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Optimizing treatments for anxiety by age and genetics

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This paper highlights recent human neuroimaging and cross-species developmental and genetic studies that examine how fear regulation varies by age and the individual, especially during the period of adolescence, when there is a peak in the prevalence of anxiety disorders. The findings have significant implications for understanding who may be at risk for anxiety disorders and for whom, and when, an exposure-based therapy may be most effective. We provide proof of concept for targeting treatment to the individual as a function of age and genetics, inferred from mouse and human studies, and suggest optimization of treatment for nonresponders.

Keywords: anxiety; development; genetics

Introduction

Adolescence is a time of significant neurobiological changes and plasticity that may facilitate adaptability to the many physical, sexual, social, and intellectual demands that characterize this period of development. Yet, adolescence is also a time when many psychiatric disorders emerge or peak (Fig. 1), with anxiety disorders being the most prevalent among young people. This paper highlights how changes in brain development during the transition into and out of adolescence, and individual variation, affect the capacity for emotion regulation, a core component of anxiety. Understanding these neurobiological changes and differences may enhance our ability to direct the type and timing of treatment for these disorders on the basis of the biological state of the developing versus the developed brain.

As depicted in Figure 2, regional changes are occurring in the stabilization and elimination of synapses, availability of neurotrophins and neurochemicals, and their receptors, in parallel with changes in white matter and metabolism.[1] These changes are occurring when there is a surge in gonadal hormones that also impact brain structure and function. Regional brain changes across development have been proposed to result in a tension or imbalance between brain regions involved in emotion reactivity and those involved in emotion regulation. It is assumed that these region-specific changes may explain nonlinear shifts in behavior as the brain adapts to the unique intellectual, physical, sexual, and social challenges of this developmental period. Environmental and genetic factors may exacerbate these imbalances and increase the risk for mental illness during this time.

Of all the mental illnesses that affect young people today, anxiety and mood disorders are the most common, affecting as many as one in four[2] and consisting of both fear-related and other cognitive symptoms, such as worry. A core fear-related feature of many of these disorders is overgeneralizing environmental cues and contexts as threatening even when no threat is present.[3] The only evidenced-based behavioral therapies for treating this fear-related component of certain anxiety disorders, such as posttraumatic stress disorder (PTSD) and social anxiety disorder, is exposure-based cognitive behavioral therapy (CBT), which identifies the source or trigger of the anxiety and then desensitizes the individual to that fear with repeated exposure to the anxiety-provoking event, in the absence of actual threat. Desensitization is based on principles of fear-extinction learning. Only about 50–60% of individuals with anxiety disorders respond

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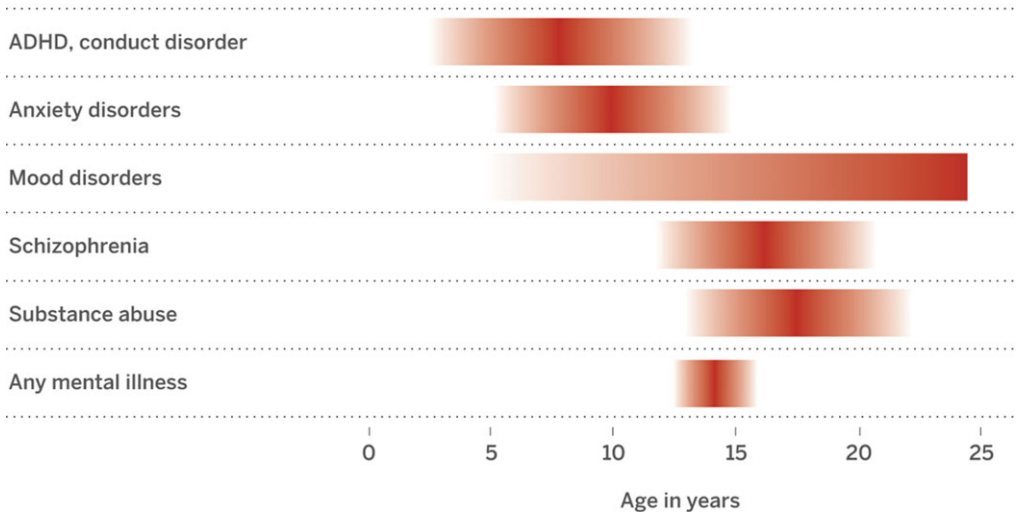

Figure 1. **Emergence and peak in mental disorders during adolescence. One in five adolescents have a mental illness that will persist into adulthood (adapted from Ref. 26, with permission).**

to this therapy.[4] This paper highlights recent human neuroimaging and cross-species behavioral and genetic studies that examine how fear regulation and extinction vary across individuals and development, especially during adolescence, when anxiety and stress-related disorders peak.

