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The Research Domain Criteria (RDoC) Project and Studies of Risk and Resilience in Maltreated Children

Joan Kaufman, PhD,
Kennedy Krieger Institute and Johns Hopkins School of Medicine, Baltimore.

Joel Gelernter, MD, **James Hudziak, MD**,
Vermont Center for Children, Youth, and Families, University of Vermont, Burlington.

Audrey R. Tyrka, MD, PhD, and
Butler Hospital Mood Disorders Research Program, Laboratory for Clinical and Translational Neuroscience, and the Alpert Medical School of Brown University, Providence, RI.

Jeremy D. Coplan, MD
State University of New York Downstate Medical Center, New York City.

Abstract

Objective—The Research Domain Criteria (RDoC) project was initiated to develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures. This article reviews the rationale behind the RDoC program, its goals, and central tenets; discusses application of an RDoC framework to research with maltreated children; and highlights some clinical implications of this work.

Method—Published RDoC papers were reviewed, together with relevant preclinical and clinical studies that guide our work on risk and resilience in maltreated children.

Results—The ultimate long-term goal of the RDoC initiative is precision medicine in psychiatry. In the interim, the RDoC initiative provides a framework to organize research to help develop the database required to derive a new psychiatric nomenclature that can appropriately match treatments to patients. The primary focus of RDoC is on neural circuitry, with levels of analyses that span from molecules to behavior. There has been some concern that the RDoC framework is reductionist, with an overemphasis on neural circuits and genetics; however, the briefly reviewed, burgeoning literature on neuroplasticity and epigenetics highlights that this concern is unwarranted, as one cannot study neural circuits and genetics without considering experience.

Conclusion—The study of maltreated children has a number of advantages for the RDoC project, including the following: study of a subset of patients who are often not responsive to standard interventions; examination of a relatively homogenous sample with onset of

Correspondence to Joan Kaufman, PhD, Kennedy Krieger Institute, Center for Child and Family Traumatic Stress, 1750 E. Fairmount Avenue, Baltimore, MD 21231; joan.kaufman@kennedykrieger.org.
At the time of the writing of this manuscript, Drs. Kaufman and Gelernter were with Yale University School of Medicine and Veteran's Administration Connecticut Health Care Center, New Haven, CT.

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psychopathology proposed to be associated with stress-related mechanisms; and well-established, relevant animal models to facilitate translational research.

Keywords

RDoC; risk and resilience; maltreated children

The brain is not organized, according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). Although the *DSM* has been an invaluable tool in establishing reliability of psychiatric diagnoses and creating a common language to facilitate communication about mental illnesses,[1,2] the validity of the *DSM* psychiatric nomenclature has come under considerable scrutiny[3,4] and has spurred the initiation of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project.[5,6] This article reviews the rationale for the NIMH RDoC program, its goals, and its central tenets (http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). It also discusses the application of an RDoC perspective in research with maltreated children.

RATIONALE FOR THE NIMH RDoC INITIATIVE

Although rates of infant mortality have dropped 50% since 1980,[7] mortality has not decreased for any psychiatric disorder, and prevalence rates are similarly unchanged.[5] Psychiatry has lagged behind multiple areas of medicine in gaining insights into the pathophysiology of disease.[8] Heterogeneity within diagnostic categories[4,9] and comorbidity among disorders[10,11] are the rule, compromising treatment efficacy and research on pathophysiology of mental illnesses. Related to this, *DSM* diagnostic classifications do not delineate distinct paths of treatment; instead, single classes of drugs, such as selective serotonin reuptake inhibitors (SSRI), are indicated for a wide range of anxiety, mood, and eating disorders.[3] Yet, although SSRIs are approved for these different conditions, treatment response is varied, and on average across diagnoses, a marketed psychiatric drug is efficacious in only half of the patients who take it.[5] The effect size for the drugs used in psychiatry range from small to large, with the efficacy of psychotropic drugs on average in the medium range, which is actually approximately comparable to the efficacy of many drugs used across multiple fields in medicine.[12] Psychiatry, like many areas of medicine, is in need of reliable diagnostic tests to better match treatments to patients. There are currently few data to guide our efforts to determine which patients will have a favorable response to any given treatment, to reliably assess risk of disorder, or to prevent or alter the course of illness onset.

GOALS AND GUIDING PRINCIPLES OF THE NIMH RDoC INITIATIVE

The ultimate long-term goal of the NIMH RDoC initiative is precision medicine in psychiatry so that clinicians can tailor treatments to optimize outcomes for individual patients.[5,8] The near-term goal is to devise a framework to organize research to help develop the database required to derive a new psychiatric nomenclature that can use the research findings to appropriately match treatments to patients.[5] It is believed that this new psychiatric nomenclature will facilitate precision medicine in psychiatry. The NIMH is

agnostic about what this new nosology will look like, but has delineated a set of guiding principles to move toward the goals of the RDoC initiative.

Central tenets of the NIMH RDoC initiative include the following: Mental illnesses are brain circuit disorders[6]; Psychopathology is conceptualized in terms of component abnormalities in discrete, but frequently highly interconnected, brain circuits[13]; Brain circuit abnormalities cut across traditional diagnostic boundaries[13]; Behaviors linked to different brain circuits vary dimensionally from impairment to healthy functioning[13]; and Brain circuit function varies across development and is significantly influenced by experience.[14] The RDoC further assumes that diagnoses based solely on observable signs and symptoms are nonspecific and inevitably reflect heterogeneity in terms of pathophysiology,[8] and that, in time, data from the fields of genetics and clinical neuroscience will yield meaningful biomarkers to augment clinical symptoms in guiding treatment.[6]

Table 1 delineates key features that distinguish RDoC from the *DSM*. First, RDoC is a research framework; it is an evolving structure designed to guide research, not replace the *DSM* as a tool for clinicians at the present time.[15] RDoC also conceptualizes mental illnesses as comprising component parts that can be represented on dimensional scales, not as categorically discrete entities. In addition, the RDoC framework takes a bottom–up approach by starting with neural circuits to understand behaviors, rather than a top–down approach of starting with symptoms to understand the pathophysiology of mental illnesses. It also aims to reflect understanding of the biology of discrete circuits and behaviors, not multifaceted clinical syndromes.

