

TOWARDS A NEUROIMAGING BIOMARKER OF DEPRESSION VULNERABILITY

Abstract

Major depressive disorder (MDD) is a pervasive and debilitating illness, with a recurrent course and chronic prognosis. Although effective treatments for MDD exist, there is a pressing need to characterize relapse vulnerability in order to design effective prophylactic care. To date, heterogeneity within depression neuroimaging research has made it difficult to establish a reliable biomarker of disorder susceptibility. In this paper, we review neuroimaging evidence for the assessment of MDD vulnerability, theorizing that current findings can be broadly distinguished between those indicating the presence of depressive episodes and those indicating MDD vulnerability during symptom remission. We argue that unlike the amygdala hyperactivity and prefrontal hypoactivity observed during MDD episodes, prefrontal hyperactivity may be a characteristic of dysphoric cognition during symptom remission that indicates MDD vulnerability and relapse risk. Drawing on current research of normative emotion regulation, we describe a potential test of MDD vulnerability, employing emotional challenge paradigms that induce cognitive reactivity - the increased endorsement of negative self-descriptions during a transient dysphoric mood. Relative to a normative model of prefrontal function, the neuroimaging assessment of cognitive reactivity may provide a reliable indicator of MDD vulnerability, advancing the field of biomarker research as well as the delivery of preventative treatment on an individual basis.

Keywords

• Depression • Functional Magnetic Resonance Imaging • Biomarker • Emotion • Reactivity • Relapse • Imaging • Major Depressive Disorder

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1. Introduction

Major depressive disorder (MDD) is a common and debilitating disorder, with prevalence rates between 3-13% [1,2] and lifetime risk estimated at 17-19% [3,4]. MDD carries enormous social costs due to its high risk for relapse and recurrence [1,5-7], and is one of the leading causes of disability worldwide [8], significantly increasing social impairment and mortality [9-11]. Despite the clinical adoption of efficacious treatments [12,13], MDD may be rising in prevalence [14], and remains a disorder of global health concern.

There are likely multiple determinants of MDD susceptibility, including genetic [15], physiological [16], psychological [17-21], and socio-economic [22,23] factors. While heritability studies suggest that while MDD has a strong genetic component [24], the majority of risk still comes from environmental factors, accounting for 60-70% of the variance in familial inheritance. This environmental contribution suggests that psychosocial interventions may

powerfully combat or even prevent MDD [25]. A major challenge in preventing MDD onset and relapse lies in identifying individuals who are at risk, in spite of not being currently symptomatic. The validation of a method for predicting MDD risk could justify the allocation of clinical resources towards the prevention of first episodes of depression or depressive relapse in remitted patients. One promising avenue for the assessment of MDD susceptibility lies in the study of neuroimaging biomarkers of MDD. This paper reviews one approach towards biomarker development: using functional magnetic resonance imaging (fMRI) to analyze patterns of emotional reactivity to stress.

Neuroimaging allows us to explore the brain mechanisms underlying psychopathology and its resolution [26-28]. In this paper, we review neuroimaging evidence for the assessment of MDD vulnerability, demonstrating how translation of the normative features of cognitive control in the brain can be applied to investigate MDD vulnerability. We argue that

a person's neural response to negative mood provocation can predict depression risk, and may substantially advance our understanding of MDD pathophysiology, the heterogeneity of clinical presentations and treatment responsiveness. Uncovering mechanisms supporting the onset of depressive symptoms would enable the targeting of preventative interventions towards individuals at increased risk for MDD [29,30].

2. MDD vulnerability and the brain

The same neural networks associated with normal emotional expression appear to be involved in affective disorders [31]. Specifically altered anatomy and neurophysiological activity has been observed throughout the prefrontal cortex (PFC), including its medial (MPFC), dorsolateral (DLPFC) and ventromedial (VMPFC) aspects, as well as in subcortical structures such as the amygdala and hippocampus [32]. Despite variability in neuroimaging research findings, considerable

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progress has been made in identifying some common functional features of MDD in the brain.

It should be made clear from the outset that the study of a biomarker of MDD susceptibility must focus on the contributing factors to episode onset rather than the detection of episode states themselves. Thus, while the traditional profile for depression in the brain is one of PFC hypoactivity and amygdala hyperactivity [33,34], the pathophysiology leading to this depressed state may be markedly different, associated with a different biomarker profile.

2.1 The amygdala and emotional salience

Most descriptions of affective dysfunction begin with the amygdala. Traditionally characterized as a threat detector [35,36], this subcortical region displays greater activity in MDD and related disorders [37-40]. However, several studies have now demonstrated greater amygdala responsiveness to emotional arousal in general than negative valence in particular [41,42]. As such, rather than dysphoric affect, the amygdala has increasingly been associated with emotional salience [43], whether positive or negative [44-46]. Indeed, amygdala reactivity may be shaped by a host of factors, including short-term goals and motivational context [47,48], chronic personality traits such as neuroticism [49], or stimulus properties such as novelty [50,51]. Thus while amygdala reactivity may be an important component of depressive information processing, we must begin to more broadly consider amygdala reactivity to emotionally-relevant stimuli, including positive and goal-relevant stimuli, to assess its precise information processing role in MDD.

Even given a bias in amygdala responsiveness to negative stimuli, it appears that the automatic categorization of emotional salience is not totally dependent upon the amygdala: in one recent study, 2 patients with bilateral amygdala lesions demonstrated enhanced memory for emotional stimuli [52], suggesting that more conceptual pathways may operate to evaluate and categorize stimuli for emotional relevance. Additionally, it may be the case that an individual with a proclivity to notice negative details may still have adequate

cognitive resources to regulate subsequent affective appraisals, thereby maintaining mental equilibrium and social function. Thus, it is important not to assume that the amygdala response can, on its own, constitute a definitive biomarker of depression risk.

Despite these caveats, amygdala reactivity to emotional stimuli may still prove to be an important biomarker of depressive information processing, particularly as it applies to the blunting of sensitivity towards positive stimulation in MDD [53,54]. This may reflect a differential tuning of the amygdala towards the salience of dysphoric relative to euphoric events. The ability to habitually and automatically represent positive emotion may also be well characterized by examination of subcortical reward centers such as the nucleus accumbens, whose activity contrasted with the amygdala response to emotionally-relevant stimuli may begin to form a more complete model of information processing bias in MDD [55]. These limitations notwithstanding, the quality of reactivity to emotional provocation in the amygdala and other subcortical structures may yet prove to be important components in developing biomarkers for MDD vulnerability.

2.2 The DLPFC and cognitive control

The response to emotional stimuli in individuals at risk for depression has been characterized by amygdala hyperactivation and PFC hypoactivation [37,38], suggesting a hyperactive subcortical affective signal that overcomes attentional resources for cognitive control. On the other hand, when people are faced with the challenge of regulating their own internal affective state during difficult task performance, increased PFC activation in MDD has been observed [56,57]. The possibility exists that these disparate research findings are driven by multiple subtypes of MDD, one of which involves overactive affective tone in the amygdala, whereas another involves maladaptive dysphoric cognition in the PFC. Another possibility is that these two patterns of activity are due to nontrivial differences in study design.

One factor that addresses the apparent inconsistency between PFC and amygdala activity findings is whether a study paradigm

probes individuals in a neutral or affectively charged state. In the absence of a strong stressor, it appears that findings of high amygdala activity but withdrawn PFC cognitive control are the norm, suggestive of the intrinsic baseline of negative affect that characterizes the disorder. However, in paradigms where participants are faced with an ongoing emotional challenge, MDD patients appear to show an exaggerated regulatory response, transiently suppressing amygdala activity through an abnormal commitment of cognitive resources. Importantly, while amygdala hyperactivity patterns may normalize following remission from depressive episode [34], the exaggerated PFC response may remain as a biomarker of depression risk [58]. Increasingly, depression vulnerability can be viewed as a disorder of cognitive elaboration rather than one driven purely by amygdala hyperactivity [59-61], although some inconsistencies in this hypothesis still exist [62].

In understanding this idea of a reactivity biomarker for MDD, it is helpful to consider emotion regulation in healthy individuals. The DLPFC is strongly associated with resolving emotional conflict, such as choosing between the equitable division of resources and maximizing self-interest [63]. Acute stress from emotional challenge reduces DLPFC activity [64], perhaps thereby compromising emotion regulation ability. Indeed, DLPFC lesions are associated with higher depression risk [65], testament to their importance for normative emotion regulation.

