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Does Anhedonia Presage Increased Risk of Posttraumatic Stress Disorder?:

Adolescent Anhedonia and Posttraumatic Disorders

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Abstract

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Anhedonia, the reduced ability to experience pleasure, is a dimensional entity linked to multiple neuropsychiatric disorders, where it is associated with diminished treatment response, reduced global function, and increased suicidality. It has been suggested that anhedonia and the related disruption in reward processing may be critical precursors to development of psychiatric symptoms later in life. Here, we examine cross-species evidence supporting the hypothesis that early life experiences modulate development of reward processing, which if disrupted, result in anhedonia. Importantly, we find that anhedonia may confer risk for later neuropsychiatric disorders, especially posttraumatic stress disorder (PTSD). Whereas childhood trauma has long been associated with increased anhedonia and increased subsequent risk for trauma-related disorders in adulthood, here we focus on an additional novel, emerging direct contributor to anhedonia in rodents and humans: fragmented, chaotic environmental signals ("FRAG") during critical periods of development. In rodents, recent data suggest that adolescent anhedonia may derive from aberrant pleasure/reward circuit maturation. In humans, recent longitudinal studies support that FRAG is associated with increased anhedonia in adolescence. Both human and rodent FRAG exposure also leads to aberrant hippocampal function. Prospective studies are underway to examine if anhedonia is also a marker of PTSD risk. These preliminary cross-species studies provide a critical construct for future examination of the etiology of trauma-related symptoms in adults and for and development of prophylactic and therapeutic interventions. In addition, longitudinal studies of reward circuit development with and without FRAG will be critical to test the mechanistic hypothesis that early life FRAG modifies reward circuitry with subsequent consequences for adolescent-emergent anhedonia and contributes to risk and resilience to trauma and stress in adulthood.

Keywords

Anhedonia; Brain circuits; Corticotropin releasing factor (CRF); Depression; Early life adversity; Posttraumatic stress disorder (PTSD); Reward circuits; Rodent; Unpredictability and fragmented sensory signals (FRAG)

1 Anhedonia, A Dimensional Construct with Transdiagnostic Relevance

Mental illness, including PTSD, depression, and suicide, afflict >20% of adolescents and young adults, with significant social and fiscal costs (Insel 2011; Merikangas et al. 2010). The origins of mental illness are complex, involving genetic and environmental contributions, specifically during sensitive developmental periods (Bale et al. 2010; Lupien et al. 2009; Nelson et al. 2007; Osborne and Monk 2013). Anhedonia, defined as a reduction in pleasure and appetitive/reward seeking behaviors, is a dimensional construct that is transdiagnostic, cutting across mood, anxiety, and substance use disorders, with clearly delineated operational measures and underlying neurocircuitry [for review, see (Pizzagalli 2014; Rizvi et al. 2016)]. Across mood and anxiety disorders, anhedonia correlates with poor treatment response, suicidality, and diminished global function (Pizzagalli 2014; Rizvi et al. 2016). Because of its association with poor treatment outcomes, it is clear that understanding mechanisms underlying anhedonia and its role in both development and maintenance of neuropsychiatric disorders may be critical for effective treatment strategies. Here, we will discuss a neurodevelopmental hypothesis of anhedonia and its contribution

to risk and resilience to stress and trauma in adulthood. Specifically, we will review the role of anhedonia and its underlying reward circuitry in trauma-related disorders, discuss its known association with early life adversity, and its link to a newly described form of early life adversity, fragmented and chaotic maternal signals (FRAG) during critical phases of development. We will describe recent cross-species evidence for this form of fragmented and chaotic maternal care to mediate anhedonia in adolescence/early adulthood (Molet et al. 2016a; Bolton et al. 2018) and discuss how this newly identified form of developmental stress might shape reward circuit development and neuropsychiatric risk. Throughout, we will identify knowledge gaps and research needed to understand how FRAG may affect reward processes and reward circuitry, and how it subsequently affects susceptibility to trauma disorders in later life.

