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Easy to remember, difficult to forget: The development of fear regulation

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ABSTRACT

Fear extinction learning is a highly adaptive process that involves the integrity of frontolimbic circuitry. Its disruption has been associated with emotional dysregulation in stress and anxiety disorders. In this article we consider how age, genetics and experiences shape our capacity to regulate fear in cross-species studies. Evidence for adolescent-specific diminished fear extinction learning is presented in the context of immature frontolimbic circuitry. We also present evidence for less neural plasticity in fear regulation as a function of early-life stress and by genotype, focusing on the common brain derived neurotrophin factor (BDNF) Val66Met polymorphism. Finally, we discuss this work in the context of exposure-based behavioral therapies for the treatment of anxiety and stress disorders that are based on principles of fear extinction. We conclude by speculating on how such therapies may be optimized for the individual based on the patient's age, genetic profile and personal history to move from standard treatment of care to personalized and precision medicine.

1. Introduction

Learning the relationship between threatening events and the cues that predict the onset of those events is an adaptive process that allows an individual to anticipate and minimize exposure to danger (Ohman and Mineka, 2001). Failure to regulate fear expression in response to a cue that no longer predicts imminent threat can lead to chronic fear expression and sustained periods of heightened anxiety. This can set the stage for the emergence of stress and anxiety-related disorders.

Research studies that explore fear regulatory processes and the role they play in the etiology of anxiety and stress-related disorders are important because the personal and societal costs of these disorders are immense. Anxiety disorders affect about 40 million American adults in a given year (Kessler et al., 2005), creating significant negative impact on quality of life for victims, as well as an enormous economic burden of more than $35 billion spent annually on treatment and indirect costs of over $4 billion per year in lost productivity (Greenberg et al., 1999). The most common evidence-based behavioral treatment of anxiety disorders is cognitive behavioral therapy (CBT) (Rothbaum and Davis, 2003). Exposure-based CBT is based on principles of fear extinction learning and involves identification of what triggers the anxiety followed by systematic desensitization (repeated exposure) to that trigger in the absence of any threat (Myers and Davis, 2002; LeDoux, 2000). Unfortunately only a little over 50% of individuals with anxiety respond to this therapy (Walkup et al., 2008).

Identifying possible causes for why some individuals are responsive to CBT and others are not is important for guiding personalized treatments (i.e., precision medicine). Whether a given individual benefits from exposure therapy may vary based on extinction learning capacity that is mediated by age, genetic profile and personal history. In

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this article, we provide a brief overview of the literature on fear extinction learning and the underlying neurocircuitry based on human and rodent studies. We examine how acquisition of fear memories and their extinction change across development in humans and rodents, focusing specifically on adolescence when anxiety disorders peak. We then examine genetic and environmental factors that contribute to individual differences in fear regulation and extinction. We conclude by discussing important implications of these findings for whom, when and what type of CBT may be most effective for a patient and suggest novel therapeutic approaches.

2. Neural circuitry underlying the regulation of fear

Fear learning is an adaptive process that allows an organism to respond appropriately to cues or contexts that predict danger. Behavioral paradigms based on the principles of classical conditioning have become the *de facto* standard for studying fear learning in animals and humans. Classical conditioning is a process based on Pavlovian learning principles in which a neutral stimulus is paired with a salient stimulus (Pavlov and Anrep, 1927). During fear conditioning, a conditioned stimulus (the cue) is repeatedly paired with an aversive event (the unconditioned stimulus), such that the presentation of the cue alone comes to elicit a fear response, indicating the acquisition of a conditioned fear response (LeDoux, 2003). Once an associative link between the cue and aversive stimulus is formed and consolidated, it becomes a stable long-term memory.

After a cue is no longer predictive of the onset of danger, however, it is maladaptive to respond as if it is still a threat. Typically a conditioned fear response can be reduced by extinction. During extinction, the cue is repeatedly presented by itself and fear expression decreases, as the animal learns that it no longer reliably predicts the aversive stimulus (Mackintosh, 1974). Early models of fear extinction learning posited that extinction involved the unlearning of associations between a cue and an aversive stimulus (Rescorla and Wagner, 1972). However, it is now accepted that extinction reflects learning of a new memory trace that now competes with the original fear memory for expression (Bouton, 2004; Myers and Davis, 2002). If the extinction memory is strong enough and can be successfully retrieved, fear expression can be suppressed. Substantial evidence shows, however, that while extinction learning can reduce the expression of conditioned fear, extinguished fear may return under a number of different circumstances including the simple passage of time (spontaneous recovery), exposure to an aversive stimulus or stressor (reinstatement) or exposure to a threat cue in a novel context (renewal) (Bouton, 2004; Myers and Davis, 2002). In adaptive terms, this computes logically as the predictive value of an extinguished threat cue might become ambiguous under these conditions, and the penalty for failure to appropriately respond to a threat cue could be injury or death. The return of extinguished fear is therefore not categorically maladaptive. However, when fear regulatory capacity is diminished an individual may respond repeatedly to cues once predictive of danger, even though danger is no longer present. Persistent fear responding to a safety cue is maladaptive and can lead to pathological states of anxiety.

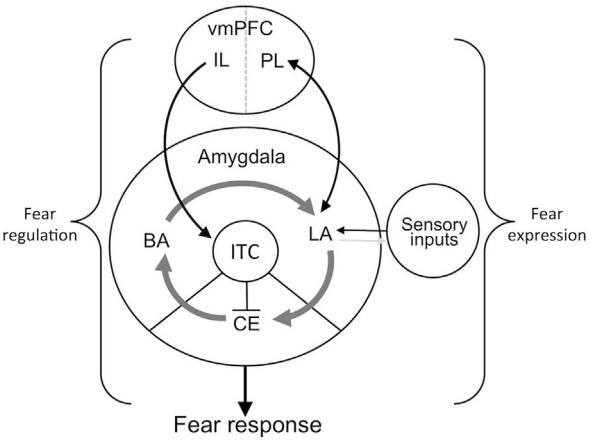

Fig. 1. Fear circuitry. A simplified diagram of the neural circuitry underlying fear expression and regulation. *Abbreviations*: IL, infralimbic prefrontal cortex; PL, prelimbic prefrontal cortex; BA, basal amygdala; LA, lateral amygdala; CE, central amygdala; ITC, intercalated cells; vmPFC, ventromedial prefrontal cortex.

Substantial research in animals and humans has characterized the neural mechanisms underlying fear acquisition and fear extinction learning (Fig. 1). The amygdala, a structure in the medial temporal lobe, is functionally segregated into subnuclei that play distinct roles in fear acquisition and expression (LeDoux, 2007). During fear learning sensory thalamic inputs converge on the lateral amygdala (LA) (Quirk et al., 1995; Collins and Pare, 2000) driving fear expression through the central nucleus (CE) of the amygdala downstream toward output systems that mediate autonomic responses (Maren, 2001). Learning has occurred when the conditioned stimulus alone is able to initiate activity in the LA and elicit a fear response, which prior to conditioning would have been elicited only by the unconditioned stimulus.