In healthy individuals, cognitive reappraisal and suppression of negative emotions may be effective regulatory strategies [66], processes driven by the DLPFC. However, just as the amygdala appears to process more than negatively-valenced information, DLPFC activation may not always indicate adaptive regulatory efforts. Causal modeling analyses that examine directionality of neural interactions have suggested that the DLPFC may act as the cognitive input for goal-relevant external information that feeds into subcortical regions [67]; if cognitive habits become tuned towards a fixation on negative events such as in depressive rumination [68], the DLPFC could exacerbate subcortical reactivity rather

than down-regulating its impact. Supporting this account, a recent study observed that MDD patients demonstrated increased DLPFC activity during a rumination task relative to healthy controls [69]. The inability to disengage from negative self-focus is an emerging theory of MDD that predicts such maladaptive DLPFC recruitment [70].

Increased PFC activity in MDD may also reflect an inefficiency of cortical processing, as depressed individuals ineffectively attempt to regulate negative emotions [56]. Thus while patients with mood disorders tend to show reduced PFC metabolism [71], this lower baseline of activity may result in greater patterns of neural reactivity when attempting to regulate negative emotion [38], particularly in the right DLPFC [72].

2.3 The VMPFC and subgenual cingulate as a subcortical-PFC bridge

The VMPFC and subgenual cingulate are anatomically situated at the nexus between subcortical structures and the PFC. The VMPFC receives connections from both exteroceptive [73] and interoceptive [74] cortices, and has been viewed as a polymodal convergence zone supporting emotional awareness [75]. Relative to the more lateral orbitofrontal aspects of the ventral forebrain, the VMPFC is particularly involved in self-referential rather than conceptual or objective estimation of emotional significance [76].

Mounting evidence suggests that MDD may be driven by compromised PFC modulation of subcortical circuitry, particularly in its treatment-resistant and recurrent cases [77,78]. In these cases the normally observed connectivity between the PFC and amygdala via the VMPFC appears to be disrupted, suggesting that conventional emotion regulation techniques may be effortfully applied without commensurate down-regulation of dysphoric tone. Indications of VMPFC or subgenual hyperactivity without signs of subcortical connectivity are therefore good candidate biomarkers for MDD vulnerability.

Fine-grained regulation of VMPFC signal appears to be important for mental health, as the VMPFC appears to control the extent

of affective influence over behavior. While VMPFC lesions are associated with reduced depression risk [65]; they are also associated with the socially unacceptable disinhibition of emotional behavior [79-81]. Volumetric reductions in the PFC are commonly observed in post mortem studies of MDD [82-84], particularly in the subgenual cingulate, a region of high interconnectivity between the VMPFC cortex and subcortical regions [85]. However, the electrical disruption of VMPFC activity, particularly in the subgenual cingulate is a promising treatment of seemingly-intractable depression [86,87]. Whether psychosocial interventions can also act upon this deregulated VMPFC-subcortical network is a question for future research.

2.4 The MPFC and self-referential focus

The anatomical and functional intermediary between DLPFC regulatory control and VMPFC affective representation lies in the MPFC. This region is associated with the 'default' mode of the brain, and is often active while individuals are at rest [88], driving automatic and habitual evaluation, and has been independently associated particularly with explicit self-evaluation [89]. Habitual, negative self-evaluation is highly prevalent in MDD in the form of rumination [68], and so maladaptive activity in the MPFC is a strong candidate mechanism supporting the chronic dysphoria observed in depression. It should be noted that it is difficult to distinguish between the MPFC and the rostral anterior cingulate as the terms are used interchangeably in the literature, and thus we will consider evidence regarding both areas in this section.

MDD participants passively viewing sad films demonstrated greater MPFC activation than controls, showing evidence of greater, and perhaps dysfunctional levels of self-referential engagement during the experience of an emotional challenge [90]. Adolescent daughters of mothers with recurrent depression demonstrated increased anterior cingulate reactivity to punishment than matched controls without a familial history of MDD, who instead demonstrated amygdala activation [91], suggesting again that risk

for depression may lead to PFC rather than subcortical reactivity in response to an emotional stressor. However, while heightened MPFC reactivity may be a sign of dysfunction, it is also one of the hallmarks of responsiveness to treatment: MPFC activity across a number of neuroscience methodologies can be a positive predictor of treatment response for patients in the midst of depressive episodes [92-100]. Thus while increased MPFC activity may be a risk factor for MDD, it also serves to identify patients who are likely to be amenable to intervention, potentially indicating cognitive engagement with one's affective status. Whether this MPFC reactivity also indicates responsiveness to preventative treatments is a subject for future investigation.

The MPFC has been argued to act as a mediator between DLPFC cognitive control and VMPFC affective tone, thereby dictating emotional expression; dysfunction in the MPFC or its interconnections is therefore a major contributor to affective psychopathology [32]. The automatic and chronic rehearsal of negative self-referential schema are theorized to modulate activity in the MPFC, leading to elevated patterns of activation that reflect maladaptive cognition rather than cognitive control [101]. This chronic and dysfunctional activation may in turn compromise regulatory processes associated with the DLPFC: while thinking about oneself normatively recruits the MPFC, MDD patients demonstrate additional spreading recruitment from the MPFC into the DLPFC [102], consistent with an account of maladaptive recruitment of DLPFC cognitive control regions during self-referential rumination.

2.5 The hippocampus and overgeneral memory

Depression is linked to subcortical changes that extend beyond the immediate attribution of emotional salience found in the amygdala. It is well-established that long term MDD is associated both with memory impairment [103,104] and with reduced hippocampal volume [105-108], and that these memory deficits are associated with reduced hippocampal activity [109]. Overgeneral memories are common in MDD, in which

patients recall general semantic facts about themselves (e.g., "I always have a bad time at the beach") rather than specific autobiographical episodes (e.g., "this one time I went to the beach and got a sunburn on my knee") [110-112]. This overgeneralization of memory appears to be driven by ruminative processes [113], and is a predictor of depression severity [110,114]. It is unclear whether these overgeneral memories are driven by hippocampal failure, leading individuals to operate on a more semantic level, or whether the constant attention towards conceptual elaboration in MDD causes hippocampal atrophy [115]. However, without a baseline measurement of hippocampal size or frequency of overgeneral memory, neither of these measures appears to have good sensitivity as a predictor of MDD vulnerability.

2.6 Sensory cortical suppression in MDD

The possibility that depression reduces the concreteness of memories suggests that a possible MDD biomarker might index disruption of basic sensory input, although this hypothesis has not been extensively tested. One study demonstrated that MDD patients suppress task-irrelevant, non-emotional information in visual cortices [116]. This visual suppression may represent the occasional distracted engagement of task-irrelevant cognitive resources, e.g. mind-wandering or rumination, or indicate a more general suppression of sensory information to accommodate bias towards cognitive-evaluative processing. In another experiment, we observed that the extent of interoceptive suppression in the right insula following emotional challenge predicted higher levels of depressive symptoms, suggesting that this sensory suppression may extend beyond visual domains [59]. Finally, patients who demonstrate a greater auditory-evoked EEG potential were more likely to respond to antidepressant treatment [117].

Together, these findings suggest that sensation may be broadly suppressed in depression, particularly in treatment-resistant presentations, and may contribute to the blunting of affective experience found in MDD. Basic research on the distinct role of positive and negative emotions in attention, suggests that contrary

to negative moods, positive states enhance sensory processing of unattended events [118], and that greater sensory processing in the face of emotion provocation may be protective against depressive relapse [58]. More research is needed to examine the influence of MDD on sensory processing, where perhaps basic alterations in perception may be present that are more amenable to measurement than tests of cognition and emotion.

3. Emotional reactivity

3.1 Reactivity in MDD

Given the multifaceted nature of risk for depression, it is thought that MDD may follow a classic diathesis-stress model, in which latent vulnerability is revealed in the face of stress [119-122]. Progress has been made in identifying the genetic basis of this vulnerability: for example, the 5-HTTLPR polymorphism is associated with biological stress reactivity, which may increase susceptibility to depression in the face of stressful life events [123]. By exposing individuals to a transient dysphoric challenge, it is possible to activate latent vulnerabilities in emotional reactivity to stress [124-126], thereby revealing individual differences in MDD susceptibility.