RDoC Matrix

As depicted in Table 2, the RDoC Matrix currently consists of 5 domains and a series of interrelated constructs. The domains and constructs were selected during a series of thoughtful workshops facilitated by NIMH over the past several years.[16] For constructs to be included in the RDoC Matrix, evidence demonstrating that they are reliable and valid behavioral functions and are subserved by an identified neural circuit was required.[14] The 5 initial domains identified by the RDoC workshops include negative valence (e.g., anxiety, loss), positive valence (e.g., reward), cognitive systems (e.g., attention, working memory), social processes (e.g., affiliation), and arousal/modulatory systems (e.g., sleep–wake). Over time, it is likely that additional domains and constructs will be added to the matrix. Although the table may appear to suggest sharp boundaries between the separate domains and constructs, research has demonstrated that the domains and constructs function interactively via highly integrated brain circuits.[17]

The primary focus of RDoC is on neural circuitry, with levels of analysis progressing in 1 of 2 directions: upward from measures of circuitry to clinical symptomatology, and downward to the genetic and molecular factors that ultimately influence function.[6] The RDoC initiative promotes the examination of each construct across 7 units of analyses: genes, molecules, cells, circuits, physiology, behavior, and self-reports. It also identifies paradigms that can be used to assess each construct. Table 3 delineates a nonexhaustive set of data for each of these units of analyses for the construct “acute threat” (or “fear”) to illustrate the clinical

utility of the RDoC perspective that calls for incorporating units of analyses from molecules to behavior, with this construct chosen, given its relevance to our work with maltreated children.

Starting with circuits, preclinical and clinical research suggest the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus are key structures within the fear circuit.[18] Moving to symptoms, deficits in fear learning and fear extinction are hypothesized to be related to the onset of posttraumatic stress disorder (PTSD) and other anxiety disorders,[19] with knowledge about fear extinction behavioral paradigms instrumental for the development of exposure therapies.[20] Moving downward, variation in polymorphisms in the serotonin transporter gene (a particular variant, *5-HTTLPR*),[21] γ-aminobutyric acid (GABA) A receptor gene α 2 (*GABRA2)*,[22] and *oFK506*-binding protein 5 (*FKBP5*) gene (the protein product that interacts with the glucocorticoid receptor[23,24]) have been found to alter risk for the development of PTSD after child abuse. These gene-by-environment studies have helped to elucidate why some individuals develop psychopathology after abuse and others do not. On the molecular level, glutamate transmission, and particularly its actions at *N*-methyl-D-aspartate (NMDA) receptors, underlies extinction learning.[25] This finding has been translated into clinical practice, with administration of the NMDA receptor partial agonist D-cycloserine (DCS) found to augment the efficacy of exposure therapy for PTSD and other anxiety disorders,[25] providing a powerful illustration of the clinical utility of the RDoC perspective, and incorporating units of analyses from molecules to behavior.

There has been some concern expressed that the RDoC framework is reductionist, with an overemphasis on neural circuits and genetics, and minimal attention to contextual factors.[26,27] The incorporation of preclinical translational studies of fear extinction at both the behavioral and molecular level into treatments (e.g., exposure therapy and DCS) demonstrates the potential value of the integrated approach proposed by RDoC, and the burgeoning literature on neuroplasticity and epigenetics further highlights that this concern is unwarranted, as one cannot study neural circuits and genetics without considering experience.[25,28] Old dichotomies of nature versus nurture, or biology versus experience, are obsolete and have been so for decades. The dynamic interactions among genes and environment, and experience and the brain, are innumerable.

RESEARCH APPLICATIONS OF THE RDoC PERSPECTIVE TO STUDIES OF MALTREATED CHILDREN

The study of maltreated children has a number of advantages for the RDoC project, including: the study of a subset of patients that are frequently treatment resistant to standard interventions;[9,29,30] examination of a relatively homogenous sample with the onset of psychopathology proposed to be associated with stress-related mechanisms;[9,31,32] and well-established, relevant animal models to facilitate translational research.[33,34] It also focuses on an exposure that impacts known neural circuits, rather than a *DSM* entity, and involves a process that occurs in a developmental context, an aspect critical to the RDoC matrix.

Children who experience maltreatment are at high risk for developing a wide range of psychiatric problems, including PTSD,[35] depression,[29] and substance use disorders.[36] These

various conditions frequently co-occur and often persist into adulthood.[9,36] Anxiety, mood, and substance use disorders are associated with alterations in interlocking brain circuits, with each of these brain circuits included in the RDoC matrix (Figure 1). As discussed previously, PTSD and other anxiety disorders are associated with alterations in fear circuitry.[18] Depressive disorders are associated with changes to the structure and function of the emotion processing circuit involving the amygdala, hippocampus, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC).[37] Substance use disorders are associated with changes to the structure and function of regions within the reward circuit, including the hippocampus, amygdala, hypothalamus, and the nucleus accumbens and ventral tegmental area (VTA), which have extensive connections with prefrontal cortex.[38] Problems in attention, memory, and impulse control, which frequently co-occur with these other trauma-related psychiatric disorders, are associated with alterations in the executive control circuit that overlaps extensively with these other brain systems.[39] In addition, as shown in Figure 1, the neural regions implicated in these psychiatric and substance use disorders are also key structures involved in the stress response.[40] Given the overlap among these neural systems and the brain regions involved in stress, it is not surprising the individuals with a history of abuse frequently meet diagnostic criteria for these multiple cooccurring conditions.[41]

