Neuroplasticity and memory formation in major depressive disorder: An imaging genetics perspective on serotonin and BDNF

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Abstract. A vast number of imaging studies have demonstrated the impact of serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) on emotion and memory-related networks in the context of Major Depressive Disorder (MDD). Underlying molecular mechanisms that affect the functionality of these networks have been examined in detail in animals and corroborate imaging findings. The crucial role of 5-HT and BDNF signaling in the context of MDD is reflected in the etiologic models of MDD such as the monoamine or neuroplasticity hypothesis as well as in pharmacological models of antidepressant response. While antidepressant drug treatment has been primarily linked to the modulation of emotion-related networks, cognitive behavioral therapy has been implicated in a top-down control of limbic structures. Initially, a simple lack of monoamines or BDNF has been proposed as causal factor of MDD etiology. However, recent findings suggest a much more complex neurobiology emphasizing epistatic and epigenetic mechanisms responsible for structural and functional changes observed in emotion and memory-related brain regions of healthy subjects and MDD patients. In this review, which focuses on neuroimaging studies in the context of MDD, the authors will provide a comprehensive overview of these networks as well as on the specific role of 5-HT and BDNF in their development and function.

Keywords: Neuroimaging, functional magnetic resonance imaging, neuroplasticity, serotonin transporter, memory, learning, epistasis, major depressive disorder, selective serotonin re-uptake inhibitor, tryptophan, SLC6A4, BDNF

1. Introduction

Major Depressive Disorder (MDD) is a clinically heterogeneous disorder of variable course that is characterized by depressive mood, lack of interest, disturbances of appetite, psychomotor function, sleep-wake-cycle, etc. (American Psychiatric Association, 2000). While most symptoms are primarily emotion-related, several cognitive symptoms are considered to be of diagnostic value, including suicidal ideation, rumination as well as a diminished ability to think or concentrate (American Psychiatric Association, 2000). In its clinically deteriorated form, MDD can present itself as "pseudo-dementia", but typically MDD is not considered to be associated with a general impairment of cognitive functioning (Foland-Ross & Gotlib, 2012). However, specific anomalies such as a deficit in cognitive control with regard to the processing of negative stimuli, or an enhanced memory for negatively valenced material are without doubt present (Foland-Ross & Gotlib, 2012). Due to MDD’s denotation as mood disorder, research has primarily focused on emotion-related brain regions, leading to the discovery of anatomical and functional alterations in limbic...
structures such as the anterior cingulate cortex (ACC), the amygdala, the hippocampus, and the orbitofrontal cortex (OFC) (Kupfer et al., 2012; Murray et al., 2011; Phillips et al., 2003a, b; Price & Drevets, 2010, 2012). Apart from their role in emotion processing, some of these structures or interacting brain systems are also involved in cognitive control, learning, or memory formation. Notably, the hippocampus (McGaugh, 2000) and the amygdala (Davis & Whalen, 2001) have been directly related to memory encoding. Others, such as the OFC and ACC, support learning (Hayden et al., 2009; Jones et al., 2012) or mediate a continuously updated prediction of future cognitive demands by retrieving memory content (Sheth et al., 2012). In addition, the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC), which are linked to memory retrieval and cognitive control are important in the regulation of subcortical limbic structures (Koenigs & Grafman, 2009; Mitchell, 2011; Price & Drevets, 2010, 2012).

Both, serotonergic neurotransmission (Homberg & Lesch, 2011; Lesch & Waider, 2012; Murphy, D.L. et al., 2008; Murphy, D.L. & Lesch, 2008) as well as secretion of brain-derived neurotrophic factor (BDNF) (Castren & Rantamaki, 2010; Duman & Monteggia, 2006; Krishnan & Nestler, 2010) have been demonstrated to modulate function and structure of memory and emotion-related brain regions in the context of MDD (Krishnan & Nestler, 2008; Kupfer et al., 2012). Serotonergic effects are predominantly considered to be in line with the "monoamine hypothesis", which postulates a lack of synaptic monoamines in MDD (Delgado, 2000; Hirschfeld, 2000; Nutt, 2008; Ruhe et al., 2007). This model is supported by the clinical efficacy of tricyclic antidepressants and especially selective serotonin re-uptake inhibitors (SSRIs), the current first-line treatment of MDD (Davidson, 2010; Gelenberg, 2010; Kupfer et al., 2012). However, neither the delayed clinical therapeutic response of antidepressants (Bartova et al., 2010) nor the efficacy of non-pharmacological treatment modalities including cognitive behavioral therapy and electroconvulsive therapy can be sufficiently explained by this hypothesis (Castren, 2005). Therefore, alternative models such as the "neuroplasticity hypothesis" of MDD have been developed (Castren & Rantamaki, 2010). Briefly, this hypothesis proposes the presence of dysfunctional neural circuitries in emotion-related brain regions in MDD that originate from defective BDNF secretion (Castren & Rantamaki, 2010). Antidepressants are thought to facilitate the re-modeling of these dysfunctional neural circuitries, which ultimately leads to a relief of depressive symptoms (Masi & Brovedani, 2011). Major support for this hypothesis stems from animal studies that found an increase of synaptic neuroplasticity during antidepressant drug treatment (Castren & Rantamaki, 2010; Masi & Brovedani, 2011; McEwen et al., 2010). Particularly, the antidepressant tianeptine has been a challenge for the monoamine hypothesis since some authors reported an enhanced 5-HT re-uptake or glutamate transmission under tianeptine treatment (McEwen et al., 2010).