Even in the absence of dysphoric challenge, altered emotional reactivity has been consistently observed in MDD through studies employing experience sampling techniques, gauging the range of emotional experience over the course of several days or weeks through random sampling. In such studies, altered reactivity sometimes manifests as a blunting of affective responses to positive and negative stimuli [127]; this reduction in emotional response has been associated with a poorer prognosis for episode recovery [128]. However, this dysthymic pattern of reactivity is not consistently observed; other studies have found increased experiences of negative emotion in MDD [129,130], suggesting again that perhaps different subtypes of MDD with respect to range of emotional experience may exist. Additionally, the protracted measurement period required for experience sampling may not always be clinically efficacious; in such situations, more carefully

controlled inductions of negative mood may be employed.

3.2 Reactivity to dysphoric challenge

An alternative technique to longitudinal experience sampling is the use of an acute mood challenge that can result in the temporary emergence of depressive symptoms. As mood challenge has been already been applied in basic emotions neuroscience research, the use of this technique allows for the translation of normative emotion regulation findings to target candidate biomarkers of MDD vulnerability in the brain. Encouragingly, powerful MDD indicators can be revealed following a short-term dysphoric mood induction: negative emotional reactivity predicts 1-year levels of depressive symptoms [131], and emotional reactivity moderates the relationship between stress and depression in adolescents [132].

One of the most promising domains of reactivity research lies in the assessment of changes in cognition in response to emotional challenge. Mounting evidence suggests that cognitive reactivity to stress is a significant predictor of depression, above and beyond blunting or intensification of mood state [133], but see [134]. MDD patients show increased elaboration of negative information, difficulty in disengaging from negative stimuli, and reduced cognitive control under dysphoric challenge [135]. For example, following mood challenge, remitted patients' amygdala response predicted their recall of negative self-referential words, a relationship not observed in healthy controls or prior to mood challenge [136]. This finding supports the idea that emotional stress reveals patterns of habitual, dysphoric attention that may normally be effectively suppressed by depressed individuals.

The theory of cognitive reactivity helps to explain the persistence of dysphoric affect in MDD, whereas normal emotional experience is subject to homeostatic resolution [137]. In vulnerable individuals, emotional stress is theorized to catalyze a cascade of negative self-evaluations, creating a static, dysphoric interpretive network that undermines the positivity of future experiences. For example, patients with MDD show a marked decrease in reward responsiveness

rather than heightened arousal to anticipated punishment [138], as though positive events no longer fit into their self-schema whereas negative events are already expected. This hypothesis is consistent with studies of depressive personality traits, in which negative traits predict an earlier onset of MDD, while a lack of positive traits predict greater duration of episode [21]. These trait-like 'depressogenic cycles' help to explain the perpetuity of dysphoric affect in MDD, and predict that increasing attentional control over this implicational layer of processing as a potential avenue for therapeutic intervention [139,140]. Critically, depressogenic cycles that dominate affective appraisals may be difficult to detect in remitted patients until they are exposed to an emotional stressor. MDD patients show poorer discrimination of emotion during episode, but better detection of emotion during remission than healthy controls, owing to a higher response bias for emotion detection [141]. This bias is however not present in patients on continuing antidepressant medication, suggesting that some addressable form of reactivity is still at play in these patients. In an EEG study of a punishment learning task, remitted patients demonstrated elevated feedback-related negativities to negative feedback than controls, despite equivalent behavioral performance [142]. When confronted with emotional information, relatively asymptomatic individuals who nonetheless are at heightened risk for MDD may begin to display altered patterns of reactivity that characterize their high risk status.

3.3 Reactivity as an MDD biomarker

Current research suggests that emotional reactivity paradigms might powerfully predict MDD susceptibility, particularly in the realm of predicting depressive relapse following symptom remission. Following the induction of a mildly dysphoric state through negative autobiographical recall, remitted patients tend to increase their endorsement of negative self-attributes [143,144]. Reactivity is associated with rumination, and predicts MDD vulnerability above and beyond baseline rumination scores [145]. Critically, cognitive reactivity directly predicts depressive relapse [146].

The research literature proposes several explanatory mechanisms for cognitive reactivity, and helps to account for other cognitive constructs' contribution to depressive affect. For instance, cognitive reactivity appears to be a mediating variable in explaining why the Big-5 personality trait of Neuroticism predisposes individuals to depression [147]. At the physiological level, tryptophan depletion appears to increase cognitive reactivity patterns and promote negative affect [148]. The centrality of reactivity for explaining mood challenge at multiple levels of analysis suggests that this phenomenon may be a powerful explanatory step in the translation of psychological and physiological factors to the subjective experience of dysphoria.

Lending credence to the importance of reactivity for determining subjective well-being, interventions that focus on cognitive reactivity to emotional provocation have also demonstrated marked success in reducing MDD vulnerability by lowering depressive relapse rates. Both Cognitive Behavioral Therapy [149] and Mindfulness-Based Cognitive Therapy [150-152] appear to reduce relapse risk by increasing metacognitive awareness, thereby disrupting habitual cognitive reactivity patterns [153]. The concept of decentering experience seems to be a candidate factor driving reduced relapse risk, reducing the obligatory connection between negative emotions and self-referential inference [154].

While cognitive reactivity may be studied through behavioral testing, it is likely that these exaggerated reactivity responses have pervasive functional biomarkers in the brain that may elucidate depressive pathophysiology. MDD episodes are characterized by hyperactive VMPFC and hypoactive DLPFC recruitment, and the normalization of these patterns is associated with successful recovery [38,155,156]. However, studies of treatment response, focusing on the determinants of disorder vulnerability, paint a different picture: emotional reactivity to a dysphoric stressor in the form of DLPFC activation is maladaptive and predicts longer depressive episodes [157]. Another study observed that patients exhibited reduced reactivity to emotional stimuli in the VMPFC and subcortical regions, but increased

reactivity in the left temporal pole and right DLPFC. Successful treatment reduced this reactivity and restored subcortical tone [158]. Rumination, a cognitive predictor of MDD, has been associated with dorsal MPFC activation in healthy individuals [159] and with both DLPFC and VMPFC activation in MDD patients [69]. This pattern of exaggerated dorsal PFC reactivity to emotional challenge appears to be a flexible indicator of depression course, and is founded upon behavioral evidence linking neural activity to maladaptive ruminative cognition. The neural signal of dorsal PFC regions during cognitive reactivity to emotional challenge is thus an exciting candidate biomarker of MDD vulnerability.

4. The biomarker approach

The validation of MDD biomarkers may help to shorten the potentially lifelong span of depression, helping clinicians to identify high-risk individuals who may benefit from proactive therapeutic intervention [160]. In recent years major health institutions have begun to acknowledge that traditional categories of mental disorders such as 'depression' or 'anxiety' may be insufficient in guiding impactful research and intervention studies. Instead, researchers are now investigating dimensions of vulnerability, pursuing the idea that symptoms of mental illness may be driven by distinct pathological changes to existing regulatory systems. Using normative research for these emotion regulation systems, it may be possible to differentiate between particular patterns of dysfunction. By eschewing the assumption that there is a unitary biomarker for a given disorder, dysfunction can be modeled along multiple aspects of a complex regulatory system; this approach then holds the promise of providing individually tailored therapeutic interventions, depending upon a person's specific biomarker.

For example, two individuals may present with similar depressive symptoms, but have different underlying causes. The first individual may have the ability to regulate his emotions but lacks the understanding that such regulation is important and must be effortfully undertaken. The second individual

may have good intentions around emotion regulation but lack the capacity to control emotions once they arise. In the first case, psychotherapy might be optimal for engaging the individual in regulation strategies. In the second case strategies exist but are ineffective—an intervention that targets the automaticity of the emotional response such as mindfulness training or pharmacotherapy may be more appropriate.

Multiple techniques have shown promise in distinguishing between patients during MDD episodes and healthy controls. Using machine learning analysis of fMRI data, one study analyzed a working memory task to try to distinguish between MDD patients and healthy controls, achieving moderate accuracy sensitivity (67%) in predicting MDD diagnosis [161]. Another machine learning study achieved 86% accuracy in distinguishing between the fMRI signal associated with viewing of emotional faces [162]. Decreases in PFC midline and right lateral EEG concordance at the start of treatment predicted patient remission with 69% accuracy [163]. In a physiological analysis, sustained cortisol response in the weeks following hospitalization predicted poorer treatment responses [164], as does the dysregulation of timing between nocturnal melatonin and cortisol release [165]. Finally, in a genetic analysis, another study achieved perfect classification by analyzing the DNA methylation of the brain-derived neurotrophic factor gene, which has been linked to MDD status, although this study did not assess MDD vulnerability in subclinical groups [166]. However, even with excellent classification as is the case with genetic analysis, few of these biomarkers directly tap into the problem of maladaptive cognition in depression, thereby missing out on the variance associated with the powerful impact of psychosocial factors on MDD vulnerability. Importantly, none of these biomarkers have been linked to the detection of MDD vulnerability in asymptomatic individuals. Seeking to capitalize on the existing behavioral literature surrounding emotional reactivity and depression risk, we performed a prospective neuroimaging study in which we observed that future relapse into MDD was predicted by neural reactivity to emotional challenge [58].