Fear regulation circuitry

Under normal circumstances, fear learning is a highly adaptive process that allows appropriate responses to threats in the environment. However, fear that persists long after the removal of any threat is often referred to as pathological. This unremitting form of fear is a core component of many anxiety and stress-related disorders. Human brain circuitry implicated in fear and anxiety include the recursive projections from the ventromedial prefrontal cortex (vmPFC; thought to be the analog of the infralimbic cortex in rodents) and the amygdala. Fear regulation or extinction is thought to be driven largely by projections of the vmPFC via inhibitory intercalated cells in the amygdala that dampen the output of the central nucleus.[5] The expression of fear is the result of central nucleus output to subcortical regions involved in the fear response, including the hypothalamus, the periaqueductal gray area, neuromodulatory systems, and the vagus nerve. Clearly, the brain circuitry involved in fear expression and fear regulation is complex. Recent work highlights the role of the prelimbic prefrontal cortex and hippocampal regions in modulating this circuit in rodents,[6] but this circuitry is less clear in humans.

Measuring fear regulation across species

Human neuroimaging studies that have examined the development of fear-related circuitry have used two different categories of behavioral paradigms. The first and most common involves the use of naturalistic cues of fear, such as fearful expressions, which, over the life span, individuals learn to associate with negative outcomes. Fear regulation is examined by measuring habituation in behavioral or neural responses to repeated presentations of these cues.[7] Yet, developmental populations have different levels of experience with these cues, depending on age, with older individuals having more experience than younger ones. As such, studies have begun to use Pavlovian conditioning to examine fear regulation across human development to address this potential confound,[8] whereby a neutral stimulus is repeatedly paired with an aversive outcome until the stimulus itself evokes a conditioned fear response. Fear regulation or extinction is then assessed by how long it takes the individual to learn that the stimulus is no longer related to threat. These studies assume relatively equal experiences of the neutral and aversive cues being paired together across development.

