Childhood Antecedents and Risk for Adult Mental Disorders

Daniel S. Pine[1] and Nathan A. Fox[2]

[1]Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland 20892; email: daniel.pine@nih.gov

[2]Department of Human Development and Quantitative Methodology, University of Maryland, College Park, Maryland 20742

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Abstract

Progress in treating and preventing mental disorders may follow from research that integrates development, genetics, and neuroscience. This review first delineates how longitudinal research has identified three particular groups of disorders shown to differ on the basis of symptom trajectories and risk-factor profiles. In the next section, the review describes how research on genetic contributions to psychopathology has elucidated the nature of risk for two groups of disorders, the neurodevelopmental and psychotic disorders. In the third section, the review describes how research on environmental contributions to psychopathology has targeted early temperament, its associated perturbations in information-processing functions, and its relations to a third group of disorders, the emotional disorders. For all three groups of disorders, such integrative research has generated ideas about novel interventions. The hope is that over the coming decade such ideas will lead to novel treatments that alter the trajectory of risk in developmental psychopathology.

Contents

INTRODUCTION

The burden of mental disorders rivals most other health problems (Collins et al. 2011). Although recognition of this burden has intensified the search for novel treatments, early promise remains unfulfilled. Steady progress in genetics and neuroscience has not improved outcomes over many decades (Insel 2009). Discoveries generating currently available, widely employed treatments occurred decades before recent advances in genetics and neuroscience.

This review focuses on two aspects of mental disorders that hinder a search for novel therapies. First, most mental disorders emerge slowly, with signs or symptoms appearing in childhood, years before individuals typically seek treatment (Rutter et al. 2006). Most research on novel treatments targets patients with entrenched disorders. Greater success might accrue by targeting the earliest signs or even the precursors of disorders. Second, definitions of mental disorders remain rooted in clinical descriptions without a corresponding grounding in neuroscience, yet individuals with similar presentations markedly differ in their outcome and treatment response. Thus, clinically defined entities probably encompass heterogeneous disorders differing on the basis of measures of brain function. This review unfolds in three stages to integrate research on development, genetics, and neuroscience. In the first section, the developmental nature of mental disorders is broadly described. Next, genetic contributions to risk are probed. Finally, neural circuitry contributions to risk are examined.

THREE PATTERNS OF DEVELOPMENTAL PSYCHOPATHOLOGY

The psychiatric nosology emerging in the late 1970s resembles the nosology in place today (Wilson 1993). Although changes occurred through 2013, these changes were minor relative to the marked changes culminating in the 1980 publication of the *Diagnostic and Statistical Manual of Mental Disorders*. Hence, stability in classification facilitated longitudinal research.

Rutter and others summarize two main conclusions arising from such longitudinal research (Costello et al. 2005, Kessler et al. 2005, Pine et al. 1998, Rutter et al. 2006, van Os et al. 2010). First, most mental disorders begin in childhood (Kessler et al. 2005). That is, approximately two-thirds of affected adults exhibit signs of a mental disorder earlier in life (Copeland et al. 2009,

Pine et al. 1998). This applies to most if not all disorders, including substance use disorders, psychosis, and emotional disorders. Second, mental disorders of adults can be distinguished by their developmental trajectory. Unique groups of disorders involve particular signs and symptoms, expressed at particular points in development, with correspondingly unique risk factor profiles.

Not all mental disorders emerge before adulthood; some involve no readily detectable childhood antecedents. Late-onset major depressive disorder (MDD) represents one such disorder (Alexopoulos & Kelly 2009). Despite similar clinical presentations, forms of MDD that arise after middle age differ from those that arise earlier on the basis of therapeutics, biology, risk factors expressed in the family, and medical history. This and other such adult-onset disorders account for about one-third of problems seen in adults. However, because the current review focuses on childhood antecedents and risk for mental disorders, these conditions are not discussed.

Rutter et al. (2006) describe distinct forms of adult disorders with childhood antecedents. These forms differ based on the nature of associated risk factors as well as the signs and symptoms that are expressed at particular ages. In this context, signs are overt expressions of psychopathology observable by the clinician, whereas symptoms are aspects of the disorder reported to the clinician by the patient or the patient's family members. Considerable literature attempts to define mental disorders on the basis of constellations of signs and symptoms. Although some disagreement persists on the precise definitions, most nosologies define mental disorders as conditions in which signs and symptoms occur at a level sufficient to interfere with function.

In terms of adult disorders with strong childhood antecedents, three particular forms have been studied in the greatest depth: (*a*) neurodevelopmental, (*b*) psychotic, and (*c*) emotional disorders. Of note, these three disorder groups exhibit both similarities and differences. Thus, the neurodevelopmental and psychotic disorders share some features, such as a strong genetic basis, that are not found in emotional disorders (Bacanu & Kendler 2013, Gejman et al. 2011, Hettema et al. 2001, Murdoch & State 2013, Rutter 2005, State & Sestan 2012). Similarly, psychotic and emotional disorders share other features, such as particular changes in clinical expressions after puberty (Angold et al. 1999, Rutter et al. 2006, van der Werf et al. 2014, van Os 2013), not found in the neurodevelopmental disorders. Such features are described below and depicted in **Figure 1**.

One set of questions arising from these observations relates to how to define particular forms of mental disorder. Consensus is emerging on the distinct nature of the three broad groups of adult mental disorders with strong antecedents in childhood described in this review. However, disagreement persists on the criteria for identifying particular disorders lying within the three broad groups. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* parses particular disorders on the basis of signs and symptoms only, but this fails to identify disorders with clearly distinct pathophysiology or therapeutics (Am. Psychiatr. Assoc. 2013). The Research Domain Criteria (RDoC) project proposes to augment clinical assessments with measures of brain function and genetics (Insel et al. 2010). Although RDoC has yet to produce clinically relevant measures, such measures might emerge through research that integrates development, genetics, and neuroscience.

A second set of questions relates to procedures for combining dimensional and categorical perspectives. Longitudinal research reveals the need for a dimensional perspective. Continuous relations exist between the severity of childhood psychopathology and level of risk for adult psychopathology, without a natural break point in long-term risk for children falling just below or above diagnostic thresholds (Costello et al. 2002, Pine et al. 1999, van Os 2013). Risk increases in a continuous, graded fashion when comparing children with few symptoms, significant but still subdiagnostic symptoms, and symptoms falling just above diagnostic thresholds. Thus, risk is probabilistic: Early problems increase the odds of later problems, but many children displaying maladaptive behaviors become healthy adults.

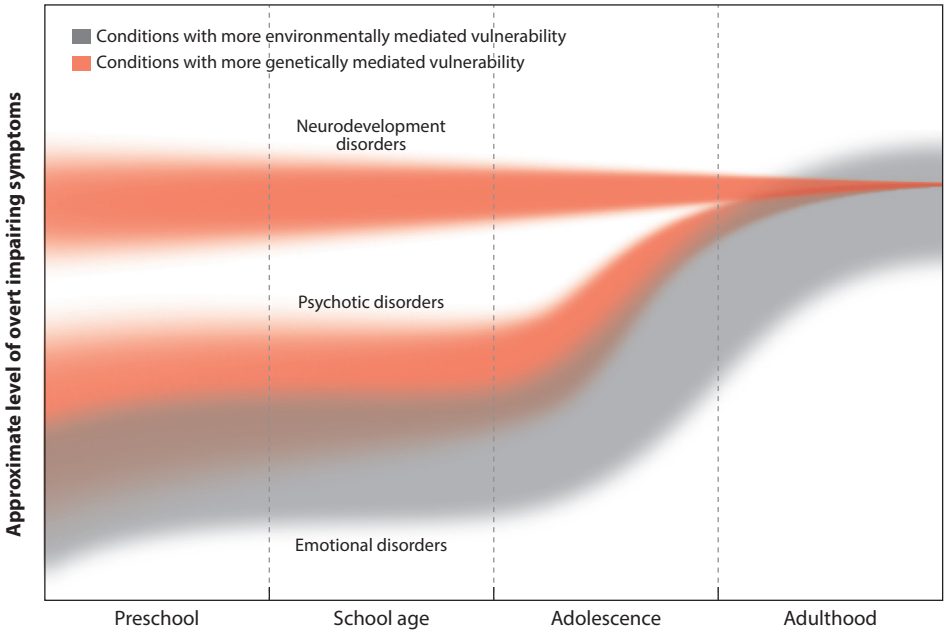

Figure 1

The features of neurodevelopmental, psychotic, and emotional disorders as they relate to levels of symptoms. Levels of symptoms are depicted only in relative terms for each group of disorders, irrespective of absolute or comparative levels across the three groups of disorders. Thus, for all three groups, the *y*-axis shows that relative severity is highest in affected adults. The first depicted feature is relative magnitude of contribution to risk from genes or the environment. This feature is depicted with red shading for neurodevelopmental and psychotic disorders, where genetic contributions are large, and with gray shading for emotional disorders, where environmental contributions are large. The second depicted feature is the relative degree of change in symptomatic expression in adolescence, as reflected by nonlinearity in each line as a function of age. Such nonlinear change occurs more prominently in the psychotic and emotional disorders than in the neurodevelopmental disorders, as reflected in a nonlinear slope through adolescence for these two groups of disorders. The third depicted feature is temporal variability in phenotypic expression, which is reflected in the thickness of the lines. Temporal variability is lowest in the neurodevelopmental disorders, as depicted by the relatively sharp line that steadily becomes even sharper through adolescence. Temporal variability is intermediate in the psychotic disorders, with decreasing variability after adolescence reflected as increasing sharpness through late adolescence. Temporal variability is consistently highest in the emotional disorders, as depicted by the consistently thick line through adulthood.