Reactivity was operationalized by contrasting patient neural activity and sadness ratings in response to viewing sad film clips, in contrast to a neutrally-valenced baseline film condition. This paradigm was previously used to demonstrate greater MPFC activation in depressed individuals relative to controls [90], and as the films produced a coherent narrative for patients, they were perhaps more externally valid cues for emotional reactivity than the static imagery often employed in affective research. Using this emotional challenge paradigm, we were able to discriminate between future relapse and sustained remission with very high (94%) accuracy, and to link rumination to MPFC reactivity in both its dorsal and ventral aspects. Importantly, this pattern of extended MPFC reactivity accounted for more variance in relapse risk than questionnaire-based assessment of rumination alone, suggesting that this candidate biomarker may be capturing unexplained depressogenic tendencies that include, but are not limited to, depressive rumination.

5. Discussion

The stress biomarker approach for understanding mental health rests on three

premises: it assumes that a person's experience of well-being is i) predicted by patterns of reactivity in the face of an emotional challenge; ii) these patterns are empirically measurable, and iii) that these patterns are reliably indicative of vulnerability to mood disorders. To this end, the use of normative patterns of emotion processing in the brain may powerfully inform the development of models for MDD vulnerability. In the present review, we have focused on one such model, suggesting that behavioral evidence of compromised cognitive control over emotion in MDD may translate into irregular neuroimaging biomarkers of PFC reactivity to emotional provocation. While MDD episodes may be characterized by an absence of such PFC control activity, MDD vulnerability may reveal a hyper-recruitment of these same prefrontal regions, perhaps due to a need for stronger effort to regulate powerful negative emotion in MDD, or perhaps due to an inefficient cognitive control system. A schematic representation of how normative models of brain activity can inform models of MDD vulnerability is presented in Figure 1.

Despite the promise of our proposed PFC biomarker, it is unlikely that a single measure will end up being the 'magic bullet' biomarker for depression; instead biomarkers will help

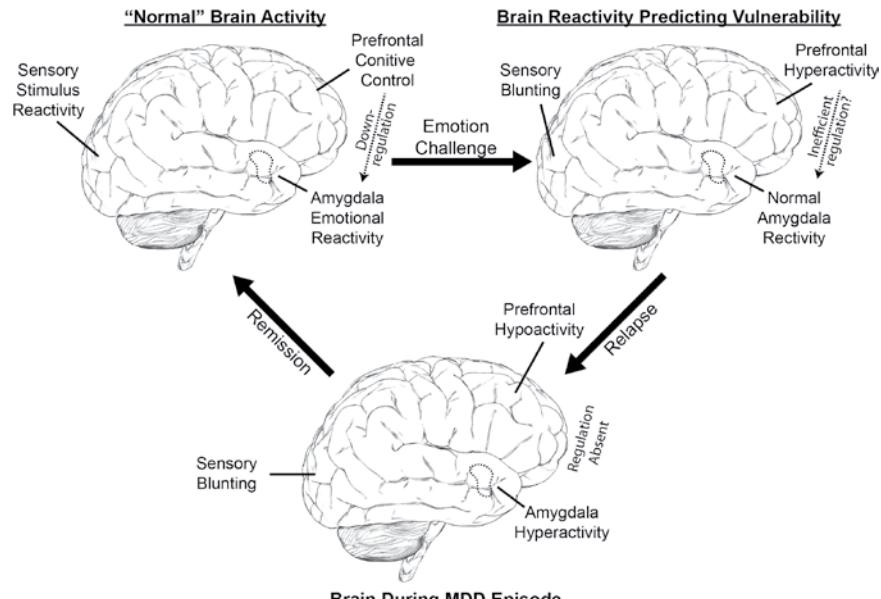


Figure 1. Schematic representation of emotion processing. Research on normative emotion processing informs abnormal patterns of cognitive reactivity following emotional challenge. Normative cognitive control regions in the DLPFC are hyperactive following mood provocation, predicting a reversal of brain reactivity during depressive episode, in which the absence of DLPFC activity is associated with amygdala dysregulation.

to distinguish between specific subtypes of depression [25]. Our model of relapse prediction for instance was obtained by examining patients with recurrent depression (3 episodes or more), who were responsive to antidepressant treatment but retained a high risk for relapse. These patients demonstrated a distinct association between rumination and clinical relapse, involving maladaptive PFC reactivity to emotional stressors. On the other hand, it may be that other types of MDD presentations will demonstrate heterogeneous patterns that do not conform to this neuroimaging biomarker, but may be detectable in terms of other neuroimaging, genetic, or chemical assessment techniques. While the heterogeneity of MDD adds complexity to the diagnostic process, this complexity also allows for the personalization of patient therapeutic interventions to match specific biomarkers or combinations thereof. Unlike other disorders such as bipolar disorder or psychosis [167], patients with MDD are all too aware of their dysphoric state. However, insight about affective state does not ensure that patients have insight into the specific mechanisms supporting their dysphoric affect, and certainly not into the mechanisms for disorder resolution. Thus the biomarker approach may be increasingly important in distinguishing between subtle differences in

MDD subtypes with large differences in optimal treatment prediction. These biomarkers may also help to inform clinical theory, perhaps distinguishing between hyperactive amygdala and hyperactive PFC subtypes of MDD, and validating both schools of research findings within a specific subpopulation. In this review we focused on one example of reactivity that may be used as a biomarker, namely PFC reactivity in response to an emotional challenge. Rather than using a data driven approach, the investigation of this biomarker is driven by a theory of affective deregulation in MDD. Recruitment of a VMPFC pathway is traditionally found during the effortful regulation of affect, attempting to form new evaluations of an aversive experience [168,169]. However, what appears to be a normative regulatory process in healthy individuals may manifest as a biomarker of psychopathology in the context of a depressive history. Furthermore, the co-activation of the VMPFC pathway with the DLPFC in depressed patients is unusual, as these regions tend to be negatively correlated in healthy individuals [170]. Thus what is normative at the level of a specific brain structure may be abnormal in the context of broad neuronal activity in a given paradigm. While the data presented in our study of PFC reactivity is exciting and appears to have

good conceptual validity with respect to the mechanisms by which reactivity promotes depressive affect, considerable research is required to render these findings clinically tractable. Even with acceptable discrimination between vulnerable and resilient individuals, any prospective biomarker would require extensive independent validation in a broader, randomly sampled cohort to establish its clinical value. However, by focusing on emotional challenge paradigms that test the reactivity of regulatory systems, it may be possible to generate meaningful indices of depression vulnerability that may one day support clinically applied biomarkers for MDD. This would go far in bolstering preventative efforts and reduce the burden associated with this all too often chronic disorder.