2 Anhedonia and Disrupted Reward Circuits as a Marker of Heterogeneity in Trauma Disorders

Posttraumatic stress (PTS) symptoms manifest after severe trauma exposure, affecting 7–8% of the US population (Seedat and Stein 2001) and up to 20% of armed service members (Thomas et al. 2010). Besides the extensive mental health service utilization required for treatment, trauma-related disorders, such as posttraumatic stress disorder (PTSD), are associated with greater overall medical service utilization due to higher rates of chronic physical illness experienced by these patients (Baker et al. 2009; O'Donnell et al. 2013). PTSD is phenotypically and etiologically heterogeneous, posing a significant challenge to identifying its biological mechanisms, creation of objective, non-symptom-based nosological categories that cut across current diagnostic boundaries, and development of novel therapeutics. Hence, the current greater focus in psychiatric research is towards identifying fundamental underlying dimensional constructs that contribute significantly to mortality, global function, and treatment response, such as anhedonia.

Anhedonia and Reward Abnormalities in Trauma-Related Disorders

Self-reported anhedonia contributes to symptom heterogeneity in PTSD; it is associated with increased risk for suicide (Spitzer et al. 2018) and social withdrawal (Cao et al. 2016) as well as reduced reward responsiveness (Nawijn et al. 2016). PTS-related anhedonic symptoms in combat veterans increase the risk for comorbidity with substance use, depression, and anxiety disorders (>50% of veterans with PTSD have at least one of these comorbidities) (Kashdan et al. 2006). Theoretically, anhedonia is derived from both reward motivation and consumption ("wanting" and "liking," respectively). A comprehensive recent review by Nawijn et al. suggests that reward abnormalities most robustly observed in trauma disorders are in reward motivation or "wanting" components of the hedonic process such a reward response and effortful-approach behavior, while arousal and valence ratings of rewarding stimuli are not different from those of controls (Nawijn et al. 2015). PTSD patients report significant reductions in the experience of pleasure, i.e., anhedonia (Vujanovic et al. 2017). PTSD patients exhibit anhedonia with or without co-occurring major depressive disorder (MDD), suggesting that anhedonia in trauma-exposed patients is not purely a function of comorbid major depression (Franklin and Zimmerman 2001).

Importantly, trauma exposure alone is not related to reduced reward functioning (Nawijn et al. 2015).

Reward Circuit Abnormalities Associated with Anhedonia and Trauma-Related Disorders

Anhedonia has been examined across multiple neuropsychiatric disorders including mood, trauma-related, and psychotic disorders. Evidence clearly indicates overlap in the circuitry mediating anhedonia and reward abnormalities across disorders, supporting that anhedonia spans classical diagnostic categories (Sharma et al. 2017; Zhang et al. 2016). Symptoms of anhedonia are robustly associated with the brain's reward processing pathways and reduced responsiveness to reward information (Berghorst et al. 2013; Bogdan and Pizzagalli 2006; Pizzagalli et al. 2008).

The brain's reward circuits consist of the ventral tegmental area (VTA) which sends dopaminergic projections to the nucleus accumbens (NAc) in the ventral striatum. VTA neurons also innervate the prefrontal cortex (PFC), the amygdala, and the hippocampus. Most of the extant literature on the reward pathway in humans comes from fMRI studies that implicate decreased activity levels in the VTA and NAc in anhedonia (Drevets et al. 1992; Lee et al. 2012; Mayberg et al. 2000; Russo and Nestler 2013). Consistent with these imaging findings, deep brain stimulation within the NAc reduces anhedonia in treatment-resistant depression (Bewernick et al. 2010, 2012; Schlaepfer et al. 2008). There is also some evidence that amygdala activation is associated with anhedonia (Kumar et al. 2014; Stuhrmann et al. 2013). Amygdala hyperactivity is one of the most robust phenotypes in PTSD (Koch et al. 2016; Etkin and Wager 2007) and may be a pre-trauma risk factor for PTSD (Stevens et al. 2017). However, there is no reliable evidence as to the level of amygdala excitability in the context of anhedonia. It is possible that amygdala hyperactivation is a distinct feature of emotional processing aberrations found in mood and trauma disorders and not reward processing per se.