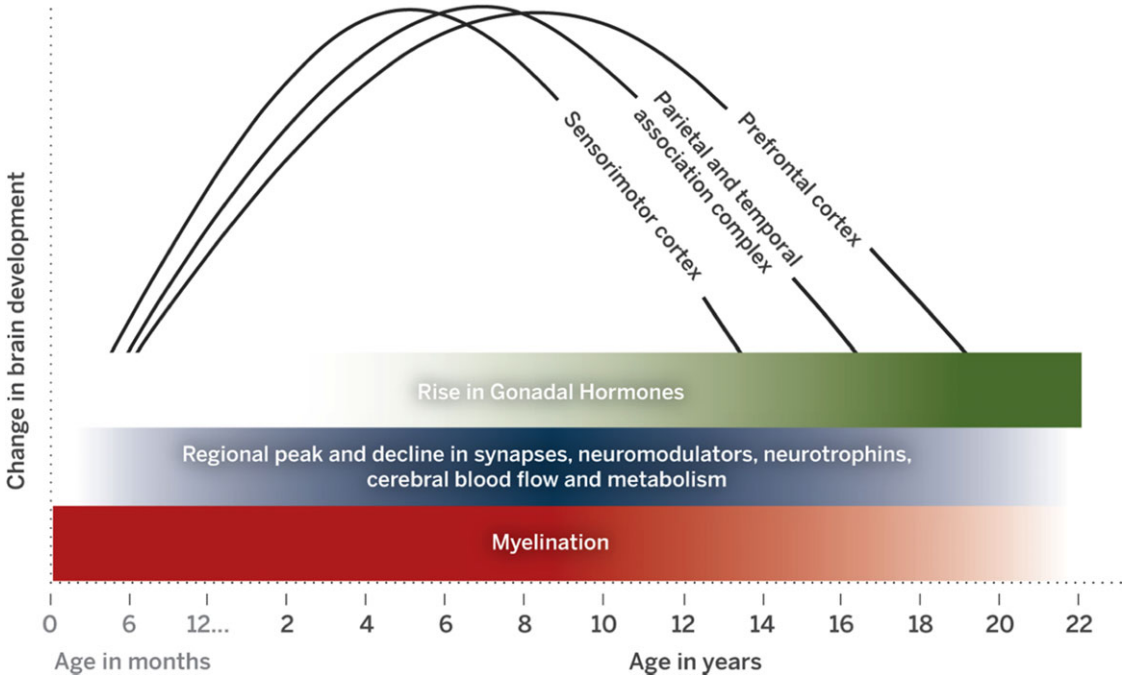

Figure 2. Developmental course of brain maturation during adolescence. Behavioral attributes are paralleled by hormonal and neurobiological changes that target specific brain regions and cell populations (adapted from Ref. 26, with permission).

Both of the described approaches provide an index of how well an individual can suppress a fear response when a threat is no longer associated with a cue. We present behavioral and neural evidence from our laboratories highlighting developmental and individual variation in fear regulation using both of these paradigms. The latter approach of conditioning is important for two reasons. First, Pavlovian conditioning can easily be examined across species, providing opportunities for a mechanistic understanding of developmental changes in fear regulation. Second, many CBTs rely on the basic principles of fear-extinction learning in desensitizing patients to triggers of anxiety with repeated exposure. Thus, this approach has important potential implications for treatment. This article begins with a select review of human imaging studies of fear regulation, followed by a review of cross-species behavioral and genetic studies of fear regulation from our laboratories. We end with a discussion of the clinical implications of these findings for the treatment of anxiety and stress-related disorders.

Human imaging studies of fear regulation

Findings from neuroimaging studies of fear regulation in humans are consistent with those from rodent studies and suggest that the circuitry supporting fear learning and regulation in animal models is largely conserved across species.[9–13] These studies highlight the importance of vmPFC–amygdala circuitry in fear regulation and how imbalances in this circuitry can contribute to pathological fear implicated in anxiety and stress-related disorders.[14–16]

Development of fear regulation

Our early work on the neural correlates of fear regulation in humans, using naturalistic cues of threat (fearful expressions), sets the stage for translational studies across species and toward treatment. First, we and other researchers have shown that adolescents, relative to children[7] or adults,[7,17,18] show an exaggerated response in the amygdala to simple passive viewing or detection of threat cues (Fig. 3A). Moreover, threat cues (fearful faces) induce slower response latencies relative to nonthreatening cues.[19]

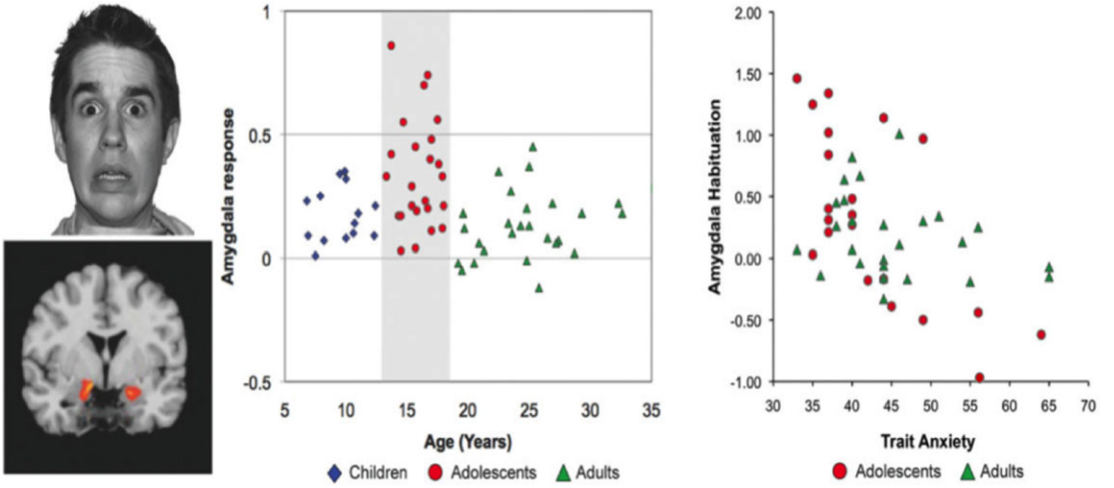

Figure 3. Developmental and individual differences in emotional reactivity to cues of threat. (A) Adolescents show greater amygdala reactivity to threat cues (fearful faces) compared to children and adults. (B) Cortical and subcortical regions associated with reaction time for fear targets. The region of the left amygdala showed a positive correlation with reaction time (top), and the region of the ventral PFC (vPFC) showed a negative correlation with reaction time (bottom). (Adapted from Ref. 7, with permission.)