The ventral medial prefrontal cortex (vmPFC) is critical for mediating fear expression and extinction (Quirk and Mueller, 2008; Phelps et al., 2004). Two distinct subregions of the rodent vmPFC, the prelimbic and infralimbic cortices, play specific functional roles in the expression and inhibition of fear, respectively (Santini et al., 2008; Sierra-Mercado et al., 2011; Sotres-Bayon and Quirk, 2010). The prelimbic cortex (PL) has been implicated in the expression of fear via bilateral projections to and from the amygdala (Milad and Quirk, 2012). The PL receives transient inputs signaling the presence of threat from the amygdala and transforms these signals into sustained firing via downward projections to the CE (Sotres-Bayon and Quirk, 2010) and toward output systems that generate fear responses. The infralimbic cortex (IL) plays a contrasting role in the storage and recall of extinction memory (Quirk and Mueller, 2008). The LA and basal nucleus (BA) of the amygdala excite cells in the IL in response to safety signals (Repa et al., 2001). Cells in the IL then modulate fear expression through projections to inhibitory (intercalated) cells in the amygdala, that in turn block activity in the

CE, suppress outputs to downstream targets and blunt fear expression and related autonomic activity (Milad and Quirk, 2012). Thus, the vmPFC does not simply play an inhibitory role in fear regulation but rather regulates low and high fear states through subnetworks defined by bilateral projections between distinct regions of the vmPFC and functionally specific nuclei in the amygdala (Sotres-Bayon and Quirk, 2010).

Many studies have shown that fear circuitry is highly conserved across species, suggesting similar neural mechanisms underlie fear learning and extinction in both mice and humans (Soliman et al., 2010; Milad et al., 2007a; Gottfried and Dolan, 2004). Technical limitations make it challenging to precisely delineate regions homologous to rodent infralimbic and prelimbic cortex in the human brain (Milad and Quirk, 2012). However, the dorsal anterior cingulate cortex (dACC) has been associated with expression of conditioned fear in humans and has been proposed as the human homologue of the rodent prelimbic cortex (Milad et al., 2007a). This is supported by fMRI BOLD data that has shown dACC activity increases with expression of conditioned (Milad et al., 2007a) and unconditioned fear (Dunsmoor et al., 2008). Numerous human studies have demonstrated the importance of the vmPFC in fear extinction learning, supporting this region as functionally and structurally homologous to the rodent infralimbic cortex. Functional imaging studies show that increased vmPFC activity is associated with less fear expression during extinction learning (Phelps et al., 2004; Kalisch et al., 2006) and better recall of extinction memory (Milad et al., 2007b). MRI-based volumetric studies show that larger vmPFC volume is associated with greater fear extinction learning (Shin et al., 2006) and better retention of extinction memory (Milad et al., 2005).

The hippocampus also plays a significant role in expression of fear memories that go beyond the current review. Studies show that contextual processing of fear memory is mediated through direct projections from the hippocampus to the amygdala and indirectly through projections to the prefrontal cortex (Sotres-Bayon et al., 2012; Phillips and LeDoux, 1992).

Together these studies demonstrate that while the amygdala plays a role in acquisition, storage and retrieval of fear memory, regulation of fear is dependent on bilateral connections between the amygdala and the vmPFC. Converging evidence has linked anxiety and anxiety-related disorder to impaired fronto-amygdala regulation. Trait anxiety has been associated with heightened amygdala activity during fear learning in human adults (Indovina et al., 2011), while individuals with increased trait anxiety show compromised fear extinction learning that appears to be driven by dysreguated interactions between frontal and amygdala regions (Indovina et al., 2011; Lissek et al., 2005). In clinical populations, PTSD patients have shown diminished prefrontal blood flow in PET studies (Bremner et al., 1999; Semple et al., 1996), reduced vmPFC activity when recalling traumatic events (Shin et al., 1999) and impaired fear extinction learning (Milad et al., 2008). In sum, these data suggest diminished functional capacity in fronto-amygdala circuitry may underlie deficits in fear extinction learning and could be a factor contributing to the onset of pathological fear and anxiety.

Anxiety disorders peak during adolescence (Merikangas et al., 2010; Costello et al., 2005). These disorders often persist into adulthood and early onset is often predictive of the most severe and disabling forms of adult psychopathology (Andersen and Teicher, 2008; Kim-Cohen et al., 2003). Adolescence is also a developmental stage during which functional immaturity of fronto-amygdala circuitry is observed with stronger connectivity between early-developing subcortical regions than in later-maturing prefrontal regions (Casey et al., 2008). Therefore, the PFC is less capable of sufficiently suppressing emotions and actions mediated by subcortical limbic structures during adolescence. In the next section, we review studies that collectively describe how functional immaturity in prefrontal-amygdala connections may underlie adolescent-specific diminished fear extinction learning.

3. Development of fear extinction learning: structural and functional changes during adolescence

There are regional structural and functional changes in brain circuitry during adolescence. Nonhuman animal work and post mortem human studies show that synaptic pruning reaches adult numbers in sensorimotor cortices before the prefrontal regions (Bourgeois et al., 1994, Huttenlocher and Dabholkar, 1997). These regional changes are paralleled by human developmental imaging studies that show peaks in cortical thickness and volume in sensorimotor cortices and subcortical regions before association cortices (Gogtay et al., 2004; Sowell et al., 1999, 2004; Mills et al., 2014). This pattern of development can result in a functional imbalance during adolescence characterized by high, subcortically driven reactivity to emotional events and low capacity to regulate emotional responses to these events through prefrontal mechanisms. Recent evidence (McCallum et al., 2010; Pattwell et al., 2012a; Hare et al., 2008) suggests that immature top down ventromedial (infralimbic) prefrontal projections to the amygdala during adolescence may lead to diminished fear extinction learning (Fig. 1).

An example of functionally altered frontolimbic activity during adolescence from our own work examined developmental changes in fMRI BOLD signal to threat-related cues (fearful faces) (Fig. 2A). We demonstrated that adolescents show heightened amygdala activity to threat cues relative to both children and adults (Hare et al., 2008; Fig. 2B). These results are consistent with other work showing that adolescents exhibit greater amygdala responses to emotional pictures than adults (Guyer et al., 2008; Monk et al., 2003).