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References

- [1] Gelenberg A.J., The prevalence and impact of depression, *J. Clin. Psychiatry*, 2010, 71, e06
- [2] Richards D., Prevalence and clinical course of depression: A review, *Clin. Psychol. Rev.*, 2011, 31, 1117-1125
- [3] Kessler R.C., McGonagle K. A., Zhao S., Nelson C. B., Hughes M., Eshleman S. et al., Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey, *Arch. Gen. Psychiatry*, 1994, 51, 8-19
- [4] Wittchen H.U., Knauper B., Kessler R. C., Lifetime risk of depression, *Br. J. Psychiatry Suppl.*, 1994, 26, 16-22
- [5] Greenberg P.E., Kessler R. C., Birnbaum H. G., Leong S. A., Lowe S. W., Berglund P. A. et al., The economic burden of depression in the United States: how did it change between 1990 and 2000?, *J. Clin. Psychiatry*, 2003, 64, 1465-75
- [6] Judd L. L., The clinical course of unipolar major depressive disorders, *Arch. Gen. Psychiatry*, 1997, 54, 989-991
- [7] Murray C.J., Lopez A. D., Mortality by cause for eight regions of the world: Global Burden of Disease Study, *Lancet*, 1997, 349, 1269-1276
- [8] Lopez A. D., Mathers C. D., Ezzati M., Jamison D. T., Murray C. J., Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data, *Lancet*, 2006, 367, 1747-1757
- [9] Angst F., Stassen H. H., Clayton P. J., Angst J., Mortality of patients with mood disorders: follow-up over 34-38 years, *J. Affect. Disord.*, 2002, 68, 167-181
- [10] Bromet E., Andrade L. H., Hwang I., Sampson N. A., Alonso J., de Girolamo G. et al., Cross-national epidemiology of DSM-IV major depressive episode, *BMC Med.*, 2011, 9
- [11] Kessler R. C., Berglund P., Demler O., Jin R., Koretz D., Merikangas K. R. et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R), *JAMA*, 2003, 289, 3095-3105
- [12] Fava G.A., Tomba E., New modalities of assessment and treatment planning in depression: the sequential approach, *CNS Drugs*, 2010, 24, 453-465
- [13] Fava G. A., Park S.K., Sonino N., Treatment of recurrent depression, *Expert Rev. Neurother.*, 2006, 6, 1735-1740

[14] Andersen I., Thielen K., Bech P., Nygaard E., Diderichsen F., Increasing prevalence of depression from 2000 to 2006, *Scand. J. Public Health*, 2011, 39, 857-863

[15] Weissman M.M., Wickeramaratne P., Nomura Y., Warner V., Verdely H., Pilowsky D. J. et al., Families at high and low risk for depression: a 3-generation study, *Arch. Gen. Psychiatry*, 2005, 62, 29-36

[16] Horstmann S., Binder E. B., Glucocorticoids as predictors of treatment response in depression, *Harv. Rev. Psychiatry*, 2011, 19, 125-143

[17] Iacoviello, B.M., Alloy L. B., Abramson L. Y., Whitehouse W. G., Hogan M. E., The course of depression in individuals at high and low cognitive risk for depression: a prospective study, *J. Affect. Disord.*, 2006, 93, 61-69

[18] Alloy L. B., Abramson L. Y., Whitehouse W. G., Hogan M. E., Panzarella C., Rose D. T., Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression, *J. Abnorm. Psychol.*, 2006, 115, 145-156

[19] Spasojevic J., Alloy L. B., Rumination as a common mechanism relating depressive risk factors to depression, *Emotion*, 2001, 1, 25-37

[20] Slavich G. M., Monroe S. M., Gotlib I. H., Early parental loss and depression history: associations with recent life stress in major depressive disorder, *J. Psychiatr. Res.*, 2011, 45, 1146-1152

[21] Robison E. J., Shankman S. A., McFarland B. R., Independent associations between personality traits and clinical characteristics of depression, *J. Nerv. Ment. Dis.*, 2009, 197, 476-483

[22] Lorant V., Croux C., Weich S., Deliège D., Mackenbach J., Ansseau M., Depression and socio-economic risk factors: 7-year longitudinal population study, *Br. J. Psychiatry*, 2007, 190, 293-298

[23] Lorant V., Deliège D., Eaton W., Robert A., Philippot P., Ansseau M., Socioeconomic inequalities in depression: a meta-analysis, *Am. J. Epidemiol.*, 2003, 157, 98-112

[24] Sullivan P. F., Neale M. C., Kendler K. S., Genetic epidemiology of major depression: review and meta-analysis, *Am. J. Psychiatry*, 2000, 157, 1552-1562

[25] Hasler G., Pathophysiology of depression: do we have any solid evidence of interest to clinicians?, *World Psychiatry*, 2010, 9, 155-161

[26] Davidson R.J., Lewis D. A., Alloy L. B., Amaral D. G., Bush G., Cohen J. D. et al., Neural and behavioral substrates of mood and mood regulation, *Biol. Psychiatry*, 2002, 52, 478-502

[27] Drevets W. C., Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders, *Curr. Opin. Neurobiol.*, 2001, 11, 240-249

[28] Drevets W. C., Raichle M. E., Neuroanatomical circuits in depression: implications for treatment mechanisms, *Psychopharmacol. Bull.*, 1992, 28, 261-274

[29] DeRubeis R. J., Siegle G. J., Hollon S. D., Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms, *Nat. Rev. Neurosci.*, 2008, 9, 788-796

[30] Mayberg H. S., Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment, *Br. Med. Bull.*, 2003, 65, 193-207

[31] Davidson R. J., Pizzagalli D., Nitschke J. B., Putnam K., Depression: perspectives from affective neuroscience, *Annu. Rev. Psychol.*, 2002, 53, 545-574

[32] Drevets W. C., Price J. L., Furey M. L., Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression, *Brain Struct. Funct.*, 2008, 213, 93-118

[33] Mayberg H. S., Liotti M., Brannan S. K., McGinnis S., Mahurin R. K., Jerabek P. A. et al., Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness, *Am. J. Psychiatry*, 1999, 156, 675-682

[34] Mayberg H. S., Limbic-cortical dysregulation: a proposed model of depression, *J. Neuropsychiatry Clin Neurosci*, 1997, 9, 471-481

[35] Amaral D. G., The amygdala, social behavior, and danger detection, *Ann. N.Y Acad. Sci.*, 2003, 1000, 337-347

[36] Ohman A., The role of the amygdala in human fear: automatic detection of threat, *Psychoneuroendocrinology*, 2005, 30, 953-958

[37] Zhong M., Wang X., Xiao J., Yi J., Zhu X., Liao J. et al., Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression, *Biol. Psychol.*, 2011, 88, 233-242

[38] Siegle G. J., Thompson W., Carter C. S., Steinhauer S. R., Thase M. E., Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features, *Biol. Psychiatry*, 2007, 61, 198-209

[39] Abler B., Erk S., Herwig U., Walter H., Anticipation of aversive stimuli activates extended amygdala in unipolar depression, *J. Psychiatr. Res.*, 2007, 41, 511-522

[40] Whalen P. J., Shin L. M., Somerville L. H., McLean A. A., Kim H., Functional neuroimaging studies of the amygdala in depression, *Semin. Clin. Neuropsychiatry*, 2002, 7, 234-242

[41] Anderson A.K., Christoff K., Stappen I., Panitz D., Ghahremani D. G., Glover G. et al., Dissociated neural representations of intensity and valence in human olfaction, *Nat. Neurosci.*, 2003, 6, 196-202

[42] Small D. M., Gregory M. D., Mak Y. E., Gitelman D., Mesulam M. M., Parrish T., Dissociation of neural representation of intensity and affective valuation in human gustation, *Neuron*, 2003, 39, 701-711

[43] Anderson A. K., Phelps E. A., Lesions of the human amygdala impair enhanced perception of emotionally salient events, *Nature*, 2001, 411, 305-309

[44] Santos A., Mier D., Kirsch P., Meyer-Lindenberg A., Evidence for a general face salience signal in human amygdala, *Neuroimage*, 2011, 54, 3111-3116

[45] Mahler S. V., Berridge K. C., Which cue to "want?" Central amygdala opioid activation enhances and focuses incentive salience on a prepotent reward cue, *J. Neurosci.*, 2009, 29, 6500-6513

[46] Liberzon I., Phan K. L., Decker L. R., Taylor S. F., Extended amygdala and emotional salience: a PET activation study of positive and negative affect, *Neuropsychopharmacology*, 2003, 28, 726-733

[47] Cunningham W. A., Van Bavel J. J., Johnsen I.R., Affective flexibility: evaluative processing goals shape amygdala activity, *Psychol. Sci.*, 2008, 19, 152-160

[48] Ousdal O. T., Jensen J., Server A., Hariri A. R., Nakstad P. H., Andreassen O. A., The human amygdala is involved in general behavioral relevance detection: evidence from an event-related functional magnetic resonance imaging Go-NoGo task, *Neuroscience*, 2008, 156, 450-455

[49] Cunningham W.A., Arbuckle N. L., Jahn A., Mowrer S. M., Abduljalil A. M., Reprint of: Aspects of neuroticism and the amygdala:

chronic tuning from motivational styles, *Neuropsychologia*, 2011, 49, 657-662

[50] Balderston N. L., Schultz D. H., Helmstetter F. J., The human amygdala plays a stimulus specific role in the detection of novelty, *Neuroimage*, 2011, 55, 1889-1898

