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Stress and depression: old questions, new approaches

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After decades in which diatheses dominated research on the diathesis–stress models of depression, increasing attention to stress and stress–depression mechanisms is in the forefront of efforts to understand depression and treat it effectively. Supplementing research on known risk factors and moderators (such as demographic, cognitive, relational, family, and personality characteristics) of the stress–depression association, much work now focuses on experiences of early life stress, acute stressors, and chronic stress and their developmental features and neurobiological mechanisms relevant to depression. The review briefly highlights the current status of risk factors, HPA axis, neural, and genetic approaches, noting conceptual and methodological challenges.

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Introduction

Stressful life events have long been recognized and studied as robust predictors of depression. However, most people who have major stressful events do not get depressed, leading researchers to refine the issue of why Person A develops depression following stressful experiences but Person B does not. Questions about the moderators of the stress–depression link have predominated until more recent years in which there has been increasing interest in mechanisms, especially biological, by which stress triggers depression. This brief review attempts to highlight recent developments and current issues for contemporary researchers in which stress is at the forefront of models of depression.

Developments in conceptualization and measurement of depression and stress

Changing constructs and methodologies applied to ‘stress’ and ‘depression’ clearly shape current research

strategies. Some of the major findings of latter part of the 20th century were enabled by development of a reliable diagnostic classification system that sparked new areas of research, rapidly generating new theories of depression and major treatment advances. Nevertheless, there is widespread recognition that diagnosis-based research in depression has obscured enormous heterogeneity, which along with comorbidity, impedes precision and reproducibility of research findings [1,2]. Future research efforts are increasingly being directed toward alternative conceptualizations of the phenotype, including refining intermediate phenotypes [3,4,5*] and relating processes to transdiagnostic conceptualizations and dimensional measures [6].

Similarly, ‘stress’ conceptualizations evolved from focus on acute negative life events and easily administered but conceptually and methodologically limited assessments including checklists and questionnaires of perceived stress [7] to a much wider array of constructs and tools. Improvements include interview-based, objective measures of negative life event occurrence and severity [7]. Notably, there has also been increasing recognition of two additional but vitally important realms of stress exposure that had long passed largely below the radar in depression research: childhood adversities such as emotional abuse, and chronic, ongoing stressful conditions. There is increasing recognition that chronic stress, such as challenging marital, financial and work conditions, is a robust predictor of depression [8], as well as other psychopathologies, maladaptive behaviors, and poorer health outcomes [9,10]. Similarly, childhood adversity exposure predicts adolescent and adult psychopathology [11,12]. The impact of cumulative stress, especially measured as allostatic load, has also been the focus of efforts to understand depression and other forms of dysfunctional behavioral and medical health [13]. Thus, stress research warrants examination of early, chronic, continuing, cumulative, and proximal acute stress exposure. Moreover, there is growing evidence of the uniquely powerful role of interpersonal types of stress such as marital, family, and social relationships, losses, conflicts, and rejection in the prediction of depression especially in women [14,15].

Important shifts in definitions of stress and depression have also been accompanied by significant changes in models of associations between stress and depression. Much of research in recent decades was dominated by diathesis–stress paradigms, in which stress *predicts* depression, moderated by key vulnerability factors. Many research programs were largely focused on the diatheses, the vulnerability factors, with typically indirect or implicit

recognition of stress. As investigators tested the diathesis–stress models directly, it became clear that the stress–depression association, however, is not unidirectional, not static, and definitely not simple. Adults and children with histories of depression generate stressors in their lives, a bidirectional pattern portending continuing experiences of depression — and continuity of stress [16,17]. Depressive symptoms themselves contribute to the occurrence of stressful events in people’s lives, but stable dysfunctional characteristics of the depressed person also predict disruptions and stressors, particularly in interpersonal relationships [18,19]. Thus, the link between stress and depression is bidirectional.

