different genes. This highlights the importance of analyzing epigenetic modifications locally at specific targets rather than globally.

Hippocampus

Contrary to the VTA-NAc, the role of the hippocampal BDNF system in the pathophysiology of depression remains unclear. On the one hand, post-mortem hippocampal BDNF levels are reduced in depressed patients (Dwivedi et al., 2003), which could be associated with the reduction of hippocampal volume and neuronal loss (Duman, 2004a; Duman, 2004b; Sheline et al., 2003; Vermetten et al., 2003). On the other hand, transgenic disruption of BDNF and TrkB expression and signaling does not consistently induce a depressive-like phenotype (Adachi et al., 2008; Monteggia et al., 2004; Monteggia et al., 2007), although one group reported anhedonia and behavioral despair following knockdown of hippocampal BDNF by RNA interference (Taliaz et al., 2013; Taliaz et al., 2010). Furthermore, such inconsistency is also observed when investigating the effects of chronic stress. Indeed, although hippocampal BDNF levels are generally downregulated by chronic stress paradigms (Bath et al., 2013), some groups report reduction, some report an increase and others report no substantial changes in BDNF expression following chronic social defeat (Coppens et al., 2011; Duclot and Kabbaj, 2013; Lagace et al., 2010; Pizarro et al., 2004; Tsankova et al., 2006). These discrepancies probably result from differences in experimental designs, animal models used or specificities between hippocampal subregions. Nevertheless, they warrant more thorough investigation of the hippocampal *BDNF* regulation in the pathophysiology of depression. The consideration of individual differences has, for instance, provided valuable information.

Similar to social defeat in mice (Krishnan et al., 2007), some rats develop depressive-like symptoms following chronic mild stress (CMS), while others remain resilient, as defined by the absence of anhedonia (Bergström et al., 2008). A comparative analysis of gene expression between these two sub-populations revealed a specific BDNF upregulation in the CA3 area of the hippocampus when compared with CMS-vulnerable rats and unstressed controls, highlighting hippocampal upregulation of BDNF as a pro-resiliency factor. In line with this observation, the viral-mediated overexpression of BDNF in the dorsal dentate gyrus (dDG) of the hippocampus prevents the development of CMS-induced anhedonia and behavioral despair in the forced-swim test (Taliaz et al., 2011). Interestingly, BDNF-overexpressing animals still exhibit lower hippocampal levels than their non-stressed controls following CMS, indicating that BDNF levels are still affected by the CMS procedure in these animals. It therefore appears that BDNF-overexpressing animals are protected from the depressive-like symptoms induced by CMS by maintaining sufficient levels of BDNF in the hippocampus to counteract the deleterious effects of CMS on hippocampal plasticity (Reich et al., 2013). Accordingly, resilience to CMS-induced anhedonia would be promoted by the maintenance of 'physiological' levels of BDNF in the hippocampus. In an attempt to model the worsening effects of past stressful experiences on the subsequent response to stress, Blugeot and colleagues submitted rats to CMS 4 weeks after being exposed to a social defeat paradigm (Blugeot et al., 2011), and found that the ability of serum and hippocampal BDNF to recover from the first social defeat stress was critical in determining subsequent vulnerability to CMS. While all animals were vulnerable to the first stressor and exhibited reduced BDNF levels 5 days after the last exposure to the stress, only those that recovered from the first stress 4 weeks later and presented with BDNF levels similar to non-stressed controls were resilient to subsequent CMS-induced anhedonia. The animals whose BDNF levels did not recover became vulnerable (Blugeot et al., 2011). While the molecular regulation of BDNF involved in this recovery remains uninvestigated, this illustrates the importance of considering the individual differences in adaptation and response of the BDNF system to a stimulus.