Past (pre)clinical and neuroimaging studies have highlighted the importance of the above mentioned brain regions as well as serotonergic neurotransmission and BDNF secretion in the neurobiology of MDD and its treatment. Given the abundance of studies that have been conducted in these fields, we intend to provide an instructive literature overview comprising major research findings. We will outline basic anatomical and functional characteristics of neural circuitries involved in memory formation and emotion processing, which have been related to MDD. Moreover, a brief synopsis on how these neural circuitries are modulated by serotonin (5-HT) transmission, BDNF secretion and their molecular interactions will be provided. Particular attention will be paid to the distinct role of the 5-HT and BDNF signaling in memory formation and molecular mechanisms of learning that contribute to neuroplasticity. Finally, imaging studies examining brain systems level effects of SLC6A4 and BDNF will be discussed.

2. Emotion-related brain regions

Several cortical regions and subcortical structures have been repeatedly reported in studies investigating MDD patients (Price & Drevets, 2010). The following section will briefly introduce their anatomy and function in the light of current concepts of MDD.

2.1. Amygdala

The amygdala is a large nuclear body consisting of several well-studied subnuclei that receive numerous cortical and subcortical inputs (LeDoux, 2000). It is considered a neural hub that is crucially involved in emotional and memory tasks such as facial emotion recognition (Adolphs et al., 1994; Morris, J.S. et al.,...
threat detection (Adolphs et al., 1995; Whalen et al., 1998), and fear conditioning (LaBar et al., 1998; LeDoux, 2007), and consequently determines behavior such as freezing or running for safety in animals. Moreover, the amygdala has been implicated in reward processing, aggression, maternal, sexual, and ingestive behaviors (LeDoux, 2007). With respect to cognitive functioning, it is thought to be involved in attention, perception, and memory formation by modulating the emotional salience of external stimuli (LeDoux, 2007). It is noteworthy that chronic stress exposure has been demonstrated to increase synaptic plasticity and reactivity of the amygdala in contrast to atrophic effects seen in the hippocampus (Pittenger & Duman, 2008; Roozenendaal et al., 2009). Given the important role of stress exposure for mental illness it is not surprising that amygdala dysfunction has been reported in various psychiatric conditions such as schizophrenia, autism, anxiety, and mood disorders (LeDoux, 2007). With respect to MDD, most studies found increased amygdala reactivity in patients with a concurrent depressive episode (Drevets et al., 2008a). Moreover, biased attention towards negative stimuli has repeatedly been shown in MDD and has been related to amygdala dysfunction (Browning et al., 2010; Everaert et al., 2012; Kupfer et al., 2012). Interestingly, the amygdala also alters anterior hippocampal activity and thereby indirectly affects memory formation (Disner et al., 2011; Fell & Axmacher, 2011; LaBar & Cabeza, 2006). However, results of morphometric studies measuring amygdala volume in MDD have been inconclusive so far (Bora et al., 2012; Drevets, 2003; Hamilton et al., 2008). Disease chronicity as well as medication status have been considered as confounding factors (Bora et al., 2012; Hamilton et al., 2008).

2.2. Cingulate cortex

The cingulate cortex (CC) comprises four anatomically distinct regions: anterior cingulate (ACC), midcingulate (MCC), posterior cingulate (PCC), and retrosplenial cortex (RSC), encompassing two subregions within each region (Palomero-Gallagher et al., 2009; Vogt, 2009). In the context of emotion and depression research, however, most attention has been paid to the subgenual ACC (sACC) and perigenual ACC (pACC), which are implicated in emotional and autonomic integration. Most importantly, the sACC has been related to processing of negative mood (Mayberg et al., 1999), deep brain stimulation (Holtzheimer et al., 2012; Mayberg et al., 2005), electroconvulsive (McCormick et al., 2007) as well as cognitive behavioral therapy (DoRebeis et al., 2008; Dosner et al., 2011). This notion has recently been supported by a publicly available meta-analytical tool that provides reverse inference of the importance of the ACC in functional neuroimaging studies thereby highlighting the relative specificity of this region for depressive mood (Yarkoni et al., 2011). Apart from that, the ACC has also been studied in the context of schizophrenia and pain (Lederbogen et al., 2011; Vogt, 2005). Furthermore, the ACC is heavily interconnected with the amygdala and other prefrontal cortical areas (Pizzagalli, 2011), thereby mediating the extinction of aversive memories (Livneh & Paz, 2012; Margulies et al., 2007). Accordingly, neuroimaging literature underscoring the importance of the amygdala-ACC circuitry has attracted significant attention in emotion research (Drevets et al., 2008b; Pezawas et al., 2005). With regard to clinical studies, sACC volume reductions (Cotter et al., 2001; Ongur et al., 1998; Yucel et al., 2008) and activation increases (Drevets et al., 1997) have been amongst the first neurobiological findings reported in samples of MDD patients (Drevets et al., 2008b). Similar morphometric results have also been found in subjects with a family history of mood disorders (Boes et al., 2008; Hajek et al., 2008; Ongur et al., 1998).

2.3. OFC

The orbitofrontal cortex (OFC) predominantly receives inputs from sensory brain regions and is heavily interconnected with emotion- and memory-related neural structures such as amygdala, ventral striatum, and ACC. Neuroimaging studies have further supported a clear distinction between medial and lateral as well as anterior and posterior portions of the OFC (Kringelbach & Rolls, 2004). In general, it is implicated in stimulus-reinforcer associations, goal-directed behavior, and reward conditioning (Kringelbach, 2005; Rolls & Grabenhorst, 2008). Furthermore, OFC and ACC share important anatomical connections and functional similarities and are suggested to be involved in similar domains such as reinforcement-guided decision making, emotion and social behavior (Rushworth et al., 2007). With respect to MDD, OFC gray matter volume loss and increased metabolism in medial and lateral posterior regions have been reported (Drevets et al., 2008a).
2.4. Hippocampus

The hippocampus consists of two main portions: the dentate gyrus and the Ammon’s horn. The latter is histologically divided into four subregions CA1–CA4 (cornu ammonis). The hippocampus receives efferents from parahippocampal, entorhinal, and perirhinal cortices and is interconnected with several cortical regions including visual and auditory association areas as well as the prefrontal and parietal cortex. The subiculum of the hippocampus subserves as an output system, predominantly targeting cortical areas. Its tight interconnections with the amygdala and the OFC reflect the importance of the hippocampus in emotion processing (Rolls, 2007).