In general, fewer studies have examined anhedonia in individuals with PTSD compared to depression and schizophrenia. The circuit activation patterns are similar across these disorders in relation to anhedonic symptoms, with altered BOLD fMRI activity levels in reward circuitry including the ventral striatum/NAc, the amygdala, and the PFC (Nawijn et al. 2016; Frewen et al. 2012). Reductions in ventral striatum/NAc activity in response to rewards is reliably associated with increased PTS symptoms or PTSD diagnosis (Admon et al. 2013a, b; Elman et al. 2009; Sailer et al. 2008). Interestingly, CT-based lesion analysis also revealed a link between anhedonia and injury to the ventrolateral PFC in Vietnam combat veterans (Lewis et al. 2015). This finding poses a potential complication in studying populations with comorbid head injury and PTSD as regional vulnerabilities in the PFC may manifest in both and may be linked to anhedonic symptoms.

3 Anhedonia, Potential Risk Factor or Marker of Symptom State in Posttraumatic Stress Disorder?

Evidence for Anhedonia as a Preexisting Risk Factor for Depression and PTSD

Substantial evidence supports anhedonia as a robust phenotype associated with reward circuit disruption in PTSD patients. However, whether anhedonia and reward dysfunction are precursors to clinical dysfunction precipitated by environmental challenges such as stress and trauma or only develop after trauma/chronic stress exposure and symptom development is unknown. Evidence for anhedonia as a risk factor is quite preliminary and still circumstantial at this stage, consisting primarily of correlational and cross-sectional findings. First, depressed and PTSD subjects continue to show deficient reward learning even after symptom remission (Whitton et al. 2016; Kalebasi et al. 2015) (note that this PTSD study is very small, $N = 12$/group). PTSD subjects also show reward processing and response abnormalities when controlling for psychoactive medication (Elman et al. 2005; Hopper et al. 2008). Potential interpretations of these findings are that anhedonia may be a more “fixed” trait that increases risk for development of PTSD, or that anhedonia is less responsive than other symptoms to current treatments. To determine if anhedonia and reward processing abnormalities are pre-trauma risk factors, twin studies and prospective longitudinal studies will be required. No studies have yet examined this question in trauma-related disorders; however, one small prospective study in adolescent girls reported that low reward sensitivity predicts later adult depression (Bress et al. 2013). To answer this question, we have used the Marine Resiliency Study (MRS) database to test a prospective role of multiple risk factors for PTSD. MRS is a prospective, longitudinal study of psychological, physiological, and biological risk factors for development of combat-related PTSD, in which infantry Marine participants (average age range 18–22) were comprehensively assessed both before leaving for a combat deployment to Iraq or Afghanistan, and 3 and 6 months after their return from deployment (Baker et al. 2012). We previously reported that childhood trauma is associated with PTSD in this population (Agorastos et al. 2014). We are currently examining if in healthy participants at pre-deployment, self-reported levels of anhedonia (as measured by the anhedonia subscale of the Beck Depression Inventory) predict increased risk for their developing PTSD after deployment. Our findings are in preparation for publication and were reported at the 2017 American College of Neuropharmacology Annual Meeting (Risbrough et al. 2017). The findings suggest that anhedonia is a significant predictor of risk, and this association is independent of self-reported depression symptoms and deployment trauma exposure. Studies such as this ongoing analysis in MRS will be required to support the hypothesis that anhedonia in late-adolescence/early adulthood may contribute to pre-trauma risk for PTS.

Might Anhedonia Mediate the Relationship Between PTSD Vulnerability and Early Life Adversity?

During early life, the fetus and infant are vulnerable to the consequences of adversity with lasting consequences for infant, toddler, child, and adolescent outcomes (Kim et al. 2014, 2016, 2017; Sandman et al. 2012, 2015; Davis et al. 2011a, b; Davis and Sandman 2006, 2010, 2012; Davis et al. 2007; Glynn et al. 2007; Howland et al. 2016; Stout et al. 2015).