Furthermore, studies revealed that the stress–depression association is not static over time, with stressors playing progressively less of a role in triggering episodes over the clinical course of depression [20–22]. Also, some individuals appear to be ‘sensitized’ by experiences such as exposure to adversity in childhood, so that they are more likely to develop depression in response to later-occurring stressors compared to those not exposed or to develop depression at lower levels of exposure [23–25]. There is a growing body of research and theory on the ways in which stressful experiences including social relationships sculpt the brain and neuroendocrine systems at different developmental periods from prenatal through adolescence [26–28].

Psychosocial moderators of associations between stress and depression

Over the past few decades several variables repeatedly emerged as robust predictors of risk for depression, both as main effects and as moderators, and sometimes mediators, of the effects of stress on depression. Demographic factors, such as female gender, younger (rather than old) age, and lower socioeconomic status predict higher rates of depressive disorders and symptoms [29,30] in part because they are associated with acute and chronic stressors.

Clinical history factors, such as having a parent, especially a mother, with depression is a major risk factor for developing depression in youth [31,32], due to both genetic and parenting mechanisms, and family stress [33]. Personal history of prior depressive episodes is also a strong predictor of the risk of future depressions [34], with successive episodes reducing the association between stress and depression in a ‘kindling’ pattern [21].

For some years there has been a particular emphasis on depression-related cognition, biased and maladaptive perceptions emphasizing low self-worth, pessimism, futility, and exaggeration of the negative impact and meaning of events. Recent research on dysfunctional information-processing among depressed individuals reveals a variety of distinctive patterns including increased accessibility of, and greater difficulties disengaging from, negative material, and deficits in cognitive

control leading to failure to inhibit irrelevant negative content, increasing the difficulty in ‘recovering’ from negative thoughts [35,36**].

Relatedly, ruminative response style is a dysfunctional trait-like pattern of response to negative experiences that typically intensifies and prolongs depressive symptoms [37]. Joining the list of prime predictors of depression or moderators of the stress–depression link, neuroticism is a core human trait reflecting the tendency to interpret the world as dangerous and threatening, coupled with negative emotional reactions in response to stress [38] and is highly predictive of mood and anxiety disorders [39,40]. Certain personality traits or interaction styles potentially predictive of dysfunctional (and stressful) interpersonal relationships have also been linked with depression outcomes, including excessive reassurance-seeking, dependency, rejection sensitivity, insecure attachment style, and related dispositions ([33]; see also [10]). Beyond the scope of the present review, a considerable amount of emerging research has focused on the genetic and neurobiological correlates of such traits and behaviors (e.g. [36**,41**]).

Research on biological risk factors and mechanisms of stress effects on depression

The various risk factors for depression and links between stress and depression are now under intense scrutiny of their biological mechanisms, foremost among them the HPA axis stress response processes, but also including imaging studies of brain structure and function, and hormonal and neurotransmitter systems, and genetic candidates that are known to be associated with stress reactivity and emotional responding. Vast volumes of human and animal research on both normal and abnormal processes are too extensive to cover, so a few brief comments focus on recent human research.

Hypothalamic-pituitary-adrenal (HPA) axis

It has long been observed that depressed adult patients show several indicators of dysregulation of the HPA axis — some state-dependent but others trait-like — including altered basal levels of cortisol, disrupted homeostatic mechanisms of the HPA axis evidenced in abnormal responses to an exogenous steroids and/or abnormal patterns of reactivity to stressors [42,43]. Glucocorticoids are widely dispersed throughout the brain, and in complex and developmentally programmed ways affect brain structures and functioning. Recent research also increasingly links HPA stress responses to immunological processes that may promote depression [14,42]. Numerous studies have explored associations between cortisol and stress, including both natural and experimentally induced social-evaluative stress, and depression. However, there have been many inconsistencies in findings likely due to variations in methods, samples, age groups, types and age of stress, and cortisol methods — as well as mediation by

genetic and biological processes (e.g. [43–46]) and it is concluded that much remains unclear about the mechanisms characterizing abnormal HPA reactions in depression [44,47].