In this study, threat cues generated behavioral inhibition, as measured by increased time to respond to threat relative to non-threat cues. Threat-related slowing in response latencies corresponded to greater amygdala and decreased vmPFC activity (Fig. 2C). This inverse pattern between the vmPFC and amygdala is consistent with the role of the prefrontal cortex in modulating and regulating the fear response via projections to inhibitory cells (intercalated cells) in the amygdala that in turn inhibit

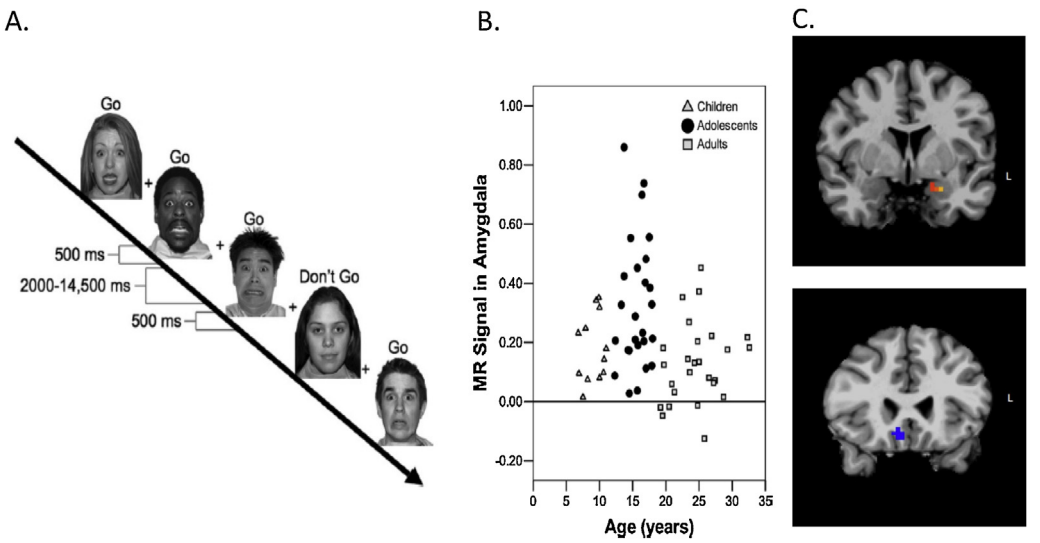

Fig. 2. Adolescent-specific differences in threat reactivity and regulation. (A) Participants were instructed to either press or not press a button in response to neutral or angry faces. (B) Adolescents show greater amygdala reactivity to threat cues (angry faces) compared to children and adults. (C) Cortical and subcortical neural regions associated with reaction time for fear targets. Region of left amygdala showed positive correlation with reaction time (top panel). Region of vPFC showed negative correlation with reaction time (bottom panel).
From Hare et al. (2008).

central nucleus output that dampens the fear response. To further constrain the interpretation of our findings we examined changes in amygdala activity as a function of time and to what extent habituation of the amygdala response over time was correlated with vmPFC activity. Greater habituation in the amygdala was associated with greater connectivity between vmPFC and amygdala, with less habituation in the amygdala response correlating with higher self-reported trait anxiety. These latter findings are consistent with studies showing that fear regulatory circuitry is functionally compromised in anxious individuals (Kim and Whalen, 2009). While this study provides support consistent with our hypothesis of diminished functional capacity of prefrontal regions to inhibit amygdala responses to threat-related cues, there are not as of yet any published studies that have directly tested this idea using associative (Pavlovian) learning paradigms in adolescent humans. For insight, we turn to human behavioral studies and rodent behavioral and neurobiological evidence that suggest adolescent-specific changes in fear regulation are mediated by a functional imbalance between prefrontal inhibitory regions and subcortical activity that drives fear expression.

3.1. Fear extinction learning in adolescents

Although there is a large body of research examining fear extinction learning in adults, there is a surprising scarcity of research pertaining to adolescents. In one of the first rodent studies to directly test adolescent fear extinction learning, Kim et al. (2011) compared the behavior of pre-adolescent (p28), adolescent (p35) and adult (p70) rats in a Pavlovian conditioning task. Although adolescent rodents showed within-session extinction equivalent to young adults and pre-adolescents, they showed attenuated extinction retention (enhanced return of fear 24 h after extinction). In other words, despite no difference in attenuating fear during extinction, adolescents showed a significant return of fear later. This study also demonstrated insufficient recruitment of the infralimbic cortex during extinction in adolescent compared to adult and preadolescent rodents.

We have recently shown diminished within- and between-session extinction learning in adolescent mice (Pattwell et al., 2012a; Fig. 3A). Adolescent mice (p29) showed increased freezing at various test points over multiple days of extinction training compared to both adults (p70) and pre-adolescents (p23) (Fig. 3A). This pattern was paralleled by diminished synaptic plasticity in infralimbic cortex of the adolescent mice compared to the pre-adolescents and adults.

To date, there have been very few studies examining fear conditioning and extinction learning in human adolescents. In one study, Haddad et al. (2011) presented teens with photographs of neutral faces paired with a negative event (angry face plus a critical comment), a positive event (happy face plus a compliment) or neutral event (neutral face plus a neutral comment). After each phase of the experiment, participants rated each stimulus for "scariness." Participants rated the faces paired with negative outcomes as significantly more scary than those paired with positive or neutral outcomes after acquisition and extinction. Although this study demonstrated that adolescents were resistant to extinction it is difficult to attribute the findings to age as there were no other age groups to which to compare the findings. Adolescent-specific diminished fear extinction learning ideally requires an adult and/or child group for comparison.

We recently examined fear extinction learning in groups of pre-adolescent, adolescent and adult humans to determine whether adolescent-specific effects observed

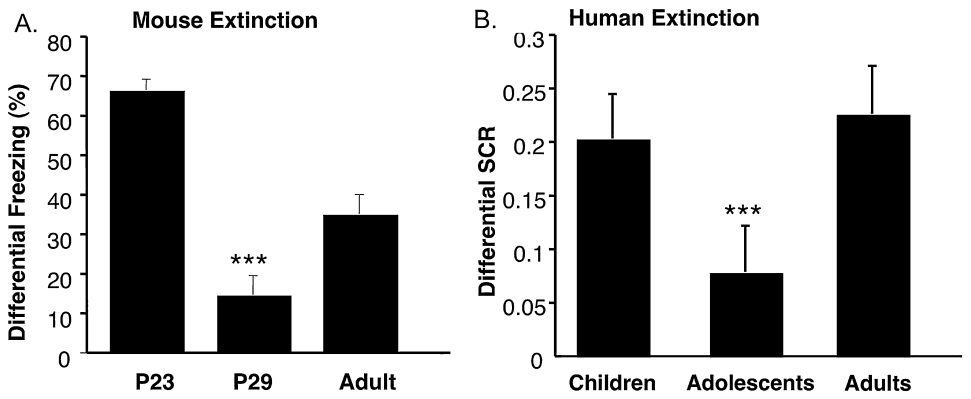

Fig. 3. Diminished fear extinction learning in adolescent mice and human. (A) Diminished extinction learning and retention of extinction memory is shown in adolescent mice compared to preadolescents and adults, as measured by freezing. (B) Similarly diminished fear extinction learning was observed in human adolescents, as indexed by changes in SCR responses from early to late extinction.
From Pattwell et al. (2012a).