The decision to intervene requires categorization of children falling along a continuum of risk, thereby imposing a dichotomous structure on phenomena that are continuous in nature. This commonly occurs in medicine, where categorization attempts to identify a point on a dimension of severity where the benefits of intervening outweigh the risks of false diagnoses. As such, classifying a child with a mental disorder is more about recognizing a break point in risk-benefit ratios than a fundamental difference in clinical presentation among healthy and disordered children. Such classification is an important part of reducing the probability of risk whenever vulnerable youth must be selected for interventions. Consensus on how to categorize at-risk youth has yet to emerge in psychopathology, at least partly due to limited understandings of pathophysiology. In other areas of medicine, biological tests supplement clinical assessments to improve outcome prediction or treatment selection. This has not yet been possible for mental disorders but is the goal of research in RDoC and other translational approaches to psychiatry.

For both sets of questions, answers could emerge through research that integrates development, genetics, and neuroscience. To parse heterogeneity, different methods may provide traction for different groups of disorders. As described below, methods focused on genetics and neurochemistry may prove most rapidly useful in the neurodevelopmental and psychotic disorders. However, methods focused on temperament, environmental risk, and cognitive neuroscience may be more rapidly useful in the emotional disorders. Similarly, in terms of imposing categories on dimensions, the decision to categorize children in need of intervention also can be organized around developmental concerns. For strongly persistent, early-emerging disorders, interventions targeting early signs of risk can be justified, even when there is some potential for adverse treatment effects. Research on genetics may provide novel ideas in this area, as described for the neurodevelopmental and psychotic disorders. For less persistent conditions, it may be preferable to target later stages of risk with treatments having the lowest potential for adverse effects. Incorporating information on brain function could aid in such applications by identifying subgroups of children at particularly elevated risk or with unique responses to particular treatments, as described below for the emotional disorders.

Neurodevelopmental Disorders

The neurodevelopmental disorders include autism spectrum disorders (ASDs) and attention-deficit/hyperactivity disorder (ADHD). The neurodevelopmental, psychotic, and emotional disorders can be differentiated from each other on the basis of five characteristics that uniquely differentiate each group of conditions.

First, for the neurodevelopmental disorders, clinical signs virtually always manifest before puberty (Lord et al. 2006, Rutter et al. 2006). Moreover, when puberty brings changes in symptomatic manifestations, such changes involve varying expressions of the same set of core symptoms rather than new onset of unique symptoms. Thus, ADHD involves a fundamental, relatively persistent disruption in attention and impulse control both before and after puberty, whereas ASDs involve a similarly fundamental persistent disruption in social relationships. Moreover, from a dimensional perspective, levels of symptoms in these neurodevelopmental disorders are relatively stable, showing low degrees of temporal variability. Thus, remission rarely occurs in children followed over a few months to a year.

Second, these disorders represent perturbed development in specific skills, such as attention or impulse control in ADHD. These skills change with development; pathology is expressed as failure or delay in the normal achievement of expectable milestones. For example, a level of sustained attention that is considered abnormally brief in a seven-year-old child with ADHD might be considered normal were it to occur in a four-year-old (Nigg 2007, Nigg & Casey 2005). Thus, symptoms of neurodevelopmental disorders arise particularly early and are expressed as failed or delayed development in cognition and behavior. These conditions are developmental in nature; they are defined as a failure to express the changes in cognition and behavior that accompany healthy development. Moreover, they emerge over the course of development and typically are not generally identified during infancy.

Third, the neurodevelopmental disorders exhibit a relatively large preponderance of males (Rutter et al. 2006). Approximately two times more boys than girls are affected in population-based studies of these disorders, a pattern shared with neurological illnesses, such as cerebral palsy, that involve abnormal development. Fourth, research demonstrates a relatively consistent and broad pattern of perturbed information processing and associated neural processes (Klin et al. 2002, 2009; Ozonoff et al. 2004). In some cases, longitudinal or family-based research demonstrates similar perturbed patterns among at-risk individuals. For example, in ADHD, executive function

differs among symptomatic children, their asymptomatic vulnerable relatives, and children with neither symptoms of nor vulnerabilities for ADHD (Castellanos & Tannock 2002). Such findings manifest in trial-by-trial variation in reaction time. Similarly, in ASDs, perturbations in brain structure and attention to social stimuli may reflect early risk. Here, ASD involves abnormal attention and neural development in the first year of life, potentially before the onset of overt clinical symptoms (Klin et al. 2009, Wolff et al. 2012).

Finally, these neurodevelopmental disorders are strongly genetic: Twin and adoption studies attribute more than half of the underlying risk to genetic factors (Rutter et al. 2006, State & Sestan 2012). This is not to say that the environment is unimportant, as it is common for symptoms of the neurodevelopmental disorders to worsen as a result of stress. Nevertheless, such worsening typically involves an exacerbation of symptoms that already are present as opposed to de novo appearance of new symptoms. In addition, findings from twin studies could minimize some environmental contributions to these disorders because twin studies attribute risk from gene-environment interactions to genes without emphasizing the role played by the environment in such scenarios (Rutter 2002). Regardless, within assumptions of behavior genetic methods, the probability of risk arises mostly from genes.

These five features influence perspectives on heterogeneity and decisions to categorize children falling on dimensions on the basis of their need for treatment. Specifically, because genetic factors heavily shape risk, attempts to understand these probabilities through research on genes and associated neural correlates hold promise. Finally, because early-emerging, serious problems often persist, justification exists for early intervention, even when it carries some risk.

Psychotic Disorders

Recent models view the psychotic disorders as lying along a continuum. The classic adult-onset disorder in this group is schizophrenia, and the other psychotic disorders are included on the basis of where they fall on the psychosis continuum. For example, this group might include schizoaffective disorder as well as forms of bipolar disorder that include prominent psychotic features. For other disorders, such as certain depressive disorders, placement may straddle the psychotic and emotional disorders. Much like the neurodevelopmental disorders, the psychotic disorders share five features.

First, clinical features of the psychotic disorders differ from those in neurodevelopmental or emotional disorders. Although subtle clinical signs may present before puberty, the core features of the psychotic disorders usually appear in the first decades after puberty (van der Werf et al. 2014, van Os 2013). Clearly, at-risk children can show signs of impairment before this developmental stage. Such prepubertal impairment typically manifests as perturbations in cognition or features of neurodevelopmental and emotional disorders, such as symptoms of ADHD or an anxiety disorder, as opposed to the core features of psychosis that manifest after puberty (Church et al. 2002, Nuechterlein et al. 2012, van Os 2013). Thus, puberty involves a fundamental change in clinical expression, which is thought to reflect fundamental changes in the brain.

Second, although reality testing shows a normal developmental trajectory, disrupted reality testing in psychotic disorders represents a more abrupt departure from typical development, for example, than does disrupted attention in ADHD (Kotov et al. 2013). Unlike the above example of brief attention in a 7-year-old patient with ADHD, florid psychosis in a 17-year-old would rarely be considered normal in a patient a few years younger.

Of note, adolescents with more subtle, nonpsychotic distortions in reality testing face a higher risk for psychosis than do adolescents without such distortions (van Os 2013). These involve exaggerated fantasies or peculiar beliefs, similar to normal, developmental fantasies. However,

when distortions are severe enough to be classified as psychosis, risk for poor outcome increases in a quantum fashion, suggesting discontinuity in the severity-risk continuum. As such, the longitudinal profile in psychotic disorders involves a more abrupt departure from typical development than does the profile in the neurodevelopmental disorders (Harvey et al. 2012, Kotov et al. 2013). Moreover, these patterns are reflected in changing temporal variability before and after adolescence. Thus, before the onset of psychosis, typically in adolescence, temporal variability is relatively high, such that large proportions of at-risk children will remain symptom free when followed through adolescence into adulthood. However, after the onset of psychosis, variability changes, such that features of these disorders show higher stability/lower variability, with low rates of remission, as found in the neurodevelopmental disorders.

Third, male preponderance in the psychotic disorders is lower than in the neurodevelopmental disorders. Moreover, the most consistent finding is earlier onset in males, at least for schizophrenia, in late adolescence, with equalizing of gender differences in incidence over the next two decades of life (van der Werf et al. 2014). Fourth, as with the neurodevelopmental disorders, research demonstrates a relatively broad, persistent pattern of perturbed information-processing and neural functions, with longitudinal or family-based research also demonstrating perturbed patterns in at-risk individuals (Carter & Barch 2007, 2012; Carter et al. 2011; Church et al. 2002; Nuechterlein et al. 2012). The deficits appear particularly broad in schizophrenia and affect executive functions, memory, and socioemotional functions. Similarly, broadly perturbed brain structure manifests in schizophrenia as well as in the neurodevelopmental disorders. However, evidence suggests that structural perturbations and associated information-processing functions can worsen well into adulthood for the psychotic disorders, a pattern not typically described for the neurodevelopmental disorders (Carter & Barch 2012). Finally, like the neurodevelopmental disorders, much of risk can be attributed to genetic factors (Bacanu & Kendler 2013).