The dynamic nature of *BDNF* regulation is therefore critical in determining the vulnerability to develop depressive-like symptoms, and places epigenetic mechanisms as interesting candidates. In mice, chronic social defeat induces a specific downregulation of *BDNF* exons IV and VI, through hypermethylation of H3K27 around their respective promoters (Tsankova et al., 2006). Notably, H3K9 methylation, histone H3 acetylation and DNA methylation remained unaffected by social defeat at *BDNF* P4 and P6. Furthermore, an acute footshock stress triggers in the hippocampus an upregulation of *BDNF* transcripts I and IV, but not VI, through local increase in histone acetylation (Fuchikami et al., 2010). These findings demonstrate a strong stimulus specificity in *BDNF* regulation in terms of transcripts and histone modifications, and highlight the importance of epigenetic mechanisms in mediating such specificity.

When exposed to the mild stress of a novel environment, rats exhibit either high rates (termed high responders, HR) or low rates (termed low responders, LR) of exploratory locomotion (Piazza et al., 1989). In addition to predicting sensitivity to drugs of abuse, this novelty-seeking phenotype also predicts subsequent vulnerability to the development of depressive-like symptoms. Following repeated exposure to social defeat, HR animals exhibit anhedonia, a marked social withdrawal, reduced body weight gain and a prolonged contextual fear, together with an impaired neuroendrocrine response, whereas LR animals remain unaffected (Calvo et al., 2011; Duclot et al., 2011). Interestingly, these behavioral differences were associated with individual differences in the hippocampal profile of histone acetylation. Although HR animals have higher histone H3 and H2B acetylation than LR rats at baseline, they exhibit a decrease in H3 and H2B acetylation following repeated social defeat, whereas only H3 acetylation was increased in LR rats (Hollis et al., 2011). Interestingly, H4 acetylation is reduced in both HR and LR animals following social defeat (Hollis et al., 2011) or chronic variable physical stress (Oztan et al., 2011), suggesting that the individual differences in response to repeated stress are mediated by acetylation of H2B and H3, but not H4. As suggested by the global pattern of histone acetylation, a different set of genes, including *Bdnf*, is affected in the hippocampus by social defeat between HR and LR animals (Duclot and Kabbaj, 2013; Kabbaj et al., 2004). Following repeated social defeat, the resilient LR animals exhibit an upregulation of BDNF mRNA and protein levels, whereas the vulnerable HR animals do not, despite higher baseline levels. Accordingly, the downstream BDNF signaling pathway TrkB–Akt–CREB is activated following social defeat in LR, but not HR animals. Notably, activating the hippocampal BDNF system with the potent BDNF mimetic and TrkB agonist 7,8-dihydroxyflavone (DHF) during each defeat encounter promotes resiliency in HR animals. Conversely, preventing its activation during each defeat session in LR animals leads to vulnerability to the induction of social avoidance by social defeat (Duclot and Kabbaj, 2013). Therefore, the *Bdnf* upregulation in LR animals in response to the social defeat exposure ensures their resilience to the social defeat stress, whereas HR animals, lacking such a protective response, are vulnerable. The differential regulation of BDNF levels between HR and LR animals is accompanied by a complex, but coherent epigenetic regulation specific to *Bdnf* P6, which has been previously suggested to be the main *Bdnf* transcript regulated by antidepressant treatment in the hippocampus (Baj et al., 2012). Following social defeat, LR animals show at *Bdnf* P6 an increase in the permissive H3K4 methylation and H3 acetylation, as well as reduced levels of the repressive H3K9 methylation, while HR animals exhibit at baseline higher H3K4

methylation and lower H3K9 methylation than their LR counterparts, without any modification after defeat (Duclot and Kabbaj, 2013). These epigenetic marks were associated with a coherent regulation of their relevant enzymes, the lysine methyltransferase Mll1, the lysine acetyltransferase CBP and the lysine demethylase Kdm3a (Duclot and Kabbaj, 2013). However, DNA methylation at *Bdnf* P6 remains unaffected in the two subpopulations of rats at baseline and after social defeat, which confirms the lack of involvement of DNA methylation in modulating *Bdnf* expression following chronic psychosocial stress in the mouse hippocampus (Tsankova et al., 2006) and *BDNF* expression in human blood following acute psychological stress (Unternaehrer et al., 2012). Although the mechanisms regulating the epigenetic factors remain to be identified, these findings illustrate how epigenetic modifications and their related factors can finely regulate *Bdnf* gene expression in a promoter-specific manner and in turn modulate the vulnerability to the development of depressive-like symptoms (Table 2).