However, the hippocampus is best known for its prominent role in explicit memory formation (McGaugh, 2000; Rolls & Kesner, 2006) as well as homeostatic adaptation to stressful environmental conditions (Kim, J.J. & Diamond, 2002; Lopez et al., 1999). With respect to MDD research, hippocampal volume reductions and functional alterations have repeatedly been found in patients (Bremner et al., 2000; Colla et al., 2007; Duman & Aghajanian, 2012; Eisch & Petrik, 2012; Masi & Brovedani, 2011). These findings are in accordance with a known dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis in MDD patients (de Kloet et al., 2005), which specifically affects the hippocampus due to its high sensitivity to glucocorticoid toxicity (McEwen, 2001). Moreover, hippocampal alterations have been related to memory deficits in MDD patients (Campbell & Macqueen, 2004; Frodl et al., 2006).

2.5. DLPFC and VLPFC

The lateral prefrontal cortex anatomically comprises the ventrolateral (VLPFC; BA 44, 45, 47) and dorsolateral (DLPFC; BA 9, 46) PFC, which receives direct afferents from the mediodorsal thalamic nucleus together with the remaining PFC. The DLPFC and VLPFC are characterized by their dense projections to subcortical regions including limbic structures (Leh et al., 2007), thereby exerting a top-down control. It is noteworthy that the lateral PFC also receives indirect inputs from several areas including visual areas, OFC as well as subcortical regions such as the amygdala and hippocampus, among others (Fuster, 2001). DLPFC and VLPFC are responsible for executive functions and the processing of external stimuli in terms of their relevance for behavioral changes (Sakagami & Pan, 2007). Together with the ACC, the VLPFC orchestrates the cognitive control of emotions, via both, bottom up and top down regulation (Ochsner et al., 2004; Price & Drevets, 2010). It is of clinical relevance that the modulation of these brain areas is thought to be crucial for the efficacy of cognitive behavioral therapy in MDD patients (Disner et al., 2011). Interestingly, the left VLPFC has foremost been implicated in cognitive control of negative and amygdala-driven emotion, whereas the right VLPFC has been associated with emotion-related motor inhibition (Levy & Wagener, 2011). Moreover, the VLPFC and the amygdala are part of a brain system that monitors and selects responses to threats (Hariri et al., 2003b). Contrarily, the DLPFC has predominantly been demonstrated to be involved in planning (Crescimonti et al., 2012), action selection (Rowe et al., 2000) and working memory (Goldman-Rakic, 1997). It is therefore considered to be “a place, where the past and the future meet”, because it creates memories from sensory inputs and it assembles a motor plan of action (Fuster, 2001). Left PFC lesions have been more frequently associated with depression than with contralateral brain lesions (Morris, M.K. et al., 1992). Additionally, decreased working memory performance in MDD patients has been related to hypoactivity and gray matter volume reduction in these areas (Goldstein et al., 2011). The latter finding is thought to result from a loss of dendritic spines, dendrites and synapses, due to decreased expression of synapse-related genes (Kang et al., 2012). Furthermore, limited evidence suggests that SSRI treatment might normalize hypoactivity (Fales et al., 2009) and gray matter loss (Kang et al., 2012) in both regions.

3. Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is primarily found in the gastrointestinal tract (Dhasmana et al., 1993), the blood platelets (Hranilovic et al., 1996), and in the brain (Barnes & Sharp, 1999). It is actively removed from extracellular space by the transmembrane 5-HT transporter protein (5-HTT), followed by monoaminooxidase-A (MAO-A) intracellular degradation (Youdim et al., 2006). Neuronal serotonergic cells project to virtually every brain area (Gaspar et al., 2003; Kyasova & Gaspar, 2011). However, 5-HTT availability is not equally distributed throughout the brain and shows high densities in subcortical limbic...
structures (e.g., hippocampus, amygdala) (O’Rourke & Fudge, 2006; Saulin et al., 2012) and cortically along the midline of the brain (Kranz et al., 2010; Yokoyama et al., 2010), and specifically in the sACC (Varnas et al., 2004). This is also supported by publicly available human gene expression maps of SLC6A4 (Hawrylycz et al., 2012). While neural 5-HTTs are terminating synaptic 5-HT actions, postsynaptic 5-HT receptors are initiating an intracellualr and mostly G-protein coupled cascade that may lead to inhibitory or excitatory neural responses (Hoyer et al., 2002). Up to now, seven 5-HT receptor families and a number of specific subtypes have been characterized (Nichols & Nichols, 2008). Similar to 5-HTT, 5-HT receptors are highly expressed in cortico-limbic regions, specifically hippocampus, ACC, and entorhinal cortex (Bose et al., 2011; Palomero-Gallagher et al., 2009), and accordingly, correlate to some degree with regional 5-HTT availability (Banerjee et al., 2007; Bose et al., 2011; Nichols & Nichols, 2008). In the context of MDD research, most attention has been paid to the 5-HT1A receptor, because it is thought to mediate antidepressant drug action (Bortolozzi et al., 2012; Lemonde et al., 2004; Melzner et al., 2004; Richardson-Jones et al., 2010; Spindelegger et al., 2009) as well as behavioral phenotypes related to MDD (Blier & Ward, 2003). It is noteworthy that 5-HT1A receptors can be found post-synaptically as well as pre-synaptically thereby controlling 5-HT transmission as auto-receptors (Albert et al., 2011; Lundberg et al., 2007; Puig & Gullidge, 2011).