Similarities in neurodevelopmental and psychotic disorders suggest the promise of searching for commonalities and differences in genetic and neural correlates of these conditions. Differences in developmental profiles, however, suggest the need for alternative approaches to categorization. Specifically, lower stability in the earliest clinical signs of risk for the psychotic than for the neurodevelopmental disorders suggests the need for a more cautious approach to early intervention.

Emotional Disorders

Emotional disorders include MDD, panic disorder, and social anxiety disorder. These disorders can be contrasted with the neurodevelopmental and psychotic disorders on the same set of five defining features described above.

First, across development and into adulthood, emotional disorders have a more varied presentation, relative to either the neurodevelopmental or psychotic disorders. Thus, some disorders present in early childhood, but, unlike for neurodevelopmental disorders, such early-life symptoms are often transient (Costello et al. 2005). Other individuals may only develop signs during school age, adolescence, or adulthood. Moreover, at all ages these syndromes involve prominent symptoms of fear, as is typical of the anxiety disorders, or sadness and irritability, as is typical of the mood disorders. Of note, such symptoms also occur in neurodevelopmental disorders, where they coexist with cognitive or social features of these disorders, and in psychotic disorders, where they may represent the first sign of risk. However, only in the emotional disorders does one observe isolated presentation of mood or anxiety symptoms.

Second, these disorders also have a unique developmental profile, as puberty signals a marked change in symptomatic expressions (Angold et al. 1999, Hayward & Sanborn 2002). Before puberty, symptoms of MDD are rare and are far less common than symptoms of anxiety disorders.

Moreover, the nature of anxiety changes fundamentally after puberty. Fears of separation and specific objects or situations are the most common normal and abnormal features of anxiety before puberty; these fears typically diminish after puberty. Whereas other phenomena, such as excessive anxiety about social scenarios or competence, also can occur before puberty, these latter forms of fear tend to increase after puberty, when rates of social anxiety disorder, generalized anxiety disorder, and panic attacks typically increase (Pine et al. 1998). In part this may be due to the change in social context with puberty and adolescence and its emphasis on the peer group and accompanying social networks.

Expressions of emotional disorders that manifest with these types of signs and symptoms appear less as perturbed development in specific skills and more as exaggerated presentations of the mild types of emotional phenomena that occur in typical development. For example, fears of specific objects and separation are a common feature of early childhood, as are concerns with social acceptance and mild dysphoria in adolescence. Emotional disorders involve exaggerated expressions of these same behaviors occurring at the age when such behaviors are most common. Relative to phenomena of typical development, disorders are defined on the basis of greater severity, frequency, and persistence of the same behaviors. Finally, from a dimensional perspective, emotional disorders are less stable than neurodevelopmental or psychotic disorders, showing relatively high degrees of temporal variability at all ages. Thus, even after adolescence, for individuals with relatively severe disorders, remission is more common in emotional disorders than in the neurodevelopmental or psychotic disorders.

Third, the emotional disorders exhibit a female preponderance, which manifests before puberty for phobias and separation anxiety disorder but after puberty for MDD and panic attacks (Hayward & Sanborn 2002, Pine et al. 1998). Fourth, research demonstrates more focused or restricted perturbations in information processing and associated brain structure or function relative to the neurodevelopmental and psychotic disorders. As noted above, neurodevelopmental and psychotic disorders involve broad perturbations in basic information-processing functions as well as in specific emotional processes. In contrast, for emotional disorders, when perturbations are found, they appear to be relatively restricted and manifest selectively in particular emotion-based information-processing functions or in specific brain structures involved in the expression or regulation of emotion (Bar-Haim et al. 2007, Pine et al. 2009). Moreover, relative to perturbations in neurodevelopmental and psychotic disorders, the perturbations that occur in emotional disorders also may be more likely to disappear with effective treatment.

Finally, the emotional disorders involve a weaker genetic component than either the neurodevelopmental or the psychotic disorders, typically with more than half of the underlying risk attributable to environmental factors (Hettema et al. 2001). Moreover, relatively specific and marked associations have been demonstrated with a range of environmental factors for the emotional disorders. In these conditions, a full-blown syndrome can arise in a child with minimal symptoms prior to stress exposure (Costello et al. 2002). This occurs most dramatically in posttraumatic stress disorder (PTSD), one of the emotional disorders where symptoms focus squarely on the environmental precipitant. This contrasts with neurodevelopmental and psychotic disorders, where environmental factors usually predict changes in preexisting symptoms.

These features influence attempts to parse heterogeneity and categorize children in need of treatment. Relative to neurodevelopmental and psychotic disorders, environmental factors account for more risk in emotional disorders. As a result, attempts to categorize risk on the basis of stress exposure and associated perturbations in information processing hold promise. Similarly, because symptoms are frequently transient, a particularly cautious approach to categorization and treatment is needed, especially for treatments that carry more than minimal levels of risk.

GENETICS AND DEVELOPMENTAL PSYCHOPATHOLOGY

Early expressions of risk complicate attempts to study pathophysiology. With each passing phase of development, interactions between genetic and environmental factors accumulate, thereby becoming increasingly complex. This produces a reverberating cycle of causes and effects that shapes individual differences in brain function and behavior. As a result, pathophysiology might be understood most completely through longitudinal studies targeting the earliest stages of risk. The strong heritability of the neurodevelopmental and psychotic disorders provides a convenient starting point in such research, through a focus on genetics. Whereas effects of the environment begin in utero, each individual's sequence of nucleotides, as codified in the genome at conception, does continue to shape risk for neurodevelopmental and psychotic disorders into adulthood, acting in concert with environmental risks. Thus, by grounding a study in an assessment of the genome, research on neurodevelopmental or psychotic disorders can leverage basic science understanding on gene function and influences of the environment through epigenetics (LaSalle et al. 2013). This ready path exists for research in humans because research in rodents charts how variations in gene structure and function, in tandem with environmental exposures, influence neural circuitry function and behavior.

Ongoing findings in genetics echo findings in developmental psychopathology. In both areas, variation in behavior arises from cascades of events operating in multiple, final-common pathways through two trajectories of risk for psychopathology: "equifinality" and "multifinality" (Cicchetti 2014). The presence of equifinality and multifinality creates tenuous ties between the behaviors expressed in psychopathology and the chains of events that produce them. The presence of such tenuous ties in turn emphasizes the need to go beyond assessments of behavior, through assessments of genetics and brain function, to understand pathophysiology.

Equifinality refers to instances in which similar behaviors arise from distinct developmental pathways. For example, adolescent conduct disorder might arise from two pathways, one related to early brain-based risk and the other related to contextual influences (Moffitt & Caspi 2001). Genetic research described below illustrates how equifinality shapes the trajectories for ASDs. Multifinality refers to instances where a specific risk factor produces multiple outcomes. For example, trauma exposure increases risk for diverse forms of psychopathology, including MDD and PTSD (Pine & Cohen 2002). Genetic research described below illustrates how multifinality shapes risk for psychotic disorders.

Equifinality, Genetics, and ASDs

ASDs comprise a family of conditions, with autism as the prototype, involving early-emerging perturbations in social communication and restricted, repetitive behaviors. From very early in life, children with ASDs face significant difficulty when attempting to develop and maintain social relationships, owing to their marked impairments in social communication. Moreover, their fixed interests and inflexibility arising from restrictive, repetitive behaviors interfere with their ability to engage in many important activities. Twin studies finding substantial heritability of ASDs as well as their individual component behaviors encouraged work on molecular genetics, which identified distinct genetic relations. The phenotypes linked to distinct genetic findings appear similar to each other; there is no one-to-one mapping between the distinct genetic findings and a distinct set of behaviors. Rather, illustrating the principle of equifinality, different genetic vulnerabilities produce the same phenotype. If similar behaviors can arise from different vulnerabilities, caution is needed when attempting to understand pathophysiology by examining behavior without reference to the risk factors that produce it.

Because the pace of discovery in ASD genetics remains brisk, conceptualizations are likely to change in the coming years. As of this writing, two sets of genetic relations have been described. One involves relatively few genes, with potentially large effects; the other involves many, relatively small, individual causative factors. These either could comprise a large number of genes, each with small effects, or a smaller set of genes that exert their effects through epistasis or interactions with the environment.

Large genetic effects in ASD arise from rare genetic mutations or large disruptions in the genetic architecture, such as deletions or copy number variations (State & Levitt 2011, State & Sestan 2012). In some instances, this produces a genetic syndrome, such as tuberous sclerosis and Rett, Phelan-McDermid, and fragile X syndromes. These syndromes involve a behavioral phenotype that closely resembles the ASD phenotype seen in other contexts. Although the prevalence of such large genetic effects remains unknown, some estimates suggest that as many as half of all ASD cases involve some major disruption in molecular genetic architecture (Coe et al. 2012). Regardless of the exact estimate, however, many other ASD cases arise from different genetic relations, involving multiple small effects, producing a phenotype labeled "idiopathic autism." Research in this area on ASD extends ideas about equifinality into the realm of neuroscience.