In opposition to the susceptible/resilient mice or CMS-resilient animal models revealing individual differences after exposure to stress, the HR/LR model thus provides the opportunity to investigate the neurobiological bases of individual differences in the development of depressive-like symptoms prior to the exposure to the stress paradigm and illustrates how the epigenome can direct such inter-individual variability. Nevertheless, the individual differences between HR and LR animals could themselves be the consequences of prior stressful experiences and thus highlight an influence of the epigenome on gene expression over an extended period of time. In humans, neglect early in life and child abuse are directly linked to negative emotional outcomes in adulthood (Bebbington et al., 2004; Kaffman and Meaney, 2007; Mullen et al., 1996) and relevant animal models uncovered a determining role of BDNF regulation via DNA methylation in the PFC (Roth et al., 2009; Roth and Sweatt, 2011). Similar to maternal separation or early-life adversity, the perinatal toxic exposure to methylmercury promotes the development of cognitive impairments and depressive-like symptoms (Onishchenko et al., 2008). In this model, methylmercury triggers a long-lasting downregulation of *Bdnf* expression in the hippocampus through an increase in H3K27 methylation, as observed following social defeat (Tsankova et al., 2006), DNA methylation and reduced histone H3 acetylation at *Bdnf* P4 (Onishchenko et al., 2008).

Epigenetic regulation of the *Bdnf* gene and response to antidepressants

As discussed earlier, the precise role of BDNF in the development of depressive-like symptoms remains unclear. However, a growing body of evidence indicates that physiological levels of BDNF and its downstream signaling are required for proper antidepressant efficacy (for a review, see Castrén and Rantamäki, 2010). A vast majority of currently available antidepressants increase BDNF expression and activate its downstream signaling pathway through TrkB (Duman and Monteggia, 2006; Martinowich et al., 2007), although some evidence exist for an activation of TrkB by antidepressants independent of BDNF (Castrén and Rantamäki, 2010). Accordingly, the potent BDNF mimetic and TrkB agonist 7,8-DHF, or transgenic overexpression of TrkB exhibits antidepressant effects in the forced-swim test (Koponen et al., 2005; Liu et al., 2010). Furthermore, the efficacy of antidepressants is greatly reduced or even abolished when BDNF expression or TrkB signaling are disrupted (Adachi et al., 2008; Ibarguen-Vargas et al., 2009; Monteggia et al., 2004). In addition to the known antidepressant effects of compounds such as HDAC inhibitors (HDACi), it is appropriate to consider that epigenetic mechanisms could, through regulation of genes such as *BDNF*, modulate the efficacy of antidepressant treatments (Table 3).

Classical antidepressants

In mice, without consideration of individual differences, chronic social defeat induces a downregulation of *Bdnf* in the hippocampus through an increase in the repressive H3K27 methylation at BDNF P4 and P6. This is associated with long-lasting depressive-like symptoms that can be reversed following chronic treatment with the tricyclic imipramine (Tsankova et al., 2006). Interestingly, imipramine does not affect H3K27 methylation, but rather enhances H3 acetylation at *Bdnf* P4 and P6 through downregulation of HDAC5. Notably, the effects of imipramine on HDAC expression differ between stressed and non-stressed animals, with a downregulation of HDAC9 and HDAC5 in controls and stressed animals, respectively (Tsankova et al., 2006). This observation is particularly interesting as it denotes a differential effect of the drug based on the prior experience of the mouse, suggesting that HDACs could bear the mark of past experiences. We could thus see HDACs as substrates for variability in response to a drug, such as an antidepressant, between two individuals with different past experiences. In line with this hypothesis, loss of HDAC5 promotes vulnerability to social-defeat-induced depressive-like symptoms (Renthal et al., 2007).