in the rodent (Kim et al., 2011; McCallum et al., 2010; Pattwell et al., 2012a) were also present in the human. During acquisition, participants were repeatedly presented a conditioned stimulus (a colored square) that was paired 50% of the time with an aversive stimulus (a loud, unpleasant noise). Participants underwent extinction 24 h later, during which they received repeated, non-reinforced presentations of the conditioned stimulus. Skin conductance response (SCR) was measured to assess fear responding during acquisition and extinction phases. Although children (5–11 years old, Pubertal Tanner stage = 1), adolescents (12–17 years old, Pubertal Tanner stage between 2 and 4) and adults (18–28 years old, Pubertal Tanner stage = 5) all showed equivalent fear acquisition, the adolescents showed attenuated fear extinction learning compared to the children and adults (Fig. 3B).

3.2. Implications of developmental findings

A primary objective of this review is to understand why some individuals respond to CBT and others do not. Given the converging evidence of diminished extinction learning during adolescence, it may follow that exposure-based forms of CBT may be less effective during this phase of development. As a proof of concept we explored this idea by examining existing clinical outcome data from a randomized placebo-controlled trial of children and adolescents with anxiety (Walkup et al., 2008; Drysdale et al., 2014). Specifically we examined the effect of CBT compared to placebo on changes in anxiety symptoms after 12 weeks of CBT or placebo as a function of age. Fig. 4A below shows effect sizes of CBT relative to placebo separately for children and adolescents. The effect size for adults was estimated from outcome measures (improvement in anxiety symptoms) of a comparable adult clinical trial study comparing CBT vs. placebo (Davidson et al., 2004). These comparisons reveal a non-significant trend of diminished treatment efficacy for adolescents relative to either children or adults (Fig. 4A). A recent meta-analysis of 16 clinical studies (Bennett et al., 2013) shows a similar, but non-significant, dip in CBT efficacy for adolescents aged 12–15 years compared to younger children and older adolescents (Fig. 4B).

While these studies suggest it may be important to consider the age of the individual when prescribing treatment, they by no means provide definitive support for such a claim. Across all the clinical trials reviewed, the forms of CBT used varied and often combined coping strategies and patient-focused activities with exposure. To test our premise of age-dependent effects of exposure therapy based on principles of extinction, we would need to test the effects of CBT specifically focused on exposure therapy rather than on the effects of CBT that rely more on coping strategies or a combination of coping and exposure-based approaches. We discuss the implications of these findings further when we discuss the potential for novel-based therapies.

4. Individual differences in fear regulation

Fear regulatory processes vary not just by age but also between individuals. However, factors that mediate variation at the individual level have not been well characterized. Below we provide examples from our own work of environmental and genetic factors that impact emotion regulation, inferred from parallel mice and human studies.

4.1. Environmental factors impacting emotion regulation

Early-life stress (ELS) such as abuse or neglect is associated with a high prevalence of later psychopathology and diminished emotion regulatory capacity (Green et al., 2010; Shonkoff et al., 2009). One extreme example of early-life stress is that of orphanage rearing, in which children are subjected to high stress and reduced child-parent interaction compared to their non-orphaned peers. Children reared in orphanages show higher incidence of psychopathology and emotion dysregulation compared to non-orphans (Casey et al., 2005; Tottenham et al., 2010; Malter-Cohen et al., 2013; Gee et al., 2013). However, it has been difficult to attribute these adverse outcomes directly to orphanage rearing because pre-existing conditions (e.g.,

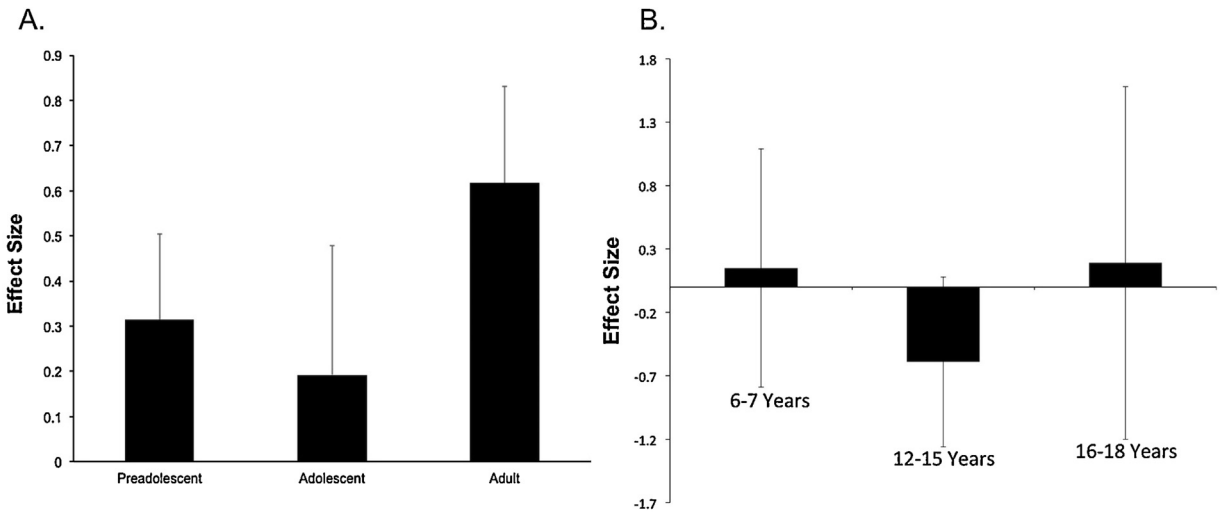

Fig. 4. Developmental effects of CBT on anxiety symptoms. (A) Adolescents showed a trend toward diminished treatment effect size after CBT compared to preadolescents or adults in anxiety symptoms (Drysdale et al., 2014) (B) Results from a meta-analysis (Bennett et al., 2013) showed a non-significant trend for diminished treatment effects of CBT in adolescents aged 12–15 years as compared to younger and older individuals. *Y*-axis indicates magnitude of treatment effect, as indexed by post-treatment anxiety disorder interview score (ADIS). (Polarity has been reversed from original scores such that positive effect sizes correspond to larger effect of treatment.). ((A) From Drysdale et al., 2014. (B) Adapted from Bennett et al., 2013).

prenatal exposure to substances or genetic abnormalities) could not be ruled out.

