Posttraumatic Stress Disorder and the Developing Adolescent Brain

Supplement

Prominent constructs for PTSD and evidence in adolescents

Threat and extinction learning

Threat and extinction learning are dominant constructs in adult PTSD neurocircuitry models and provide intuitive, though overly simplistic (1–3), laboratory models for the development and retention of threat reactions to trauma cues in individuals who develop PTSD as well as for exposure-based treatments of PTSD (4,5). While healthy adolescents are capable of threat acquisition and extinction learning (6–9), they exhibit potentially important differences from adults that may factor into PTSD risk and treatment effectiveness. Notably, adolescents show attenuated contextual extinction learning which has been attributed to reduced prefrontal plasticity (8,10). Consistent with this notion, adolescents have been shown to have greater amygdala and hippocampal recruitment, but less discriminative prefrontal responses to threat learning compared to adults (11–13). Prior work implicates threat extinction deficits in adolescent anxiety disorders (14) but with potentially differential prefrontal recruitment during threat discrimination compared to anxious adults including increased, rather than decreased, amygdala-ventromedial prefrontal cortex (vmPFC) connectivity (12,13). While no studies have specifically examined threat learning in adolescent PTSD, some have examined relationships with PTSD symptoms and found inconsistent relationships for fear acquisition with trauma load and PTSD symptoms, and no relationships with extinction (15,16). Overall, the dearth of information on threat learning in adolescent PTSD remains an important knowledge gap, and one we are actively aiming to address in an ongoing psychophysiology and neuroimaging study. Potential sex differences on threat learning in adolescence are also particularly important given the increased prevalence of PTSD in adolescent females compared to males and the

recent evidence for estradiol modulating extinction learning (17,18). How estrogen and other pubertal hormones impact PTSD risk and threat and extinction learning in adolescence remains an open question.

Threat attentional bias

Threat attentional bias refers to bias in the allocation of attention towards threat-related stimuli and, depending on the stage of processing, can manifest as heightened orientation of attention towards threat, delayed disengagement from threat, or avoidance of threat (19). Attentional threat bias in PTSD was initially conceptualized as automatic orienting towards threat, consistent with hypervigilance symptoms. However, meta-analyses in adult PTSD do not provide support for automatic threat orienting and instead suggest that attentional threat bias operates at a strategic level consistent with delayed disengagement (20). To date, only two studies have examined threat bias in pediatric PTSD. A study of maltreated youth showed that both maltreatment exposure and PTSD were associated with attentional avoidance of angry, but not happy faces, relative to neutral faces (21). On the other hand, a recent study in pre- and early adolescents showed that while trauma exposure was associated with attentional bias towards angry faces, PTSD symptoms were associated with bias towards happy faces (22). Further research is needed to determine the contributions of attentional threat bias to adolescent PTSD. Such studies would ideally include consideration of developmental patterns and sex differences conferring PTSD risk, emergent sex differences in threat bias.

Emotion regulation

Deficits in the regulation of negative emotion have been implicated as a key mechanism linking childhood trauma exposure to a broad array of psychiatric disorders, including PTSD [see also this issue (23)]. Emotion regulation incorporates several processes including emotion awareness and understanding, acceptance/tolerance of emotions, control of impulsive behaviors to reach desired goals, and flexible,

contextually appropriate deployment of regulation strategies during emotional distress (24). Adolescence is a key period of emotion regulation development, and under healthy conditions is characterized by decreased self-reported reactivity to negative stimuli with age (25). Furthermore, healthy adolescents show enhanced cognitive control of negative emotion with age under implicit cognitive-emotional interference tasks (26–29), as well as greater downregulation of negative affect under explicit reappraisal tasks (30–32) (though see (33,34)). In contrast, abuse has been associated with poorer emotion regulation capacity in youth, which mediates risk for adolescent psychopathology including PTSD symptoms (35–39). However, adolescents who are largely resilient show evidence of normative self-reported reactivity and reappraisal of negative emotion (40). Finally, improvements in self-reported emotion regulation during TF-CBT are associated with reduced PTSD symptoms in adolescents (41). These studies suggest that emotion regulation may be an important mechanism linking trauma exposure to resilience or risk for, and recovery from, PTSD in adolescents.