Finally, the selective serotonin re-uptake inhibitor fluoxetine triggers an epigenetic response similar to that of imipramine (Tsankova et al., 2006), because chronic treatment reverses the depressive-like symptoms induced by perinatal exposure to

Table 2. Epigenetic regulation of *Bdnf* and vulnerability/resilience to depressive-like symptoms in rodents

Experimental paradigm	Effects on BDNF levels	Region	Epigenetic marks on *bdnf*	Associated with vulnerability or resilience	References
Chronic social defeat (CSD)	↑	NAc	n.d.	Vulnerability	Krishnan et al., 2007
BDNF overexpression, 7,8-DHF, CMS, CSD	↑	HPC	n.d.	Resilience	Bergstrom et al., 2008; Blugeot et al., 2011; Taliaz et al., 2011; Duclot and Kabbaj, 2013
BDNF-shRNA, TrkB-Fc, CMS, CSD	↓	HPC	n.d.	Vulnerability	Bergstrom et al., 2008; Blugeot et al., 2011; Taliaz et al., 2011; Duclot and Kabbaj, 2013
CSD	↓	HPC	↑ H3K27me at P4 + P6	Vulnerability	Tsankova et al., 2006
Repeated social defeat	↑	HPC	↑ H3K4me and ↑ H3Ac ↓ H3K9me at P4 + P6	Resilience	Duclot et al., 2013
Perinatal methylmercury exposure	↓	HPC	↑ H3K27me at P4	Vulnerability	Onishchenko et al., 2008

7,8-DHF, 7,8-dihydroxyflavone (TrkB agonist and BDNF mimetic); BDNF, brain-derived neurotrophic factor; CMS, chronic mild stress; HPC, hippocampus; NAc, nucleus accumbens; n.d., not determined; P4,P6, *Bdnf* promoters 4 and 6; PFC, prefrontal cortex.

Table 3. Epigenetic regulation of *Bdnf* and antidepressant response in rodents

Treatment	Duration	Epigenetic marks on *Bdnf*	Effects on BDNF levels	Region	References
Imipramine	4 weeks	↑ H3Ac at P4 + P6	↑	HPC	Tsankova et al., 2006
Fluoxetine	3 weeks	↑ H3Ac at P4 + P6	↑	HPC	Onishchenko et al., 2008
ECT	Once daily for 7 days	↑ H3Ac at P4	↑	HPC	Tsankova et al., 2004
HDAC inhibitor (SAHA)	1 to 3 hours	↑ H3Ac + ↑ H4Ac at P1 + P4	↑	Cortical neurons	Koppel and Timmusk et al., 2013
Environmental enrichment	4 weeks	↑ H3K4me at P3 + P6 ↓ H3K9me at P4 ↓ H3K27me at P3 + P4	↑	HPC	Kuzumaki et al., 2011
Exercise	1 week	↓ DNA methylation at P4 ↑ Global H3Ac, but not H4Ac	↑	HPC	Gomez-Pinilla et al., 2011
Exercise	3 weeks	↑ Global H4K8Ac	↑	HPC	Intlekofer et al., 2013

BDNF, brain-derived neurotrophic factor; ECT, electroconvulsive therapy; HDAC, histone deacetylase; HPC, hippocampus; P1, P3, P4, P6: *Bdnf* promoters 1, 3, 4 and 6; SAHA, suberoylanilide hydroxamic acid.

methylmercury through an increase in histone H3 acetylation at *Bdnf* P4 in the hippocampus without alteration of H3K27 methylation (Onishchenko et al., 2008). Notably, such fluoxetine-induced hippocampal increase in BDNF is not consistently observed in the literature, which may be due to the variety of experimental designs (especially time of measurement) and conditions (Coppell et al., 2003; de Foubert et al., 2004; First et al., 2011; Mitic et al., 2013).