Neural structure and function

Linkages of the HPA axis with multiple brain regions and functions, and a focus on emotion-relevant limbic structures in the brain, have led to emphasis on both structural/functional consequences of excessive corticosteroid levels associated with major depression, and on abnormalities in neural networks encompassing the medial prefrontal cortex and limbic and striatal areas and particularly the amygdala and hippocampus. Frodyl and O’Keane [42] review evidence supporting the glucocorticoid cascade hypothesis, including changes in synaptic plasticity, reduced neurogenesis, and neuronal atrophy in which excessive stress exposure causes structural and functional neural damage mediated by excess cortisol. Such processes affect brain regions relevant to cognitive and emotional functioning, as well as neuroendocrine and autonomic functioning [48,49]. Reviewers of the voluminous research acknowledge the complexity and often inconsistency of results, and tendencies toward reductionistic and unproven assumptions of causality are sometimes evident. Treadway and Pizzagalli [50] note that the differences between depressed and control samples are often contradictory across studies, and researchers thus have been unable to identify specific neural biomarkers that have treatment utility, and call for conceptual and methodological improvements [51**].

Genetic factors

It has long been known that depression runs in families, and is moderately heritable [52]. However, modern molecular genetic studies of candidate genes and gene-finding methods have so far failed to find replicated evidence of single genes, and it is presumed that genetic influences are due to small effects of multiple genes, operating in complex ways in concert with neurobiological and environmental/experiential processes.

Candidate genes associated with stress and depression have become a major focus of attention. Hormung and Heim [53**] review evidence emerging from numerous gene–environment (early life stress) interaction studies on SNPs of several genes apparently relevant to depressive phenomena. Their review also highlights the interaction of these genes and early life stress predicting putative intermediate phenotypes of depression, such as HPA axis responses to psychosocial stress in the laboratory, and structural and functional characteristics of the brain such as amygdala reactivity and hippocampal volume [53**]. Interactions of multiple genes and stressors, issues of measurement quality, and sample size and replicability remain important considerations in this developing field, but it does seem evident that genetic

factors help to explain variation in individual sequelae of early life stress.

Developments in the study of epigenetic processes are helping to illuminate the mechanisms by which stressful conditions affect outcomes. Increasingly applied to humans, these studies investigate stress-induced DNA methylation (and other) processes in the brain that alter gene expression. These studies focus largely on genes related to HPA axis functions, neurotransmission, and neuroplasticity [54]. Environmentally (stress) induced DNA methylation has been shown to have both short-term and long-term effects and in some instances intergenerational effects [55**].

Integrative perspectives

Calls for integrative research across multiple levels of analysis have increased in frequency in recent years especially among those with developmental perspectives [41**,56–58]. Many studies combine environmental and biological levels of analysis but results are generally incremental, based on small, heterogeneous samples, often cross-sectional designs, with a vast array of paradigms intended to assess similar constructs but differing enough to make it difficult to compare results and evaluate impact, and many not specifically including stress.

Research integrating across multiple levels has also emphasized the association among social and biological risk factors and mechanisms, specifically the effects of social interactions on stress processes and stress reactivity. The role of early life stress on HPA axis functioning and brain development contributing to stress reactivity and psychopathology [26–28] makes salient the likelihood that effects of the early environment on the developing child are mediated extensively through maternal care (e.g. [59]). The quality of this intimate relationship has a powerful effect on infant and child outcomes and HPA axis development, and Hostinar and Gunnar [27] argue that social relationships are regulators of HPA axis functioning, including the ability to benefit from social supports during stress.

There are numerous recent and ongoing examples of integrative research (e.g. review by Gibb *et al.* [41**] on gene \times cognition \times environment; see also [60–63]). Larger-scale longitudinal studies of multiple variables are among promising examples (e.g. Waters *et al.* [44], and Washington University investigators [64**]). The stress–depression field is in the early phases of an exhilarating era of creative integration.