Serotonin signaling modulates neuronal processing of crucial vegetative and emotional functions including mood, anxiety, appetite, sexual drive and function, and sleep-wake cycle (Canli & Lesch, 2007) as well as executive functions and memory (Puig & Gullidge, 2011). Furthermore, 5-HT is a neurodevelopmental factor (Gaspar et al., 2003; Gross & Hen, 2004; Lesch & Waider, 2012), relevant for the development of glutamatergic projection neurons (Dooley et al., 1997), migration of serotonergic and non-serotonergic cells (Riccio et al., 2009), and the modulation of fetal forebrain development via a transient placental source (Bonnin et al., 2011). Interestingly, 5-HTT is additionally expressed in non-serotonergic neurons during early-life stages thereby promoting these developmentental effects (Gaspar et al., 2003). On a behavioral level, it has been demonstrated that a transient pharmacological inhibition of 5-HTT in early-life alters emotional behavior in adult mice (Ansorge et al., 2004). Additionally, 5-HTT is also implicated in neuroplasticity in adults (Lesch & Waider, 2012) and animal work has demonstrated that SSRI-induced neuroplasticity can be blocked by drugs which decrease neural activity (Maya Vetencourt et al., 2008). Apart from that, reduced synaptic 5-HT availability induced by acute tryptophan depletion (ATD) has been associated with depressed mood in human adults (Ruhe et al., 2007), specifically in subjects at high risk for MDD (Feder et al., 2011; Neumeister et al., 2004). Similarly, ATD has been found to increase anxiety but not fear (Robinson et al., 2012). Compellingly, memory processes such as fear conditioning have been reported to be attenuated (Hindi Attar et al., 2012), which contrasts with findings in other memory domains including autobiographical (Haddad et al., 2009) and episodic memory (Ruhe et al., 2012). Eventually, ATD has been linked to alterations of stimulus-reward association (Rogers et al., 1999), emotional (Merens et al., 2008), reversal (Murphy, F.C. et al., 2002), and verbal learning (Evers et al., 2005).

Since the 5-HTT is the “bottle-neck” for the termination of neural 5-HT actions, it is not surprising that its pharmacological inhibition by SSRIs emerged as first-line treatment of MDD (American Psychiatric Association, 2010). Maximal synaptic 5-HT concentrations occur immediately after acute SSRI administration and behavioral changes such as increased anxiety (Browning et al., 2007; Burghardt et al., 2007) or even suicidal behavior (Hetrick et al., 2007) have been reported. However, clinically observable antidepressant effects such as decreas in anxiety and a normalization of depressive mood do not occur before the second week of treatment (Kupfer et al., 2012). Contrarily, on a brain level, 5-HT-induced neural activation can already be detected ahead of the clinical response with fMRI (Klomp et al., 2012). Maximal synaptic 5-HT concentrations occur immediately after acute SSRI administration and behavioral changes such as increased anxiety (Browning et al., 2007; Burghardt et al., 2007) or even suicidal behavior (Hetrick et al., 2007) have been reported. However, clinically observable antidepressant effects such as decrease in anxiety and a normalization of depressive mood do not occur before the second week of treatment (Kupfer et al., 2012). Contrarily, on a brain level, 5-HT-induced neural activation can already be detected ahead of the clinical response with fMRI (Klomp et al., 2012). Maximal synaptic 5-HT concentrations occur immediately after acute SSRI administration and behavioral changes such as increased anxiety (Browning et al., 2007; Burghardt et al., 2007) or even suicidal behavior (Hetrick et al., 2007) have been reported. However, clinically observable antidepressant effects such as decrease in anxiety and a normalization of depressive mood do not occur before the second week of treatment (Kupfer et al., 2012). Contrarily, on a brain level, 5-HT-induced neural activation can already be detected ahead of the clinical response with fMRI (Klomp et al., 2012).
been found for the so-called LA allele, which contrasts the LG allele that is more similar to the S allele (Bevilacqua & Goldman, 2011; Hu & Russek, 2008). Frequencies of the S allele vary dramatically between ethnicities, with about two thirds of S allele carriers of European ancestry and significantly higher numbers in Asian populations (Kunugi et al., 1997). With regard to behavioral correlates of 5-HTTLPR, predominately increased neuroticism in S allele carriers has been reported (Lesch et al., 1996; Schinka et al., 2004; Sen et al., 2004; Shifman et al., 2008), although effect sizes appear to be small on a behavioral level (Murphy, S.E. et al., 2012; Shifman et al., 2008). While neuroticism is only considered to be a risk factor for MDD (Kendler et al., 2004), the development of the full-blown picture of MDD has been described in S allele carriers in the presence of environmental adversity (Caspi et al., 2003). This gene-environment interaction has been replicated in several studies (Eley et al., 2004) along with comparable results in PTSD investigating effects of childhood adversity (Xie et al., 2012). However, some studies failed to find a 5-HTTLPR-environment interaction (Levinson, 2006). Given this inconsistency, meta-analytical studies have been conducted, some of which did not support such an effect (Munafo et al., 2009; Risch et al., 2009). These findings have been challenged by a recent meta-analysis that identified the presence of a selection bias within previous meta-analyses, thereby supporting the original finding of 5-HTTLPR-environment interactions (Karg et al., 2011). This conclusion should be corroborated by future animal work investigating the molecular mechanisms of such a gene-environment interaction (Alasaari et al., 2012; Caspi et al., 2010; Jasinska et al., 2012; Miller et al., 2012). 5-HTTLPR genotyping has also been linked to SSRI treatment response in several pharmacogenetic association studies (Serretti et al., 2010), however conflicting results exist (Rabl et al., 2010). Apart from replicated 5-HTTLPR effects on limbic structures, evidence from recent animal studies hints at 5-HTTLPR mediated effects on prefrontal executive areas that show beneficial impacts of the S allele on cognitive processes such as reversal learning (Finger et al., 2007; Homberg & Lesch, 2011). This finding might also serve as a possible explanation, why the common S allele has been selected by evolutionary pressure (Homberg & Lesch, 2011).