Consistent with research in the field, in our prior studies of this population, PTSD was the most common diagnosis experienced by the children, present in more than half of the maltreated cohort.[35] The maltreated children in our prior studies also had high rates of clinically significant depression[42,43]; and, at longitudinal follow-up, 29% of our predominantly preadolescent and young adolescent maltreated cohort reported alcohol use, a rate more than 7 times the rate observed in controls. Maltreated children also had a full drink of alcohol, on average, more than 2 years earlier than controls (11.2 versus 13.5 years), and at the time of follow-up, 15% had already experienced an episode of being intoxicated.[44]

Given the role of fear conditioning in the neurobiology of PTSD,[19,45–47] we are presently studying the RDoC construct acute threat, or fear, using an emotional Go–No Go task developed by Casey *et al.*[48] in a new cohort that we are currently recruiting. We are also collecting structural, diffusion tensor, and resting-state imaging data that will allow us to examine the impact of child maltreatment on other brain circuits implicated in the regulation of relevant RDoC domains that are also altered in response to child maltreatment—even independent of psychopathology.[49,50] Inclusion criteria for the study are not set by *DSM* diagnostic categories but, rather, by a history of child maltreatment to identify a relatively homogenous sample with the onset of psychopathology proposed to be associated with stress-related mechanisms.[9,31,32] Maltreatment and other adverse childhood experiences are being quantified, dimensionally integrating information derived from multiple informants and data sources[51]: symptoms across a wide range of domains and constructs are being collected, using dimensional rating scales and computerized tasks, and a range of genetic and environmental factors are being collected to better understand risk and resilience in this population.

CHILD ABUSE AND GENETICS RESEARCH IN AN RDoC ERA

There is emerging evidence that alternations in stress-reactivity and many of the structural and functional changes in the brain that are associated with early adversity are mediated by epigenetic mechanisms.[52–54] Epigenetics refers to functionally relevant modifications to the genome that do not involve a change in DNA nucleotide sequence.[53] These modifications can alter gene activity and play roles in acute regulation of genes in response to changes in the environment.[55]

In our current research, we aim to replicate our recently published findings that showed that depression symptoms in maltreated children are associated with epigenetic changes in 3 genes: DNA binding protein inhibitor ID-3 (*ID3*), Tubulin Polymerization Promoting Protein (*TPPP)*, and a Glutamate NMDA Receptor subunit (*GRIN1*).[56] Methylation changes in these genes appear to be independent predictors of depression, above and beyond the effects of maltreatment history. These genes are all biologically relevant: they are involved in the stress response, neural plasticity, and neural circuitry, as follows. *ID3* is upregulated in the pituitary in response to chronic stress.[57] It is also upregulated with stimulation by pituitary adenylate cyclise-activating polypeptide (PACAP).[58] This is interesting, as levels of PACAP in peripheral blood have been linked to PTSD symptoms in females,[59] and variation in the gene that encodes the PACAP receptor has been associated with risk for PTSD in some[59–61] but not all[62] studies. PACAP genetic variation has also been associated with individual differences in brain activation and connectivity within the fear circuit.[63] *ID3* is also involved in neurogenesis and has been implicated in neural plasticity.[64] *TPPP* is critical for oligodendrocyte differentiation,[65] and the protein TPPP is present in myelinating oligodendrocytes and is believed to have a role in development and maintenance of white matter tracts in brain.[66,67] *GRIN1* transcription is downregulated in frontal cortex in response to stress in animal models of depression[68]; glutamate is implicated in the pathophysiology of depression and anxiety disorders[69,70]; and NMDA receptors play a critical role in synaptic plasticity, memory, and fear conditioning.[71]

The field of psychiatric genetics is evolving, and it is becoming increasingly evident that the genetic architecture of psychiatric illness does not map onto the *DSM*.[72–74] There is also emerging evidence for a role of mitochondrial DNA,[75,76] tissue-specific mutations,[77] and noncoding DNA regulatory elements[78] in the etiology of psychiatric illnesses. Less than 2% of the more than 3 billion DNA base pairs in human genome code for proteins, and many sites in intergenic regions are enriched for transcription factor binding sites that influence the 3-dimensional organization of the genome and play key roles in gene regulation.[79,80] Transcription factor binding sites and chromatin insulators within intergenic regions are believed to mediate intra- and interchromosomal interactions, affecting gene expression at both proximal and distal locations.[80] There are numerous instances in which intergenic genetic variation is associated with disease risk,[81] and methylation in intergenic regions has been implicated in neuropsychiatric[82] and other diseases. Novel methods have been developed to characterize the 3-dimensional configuration of the genome, and a better understanding of the regulatory role of these 3-dimensional changes will open up new frontiers in human brain research and psychiatric genetics.[78]

CHILD ABUSE AND RESILIENCE RESEARCH IN AN RDoC ERA

Data collected in Connecticut in 2007 found that children committed to protective services due to abuse or neglect made up approximately 65% of all admissions to psychiatric hospitals, despite comprising only about 1% of the child population.[83] With an infusion of state, federal, and private foundation dollars, Connecticut recently implemented a trauma-informed system of care. Child welfare administrators, caseworkers, and contracted mental health providers received training on trauma-informed practices. Learning collaboratives were created to disseminate evidenced-based psychotherapies to treat PTSD and other trauma-related psychiatric problems in children. Although correlation does not imply causality, since the training of providers around the state to assess for and treat PTSD in children, there has been a contemporaneous change such that children committed to protective services due to abuse or neglect now make up only 30% instead of 65% of all admissions to psychiatric hospitals.[84]

There is emerging evidence that the clinical benefits of cognitive-behavioral therapy (CBT) interventions may be mediated by adaptive changes in brain circuits that control emotion regulation.[85–87] Although the reduction in rates of inpatient care among children committed to the state is praiseworthy, even with the improvement in the system of care, these children remain at inordinately high risk for significant psychiatric problems serious enough to warrant inpatient hospitalization—a rate about 30 times greater than expected by population estimates. Evidence-based treatments work better than other practices, but, as discussed previously, there is no treatment in psychiatry that works for all patients with a given mental health condition.

