Functional neuroimaging biomarkers of resilience in major depressive disorder

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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 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, will advance our understanding of resilience and improve approaches to prevention and treatment of MDD.

Keywords
functional neuroimaging biomarkers, major depressive disorder (MDD), resilience

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 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-fold to 10-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.* [9]); rarely do they focus on resilience to MDD. It is noteworthy that while studies delineating the neurobiology of resilience 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 [10]. In this article, we discuss resilience in the context of MDD, review recent developments

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KEY POINTS

- Recent psychiatric neuroimaging and clinical trials research has focused on factors that confer resilience to MDD.
- Resilience to MDD is characterized by dissociable profiles of activation and functional connectivity 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 to 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.

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, multidimensional 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 multifactorial 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 (e.g., having a first-degree relative with MDD); and examining the neural signatures of depressed individuals with a favorable illness trajectory.

Resilience to major depressive disorder 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 offer 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 profiles within limbic, salience, and executive control networks 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 functional connectivity 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 *et al.* [19▪] also reported findings from a study of youth at risk for MDD who were

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assessed 3-4 years later for conversion to MDD. At baseline, resilient youth had greater functional connectivity between the left and right dorsolateral prefrontal cortex (DLPFC), whereas youth who converted had greater negative functional connectivity between these regions. Resilient youth also had greater functional connectivity between the subgenual ACC and right precentral gyrus. Given that the subgenual ACC [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 the DLPFC [part of the executive control network (ECN)] are anticorrelated in healthy individuals, these results suggest that resilience involves neuro-compensation and is not characterized by 'normal' connectivity profiles characteristic of low-risk healthy controls.

In another recent study assessing resilience to MDD over 2 years, Rodman *et al.* [20▪▪] characterized differences in neural activation during an emotion regulation task between youth with and without a history of childhood maltreatment. 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, there was no association between neural activation during reappraisal and depressive symptoms in youth without a history of childhood maltreatment. 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 major depressive disorder in adults

Researchers have also investigated neural markers of resilience in adults with first-degree relatives with MDD. Barbour *et al.* [21▪] examined the association between amygdala activity during processing of neutral facial stimuli and scores on the Connor-Davidson Resilience Scale (CD-RISC [22]) in adults with and without a family history of MDD. 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 *et al.* [23] similarly found that CD-RISC scores were negatively correlated with amygdala activity and functional connectivity with the DMN; in addition, depression scores were negatively associated with amygdala-ECN functional connectivity. Wackerhagen *et al.* [24▪] recruited adult patients with MDD, their unaffected (i.e., resilient) first-degree relatives, and low-risk healthy controls and assessed neural activation and functional connectivity during a face-matching task. Resilient individuals had greater functional connectivity among the amygdala, perigenual ACC, and superior frontal gyrus compared with their depressed first-degree relatives and controls. Finally, Nord *et al.* [25▪] recruited unmedicated depressed adults, their unaffected first-degree relatives, and healthy controls and found that unaffected relatives and healthy comparison adults had significantly greater activation of the DLPFC during a working memory task than did depressed participants. 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 major depressive disorder

Researchers have characterized illness trajectory in MDD, attempting to differentiate individuals with a favorable course from those who develop a chronic, refractory illness. Frässle *et al.* [26▪] used generative embedding (a form of machine learning) with neural activation and functional connectivity 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. 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 *et al.* [27▪] examined whether neural activation and functional connectivity related to cognitive control could predict relapse at 1-year follow-up in adults with a history of MDD who were in remission at study entry. Similar to healthy comparison individuals, participants who were resilient to relapse had greater neural activation of the middle frontal gyrus (MFG) when making commission errors during the Go/No-Go task, and greater MFG functional connectivity 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

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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 functional connectivity between the ECN and the DMN was associated with greater likelihood of response to ADM [28▪▪]. Greater functional connectivity 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 (ECN region) 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 functional connectivity 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 *et al.* [31▪▪] found that pre-treatment ventral striatal dynamic response to reward expectancy and prediction error modulated likelihood of treatment response to ADM. In addition to its association with treatment response, pre-to-post ADM treatment increases in nucleus accumbens (NAcc, encompassed within the ventral striatum) functional connectivity was associated with improved functioning in quality of life domains: *environmental* (NAcc-ventral ACC), *social* (NAcc-paracingulate gyrus), and *physical* (NAcc-thalamus) [32]. Early changes in reward circuit functional connectivity [33▪] and activation during anticipation of 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. Queirazza *et al.* [35▪▪] found that greater baseline striatum and amygdala activation during a probabilistic reversal learning task predicted response to cognitive behavioral therapy in unmedicated depressed women. Further, a study of neural predictors of response to behavioral activation found that baseline functional connectivity 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 in activation of the DLPFC and precuneus during processing of negative stimuli pre-to-post treatment were associated with a greater likelihood of response to cognitive behavioral therapy [37▪].