Over the past decade, numerous functional and anatomical neuroimaging studies have investigated 5-HTTLPR brain effects by applying an “imaging genetics” approach (Scharinger et al., 2010) (Fig. 1). Originally, healthy S allele carriers have been found to exhibit an exaggerated amygdala response induced by the presentation of fearful faces (Hariri et al., 2002), a finding that has repeatedly been replicated (Scharinger
Fig. 1. Overview of functional and structural 5-HTTLPR and Val66Met BDNF effects in healthy subjects reported by imaging genetics studies. 5-HTTLPR (S allele): S allele > L/L genotype of 5-HTTLPR; Val66Met BDNF (Met): Met allele > Val/Val genotype of Val66Met BDNF; Epistasis: Epistasis between \textit{SCL6A4} and \textit{BDNF}; arrow direction indicates increase or decrease of BOLD signal or gray matter volume; arrow thickness indicates number or significance of study results; vertical double arrows indicate significant epistasis effects; horizontal double arrows indicate inconclusive or lacking results. Gray arrows represent results of structural studies and white arrows represent results of functional studies.

et al., 2010). Similarly, increased amygdala activation during rest has been found in S allele carriers (Canli et al., 2005; Rao et al., 2007; von dem Hagen et al., 2011). Meta-analytic data suggest that gene effects of this kind are overall smaller than originally anticipated (Murphy, S.E. et al., 2012). Furthermore, functional connectivity studies have highlighted a reduced coupling of amygdala and sACC activity in 5-HTTLPR S allele carriers (Heinz et al., 2005; Lemogne et al., 2011; Pezawas et al., 2005; Roiser et al., 2009; Shah et al., 2009), while one study failed to detect a genotype-driven alteration of amygdala-sACC connectivity (O’Nions et al., 2011). This reduction of amygdala-sACC coupling seems to be primarily driven by developmental effects of 5-HTTLPR on sACC volume (Frodl et al., 2008a; Jedema et al., 2010; Migliarini et al., 2012; Pezawas et al., 2005; Selvaraj et al., 2011), which accords with behavioral changes such as increased neuroticism (Cremers et al., 2010; Haas et al., 2007; Pezawas et al., 2005). Previous studies have shown that a reduction of amygdala-sACC coupling leads to dis-inhibition of a feedback loop resulting in increased amygdala activity (Hariri et al., 2002; Heinz et al., 2005; Munafò et al., 2008; Pezawas et al., 2005). Additionally, imaging genetics studies have examined 5-HTTLPR effects on brain areas involved in executive functions (Homberg & Lesch, 2011). Results show increases in DLPFC activity in S allele carriers during a working memory task (Jonassen et al., 2012) and in VLPFC activity during cognitive appraisal of emotions (Firk et al., 2012; Surguladze et al., 2008). Besides, hippocampal activation increases have been reported during threat anticipation (Dreabant et al., 2012; Smolka et al., 2007), whereas volumetric reductions have been observed in healthy S-allele carriers (Frodl et al., 2008a) in this region. Yet, patient studies revealed opposing results and showed hippocampal volume loss for L homozygote patients (Frodl et al., 2004; Frodl et al., 2008b), which is not surprising given the role of stress-related methylation (Alasaari et al., 2012; Kinnally et al., 2010; van IJzendoorn et al., 2010). Finally, supportive evidence exists for an increased vulnerability of the hippocampus with regard to environmental adversity in S allele carriers (Canli et al., 2006; Frodl et al., 2010).
4. BDNF

Human brain tissue expresses four different neurotrophins (Lu, B. et al., 2005). The most extensively investigated neurotrophin, BDNF, exhibits its highest expression in the hippocampus, amygdala, neocortex, and the cerebellum (Lessmann et al., 2003). BDNF is an important neurodevelopmental factor and essential for cholinergic, GABAergic, dopaminergic, as well as serotonergic neuronal development and survival. This highlights its tight relationship to neuropsychiatric diseases such as schizophrenia, mood disorders, Huntington’s disease, Alzheimer’s disease etc. (Autry & Monteggia, 2012). The BDNF protein is coded by a single gene (BDNF), which undergoes a complex transcription process before its mature form is made available. Its expression is activated and regulated by activity- and calcium-sensitive transcription factors including the cAMP response-element binding protein (CREB) (Autry & Monteggia, 2012).