Different genetic contexts produce different anatomical profiles. This is illustrated by findings from a recent structural magnetic resonance imaging (MRI) study comparing brain volumes in 63 children with idiopathic autism, 52 children with fragile X, and 50 children with neither fragile X syndrome or autism (Hoeft et al. 2008). Fragile X syndrome results from a specific genetic disruption in the fragile X mental retardation 1 (*FMR1*) gene located on the X chromosome. This produces a syndrome with both somatic and behavioral manifestations. Somatic manifestations include an elongated face, misshapen ears, low muscle tone, and macroorchidism. Behavioral manifestations include high risk for ASDs and intellectual disability. In fact, fragile X syndrome is the most common single-gene cause of autism and the most common inherited form of intellectual disability. This structural MRI study is important for revealing differences between children with autism associated with fragile X and children with autism arising from other genetic pathways. Despite similar clinical ASD phenotypes, neuroanatomical profiles in the two ASD groups differed from each other and from the comparison group. Relative to nonaffected children, idiopathic autism is associated with elevated brain volume in diverse expanses of frontal and temporal association cortex. In contrast, fragile X syndrome is associated with the opposite pattern: reduced volumes in these same structures, even in cases with ASD. Thus, two different genetic contexts produce similar clinical phenotypes and distinct anatomical correlates.

Research on ASD also delineates the ways that neurochemistry relates to equifinality and novel treatments. More than half of children with fragile X syndrome have an ASD. Disruption in the *FMR1* gene involves an expanding trinucleotide repeat in the gene's 5′-untranslated region, which is thought to produce hyperactivity of the metabotropic glutamate receptor type 5 (mGluR5) signaling pathway (Veenstra-VanderWeele & Blakely 2012). Effective treatment for ASD symptoms in fragile X syndrome might utilize antagonists at this glutamate receptor. Conversely, tuberous sclerosis is another single-gene condition where similarly large proportions of children are affected by an ASD (Auerbach et al. 2011). In contrast to mGluR5 hyperactivity in fragile X syndrome, tuberous sclerosis may result in mGluR5 hypoactivity. Similar findings may occur for other molecular targets, such as cascades activated by SHANK3, where similar phenotypes arise from opposing chemical profiles (Han et al. 2013, Shcheglovitov et al. 2013).

In these instances, novel treatments target unique forms of disruption rather than symptomatic presentations. Of note, preliminary attempts to treat ASD based on these principles have been disappointing (Veenstra-VanderWeele & Blakely 2012), but the broader framework for medication discovery remains promising. This approach is justifiable because of the early-appearing

persistent course of severe ASDs. However, such treatments also could carry unknown risks, given evidence in basic research of the fine balance between expressions of gene products and normal development.

Research on equifinality in ASD is most notable for the framework that it provides. In this framework, basic research demonstrates how changes in genetic expression disrupt brain function and associated behaviors with high penetrance; clinical research defines risk alleles to be pursued in other basic research studies. Attempts to link specific changes in genetic expression to clinical symptoms generate ideas on novel treatments targeted toward the specific causes of a syndrome rather than the overt expressions of pathology. Finally, these ideas suggest novel medications to extend translational research in genetics. However, other pathways of treatment discovery also hold promise. For example, novel therapies could emerge through cognitive neuroscience, where research in ASDs finds disruptions in learning or attention that provide other treatment targets (Klin et al. 2009). This pathway is described below for the emotional disorders, where more randomized controlled trials (RCTs) demonstrate efficacy than is true for the ASDs.

Multifinality, Genetics, and Psychotic Disorders

Schizophrenia is a prototypical psychotic disorder targeted in genetics and neuroscience research. It involves a constellation of positive symptoms, such as delusions; negative symptoms, such as social withdrawal; and cognitive symptoms, such as disruptions in attention and memory. As with neurodevelopmental disorders, substantial heritability suggests the potential utility of genetic research.

Recent reviews of schizophrenia genetics describe findings that are broadly similar to those in ASDs, with evidence of rare genetic variants producing large effects and more common genetic variants producing small effects (Bacanu & Kendler 2013, Gejman et al. 2011, Owen et al. 2010). Moreover, as in ASDs, some genetic associations manifesting with large effects arise from structural disruptions in genetic architecture, whereas those with small effects arise in genome-wide association studies (GWAS). For large-effect-size findings, risk conferred to the individual patient is high, suggesting avenues for interventions. However, for small effects in GWAS, clinical relevance arises less from a genetic assessment in an individual patient and more from programmatic research.

One possible example of programmatic research could arise from GWAS research implicating a region on chromosome 6 in schizophrenia (Walters et al. 2013). This region encompasses the major histocompatibility complex, which influences both immune function and neuronal plasticity; pharmacologic manipulations of chemicals interacting with the major histocompatibility complex could have therapeutic potential (Shatz 2009). Nevertheless, the relevance of research on such manipulations for the treatment of psychosis remains indirect due to the small level of risk associated with genetic variation on this chromosomal 6 region. Because large-effect-size findings may be more immediately relevant for treatment, this review focuses on such findings. Nevertheless, even here, multifinality complicates attempts to generate novel therapies.

Some large-effect-size findings in psychosis relate to genetic syndromes. For example, velo-cardio-facial (VCF) syndrome results from a hemizygous deletion on the long arm of chromosome 22, which can encompass between 1.5 and 3 million bases. VCF involves somatic features and a complex psychiatric phenotype, with a particularly strong risk for psychosis, usually occurring after puberty (Jonas et al. 2014). However, a sizable minority of children with VCF does not develop psychosis but rather suffers from emotional or neurodevelopmental disorders. This illustrates the principle of multifinality.

Research on VCF searches for genes in the deleted region that could produce multifinality. Attention has focused on the gene for catechol-O-methyl-transferase (COMT), which metabolizes

catecholamines to influence cognition and emotion. Initial work suggested that naturally occurring COMT variants also might influence risk for psychosis in people without the VCF deletion, but subsequent research failed to confirm these findings. Regardless, this work does illustrate one pathway to multifinality, where COMT was shown to affect attention, anxiety, and other domains of function (Bilder et al. 2004). Moreover, this work identified medications that, through their effects on COMT, might have similarly broad effects on a range of parameters. Thus, different treatment implications arise from instances of multifinality, where medications with broad effects might be identified, as opposed to equifinality, where medications with relatively specific effects might be identified, based on their ability to treat forms of ASD that arise in particular genetic contexts.

Finally, beyond a shared focus on genetic syndromes, other research on large-effect-size findings in schizophrenia parallels research in ASDs. For example, copy number variations occur in ASDs and schizophrenia, as well as in other syndromes, such as ADHD and intellectual disability (Gejman et al. 2011, Owen et al. 2010). This demonstrates multifinality, where the same set of risk factors produces varied phenotypes.

TEMPERAMENT AND DEVELOPMENTAL PSYCHOPATHOLOGY

The term "temperament" refers to a stable, enduring style of behavior expressed within the first years of life, typically in reaction to novel stimuli or unfamiliar circumstances. Research on emotional disorders targets specific types of temperament and their link to brain function to address a key problem in research on risk for disorders. A focus on the genome provides a convenient starting point in neurodevelopmental and psychotic disorders, but emotional disorders involve less defined genetic components, a greater influence of environmental context, and greater fluctuations in symptoms; complete remission is more common in emotional than neurodevelopmental or psychotic disorders. Thus, genetics paradigms successfully used in neurodevelopmental and psychotic disorders are not easily applied in emotional disorders. Research on temperament provides an alternative paradigm that quantifies differences in reactivity from an early age. Such research charts how early temperament interacts with specific types of environment. This approach recognizes the salience of environmental risk in emotional disorder vulnerability and extends basic work suggesting that environmental events exert a particularly strong impact on temperamentally reactive organisms.

Emotional disorders, particularly anxiety disorders, relate to one specific temperament, behavioral inhibition (BI). Relative to children without BI, children with BI show more fear when encountering novel stimuli, particularly novel social stimuli (Fox et al. 2005). Fear manifests in children's observed behavior in laboratory settings and in children's behavior over more extended periods, as rated by parents or teachers. Children with BI face a higher risk than children without BI for various psychiatric disorders, particularly anxiety disorders (Clauss & Blackford 2012), and higher rates of BI occur in offspring of parents with emotional disorders than in offspring of healthy parents (Rosenbaum et al. 2000). However, this risk is probabilistic; only about half of children vulnerable due to BI ultimately develop an anxiety disorder. This raises questions on moderators that predict outcome and identify those children with BI at particularly high risk for anxiety disorders.

