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## Functional Neuroimaging Biomarkers of Resilience in Major Depressive Disorder

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### Abstract

**Purpose of review:** In this review we provide an overview of definitions and determinants of resilience in the context of neuroimaging research in Major Depressive Disorder (MDD). We summarize emerging literature on functional neuroimaging biomarkers of resilience in MDD and discuss their clinical relevance and implications for future research.

**Recent findings:** Resilience in MDD is characterized by dissociable profiles of activation and functional connectivity within brain networks involved in cognitive control, emotion regulation, and reward processing. Increased activation of frontal cortical brain regions implicated in cognitive appraisal and emotion regulation is a common characteristic of resilient individuals at high risk for MDD and of individuals with MDD with a favorable illness course. Furthermore, significant associations between fronto-striato-limbic functional connectivity and both positively-interpreted stressful life events in resilient high-risk individuals and a favorable response to first-line treatments in depressed individuals suggest that neuro-compensatory changes and experience-dependent plasticity underlie resilience in MDD.

**Summary:** Emerging research has identified putative functional neuroimaging biomarkers of resilience in MDD. A continued focus on identifying neurobiological underpinnings of resilience, in the context of dynamic environmental and developmental influences on MDD, will advance our understanding of resilience in this disorder and improve approaches to prevention and treatment.

### Keywords

Resilience; Major Depressive Disorder (MDD); Functional neuroimaging (fMRI) biomarkers

### Introduction

Major Depressive Disorder (MDD) is among the most prevalent and debilitating of all psychiatric illnesses; it is characterized by pervasive decreases in mood and/or in the ability

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Conflicts of interest

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to experience pleasure (1). MDD affects over 17 million Americans annually (2). In fact, MDD is the leading cause of global disability and is associated with significant morbidity and mortality (3). The peak incidence of MDD occurs in adolescence and young adulthood (4), with earlier onset associated with greater recurrence and a more refractory illness course (5). Offspring of depressed parents are at particularly high risk, experiencing a six- to ten-fold increase in risk for MDD (6, 7). Importantly, MDD is associated with persistent impairments in well-being and quality of life, even with successful treatment of depressive symptoms (8).

To date, most neuroimaging studies have focused on elucidating neural markers of risk and pathology in MDD (for a systematic review and meta-analysis; Kennis et al., 2020 (9)); rarely do they focus on resilience to MDD. It is noteworthy that while studies delineating the neurobiology of resilience (10) are important, they cannot adequately characterize broader aspects of resilience in MDD, including cognitive reappraisal, emotion regulation, a positive outlook, self-efficacy, or finding meaning in the face of hardship. In this paper we discuss resilience in the context of MDD, review recent developments in neuroimaging biomarkers of resilience, and outline clinical considerations and promising directions for future research.

## Defining Resilience

The American Psychological Association broadly defines resilience as “bouncing back” from difficult life experiences and “adapting well” to stress or adversity (11). Resilience may be best conceptualized as a dynamic, multi-dimensional capacity with biological, psychological, and socio-cultural contributions (12, 13). We and others have taken a developmental approach to investigating biomarkers of resilience in MDD. In this context, we define resilience in MDD as not developing depression or other psychopathology despite having a first-degree relative with MDD (e.g., (14, 15)). While this definition does not fully capture the dynamic and multi-factorial determinants of resilience, it provides a clear approach to characterizing relevant neural processes in the context of developmental factors and stressors that also contribute to resilience in MDD. Identifying biomarkers of resilience in MDD holds promise for the development of novel interventions that target and strengthen adaptive processes.

## Functional Neuroimaging Biomarkers of Resilience in Depression

There are two broad categories of research on resilience to MDD: assessing factors that contribute to resilience despite being at high risk (having a first-degree relative with MDD); and examining the neural signatures of depressed individuals with a favorable illness trajectory.

### Resilience to MDD in High-Risk Youth

Adolescence is characterized by rapid neurobiological and socio-emotional change, and consequently, is a peak risk period for MDD. At the same time, neural plasticity during this period facilitates greater learning, flexibility, and adaptive coping, and thus, may offers higher potential for resilience to MDD. Indeed, in adolescence there is significant maturation of neural networks involved in cognitive control and emotion regulation (16, 17), as well as

experience-dependent plasticity of brain networks (18). Thus, elucidating biomarkers of resilience to adolescent-onset MDD may help researchers develop more targeted and neurobiologically-focused approaches to prevention and intervention that enhance resilience to MDD.