We recently examined the effect of early-life stress on emotion regulation and the underlying neural substrates in parallel studies in humans and mice (Malter-Cohen et al., 2013). Mice allow for the control of environmental and genetic backgrounds that often confound naturalistic studies in humans. Children (aged 5–11) performed an emotion regulation task as part of a functional imaging study. The task was designed to assess response latency to approach recurrent neutral cues in anticipation of a rare threat cue (fearful face). Children reared in the orphanage were slower than non orphanage-reared children to approach (detect) cues in the context of impending threat (Fig. 5A). This slower response latency was paralleled by greater fMRI BOLD amygdala activity in response to threat cues (Fig. 5B and C). In a parallel study, pre-adolescent mice were subjected to stress by means of limiting nesting material available to the dam, while the control group's rearing environment was not disrupted. This manipulation led to the dam spending less time with her pups to mimic aspects of orphanage care. We then tested these mice post weaning in a task conceptually similar to the human task. In order to get the mice to approach potential threat, we used one of their favorite cocktails of sweetened condensed milk. The mice were trained to obtain the milk from a nozzle over several days in their home cage (i.e., approach a cue). On the last day the context was changed to a well-lit, odor-barren novel cage, an environment of potential threat for rodents. Thus like the human, the mouse had to approach a cue (nozzle) in the face of potential threat (brightly lit, novel environment). Early-life stress altered fear regulation in the postweaned mice, as measured by longer approach latencies to the nozzle in the novel cage (Fig. 5D). This behavioral pattern was mirrored by enhanced C-Fos activity in the amygdala to threat cues in pre-adolescent mice (Fig. 5E and F), paralleling the human findings.

How persistent are these changes? Given that mice age more quickly than humans, we tracked the effects of early-life stress into adulthood (i.e., postnatal day 70). We found that the atypical behavior and brain activity persisted long after the stressor was removed and even with development of prefrontal regulatory regions. These results are consistent with other animal studies that have shown chronic stress exposure mediates long-term amygdala reactivity and anxiety-like behavior in adulthood (Vyas et al., 2002).

In an independent study of emotion regulation in children adopted from orphanages abroad, Gee et al. (2013) showed that children reared in orphanages have altered frontolimbic circuitry relative to nonadopted children. While this study did not directly test whether early-life stress mediated changes in fear extinction learning per se, it demonstrated heightened amygdala-driven reactivity to repeated presentations of empty threat. This pattern coupled with immaturity of prefrontal control regions and inputs may diminish emotion regulation and set the stage for long lasting emotion dysregulation.

4.2. Implications of environmental studies

Together the developmental findings from rodent and human studies highlight how early-life stress can lead to emotional dysregulation and altered connectivity of frontolimbic circuitry that may increase the risk for psychopathology. Previous animal work examining the effects of early-life stress (e.g. maternal deprivation) on long-term outcomes have shown altered social and fear behaviors and fronto-amygdala circuitry (Hofer, 1996; Romeo et al., 2003; Callaghan and Richardson, 2011). Our findings are similar to these reports and have been extended by Gee et al. (2013) who show a shift in the typical development of fronto-amygdala connectivity that is associated with anxiety-like behavior in orphanage-reared children. These findings suggest the importance of early interventions or rescue from

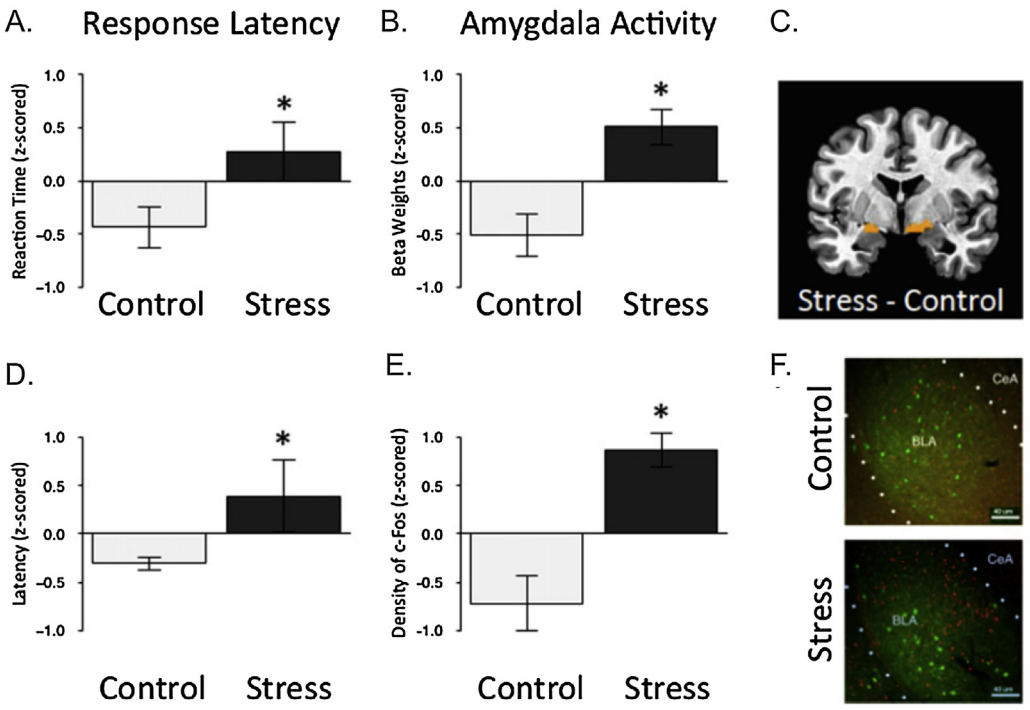

Fig. 5. Increased amgydala activity after ESL in mice and humans. (A) Children with a history of early-life stress showed increased latency to detect neutral targets in the context of threat compared to non-stressed peers. (B) Stressed preadolescent humans showed greater amygdala activity to threat cues relative to standard-reared preadolescents. (C) Greater bilateral amygdala activity in response to threat was shown in stressed relative to non-stressed children. D. Stressed mice took longer to approach a cue in a novel (threatening) environment than controls mice. E. Stressed mice showed greater c-Fos density in amygdala following threat exposure relative to control mice. F. Representation of an individual slice cut through the amygdala (green = PVA, red = c-Fos). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
From Malter-Cohen et al. (2013).

early-life stress to prevent atypical wiring of frontoamgydala circuitry that can lead to patterns of pathological fear responding. Evidence in support of early intervention is provided by findings that children adopted within 12–24 months of age from the orphanage environment appear more resilient than those adopted later (Tottenham et al., 2010; Rutter and O'Connor, 2004; Rutter et al., 2010; Gunnar et al., 2000; Gunnar and van Dulmen, 2007; Nelson et al., 2007).