Cognitive neuroscience research provides clues on moderators. Similar information-processing and neural perturbations occur in anxiety disorders and BI (Pine et al. 2009, Shechner et al. 2012). Moreover, among children with BI, the presence of such perturbations predicts risk for anxiety disorders (McDermott et al. 2009, Reeb-Sutherland et al. 2009). This suggests that the very same information-processing and neural perturbations that occur in the anxiety disorders moderate risk

among children with BI. There also is evidence that these relations are unique to anxiety and other emotional disorders. This is because information-processing and neural perturbations in anxiety disorders are more restrictive than in the neurodevelopmental or psychotic disorders (Salum et al. 2012). When such perturbations do occur in emotional disorders, they appear to manifest with large effect sizes. Thus, whereas genetics provides a fulcrum for translational research on neurodevelopmental and psychotic disorders, cognitive neuroscience provides a similar foundation in the emotional disorders.

Research on BI is described below as it relates to expressions of risk and three specific areas of cognitive neuroscience. Research on fear learning is described in an initial section, followed by a description of research on attention orienting in the next section. In both areas, research has led to RCTs for novel treatments. Finally, research on cognitive control is described, an area less well developed than fear learning or attention orienting. Each instance provides brief descriptions rather than exhaustive reviews to illustrate conceptualizations of risk as it relates to BI.

Fear Learning

Various forms of fear learning can be studied in laboratory settings. Such research illustrates how experience influences knowledge and sculpts risk. This effectively maps the ways that environments change behavior through epigenetics and associated effects on neural circuits. As such, much in the way that basic research elucidates genetic contributions to vulnerability in neurodevelopmental and psychotic disorders, basic research on fear learning elucidates environmental contributions to vulnerability in emotional disorders. Such basic research shows that early-life stress has lasting effects on behavior by shaping functioning in circuits that support fear learning (Meaney 2001). This has clinical parallels in work linking early-life stress to long-term risk for emotional disorders. Among many processes targeted in translational research, conditioning and extinction have generated the most interest.

Conditioning and extinction. Fear conditioning refers to the process whereby a neutral conditioned stimulus (CS+) acquires the capacity to evoke fear when it is paired with an aversive, unconditioned stimulus (UCS). Extinction occurs after conditioning, when the CS+ is presented repeatedly in the absence of the UCS, which leads to a reduction in fear. As illustrated in **Figure 2**, investigators monitor both the acquisition of extinction, occurring across repeated unreinforced CS+ presentations, and its maintenance, tested on extinction recall paradigms, where organisms encounter the CS+ days after it has been extinguished.

Cross-species similarities exist in the neural architecture of these processes. Whereas both conditioning and extinction depend heavily on the various amygdala nuclei, the ventromedial prefrontal cortex (vmPFC) and hippocampus play a stronger role in the maintenance of extinction than in conditioning (Quirk & Mueller 2008). Beyond differences in circuitry, conditioning and extinction differ in other ways. For example, extinction tends to be maintained less stably than conditioning and shows more dramatic variation with changes in context. These findings may reflect the fact that during extinction recall paradigms, subjects encounter threat cues that are more ambiguous than those encountered during conditioning (Bouton 2002). Responses to such ambiguous cues are highly relevant to risk for emotional disorders.

Individual differences. As reviewed elsewhere, considerable work charts relations between fear learning and emotional disorders (Lissek et al. 2005). To understand risk, it is important to compare not only low and high risk but also unaffected and affected individuals. For ambiguous threats, similar profiles on functional magnetic resonance imaging (fMRI) in high-risk and affected

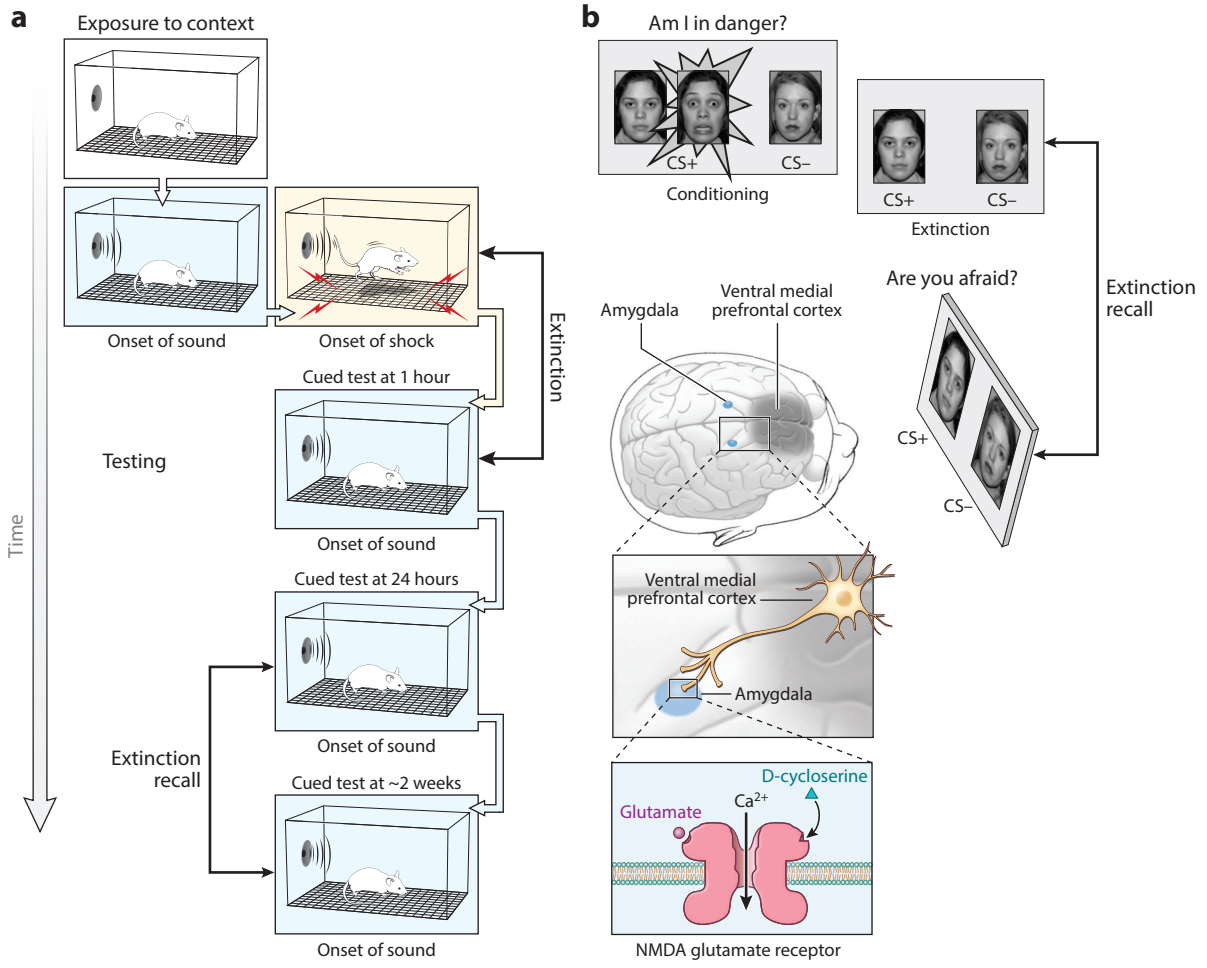

Figure 2

Procedures and circuitry in research on conditioning, extinction, and extinction recall in rodents and humans. **Figure 2*a*** depicts a conditioning procedure in a study with rodents in which a sound conditioned stimulus (CS+) is paired with a shock unconditioned stimulus (UCS) in the yellow box. This is followed by extinction one hour after conditioning and then extinction recall over subsequent days in the blue boxes below the yellow box. **Figure 2*b*** depicts the procedures for studying developmental psychopathology, conditioning, and extinction using the paradigm in Britton et al. (2013b) and in Lau et al. (2011). This paradigm pairs a neutral face CS+ with an aversive scream and a fearful face UCS during conditioning, followed in extinction by presentation of unpaired CS+ and nonconditioned stimulus (CS−). Finally, during extinction recall, research participants view the CS− and extinguished CS+ in the scanner, during which time participants are asked to rate their level of experienced fear. This engages ventral medial prefrontal cortex (vmPFC), as shown in the schematic for the depicted child participant. The lower two figure panels depict the associated neural circuitry connecting vmPFC to the amygdala, where glutamate release occurs in the synapse connecting axons of pyramidal vmPFC neurons to dendrites on cell bodies of the intercalated cells proximal to the amygdala basolateral nucleus. Abbreviations: Ca^{2+}, calcium ion; NMDA, *N*-methyl-D-aspartate.

groups, which both differ from the profile in a low-risk unaffected group, suggest that interventions effective in affected children also may be useful in prevention among vulnerable, unaffected youth.