[51] Blackford J. U., Buckholtz J. W., Avery S. N., Zald D. H., A unique role for the human amygdala in novelty detection, *Neuroimage*, 2010, 50, 1188-1193

[52] Bach, D.R., Talmi D., Hurlemann R., Patin A., Dolan R. J., Automatic relevance detection in the absence of a functional amygdala, *Neuropsychologia*, 2011, 49, 1302-1305

[53] Versace A., Thompson W. K., Zhou D., Almeida J. R., Hassel S., Klein C. R. et al., Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder, *Biol. Psychiatry*, 2010, 67, 422-431

[54] Almeida J. R., Versace A., Mechelli A., Hassel S., Quevedo K., Kupfer D. J. et al., Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression, *Biol. Psychiatry*, 2009, 66, 451-459

[55] Monk, C.S., Klein R. G., Telzer E. H., Schroth E. A., Mannuzza S., Moulton J. L. 3rd et al., Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression, *Am. J. Psychiatry*, 2008, 165, 90-98

[56] Wagner G., Sinsel E., Sobanski T., Köhler S., Marinou V., Mentzel H. J. et al., Cortical inefficiency in patients with unipolar depression: an event-related fMRI study with the Stroop task, *Biol. Psychiatry*, 2006, 59, 958-965

[57] Walter H., Wolf R. C., Spitzer M., Vasic N., Increased left prefrontal activation in patients with unipolar depression: an event-related, parametric, performance-controlled fMRI study, *J. Affect. Disord.*, 2007, 101, 175-185

[58] Farb N. A., Anderson A. K., Bloch R. T., Segal Z. V., Mood-linked responses in medial prefrontal cortex predict relapse in patients with recurrent unipolar depression, *Biol. Psychiatry*, 2011, 70, 366-372

[59] Farb N. A., Anderson A. K., Mayberg H., Bean J., McKeon D., Segal Z. V., Minding one's emotions: mindfulness training alters the neural expression of sadness, *Emotion*, 2010, 10, 25-33

[60] Sheline Y. I., Barch D. M., Price J. L., Rundle M. M., Vaishnavi S. N., Snyder A. Z. et al., The default mode network and self-referential processes in depression, *Proc. Natl. Acad. Sci. U S A*, 2009, 106, 1942-1947

[61] Sheline, Y.I., Price J. L., Yan Z., Mintun M. A., Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus, *Proc. Natl. Acad. Sci. U S A*, 2010, 107, 11020-11025

[62] Hooley J. M., Gruber S. A., Parker H. A., Guillamot J., Rogowska J., Yurgelun-Todd D. A., Cortico-limbic response to personally challenging emotional stimuli after complete recovery from depression, *Psychiatry Res.*, 2009, 172, 83-91

[63] Baumgartner T., Knoch D., Hotz P., Eisenegger C., Fehr E., Dorsolateral and ventromedial prefrontal cortex orchestrate normative choice, *Nat. Neurosci.*, 2011, 14, 1468-1474

[64] Qin S., Hermans E. J., van Marle H. J., Luo J., Fernández G., Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex, *Biol. Psychiatry*, 2009, 66, 25-32

[65] Koenigs M., Huey E. D., Calamia M., Raymond V., Tranel D., Grafman J., Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression, *J. Neurosci.*, 2008, 28, 12341-12348

[66] Goldin P. R., McRae K., Ramel W., Gross J. J., The neural bases of emotion regulation: reappraisal and suppression of negative emotion, *Biol. Psychiatry*, 2008, 63, 577-586

[67] Ballard I.C., Murty V.P., Carter R.M., MacInnes J.J., Huettel S.A., Adcock R.A., Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior, *J. Neurosci.*, 2011, 31, 10340-10346

[68] Nolen-Hoeksema S., The role of rumination in depressive disorders and mixed anxiety/depressive symptoms, *J. Abnorm. Psychol.*, 2000, 109, 504-511

[69] Cooney R. E., Joormann J., Eugène F., Dennis E. L., Gotlib I. H., Neural correlates of rumination in depression, *Cogn. Affect. Behav. Neurosci.*, 2010, 10, 470-478

[70] Koster E. H., De Lissnyder E., Derakshan N., De Raedt R., Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis, *Clin. Psychol. Rev.*, 2011, 31, 138-145

[71] Baxter L.R. Jr., Schwartz J. M., Phelps M. E., Mazziota J. C., Guze B. H., Selin C. E. et al., Reduction of prefrontal cortex glucose metabolism common to three types of depression, *Arch. Gen. Psychiatry*, 1989, 46, 243-250

[72] Grimm S., Beck J., Schuepbach D., Hell D., Boesiger P., Bermpohl F. et al., Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder, *Biol. Psychiatry*, 2008, 63, 369-376

[73] Barbas H., Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices, *Brain Res. Bull.*, 2000, 52, 319-330

[74] Carmichael S.T., Price J. L., Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys, *J. Comp. Neurol.*, 1995, 363, 615-641

[75] Rolls E.T., Convergence of sensory systems in the orbitofrontal cortex in primates and brain design for emotion, *Anat. Rec. Part A*, 2004, 281, 1212-1225

[76] Bouret S., Richmond B. J., Ventromedial and orbital prefrontal neurons differentially encode internally and externally driven motivational values in monkeys, *J. Neurosci.*, 2010, 30, 8591-8601

[77] Johnstone T., van Reekum C. M., Urry H. L., Kalin N. H., Davidson R. J., Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression, *J. Neurosci.*, 2007, 27, 8877-8884

[78] Ressler K. J., Mayberg H. S., Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic, *Nat. Neurosci.*, 2007, 10, 1116-1124

[79] Damasio H., Grabowski T., Frank R., Galaburda A. M., Damasio A. R., The return of Phineas Gage: clues about the brain from the skull of a famous patient, *Science*, 1994, 264, 1102-1105

[80] Beer J. S., Heerey E. A., Keltner D., Scabini D., Knight R. T., The regulatory function of self-conscious emotion: insights from patients with orbitofrontal damage, *J. Pers. Soc. Psychol.*, 2003, 85, 594-604

[81] Beer J. S., John O. P., Scabini D., Knight R. T., Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions, *J. Cogn. Neurosci.*, 2006, 18, 871-879

[82] Hercher C., Turecki G., Mechawar N., Through the looking glass: examining neuroanatomical evidence for cellular alterations in major depression, *J. Psychiatr. Res.*, 2009, 43, 947-961

[83] Rajkowska G., Miguel-Hidalgo J. J., Wei J., Dilley G., Pittman S. D., Meltzer H. Y. et al., Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression, *Biol. Psychiatry*, 1999, 45, 1085-1098

[84] Rajkowska G., Depression: what we can learn from postmortem studies, *Neuroscientist*, 2003, 9, 273-284

[85] Price J. L., Drevets W. C., Neurocircuitry of mood disorders, *Neuropsychopharmacology*, 2010, 35, 192-216

[86] Hamani C., Machado D. C., Hipólido D. C., Dubiela F. P., Susecki D., Macedo C. E. et al., Deep Brain Stimulation Reverses Anhedonic-Like Behavior in a Chronic Model of Depression: Role of Serotonin and Brain Derived Neurotrophic Factor, *Biol. Psychiatry*, 2011, Epub ahead of print

[87] Mayberg H. S., Lozano A. M., Voon V., McNeely H. E., Seminowicz D., Hamani C. et al., Deep brain stimulation for treatment-resistant depression, *Neuron*, 2005, 45, 651-660

[88] Gusnard D. A., Akbudak E., Shulman G. L., Raichle M. E., Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function, *Proc. Natl. Acad. Sci. U S A*, 2001, 98, 4259-4264

[89] Kelley W. M., Macrae C. N., Wyland C. L., Caglar S., Inati S., Heatherton T. F., Finding the self? An event-related fMRI study, *J. Cogn. Neurosci.*, 2002, 14, 785-794

[90] Beauregard M., Leroux J. M., Bergman S., Arzoumanian Y., Beaudoin G., Bourgouin P. et al., The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm, *Neuroreport*, 1998, 9, 3253-3258

[91] Gotlib I. H., Hamilton J. P., Cooney R. E., Singh M. K., Henry M. L., Joormann J., Neural processing of reward and loss in girls at risk for major depression, *Arch. Gen. Psychiatry*, 2010, 67, 380-387