This behavioral inhibition to cues of threat positively correlates with the degree of amygdala activity but negatively correlates with activity in the vmPFC.[7] These findings suggest an inverse association between the prefrontal cortex and amygdala in modulating fear responses and the need for a balance between these regions in regulating emotional behavior across contexts.

Individual variation in fear regulation

We have shown previously that the magnitude of the amygdala response to cues of threat is associated with everyday ratings of symptoms of anxiety in children and adolescents with anxiety disorders.[20] However, by examining the temporal dynamics of the amygdala response with repeated presentations to cues of threat, we found that habituation of the response, rather than the magnitude of the response, was driving this association. Specifically, we showed that those individuals who failed to show a decrease in amygdala activity with repeated presentations to empty threat had the highest ratings of everyday anxiety (Fig. 3B). This failure of the amygdala response to return to baseline over time was associated with negative coupling between this region and the vmPFC (Fig. 4), further highlighting the importance of a balance between top-down prefrontal projections to primitive emotional centers of the brain in regulating emotion and how an imbalance in this circuitry may serve as a pathway to pathological states of emotional dysregulation. These results are consistent with a growing body of evidence for the role of an imbalance in frontoamygdala networks and mood and anxiety disorders.[21,22]

Parallel mouse and human studies of fear extinction

The preceding studies highlight the importance of frontoamygdala circuitry in fear and anxiety, and how naturalistic cues of threat (fearful expressions) that, over the life span, come to be associated with threat, can inform our understanding of both typical and atypical human development. However, our experiences with such naturalistic cues varies by age and our experiences of threatening situations. As such, recent developmental work has moved toward the use of neutral cues that are paired with aversive stimuli during Pavlovian fear condition in order to better measure developmental differences in fear regulation.

Development of fear extinction

Recently, we performed mouse and human studies to examine the development of fear regulation using a cued fear-extinction paradigm. In mice, we paired a tone with three mild foot shocks and then measured the amount of freezing on

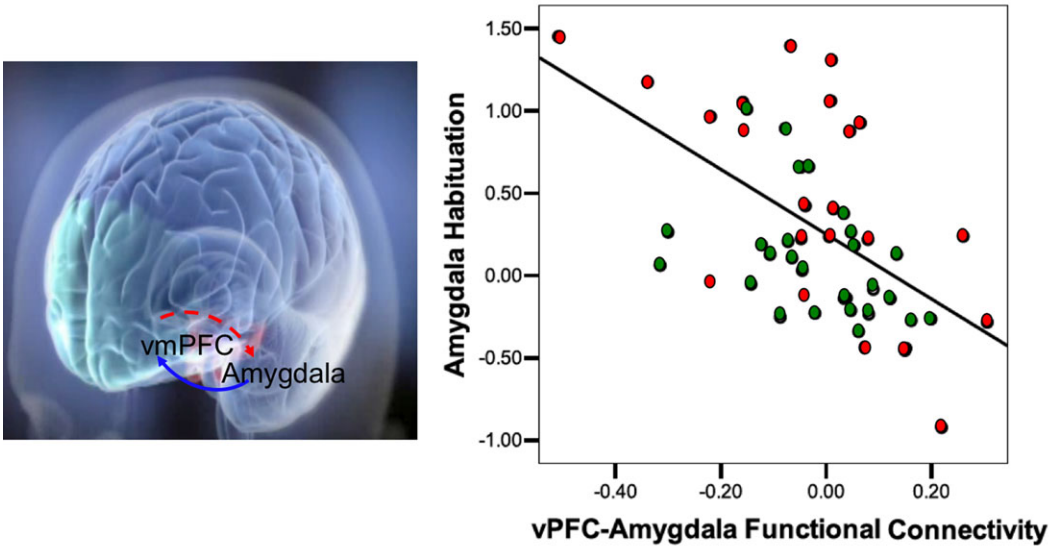

Figure 4. Emotion regulation involves negative coupling of ventromedial frontoamygdala circuitry. (Adapted from Refs. 7 and 25, with permission.)