Fear-learning perturbations are subtle in the anxiety disorders. Individual differences in anxiety generally show no relation to individual differences in fear conditioning, regardless of how

anxiety and conditioning are quantified (Lissek et al. 2005). Of note, on diverse emotional-reactivity paradigms, findings suggest that anxiety disorders involve perturbed processing only for relatively subtle as opposed to more overt forms of threat (Lissek et al. 2006). Fear conditioning studies typically utilize overt forms of threat to instantiate robust degrees of conditioned fear. Thus, conditioning in anxiety disorders may reflect a normal response to dangers that are clearly identifiable. Although conditioning typically is normal in anxiety disorders, perturbations do occur with some consistency to ambiguous cues that appear in extinction recall, stimulus generalization, and inhibition of fear paradigms (Britton et al. 2013b, Graham & Milad 2011, Lissek et al. 2010). Associations with anxiety on such paradigms manifest with skin conductance, startle responding, and self-reported fear. Moreover, findings suggest some specificity, as perturbations in the emotional disorders appear to differ from those in psychotic and neurodevelopmental disorders (Blair et al. 2005). Finally, similarly perturbed fear responding may occur in affected and unaffected individuals at high risk for emotional disorders (Craske et al. 2012, Grillon et al. 2005, Reeb-Sutherland et al. 2009).

Such research on risk for emotional disorders has used various research designs. In family-based studies, children born to parents with emotional disorders have been shown to exhibit forms of perturbed responding that also occur in anxiety disorders (Grillon et al. 2005). This involves normal responding to overt threats but heightened responding to ambiguous threats. Similarly, longitudinal studies quantify threat responding in unaffected adolescents and follow them prospectively. In such work, a tendency to respond with fear to an ambiguous threat at one point in time predicts risk for anxiety disorders at later points in time (Craske et al. 2012). Finally, two studies show that the response to ambiguous threats is different in children with BI than in children without BI (Barker et al. 2014, Reeb-Sutherland et al. 2009). This pattern of findings suggests that a tendency to respond with fear to ambiguous threats manifests in some unaffected at-risk youth.

This tendency to respond with elevated fear to an ambiguous threat may place behaviorally inhibited children at risk during particular phases of development. Adolescence may be one such phase, representing an inflection point in development. For symptomatic children, the ability to overcome earlier problems during adolescence may portend persistent remission, whereas children who remain symptomatic may face particularly elevated risks for adult emotional disorders. The importance of adolescence for behavioral trajectories may relate to unique experiences, such as the stressful nature of adolescence for organisms adjusting to a changing social milieu and confronting both overt and more ambiguous threats. As such, changes in symptoms may relate to the unique social challenges of adolescence. Alternatively, this could relate to critical aspects of brain development occurring in adolescence. As such, adolescence may involve changes in brain organization that influence responding to ambiguous threats. Such changes could occur specifically at puberty, when alterations in the hormonal milieu signal the beginning of adolescence.

Healthy adolescent development may sharpen the individual's ability to differentiate between overt and ambiguous threats. Existing data suggest that such development may specifically involve learning to inhibit fear responses to ambiguous threats (Lau et al. 2011). Children who fail to acquire this skill may face particular difficulty during this stressful transition point. Thus, heterogeneity in emotional disorders may be parsed based on symptom trajectories and associated information-processing profiles. In particular, the subgroup of children with BI who enter adolescence with a tendency to respond with fear to ambiguous threats may differ from other children. This unique group is hypothesized to face a particularly high risk for persistent anxiety when exposed to the stress of adolescence.

Tests of such hypotheses relating early temperament, threat responding, adolescence, and persistence of emotional problems ideally would rely on brain-imaging measures because they are

more sensitive than behavioral or psychophysiological measures to individual differences in threat responding (Britton et al. 2013b). However, no imaging studies compare response to ambiguous threats among affected, high-risk, and low-risk samples. Studies in affected subjects implicate deficient vmPFC function in response to ambiguous threats, and, based on findings from psychophysiology studies, one might expect similar findings in at-risk youth.

Findings that most directly extend basic research on fear learning utilize extinction recall paradigms. In this research, fMRI studies compare anxious and healthy subjects. These studies find reduced vmPFC function to previously extinguished, ambiguous CS+ cues in anxious versus nonanxious individuals. This pattern has been documented in studies among adults and adolescents with various forms of anxiety, including social anxiety disorder, generalized anxiety disorder, and PTSD (Britton et al. 2013b, Graham & Milad 2011). **Figure 2** illustrates the general design in one such study, in which conditioning involves the pairing of a CS+ facial photograph with an aversive scream, followed by extinction. Two weeks later, the research subject is exposed to the extinguished CS+ while their level of experienced fear is monitored. In this context, healthy adolescents and adults, but neither adolescents nor adults with social anxiety or generalized anxiety disorder, exhibit vmPFC engagement.

It remains unclear the degree to which development impacts the association between anxiety and deficient vmPFC function. Studies in rodents and healthy subjects do document age-related differences in vmPFC function in fear-learning paradigms (Casey et al. 2013). This suggests that age-related changes in vmPFC function might contribute to extinction and remission of emotional problems in adolescence. However, only one study of extinction in patients directly compares healthy and anxious adolescent and adults (Britton et al. 2013b). This study found that one aspect of vmPFC function relates to development, whereas a different aspect of vmPFC function relates to clinical anxiety. Thus, different aspects of brain function might relate to healthy and pathological development.

Treatment implications. Studies on fear learning inform treatments, showing how neuroscience can impact clinical research. Such research also informs attempts to reduce risk for emotional disorders and treat early markers of mental disorders to minimize impact on later development.

Some research relevant to treatment and risk is based on the temperament of BI. As noted above, children with BI face a high risk for clinical anxiety disorders and respond with fear to ambiguous threats. Moreover, one study found that such perturbed responding only occurs in the subset of children with BI who also suffer from an anxiety disorder (Reeb-Sutherland et al. 2009); in this study, children with an anxiety disorder without BI exhibited normal responding. Hence, perturbed responding to ambiguous threats may be most closely tied to anxiety disorders occurring in at-risk individuals. Moreover, before clinical anxiety disorders are expressed, this at-risk subset might be identifiable on the basis of their responses to ambiguous threats and might benefit from treatments specifically designed to correct such aberrant responding. Ideally, such responding would index vmPFC engagement to ambiguous threats with fMRI.

Preliminary work in BI indirectly suggests that interventions targeting perturbed threat responding impact risk outcomes. Children with BI raised by parents who place their children in peer contexts early in life, such as day care, or encourage their children to confront mildly fearful situations are less likely to develop anxiety than are children with BI raised by parents who fail to do so (Lewis-Morrarty et al. 2012). This suggests that exposure reduces fear. When combined with experimental stress-exposure research in nonhuman primates (Parker et al. 2006), these observational data on BI suggest that resilience arises through extinction of fear in children with BI. Similarly, cognitive behavioral therapy (CBT) is a treatment that uses the principles of extinction to reduce anxiety by teaching children how to differentiate overt from ambiguous threats and

by then exposing children to ambiguous threats. Consistent with observational data on threat exposure in children with BI, CBT also reduces risk for anxiety in children with BI (Rapee 2013).

Of note, such research raises fundamental questions about risk, disorders, and interventions. One set of questions relates to differences between risk factors and disorders. Traditionally, CBT is provided to patients with impairing psychopathology. However, in this context, CBT was provided to unimpaired children with signs of extreme threat responding in the form of BI. The intervention reduced long-term risk, as reflected in later impairing anxiety disorders. This suggests that the criteria currently used to categorize children as suffering from a disorder can sometimes differ from the criteria used to select children for an intervention. This raises questions about when similar or different criteria should be used for these two groups of children. Other questions follow related to interventions. Rapee (2013) found that many children with BI who did not receive CBT matured to be healthy adolescents, which suggests that at least some of the children in the study received CBT unnecessarily. This raises questions on how to distinguish the unique group of at-risk children most in need of intervention.

Of note, none of these studies directly evaluate threat responding using paradigms from cognitive neuroscience. Thus, it remains unclear if parenting behavior or CBT specifically moderate outcome in a subset of children with BI with perturbed threat responding. Future studies could address such questions by directly assessing threat responding in children with BI. Moreover, because only a subset of children with BI face elevated risk, future studies also could attempt to identify and treat this subset through such direct assessments of threat responding.

Other research examines patients with anxiety disorders. In one area, medications that target threat response deficiencies are administered as part of CBT to facilitate extinction (Pine et al. 2009). These medications include D-cycloserine, oxytocin, and yohimbine. The circuitry on which D-cycloserine and other medications act is illustrated in **Figure 2**. In this figure, the circuitry connecting the vmPFC to the basolateral nucleus of amygdala is depicted, revealing the site at which D-cycloserine is thought to act. In another area of research, the format of CBT is tailored to fear-learning deficits. For example, conducting exposure in multiple contexts addresses the sensitivity of extinction to context.

Much as in genetics research on ASDs, the importance of this work emerges less from the findings it has already generated and more from the pathway for discovery it elucidates. Treatments such as D-cycloserine appear to provide no more than modest clinical benefit. However, these treatments target the neural substrate that creates risk. Findings in other areas of medicine suggest that such a direct targeting of pathophysiological processes provides a sound avenue for therapeutic discovery. Although few of these studies target youth and none have changed clinical practice, they represent important instances where research in neuroscience generates promising initial results in a programmatic set of therapeutic studies.