4.3. Genetic factors

Emerging evidence suggests that fear learning is heritable (Hettema et al., 2003). As the neural circuitry underlying fear learning and regulation is quite complex, it is reasonable to assume that heritable influences on these processes involve multiple genes, each of which (or combinations thereof) possesses different functional roles. In this section we focus on how variability in the gene encoding for brain-derived neurotrophic factor (BDNF) influences fear extinction learning, again using parallel mouse and human studies to control for the high degree of environmental and genetic variability in humans. BDNF is a neurotrophin with a key role in mediating plasticity in the brain and regulating various learning and memory processes (Bramham and Messaoudi, 2005; Mahan and Ressler, 2012), including fear extinction learning (Peters et al., 2010; Egan et al., 2003). In humans, the BDNF gene contains a single-nucleotide polymorphism (SNP) at codon 66 that leads to a valine to methionine substitution (val66met). The presence of this SNP leads to decreased activity-dependent release of BDNF (Egan et al., 2003). One of the behavioral consequences of this SNP was highlighted by a study showing increased anxiety-like behavior in genetically modified Val66Met mice (with a methionine substitution at codon 66) compared to wild types (Chen et al., 2006), with the Val66Met mice spending less time in the open arms of a T-maze.

Because dysregulated fear expression is a fundamental component of anxiety-related behavior, we conducted a parallel study in mice and humans to test whether BDNF might exert an influence on fear extinction learning and associated neurobiological substrates (Soliman et al., 2010). In both mice and humans, the Met allele carriers showed less extinction learning than non-Met allele carriers (Fig. 6A and B). Humans showed concordant alterations in fMRI BOLD activity in fear regulatory circuitry, with Met allele carriers showing less vmPFC and greater amygdala activity during extinction than non-Met allele carriers (Fig. 6C and D).

Subsequent rodent studies have attributed this BDNF-mediated impairment in extinction learning to diminished synaptic plasticity in infralimbic cortex (Pattwell et al., 2012b). Decreased capacity to extinguish fear memories can be rescued by infusion of BDNF into this same region (Peters et al., 2010).

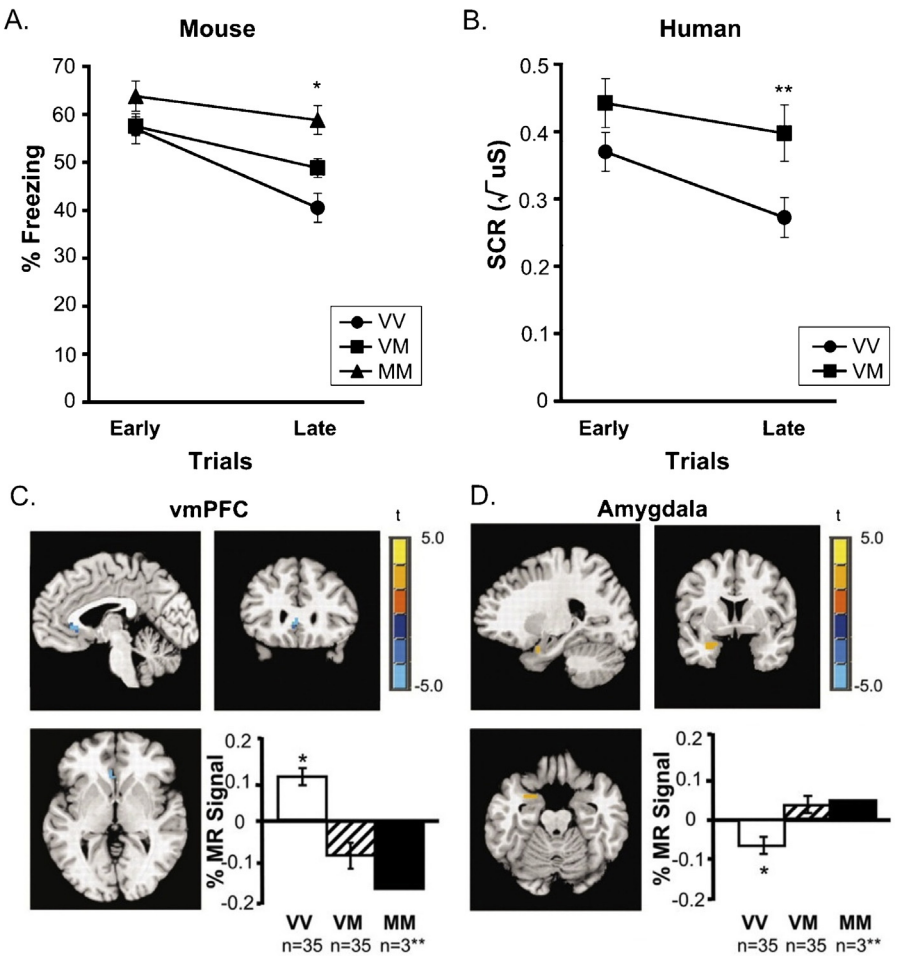

Fig. 6. Altered extinction learning in mouse and human Met allele carriers. (A) Diminished extinction in mice with BDNF Val66Met as indexed by changes in freezing across extinction. (B) Similar effects were shown in human Met allele carriers, as measured by changes in skin conductance response (SCR) during extinction. (C) Human Met allele carriers showed less BOLD activity in the vmPFC during extinction. (D) Humans with BDNF Val66Met showed increased amygdala activity compared to val/val homozygotes.
From Soliman et al. (2010).

These findings are concordant with studies that have linked BDNF genotype to increased stress reactivity underlying posttraumatic stress disorder (PTSD), a pathological condition characterized by impaired fear extinction learning. Met carriers have an increased risk for PTSD compared to non-Met allele carriers (Rakofsky et al., 2012) with a 3-fold increase in carriers homozygous for the Met allele (Zhang et al., 2014). Together these findings underscore the importance of neurotrophin factor in learning when cues of potential danger are no longer a threat. These findings further suggest that decreased available BDNF may play an important role in vulnerability to anxiety and stress-related disorders due to less capacity to regulate fears and emotions.

4.4. Implications of genetic findings

A key theme of this review is why some individuals respond to CBT and others do not. Given the converging evidence of diminished extinction learning in mice and humans with the single-nucleotide polymorphism on the BDNF gene, it may follow that exposure-based forms of CBT may be less effective for individuals with this genotype. Recently, Felmingham et al. (2013) tested this hypothesis. Specifically they examined the efficacy of CBT in adults with PTSD in an 8-week program of once-weekly 90-min CBT sessions based on their genotype. Treatment response was assessed within 2 weeks of the cessation of treatment. BDNF Met allele carriers had poorer responses to exposure therapy than non-Met carriers (Fig. 7).

These findings suggest that genotype could be an informative predictor of response to clinical treatment and help guide clinicians in identifying patients for whom more efficacious treatment approaches or additional therapeutic sessions might be necessary.