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

DISCUSSION

In this article, we reviewed recent findings relevant to functional neuroimaging biomarkers of resilience in MDD. Accumulating data suggest that resilience is not necessarily characterized 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 also have distinct neural activation patterns in cognitive control, emotion regulation, and reward circuitry that may reflect compensation, including increased activity in, and functional connectivity 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 have highlighted the importance of personal growth, self-actualization, and generating meaning from stressful life experiences in the treatment of depression. 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 prevention and treatment approaches 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 self-efficacy, and have ongoing and pervasive impairments in well-being [8,40].

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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 future direction is to leverage large, longitudinal multimodal 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 begun to identify 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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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). American Psychiatric Pub; 2013 May 22.
2. National Institutes of Health (NIH). Prevalence of Major Depressive Episode Among Adults. National Institute of Mental Health (NIMH); 2019; Available from: https://www.nimh.nih.gov/health/statistics/major-depression.shtml#part_155029 Accessed February 9, 2020.
3. Global Burden of Disease Study Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study. Lancet 2015; 386:743–800.
4. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health 2013; 34:119–138.
5. Wilson S, Hicks BM, Foster KT, *et al.* Age of onset and course of major depressive disorder: associations with psychosocial functioning outcomes in adulthood. Psychol Med 2015; 45:505–514.
6. Breslau J, Gilman SE, Stein BD, *et al.* Sex differences in recent first-onset depression in an epidemiological sample of adolescents. Transl Psychiatry 2017; 7:e1139.
7. Weissman MM, Wickramaratne P, Gameroff MJ, *et al.* Offspring of depressed parents: 30 years later. Am J Psychiatry 2016; 173:1024–1032.
8. Rhebergen D, Beekman AT, de Graaf R, *et al.* Trajectories of recovery of social and physical functioning in major depression, dysthymic disorder and double depression: a 3-year follow-up. J Affect Disord 2010; 124:148–156.
9. Kennis M, Gerritsen L, van Dalen M, *et al.* Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. Mol Psychiatry 2020; 25:321–338.

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10. Cathomas F, Murrough JW, Nestler EJ, *et al.* Neurobiology of resilience: interface between mind and body. Biol Psychiatry 2019; 86:410–420.

11. American Psychological Association (APA). The road to resilience [Available from: https://www.apa.org/topics/resilience]. Accessed September 2, 2020.

12. Feder A, Fred-Torres S, Southwick SM, Charney DS. The biology of human resilience: opportunities for enhancing resilience across the life span. Biol Psychiatry 2019; 86:443–453.

13. Southwick SM, Bonanno GA, Masten AS, *et al.* Resilience definitions, theory, and challenges: interdisciplinary perspectives. Eur J Psychotraumatol 2014; 5:25338.

14. ▪ Fischer AS, Camacho MC, Ho TC, *et al.* Neural markers of resilience in adolescent females at familial risk for major depressive disorder. JAMA Psychiatry 2018; 75:493–502.

The study demonstrated that 'normative' reward processing may not be a prerequisite for resilience, and that resilient individuals at high-familial risk for major depressive disorder (MDD) appear to develop adaptive compensatory processes to remain healthy despite deficits in reward processing.

15. ▪ Fischer AS, Ellwood-Lowe ME, Colich NL, *et al.* Reward-circuit biomarkers of risk and resilience in adolescent depression. J Affect Disord 2019; 246:902–909.

The study identified differential pre-to-post treatment changes in cortico-striatal functional connectivity within reward circuitry suggestive of a mechanism of favorable treatment response with respect to depressive symptoms and quality of life.

16. Giedd JN, Blumenthal J, Jeffries NO, *et al.* Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999; 2:861–863.

17. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol 2002; 453:116–130.

18. McEwen BS. The brain on stress: toward an integrative approach to brain, body, and behavior. Perspect Psychol Sci 2013; 8:673–675.

19. ▪ Hirshfeld-Becker DR, Gabrieli JDE, Shapero BG, *et al.* Intrinsic functional brain connectivity predicts onset of major depression disorder in adolescence: a pilot study. Brain Connect 2019; 9:388–398.