The BDNF protein itself evolves from its precursor pro-BDNF and is synthesized in the endoplasmic reticulum. Thereafter, it is packed into neuronal vesicles and forwarded to axonal terminals or dendrites, where it is released in an activity-dependent manner (Lu, B. et al., 2005). Notably, selective expression and secretion of pro-BDNF and mature BDNF are cell type dependent and activate two different signaling pathways, where pro-BDNF has been found to induce apoptosis by selectively activating the low-affinity p75 neurotrophin receptor (p75NTR). Mature BDNF, on the other hand, promotes neurotrophic and anti-apoptotic effects by binding to the high-affinity tropomysin-related kinase receptor type B (TrkB) receptor, located at pre- as well as postsynaptic sites (Autry & Monteggia, 2012). The independent reciprocal effects of pro- and mature BDNF have been called ‘yin & yang’ principle (Lu, B. et al., 2005) since both constitute a potential mechanism for essential structural and functional alterations during development but also in the context of neuroplasticity in the adult brain (Autry & Monteggia, 2012; Poo, 2001). Moreover, BDNF has also been implicated in the biological mechanism of long-term memory formation (Barco et al., 2005). While mature BDNF has been associated with long-term potentiation (LTP), an electrophysiological correlate of long-term memory consolidation and learning, pro-BDNF signaling has been related to long-term depression (LTD) representing memory extinction and impairment (Autry & Monteggia, 2012; Lu, B. et al., 2005; Lu, Y. et al., 2008; Malenka & Bear, 2004).

In line with these molecular neuroplasticity effects, altered regional BDNF concentrations have been suggested to impact on episode onset, re-occurrence, and treatment response of mood disorders via sensitization and kindling-like mechanisms (Post, 2007). BDNF alterations were further found in the reward and motivation regions of the brain such as the nucleus accumbens (NAcc) in mice that have been exposed to social defeat stress (Krishnan et al., 2007). These findings are in accordance with postmortem data of NAcc brain tissue in depressed humans (Krishnan et al., 2007). Eventually, it has already been recognized that hippocampal BDNF transcription significantly decreases during stress, which is accompanied by a reduction of BDNF blood levels, specifically in MDD patients (Bartova et al., 2010; Molendijk et al., 2011; Schmidt et al., 2011). While some authors consider observed BDNF alterations to be a state feature reflecting biological changes accompanying acute stress (Bocchio-Chiavetto et al., 2010; Molendijk et al., 2011), others suggest that such alterations rather represent a trait marker of MDD (Piccini et al., 2008). Complementary evidence stems from antidepressant drug treatment and electroconvulsive therapy studies in animals that found increased BDNF expression (Duman et al., 2000), whereas human studies found a normalization of BDNF plasma levels (Brunoni et al., 2008) that predicted antidepressant treatment outcome (Dreimuller et al., 2012). This modulatory effect of BDNF on antidepressant drug response is supported by animal studies that demonstrated its dependence on BDNF genotypes in BDNF-knockout mice models (Saarelainen et al., 2003). Furthermore, intra-cerebral BDNF infusion in animals has shown to facilitate the efficacy of antidepressants (Koiriesek et al., 2008). However, several animal and human studies have not been able to detect or replicate such effects (Groves, 2007; Schmidt et al., 2011). Therefore, final conclusions with regard to the validity of the neuroplasticity hypothesis of depression and its biological mechanisms cannot be drawn at this moment. Hence, further evidence is needed, before plasma BDNF levels can possibly be used for clinical applications such as diagnostics or personalized treatment regimes (Hashimoto, K., 2010; Kapur et al., 2012; Nagahara & Tiusynski, 2011). Recent research indicates that the relationship between BDNF secretion and clinically depressive phenotypes is far more complex than originally anticipated.
A genomic deletion of a region including BDNF assessed by a microarray study has been described as highly penetrant, and hemizygosity of BDNF has been found to contribute to variable psychiatric phenotypes including anxiety, behavioral, and mood disorders (Ernst et al., 2012). However, previous studies have predominantly focused on investigating functional polymorphisms within BDNF, and several genetic variants of BDNF have been identified so far (Licinio et al., 2009). Notwithstanding, only Val66Met BDNF, a substitution polymorphism in the 5’ pro-domain of BDNF, has been thoroughly explored. The Met allele of Val66Met BDNF has clearly been linked to defective BDNF signaling on a cellular level showing reduced intracellular trafficking to distal dendrites, failure to distribute BDNF to secretory granules, and lower depolarization-induced secretion (Chen, Z.Y. et al., 2006), whereas most human fMRI studies ported Met allele induced amygdala reactivity (Chen, Z.Y. et al., 2012). Moreover, only one animal study supported Val66Met BDNF effects on working (Hansell et al., 2007) or verbal memory (Matsuo et al., 2009) as well as other memory-related tasks (Karnik et al., 2010). This is further supported by a recent meta-analysis, which found lacking evidence for Val66Met BDNF mediated impairment in memory processing, general cognitive ability, cognitive fluency, visual processing, and executive functioning (Mandelman & Grigorenko, 2012).

In contrast, other limbic structures have less consistently been related to differential effects of BDNF genotypes. While the majority of studies found no evidence for amygdala volume reductions (Fredri et al., 2007; Gerritsen et al., 2012; Matsuo et al., 2009; Pezawa et al., 2004; Schottfeld et al., 2009), few authors observed amygdala volume loss in healthy Met allele carriers (Gatt et al., 2009; Sublette et al., 2008). Similarly, conflicting results exist with respect to amygdala function and the specific role of Val66Met BDNF genotypes (Gasic et al., 2009; Montag et al., 2008; Wang et al., 2012). Moreover, only one animal study supports Met allele induced amygdala reactivity (Chen, Z.Y. et al., 2006), whereas most human fMRI studies considered to be conclusive (Hajek et al., 2012; Kambeitz et al., 2012), no conclusions can be drawn from patient studies yet (Scharinger et al., 2010). This might be due to diagnostic heterogeneity of MDD, disease course and medication effects (Bigos & Weinberger, 2010), and to a lesser degree to stress-related epigenetic effects (Unternaehrer et al., 2012). These findings are further underlined by studies reporting BDNF interactions with diagnosis (Koolschijn et al., 2010), personality (Joffe et al., 2009), and life events (Gatt et al., 2009). Moreover, Val66Met BDNF genotypes have shown to affect hippocampal function within several memory paradigms (Egan et al., 2003; Hariri et al., 2003a; Hashimoto, R. et al., 2008; Schottfeld et al., 2009). On a behavioral level, particularly Met carriers of Val66Met BDNF have shown reductions in episodic memory (Dempster et al., 2005; Egan et al., 2003; Hariri et al., 2003a), working memory (Gatt et al., 2009; Richter-Schmidinger et al., 2011), and verbal learning (Cathomas et al., 2010; Goldberg et al., 2008; Ho et al., 2006; Schottfeld et al., 2009). These findings are in line with animal studies highlighting a specific role of BDNF in the preservation of hippocampal functional integrity that is related to memory processing and depressive mood (Heldt et al., 2007; Molendijk et al., 2012b; Monteggia et al., 2004; Saxe et al., 2006). Yet, some studies failed to detect Val66Met BDNF effects on working (Hansell et al., 2007) or verbal memory (Matsuo et al., 2009) as well as other memory-related tasks (Karnik et al., 2010). This is further supported by a recent meta-analysis, which found lacking evidence for Val66Met BDNF mediated impairment in memory processing, general cognitive ability, cognitive fluency, visual processing, and executive functioning (Mandelman & Grigorenko, 2012).