[92] Fu C. H., Williams S. C., Cleare A. J., Brammer M. J., Walsch N. D., Kim J. et al., Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study, *Arch. Gen. Psychiatry*, 2004, 61, 877-889

[93] Chen C. H., Ridler K., Suckling J., Williams S., Fu C. H., Merlo-Pich E. et al., Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment, *Biol. Psychiatry*, 2007, 62, 407-414

[94] Wu J. C., Gillin J. C., Buchsbaum M. S., Hershey T., Johnson J. C., Bunney W. E. Jr., Effect of sleep deprivation on brain metabolism of depressed patients, *Am. J. Psychiatry*, 1992, 149, 538-543

[95] Ebert D., Feistel H., Barocka A., Kaschka W., Increased limbic blood flow and total sleep deprivation in major depression with melancholia, *Psychiatry Res.*, 1994, 55, 101-109

[96] Brody A. L., Saxena S., Silverman D. H., Alborzian S., Fairbanks L. A., Phelps M. E. et al., Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine, *Psychiatry Res.*, 1999, 91, 127-139

[97] Wu J., Buchsbaum M. S., Gillin J. C., Tang C., Cadwell S., Wiegand M. et al., Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex, *Am. J. Psychiatry*, 1999, 156, 1149-1158

[98] Pizzagalli D., Pascual-Marqui R. D., Nitschke J. B., Oakes T. R., Larson C. L., Abercrombie H. C. et al., Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis, *Am. J. Psychiatry*, 2001, 158, 405-415

[99] Davidson R. J., Irwin W., Anderle M. J., Kalin N. H., The neural substrates of affective processing in depressed patients treated with venlafaxine, *Am. J. Psychiatry*, 2003, 160, 64-75

[100] Mayberg H. S., Brannan S. K., Mahurin R. K., Jerabek P. A., Brickman J. S., Tekell J. L. et al., Cingulate function in depression: a potential predictor of treatment response, *Neuroreport*, 1997, 8, 1057-1061

[101] Lemogne C., Delaveau P., Freton M., Guionnet S., Fossati P., Medial prefrontal cortex and the self in major depression, *J. Affect. Disord.*, 2012, 136, e1-e11

[102] Lemogne C., le Bastard G., Mayberg H., Volle E., Bergouignan L., Lehéricy S. et al., In search of the depressive self: extended medial prefrontal network during self-referential processing in major depression, *Soc. Cogn. Affect. Neurosci.*, 2009, 4, 305-312

[103] Raes F., Hermans D., Williams J. M., Demyttenaere K., Sabbe B., Pieters G. et al., Is overgeneral autobiographical memory an isolated memory phenomenon in major depression?, *Memory*, 2006, 14, 584-594

[104] Reppermund S., Brodaty H., Crawford J. D., Kochan N. A., Slavin M. J., Trollor J. N., et al., The relationship of current depressive symptoms and past depression with cognitive impairment and instrumental activities of daily living in an elderly population: The Sydney Memory and Ageing Study, *J. Psychiatr. Res.*, 2011, 45, 1600-1607

[105] Bellani M., Baiano M., Brambilla P., Brain anatomy of major depression - I. Focus on hippocampus, *Epidemiol. Psychiatr. Soc.*, 2010, 19, 298-301

[106] Campbell S., Macqueen G., The role of the hippocampus in the pathophysiology of major depression, *J. Psychiatry Neurosci.*, 2004, 29, 417-426

[107] Xia J., Chen J., Zhou Y., Zhang J., Yang B., Xia L. et al., Volumetric MRI analysis of the amygdala and hippocampus in subjects with major depression, *J. Huazhong Univ Sci Technolog Med Sci*, 2004, 24, 500-502, 506

[108] Sheline Y. I., Mittler B. L., Mintun M. A., The hippocampus and depression, *Eur. Psychiatry*, 2002, 17 (Suppl. 3), 300-305

[109] Young K. D., Erickson K., Nugent A. C., Fromm S. J., Mallinger A. G., Furey M. L. et al., Functional anatomy of autobiographical memory recall deficits in depression, *Psychol. Med.*, 2011, 1-13

[110] Hermans D., Vandromme H., Debeer E., Raes F., Demyttenaere K., Brunfaut E., et al., Overgeneral autobiographical memory predicts diagnostic status in depression, *Behav. Res. Ther.*, 2008, 46, 668-677

[111] Dalglish T., Williams J. M., Golden A. M., Perkins N., Barrett L. F., Barnard P. J., et al., Reduced specificity of autobiographical memory and depression: the role of executive control, *J. Exp. Psychol. Gen.*, 2007, 136, 23-42

[112] Nandrino J. L., Pezard L., Posté A., Réveillère C., Beaune D., Autobiographical memory in major depression: a comparison between first-episode and recurrent patients, *Psychopathology*, 2002, 35, 335-340

[113] Watkins E., Teasdale J. D., Rumination and overgeneral memory in depression: effects of self-focus and analytic thinking, *J. Abnorm. Psychol.*, 2001, 110, 353-357

[114] Sumner J. A., Griffith J. W., Mineka S., Overgeneral autobiographical memory as a predictor of the course of depression: a meta-analysis, *Behav. Res. Ther.*, 2010, 48, 614-625

[115] Sheline Y. I., Depression and the hippocampus: cause or effect?, *Biol. Psychiatry*, 2011, 70, 308-309

[116] Desseilles M., Balteau E., Sterpenich V., Dang-Vu T. T., Darsaud A., Vandewalle G. et al., Abnormal neural filtering of irrelevant visual information in depression, *J. Neurosci.*, 2009, 29, 1395-1403

[117] Mulert C., Juckel G., Brunnmeier M., Karch S., Leicht G., Mergl R. et al., Prediction of treatment response in major depression: integration of concepts, *J. Affect. Disord.*, 2007, 98, 215-225

[118] Schmitz T. W., De Rosa E., Anderson A. K., Opposing influences of affective state valence on visual cortical encoding, *J. Neurosci.*, 2009, 29, 7199-7207

[119] Keenan K., Hipwell A., Feng X., Rischall M., Henneberger A., Klosterman S., Lack of assertion, peer victimization, and risk for depression in girls: testing a diathesis-stress model, *J. Adolesc. Health*, 2010, 47, 526-528

[120] Kercher A., Rapee R. M., A test of a cognitive diathesis-stress generation pathway in early adolescent depression, *J. Abnorm. Child Psychol.*, 2009, 37, 845-855

[121] Abela J. R., D'Alessandro D. U., Beck's cognitive theory of depression: a test of the diathesis-stress and causal mediation components, *Br. J. Clin. Psychol.*, 2002, 41, 111-128

[122] Spangler D. L., Simons A. D., Monroe S. M., Thase M. E., Evaluating the hopelessness model of depression: diathesis-stress and symptom components, *J. Abnorm. Psychol.*, 1993, 102, 592-600

[123] Gotlib I. H., Joormann J., Minor K. L., Hallmayer J., HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression, *Biol. Psychiatry*, 2008, 63, 847-851

[124] Miranda J., Gross J. J., Persons J. B., Hahn J., Mood matters: negative mood induction activates dysfunctional attitudes in women vulnerable to depression, *Cognitive Ther. Res.*, 1998, 22, 363-376

[125] Miranda J., Persons J. B., Dysfunctional attitudes are mood-state dependent, *J. Abnorm. Psychol.*, 1988, 97, 76-79

[126] Hedlund S., Rude S. S., Evidence of latent depressive schemas in formerly depressed individuals, *J. Abnorm. Psychol.*, 1995, 104, 517-525

[127] Bylsma L. M., Morris B. H., Rottenberg J., A meta-analysis of emotional reactivity in major depressive disorder, *Clin. Psychol. Rev.*, 2008, 28, 676-691

[128] Peeters F., Berkhof J., Rottenberg J., Nicolson N. A., Ambulatory emotional reactivity to negative daily life events predicts remission from major depressive disorder, *Behav. Res. Ther.*, 2010, 48, 754-760

[129] Bylsma L. M., Taylor-Clift A., Rottenberg J., Emotional reactivity to daily events in major and minor depression, *J. Abnorm. Psychol.*, 2011, 120, 155-167

[130] Thompson R. J., Berenbaum H., Bredemeier K., Cross-sectional and longitudinal relations between affective instability and depression, *J. Affect. Disord.*, 2011, 130, 53-59

[131] Kuehner C., Liebsch K., Huffziger S., Research letter: emotional reactivity to induced rumination predicts 1-year levels of depressive symptoms, *Psychol. Med.*, 2009, 39, 1226-1228

