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## Transitional and translational studies of risk for anxiety

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### Summary

Adolescence reflects a period of increased rates of anxiety, depression and suicide. Yet most teens emerge from this period with a healthy, positive outcome. In this paper, we identify biological factors that may increase risk for some individuals during this developmental period by: 1) examining changes in neural circuitry underlying core phenotypic features of anxiety as healthy individuals **transition** into and out of adolescence; 2) examining genetic factors that may enhance risk for psychopathology in one individual over another using **translation** from mouse models to human neuroimaging and behavior; and 3) examining the effects of early experiences on core phenotypic features of anxiety using human neuroimaging and behavioral approaches. Each of these approaches alone provides only limited information on genetic and environmental influences on complex human behavior across development. Together, they reflect an emerging field of translational developmental neuroscience in forming important bridges between animal models of neurodevelopmental and neuropsychiatric disorders.

### INTRODUCTION

Adolescence is a time of mental, physical, neurobiological and hormonal changes that often correspond with an increased drive toward independence and peers, often accompanied by heightened emotionality. Historically this developmental period has been characterized as one of ‘storm and stress’ (Hall, 1904). The controversial ‘storm and stress’ characterization is supported by the increase in onset of many psychiatric illnesses and the alarming US health statistics on mortality associated with this period (Casey et al., 2010). Yet, the majority of adolescents experience and emerge from this period in a healthy positive manner (Lerner & Israeloff, 2007).

This review offers new insights from both *transitional* and *translational* studies for why some individuals may be at greater risk for developing psychopathologies during the adolescent years than others. These studies reflect an emerging field of *translational developmental neuroscience*- a collaborative science of how the healthy brain develops, how development of the brain may go awry in mental illness, and potentially how to alter this development on a healthy trajectory through early identification and intervention (NIMH, NIMH, 2007).

We highlight three approaches that examine neural circuitry underlying core phenotypic features of anxiety (e.g., suppression of fear response) that exemplify transitional and translational approaches. First, we describe findings from human imaging studies that show changes in neural circuitry underlying core phenotypic features of anxiety in healthy individuals **during the transition into and out of adolescence**. Second, we describe a recent study examining **genetic factors** that may enhance risk for anxiety and alter underlying neural circuitry using **translation from mouse models to human** behavior.

Finally, we provide evidence for alterations in neural circuitry underlying core phenotypic features of anxiety as a result of early postnatal **experiences** using human imaging and behavioral approaches.

Each of the approaches described, including human behavioral, clinical, and developmental studies; human behavioral and imaging genetics; and studies of genetically modified mice, alone provide only limited information on genetic and environmental influences on complex human behavior across development, and risk for psychopathology. However, together, these approaches are building important bridges between animal models and human psychiatric and developmental disorders. Collectively, these studies provide converging methods for understanding the highly variable positive and negative experiences of adolescence and genetic and environmental factors that may increase the risk for anxiety during this period of life.

### Core phenotypic features of anxiety

Understanding the neurobiology of anxiety disorders requires the identification of core phenotypes that can be measured across development, are more precisely measured than categorical disorder phenotypes, and relate to underlying biological processes. These *endophenotypes* should be state-dependent and heritable. Specifically, they should: 1) reflect a biological process that is a core component of the more complex disorder phenotype; 2) be more biologically simple than the disorder phenotype to ensure that the effect size of any particular risk factor is relatively large; and 3) be understood well enough at the biological level that they can be related to specific candidate risk factors including genetic, environmental, and developmental ones. These criteria are particularly important for imaging genetic studies where the neurobiological findings are dependent upon validity of the behavioral activation paradigm (Casey et al., 2010).

A core feature of anxiety disorders is difficulty learning which contexts or cues may signal safety and which signal a threat (fear conditioning), and learning to suppress these associations when they no longer apply (fear extinction). These forms of learning reflect adaptation to environmental change/stress (e.g., fear conditioning) that appear to lie at the very core of a number of clinical disorders (Charney & Manji, 2004; Duman et al., 1997; Nestler et al., 2002; Pine, 2007). Importantly, these measures can be tested across species, throughout development and have known underlying biological substrates. These genetically influenced forms of learning include those that capture the difficulties some individuals have in: 1) adjusting to new environments (contextual learning); 2) recognizing signals of safety or danger (cued learning); and 3) learning to adjust behavior when actual associations no longer exist (extinction). Unlike disease states, the tasks that examine these types of learning can be assessed equivalently in typically and atypically developing humans and mice. Using such measures across development and under varying degrees of stress, may ultimately allow us to examine vulnerability and protection across development.

As described by Britton et al. (this issue), the literature has been mixed on whether simple fear conditioning has significant relevance to understanding anxiety disorders. In this review, we focus on fear learning that is specific to adjustment of behavior when fear associations no longer exist (i.e., extinction). This form of fear learning is emphasized for three reasons. First, evidence provided from therapeutic effects of exposure therapy in treating certain forms of anxiety disorders such as post traumatic stress disorder are based on principles of extinction learning (Taylor et al., 2003). This therapy involves teaching the patient to acquire new associations between a cue previously associated with threat to a new association of safety. Successful treatment results in activation of the safe association over the threatening one and thus a diminished fear response. Second, this aspect of fear learning requires cortical top down-regulation of autonomic responses related to the expression of

fear (Phelps et al., 2004). Rodent work suggests that this cortical circuitry continues to develop during adolescence (Bouwmeester et al., 2002; Cunningham et al., 2002) and that extinction may be attenuated during this developmental period, as evidenced by sustained freezing behavior, and requiring twice as many extinction trials to diminish the freezing behavior relative to adult rodents (McCallum et al., 2010). Third, given the high heritability of anxiety disorders (Thapar & McGuffin, 1995), we focus on a form of fear learning shown to be altered in genetically altered mice and in humans with a common single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene that leads to a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met). This polymorphism is associated with impaired activity-dependent release of neurotrophic factor in the brain, treatment resistant forms of anxiety-like behavior (Chen et al., 2006) and, for the purposes of this review, altered extinction in mice and humans (Yu et al., 2009; Soliman et al., 2010). Thus, in this review we highlight human imaging studies that use extinction (or repeated presentations of cues of empty threat) to assess individual and developmental differences in suppressing the fear response as our primary phenotypic measure of anxiety-like behavior.