Conclusions

It was not long ago that stress was a silent partner in the diathesis–stress models of depression but is currently at the forefront as developmental and psychobiological models and methods bring new perspectives and techniques to the

question of how and for which individuals do stressful conditions eventuate in depression. Future research needs to refine the phenotypes relevant to depression, increase relevance by using multiple levels of analysis (within individuals and across time/development), and promote communicability based on valid and shared methods in carefully characterized human samples with studies subjected to replication and aggregation. Critical elements pertinent to capturing bidirectional effects must be addressed to clarify causal and developmentally sensitive processes, and models need to be capable of exploring dynamic and transactional, rather than static and unidirectional, associations between elements. It cannot be assumed that predictors of child-adolescent onset are the same as adult onset, or that first onsets are the same as recurrent episodes. It must be recalled that stress effects are not specific to depression, and if linked to intermediate phenotypes will then require the search for applications to clinically significant chronic and recurrent depression. Much basic research is required to fill in gaps in essential knowledge of complex processes but ultimately the essential test should be whether our efforts are achieving understanding that leads to new and effective treatments for the widespread, debilitating and intergenerationally propagated phenomena of depression.

Conflict of interest

No conflicts to declare.

References and recommended reading

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

- of special interest
- of outstanding interest

1. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine D, Quinn K, Sanislow C, Wang P: **Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders.** *Am J Psychiatry* 2010, **167**:748-751.
 2. Kendler K, Aggen SH, Neale MC: **Evidence for multiple genetic factors underlying DSM-IV criteria for major depression.** *JAMA Psychiatry* 2013, **70**:599-607.
 3. Goldstein B, Klein D: **A review of selected candidate endophenotypes for depression.** *Clin Psychol Rev* 2014, **34**:417-427.
 4. Hasler G, Drevets W, Manji H, Charney D: **Discovering endophenotypes for major depression.** *Neuropsychopharmacology* 2004, **29**:1765-1781.
 5. Pizzagalli D: **Depression, stress, and anhedonia: toward a synthesis and integrated model.** *Annu Rev Clin Psychol* 2014, **10**:393-423.
- Viewing anhedonia as an endophenotype for depression, the article reviews elements of a proposed model of depression in which anhedonia arises from dysfunctional interactions between stress and brain reward systems. An integrated model links four bodies of research: anhedonia, dopamine transmission and function, stress (including early and recent stress), and animal data on stress effects on mesocorticolimbic dopaminergic pathways relevant to reinforcement learning and incentive motivation. Critical gaps and future directions for research are noted.
6. Blanco C, Krueger R, Hasin D, Liu S-M, Wang S, Kerridge B, Saha T, Olfson M: **Mapping common psychiatric disorders: structure and predictive validity in the national epidemiologic survey on alcohol and related conditions.** *JAMA Psychiatry* 2013, **70**:199-208.
 7. Monroe S: **Modern approaches to conceptualization and measurement of human stress.** *Annu Rev Clin Psychol* 2008, **4**:33-52.
 8. Hammen C: **Stress and depression.** *Annu Rev Clin Psychol* 2005, **1**:293-319.
 9. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB: **Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk.** *Proc Natl Acad Sci U S A* 2012, **109**:5995-5999.
 10. Marin T, Miller GE: **The interpersonally sensitive disposition and health: an integrative review.** *Psychol Bull* 2013, **139**:941-984.
 11. McLaughlin K, Green J, Gruber N, Sampson N, Zaslavsky A, Kessler R: **Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) III: associations with functional impairment related to DSM-IV disorders.** *Psychol Med* 2012, **40**:847-859.
 12. Kessler R, McLaughlin K, Green J, Gruber N, Sampson N, Zaslavsky A, Aguilar-Gaxiola J, Alhamzawi A, Alonso J, Angermeyer M et al.: **Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys.** *Br J Psychiatry* 2010, **197**:378-385.
 13. McEwen BS: **Mood disorders and allostatic load.** *Biol Psychiatry* 2003, **54**:200-207.
 14. Slavich G, Irwin M: **From stress to inflammation and major depressive disorder: a social signal transduction theory of depression.** *Psychol Bull* 2014, **140**:774-815.
 15. Kendler K, Gardner C: **Sex differences in the pathways to major depression: a study of opposite-sex twin pairs.** *Am J Psychiatry* 2014, **171**:426-435.
 16. Hammen C: **The generation of stress in the course of unipolar depression.** *J Abnorm Psychol* 1991, **100**:555-561.
 17. Hammen C, Hazel N, Brennan P, Najman J: **Intergenerational transmission and continuity of stress and depression: depressed women and their offspring in 20 years of follow-up.** *Psychol Med* 2012, **42**:931-942.
 18. Liu R: **Stress generation: future directions and clinical implications.** *Clin Psychol Rev* 2013, **33**:406-416.
 19. Wichers M, Maes H, Jacobs N, Derom C, Thiery E, Kendler K: **Disentangling the causal inter-relationship between negative life events and depressive symptoms in women: a longitudinal twin study.** *Psychol Med* 2012, **42**:1801-1814.
 20. Post RM: **Transduction of psychosocial stress into the neurobiology of recurrent affective disorder.** *Am J Psychiatry* 1992, **149**:999-1010.
 21. Kendler KS, Thornton LM, Gardner CO: **Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis.** *Am J Psychiatry* 2000, **157**:1243-1251.
 22. Stroud C, Davila J, Hammen C, Vrsheck-Schallhorn S: **Severe and nonsevere events in first onsets and recurrences of depression: evidence for stress sensitization.** *J Abnorm Psychol* 2011, **120**:142-154.
 23. Hammen C, Henry R, Daley S: **Depression and sensitization to stressors among young women as a function of childhood adversity.** *J Consult Clin Psychol* 2000, **68**:782-787.
 24. McLaughlin K, Conron K, Koenen K, Gilman S: **Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults.** *Psychol Med* 2010, **40**:1647-1658.
 25. Shapero B, Black S, Liu R, Klugman J, Bender R, Abramson L, Alloy L: **Stressful life events and depression symptoms: the effect of childhood emotional abuse on stress reactivity.** *J Clin Psychol* 2014, **70**:209-223.