Recently, we sought to identify neural markers that distinguish resilient adolescents at high risk for MDD. We investigated neural signatures of resilience in high-risk adolescent females (biological offspring of mothers with recurrent MDD) relative to low-risk adolescents, following them from ages 10–14 through age 18. We found unique functional connectivity (FC) profiles within limbic, salience, and executive control networks (ECNs) that distinguished high-risk resilient adolescents from both high-risk adolescents who developed MDD and low-risk healthy controls (14). Moreover, there was a significant association between amygdala-orbitofrontal cortex FC and positively-interpreted – albeit stressful – life events in the resilient adolescents. We also identified distinct patterns of neural activation in reward circuitry that appear to be biomarkers of resilience in MDD. Both high-risk resilient and high-risk converted adolescents had blunted activation in the striatum and ventral anterior cingulate cortex (ACC) during anticipation of reward, relative to low-risk controls (15). Resilient adolescents had *greater* frontal cortical activation than did adolescents who developed MDD during reward anticipation, *and decreased* activation in the superior frontal gyrus and cuneus during reward outcome (15). These findings suggest that ‘normative’ reward processing is not a prerequisite for resilience in high-risk offspring, and that high-risk resilient individuals can develop adaptive compensatory processes to remain healthy despite deficits in reward processing.

Hirshfeld-Becker and colleagues also reported findings from a study of youth at risk for MDD followed up 3–4 years later to assess conversion to MDD (19). At baseline, resilient youth had greater FC between the left and right dorsolateral prefrontal cortex (DLPFC), whereas youth who converted had greater negative FC between these regions. Resilient youth also had greater FC between the subgenual ACC (sgACC) and right precentral gyrus. Given that the sgACC (part of the default mode network [DMN], found to be hyperactive and hyperconnected in MDD in association with aberrant self-referential and ruminative thoughts), and DLPFC (part of the ECN) are anticorrelated in healthy individuals, these results suggest that resilience involves neuro-compensation and is not characterized by ‘normal’ connectivity profiles of low-risk healthy controls.

In another recent study assessing resilience to MDD over two years, Rodman and colleagues characterized differences between youth with and without a history of childhood maltreatment in neural activation during an emotion regulation task (20). Resilient youth with a history of maltreatment had greater prefrontal cortical activation and a greater capacity to modulate amygdala activity during a cognitive reappraisal task than did maltreated youth who developed MDD. Moreover, in youth without a history of childhood maltreatment there was no association between neural activation during reappraisal and depressive symptoms. These findings support the formulation that emotion regulation strategies such as cognitive reappraisal bolster resilience and help prevent MDD, particularly in high-risk youth.

## Resilience Against MDD in Adults

Researchers have also investigated neural markers of resilience in adults with first-degree relatives with MDD. Barbour et al. examined the association between amygdala activity during processing of neutral facial stimuli and scores on the Connor-Davidson Resilience Scale (CD-RISC; (21)) in adults with and without a family history of MDD (22). Participants with a family history of MDD had greater amygdala activity during processing of looming neutral faces than did participants with no family history; activation was negatively related to CD-RISC scores. In a study of late-life depression, Leaver and colleagues similarly found that CD-RISC scores were negatively correlated with amygdala activity and FC with the DMN; in addition, depression scores were negatively associated with amygdala-ECN FC (23). Wackerhagen and colleagues recruited adult patients with MDD, their unaffected (i.e., resilient) first-degree relatives, and low-risk healthy controls and assessed neural activation and FC during a face-matching task (24). Resilient individuals had greater FC among the amygdala, perigenual ACC, and superior frontal gyrus compared to their depressed first-degree relatives and controls. Finally, Nord et al. recruited unmedicated depressed adults, their unaffected first-degree relatives, and healthy controls and found that relatives and healthy comparison adults had significantly greater activation of the DLPFC during a working memory task than did depressed patients (25). Collectively, these findings suggest that reduced amygdala activity and greater ECN activity underlie more positive ‘bottom-up’ generation of emotion and ‘top-down’ interpretation of emotion-laden stimuli, respectively, contributing to resilience in MDD.