### Neural circuitry underlying core phenotypic behaviors

Figure 1 is a simplified diagram of the neural circuitry of fear conditioning and extinction that has been delineated in human and rodent studies (Davis & Whalen, 2001; LeDoux, 2000). This diagram illustrates how top-down prefrontal input to the amygdala, a region important for detecting cues of safety and threat, can reduce the fear response. Sensory input is received primarily by the lateral nuclei of the amygdala. The lateral nuclei project to the basal and central nuclei of the amygdala. The basal nuclei project predominantly to cortical regions (e.g., ventromedial prefrontal cortex) and striatum, whereas the central nuclei project mainly to subcortical regions involved in the fear response, including neuromodulatory systems, the hypothalamus, periaquiductal gray, and vagus. The ventromedial prefrontal cortex (vmPFC) projects to the amygdala and dampens its response via projections to inhibitory intercalated cells at the level of the central and basal nuclei. Thus, the amygdala can both signal the vmPFC of the significance of a cue and receive input from the vmPFC that dampen the fear response by suppressing output from the amygdala to neuromodulatory systems, the hypothalamus, periaqueductal gray, and vagus (LeDoux, 2000; Phelps et al., 2004). This cortical signaling is the emphasis of the current review.

Recently we have put forth a testable model of brain development that may account for heightened emotional responsivity during adolescence (Casey et al., 2008). This review highlights empirical data that go beyond simple characterizations of adolescence relative to adulthood, but rather, use a transitional approach. As such, we illustrate not simple linear changes, but inflections in behavior and in the brain during transitions into adolescence from childhood, and out of adolescence, to adulthood. The imbalance model underscores the importance of empirical characterization of the development of limbic subcortical regions involved in desire, fight and flight – which are reminiscent of teens' heightened emotional reactions – together with the development of prefrontal top-down control regions across the pre-, peri- and post- adolescence. Different developmental trajectories for the neural substrates of these systems, with limbic systems maturing earlier than prefrontal control regions, are suggested to result in an imbalance between these systems. This 'imbalance' model proposes that during adolescence, differential timing of brain development induces a disparity between the structural and functional maturity of brain systems critical to affective processing (e.g., subcortical regions including the amygdala), relative to cortical regions of the brain important in control over emotional responses (e.g., the prefrontal cortex). Differential developmental timing of these regions is consistent with nonhuman primate and human postmortem studies showing that the prefrontal cortex is one of the last brain regions to mature (Bourgeois et al., 1994; Huttenlocher, 1979) while subcortical and sensorimotor

regions mature sooner as indexed by peaks in synaptogenesis and subsequent synaptic pruning. Our work is similar yet discrete from many others' in that it provides a working framework from which to test changes in the brain and in behavior both before, during and following adolescence.

We provide empirical support for our imbalance model from recent behavioral and human imaging studies on the development of emotion regulation and suggest that it is the suppression of the emotional response rather than the transient heightened reactivity that is related to anxiety. We then provide data from human imaging and mouse studies to illustrate how genetic factors may exacerbate or diminish this ability to suppress an emotional response. Finally, we provide examples of environmental factors that may exacerbate imbalances in emotion related brain circuitry and lead to long-term upregulation of this circuitry. Together, these studies provide a converging methods approach for understanding the highly variable experience of adolescence among our teens and dissociate aspects of emotional responses that are typical versus those which may put an individual at risk.

### **Changes in Neural Circuitry during Transitions into and out of Adolescence**

In a series of neuroimaging studies of adolescents, we have used a transitional approach to understand inflections in behavior during this developmental window relative to those preceding or following it (Galvan et al., 2006; Hare et al., 2008; Somerville & Casey, 2010). In the most relevant of these studies to the focus of this review on anxiety disorders, we examined emotion responses in 60 children, adolescents, and adults with functional magnetic resonance imaging (fMRI). We went beyond examining the magnitude of brain activity that has been shown by several groups to be higher in adolescents than in adults (Ernst et al., 2005; Guyer et al., 2008a; Guyer et al., 2009; Guyer et al., 2008b; Monk et al., 2003b; Rich et al., 2006; Williams et al., 2006) to: 1) show specific changes in the brain and behavior in adolescents relative to both adults and children; and 2) examined not only transient patterns of frontoamygdala activity, but changes in activity over time (Hare et al., 2008). Finally, to assess individual differences in emotional reactivity that might put some teens at greater risk during this sensitive transition in development for anxiety, we assessed everyday anxiety using the Spielberger Trait Anxiety Inventory.

Our results showed that adolescents have an initial exaggerated amygdala response to cues that signal possible threat (fearful faces) relative to children and adults (see Figure 2, Hare et al., 2008). This initial heightened response in amygdala activity is age-dependent and does not correlate with trait anxiety. Moreover, while several groups have shown elevated amygdala activity to emotional pictures in adolescents relative to adults (Guyer et al., 2008b; Monk et al., 2003a); these data showed a distinct pattern in adolescents from both children and adults and showed specific correlations in frontoamygdala activity and response latencies to cues of potential threat (see Figure 3, Hare et al., 2008).

Examination of the MR signal in the amygdala with repeated presentation of the fearful face (i.e., exposure to empty threat) across experimental trials showed attenuation over time (i.e. habituation). The extent to which activation of this region diminished with repeated trials was correlated with anonymous self-report ratings of everyday anxiety. This measure was calculated by subtracting average MR signal in late trials of the experiment from early trials of the experiment (i.e., the larger the value, the greater the suppression of the amygdala response). Negative values indicate an actual increase in amygdala activity over time). Individuals with higher trait anxiety showed less suppression of the amygdala response over time (Figure 2, right panel). The failure of the amygdala response to return to baseline over time was associated with coupling of frontoamygdala activity. Specifically inverse functional coupling of these regions, consistent with greater top-down regulation (higher vmPFC activity) of the amygdala, was correlated with greater diminished signal in the

amygdala (i.e., negative values indicate inverse coupling, whereas a lack of coupling was indicated by values of 0 or slightly positive, see Figure 2, right panel, Hare et al., 2008). The association of inverse coupling of the vmPFC and the amygdala with downregulation of the amygdala to repeated presentations of empty threat is consistent with the previously described rodent and adult human studies on extinction learning and the underlying neural circuitry delineated earlier in Figure 1.

These findings suggest that initial emotional reactivity as indexed by elevated amygdala activity may be typical of or normal for adolescence, but that failure of this response to subside over time with no impending threat is atypical and may be indicative of anxiety. Clinical imaging data using similar paradigms with older children and adolescents diagnosed with anxiety and depression show elevated amygdala activity to fearful faces (Thomas et al., 2001). These findings may be due to persistent activation of this region with repeated exposures as seen in adolescent females who are at greater risk of these disorders relative to males (Thomas et al., 2001) rather than elevated activations per se. Future studies of populations at risk for anxiety will need to examine carefully not only what triggers a heightened threat response in the amygdala, but also the brain processes that support anxiety responses that are sustained over time (Somerville et al., 2010).