Trauma-related cognitions

Maladaptive belief systems are a central component of psychological theories of PTSD (2,42,43). Much of this work has focused on adults and demonstrates that individuals with PTSD demonstrate negative beliefs about the self (e.g., “I’m damaged”), negative beliefs about the world (e.g., “the world is a dangerous place”), and self-blame (e.g., “the trauma happened because of me”) (44,45). Cognitive theories of PTSD generally posit that these negative beliefs developed following the trauma thereby conferring risk for PTSD (42), though some prospective studies have demonstrated that higher pre-trauma maladaptive beliefs predict greater PTSD symptoms following trauma (46) and thereby also implicate these beliefs as risk factors. Cognitively-oriented treatments for PTSD attempt to identify and challenge these negative beliefs (43). Indeed, dismantling studies have found that sole focus on challenging these beliefs results in greater symptom reduction than narrative exposure therapy (47), and symptom reduction during

prolonged exposure therapy that does not explicitly focus on negative beliefs may nonetheless occur due to changes in negative beliefs (48). While most of this research has been conducted among adults, this work has also been extended to adolescent PTSD (49,50). Meta-analyses also demonstrate heightened negative beliefs about the self, world, and self-blame in adolescent PTSD (45), and degree of these negative beliefs in acutely traumatized children and adolescents prospectively predicts subsequent PTSD symptom (51,52). The gold standard treatment for youth with PTSD, trauma focused cognitive behavioral therapy, involves creation of a trauma narrative and explicit focus on identifying and challenging unhealthy beliefs related to the trauma (49). Further, degree of negative beliefs expressed during TF-CBT, coded through audio recordings of the exposure sessions, predicted degree of symptom improvement up to one year later (53). Continued mechanistic and treatment-oriented research on these higher-order belief systems, couched within normative developmental models of cognitive development, will be important for further improving treatment outcomes.

Emerging directions in adolescent PTSD: Additional domains

Large scale network abnormalities in adolescent PTSD

Complementing prefrontal-amygdala and -hippocampal findings, recent work increasingly implicates abnormalities in larger brain networks in adolescent PTSD. Core functional brain networks include the default mode network (DMN), involved in self-referential thought and processing, the salience network (SN), involved in detection of relevant internal or external cues including threat, and the central executive network (CEN), involved in goal-directed behavior and emotion regulation (54). To date, few studies have examined large-scale network function in adolescent PTSD. In an initial resting-state study (n=29 PTSD, 30 TD), we found increased within-DMN connectivity (posterior cingulate cortex [PCC] to inferior parietal gyrus), increased within-DMN connectivity with age (PCC to vmPFC), and greater anti-correlation between the PCC and CEN/SN regions in adolescents with PTSD (55). Another resting-state study of adolescent

PTSD showed no differences in PCC connectivity, though may have been limited by small sample size (n=14 PTSD, 24 TD) (56). While further work is needed, these initial findings suggest a pattern of DMN network development which may differ between adolescent and adult PTSD and are consistent with studies above highlighting the role of CEN nodes in emotion regulation.

In addition to resting-state seed-based approaches, studies using graph theoretical approaches suggest alterations in global brain organization among traumatized youth. One such measure is modularity, which refers to greater connectivity among nodes within a network relative to nodes between networks, enabling functional specialization (57–59). In an initial study of 20 adolescent girls with PTSD who performed an emotion processing task before and after TF-CBT, we found that girls with less whole-brain modularity pre-treatment relative to TD girls predicted worse treatment outcomes (60). These findings suggest that intact modular brain organization, and presumably functional specialization, during emotion processing enables better adaptive learning during TF-CBT. These data are also consistent with normative developmental studies demonstrating increasing brain modularity across adolescence, which predicts developmental increases in executive function (57). In a subsequent expanded study of adolescent girls (n=29 TD, n=59 assault victims), we found that maltreatment severity scaled with greater whole-brain modularity during an emotion processing task (61). Controlling for maltreatment severity, girls with PTSD (n=38) had even greater modular brain organization. In the context of normative increases in brain modularity across adolescence, these data could suggest that increased brain modularity in trauma-exposed adolescents, and presumably increased functional specialization, could be adaptive up to a certain point, while overspecialization, as is seen in PTSD and severe early life trauma, becomes maladaptive. In a subset of this sample of individuals completing resting-state fMRI (n=56), we again found that maltreatment was associated with greater whole-brain modularity. Encouragingly, data from a small Chinese sample also found increased global segregation in resting-state connectivity among children with