Atypical antidepressants

One of the most effective treatments for MDD aside from classical antidepressants is electroconvulsive therapy (ECT), which causes substantial side effects (Berton and Nestler, 2006). In rats, ECT leads to a chronic upregulation of BDNF levels in the hippocampus, associated with hyperacetylation of histone H3 at *Bdnf* P4 (Tsankova et al., 2004), which is similar to the effects of chronic imipramine treatment in mice (Tsankova et al., 2006). In light of the differences in treatment efficacy between the two therapies, it is surprising to see such a resemblance. Nevertheless, a recent study in rats revealed that ECT up- and downregulates BDNF levels in the hippocampus and the VTA, respectively (Taliaz et al., 2013), in line with the known antidepressant and prodepressant roles of BDNF in these two structures. Interestingly, viral-mediated overexpression of BDNF in the VTA blocked the antidepressant effects of ECT, whereas the knockdown of BDNF in the hippocampus had little effect on ECT efficacy (Taliaz et al., 2013). These findings thus suggest that BDNF regulation in the VTA, but not the hippocampus, is critical in mediating the antidepressant effect of ECT in rats, and shed some light on why ECT and imipramine treatments vary greatly in efficacy despite inducing a similar epigenetic regulation of *Bdnf* in the hippocampus.

In line with the changes in histone acetylation observed following the induction of depressive-like symptoms, HDACi exhibit interesting antidepressant properties (Schroeder et al., 2007). By inhibiting HDACs, these compounds promote histone acetylation throughout the genome, with a surprising specificity (Halsall et al., 2012; Weaver et al., 2006). In cortical neurons, HDACi treatment resulted in a rapid upregulation of *Bdnf* mRNA levels through hyperacetylation of histones H3 and H4 mainly localized at *Bdnf* P1 and P4 (Koppel and Timmusk, 2013), as seen after imipramine treatment (Tsankova et al., 2006). Furthermore, the mood stabilizers lithium and valproate, widely used clinically for treatment of bipolar disorders, also possess HDACi activity, and can activate transcription of *BDNF* exon IV through interaction with GSK-3, an effect also observed following treatment with the other HDACi sodium butyrate and trichostatin A (Yasuda et al., 2009).

In addition to histone modifications, some animal models of depression also reveal an altered pattern of DNA methylation. Interestingly, the DNMT inhibitor RG108 reverses social-defeat-induced social avoidance to a similar extent as chronic treatment with the classical antidepressant fluoxetine (LaPlant et al., 2010). Moreover, the DNMT inhibitors 5-azaD, 5-azaC and RG108 exhibit antidepressant activity in the forced-swim test when injected systemically or in the hippocampus of rats (Sales et al., 2011), suggesting that hippocampal inhibition of DNMT is sufficient to exert antidepressant effects. Mechanistically, the targets of DNMT inhibitors mediating their antidepressant effects remain to be investigated. Nevertheless, 5-azaC potentiates the activity-driven demethylation of BDNF P1 in hippocampal cultures (Nelson et al., 2008). Furthermore, classical antidepressants can influence DNMT expression directly, and histone methylation indirectly via interaction with G9a. In primary astrocytes from the rat cortex, the classical antidepressant amitriptyline downregulates DNMT activity by reducing the interaction with G9a, a known activator of DNMT1 (Zimmermann et al., 2012). It is thus reasonable to hypothesize that part of the therapeutic effect of classical antidepressants is mediated by the regulation of DNMT, and subsequent DNA methylation, indirectly through the histone methyltransferase G9a. Given the critical role played by G9a in vulnerability to the induction of depressive-like symptoms (Covington, III et al., 2011), this interaction between epigenetic factors could provide a method of determining antidepressant efficacy.

Environmental factors

Environmental enrichment (EE) is an experimental paradigm in which animals are group-housed in large cages promoting social interaction, with free access to several environmental stimuli, such as toys and running wheels. Prolonged housing in such conditions exerts antidepressant effects mainly through neuromorphological and neurogenic adaptations, which suggests the involvement of neurotrophins such as BDNF. Accordingly, several weeks of EE can rescue depression-like behaviors, and upregulate hippocampal BDNF expression through hypermethylation of the permissive H3K4 at *Bdnf* P3 and P6, associated with a coherent reduction in repressive methylation of H3K9 at *Bdnf* P4 and H3K27 at *Bdnf* P3 and P4 (Jha et al., 2011; Kuzumaki et al., 2011). Although these modifications have yet to be directly linked to the antidepressant properties of EE, these findings illustrate how epigenetic mechanisms translate environmental cues into long-lasting changes in gene expression. Nevertheless, it is important to note that EE is composed of a multitude of sensorial and social stimuli, combined

with a physical component represented by higher levels of activity and exercise (running wheel).