The observation of imbalanced activity in the amygdala-vPFC network as shown by elevated amygdala and less vmPFC activity in high anxious individuals, is consistent with a variety of work in animals (Baxter et al., 2000; Milad & Quirk, 2002) humans (Delgado et al., 2006; Etkin et al., 2006; Haas et al., 2007; Johnstone et al., 2007; Urry et al., 2006), and in childhood and adolescent mood and anxiety disorders (Guyer et al., 2008a; Monk et al., 2008) implicating an inverse relationship between these structures that governs affective output. In particular, increased response in the vPFC is inversely correlated with responding in the amygdala, and predicts behavioral outcomes such as fear extinction, downregulation of autonomic responses (Phelps et al., 2004) and more positive interpretations of emotionally ambiguous information (Kim et al., 2004). Thus, inverse functional coupling of these structures is key for down-regulation of heightened emotional responses. During adolescence when the amygdala response is heightened, relative to that observed in children and adults (imbalance), more top down control is needed. A lack of coupling between these regions with development to help provide that down-regulation may lead to symptoms and ultimately diagnosis of anxiety.

### **Translation from Genetic Mouse Model to Human**

A number of human genetic studies have begun to identify candidate genes that may play a role in increased risk for anxiety. The main avenues for understanding gene function in these disorders have been in behavioral genetics on one end and on the other end, molecular mouse models. Attempts to bridge these approaches have used brain imaging to conveniently link anatomical abnormalities seen in knockout/transgenic mouse models and abnormal patterns of brain activity seen in humans. Recently we completed a study using parallel analysis of behavioral and imaging genetics in humans and a genetic knock-in mouse model of a human polymorphism. The respective strengths of different levels of analysis from molecular to neural to behavioral, all provide external validation for the findings of any single genetic analysis (Casey et al., 2010). Moreover, this integrative approach provides bridges between the intrinsically relevant but complex and imprecise phenomenology of human behavior and the solid findings of rodent neurobiology that can be difficult to extrapolate to human behavior and disease.

Our translational study focused on a common single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene that leads to a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met). This polymorphism leads to decreased

trafficking of the signaling neuropeptide BDNF into the regulated secretory pathway, which in turn leads to impaired activity-dependent release of BDNF. In an inbred genetic knock-in mouse strain that expresses the variant BDNF<sub>Met</sub> allele to recapitulate the specific phenotypic properties of the human BDNF Val66Met polymorphism *in vivo*, we found the Met allele was associated with treatment resistant forms of anxiety-like behavior (Chen et al., 2006). As described earlier, a key feature of anxiety is difficulty in learning of cues that signal safety versus threat and in learning new associations when a previous threat cue is no longer associated with that threat (i.e., extinction). Thus, the objective of our study was to test if the BDNF<sub>Met</sub> genotype could impact extinction learning in the mouse model, and if such findings could be generalized to human populations.

We examined the impact of the variant BDNF on fear conditioning and extinction paradigms (Soliman et al., 2010). Approximately 70 mice and 70 humans were tested. The human sample included 36 Met allele carriers (heterozygotes and Met allele homozygotes) and 36 nonMet allele carriers (Val allele homozygotes) group-matched on age, gender and ethnic background. Fear conditioning consisted of pairing a neutral cue (i.e., conditioned stimulus or CS) with an unconditioned aversive stimulus (US) until the cue itself took on properties of the US of an impending aversive event. The extinction procedure consisted of repeated presentations of the CS alone. Behavioral responses of percentage of time freezing in the mouse and amplitude of the galvanic skin response in the human were the dependent measures. In addition, we collected brain imaging data using fMRI with the human sample.

Both in the mice and humans, we observed less extinction in Met allele carriers than in nonMet allele carriers as shown in Figure 4A and B below (Hajcak et al., 2009). Moreover, human fMRI data provided neuroanatomical validation of the cross species translation. Specifically, we showed alterations in frontoamygdala circuitry, shown to support fear conditioning and extinction in previous rodent (LeDoux, 2000; Myers & Davis, 2002) and human (Delgado et al., 2008; Gottfried & Dolan, 2004; LaBar et al., 1998; Phelps et al., 2004) studies, as a function of BDNF genotype. Met allele carriers showed less ventromedial prefrontal cortical (vmPFC) activity during extinction relative to nonMet allele carriers (Figure 4C), but greater amygdala activity relative to nonMet allele carriers (Figure 4D). These findings suggest that cortical regions essential for extinction in animals and humans are less responsive in Met allele carriers. Moreover, amygdala recruitment which should show diminished activity during extinction was elevated in Met allele carriers, suggesting less dampening by vmPFC and more fear response as generated by amygdala output to neuromodulatory systems, the hypothalamus, periaquiductal gray, and vagus (LeDoux, 2000; Phelps et al., 2004).

These findings are provocative as they provide an example of bridging human behavioral and imaging genetics with a molecular mouse model to suggest a role for BDNF in anxiety for adults. In the context of our neurobiological model of adolescence, individuals with the BDNF Met allele may be more vulnerable for developing symptoms of anxiety as teens, in that they show higher and prolonged patterns of amygdala activity and less vPFC activity to emotional cues. During a period when evaluating social cues from peers is essential in forming and maintaining healthy peer relationships, the failure to suppress heightened emotional responses to empty threat in these interactions (e.g., failure of a peer to notice or smile at a teenager, without any negative intent) could lead to over interpretation and ruminations of self doubt. The genetic data provide an example then of how an imbalance in amygdala-PFC coupling during typical development could be exacerbated and lead to clinical symptoms of anxiety. This interpretation is strengthened by recent animal research showing slower extinction in adolescent rats relative to adult rats (McCallum et al., 2010). Thus, these data may have important implications for the efficacy of treatments for anxiety disorders in children that rely on extinction mechanisms such as exposure therapy in terms

of who will be responsive and when. Consistent with this view are findings from recent studies showing that Selective Serotonin Reuptake Inhibitors (SSRIs) in combination with exposure therapy in children are more beneficial than either of these two treatments alone (Walkup et al., 2008).