PTSD following an earthquake (62), albeit using a different network measure of segregation (global clustering coefficient). While further research is warranted to delineate the impact of trauma on large-scale brain organization in youth, these studies, along with recent work in adults (63), suggest that modularity and other brain network properties could be used to identify early patterns of risk and resilience in adolescents, and potentially serve as informative treatment biomarkers.

Social cognition and reorienting

Adolescence is characterized marked changes in social cognition, social brain development, and reorientation towards peer relationships [this issue (64)]. In particular, adolescents show development of more complex social cognitive processes allowing inference of emotional states, motivations, and intentions of others (i.e. mentalizing). These changes are accompanied by structural and functional changes in the "social brain" including the temporoparietal junction, temporal pole, precuneus, and dmPFC. As highlighted in a recent review and meta-analysis, perceived social support is an important buffer against PTSD in the peri-traumatic period, and is a key component in recovery from PTSD (65). This meta-analysis showed that adult PTSD is characterized by deficits in emotion recognition and mentalizing, findings that were not present in traumatized individuals without PTSD.

While gaining increasing study in adolescent populations, little is known about social cognition in adolescent PTSD. A study of inpatient adolescent PTSD found that secure caregiver attachment was positively associated with mentalizing performance, while mentalizing mediated the relationship between attachment and PTSD severity and treatment outcome (66). Studies of emotion recognition in adolescent PTSD are few and show conflicting findings to date. A study of maltreated youth (8-15 years) with and without PTSD found faster recognition of fearful, but not happy or neutral, faces compared to non-maltreated youth, with no effect of PTSD status (67). In contrast, a sample of adolescent boys in

therapeutic day school with and without PTSD found that PTSD symptoms were associated with less accurate recognition of angry relative to fearful, but not sad, faces (68). A recent study by our group found that adolescents with PTSD show reduced accuracy for angry, disgust, and neutral (but not happy or sad) faces compared to TD adolescents and in the absence of visual attention or gender recognition differences (Heyn et al., under review). Surprisingly, PTSD severity was associated with improved accuracy for angry, disgust, and neutral faces, suggesting that impaired emotion recognition may be a predisposing factor for PTSD which, in turn, counteracts recognition deficits. Given the mixed findings to date, however, further study is needed to definitively characterize social cognition performance in adolescent PTSD.

Contrary to what would be expected given hypervigilance, avoidance, and heightened threat interpretations in PTSD, there is a consistent literature, mostly among college aged women, demonstrating significant deficits in risk perceptions of social situations and increased risky social behavior among violence victims. One study among young women examined judgments of written descriptions of social situations with sexual victimization risk and found that greater histories of interpersonal violence were associated with higher thresholds for judging a situation as risky (69). Moreover, another study found that the latency with which victimized young adult women decided to leave hypothetical risky social situations escalating towards rape significantly predicted subsequent revictimization (70). Data also suggests that college age women with histories of interpersonal violence demonstrate less response effectiveness and less response refusal in sexually risky situations (71), less overall sexual assertiveness (72), and greater risky sexual behavior (e.g., number of sexual partners, frequency of unprotected sex, etc.) (73). Building on this literature, we compared social decision-making in victimized adolescent girls using laboratory behavioral tasks. We found that increasing severity of early life abuse, but not clinical symptom severity, was associated with decreased ability to correctly identify trustworthy conspecifics and decreased salience network encoding of unexpectedly bad social outcomes (i.e., negative predictors

errors) in a social version of a probabilistic learning task (74–76). In the neuroeconomic "trust game" task, victimized adolescent girls with no current mental health disorders (i.e., resilient) demonstrated decreased trust behavior compared to victimized girls with anxiety disorders (including PTSD). Victimized girls with anxiety/PTSD also demonstrated globally increased social reciprocity compared to both healthy non-traumatized and resilient girls (77). Overall, these data suggest that early life victimization may create a "vicious cycle", such that the social deficits consequent to victimization and development of anxiety symptoms may increase likelihood of additional victimization, further increasing risk of mental and physical health problems. Additionally, altered social functioning may prevent development of healthy relationships that provide sources of social support that could promote recovery from PTSD. Further investigation of social functioning, including potential sex differences, in trauma-exposed adolescents will be important for better understanding risk for and maintenance of PTSD.