Beyond clinical treatment, research data now also show that there are other experiences that can promote positive brain changes via neuroplasticity, including exercise,[88] mindfulness and meditation,[88] and music training.[89] There is growing interest in understanding sensitive time windows when the brain is more responsive to experiential inputs[90] and the mechanisms necessary to reopen and strengthen windows of plasticity.[88] Investigations of underlying mechanisms for the re-establishment of new windows of plasticity are focusing on the balance between excitatory and inhibitory transmission and removing molecules that limit plasticity.[88]

The availability of positive social supports is also believed to facilitate neuroplasticity.[91] Studies have repeatedly documented that the availability of positive social supports is 1 of the most important factors in promoting resilience in maltreated children and other traumatized populations.[92] In our studies, the availability of a positive adult support was found to ameliorate risk for depression associated with maltreatment, with the positive effect of social support most beneficial for those children at elevated genetic risk for depression.[42,43] Studies with socially monogamous prairie vole have demonstrated that paraventricular nucleus oxytocin is a critical component of the neurobiological mechanisms by which social supports can alleviate the negative effects of stress, and it has therefore been suggested that oxytocin may be a target for treatment of stress-related disorders.[91] Ongoing translational research studies using an RDoC perspective, from molecules to behavior, may

help to elucidate novel therapeutic approaches for the prevention and treatment of stress-related psychiatric disorders.

In addition to psychiatric and substance use outcomes, our group is also interested in the effects of stress on health outcomes.[93–95] There is a robust literature documenting that adverse early life experiences increase risk for a broad range of health problems,[95] and data suggesting that social supports can help to buffer against the negative health effects associated with stress as well.[92] Common biological mechanisms may or may not be involved in promoting psychological and physical well-being after early adversity, and ongoing multidisciplinary and translational research will help to address these questions.

When we conducted our whole-genome methylation study, given preclinical research findings on the effects of adverse early rearing experiences on the glucocorticoid receptor and other stress-related genes,[54] we expected to see epigenetic changes in genes known to be involved in the stress response. Although we did see maltreatment-related group differences in certain of these genes, after controlling for whole-genome multiple comparisons, maltreated and control children had significantly different methylation values at 2,868 methylation sites. The gene set showing differential methylation between the maltreated and comparison children contained genes involved not only in biological processes relevant to psychiatric and substance use disorders (e.g., neurogenesis, axonal guidance), but also heart disease (e.g., cardiac development), stroke (development of blood vessel morphogenesis), respiratory disease (e.g., interleukin regulation), diabetes (e.g., leptin signaling), and cancer (e.g., WNT signaling, NOTCH signaling)—all medical illnesses that have been associated with a history of adverse childhood experiences.[96]

Data frequently lead to surprises. The explosion of large-scale, high-throughput technologies has necessitated a shift away from reductionism and fueled the development of new computational tools.[97,98] As Schadt *et al.* stated,

> … future successes in biomedical research will likely demand a more comprehensive view of the complex array of interaction in biological systems and how such interactions are influenced by genetic background, infection, environmental states, lifestyle choices, and social structures more generally. This holistic view requires embracing complexity in its entirety, so that complex biological systems are beginning to be seen as dynamic, fluid systems that are able to reconfigure themselves as conditions demand.[98]

There is no area of medicine in which this holds more truth than in psychiatry.

CONCLUDING REMARKS

As discussed at the outset of this article, the long-term goal of the RDoC initiative is precision medicine in psychiatry, so clinicians can tailor treatments to optimize outcomes for individual patients. The study of maltreated children is important for the RDoC project, as patients with a history of child abuse are often not responsive to standard interventions. The near-term goal of the RDoC initiative is to devise a framework to organize research based on dimensions of observable behavior and neurobiological measures. The primary focus of

RDoC is on neural circuitry, with levels of analysis progressing upward from measures of circuitry to clinical symptomatology, and downward to the genetic and molecular factors that ultimately influence function. Maltreated children comprise a relatively homogenous sample with the onset of psychopathology proposed to be associated with stress-related mechanisms, with well-established relevant animal models to facilitate translational research. In the current paper, the anticipated value of the RDoC framework that extends from molecules to behavior was highlighted with clinical and research examples. RDoC and the tools used within this framework will continue to evolve, and if the aims of the RDoC initiative are attained, morbidity and rates of mortality associated with psychiatric illnesses will at last decrease.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edition. DSM-5. Washington, DC: American Psychiatric Publishing; 2013.
2. Insel TR, Wang PS. Rethinking mental illness. JAMA. 2010; 303:1970–1971. [PubMed: 20483974]
3. Regier DA, Narrow WE, Kuhl EA, Kupfer DJ. The conceptual development of DSM-V. Am J Psychiatry. 2009; 166:645–650. [PubMed: 19487400]
4. Keshavan MS, Ongur D. The journey from RDC/DSM diagnoses toward RDoC dimensions. World Psychiatry. 2014; 13:44–46. [PubMed: 24497246]
5. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013; 11:126. [PubMed: 23672542]
6. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]
7. Centers for Disease Control and Prevention. NCfHS. Infant Mortality Rates, 1950–2010. From Health, United States, Vital Statistics Report. http://www.infoplease.com/ipa/A0779935.html. Published 2012.
8. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. Am J Psychiatry. 2014; 171:395–397. [PubMed: 24687194]
9. Teicher MH, Samson JA. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am J Psychiatry. 2013; 170:1114–1133. [PubMed: 23982148]