### Effects of Early Experiences on Later Development

The variability observed in both our developmental and genetic studies of emotion regulation may in part be due to variation in individuals' experiences. A number of studies have shown the significance of environmental factors such as early adversity and stress on the brain and behavior (Liston et al., 2009; Liston et al., 2006; Tottenham et al., 2010; Tottenham et al., 2009) and risk for psychopathology. In the context of our neurobiological model of adolescence, individuals who experience adversity during this period, or who have experienced adversity or multiple traumas earlier in development, may be especially vulnerable for developing symptoms of anxiety or depression as teens or adults. There is a large epidemiological and clinical literature supporting this claim (Brown et al., 1999; Heim & Nemeroff, 2001; Pine & Cohen, 2002; Yule et al., 2000). Our model simply provides a biological basis for this vulnerability. In other words, while heightened emotional reactivity is typical during the period of adolescence, failure to suppress that emotional reactivity over time when there is no impending threat is associated with symptoms of anxiety.

Early postnatal life is a time of both developmental opportunity and vulnerability, and the timing of experiences is critical for developmental outcome. Non-human animal studies have shown that early rearing conditions can have long-term consequences on emotional behavior and the effects of early experience can be more significant than later experiences (Sabatini et al., 2007). Many of these behavioral outcomes are associated with changes in limbic circuitry described previously (see Figure 1). Within that circuitry, the region of the amygdala and its growth and hyperactivity have been shown to mediate the expression of hyperemotionality as measured by increased anxiety-like behaviors in animals (Vyas & Chattarji, 2004). The primate amygdala develops early in life (Humphrey, 1968; Ulfig et al., 2003) with the most rapid rate of development occurring during the early postnatal period (Payne et al., 2009), a rate which may heighten the vulnerability of the amygdala to environmental exposures (Lupien et al., 2009). A number of animal studies have shown that the amygdala is particularly sensitive to early life rearing conditions (Kikusui & Mori, 2009; Plotsky et al., 2005; Sabatini et al., 2007).

A naturally occurring example of poor early care in humans that affects millions of children worldwide (<http://www.hrw.org>) is that of rearing in an orphanage. Socio-emotional behavior is especially vulnerable to early-life adversity, and often these children exhibit elevated emotional reactivity (Colvert et al. 2008) and low social competence (Hodges & Tizard, 1989). They exhibit more anxiety (Casey et al., 2009; Zeanah et al., 2009), internalizing problems (Juffer & van Ijzendoorn, 2005) and difficulty regulating behavior in emotionally arousing contexts (Tottenham et al., 2009). This emotional profile persists for many years. The means by which the early care giving environment influences neural development and associated behaviors in humans are not well understood. However, given the central role of frontoamygdala circuitry in fear learning that is specific to adjustment of behavior when prior associations or contexts no longer exist begs the questions of how well these children can adjust their emotional responses when aversive cues or contexts no longer exist (i.e., extinction)

Recently, we examined the long-term neural correlates of early suboptimal rearing conditions on later emotional development in humans. Specifically we examined children adopted to the US from orphanages abroad using the same paradigm as that described earlier by Hare et al. (2008). Imaging and behavioral data were collected from nearly 60 children

(28 internationally adopted children and 27 nonadopted children with mean age of 10 and mean age of adoption 2 years (Tottenham et al., 2010).

Our results showed that adverse rearing conditions in the postnatal period are associated with heightened amygdala activity when suppressing an attentional response to a fearful expression late childhood and adolescence, especially in later adopted children. Non-human animal studies suggest the early, rapid development of the amygdala (Avishai-Eliner et al., 1996; Payne et al., 2009; Vazquez et al., 2006) may increase its vulnerability to environmental pressures, resulting in elevated endogenous stress hormones, altered gene expression, precocious structural development, and altered future functioning (Becker et al., 2007; Kikusui & Mori, 2009; Moriceau et al., 2009; Plotsky et al., 2005; Sabatini et al., 2007). Consistent with these animal models, human imaging studies have revealed amygdala structural atypicalities and associated emotion difficulties following adverse early caregiving environments that are observable years after the removal from these conditions (Mehta et al., 2009; Tottenham et al., 2010; Tottenham et al., 2009).

Most striking of our results from this study was an association between patterns of brain activity and measures of live dyadic interaction between the child and the parent. Specifically, we used video recordings of dyadic interaction and eye-tracking of gaze on a laboratory task of simple face stimuli to examine if early life adversity were related to basic components of social interaction and emotional processing such as eye contact and gaze. We found that activity within the amygdala was associated with decreased eye gaze on both the laboratory task as measured by eye-tracking methods and during a live dyadic interaction with one of their parents (see Figure 5). This finding was greatest in those children adopted later in life. Individual differences in amygdala activity have been associated with directing gaze away from arousing (and informative) aspects of human faces (Dalton et al., 2005), even though doing so can interfere with successful interpersonal communication (Adolphs et al., 2005). Shy individuals, who make less eye contact than their non-shy peers (Pilkonis, 1977), show impairments in face recognition (Brunet et al., 2009) and expression classifications (Battaglia et al., 2004). In typical populations, higher amounts of eye-contact have been associated with social competence and skill, as well as serving a number of social functions like expressing intimacy, exchanging social information, and regulating social exchanges (reviewed in Kleinke 1986).

In our study, children reared in orphanages showed increased amygdala signal to emotional distracter stimuli relative to a comparison sample of children reared with their biological families. The elevated amygdala response may suggest that the comparison children were better able to ignore or suppress the irrelevant emotional content of the distracter stimuli, while the previously institutionalized children were not. Examination of ventromedial prefrontal regions that play a modulatory role in suppressing amygdala outputs that lead to an emotional response (Phelps et al., 2004; Quirk & Beer, 2006) showed atypical activity. Specifically, unlike the comparison children, the orphanage reared children showed no change in vmPFC with increased amygdala activity to fearful stimuli. In healthy populations, the amygdala and vmPFC show inverse activity (Hare et al., 2008; Phelps et al., 2004), which might be mediated by the integrity of the white matter tracts between them (Kim & Whalen, 2009). However, pathological populations show less inverse coupling between the two regions (Marsh et al., 2008; Shin et al., 2006), and decreased coupling has been associated with increased trait anxiety (Hare et al., 2008). Thus our findings are consistent with poor communication between the two regions in the previously institutionalized children, and recent diffusion tensor imaging has identified reduced white matter between amygdala and prefrontal cortex in children previously reared in orphanages (Govindan et al., 2009).

These findings are consistent with a model of heightened amygdala reactivity following chronic stress exposure, with relatively slow recovery, similar to that reported in animal studies (Adamec et al., 2005; Vyas et al., 2002). Moreover, the results underscore the importance of top down modulation of subcortical limbic regions in healthy emotional development. Yet, the orphanage environment is more than a simple or single stressor. Specifically, not only are there mismatches between the child's needs and the caregiver's responses resulting in dysregulation, but there is a mismatch in the expected environment based on a long evolutionary history and the actual one, that must be considered in the how these neural systems develop and behaviors emerge.