Sleep biology

Sleep is a fundamental process proposed to maintain overall synaptic homeostasis following the wake period, allowing for proper function in multiple domains including learning and memory, executive function, and emotion regulation (78). Subjective sleep complaints are associated with both trauma exposure and PTSD in adolescents (79). Furthermore, peri-traumatic sleep disturbances appear to increase the risk of PTSD (80), including in adolescents (81). Experimental evidence indicates that impaired sleep is associated with increased reactivity to negative stimuli, reduced emotion regulation, poorer emotion discrimination, and reduced extinction recall (82–84). When exposed to negative stimuli, sleep deprived adults exhibit elevated amygdala reactivity and reduced functional connectivity between the amygdala and the medial prefrontal cortex (85), suggesting acute changes in the neural circuitry underlying emotion regulation and extinction. While such studies implicate sleep disruption as a potential contributor to adolescent PTSD, little is known about the underlying changes in sleep biology in

adolescents following trauma, and how these differ from normative adolescent development. Normative developmental studies have recently highlighted the role of regional slow wave sleep in cortical development. For example, slow wave activity (SWA) is most prominent over posterior regions at early ages, but shifts to prefrontal regions by late adolescence, consistent with synaptic activity and pruning in later maturing cortical regions involved in executive function and emotion regulation (86). At present, no studies have examined regional cortical sleep development in trauma-exposed adolescents or adolescent PTSD. Furthermore, the contribution of cortical sleep abnormalities to neural dysfunction and development, and their related deficits in functional domains, remains an open area of investigation in youth. Preliminary work from our group suggests that cortical SWA may be impaired in adolescents with PTSD, particularly over prefrontal cortical regions (Jones et al., under review). Impairments in prefrontal SWA appear to be further associated with impaired downregulation of affective reactivity to negative stimuli. While early, these and future studies may offer new insights on biological sleep mechanisms in adolescent PTSD and could point to novel interventions targeting sleep consolidation or enhancement to boost emotion regulation and extinction learning.

Other domains

The socioenvironmental factors, biological systems, and functional domains discussed so far are meant to highlight potentially fruitful areas of research to understand the underlying mechanisms of adolescent PTSD but are by no means exhaustive. There are other neurobiological systems and functional domains which have received limited to no study in adolescent PTSD, some of which we will mention here. One example of such a knowledge gap is the genetic and epigenetic underpinnings of adolescent PTSD. While extensive work has been undertaken to explore risk genes and epigenetic modifications contributing to adult PTSD (87), and some work in trauma-exposed youth, to date no studies have examined these processes in adolescent PTSD (88). Such work is inherently limited by the typically modest sample sizes

of this difficult to recruit population and will ultimately require pooling of data as has been done for adult disorders in the Psychiatric Genomics Consortium. Such studies would also benefit from inclusion of caregiver genetic data, given increasing evidence of intergenerational transmission of epigenetic trauma effects (89). Other potentially key knowledge gaps in adolescent PTSD include the role of neuroinflammation, which may link childhood trauma exposure to later psychopathology (90) and the gut microbiome-brain axis, which can influence stress and inflammatory responses with additional potential for intergenerational transmission (91). Additionally, no studies have examined reward processing specifically in adolescent PTSD, an area that would warrant further exploration particularly given the alterations in mood characteristic of PTSD, and its high comorbidity with depressive disorders. Finally, little remains known about sex differences in mechanisms contributing to the heightened risk of PTSD in adolescent females, as well as sex differences in the underlying neurobiology of adolescent PTSD (92–94). Ultimately, increasing knowledge in all domains mentioned above, as well as others, will be crucial in developing a precision medicine approach to mitigate risk and improve treatments for adolescent PTSD.

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