Attention Orienting

In a range of mammalian species, overtly threatening stimuli exhibit the capacity to capture attention (Bar-Haim et al. 2007). For example, on various experimental paradigms, the appearance of a task-irrelevant threat can elicit a saccade or interrupt a motor response. To assess attention, researchers most frequently employ paradigms that utilize adaptations of the Posner cueing paradigm, where subjects engage in a neutral, repetitive task. For example, they might be required to indicate the box in which a neutral target appears. On select trials, a distracting task-irrelevant threat appears immediately before the target. This might include a negative-valence word or a mildly aversive picture. In some trials, the threat appears in the box where the target subsequently appears; in other trials, the target appears in the box opposite from where the target subsequently

appears. Attention orienting to threat is indexed based on the capacity for threats to influence performance on the neutral task across these two types of trials. Whereas extreme threats capture attention in most individuals, mild threats typically elicit no such effects (Bar-Haim et al. 2007).

Individual differences. As reviewed elsewhere (Bar-Haim et al. 2007, Shechner et al. 2012), biased attention orienting represents the most consistently replicated information-processing correlate of individual differences in anxiety. This bias manifests on tasks where threats influence anxious but not nonanxious subjects. As shown in **Figure 3**, an overt threat, such as a snake that suddenly appears, has the capacity to capture attention. However, subtle or ambiguous threats exert less robust effects on attention orienting. For example, in a safe, nonthreatening environment, where the probability of encountering danger is very low, a picture of an angry face could represent a subtle or ambiguous threat. Such stimuli capture attention more readily in anxious than nonanxious individuals. Thus, much as in findings on fear-learning paradigms for ambiguous as opposed to overt threats, individual differences in attention manifest in scenarios where mild threats influence performance more profoundly in anxious than in nonanxious individuals.

These individual differences manifest on cueing tasks. For example, whereas mild threats typically exert no measurable effect on orienting in healthy people, such threats affect task performance in a measurable way among people with high levels of anxiety. These associations have been found using a range of paradigms; they have been documented for a range of behaviors, including reaction time and saccade latency; and they have been detected for diverse threats, including mildly aversive words or pictures. Such a paradigm is also depicted in **Figure 3**. Moreover, associations are observable with diverse individual-difference measures. These include a diagnosis of an anxiety disorder, high levels of symptoms on a rating scale, or various measures of risk for or presence of anxiety disorders (Bar-Haim et al. 2007, Shechner et al. 2012). There is modest specificity in these associations; attention biases typically do not occur for phenotypes outside of the emotional disorders (Salum et al. 2012), such as some neurodevelopmental disorders. However, attention biases manifest similarly in many emotional disorders that are classified as distinct. This includes most if not all of the specific anxiety disorders, such as phobias or social anxiety disorder. Finally, these associations generally manifest with an effect size in the medium-to-large range.

Given the strong role of environmental factors in risk for emotional disorders, studies have attempted to link environmental risks to attention orienting. Such research has revealed a unique relation between attention bias and stress exposures, relative to other forms of risk for emotional disorders. This unique pattern is illustrated in findings on the ways that temperament and other risk factors relate to patterns on attention bias and fear-learning tasks. For fear-learning tasks, perturbations generally manifest similarly among patients affected by anxiety disorders and individuals identified as temperamentally at risk for disorders using diverse research designs. This includes individuals characterized in early childhood with BI. For attention orienting, in contrast, findings differ based on the nature of the risk. That is, children with BI, like children with anxiety disorders, tend to orient attention toward threat; in contrast, healthy children at low risk for anxiety show no bias either toward or away from threat (Shechner et al. 2012). However, relative to other groups, children and adults who are at risk due to stress exposure exhibit a unique attention profile. Such vulnerable individuals tend to orient their attention away from threat (Wald et al. 2013). These variable findings could inform attempts to apply novel therapies in particular types of vulnerable populations.

Relations among attention orienting, anxiety, and probabilities of risk are thought to arise from dysfunction in a neural circuit that is related to but also distinguishable from the circuit implicated in fear-learning perturbations. Both attention orienting and fear-learning perturbations have been shown to involve dysfunction in circuits that connect the amygdala and prefrontal cortex (PFC).

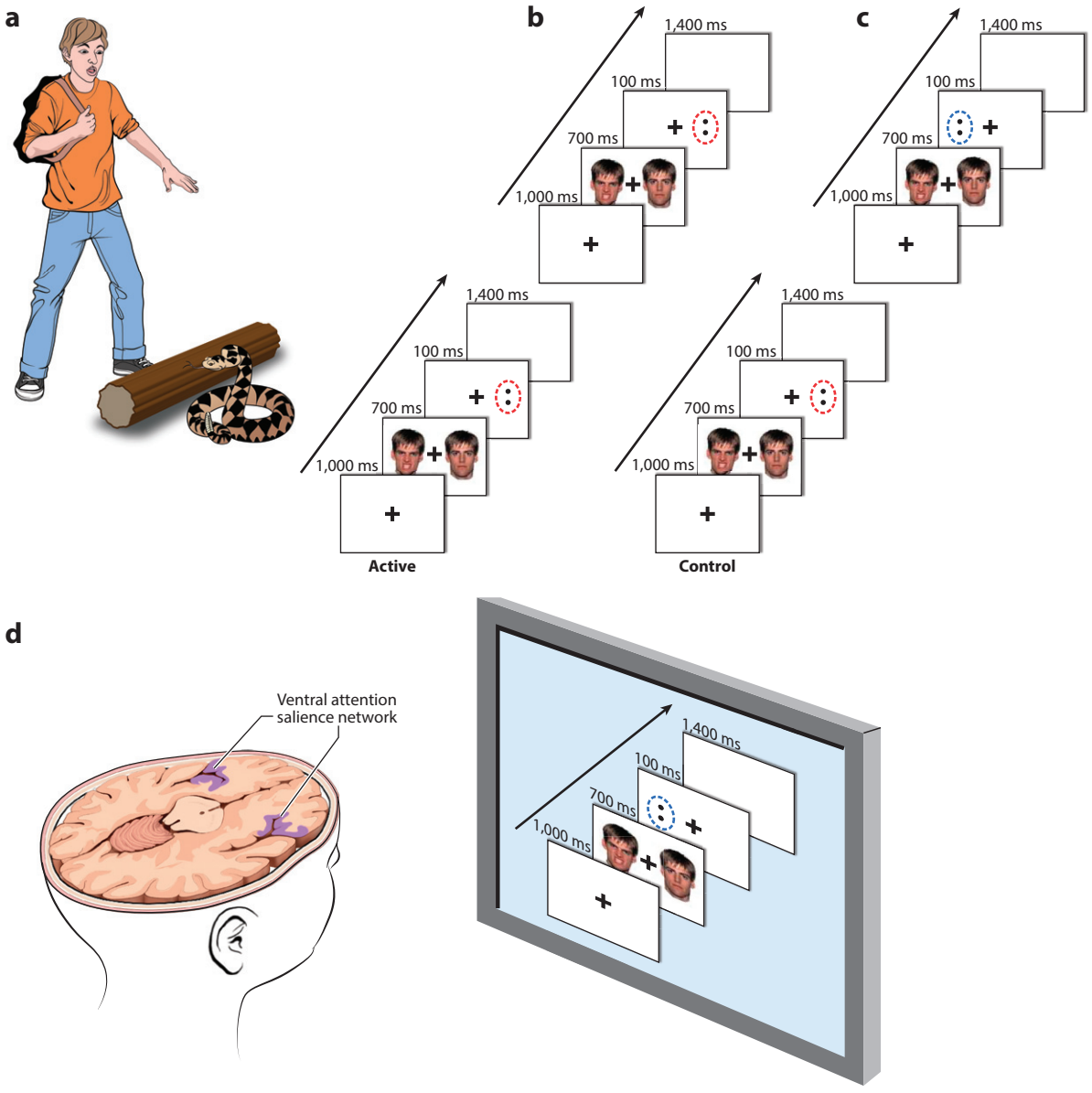

Figure 3

Procedures for examining the effect of threat on attention orienting. **Figure 3*a*** depicts a scenario in which an unexpected threat, in the form of a snake, influences attention orienting, arresting motor behavior and capturing attention. Both an active (*b*) and a control (*c*) regimen for attention bias modification treatment are shown in the adjacent pictures depicting sets of task trials. In both sets, subjects must identify a semicolon target, as indicated by dashed circles. In the active condition (*b*), this target is indicated by a red dashed circle; here this target always appears behind the neutral face, opposite from the threat face. Over time, with training, the consistent location of this target leads subjects to orient away from threat faces. In the control condition (*c*), the target appears behind the neutral face in half of the trials, but it appears behind the threat face, as indicated by a blue dashed circle, in the other half. Finally, **Figure 3*d*** shows the locations of the ventral attention salience network engaged by such attention-orienting tasks. The ventrolateral prefrontal cortex and adjacent insula are depicted in purple.

However, these two information-processing functions involve different components of the ventral PFC and different extra-PFC structures. Specifically, fear-learning perturbations have been tied to perturbations specifically in the vmPFC as well as the hippocampus (Quirk & Mueller 2008). In contrast, perturbations in attention orienting typically have not involved either the vmPFC or the hippocampus. Rather, they are more frequently linked to perturbations within distinct components of the PFC (Pine et al. 2009). These include the ventrolateral PFC (vlPFC), encompassing the anterior insula cortex to form key components of the ventral attention salience network, and the dorsolateral PFC (dlPFC). **Figure 3*d*** illustrates the vlPFC component of this circuit. Within this circuit, amygdala dysfunction on orienting tasks is thought to support a heightened tendency in anxious individuals to react to a task-irrelevant threat cue. In contrast, varying levels of engagement in vlPFC, insula, and dlPFC are thought to reflect varying abilities to engage attention-regulatory functions and maintain goal-related behavior to compensate for such heightened amygdala-related threat reactivity and maintain representations of task-related goals.