## CONCLUSIONS

In this review, we described three approaches that examine neural circuitry underlying core phenotypic features of anxiety (e.g., suppression of fear response) that exemplify translational and translational approaches. First, we described findings from human imaging studies that showed changes in neural circuitry underlying core phenotypic features of anxiety in healthy individuals during the transition into and out of adolescence. Second, we described a recent study examining genetic factors that may enhance risk for anxiety and alter underlying neural circuitry using translation from mouse models to human behavior. Finally, we provided evidence for alterations in neural circuitry underlying core phenotypic features of anxiety as a result of early postnatal experiences using human imaging and behavioral approaches. Taken together, the findings synthesized here indicate that increased risk in adolescence appears to be associated with different developmental trajectories of subcortical emotional systems relative to cortical control regions involved in suppressing emotional responses. This differential development can lead to an imbalance in control by subcortical regions over prefrontal ones leading to heightened emotional reactivity. Although elevated emotional reactivity appears to a typical part of development during the period of adolescence, failure to suppress that emotional reactivity over time seems to be associated more with individual differences in, or symptoms of, anxiety. Both environmental and genetic factors can exacerbate the imbalance between limbic and cortical regions resulting in dysregulation of limbic circuitry and sustained rather than transient emotional responses to cues of threat. Our findings suggest that it is sustainment of the emotional response that leads to anxiogenic feelings and possible risk for anxiety disorders.

Together, our studies provide a converging methods approach for understanding the highly variable experiences and outcomes of adolescence. Each of these approaches alone provides limited information on genetic and environmental influences on complex human behavior across development. Together, they reflect an emerging field of translational developmental neuroscience in forming important bridges between animal models of neurodevelopmental and neuropsychiatric disorders. Important future directions will be to consider how genetic, environmental and developmental factors inter-relate in sufficiently large samples to directly test these effects from a developmental perspective. Such genetic studies will need to entertain dynamic models that capture the effects of changing environmental and developmental conditions or contexts, rather than relying on static models.

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## References

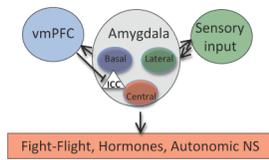
- Adamec RE, Blundell J, Burton P. Neural circuit changes mediating lasting brain and behavioral response to predator stress. *Neurosci Biobehav Rev.* 2005; 29(8):1225–41. [PubMed: 16099042]
- Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR. A mechanism for impaired fear recognition after amygdala damage. *Nature.* 2005; 433(7021):68–72. [PubMed: 15635411]
- Avishai-Eliner S, Yi SJ, Baram TZ. Developmental profile of messenger RNA for the corticotropin-releasing hormone receptor in the rat limbic system. *Brain Res Dev Brain Res.* 1996; 91(2):159–63.
- Battaglia M, Ogliari A, Zanoni A, Villa F, Citterio A, Binaghi F, Fossati A, Maffei C. Children's discrimination of expressions of emotions: relationship with indices of social anxiety and shyness. *J Am Acad Child Adolesc Psychiatry.* 2004; 43(3):358–65. [PubMed: 15076270]
- Baxter MG, Parker A, Lindner CC, Izquierdo AD, Murray EA. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Neurosci.* 2000; 20(11):4311–9. [PubMed: 10818166]
- Becker K, Abraham A, Kindler J, Helmeke C, Braun K. Exposure to neonatal separation stress alters exploratory behavior and corticotropin releasing factor expression in neurons in the amygdala and hippocampus. *Dev Neurobiol.* 2007; 67(5):617–29. [PubMed: 17443812]
- Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. *Cereb Cortex.* 1994; 4(1):78–96. [PubMed: 8180493]
- Bouwmeester H, Wolterink G, Van Ree JM. Neonatal development of projections from the basolateral amygdala to prefrontal, striatal, and thalamic structures in the rat. *Journal of Comparative Neurology.* 2002; 442(3):239–49. [PubMed: 11774339]
- Brown J, Cohen P, Johnson JG, Smailes EM. Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. *J Am Acad Child Adolesc Psychiatry.* 1999; 38(12):1490–6. [PubMed: 10596248]
- Brunet PM, Mondloch CJ, Schmidt LA. Shy children are less sensitive to some cues to facial recognition. *Child Psychiatry Hum Dev.* 2009; 41(1):1–14. [PubMed: 19590948]
- Casey BJ, Glatt CE, Tottenham N, Soliman F, Bath K, Amsos D, Altemus M, Pattwell S, Jones R, Levita L, et al. Brain-derived neurotrophic factor as a model system for examining gene by environment interactions across development. *Neuroscience.* 2009; 164(1):108–20. [PubMed: 19358879]
- Casey BJ, Jones RM, Hare TA. The adolescent brain. *Ann N Y Acad Sci.* 2008; 1124:111–26. [PubMed: 18400927]
- Casey BJ, Jones RM, Levita L, Libby V, Pattwell SS, Ruberry EJ, Soliman F, Somerville LH. The storm and stress of adolescence: Insights from human imaging and mouse genetics. *Dev Psychobiol.* 2010; 52(3):225–235. [PubMed: 20222060]
- Casey BJ, Soliman F, Bath KG, Glatt CE. Imaging genetics and development: challenges and promises. *Human Brain Mapping.* 2010; 31:838–51. [PubMed: 20496375]
- Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. *Science's STKE: signal transduction knowledge environment* 2004. 2004; 2004(225):re5.
- Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science.* 2006; 314(5796):140–3. [PubMed: 17023662]
- Colvert E, Rutter M, Beckett C, Castle J, Groothues C, Hawkins A, Kreppner J, O'Connor TG, Stevens S, Sonuga-Barke EJ. Emotional difficulties in early adolescence following severe early deprivation: findings from the English and Romanian adoptees study. *Dev Psychopathol.* 2008; 20(2):547–67. [PubMed: 18423094]
- Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: Implications for the development of normal and abnormal function during adolescence. *Journal of Comparative Neurology.* 2002; 453(2):116–30. [PubMed: 12373778]
- Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, Alexander AL, Davidson RJ. Gaze fixation and the neural circuitry of face processing in autism. *Nat Neurosci.* 2005; 8(4):519–26. [PubMed: 15750588]