Findings from this study suggest that resilience against depression involves greater connectivity between the left and right dorsolateral prefrontal cortex and between the subgenual anterior cingulate cortex and precentral gyrus, brain regions that are typically anticorrelated in healthy individuals. Thus, results of this study lend support to the notion that resilience may involve neuro-compensation.

20. ▪▪ Rodman AM, Jenness JL, Weissman DG, *et al.* Neurobiological markers of resilience to depression following childhood maltreatment: the role of neural circuits supporting the cognitive control of emotion. Biol Psychiatry 2019; 86:464–473.

The study found that resilient youth with a history of maltreatment showed increased prefrontal cortical activation and a greater capacity to modulate amygdala activity during a cognitive reappraisal task relative to those who developed MDD. These findings suggest that cognitive reappraisal may bolster resilience and help prevent MDD, particularly among high-risk youth.

21. ▪ Barbour T, Holmes AJ, Farabaugh AH, *et al.* Elevated amygdala activity in young adults with familial risk for depression: a potential marker of low resilience. Biol Psychiatry Cogn Neurosci Neuroimaging 2020; 5:194–202.

The study examined dimensional resilience scores in relation to neural activation in response to 'looming' neutral-valence facial stimuli in young adults with and without a family history of MDD, highlighting the utility of incorporating a dimensional measure of resilience.

22. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003; 18:76–82.

23. Leaver AM, Yang H, Siddarth P, *et al.* Resilience and amygdala function in older healthy and depressed adults. J Affect Disord 2018; 237:27–34.

24. ▪ Wackerhagen C, Veer IM, Erk S, *et al.* Amygdala functional connectivity in major depression – disentangling markers of pathology, risk and resilience. Psychol Med 2019; 1–11.

The study examined task-dependent and independent functional connectivity in adults with MDD and their unaffected first-degree relatives. Findings suggest increased integration of executive and salience networks in adults resilient to MDD.

25. ▪ Nord CL, Halahakoon DC, Lally N, *et al.* The neural basis of hot and cold cognition in depressed patients, unaffected relatives, and low-risk healthy controls: an fMRI investigation. J Affect Disord 2020; 274:389–398.

The study examined neural activation during working memory and emotional processing tasks in adults with depression, their unaffected (i.e., resilient) first-degree relatives, and healthy comparison adults. Findings from this study lend further support to the idea that resilience may involve neuro-compensation.

26. ▪ Frässle S, Marquand AF, Schmaal L, *et al.* Predicting individual clinical trajectories of depression with generative embedding. Neuroimage Clin 2020; 26:102213.

These authors combined functional MRI data and machine learning to predict whether individuals with MDD would remit or develop a chronic course, thereby highlighting the utility of integrating machine learning and neuroimaging to identify resilience in individuals with MDD with a favorable treatment course.

27. ▪ Langenecker SA, Jenkins LM, Stange JP, *et al.* Cognitive control neuroimaging measures differentiate between those with and without future recurrence of depression. Neuroimage Clin 2018; 20:1001–1009.

The study showed that decreased activation of brain regions implicated in cognitive control at baseline was associated with MDD recurrence in young adults with a history of MDD, highlighting that increased 'top-down' cognitive control appears to be a marker of resilience.

28. ▪▪ Chin Fatt CR, Jha MK, Cooper CM, *et al.* Effect of intrinsic patterns of functional brain connectivity in moderating antidepressant treatment response in major depression. Am J Psychiatry 2020; 177:143–154.

The study identified specific functional connectivity moderators of antidepressant medication (ADM) treatment outcomes within cognitive control and default mode networks that appear to play an important role in identifying favorable ADM treatment response in MDD.

29. ▪ Tozzi L, Goldstein-Piekarski AN, Korgaonkar MS, Williams LM. Connectivity of the cognitive control network during response inhibition as a predictive and response biomarker in major depression: evidence from a randomized clinical trial. Biol Psychiatry 2020; 87:462–472.

The study found that baseline functional connectivity of cognitive control regions implicated in cognitive reappraisal and modulating emotional responses may assist in the prediction of successful treatment response to ADM, thereby demonstrating the utility of functional neuroimaging biomarkers in the identification of a more resilient course in MDD.

30. ▪▪ Meyer BM, Rabl U, Huemer J, *et al.* Prefrontal networks dynamically related to recovery from major depressive disorder: a longitudinal pharmacological fMRI study. Transl Psychiatry 2019; 9:64.