subsequent days to the tone alone. A parallel study in humans paired a yellow or blue square with an aversive noise and then measured the skin conductance response (SCR) to viewing the squares on the subsequent day. Children, adolescents, and adults showed equal acquisition to the conditioned stimulus (colored square paired to the aversive sound relative to the square never paired with the sound).[8] However, when we tested extinction learning to the conditioned stimulus, adolescent humans and mice differed from preadolescents and adults in their conditioned responses. Specifically, they showed diminished extinction with high levels of freezing and SCRs to the conditioned stimulus with repeated presentations (Fig. 5A and B). These findings are consistent with previous reports of less fear-extinction retention in adolescent rats compared to younger and older rats.[23]

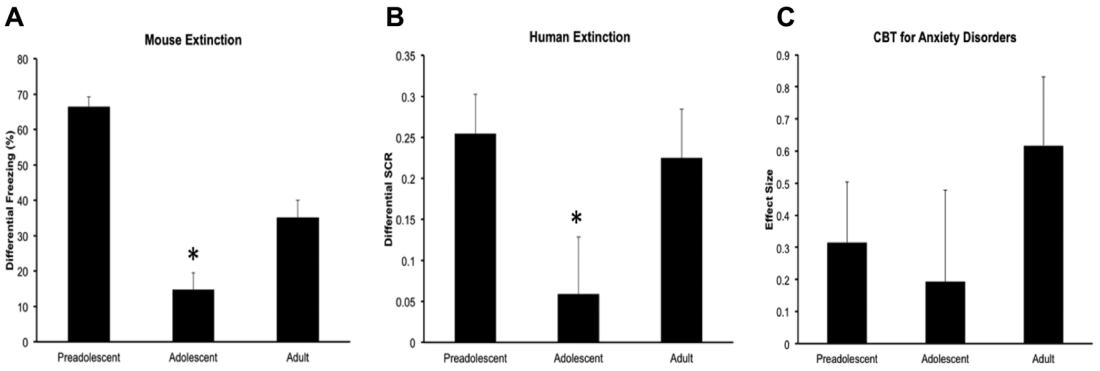

Figure 5. Diminished fear extinction and anxiety symptoms following cognitive behavioral therapy (CBT) during adolescence. (A) Diminished extinction learning and retention of extinction memory is shown in adolescent mice compared to preadolescents and adults, as measured by freezing (taken from Ref. 8, with permission). (B) Similarly diminished fear-extinction learning was observed in human adolescents, as indexed by changes in skin conductance responses (SCRs) from early to late extinction (taken from Ref. 8, with permission). (C) Adolescents showed a trend toward diminished treatment effect size for anxiety symptoms after CBT compared to preadolescents or adults (taken from Ref. 25, with permission).

The findings of diminished fear extinction in adolescents have important clinical implications and suggest that exposure therapies that build on principles of fear extinction may be less effective for adolescents than for children and adults. To provide proof of concept for this hypothesis, we examined existing data from a clinical pediatric trial for anxiety disorders that had both a standard manualized CBT and a placebo arm.[4,24] There was a nonsignificant decrease in effect size of CBT relative to placebo in adolescents compared to children or adults (Fig. 5C).[25] This work illustrates the importance of age as a potential predictor of treatment and highlights the need for treatments to target the biological state of the developing, rather than the developed, brain.[26]

Individual variation in fear extinction

The previous sections suggest the important role of developmental factors in the risk for, and treatment of, anxiety disorders. Although the adolescent period has been suggested to be a time of storm and stress,[27] clearly not all adolescents meet criteria for a mental illness. Environmental and genetic factors may exacerbate these imbalances and increase the risk for mental illness during this time. We illustrate the role of individual genetic variation by studying the effect of a common single nucleotide polymorphism (SNP) in the human gene for brain-derived neurotrophic factor (BDNF), a key growth factor that has been shown to mediate neuronal differentiation and synaptic plasticity[28]—core aspects of associative learning. The BDNF Val66Met SNP (dbSNP ID:rs6265) codes for the replacement of an evolutionarily conserved valine amino acid residue with a methionine at position 66 in the BDNF protein. The BDNF Val66Met polymorphism is common in most human populations with the minor allele frequency of 0.2 in European populations.[29] *In vitro* analyses have demonstrated that the variant BDNF Met protein is less efficiently targeted to the regulated secretory pathway leading to decreased activity-dependent secretion.[30,31] We utilized a vertically integrated translational approach and introduced into the genome of inbred mouse strains the BDNF SNP,[32] allowing for controlled experiments to understand the phenotypic effects of that variation at different levels of complexity and relate them to one another.