- Davis M, Whalen PJ. The amygdala: vigilance and emotion. *Mol Psychiatry*. 2001; 6(1):13–34. [PubMed: 11244481]
- Delgado MR, Nearing KI, Ledoux JE, Phelps EA. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron*. 2008; 59(5):829–38. [PubMed: 18786365]
- Delgado MR, Olsson A, Phelps EA. Extending animal models of fear conditioning to humans. *Biol Psychol*. 2006; 73(1):39–48. [PubMed: 16472906]
- Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry*. 1997; 54(7):587–606.
- Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, Blair J, Pine DS. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage*. 2005; 25(4):1279–91. [PubMed: 15850746]
- Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*. 2006; 51(6):871–82. [PubMed: 16982430]
- Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *J Neurosci*. 2006; 26(25):6885–92. [PubMed: 16793895]
- Gottfried JA, Dolan RJ. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. *Nat Neurosci*. 2004; 7(10):1144–52. [PubMed: 15361879]
- Govindan RM, Behen ME, Helder E, Makki MI, Chugani HT. Altered water diffusivity in cortical association tracts in children with early deprivation identified with Tract-Based Spatial Statistics (TBSS). *Cereb Cortex*. 2009; 20(3):561–9. [PubMed: 19546156]
- Guyer AE, Lau JY, McClure-Tone EB, Parrish J, Shiffrin ND, Reynolds RC, Chen G, Blair RJ, Leibenluft E, Fox NA, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch Gen Psychiatry*. 2008a; 65(11):1303–12. [PubMed: 18981342]
- Guyer AE, McClure-Tone EB, Shiffrin ND, Pine DS, Nelson EE. Probing the neural correlates of anticipated peer evaluation in adolescence. *Child Dev*. 2009; 80(4):1000–15. [PubMed: 19630890]
- Guyer AE, Monk CS, McClure-Tone EB, Nelson EE, Roberson-Nay R, Adler AD, Fromm SJ, Leibenluft E, Pine DS, Ernst M. A developmental examination of amygdala response to facial expressions. *J Cogn Neurosci*. 2008b; 20(9):1565–82. [PubMed: 18345988]
- Haas BW, Omura K, Constable RT, Canli T. Emotional conflict and neuroticism: personality-dependent activation in the amygdala and subgenual anterior cingulate. *Behav Neurosci*. 2007; 121(2):249–56. [PubMed: 17469914]
- Hajcak G, Castille C, Olvet DM, Dunning JR, Hatchwell E. Genetic variation in brain-derived neurotrophic factor and human fear conditioning. *Genes, Brain and Behavior*. 2009; 8(1):80–85.
- Hall, GS. Adolescence: Its psychology and its relation to physiology, anthropology, sociology, sex, crime, religion, and education (Vols I & II). Englewood Cliffs, NJ: Prentice-Hall; 1904.
- Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biol Psychiatry*. 2008; 63(10):927–34. [PubMed: 18452757]
- Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry*. 2001; 49(12):1023–39. [PubMed: 11430844]
- Hodges J, Tizard B. Social and family relationships of ex-institutional adolescents. *J Child Psychol Psychiatry*. 1989; 30(1):77–97. [PubMed: 2925822]
- Humphrey T. The development of the human amygdala during early embryonic life. *J Comp Neurol*. 1968; 132(1):135–65. [PubMed: 5732427]
- Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res*. 1979; 163(2):195–205. [PubMed: 427544]
- Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci*. 2007; 27(33):8877–84. [PubMed: 17699669]

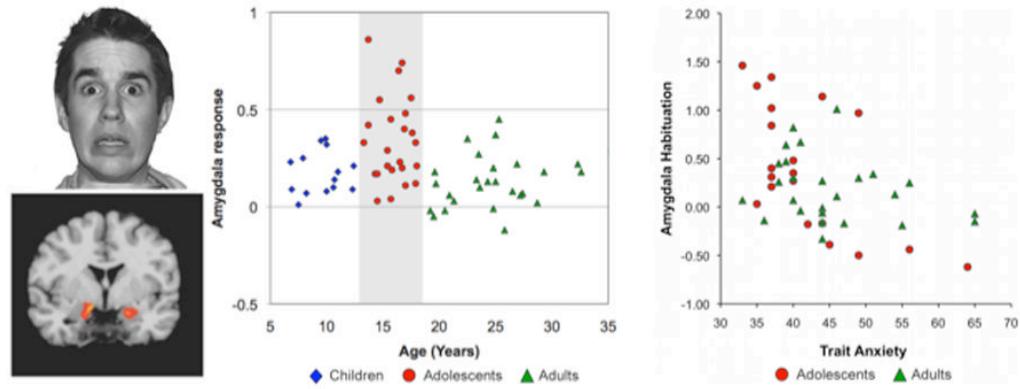
- Juffer F, van Ijzendoorn MH. Behavior problems and mental health referrals of international adoptees: a meta-analysis. *JAMA*. 2005; 293(20):2501–15. [PubMed: 15914751]
- Kikusui T, Mori Y. Behavioural and neurochemical consequences of early weaning in rodents. *J Neuroendocrinol*. 2009; 21(4):427–31. [PubMed: 19207810]
- Kim H, Somerville LH, Johnstone T, Polis S, Alexander AL, Shin LM, Whalen PJ. Contextual modulation of amygdala responsivity to surprised faces. *J Cogn Neurosci*. 2004; 16(10):1730–45. [PubMed: 15701225]
- Kim MJ, Whalen PJ. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. *Journal of Neuroscience*. 2009; 29(37):11614–11618. [PubMed: 19759308]
- Kleinke CL. Gaze and eye contact: a research review. *Psychol Bull*. 1986; 100(1):78–100. [PubMed: 3526377]
- LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron*. 1998; 20(5):937–45. [PubMed: 9620698]
- LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000; 23:155–84. [PubMed: 10845062]
- Lerner, RM.; Israeloff, R. *The good teen : rescuing adolescence from the myths of the storm and stress years*. New York: Stonesong Press Book/Crown Pub; 2007. p. 25
- Liston C, McEwen BS, Casey BJ. Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proc Natl Acad Sci U S A*. 2009; 106(3):912–7. [PubMed: 19139412]
- Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci*. 2006; 26(30):7870–4. [PubMed: 16870732]
- Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009; 10(6):434–45. [PubMed: 19401723]
- Marsh AA, Finger EC, Mitchell DG, Reid ME, Sims C, Kosson DS, Towbin KE, Leibenluft E, Pine DS, Blair RJ. Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry*. 2008; 165(6):712–20. [PubMed: 18281412]
- McCallum J, Kim JH, Richardson R. Impaired extinction retention in adolescent rats: effects of D-cycloserine. *Neuropsychopharmacology*. 2010; 35(10):2134–42. [PubMed: 20592716]
- Mehta MA, Golembi NI, Nosarti C, Colvert E, Mota A, Williams SC, Rutter M, Sonuga-Barke EJ. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *J Child Psychol Psychiatry*. 2009; 50(8):943–51. [PubMed: 19457047]
- Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*. 2002; 420(6911):70–4. [PubMed: 12422216]
- Monk CS, Grillon C, Baas JM, McClure EB, Nelson EE, Zarahn E, Charney DS, Ernst M, Pine DS. A neuroimaging method for the study of threat in adolescents. *Developmental Psychobiology*. 2003a; 43(4):359–66. [PubMed: 15027419]
- Monk CS, McClure EB, Nelson EE, Zarahn E, Bilder RM, Leibenluft E, Charney DS, Ernst M, Pine DS. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage*. 2003b; 20:420–428. [PubMed: 14527602]
- Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, Chen G, McClure-Tone EB, Ernst M, Pine DS. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Arch Gen Psychiatry*. 2008; 65(5):568–76. [PubMed: 18458208]
- Moriceau S, Rainecki C, Holman JD, Holman JG, Sullivan RM. Enduring neurobehavioral effects of early life trauma mediated through learning and corticosterone suppression. *Front Behav Neurosci*. 2009; 3:22. [PubMed: 19750195]
- Myers KM, Davis M. Behavioral and neural analysis of extinction. *Neuron*. 2002; 36(4):567–84. [PubMed: 12441048]
- Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of Depression. *Neuron*. 2002; 34(1):13–25. [PubMed: 11931738]