## Resilience in MDD

Researchers have characterized illness trajectory in MDD, attempting to differentiate individuals with a favorable course from those who develop a chronic, refractory illness. Frässle and colleagues used generative embedding (a form of machine learning) with neural activation and FC during an emotion face-processing task to predict who would remain in remission from MDD and who would develop a chronic illness course at 2-year follow-up (26). Individuals who showed stronger modulation of emotion in face processing (occipital and fusiform face areas) and limbic (amygdala) regions were more likely to remain in remission at follow-up. Similarly, Langenecker and colleagues examined whether neural activation and FC related to cognitive control predict relapse at a one-year follow-up in adults with a history of MDD who were in remission at study entry (27). Similar to healthy comparison subjects, participants who were resilient to relapse at follow-up had greater neural activation of the middle frontal gyrus (MFG) when making commission errors during a go/no-go task, and greater MFG FC with the inferior frontal gyrus, inferior parietal lobule and striatal regions, relative to individuals who experienced MDD recurrence.

Recent findings from clinical trials that have incorporated functional neuroimaging are relevant to understanding the neural basis of resilience in MDD. Increased plasticity of brain networks subserving cognition, emotion, and reward processing appears to affect the likelihood of recovery from depression with both antidepressant medication (ADM) and psychotherapy. Randomized clinical trials of first-line ADM have reported that increased prefrontal and frontal cortical function, implicated in cognitive reappraisal and modulating emotional responses and self-referential processing, is associated with improved treatment

response. Specifically, greater baseline FC between the ECN and the DMN was associated with greater likelihood of response to ADM (28). Greater FC among DLPFC, supramarginal gyrus, and MFG during response inhibition predicted successful ADM response in depressed individuals (29). Enhanced deactivation of the anterior medial PFC (DMN region) and greater DLPFC activation and anticorrelation with the DMN were also associated subsequent improvement in depressive symptoms and working memory (30). These findings suggest that greater ECN activation and FC portend a more favorable treatment course in MDD.

Reward circuitry has also been implicated in distinguishing a favorable response to treatment from a more refractory illness course. Greenberg and colleagues found that pre-treatment ventral striatal (VS) dynamic response to reward expectancy and prediction error modulated likelihood of treatment response to ADM (31). In addition to its association with treatment response, pre-to-post ADM treatment increases in nucleus accumbens (NAcc, encompassed within the VS) FC was also associated with improved functioning in quality-of-life domains: *environmental* (NAcc-vACC), *social* (NAcc-paracingulate gyrus), and *physical* (NAcc-thalamus) (32). Early changes in reward circuit FC (33) and activation during anticipation of monetary reward after 2-weeks of ADM have also been associated with treatment response at 8-week follow-up (34). These findings suggest that differential reward circuitry profiles are linked to a favorable treatment course in MDD with respect symptoms and quality-of-life outcomes.

Similar brain regions have been implicated in response to psychotherapy. Quierazza and colleagues found that greater baseline striatum and amygdala activation during probabilistic reversal learning predicted response to cognitive-behavioral therapy in unmedicated depressed women (35). Further, a study of neural predictors of response to behavioral activation found that baseline FC between the MFG and temporoparietal regions during an emotion regulation task predicted a greater treatment-related reduction in anhedonia in depressed adults (36). Another study found that greater decreases from pre-to-post cognitive-behavioral therapy in activation of the DLPFC and precuneus during processing of negative stimuli were associated with better treatment response (37).

Although these clinical trials assessed relatively short-term treatment outcomes, they highlight promising targets for networks that may be implicated in resilience to MDD.