We conducted a parallel study in adult knock-in mice and human carriers to test the effects of BDNF Val66Met polymorphism on fear-extinction learning and the underlying neural circuitry using Pavlovian conditioning paradigms similar to those described earlier.[33] In both mice and humans, the BDNF Met allele was associated with reduced efficiency of fear-extinction learning, as indexed by less decrease in freezing and SCRs with repeated exposure to the conditioned stimulus alone (Fig. 6A and B). In mice, we were able to identify a dosage effect of the Met allele on fear-extinction learning (Fig. 6A), but, as is often the case with human population samples, there were too few Met allele homozygotes to allow a meaningful statistical analysis and they were pooled with BDNF Val66Met heterozygotes in human analyses.[33]

We then sought to understand the effects of the BDNF SNP on adult neural circuitry underlying the altered fear-extinction learning that we observed in human carriers.[33] We assessed activation of the amygdala and vmPFC during fear-extinction learning in humans as a function of the BDNF Val66Met genotype using functional magnetic resonance imaging (fMRI). Consistent with the behavioral results, human Met allele carriers displayed elevated activation in the amygdala and decreased activation in the vmPFC during fear-extinction learning (Fig. 6B),[33] suggesting that the behavioral effects of BDNF Val66Met on extinction learning are because of reduced extinction-activated plasticity in the vmPFC, impairing its ability to regulate amygdala responses during fear-extinction learning.[34] These findings suggest that prefrontal cortical regions essential for extinction are less responsive in Met allele carriers. Moreover, amygdala activity, which should be diminished during extinction remains elevated in Met allele carriers, suggesting less top-down regulation by the prefrontal cortex. Our parallel mouse and human genetic findings provide an example of how an imbalance in amygdala–prefrontal cortex coupling could predispose to heightened risk for anxiety disorders. In this context, recently, it has been shown that there is an association between BDNF Val66Met genotype and PTSD, with Met allele carriers showing a threefold increase in PTSD relative to noncarriers.[35] In addition, these Met carriers with PTSD also have an exaggerated startle response, a core symptom of PTSD.[35,36]

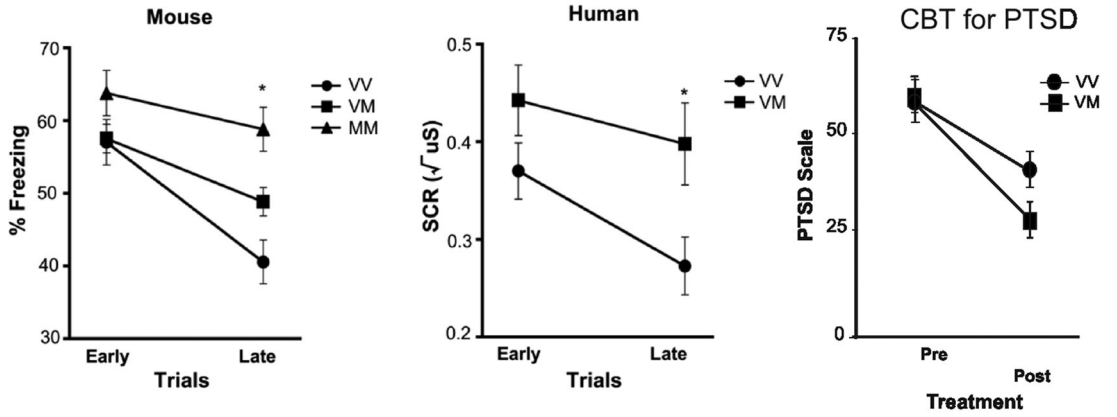

Figure 6. BDNF Val66Met polymorphism diminishes fear-extinction learning and efficacy of exposure therapy for PTSD. (A) Diminished extinction in adult knock-in mice with the BDNF Val66Met SNP as indexed by changes in freezing across extinction (taken from Ref. 33, with permission). (B) Similar effects were shown in human Met allele carriers, as measured by changes in skin conductance response (SCR) during extinction (taken from Ref. 33, with permission). (C) Met carriers showed less improvement after 8 weeks of CBT compared to non-Met carriers, as indexed by pre- and posttreatment scores on the Clinician-Administered PTSD Scale (adapted from Ref. 37, with permission).