Originally established in cardiovascular health, voluntary exercise has now attracted great interest in the context of psychiatric disorders because of its numerous beneficial effects on brain health, cognitive function and psychological status (Ma, 2008). For instance, a growing body of evidence now clearly demonstrates the significant effects of exercise on post-stroke depressive symptoms in the early and late stages of recovery (Eng and Reime, 2014). The underlying neurobiological correlates are common with antidepressant treatments and mainly include the BDNF and monoaminergic systems (Ma, 2008). Notably, exercise remained ineffective in alleviating behavioral despair in the forced-swim test in BDNF heterozygous animals, indicating that the physiological levels of BDNF are required for the antidepressant effects of voluntary exercise (Duman et al., 2008). In mice and rats, free access to a running wheel for 1 week increases BDNF levels in the hippocampus and induces a variety of epigenetic alterations. HDAC5, HDAC7, HDAC8, DNMT1, DNMT3a and DNMT3b expression is reduced when compared with sedentary animals (Abel and Rissman, 2013; Gomez-Pinilla et al., 2011) and is associated with a coherent demethylation of *Bdnf* P4 and hyperacetylation of histone H3, but not H4 (Gomez-Pinilla et al., 2011). Following 3 weeks of voluntary running, hippocampal BDNF levels remain higher than in sedentary animals, but a hyperacetylation of histone H4K8 can now be detected (Intlekofer et al., 2013). This epigenetic regulation of *Bdnf* following exercise remains to be directly linked to the antidepressant effects of voluntary exercise. However, it is important to note that this profile of regulation strongly resembles the epigenetic *Bdnf* regulation observed in the hippocampus following imipramine treatment (Tsankova et al., 2006).

Concluding remarks and therapeutic outcomes

Not all individuals are equal when facing adverse life experiences, and while some individuals remain unaffected, others are at greater risk of developing a serious pathological condition such as MDD. As a mediator of environmental influences on gene expression, the epigenome has lent valuable insight into the molecular substrates of inter-individual differences in vulnerability to depression and antidepressant response. The investigation of the epigenetic regulation of *BDNF* has provided valuable understanding into its role in shaping an individual's response to environmental stimuli, stress or antidepressants. Nevertheless, the number of studies taking into consideration such individual differences remains relatively low and further effort is needed to gain additional knowledge in both the vulnerability to depression and antidepressant response. For this reason, a comparison between clinical and pre-clinical data are difficult to perform as, in most cases, human and rodents studies differ in terms of structure and epigenetic marks investigated.

In this review, we focus on the direct epigenetic regulation of *BDNF* in the pathophysiology of depression and in the response to antidepressants, and highlight a pivotal role of the epigenome in determining the individual response to a given stimulus. However, in a therapeutic context, future research will have to overcome several obstacles. First, because the only readily available material in the clinical environment is blood, the validity of serum measurements in reflecting events in relevant brain structures will need to be carefully assessed, which could prove particularly challenging because of the high tissue-specificity of *BDNF* regulation. Second, the candidate profile of epigenetic modifications will need specificity towards depression rather than other neuropsychiatric disorders. Finally, initial individual differences in the epigenome will need to be taken into consideration in order to search for accurate predictors adapted to the patient. Interestingly, some encouraging clinical evidence already exists in the finding that the status of DNA methylation at *BDNF* P4 in depressed individuals with suicidal behavior predicts the subsequent response to classical antidepressant treatment (Kang et al., 2013).

Acknowledgements

The authors would like to thank Samantha Saland for manuscript editing.

Competing interests

The authors declare no competing financial interests.

Author contributions

F.D. and M.K. participated equally in the paper design and outline; F.D. then wrote the first draft. After a few revisions and editing by both authors, the paper was submitted.

Funding

This work was supported by the National Institute of Mental Health (NIMH) [grant numbers R01 MH087583, R21 MH081046 and R21 MH083128 to M.K.], as well as the department of Biomedical Sciences at Florida State University. Deposited in PMC for release after 12 months.

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