10. Kessler RC, Avenevoli S, McLaughlin KA, et al. Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). Psychol Med. 2012; 42:1997–2010. [PubMed: 22273480]
11. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994; 51:8–19. [PubMed: 8279933]
12. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012; 200:97–106. [PubMed: 22297588]
13. Etkin A, Cuthbert B. Beyond the DSM: development of a transdiagnostic psychiatric neuroscience course. Acad Psychiatry. 2014; 38:145–150. [PubMed: 24493358]
14. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. World Psychiatry. 2014; 13:28–35. [PubMed: 24497240]
15. Simmons JM, Quinn KJ. The NIMH Research Domain Criteria (RDoC) Project: implications for genetics research. Mamm Genome. 2014; 25:23–31. [PubMed: 24085332]
16. NIMH. [Accessed January 2015] NIMH RDoC Worshop Proceedings. 2012. Available at: http://www.nimh.nih.gov/research-priorities/rdoc/nimh-rdoc-workshop-proceedings.shtml.
17. Ford JM, Morris SE, Hoffman RE, et al. Studying hallucinations within the NIMH RDoC framework. Schizophr Bull. 2014; 40(Suppl 4):S295–S304. [PubMed: 24847862]
18. Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. Neuropsychopharmacology. 2010; 35:136–146. [PubMed: 19710632]
19. Milad MR, Pitman RK, Ellis CB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009; 66:1075–1082. [PubMed: 19748076]
20. Foa EB. Prolonged exposure therapy: past, present, and future. Depress Anxiety. 2011; 28:1043–1047. [PubMed: 22134957]
21. Xie P, Kranzler HR, Poling J, et al. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch Gen Psychiatry. 2009; 66:1201–1209. [PubMed: 19884608]
22. Nelson EC, Agrawal A, Pergadia ML, et al. Association of childhood trauma exposure and GABRA2 polymorphisms with risk of posttraumatic stress disorder in adults. Mol Psychiatry. 2009; 14:234–235. [PubMed: 19229201]
23. Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008; 299:1291–1305. [PubMed: 18349090]
24. Xie P, Kranzler HR, Poling J, et al. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. Neuropsychopharmacology. 2010; 35:1684–1692. [PubMed: 20393453]
25. Krystal JH, Tolin DF, Sanacora G, et al. Neuroplasticity as a target for the pharmacotherapy of anxiety disorders, mood disorders, and schizophrenia. Drug Discov Today. 2009; 14:690–697. [PubMed: 19460458]
26. Frances A. RDoC is necessary, but very oversold. World Psychiatry. 2014; 13:47–49. [PubMed: 24497248]
27. Parnas J. The RDoC program: psychiatry without psyche? World Psychiatry. 2014; 13:46–47. [PubMed: 24497247]
28. Turecki G, Ota V, Belangero S, Jackowski A, Kaufman J. Early life adversity, genomic plasticity, and psychopathology. Lancet Psychiatry. 2014; 1:461–466.
29. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry. 2012; 169:141–151. [PubMed: 22420036]
30. Tyrka AR, Burgers DE, Philip NS, Price LH, Carpenter LL. The neurobiological correlates of childhood adversity and implications for treatment. Acta Psychiatr Scand. 2013; 128:434–447. [PubMed: 23662634]

31. Kaffman A, Meaney MJ. Neurodevelopmental sequelae of postnatal maternal care in rodents: clinical and research implications of molecular insights. J Child Psychol Psychiatry. 2007; 48:224–244. [PubMed: 17355397]
32. Kaufman J, Plotsky P, Nemeroff C, Charney D. Effects of early adverse experience on brain structure and function: clinical implications. Biol Psychiatry. 2000; 48:778–790. [PubMed: 11063974]
33. Gorman JM, Mathew S, Coplan J. Neurobiology of early life stress: nonhuman primate models. Semin Clin Neuropsychiatry. 2002; 7:96–103. [PubMed: 11953933]
34. Stevens HE, Leckman JF, Coplan JD, Suomi SJ. Risk and resilience: early manipulation of macaque social experience and persistent behavioral and neurophysiological outcomes. J Am Acad Child Adolesc Psychiatry. 2009; 48:114–127. [PubMed: 19127170]
35. Grasso D, Boonsiri J, Lipschitz D, et al. Posttraumatic stress disorder: the missed diagnosis. Child Welfare. 2009; 88:157–176. [PubMed: 20405781]
36. Afifi TO, Henriksen CA, Asmundson GJ, Sareen J. Childhood maltreatment and substance use disorders among men and women in a nationally representative sample. Can J Psychiatry. 2012; 57:677–686. [PubMed: 23149283]
37. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct. 2008; 213:93–118. [PubMed: 18704495]
38. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008; 455:894–902. [PubMed: 18923511]
39. Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW. CNTRICS final task selection: executive control. Schizophr Bull. 2009; 35:115–135. [PubMed: 19011235]
40. Kaufman, J.; Weder, N. Neurobiology of early life stress: evolving concepts. In: Martin, A.; Scahill, L.; Kratochvil, CJ., editors. Pediatric Psychopharmacology. Second ed.. New York: Oxford University Press; 2010. p. 112-123.
41. McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. Arch Gen Psychiatry. 2010; 67:124–132. [PubMed: 20124112]
42. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry. 2006; 59:673–680. [PubMed: 16458264]
43. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci U S A. 2004; 101:17316–17321. [PubMed: 15563601]
44. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Genetic and environmental predictors of early alcohol use. Biol Psychiatry. 2007; 61:1228–1234. [PubMed: 17123474]
45. Johnson LR, McGuire J, Lazarus R, Palmer AA. Pavlovian fear memory circuits and phenotype models of PTSD. Neuropharmacology. 2011; 20:20.
46. Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends Neurosci. 2012; 35:24–35. [PubMed: 21798604]
47. Rougemont-Bucking A, Linnman C, Zeffiro TA, et al. Altered processing of contextual information during fear extinction in PTSD: an fMRI study. CNS Neurosci Ther. 2011; 17:227–236. [PubMed: 20406268]
48. Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go–no-go task. Biol Psychiatry. 2008; 63:927–934. [PubMed: 18452757]
49. Philip NS, Kuras YI, Valentine TR, et al. Regional homogeneity and resting state functional connectivity: associations with exposure to early life stress. Psychiatry Res. 2013; 214:247–253. [PubMed: 24090510]
50. Philip NS, Valentine TR, Sweet LH, Tyrka AR, Price LH, Carpenter LL. Early life stress impacts dorsolateral prefrontal cortex functional connectivity in healthy adults: informing future studies of antidepressant treatments. J Psychiatr Res. 2014; 52:63–69. [PubMed: 24513500]