Findings on the chronometry of these attention tasks document the precisely orchestrated series of events that produce attention biases. Behavioral expressions of attention biases vary when key task parameters are subtly manipulated. For example, on some tasks producing no bias among healthy subjects, biases in anxious individuals change when task parameters change; a bias toward threat typically appears in anxious subjects when neutral targets immediately follow 500-millisecond threat exposures. However, no bias may appear with briefer threat exposures, and attention avoidance may occur with longer threat exposures (Shechner et al. 2012). Data from brain imaging studies suggest that such effects relate to the rapid and exquisitely timed coordination of events that produce the attention-orienting response. Amygdala activation is thought to occur within milliseconds of threat exposure, whereas deployment of PFC-based regulatory functions is thought to occur later, only after a target appears to provide a specific behavioral goal. Tasks with parameters other than a 500-millisecond threat exposure, followed immediately by a neutral target, may miss the brief, precisely timed window where individual differences in threat monitoring manifest or, if threats extend beyond 500 milliseconds, may produce avoidance.

Due to the speed with which these events unfold, humans remain incompletely aware of the components that produce an attention-orienting response. The rapid pace during which these events unfold prevents humans from fully monitoring their responses, complicating attempts to sculpt an individual's perturbed attention-orienting responses by describing adaptive attention-orienting behavior. Rather, as with other rapidly deployed responses, efficient means for training attention orienting may use methods known to shape implicit processes. These considerations led to the development of a novel treatment called attention bias modification training (ABMT) (Hakamata et al. 2010). Much like changes to CBT that are based on research on fear learning, the development and refinement of ABMT represents an instance in which neuroscience informs therapeutics.

Treatment implications. Rather than instructing individuals on how to deploy their attention, as is done in CBT, ABMT trains attention by having subjects complete hundreds of trials in which task parameters influence attention. For example, an ABMT regimen designed to shift attention away from threat repeatedly presents a neutral target in the opposite spatial hemifield in which a threat appears (Hakamata et al. 2010). This regimen is depicted in **Figure 3**, along with a control regimen, in which threats appear randomly behind a threat in half of the trials and in the opposite spatial hemifield in the other half. This repeated juxtaposition of threats and targets leads the subject to reflexively shift attention away from a threat. A growing series of RCTs examines efficacy of ABMT for various anxiety-related problems, as reviewed in three recent papers (Beard et al. 2012, Hakamata et al. 2010, Van Bockstaele et al. 2013). In general,

although data for ABMT appear promising, there is marked variability in responding across the many studies, and the results remain too preliminary to support routine clinical use. Moreover, major questions remain regarding the most effective training regimens.

One set of questions relates to the associations between pretreatment attention bias and response to ABMT. Only a subset of anxious patients exhibits a bias toward threat, and one might expect the nature of the pretreatment bias to moderate outcome. Findings are inconsistent in this area. Moreover, RCTs in patients target behavioral expressions of attention bias. Brain-imaging studies indicate that neural expressions of attention bias may be more stable and more responsive to ABMT than are behavioral expressions of attention bias (Britton et al. 2013a). This finding suggests the need to combine brain imaging and clinical measures in an RCT of ABMT in anxious individuals. A second set of questions relates to circumstances in which the direction of training may vary with the nature of risk. As noted above, children with BI and individuals with anxiety disorders typically attend toward threats, whereas individuals exposed to stress often exhibit attention avoidance of threats. These groups may require different types of ABMT, but minimal research evaluates this possibility. Finally, ABMT may operate on one set of risk factors in anxious or at-risk groups, whereas other treatments, such as CBT or medication, may operate on another set of factors. This suggests that combining ABMT with other treatments, such as CBT, may produce greater benefits than utilizing either treatment alone. Again, minimal research evaluates this possibility, and preliminary findings are encouraging albeit inconsistent in terms of the benefits of ABMT (Shechner et al. 2014).

Cognitive Control

Cognitive control allows an organism to flexibly select from a range of possible motor programs in the face of conflicting demands. Considerable work on cognitive control utilizes the "flanker" task, in which a research participant must indicate the direction (e.g., right or left) toward which an arrow points (McDermott et al. 2009). On some trials, cognitive conflict occurs on so-called incongruent trials, where one rightward-pointing target arrow appears amid a group of other, leftward-pointing distracter arrows. On other trials, no such conflict occurs, such as when a rightward-pointing target arrow appears alone or when it appears amid a number of other identically appearing rightward-pointing distractor arrows. Paradigms such as the flanker task index cognitive control on the basis of measures of conflict processing, which can be indexed as a reaction-time slowing to the incongruent relative to other trials, or measures of conflict adjustment, which can be indexed by trial-by-trial variations in reaction time following incongruent or errant trials. Finally, some conflict tasks include stimuli of varying emotional valence to further examine the ways in which conflict and errors manifest on differentially valenced trials (Jarcho et al. 2013).

Individual differences. Results from studies on associations between individual differences in cognitive control and anxiety generally are less consistent than from studies on fear learning or attention orienting. Two sets of contradictory findings emerge in this research.

One set of studies finds signs of reduced cognitive control in anxious relative to nonanxious individuals. Such findings occur in both behavioral studies of reaction-time adjustments and brain-imaging studies of cortical response to conflict or errors (Etkin et al. 2010). However, in general, results are more consistent in a second set of studies, which finds signs of enhanced cognitive control in anxious relative to nonanxious individuals (Jarcho et al. 2013). Such enhanced control has been found in measures of behavior, such as reduced error rates, greater post-error adjustments, or more flexible behavior in the face of changing task instructions, as well as in measures of brain imaging. The most consistent evidence of an association between

elevated levels of cognitive control and anxiety arises for one particular electrophysiological measure, the error-related negativity (ERN) (Moser et al. 2013). The ERN is a negative-voltage event-related potential (ERP) that occurs between 50 and 100 milliseconds after the execution of an errant motor response. The ERN typically appears with maximal amplitude in midline frontal electrodes, and this ERP is thought to represent engagement of a neural circuit that encompasses medial frontal regions, dorsolateral PFC, and the striatum. Some fMRI research, which has better spatial resolution than most electrophysiological techniques, demonstrates greater engagement of these regions in anxious relative to nonanxious individuals studied with cognitive control tasks.

Findings are similarly inconsistent in research on children at risk for emotional disorders. For example, one study of 110 children found that risk, as indicated by parental history of an anxiety disorder, predicted reduced ERN, whereas a personal history of anxiety in the same children predicted the opposite pattern, an elevated ERN (Torpey et al. 2013). As noted above, other studies among children with BI found that risk was associated with elevated ERN. Indeed, in two independent studies by McDermott et al. (2009) and Lahat et al. (2014), children with BI displayed heightened ERN amplitudes, and this amplitude moderated the relations between BI and clinical manifestations of anxiety.

Treatment implications. Less research examines the treatment relevance of research on cognitive control than on fear learning or attention orienting. Techniques have been developed for improving cognitive control using regimens that are at least superficially similar to the regimens used to shape attention through ABMT (Jaeggi et al. 2014). Moreover, it does appear as if such regimens can potentially improve cognitive control and alter brain function in the frontostriatal circuitry implicated in cognitive control. However, as of this writing, such techniques have been used predominantly in neurodevelopmental or psychotic disorders. No evidence exists to suggest that training of cognitive control reduces anxiety. Moreover, given inconsistencies in the literature on anxiety, debate persists on the most appropriate cognitive-control training regimen for anxiety. Findings on reduced ERN suggest a hypersensitivity to performance monitoring or errors. Such findings might encourage training regimens that reduce the anxious subjects' tendency to closely monitor their performance. In contrast, findings on reduced conflict adjustment and PFC activation on fMRI might encourage the opposite, regimens that enhance performance monitoring or other aspects of cognitive control.

CONCLUSIONS

Progress in treating and preventing mental disorders may follow from research that integrates development, genetics, and neuroscience. Such integration is difficult owing to the complexity of each individual area considered in isolation, which only increases as research tries to integrate perspectives across the three areas. The current review first delineates how research over the past 20 years has identified three particular groups of disorders studied in considerable depth and shown to differ based on symptom trajectories and risk factor profiles. For genetic contributions, research on probabilities of risk is beginning to integrate across multiple levels by targeting the neurodevelopmental and psychotic disorders. For contributions from the environment, research on risk is beginning to integrate across multiple levels by targeting early temperament and its relation to emotional disorders. For all three groups of disorders, such integrative research has generated ideas about novel interventions. Over the coming decade, as these ideas are tested using RCTs and other well-worn methods of the past 20 years, the hope is that both currently available treatments as well as novel interventions will be applied during childhood in ways that will begin to impact long-term risk for mental disorders.

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