5. Memory reconsolidation: a potential target for attenuating fear memory?

Taken collectively, our findings thus far point to developmental stage, personal history and heritability profile as factors that can mediate a given individual's

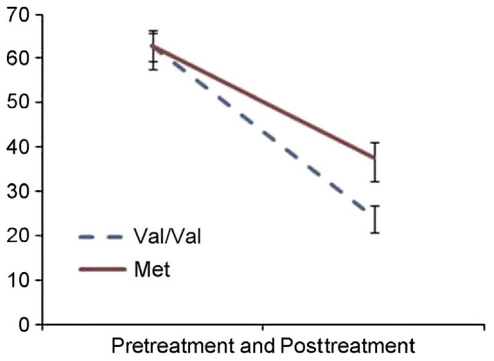

Fig. 7. Effect of BDNF genotype on response to CBT in PTSD patients. Met carriers showed less improvement after 8 weeks of CBT compared to non-Met carriers, as indexed by pre and post-treatment scores on the Clinician Administered PTSD Scale.
From Felmingham et al. (2013).

capacity to efficiently and adaptively regulate fear expression. Mechanistically, this can be attributed to a lack of top down regulation of amygdala output by prefrontal regions. In addition, extinction learning does not persistently attenuate fear. Fear responses often return after extinction (Bouton, 2004). Finding alternative interventions that potentially bypass prefrontally mediated fear regulation may be beneficial for attenuating fear memories in populations with diminished extinction learning. One such alternative relies on reconsolidation update, an approach based on the principles of memory reconsolidation.

The traditional view of memory formation is that it involves a one-time consolidation process, after which a memory becomes stable and no longer prone to interference (Squire and Davis, 1981; McGaugh, 2000). Research has demonstrated that consolidation of a new long-term memory could be disrupted by blocking protein synthesis (Schafe et al., 1999) or pharmacological intervention (Pitman et al., 2002; Vaiva et al., 2003), but only if the intervention occurred shortly after training and not several hours later. This approach has limited clinical utility because it is difficult to get access to patients immediately following a traumatic event. Therefore, an increasing amount of interest has been focused on reconsolidation as a temporal target for interfering with or attenuating fear memories.

The memory reconsolidation hypothesis suggests that every time a memory is retrieved it becomes unstable (Misanin et al., 1968; Sara, 2010) and dependent on *de novo* protein and RNA synthesis for restabilization (Dudai, 2006; Nader et al., 2000). The plasticity induced by memory retrieval opens up a "reconsolidation window" during which a memory becomes prone to disruption (Dudai, 2006). This plasticity has been demonstrated by findings in rats that showed fear memory erasure could be induced after post-retrieval intra-amygdala infusion of protein synthesis inhibitors anisomycin (Nader et al., 2000; Duvarci and Nader, 2004) and U0126 (Doyere et al., 2007), and NMDA receptor antagonist MK-801 (Lee et al., 2006). Unfortunately, these compounds are toxic and not safe for use in humans (Duvarci and Nader, 2004).

Dębiec and Ledoux (2004) showed that intra-amygdala and systemic infusion of beta-adrenergic receptor blocker propanalol (non-toxic and safe in humans) could disrupt fear memory reconsolidation in rats. This finding was recently extended to humans using systemic treatment (Kindt et al., 2009). In this study, participants who received propranolol prior to retrieval of a conditioned fear memory showed persistent attenuation of fear response on a subsequent fear recovery test (but see Schiller and Phelps, 2011). Another promising approach to attenuating fear memory was recently tested by Graff et al., 2014, with evidence suggesting epigenetic mechanisms can be targeted, in combination with extinction training, to permanently modify fear memories during reconsolidation in rodents. Even if pharmacological or epigenetic approaches proved safe in humans and effective in disrupting reconsolidation, a behavioral procedure would still be preferable due to possible off-target effects, assuming similar effects could be obtained with behavioral methods.

Such a procedure was introduced by Monfils et al. (2009) and has recently been tested in human adults (Schiller et al., 2010). This method involves activation of a fear memory by presentation of an isolated retrieval cue followed by an extinction session that takes place during the subsequent reconsolidation window. The precise temporal duration of this window is not precisely known but is thought to be from 10 min to up to at least an hour and not more than 6 h after retrieval (Monfils et al., 2009). If extinction occurs during the temporal window during which the fear memory is reconsolidating, the memory can be updated and fear prevented from returning at a subsequent fear recovery test (Steinfurth et al., 2014; Oyarzun et al., 2012; Agren et al., 2012, but also see Kindt and Soeter, 2013; Golkar et al., 2012).

In the study that first demonstrated this effect in humans, Schiller et al. (2010) designed two experiments to test whether behavioral extinction training during memory reconsolidation would lead to persistent attenuation of fear. Three groups of participants were differentially conditioned to acquire fear by pairing a colored square (the conditioned stimulus) with an aversive reinforcer (an electric shock) while another colored square was never paired with the electric shock (experimental day 1). Twenty-four hours later (experimental day 2), participants underwent an extinction session during which both conditioned stimuli were presented repeatedly unpaired with the electric shock. All participants showed significant fear extinction, as indexed by decreases in skin conductance response (SCR) to the conditioned stimulus. In two groups, the conditioned stimulus was reminded prior to extinction via a single presentation trial. One group received the reminder trial 10 min before extinction, while the other group received the reminder trial 6 hours before extinction. The third group did not receive a reminder trial prior to extinction. Another 24 hours later (experimental day 3), participants returned to test for spontaneous recovery of the conditioned fear response. Participants who weren't reminded of the conditioned stimulus prior to extinction or who were reminded but extinguished outside of the reconsolidation window showed robust recovery of fear for the conditioned stimuli, but there was no spontaneous

recovery of fear in participants for whom the CS+ was reactivated 10 min prior to extinction. Attenuation of conditioned fear was still present when participants returned for a fear recovery test one year later, demonstrating the persistence of this effect (Schiller et al., 2010).

A second experiment (Schiller et al., 2010) used a within-subject design to control for the possibility of unintended group effects and allow for direct comparison of the return of fear with or without reconsolidation update. Participants were conditioned to two different colored squares (conditioned stimuli) via partial reinforcement with electric shock, while a third square was never paired with the shock. Prior to extinction, one of the conditioned stimuli was reminded via a single presentation trial, while the other was not. Recovery of fear was elicited via four unsignaled presentations of the US prior to the fear recovery test (reinstatement), which has been demonstrated as a robust method to elicit the return of an extinguished fear memory (Bouton, 2004). Participants only showed a reinstated fear response to the conditioned stimulus that was not reminded prior to extinction. These studies collectively support the notion that behavioral extinction during reconsolidation can lead to persistent attenuation of conditioned fear.