The diminished extinction learning in mice and humans with the BDNF SNP has important implications for treatment and suggests less efficacy of exposure therapy for human Met allele carriers. Recently, Felmingham *et al.*[37] tested this hypothesis in adult PTSD patients receiving exposure-based CBT during an 8-week program. Symptoms were measured using the Clinician-Administered PTSD Scale as a function of BDNF Val66Met genotype posttreatment. BDNF Met allele carriers had a diminished response to exposure-based CBT compared to non-Met carriers (Fig. 6C). These findings suggest that genetic factors can provide predictive validity for treatment and may lead to more precise prescription of treatments to the individual on the basis of genetic makeup.

Novel mechanisms for fear reduction

The empirical work presented above suggests that there are both developmental time points and genetic factors that may reduce the effectiveness of exposure-based treatments for particular individuals. In these cases, alternative or optimized evidence-based treatments are warranted. As an example, pharmacological treatments have been shown to enhance fear regulation. One such treatment is that of D-cycloserine (DCS), a glutamate receptor modulator, which has been shown to enhance long-term fear extinction in both adolescent and adult rats.[23,38] Comparable results have been shown with selective serotonin reuptake inhibitors, which, when administered chronically in combination with extinction training, prevent the return of fear memory in mice.[39,40] These results are promising, but nonpharmacological treatments may be optimal or preferred for treating the developing brain.

A novel area of exploration for behaviorally guided treatments builds on principles of memory reconsolidation. Historically, memories were thought to be static and remain constant each time a memory was retrieved, but it is now known that memories are dynamic.[41,42] Each time we retrieve a memory, it becomes unstable.[43,44] The plasticity induced by memory retrieval is thought to open up a window of reconsolidation when the memory is prone to disruption.[45] Recent rodent and human studies[46,47] based on this reconsolidation-of-memory hypothesis have shown that retrieval of a fear memory 10 min to a few hours before extinction training results in an alteration of fear memory, presumably by reconsolidation or overwriting of the original fear memory with a new safety association. Imaging studies in humans have shown that this process, unlike extinction learning, appears to be amygdala dependent, circumventing the need for prefrontally mediated suppression of competing memories.[48,49] Memory reconsolidation

may provide the basis for novel therapeutic tools and improve existing behavioral treatments for anxiety by optimizing the timing of exposure-based therapy. Accordingly, the clinician would begin a session by first reminding the patient why she/he was there (i.e., reminder cue to activate the original fear memory) and would then engage in establishing a positive and safe setting for the next 10 min (i.e., delay needed to induce reconsolidation update). The clinician would then begin the desensitization process of repeated exposure to cues or contexts that trigger the patient's anxiety (i.e., learning the new safe association and thereby replacing or altering the original fear memory). This therapeutic approach may already be in use by many clinicians when administering exposure-based therapy, which may explain the nonsignificant decreases in effect sizes between groups who show diminished extinction learning (e.g., adolescents and BDNF Met allele carriers) and those who do not. The preclinical data described earlier provide an empirical basis for optimization of therapeutic approaches that rely on exposure-based methods to potentially enhance the effectiveness of the treatments.

Conclusions

Our findings have significant implications for understanding who may be at risk for anxiety disorders and for whom, and when, an exposure-based therapy may be most effective. We provide proof of concept for targeting treatment to the individual as a function of age and genetics, inferred from mice and human studies. A priority for future research will be to delineate treatments targeted to the biological state of the developing brain to maximize effectiveness and to continue developing research strategies to bridge discoveries in humans and animal model systems at genetic, molecular, circuit, and behavioral levels in order to guide novel interventions.

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Conflicts of interest

The authors declare no conflicts of interest.

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