51. Holbrook, H.; O'Loughlin, L.; Althoff, RR.; Douglas-Palumberi, HJK.; Hudziak, J. American Academy of Child and Adolescent Psychiatry. San Diego, CA: 2014 Oct. The Yale-Vermont Adversity in Childhood Scale: a quantitative approach to adversity assessment.
52. McGowan PO, Sasaki A, D'Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009; 12:342–348. [PubMed: 19234457]
53. Zhang TY, Meaney MJ. Epigenetics and the environmental regulation of the genome and its function. Annu Rev Psychol. 2010; 61:439–466. [PubMed: 19958180]
54. Kundakovic M, Champagne FA. Early-life experience, epigenetics, and the developing brain. Neuropsychopharmacology. 2015; 40:141–153. [PubMed: 24917200]
55. Nestler EJ. Epigenetic mechanisms in psychiatry. Biol Psychiatry. 2009; 65:189–190. [PubMed: 19146997]
56. Weder N, Zhang H, Jensen K, et al. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. J Am Acad Child Adolesc Psychiatry. 2014; 53:417–424. [PubMed: 24655651]
57. Konishi H, Ogawa T, Nakagomi S, Inoue K, Tohyama M, Kiyama H. Id1, Id2 and Id3 are induced in rat melanotrophs of the pituitary gland by dopamine suppression under continuous stress. Neuroscience. 2010; 169:1527–1534. [PubMed: 20600660]
58. Ghzili H, Grumolato L, Thouennon E, Vaudry H, Anouar Y. Possible implication of the transcriptional regulator Id3 in PACAP-induced prosurvival signaling during PC12 cell differentiation. Regul Pept. 2006; 137:89–94. [PubMed: 16928405]
59. Ressler KJ, Mercer KB, Bradley B, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature. 2011; 470:492–497. [PubMed: 21350482]
60. Almli LM, Mercer KB, Kerley K, et al. ADCYAP1R1 genotype associates with post-traumatic stress symptoms in highly traumatized African-American females. Am J Med Genet B Neuropsychiatr Genet. 2013; 162B:262–272. [PubMed: 23505260]
61. Uddin M, Chang SC, Zhang C, et al. Adcyap1r1 genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. Depress Anxiety. 2013; 30:251–258. [PubMed: 23280952]
62. Chang SC, Xie P, Anton RF, et al. No association between ADCYAP1R1 and post-traumatic stress disorder in two independent samples. Mol Psychiatry. 2012; 17:239–241. [PubMed: 21912390]
63. Stevens JS, Almli LM, Fani N, et al. PACAP receptor gene polymorphism impacts fear responses in the amygdala and hippocampus. Proc Natl Acad Sci U S A. 2014; 111:3158–3163. [PubMed: 24516127]
64. Farioli-Veccochioli S, Saraulli D, Costanzi M, et al. Impaired terminal differentiation of hippocampal granule neurons and defective contextual memory in PC3/Tis21 knockout mice. PLoS One. 2009; 4:e8339. [PubMed: 20020054]
65. Lehotzky A, Lau P, Tokési N, Muja N, Hudson LD, Ovádi J. Tubulin polymerization-promoting protein (TPPP/p25) is critical for oligodendrocyte differentiation. Glia. 2010; 58:157–168. [PubMed: 19606501]
66. Goldbaum O, Jensen PH, Ritcher-Landsberg C. The expression of tubulin polymerization promoting protein TPPP/p25alpha is developmentally regulated in cultured rat brain oligodendrocytes and affected by proteolytic stress. Glia. 2008; 56:1736–1746. [PubMed: 18563798]
67. Vincze O, Oláh J, Zádori D, Klivényi P, Vécsei L, Ovádi J. A new myelin protein, TPPP/p25, reduced in demyelinated lesions is enriched in cerebrospinal fluid of multiple sclerosis. Biochem Biophys Res Commun. 2011; 409:137–141. [PubMed: 21565174]
68. Tordera RM, Garcia-García AL, Elizalde N, et al. Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. Eur Neuropsychopharmacol. 2011; 21:23–32. [PubMed: 20937555]
69. Krystal JH, Mathew SJ, D'Souza DC, Garakani A, Gunduz-Bruce H, Charney DS. Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. CNS Drugs. 2010; 24:669–693. [PubMed: 20658799]

70. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2011; 3:3.
71. Blair HT, Schafe GE, Bauer EP, Rodrigues SM, LeDoux JE. Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn Mem. 2001; 8:229–242. [PubMed: 11584069]
72. Consortium CDGotPG. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013; 381:1371–1379. [PubMed: 23453885]
73. Stringaris A. Here and There: Gene effects cross the boundaries of psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2013; 52:557–558. [PubMed: 23702441]
74. Thapar A, Cooper M. Copy number variation: what is it and what has it told us about child psychiatric disorders? J Am Acad Child Adolesc Psychiatry. 2013; 52:772–774. [PubMed: 23880486]
75. Anglin RE, Mazurek MF, Tarnopolsky MA, Rosebush PI. The mitochondrial genome and psychiatric illness. Am J Med Genet B Neuropsychiatr Genet. 2012; 159B:749–759. [PubMed: 22887963]
76. Tyrka AR, Parade SH, Price LH, et al. Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. Biol Psychiatry. 2015 Jan 15. [epub ahead of print]. pii: S0006- 3223(15) 00041-4.
77. Insel TR. Brain somatic mutations: the dark matter of psychiatric genetics? Mol Psychiatry. 2014; 19:156–158. [PubMed: 24342990]
78. Mitchell AC, Bharadwaj R, Whittle C, et al. The genome in three dimensions: a new frontier in human brain research. Biol Psychiatry. 2014; 75:961–969. [PubMed: 23958183]
79. Hodges E, Molaro A, Dos Santos CO, et al. Directional DNA methylation changes and complex intermediate states accompany lineage specificity in the adult hematopoietic compartment. Mol Cell. 2011; 44:17–28. [PubMed: 21924933]
80. Yang J, Corces VG. Chromatin insulators: a role in nuclear organization and gene expression. Adv Cancer Res. 2011; 110:43–76. [PubMed: 21704228]
81. Cotnoir-White D, Laperriere D, Mader S. Evolution of the repertoire of nuclear receptor binding sites in genomes. Mol Cell Endocrinol. 2011; 334:76–82. [PubMed: 21056084]
82. Qureshi IA, Mattick JS, Mehler MF. Long non-coding RNAs in nervous system function and disease. Brain Res. 2010; 1338:20–35. [PubMed: 20380817]
83. Schaefer, M. Zigler Center in Child Development and Social Policy Colloquium Series. New Haven, CT: 2007 Nov 9. Public Sector Behavioral Health for Children and Families: Aligning Systems and Incentives.
84. Gruendel, J. Young children and inpatient care: an analysis of HUSKY data; Presentation by Deputy Commissioner of the Department of Children and Families of Connecticut; March 15, 2013; Rocky Hill, CT.
85. Goldin PR. Elucidating the neural mechanisms of cognitive-behavioral therapy: a commentary on treatment changes in neural correlates of subliminal and supraliminal threat in individuals with spider phobia. Biol Psychiatry. 2014; 76:836–837. [PubMed: 25439998]
86. Goldin PR, Ziv M, Jazaieri H, Hahn K, Heimberg R, Gross JJ. Impact of cognitive behavioral therapy for social anxiety disorder on the neural dynamics of cognitive reappraisal of negative self-beliefs: randomized clinical trial. JAMA Psychiatry. 2013; 70:1048–1056. [PubMed: 23945981]
87. Lipka J, Hoffmann M, Miltner WH, Straube T. Effects of cognitive-behavioral therapy on brain responses to subliminal and supraliminal threat and their functional significance in specific phobia. Biol Psychiatry. 2014; 76:869–877. [PubMed: 24393393]
88. Davidson RJ, McEwen BS. Social influences on neuroplasticity: stress and interventions to promote well-being. Nat Neurosci. 2012; 15:689–695. [PubMed: 22534579]
89. Hudziak JJ, Albaugh MD, Ducharme S, et al. Cortical thickness maturation and duration of music training: health-promoting activities shape brain development. J Am Acad Child Adolesc Psychiatry. 2014; 53:1153–1161. [PubMed: 25440305]
90. Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the Research Domain Criteria (RDoC) framework. Biol Psychiatry. 2014; 76:350–353. [PubMed: 25103538]

91. Smith AS, Wang Z. Hypothalamic oxytocin mediates social buffering of the stress response. Biol Psychiatry. 2014; 76:281–288. [PubMed: 24183103]

92. Cohen H, Liberzon I, Matar MA. Translational implications of oxytocin-mediated social buffering following immobilization stress in female prairie voles. Biol Psychiatry. 2014; 76:268–269. [PubMed: 25060784]

93. Gohil BC, Rosenblum LA, Coplan JD, Kral JG. Hypothalamic-pituitary-adrenal axis function and the metabolic syndrome × of obesity. CNS Spectr. 2001; 6:581–586. 589. [PubMed: 15573024]

94. Kaufman D, Banerji MA, Shorman I, et al. Early-life stress and the development of obesity and insulin resistance in juvenile bonnet macaques. Diabetes. 2007; 56:1382–1386. [PubMed: 17470564]

95. Yang B-Z, Zhang H, Ge W, et al. Child abuse and epigenetic mechanisms of disease risk. Am J Prev Med. 2013; 44:101–107. [PubMed: 23332324]

96. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998; 14:245–258. [PubMed: 9635069]

97. Chang R, Karr JR, Schadt EE. Causal inference in biology networks with integrated belief propagation. Pac Symp Biocomput. 2015; 20:359–370. [PubMed: 25592596]

98. Schadt EE, Sachs A, Friend S. Embracing complexity, inching closer to reality. Sci STKE. 2005; 2005:pe40. [PubMed: 16077086]

99. Spielberger, CD. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.

100. Birmaher B, Khetarpol S, Brent D, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric properties. J Am Acad Child Adolesc Psychiatry. 1997; 36:545–553. [PubMed: 9100430]

101. March JS, Parker JD, Sullivan K, Stallings P, Conners CK. The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. J Am Acad Child Adolesc Psychiatry. 1997; 36:554–565. [PubMed: 9100431]

Clinical Guidance

- Think dimensionally, and develop interventions to target discrete domains.
- Remember that risk, whether due to genetic or environmental factors, is dynamic. There are multiple approaches that can be used to promote resilience and recovery (e.g., evidence-based treatment strategies, facilitating positive attachments and social supports, and wellness interventions).