- NIMH. Transformative Neurodevelopmental Research in Mental Illness: Report of the National Advisory Mental Health Council's Workgroup. 2007
- Payne C, Machado CJ, Bliwise NG, Bachevalier J. Maturation of the hippocampal formation and amygdala in *Macaca mulatta*: A volumetric magnetic resonance imaging study. *Hippocampus*. 2009
- Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron*. 2004; 43(6):897–905. [PubMed: 15363399]
- Pilkonis P. The behavioral consequences of shyness. *Journal of Personality*. 1977; 45(4):596–611.
- Pine D. A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry*. 2007; 48(7):631–48. [PubMed: 17593144]
- Pine DS, Cohen JA. Trauma in children and adolescents: risk and treatment of psychiatric sequelae. *Biol Psychiatry*. 2002; 51(7):519–31. [PubMed: 11950454]
- Plotsky PM, Thrivikraman KV, Nemeroff CB, Caldji C, Sharma S, Meaney MJ. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. *Neuropsychopharmacology*. 2005; 30(12):2192–204. [PubMed: 15920504]
- Quirk GJ, Beer JS. Prefrontal involvement in the regulation of emotion: Convergence of rat and human studies. *Current Opinion in Neurobiology*. 2006; 16:723–727. [PubMed: 17084617]
- Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proceedings of the National Academy of Sciences, USA*. 2006; 103(23):8900–5.
- Sabatini MJ, Ebert P, Lewis DA, Levitt P, Cameron JL, Mirnics K. Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. *J Neurosci*. 2007; 27(12):3295–304. [PubMed: 17376990]
- Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci*. 2006; 1071:67–79. [PubMed: 16891563]
- Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, Jing D, Tottenham N, Amso D, Somerville LH, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science*. 2010; 327(5967):863–6. [PubMed: 20075215]
- Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. *Current Opinion in Neurobiology*. 2010; 20:1–6.
- Somerville LH, Whalen PJ, Kelley WM. Human Bed Nucleus of the Stria Terminalis Indexes Hypervigilant Threat Monitoring. *Biol Psychiatry*. 2010
- Taylor S, Thordarson DS, Maxfield L, Federoff IC, Lovell K, Ogrodniczuk J. Comparative efficacy, speed, and adverse effects of three PTSD treatments: exposure therapy, EMDR, and relaxation training. *Journal of Consulting and Clinical Psychology*. 2003; 71(2):330–38. [PubMed: 12699027]
- Thapar A, McGuffin P. Are anxiety symptoms in childhood heritable? *Journal of Child Psychology and Psychiatry*. 1995; 36(3):439–447. [PubMed: 7782407]
- Thomas KM, Drevets WC, Whalen PJ, Eccard CH, Dahl RE, Ryan ND, Casey BJ. Amygdala response to facial expressions in children and adults. *Biological Psychiatry*. 2001; 49:309–316. [PubMed: 11239901]
- Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, Axelson D, Whalen P, Casey BJ. Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry*. 2001; 58:1057–63. [PubMed: 11695953]
- Tottenham N, Hare T, Millner A, Gilhooly T, Zevin JD, Casey BJ. Elevated Amygdala Response to Faces Following Early Deprivation. *Developmental Science*- electronic access. 2010
- Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti IM, et al. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci*. 2009; 13(1):46–61. [PubMed: 20121862]
- Ulfing N, Setzer M, Bohl J. Ontogeny of the human amygdala. *Ann N Y Acad Sci*. 2003; 985:22–33. [PubMed: 12724145]

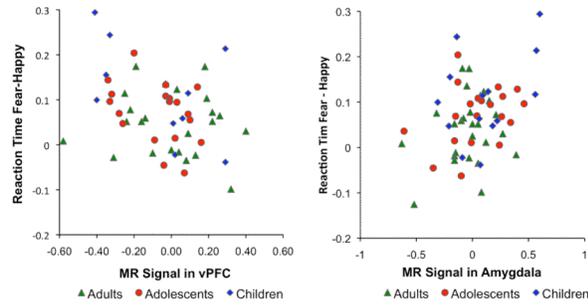
- Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, Jackson CA, Frye CJ, Greischar LL, Alexander AL, et al. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J Neurosci.* 2006; 26(16):4415–25. [PubMed: 16624961]
- Vazquez DM, Bailey C, Dent GW, Okimoto DK, Steffek A, Lopez JF, Levine S. Brain corticotropin-releasing hormone (CRH) circuits in the developing rat: effect of maternal deprivation. *Brain Res.* 2006; 1121(1):83–94. [PubMed: 17055465]
- Vyas A, Chattarji S. Modulation of different states of anxiety-like behavior by chronic stress. *Behav Neurosci.* 2004; 118(6):1450–4. [PubMed: 15598155]
- Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci.* 2002; 22(15):6810–8. [PubMed: 12151561]
- Walkup JT, Albano AM, Piacentini J, Birmaher B, Compton SN, Sherrill JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med.* 2009; 359(26):2753–2766. [PubMed: 18974308]
- Williams LM, Brown KJ, Palmer D, Liddell BJ, Kemp AH, Olivieri G, Peduto A, Gordon E. The mellow years? Neural basis of improving emotional stability with age. *Journal of Neuroscience.* 2006; 26(24):6422–6430. [PubMed: 16775129]
- Yu H, Wang Y, Pattwell S, Jing D, Liu T, Zhang Y, Bath KG, Lee FS, Chen Z. Variant BDNC Val66Met polymorphism affects extinction of conditioned aversive memory. *Journal of Neuroscience.* 2009; 29(13):4056–64. [PubMed: 19339601]
- Yule W, Bolton D, Udwin O, Boyle S, O’Ryan D, Nurrish J. The long-term psychological effects of a disaster experienced in adolescence: I: The incidence and course of PTSD. *J Child Psychol Psychiatry.* 2000; 41(4):503–11. [PubMed: 10836680]
- Zeanah CH, Egger HL, Smyke AT, Nelson CA, Fox NA, Marshall PJ, Guthrie D. Institutional rearing and psychiatric disorders in Romanian preschool children. *Am J Psychiatry.* 2009; 166(7):777–85. [PubMed: 19487394]