The study showed that prefrontal network connectivity and activation profiles are dynamically related to likelihood of recovery and favorable illness course with antidepressant mediation.

31. ▪▪ Greenberg T, Fournier JC, Stiffler R, *et al.* Reward related ventral striatal activity and differential response to sertraline versus placebo in depressed individuals. Mol Psychiatry 2020; 25:1526–1536.

Findings from this study suggest that baseline ventral striatal activity in response to rewards may help determine a favorable treatment response to ADM. Thus, pretreatment measures of reward circuit function may serve as a neural biomarker that helps in treatment selection and determining the likelihood of treatment response.

32. Fischer AS, Holt-Gosselin B, Fleming SL, Hack LM, *et al.* Intrinsic reward circuit connectivity profiles underlying symptom and quality of life outcomes following antidepressant medication: A report from the iSPOT-D trial. Neuropsychopharmacology 2020: in press.

33. ▪ An J, Li L, Wang L, *et al.* Striatal functional connectivity alterations after two-week antidepressant treatment associated to enduring clinical improvement in major depressive disorder. Front Psychiatry 2019; 10:884.

The study demonstrated that early change in cortical-striatal functional connectivity following 2 weeks of ADM may assist in identifying patients with MDD who are likely to show enduring improvement in depressive symptoms.

34. ▪▪ Dunlop K, Rizvi SJ, Kennedy SH, *et al.* Clinical, behavioral, and neural measures of reward processing correlate with escitalopram response in depression: a Canadian Biomarker Integration Network in Depression (CAN-BIND-1) Report. Neuropsychopharmacology 2020; 45:1390–1397.

The study demonstrated that early treatment changes in reward processing (after 2 weeks of ADM) was associated with longer term response to ADM and, thus, may serve as an important neuroimaging biomarker of favorable response early in the course of treatment.

35. ▪▪ Queirazza F, Fouragnan E, Steele JD, *et al.* Neural correlates of weighted reward prediction error during reinforcement learning classify response to cognitive behavioral therapy in depression. Sci Adv 2019; 5:eaav4962.

The study showed that cognitive behavioral therapy responders and nonresponders had dissociable profiles of neural activation in the striatum and amygdala during a probabilistic reversal learning task administered pretreatment, suggesting predictive validity of the task for classifying response.

36. ▪▪ Walsh EC, Eisenlohr-Moul TA, Minkel J, *et al.* Pretreatment brain connectivity during positive emotion upregulation predicts decreased anhedonia following behavioral activation therapy for depression. J Affect Disord 2019; 243:188–192.

The study suggests that neuroimaging biomarkers can be used to predict response to behavioral activation therapy for depression, and pretreatment decreased connectivity of the middle frontal gyrus with temporoparietal regions during emotion regulation may be a marker of response to behavioral activation.

37. ▪ Rubin-Falcone H, Weber J, Kishon R, *et al.* Neural predictors and effects of cognitive behavioral therapy for depression: the role of emotional reactivity and regulation. Psychol Med 2020; 50:146–160.

The study found that increased modulation of neural circuits involved in emotion regulation pre-to-post treatment is associated with better response to cognitive-behavioral therapy, suggesting that treatments that enhance modulation of emotion regulation may be particularly effective for treating MDD.

38. Gaffrey MS, Luby JL, Barch DM. Towards the study of functional brain development in depression: an interactive specialization approach. Neurobiol Dis 2013; 52:38–48.

39. Bessette KL, Burkhouse KL, Langenecker SA. An interactive developmental neuroscience perspective on adolescent resilience to familial depression. JAMA Psychiatry 2018; 75:503–504.

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40. Chevance A, Ravaud P, Tomlinson A, *et al.* Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: qualitative content analysis of a large international online survey. Lancet Psychiatry 2020; 7:692–702.

41. Jernigan TL, Brown SA, Dowling GJ. The adolescent brain cognitive development study. J Res Adolesc 2018; 28:154–156.

42. Schulz KM, Sisk CL. The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. Neurosci Biobehav Rev 2016; 70:148–158.

43. Lambert K, Hunter RG, Bartlett AA, *et al.* In search of optimal resilience ratios: differential influences of neurobehavioral factors contributing to stress-resilience spectra. Front Neuroendocrinol 2020; 56:100802.

44. Xiao H, Carney DM, Youn SJ, *et al.* Are we in crisis? National mental health and treatment trends in college counseling centers. Psychol Serv 2017; 14:407–415.

45. Feldman R. What is resilience: an affiliative neuroscience approach. World Psychiatry 2020; 19:132–150.

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