26. Eiland L, Romeo RD: **Stress and the developing adolescent brain.** *Neuroscience* 2013, **249**:162-171.
27. Hostinar C, Gunnar M: **Future directions in the study of social relationships as regulators of the HPA axis across development.** *J Clin Child Adolesc Psychol* 2013, **42**:564-575.
28. Karmiloff-Smith A, Casey BJ, Massand E, Tomalski P, Thomas M: **Environmental and genetic influences on neurocognitive development: the importance of multiple methodologies and time-dependent intervention.** *Clin Psychol Sci* 2014, **2**:628-637.
29. Hasin D, Goodwin R, Stinson F, Grant B: **Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions.** *Arch Gen Psychiatry* 2005, **62**:1097-1106.
30. Seedat S, Scott K, Angermeyer M, Berglund P, Bromet E, Brugha T, Demytteraere K, Girolama G, Haro JM, Jin R *et al.*: **Cross-national associations between gender and mental disorders in the World Health Organization World Mental Health Surveys.** *Arch Gen Psychiatry* 2009, **66**:785-795.
31. Gotlib I, Colich N: **Children of parents with depression.** In *Handbook of Depression*, edn 3. Edited by Gotlib I, Hammen C. Guilford Press; 2014:240-258.
32. Goodman S, Rouse M, Connell A, Broth M, Hall C, Heyward D: **Maternal depression and child psychopathology: a meta-analytic review.** *Clin Child Fam Psychol Rev* 2011, **14**:1-27.
33. Hammen C, Shih J: **Depression and interpersonal processes.** In *Handbook of Depression*, edn 3. Edited by Gotlib I, Hammen C. Guilford Press; 2014:277-295.
34. Monroe S, Slavich G, Gotlib I: **Life stress and family history for depression: the moderating role of past depressive episodes.** *J Psychiatr Res* 2014, **49**:90-95.
35. Gotlib I, Joorman J: **Cognition and depression: current status and future directions.** *Annu Rev Clin Psychol* 2010, **6**:285-312.
36. Foland-Ross L, Gotlib I: **Cognitive and neural aspects of information processing in major depressive disorder: an integrative perspective.** *Front Psychol* 2012, **3**:1-17.
- This review article does not specifically address stress phenomena, but covers diverse aspects of information processing and associated neural differences during performance tasks in depressed compared to non-depressed samples. The authors note the limited body of research available on cognitive and neural markers evident before depression and urge longitudinal studies to resolve issues of causality and predictive utility.
37. Nolen-Hoeksema S: **The role of rumination in depressive disorders and mixed anxiety/depressive symptoms.** *J Abnorm Psychol* 2000, **109**:504-511.
38. Barlow D, Ellard K, Sauer-Zavala S, Bullis J, Carl J: **The origins of neuroticism.** *Perspect Psychol Sci* 2014, **9**:481-496.
39. Griffith J, Zinbarg R, Craske M, Mineka S, Rose R, Waters A, Sutton J: **Neuroticism as a common dimension in the internalizing disorders.** *Psychol Med* 2010, **40**:1125-1136.
40. Lahey B: **Public health significance of neuroticism.** *Am Psychol* 2009, **64**:241-256.
41. Gibb B, Beevers C, McGeary J: **Toward and integration of cognitive and genetic models of depression.** *Cogn Emot* 2013, **27**:193-216.
- Reviews studies of information processing biases as genetically linked intermediate phenotypes of risk for depression, and gene-environment studies of cognitive bias. The article proposes and reviews preliminary evidence of a gene × cognition × environment model of depression in which genetic influences on cognition contribute to reactivity to stress. The article contains a thoughtful discussion of the limitations and future directions relevant to the integration of cognitive and genetic risk (and plasticity) factors, and a framework for a promising approach to much-needed multiple levels of analysis perspective on depression.
42. Frodl T, O'Keane V: **How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans.** *Neurobiol Dis* 2013, **52**:24-37.