## Discussion

In this paper we reviewed recent findings relevant to functional neuroimaging biomarkers of resilience in MDD. Accumulating data suggest that resilience is not necessarily characterized not by “normal” patterns of brain activation, but rather, by neural profiles that distinguish resilient individuals from those who develop MDD, those who experience a refractory illness course, and from healthy comparison individuals. While resilient individuals may have altered neural activation similar to that seen in MDD, they have also been found to have distinct neural activation patterns in cognitive control, emotion regulation, and reward circuitry that reflect compensation, including increased activity in, and FC with, prefrontal and frontal-cortical brain regions implicated in top-down cognitive

control and emotion regulation. Finally, emerging studies of neural biomarkers of resilience have begun to illuminate the complex relation between genetic and environmental risk, and the uniquely human characteristics that contribute to resilience to MDD. These findings highlight the importance of continuing to investigate neurobiological underpinnings of resilience in depression in relation to complex and dynamic environmental and developmental influences.

Enhancing resilience has long been a central tenet of psychotherapy for depression. Psychoanalysts highlighted the importance to the treatment of depression of personal growth, self-actualization, and generating meaning from stressful life experiences. Yet, few treatment trials or neuroimaging studies of MDD have focused on resilience. Research is needed that takes a dimensional approach to investigating biomarkers of resilience in MDD in order to characterize foundational traits of resilience as well as dynamic, evolving contributors to resilience at different developmental stages (38, 39). A dimensional approach may also yield an alternative approach to assessing the efficacy of preventions and treatments for depression, conceptualizing resilience as an outcome that extends beyond more narrowly defined response/remission criteria. Indeed, despite improvement in clinical symptoms of depression, many patients with MDD continue to struggle with adaptive coping, optimism, and a sense of self-efficacy, and have ongoing and pervasive impairments in well-being (8, 40).

Another unexplored area of investigation involves the question of whether altering neural circuitry can augment resilience and reduce depression severity. We are beginning to gain a more comprehensive understanding of the underlying connectivity, activation, and plasticity of neural networks that may contribute to resilience in MDD. As we highlighted here, recent studies examining resilience to MDD in high-risk individuals have identified alterations in neural networks – particularly in circuitry implicated in emotion regulation, reward processing, and cognitive control – that characterize individuals who are resilient to MDD. Continuing to focus on identifying biomarkers of resilience, particularly in high-risk individuals, and on strengthening network connectivity and plasticity underlying resilience instead of targeting pathologic connectivity, may facilitate the development of novel approaches to prevent and treat depression.

The findings reviewed here are important for the study of neural markers of resilience to depression. One critical direction is to leverage large, longitudinal multi-modal datasets, such as the Adolescent Brain Cognitive Development cohort (41), to increase our understanding of the complex and multifactorial contributors to resilience to depression and their evolution across development. Relatedly, we need research investigating the interactive effects of stress-axis and gonadal hormones in relation to resilience to MDD. Indeed, changes in resilience are particularly likely during developmental transitions in which new risk and protective factors emerge in the context of hormonal effects on brain organization (42, 43).

Another understudied risk period during which resilience to MDD should be examined is the transition to adulthood. Transition-age youth have newly acquired independence from both pathological and protective familial environmental influences, but also experience unique

and specific stressors. This is important, as we see rates of depression increase in this age group (44). More broadly, investigations are needed to elucidate the relation between both internal characteristics, such as optimism, spirituality, flexible adaptation, and ‘meaning-making’ (attributing significance to adversity) (45) and environmental influences, such as family dynamics, peer relationships and role-models, and specific life events and their meaning, and neurobiological processes.

## Conclusion

Emerging research has identified putative functional neuroimaging biomarkers of resilience to depression that are promising targets for novel approaches to prevention and treatment for MDD. A continued focus on identifying neuroimaging biomarkers of resilience in depression, particularly in high-risk individuals and those with MDD who have a favorable illness trajectory, will advance our understanding of how best to promote resilience to depression.

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### Key Points

- Recent psychiatric neuroimaging and clinical trials research has focused on factors that confer resilience to Major Depressive Disorder (MDD).
- Resilience to MDD is characterized by dissociable profiles of activation and FC within cognitive control, emotion regulation, and reward networks in the brain, relative to individuals who develop MDD, who experience a chronic course of MDD, and healthy comparison individuals.
- Increased activation of frontal cortical brain regions, implicated in cognitive appraisal and emotion regulation, appears to characterize resilience in MDD.
- An emerging focus on the investigation of neural biomarkers of resilience in relation dynamic environmental stressors and experiences over development is illuminating the complex relation between genetic and environmental risk and the uniquely human elements of resilience to MDD.