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report no influence of Val66Met BDNF on amygdala activation (Egan et al., 2003; Hariri et al., 2003a; Hashimoto, R. et al., 2008; Schofield et al., 2009). However, Val66Met BDNF seems to shape amygdala-dependent extinction learning (Soliman et al., 2010) and memory formation for biologically salient stimuli (van Wingen et al., 2010). Additionally, limited evidence is available suggesting that Val66Met BDNF impacts on ACC structure (Gerritsen et al., 2012) and function (Soliman et al., 2010). Furthermore, no conclusions can be currently drawn from imaging studies investigating white matter tract connectivity (Chiang et al., 2011; Montag et al., 2010). Eventually, pilot data suggest that Val homoygotes exhibit stronger resting state functional connectivity between PCC and pre-cuneus, a neural circuitry involved in episodic memory retrieval (Jang et al., 2012).

5. Complex interactions of SLC6A4 and BDNF

Acute episodes of MDD are frequently triggered by adverse life-events (Kupfer et al., 2012). Apart from that, MDD is undoubtedly heritable, given the known accumulation of cases in families (Kupfer et al., 2012; Wong & Licinio, 2001). However, the identification of the genetic origin of MDD is challenging since single genetic variants explain only a very small proportion of the variance of this psychiatric entity (Rabl et al., 2010). Therefore, it is necessary to consider the full complexity of gene effects and their linkage to psychopathology (Meyer-Lindenberg, 2012). Examples depicting the biological complexity of clinical phenotypes are gene-environment interactions, pleiotropy, imprinting, epistasis, epigenetics, heterogeneity, and polygenicity (Badcock & Crespi, 2008; Goldman et al., 2005; Houston et al., 2013; Levenson & Sweat, 2005; Moore et al., 2013; Puckett & Lubin, 2011; Skipper, 2011; Sultan & Day, 2011; Tsankova et al., 2005; Houston et al., 2013; Levenson & Sweatt, 2003). This finding corroborates the hypothesis that SLC6A4 x BDNF interactions specifically affect negative emotion processing (Pezawas et al., 2008). This finding also suggests that SLC6A4 x BDNF interactions specifically affect negative emotion processing (Pezawas et al., 2008). However, opposing imaging results exist for functional (Wang et al., 2012) as well as for structural studies (Cole et al., 2011). Notably, other imaging modalities such as manual tracing or 3D-shape analysis have been used in this structural study (Cole et al., 2011), which differs from the original report utilizing voxel-based morphometry (Pezawas et al., 2008).

Another complex genetic mechanism, the gene-environment (GxE) interaction, has been also studied...
arguing that genetic variability of more elaborated model has been recently proposed to antidepressants in animals (Yu et al., 2012). A been shown to alter stress vulnerability and response to antidepressants in animals (Yu et al., 2012). A more elaborated model has been recently proposed arguing that genetic variability of SLC6A4 resulting in individual 5-HT re-uptake efficiency alters the balance in the amygdala-ventromedial prefrontal cortex (VMPFC)-dorsal raphe (DR) circuitry underlying stressor reactivity and emotion regulation (Jasinska et al., 2012). The repeated exposure to uncontrollable stressors in MDD patients leads then to hyperreactivity to stress in the amygdala and hyporeactivity of the regulation of emotion in the VMPFC, which is mediated by activity-dependent neuroplasticity (Jasinska et al., 2012). Thus, neuronal S-HTTLPR effects depend on exposure to stressors (Jasinska et al., 2012), which is in accordance with clinical studies that reported 5-HTTLPR S allele carriers to be at an increased risk for depressive symptoms including suicidal ideation in the presence of environmental adversity (Caspi et al., 2003). It has further been pointed out that 5-HTTLPR x stress interaction depends on age or developmental stage (Lindell et al., 2012). Since neuroplastic mechanisms are involved in the hardwiring of 5-HTTLPR x environment interactions as mentioned above (Jasinska et al., 2012), genetic variability of BDNF might further be considered as a modifying factor (Grabe et al., 2012; Yu et al., 2012). Accordingly, three-way interactions between SLC6A4, BDNF, and environmental adversity have been reported in S and Met allele carrying children that exhibited the highest risk of depression (Aguilera et al., 2009; Kaufman et al., 2006; Kim, J.M. et al., 2007; Wichers et al., 2008). Although no such effects were found by a recent large-scale study (Nederhof et al., 2010b), Effortful control is thought to foster adaptive action by suppression of a dominant response in favor of a more goal-directed behavior and may thereby protect individuals against anxious inhibition and focus on their own distress (Oldehinkel et al., 2011). In terms of cognitive symptoms, healthy BDNF Val/Val and 5-HTTLPR S allele carriers developed more rumination while experiencing stressful life events (Clasen et al., 2011). Moreover, S homozygotes presented reduced cognitive reactivity, a decrease in dysfunctional thinking in the presence of at least one BDNF Met allele (Wells et al., 2010).

