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...
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; 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 matura-

tion 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 adoles-
cents 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...
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
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].
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. Relatively, 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.

Acknowledgements
We thank our patients and study participants for guiding and challenging our research focus to incorporate dynamic and multifaceted determinants of resilience in depression, and for continually inspiring us to develop improved interventions that focus on bolstering our strengths. We also thank members of our lab for their ongoing efforts to advance the current field with respect to examining resilience and preventive biomarkers in depression.

Financial support and sponsorship
The research described in this article was facilitated by funding from NIMH T32-MH019938 (A.S.F.), NIMH T32-MH096679 (K.E.H.), the Klingenstein Third Generation Foundation Fellowship in Adolescent Depression (A.S.F.), and NIMH R37-MH101495 (I.H.G.).

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

Neural correlates of weighted et al. Gaffrey MS, Luby JL, Barch DM. Towards the study of functional brain
ght dorsolateral prefrontal cortex and
et al. McEwen BS. The brain on stress: toward an integrative approach to brain,
www.co-psychiatry.com American Psychological A
Brain development during child-
et al. Giedd JN, Blumenthal J, Jeffries NO,
to resilience [Available
et al. Elevated amygdala activity in
Pretreatment brain connectivity
The neural basis of hot and cold
et al. Fischer AS, Camacho MC, Ho TC, et al. Neural markers of resilience in
et al. Wackerhagen C, Veer IM, Erk S,
et al. 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.
et al. 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.
et al. 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 temporal/parietal regions during emotion regulation may be a marker of response to behavioral activation.
et al. 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.