43. Pariante C, Lightman S: **The HPA axis in major depression: classical theories and new developments.** *Trends Neurosci* 2008, **31**:464-468.
44. Waters C, van Goozen S, Phillips R, Swift N, Hurst S-L, Mundy L, Jones I, Goodyer I, Hay D: **Infants at familial risk for depression show a distinct pattern of cortisol response to experimental challenge.** *J Affect Disord* 2013, **150**:955-960.
45. Morris M, Rao U, Wang L, Garber J: **Cortisol reactivity to experimentally manipulated psychosocial stress in youth adults at varied risk for depression.** *Depress Anxiety* 2014, **31**:44-52.
46. Staufenbiel S, Penninx B, Spijker A, Elzinga B, von Rossum E: **Hair cortisol, stress exposure, and mental health in humans: a systematic review.** *Psychoneuroendocrinology* 2013, **38**:1220-1235.
47. Baumeister D, Lightman S, Pariante C: **The interface of stress and the HPA axis in behavioural phenotypes of mental illness.** *Curr Top Behav Neurosci* 2014, **18**:12-24.
48. McEwen B, Morrison J: **The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course.** *Neuron* 2013, **79**:16-29.
49. Price J, Drevets W: **Neural circuits underlying the pathophysiology of mood disorders.** *Trends Cogn Sci* 2011, **16**:61-71.
50. Treadway M, Pizzagalli D: **Imaging the pathophysiology of major depressive disorder – from localist models to circuit-based analysis.** *Biol Mood Anxiety Disord* 2014, **4**:1-13.
51. Russo S, Nestler E: **The brain reward circuitry in mood disorders.** *Nat Rev Neurosci* 2013, **14**:609-625.
- Detailed and balanced review of circuits related to reward processing thought to be relevant to emotional processing and stress reactivity. Includes animal and recent human studies, noting 'unexpectedly complicated' patterns, and identifies methodological challenges.
52. Sullivan P, Neale M, Kendler K: **Genetic epidemiology of major depression: review and meta-analysis.** *Am J Psychiatry* 2000, **157**:1552-1562.
53. Homung O, Heim C: **Gene-environment interactions and intermediate phenotypes: early trauma and depression.** *Front Endocrinol* 2014, **5**:1-12.
- Reviews gene-environment interaction studies of early life stress exposure predicting depression, focusing on an array of candidate genes. Also reviews gene-early stress environment interaction studies predicting depression-related intermediate phenotypes, including neuroendocrine, hippocampal volume, amygdala reactivity, social-emotional processing, reward learning, and HPA axis activity.
54. Hing B, Gardner C, Potash J: **Effects of negative stressors on DNA methylation in the brain: implications for mood and anxiety disorders.** *Am J Med Genet B* 2014, **165B**:541-554.
55. Griffiths B, Hunger R: **Neuroepigenetics of stress.** *Neuroscience* 2014, **275**:420-435.
- Review of emerging body of research on epigenetic processes of responses to stress. Includes animal and human studies, and notes effects for acute and chronic stressors that may differ. Technically complex but useful.
56. Hankin B: **Future directions in vulnerability to depression among youth: integrating risk factors and processes across multiple levels of analysis.** *J Clin Child Adolesc Psychol* 2014, **55**:1279-1287.
57. Cicchetti D, Dawson G: **Editorial: multiple levels of analysis.** *Dev Psychopathol* 2002, **14**:417-420.
58. Doom J, Gunnar M: **Stress physiology and developmental psychopathology: past present, and future.** *Dev Psychopathol* 2013, **25**:1359-1373.
59. Tang A, Reeb-Sutherland B, Romeo R, McEwen B: **On the causes of early life experience effects: evaluating the role of mom.** *Front Neuroendocrinol* 2014, **35**:245-251.
60. Bufferd S, Dougherty L, Olino T, Dyson M, Laptook R, Carlson G, Klein D: **Predictors of the onset of depression in young**