[132] Charbonneau A. M., Mezulis A. H., Hyde J. S., Stress and emotional reactivity as explanations for gender differences in adolescents' depressive symptoms, *J. Youth Adolesc.*, 2009, 38, 1050-1058

[133] Scher C. D., Ingram R. E., Segal Z. V., Cognitive reactivity and vulnerability: empirical evaluation of construct activation and cognitive diatheses in unipolar depression, *Clin. Psychol. Rev.*, 2005, 25, 487-510

[134] Lethbridge R., Allen N. B., Mood induced cognitive and emotional reactivity, life stress, and the prediction of depressive relapse, *Behav. Res. Ther.*, 2008, 46, 1142-1150

[135] Gotlib I. H., Joormann J., Cognition and depression: current status and future directions, *Annu. Rev. Clin. Psychol.*, 2010, 6, 285-312

[136] Ramel W., Goldin P. R., Eyer L. T., Brown G. G., Gotlib I. H., McQuaid J. R., Amygdala reactivity and mood-congruent memory in individuals at risk for depressive relapse, *Biol. Psychiatry*, 2007, 61, 231-239

[137] Fredrickson B. L., Levenson R. W., Positive emotions speed recovery from the cardiovascular sequelae of negative emotions, *Cogn. Emot.*, 1998, 12, 191-220

[138] McFarland B. R., Klein D. N., Emotional reactivity in depression: diminished responsiveness to anticipated reward but not to anticipated punishment or to nonreward or avoidance, *Depress. Anxiety*, 2009, 26, 117-122

[139] Teasdale J. D., Segal Z., Williams J. M., How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help?, *Behav. Res. Ther.*, 1995, 33, 25-39

[140] Teasdale J. D., Moore R. G., Hayhurst H., Pope M., Williams S., Segal Z. V., Metacognitive awareness and prevention of relapse in depression: empirical evidence, *J. Consult. Clin. Psychol.*, 2002, 70, 275-287

[141] Anderson I. M., Shippen C., Juhasz G., Chase D., Thomas E., Downey D. et al., State-dependent alteration in face emotion recognition in depression, *Br. J. Psychiatry*, 2011, 198, 302-308

[142] Santesso D. L., Steele K. T., Bogdan R., Holmes A. J., Deveney C. M., Meites T. M. et al., Enhanced negative feedback responses in remitted depression. *Neuroreport*, 2008, 19, 1045-1048

[143] Williams J. M., Healy D., Teasdale J. D., White W., Paykel E. S., Dysfunctional attitudes and vulnerability to persistent depression, *Psychol. Med.*, 1990, 20, 375-381

[144] Teasdale J. D., Dent J., Cognitive vulnerability to depression: an investigation of two hypotheses, *Br. J. Clin. Psychol.*, 1987, 26, 113-126

[145] Moulds M. L., Kandris E., Williams A. D., Lang T., Yap C., Hoffmeister K., An investigation of the relationship between cognitive reactivity and rumination, *Behav. Ther.*, 2008, 39, 65-71

[146] Segal Z. V., Kennedy S., Gemar M., Hood K., Pedersen R., Buis T., Cognitive reactivity to sad mood provocation and the prediction of depressive relapse, *Arch. Gen. Psychiatry*, 2006, 63, 749-755

[147] Barnhofer T., Chittka T., Cognitive reactivity mediates the relationship between neuroticism and depression, *Behav. Res. Ther.*, 2010, 48, 275-281

[148] Firk C., Markus C.R., Mood and cortisol responses following tryptophan-rich hydrolyzed protein and acute stress in healthy subjects with high and low cognitive reactivity to depression, *Clin. Nutr.*, 2009, 28, 266-271

[149] Segal Z. V., Bizzini L., Bondolfi G., Cognitive behaviour therapy reduces long term risk of relapse in recurrent major depressive disorder, *Evid. Based Ment. Health*, 2005, 8, 38

[150] Segal Z.V., Bieling P., Young T., MacQueen G., Cooke R., Martin L. et al., Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression, *Arch. Gen. Psychiatry*, 2010, 67, 1256-1264

[151] Bondolfi G., Jermann F., der Linden M. V., Gex-Fabry M., Bizzini L., Rouget B. W. et al., Depression relapse prophylaxis with Mindfulness-Based Cognitive Therapy: replication and extension in the Swiss health care system, *J. Affect. Disord.*, 2010, 122, 224-231

[152] Teasdale J. D., Segal Z. V., Williams J. M., Ridgeway V. A., Soulsby J. M., Lau M. A., Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy, *J. Consult. Clin. Psychol.*, 2000, 68, 615-623

[153] Raes F., Dewulf D., Van Heeringen C., Williams J. M., Mindfulness and reduced cognitive reactivity to sad mood: evidence from a correlational study and a non-randomized waiting list controlled study, *Behav. Res. Ther.*, 2009, 47, 623-627

[154] Fresco D.M., Segal Z. V., Buis T., Kennedy S., Relationship of posttreatment decentering and cognitive reactivity to relapse in major depression, *J. Consult. Clin. Psychol.*, 2007, 75, 447-55

[155] Koenigs M., Grafman J., The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex, *Behav. Brain Res.*, 2009, 201, 239-243

[156] Gotlib I. H., Hamilton P. J., Neuroimaging and Depression: Current Status and Unresolved Issues, *Curr. Dir. Psychol. Sci.*, 2008, 17, 159-163

[157] Lemogne C., Mayberg H., Bergouignan L., Volle E., Delaveau P., Lehéricy S. et al., Self-referential processing and the prefrontal cortex over the course of depression: a pilot study, *J. Affect. Disord.*, 2010, 124, 196-201

[158] Ritchey M., Dolcos F., Eddington K. M., Strauman T. J., Cabeza R., Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response, *J. Psychiatr. Res.*, 2011, 45, 577-587

[159] Denson T. F., Pedersen W. C., Ronquillo J., Nandy A. S., The angry brain: neural correlates of anger, angry rumination, and aggressive personality, *J. Cogn. Neurosci.*, 2009, 21, 734-744

[160] Coie J. D., Watt N. F., West S. G., Hawkins J. D., Asarnow J. R., Markman H. J. et al., The science of prevention. A conceptual framework and some directions for a national research program, *Am. Psychol.*, 1993, 48, 1013-1022

[161] Marquand A. F., Mourão-Miranda J., Brammer M. J., Cleare A. J., Fu C. H., Neuroanatomy of verbal working memory as a diagnostic biomarker for depression, *Neuroreport*, 2008, 19, 1507-1511

[162] Fu C. H., Mourão-Miranda J., Costafreda S. G., Khanna A., Marquand A. F., Williams S. C. et al., Pattern classification of sad facial processing: toward the development of neurobiological markers in depression, *Biol. Psychiatry*, 2008, 63, 656-662

[163] Cook I. A., Hunter A. M., Abrams M., Siegman B., Leuchter A. F., Midline and right frontal brain function as a physiologic biomarker of remission in major depression, *Psychiatry Res.*, 2009, 174, 152-157

[164] Ising M., Horstmann S., Kloiber S., Lucae S., Binder E. B., Kern N. et al., Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression - a potential biomarker?, *Biol. Psychiatry*, 2007, 62, 47-54

[165] Buckley T. M., Schatzberg A. F., A pilot study of the phase angle between cortisol and melatonin in major depression - a potential biomarker?, *J. Psychiatr. Res.*, 2010, 44, 69-74

[166] Fuchikami M., Morinobu S., Segawa M., Okamoto Y., Yamawaki S., Ozaki N. et al., DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression, *PLoS One*, 2011, 6, e23881

[167] Peralta V., Cuesta M. J., Lack of insight in mood disorders, *J. Affect. Disord.*, 1998, 49, 55-58

[168] Ochsner K. N., Hughes B., Robertson E. R., Cooper J. C., Gabrieli J. D., Neural systems supporting the control of affective and cognitive conflicts, *J. Cogn. Neurosci.*, 2009, 21, 1842-1855

[169] Piech R. M., Lewis J., Parkinson C. H., Owen A. M., Roberts A. C., Downing P. E. et al., Neural correlates of affective influence on choice, *Brain Cogn.*, 2010, 72, 282-288

[170] Pizzagalli D. A., Frontocingulate dysfunction in depression: toward biomarkers of treatment response, *Neuropsychopharmacology*, 2011, 36, 183-206