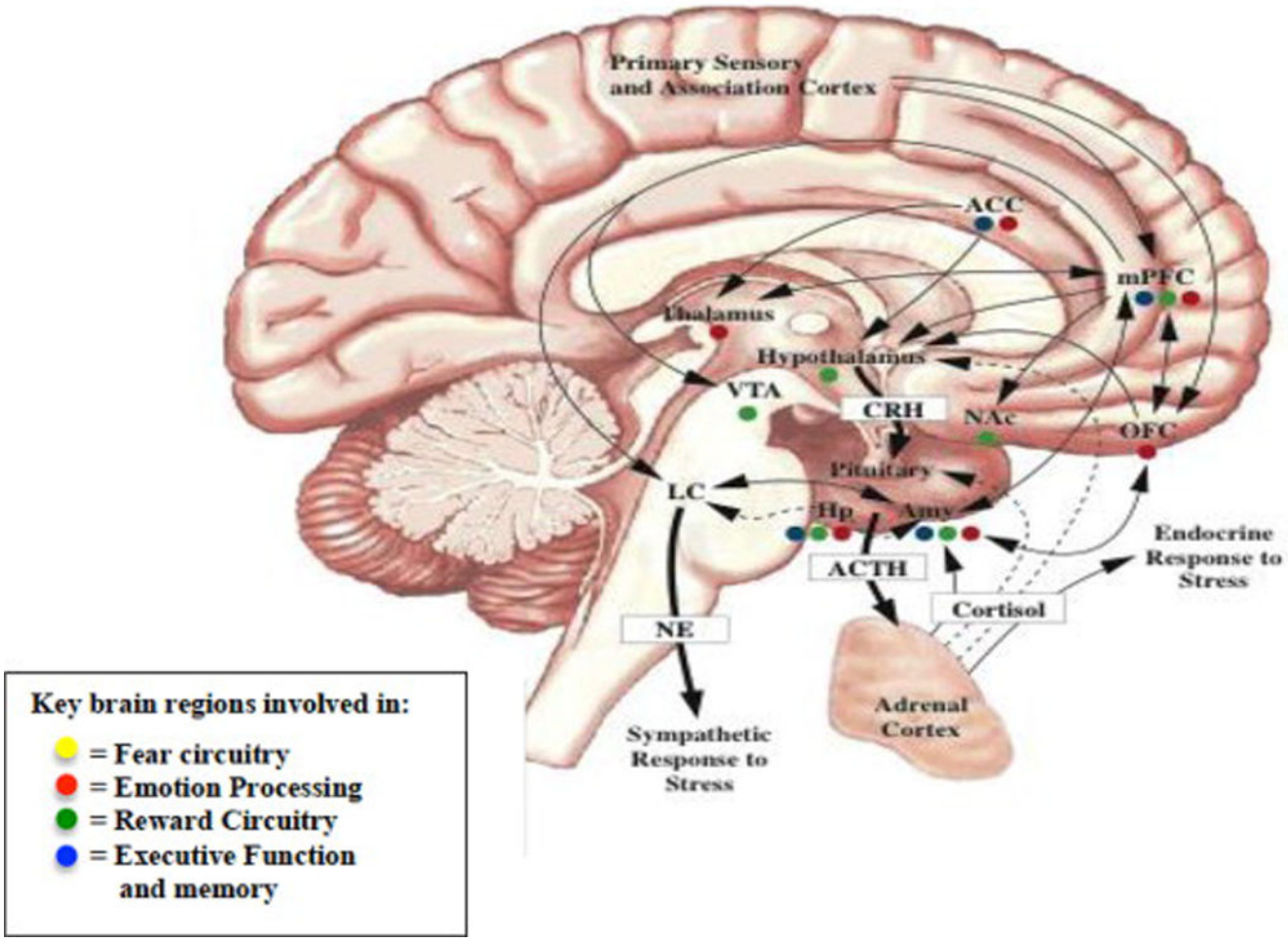

FIGURE 1.

Overlap in brain regions involved in the stress response and brain circuits implicated in stress-related psychiatric syndromes. Note: Several brain regions that are a part of interconnected neural circuits that regulate fear, emotion, reward, and executive function are also involved in the stress response. The stress response is initiated with the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the release of adrenocorticotropin hormone (ACTH) from the pituitary, which causes the release of cortisol from the adrenals, and a cascade among the multiple brain structures indicated above with the black arrows. ACC = anterior cingulate cortex; Amy = amygdala; Hp = hippocampus; LC = locus coeruleus; mPFC = medial prefrontal cortex; NAc = nucleus accumbens; OFC = orbitofrontal cortex; vmPFC = ventral medial prefrontal cortex; VTA = ventral tegmental area. Reprinted by permission of Oxford University Press, Inc. as Fig: 8.1 in Kaufman J,Weder N. Neurobiology of Early Life Stress: Evolving Concepts. Martin A, Scahill L, Kratochvil CJ, eds. Pediatric Psychopharmacology. Second ed. New York: Oxford University Press; 2010:112–123. (http://ukcatalogue.oup.com/p2p/endecaSearch.do?keyword=9780195398212). This figure does not come under a Creative Commons license (http://creativecommons.org/licenses/), or any other open access license that would allow

TABLE 1

Primary Distinctions Between the DSM and the National Institute of Mental Health's Research Domain Criteria (RDoC)

DSM	RDoC
Clinical nosology	Research framework
Categorical approach	Dimensional approach
Symptom-based definitions of disorders	Neural circuit-based delineation of behaviors

TABLE 2

Research Domain Criteria Domains and Constructs

Negative Valence Systems	Positive Valence Systems	Cognitive Systems	Systems for Social Processes	Arousal/Regulatory Systems
Acute Threat (Fear)	Approach Motivation	Attention	Affiliation and Attachment	Arousal
Potential Threat (Anxiety)	Initial Responsiveness to Reward	Perception	Social Communication	Biological Rhythms
Sustained Threat	Sustained Responsiveness to Reward	Working Memory	Perception and Understanding of Self	Sleep-Wake
Loss	Reward Learning	Declarative Memory	Perception and Understanding of Other	
Frustrative Nonreward	Habit	Language Behavior		
		Cognitive (Effortful) Control		

TABLE 3

Research Domain Criteria Units of Analyses for Acute Threat (“Fear”)

Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
5-HTTLPR	NMDA Receptors	Neurons	Fear Circuit: vmPFC	Fear Potentiated	Avoidance	STAI[99]	Fear Learning
GABRA2	Glutamate	Glia	Hippocampus	Startle	Freezing	SCARED[100]	Extinction Paradigms
CRH	Glycine	Pyramidal cells	Amygdala	Heart Rate		MASC[101]	Exposure Therapy
FKBP5							

Note: 5-HTTLPR = serotonin-transporter-linked polymorphic region; CRH = corticotropin releasing hormone; FKBP5 = FK506 binding protein 5; GABRA2 = gamma-aminobutyric acid receptor subunit alpha-2; MASC = Multidimensional Anxiety Scale for Children; NMDA = N-methyl-D-aspartate; SCARED = Screen for Child Anxiety Related Emotional Disorders; STAI = State-Trait Anxiety Inventory; vmPFC = ventromedial prefrontal cortex.