Evidence from rodents has shown that the neural mechanism of action for the reconsolidation of fear memories is a cascade of molecular events taking place in the lateral nucleus of the amygdala (Monfils et al., 2009; Nader et al., 2000; Duvarci and Nader, 2004; Dębiec and Ledoux, 2004). Recent human imaging studies have reiterated this finding by demonstrating behavioral interference during reconsolidation led to persistently attenuated fear at a subsequent recovery test, independent of PFC involvement (Agren et al., 2012), as well as showing that if fear extinction occurred during reconsolidation, decreases in fear response were not mediated by prefrontal activity (Schiller et al., 2013). These findings support the notion that reconsolidation update is a method of fear regulation that is independent of the prefrontal cortex. This makes it a potentially attractive alternative to extinction for adolescents, a developmental group characterized by protracted development of prefrontal regions upon which successful extinction is dependent (McCallum et al., 2010). It may also be helpful for individuals with diminished learning due to genetic and environmental factors, who may not respond well to exposure-based therapies that presumably rely on prefrontally mediated regulation of fear.

6. Beyond extinction: cognitive forms of fear regulation

While the efficacy of exposure-based CBT depends on the ability of a given individual to acquire and retrieve extinction memories (Berry et al., 2009), cognitive strategies can also be employed to regulate conditioned fear responding. Standard CBT protocols generally include a cognitive component in which patients are directed to strategically reframe anxiety-provoking situations in order to reduce the negative emotional responses that these situations elicit (Beck et al., 1985). One form of cognitive regulation is emotional reappraisal, in which an automatic emotional response to an emotional event is controlled through conscious transformation of its meaning (Gross, 2001). Human fMRI studies have shown that successful reappraisal of negatively valenced stimuli is dependent upon recruitment of prefrontal and cingulate regions associated with cognitive control (Ochsner et al., 2004). However, the prefrontal cortex is still maturing into early adulthood, suggesting that children and adolescents might show diminished reappraisal capacity compared to adults. Recent studies have presented some evidence to this effect, with reappraisal success positively correlating with age across adolescence (Silvers et al., 2012; McRae et al., 2012). Although only a small number of studies have examined reappraisal of threat across development, future pre-clinical research that tests different forms of reappraisal across childhood and adolescence will help shed light on which reappraisal strategies might be most effective at any given developmental stage.

Another important cognitive factor mediating fear regulation is attentional control. The ability to increase attention to threat stimuli is an adaptive function that facilitates the detection of danger (LeDoux, 2000). However, devoting an inappropriate amount of attentional resources to non-significant or low-level threats can be maladaptive. This notion is supported by research providing strong evidence for a positive correlation between threat-related attentional bias and anxiety (Bar-Haim et al., 2007; Mathews and MacLeod, 1985; Monk et al., 2008). Emerging data suggests that reductions in attentional threat bias can be achieved through attentional bias modification therapy (Hakamata et al., 2010; Bar-Haim, 2010; MacLeod and Mathews, 2012), which involves teaching individuals to shift attention away from threat-related stimuli through repetitive, computer-based training (MacLeod, 1995; MacLeod and Mathews, 2012). While attentional bias modification therapy has been shown to lead to decreases in threat bias as well as diminished anxiety symptoms (Hakamata et al., 2010), treatment outcomes across studies are inconsistent (Mogoaşe et al., 2014), suggesting further research will be necessary in order to optimize these techniques and determine when, and for whom, attention-based therapy will be most beneficial.

A comprehensive discussion of cognitive factors that mediate fear regulation ability is beyond the scope of this review. However, it is important to note that clinical therapies based on cognitive approaches may be more effective for some individuals than others. It is important that future research identifies factors that mediate any given individual's capacity to successfully employ cognitive strategies, such as reappraisal or threat bias modification, to regulate fear. Identifying such factors may inform personalized cognitive therapies, which could be used in combination with exposure-based methods to maximize positive treatment outcomes.

7. Implications for novel treatments: where do we go from here?

The studies presented here suggest there are developmental time points, as well as genetic and environmental factors, that may reduce the efficacy of exposure

therapy for particular individuals. In these cases, alternative evidence-based treatments might be employed.

Pharmacological interventions offer one alternative approach. D-Cycloserine (DCS) has been shown to enhance extinction retrieval in adolescent and adult rats (McCallum et al., 2010; Baker et al., 2012). Serotonin selective reuptake inhibitors (SSRIs) have demonstrated similar results, with one study showing that chronic administration of SSRIs in combination with extinction training prevented the return of fear in mice (Karpova et al., 2011; Deschaux et al., 2011). While these results are promising, non-pharmacological approaches may be preferable when treating the developing brain. Rodent studies have demonstrated that adolescents can benefit from an increased number of exposure trials during extinction (McCallum et al., 2010). However, this approach may not be ideal for adolescents with anxiety disorders as it would require additional time and money and could lead to higher attrition rates and increased failure to complete treatment.

Memory reconsolidation may provide a basis from which new therapeutic tools might be developed to improve clinical treatment of anxiety disorders in adolescents (Monfils et al., 2009; Schiller et al., 2010). These studies have shown that reactivating a conditioned stimulus opens a temporal window during which a fear memory becomes labile and prone to disruption. Extinction during this window leads to enhanced attenuation of fear memory. In therapeutic terms, this approach may already be in use in the clinic without explicit knowledge for why CBT may work for some patients or in some contexts or by some therapists and not others. For example, once identifying the triggers for anxiety in a patient the therapist subsequently meets with the patient. When the patient comes into the office, the clinician may remind the patient of why they are there (activation of a fear memory by presentation of an isolated retrieval cue). Then the clinician builds a rapport with the patient on what may be going well or what puts him/her as ease for at least 10 min (i.e., waiting for the reconsolidation window) before beginning desensitization (i.e., extinction during the reconsolidation window). This approach could be translated into a three-step clinical protocol whereby a clinician would: (1) reactivate a patient's traumatic or fear memory; (2) engage the patient in an unrelated, nonthreatening activity for 10–15 min; and then (3) initiate the exposure therapy session. This could lead to enhanced or persistent attenuation of the fear/trauma.

8. Conclusion

Substantial research has demonstrated that developmental, genetic and experiential factors can significantly affect any given individual's capacity to regulate fear. Current standards of care for treating anxiety-related disorders, such as exposure-based CBT, may not be optimal for such individuals. Novel therapies that augment prefrontally mediated fear regulation, or bypass prefrontal mechanisms altogether, could prove useful when targeted to specific individuals as a function of the developmental stage at which they are seeking treatment, as well as their genetic profile and experiential history (i.e., personalized medicine). Pre-clinical research studies, such as those described here, can help identify at-risk individuals and help to inform precise, evidence-based therapeutic approaches that could lead to more effective treatments for anxiety and stress-related disorders.

Conflicts of interest statement

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