**Figure 1. Cartoon of frontoamygdala circuit**

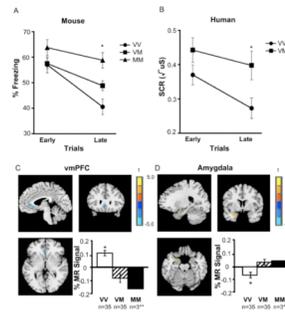


**Figure 2. Amygdala response to empty threat as a function of age and trait anxiety**  
*Left:* Depiction of threat stimulus and location of activation in the amygdala. *Middle:* Amygdala activity to empty threat (fearful faces) plotted as a function of age. *Right:* Scatter plot of the correlation between Spielberger trait anxiety scores and habituation (decrease from early to late trials) of amygdala activity for teens and adults (note: anxiety scale was not appropriate for under 13 years)  $r = -.447$ ,  $p < 0.001$ . Adapted from Hare et al., 2008.



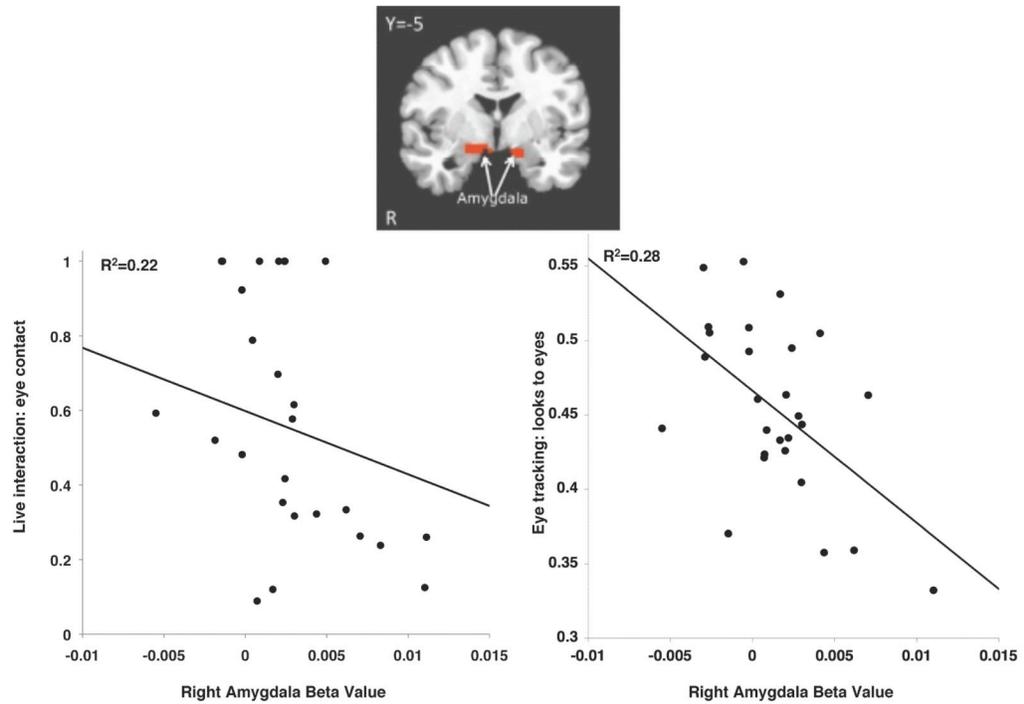
**Figure 3. Frontoamygdala activity is associated with response latency to threat stimuli**

*Left:* Scatter plot of the correlation between response latency to a cue of threat and amygdala activity ( $r = .418$ ;  $p < .001$ ). *Right:* Scatterplot of association between response latency to a cue of threat and vmPFC activity ( $r = -.411$ ,  $p < .001$ ). Adapted from Hare et al., 2008.



**Figure 4. Altered behavior and neural circuitry underlying extinction in adult mice and humans with BDNF Val66Met**

Impaired extinction in Met allele carriers (Val/Met and Met/Met) as a function of time in 68 mice (A) and 72 humans (B) as indexed by percent time freezing in mice and skin conductance response (SCR) in humans to the conditioned stimulus when it was no longer paired with the aversive stimulus. (C) Brain activity as indexed by percent change in MR signal during extinction in the ventromedial prefrontal cortex (vmPFC) by genotype ( $xyz = -4, 24, 3$ ), with Met allele carriers having significantly less activity than Val/Val homozygotes [VM < VV = blue], image threshold  $p < 0.05$ , corrected. (D) Genotypic differences in left amygdala activity during extinction ( $xyz = -25, 2, -20$ ) in 70 humans, with Met allele carriers having significantly greater activity than Val/Val homozygotes [VM > VV = orange], image threshold  $p < 0.05$ , corrected. \* $p < 0.05$ . \*\*MM were included in the analysis with VM, but plotted separately to see dose response. All results are presented as a mean  $\pm$  SEM. VV = Val/Val; VM = Val/Met; MM = Met/Met (From Soliman et al. 2010).



**Figure 5. Amygdala response to emotional faces and eye contact in children adopted from orphanages abroad**

*Left.* Amygdala response to emotional stimuli was inversely correlated with amount of eye-contact with parent in during live interaction *Right.* Amygdala response to emotional stimuli was inversely correlated with amount of eye-contact children made during eye-tracking (proportion of frames spent looking at the eye region of face stimuli). (Adapted from Tottenham et al., 2010)