Today study results investigating SLC6A4 and BDNF epistasis are rather conclusive on an animal level, but still preliminary on a clinical level. This is not surprising given the tight and complex coupling between SLC6A4, BDNF, and environmental factors. Hence, inconsistencies with regard to human studies related to BDNF and SLC6A4 epistasis are likely caused by either lacking or varying control of environmental factors.

6. Conclusion

Over the past decades depression research has made great strides forward resulting in numerous models of its putative underlying neurobiological mechanisms including the monoamine deficiency and neuroplasticity hypothesis (Krishnan & Nestler, 2010; Kapfer et al., 2012; Wong & Licinio, 2001). However, its clinical translation is still in its infancy (Berton et al., 2012; Insel, 2012). Major reasons for the encountered difficulties include suboptimal animal models and the purely descriptive operationalization of MDD, which likely comprises various biologically heterogeneous pathological entities (Insel, 2012; Pezawas & Meyer-Lindenberg, 2010). Nevertheless, neuroimaging studies have been able to identify distinctive brain circuitries related to MDD and imaging genetics studies accomplished to trace subtle effects of candidate genes such as SLC6A4 and BDNF on these circuitries (Buckholtz & Meyer-Lindenberg, 2012; Scharinger et al., 2010). Moreover, substantial efforts have been undertaken by large gene-discovery consortia such as ENIGMA, ADNI, or IMAGEN that provide imaging genetics results collected in large samples (Novak et al., 2012; Potkin et al., 2009; Schumann et al., 2010; Stein et al., 2012; Whelan et al., 2012). In contrast, complex genetic models such as epistasis or haplotype analyses that exhibit larger effect sizes have only been employed in few studies (Code et al., 2011; Meyer-Lindenberg & Weinberger, 2006;
Pezawas et al., 2008; Wang et al., 2012). Thus, future research should facilitate the investigation of epistasis and haplotypes, an approach that is also lacking in current genome-wide association (GWA) imaging genetics studies (Pezawas & Meyer-Lindenberg, 2010). Therefore, it is not surprising that no converging findings emerged in genome-wide MDD research so far (Demirkan et al., 2011; Sullivan et al., 2009; Wray et al., 2012), which has been quantified by a recent meta-analysis (Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2012). Biological heterogeneity and low heritability of the MDD phenotype are putative causes, which might have ultimately driven these inconsistencies (Wray et al., 2012). Furthermore, given the acknowledged interaction between environmental adversity and genotype (Caspi et al., 2003), MDD is currently considered as a multifactorial disorder originating from both, environmental as well as genetic factors. So far, study results indicate a substantial influence of SLC6A4 and BDNF on emotion and memory-related brain regions. While emotion regulation seems to provide a direct link to mood disorders, it is less elaborated how structural and functional alterations in memory networks impact on the clinical phenotype of MDD. Clearly, the serotonergic and neurotrophic system impact on neuroplasticity, specifically, in neural domains involved in learning and memory formation. Moreover, both are also fundamental to the adaptation to environmental adversity and are therefore possible components in the etiology of mood disorders. Thus, addressing the complexity of the underlying neurobiology by examining single gene effects, epistasis, and environmental factors in human neuroimaging studies would presumably enrich the clinical value of study results in MDD research. Unfortunately, this comprehensive research strategy adds further sophistication to clinical study designs. Also, it calls for considerably larger sample sizes of neuroimaging studies than typically needed. Epigenetics is another emerging area that promises a better understanding of the translation of environmental factors into molecular signaling pathways that ultimately impact on the development and function of neural circuitries (Badcock & Crespi, 2008; Houston et al., 2013; Levenson & Sweatt, 2005; Moore et al., 2013; Puckett & Lubin, 2011; Skipper, 2011; Sultan & Day, 2011; Tsankova et al., 2007). However, while significant progress has already been made in animal experiments, results in human neuroimaging studies that clinically validate these findings are still scarce (Wiers, 2012). Apart from studies that have been able to associate BDNF and SLC6A4 with clinical phenotypes as well as with neural structure and function, both genes have successfully been linked to other ‘phenotypes’ such as antidepressant drug response and tolerability within pharmacogenomic association studies (Rabl et al., 2010). However, only very few pilot studies have applied an imaging genetics approach to drug treatment studies yet (Rabl et al., 2010). Such a pharmacological imaging genetics strategy utilizing known intermediate imaging phenotypes would foster the neurobiological understanding of antidepressant drug response and tolerability, thereby paving the way for the development of personalized treatments.

Summing up, a vast number of clinical studies demonstrated the impact of SLC6A4 and BDNF on neural circuitries related to MDD in emotion and memory-related networks. Molecular and animal studies have suggested that biological mechanisms are much more complex than originally anticipated, including epistasis and epigenetics. However, the clinical translation and its possible use for diagnostics and treatment have not been carried out yet. Moreover, a brain systems level understanding of antidepressant drug response and its genetic underpinnings is still lacking and should be addressed in future studies. Finally, we suggest the investigation of the specific role of executive networks in the pathobiology of MDD with imaging methods and its genetic determinants. This would not only contribute to a more thorough knowledge of affected neural networks in MDD, but also provide new approaches in the development of new pharmacological and psychotherapeutic strategies in the treatment of MDD.

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References


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