- children: a multi-method, multi-informant longitudinal study from ages 3 to 6.** *J Child Psychol Psychiatry* 2014, **55**:1279-1287.
61. Silk J, Siegle G, Lee KW, Nelson E, Stroud L, Dahl R: **Increased neural response to peer rejection associated with adolescent depression and pubertal development.** *Soc Cogn Affect Neurosci* 2014, **9**:1798-1807.
62. Nusslock R, Shackman A, Harmon-Jones E, Alloy L, Coan J, Abramson L: **Cognitive vulnerability and frontal brain asymmetry: common predictors of first prospective depressive episode.** *J Abnorm Psychol* 2011, **120**:497-503.
63. Treadway M, Waskom J, Dillon D, Holmes A, Park MT, Chakravarty M, Dutra S, Polli F, Iosifescu D, Fava M *et al.*: **Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression.** *Biol Psychiatry* 2014 <http://dx.doi.org/10.1016/j.biopsych.2014.06.018>. (in press).
64. Pagliaccio D, Luby J, Bogdan R, Agrawal A, Garrey M, Belden A, Botteron K, Harms M, Barch D: **Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children.** *Neuropsychopharmacology* 2014, **39**:1245-1253.
- Results from a longitudinal study examining associations among cortisol patterns, genetic profiles featuring four stress-system genes, and early life stress in a sample of over 100 preschoolers to predict hippocampal and amygdala volume characteristics typically associated with adult depression when the children were between 7 and 12. The interaction of genetic profile score and early life stress predicted left hippocampal and amygdala volumes, and cortisol partially mediated the effects especially left amygdala volume.