The evidence that early experiences including maternal mental health (Goodman and Gotlib 1999; Oberlander et al. 2008; Monk 2001; Monk et al. 2011; Plant et al. 2015), quality of maternal care (Belsky and Fearon 2002; NICHD Early Child Care Research Network 1999, 2006; Masur et al. 2005; Hane et al. 2010; Feldman 2007, 2010, 2015), trauma (Treadway et al. 2009; Rao et al. 2010; Copeland et al. 2007; Mulvihill 2005; Pynoos et al. 1999; Young et al. 2017; Nelson 2013; McLaughlin et al. 2010), and poverty (Kim et al. 2013; Evans and Kim 2007, 2012; Barch et al. 2016; Javanbakht et al. 2016; Noble et al. 2015; Johnson et al. 2016; Does amount of time spent in child care predict socioemotional adjustment during the transition to kindergarten? 2003) profoundly influence later mental health is undisputed. There is also emerging research implicating exposure to early life adversity in dysfunction of reward-related circuitry (Pechtel and Pizzagalli 2011), particularly in response to adversity during early childhood (Hanson et al. 2016). Developmental trajectories of reward-related ventral striatum (VS) activity mediate the relationship between early life stress and mood disorders in adolescence (Hanson et al. 2015). Childhood trauma, for example, is a well-known risk factor for increased depression, PTSD, and physical health problems (Agorastos et al. 2014), yet it can also increase resilience in some populations (Liu et al. 2017). Others have shown that the strongest correlation of aspects of early life trauma to subsequent PTSD (Lowe et al. 2016) was indication of safety or lack thereof. Childhood trauma is also linked to anhedonia and aberrant reward processing in later life [e.g., (Frewen et al. 2012; Pechtel and Pizzagalli 2013)]. But, trauma exposure is not the only factor that can alter reward processing in development; both children and adults exposed to early social deprivation also exhibit altered reward processing and reduced activity in corticostriatal circuits (Dillon et al. 2009; Mehta et al. 2010; Goff et al. 2013; Guyer et al. 2006; Hanson et al. 2017). Crucially, the scope and trajectory of differential developmental effects of early life experiences and mechanisms associated with resilience vs. risk are still being elucidated. We and others have shown that maternal signals alone can have profound developmental effects on neural circuit development, including small-world network architecture, rich-club organization, and distinct modular structure (Kim et al. 2014, 2016, 2017; Sandman et al. 2012, 2015; Davis et al. 2007, 2011a, b; Davis and Sandman 2006, 2010, 2012; Glynn et al. 2007; Howland et al. 2016; Stout et al. 2015). We have recently identified a novel source of early life adversity across rodent models and humans: unpredictable and fragmented sensory signals (FRAG), particularly those derived from maternal care and the home environment. We have proposed that this relatively unexamined component of early developmental experience may be critical in shaping neural circuits underlying risk for neuropsychiatric disorders in adulthood (Baram et al. 2012). In humans, FRAG is assessed in two broad manners. Prenatally, inconsistency and fragmentation of maternal mood is examined via questionnaires and analyzed by applying Shannon’s entropy to the distribution of self-reported mood over multiple time points both in pregnancy and after birth (Glynn et al. 2017). In addition, unpredictability of maternal care sequences is examined using behavioral observations of the mother’s interactions with her infant (Molet et al. 2016a; Davis et al. 2017). In animals, fragmentation of maternal care behaviors is measured via assessment of duration of stereotyped maternal behavior bouts (e.g., nursing and grooming). In addition, unpredictability of the sequences of maternal care behaviors is examined via observations, and analyzed using Shannon’s entropy, as done for humans (Guyer et al. 2006; Hanson et al. 2017). This new construct, predictability of maternal and environmental

signals during early development, may be a vital factor that influences synapse strengthening and circuit maturation of reward processing and related circuitry.

4 Anhedonia Develops in Adolescent/Young Adult Rodents as a Result of FRAG

Because of the links between poverty, neglect, abuse, and other forms of childhood trauma with neuropathology and psychiatric symptoms in adulthood, numerous animal models of early life adversity have been developed. However, effects of early life stress on anhedonia in animal models have been conflicting, potentially because of their variable effects on the prime determinant of adversity: maternal care. Maternal care has been well recognized as influencing offspring outcome: Gene expression within the brain and the long-lasting emotional and cognitive consequences of early life experience are governed primarily by sensory signals derived from *active* maternal nurturing behaviors (Baram et al. 2012; Champagne et al. 2003; Raineki et al. 2012; Weaver et al. 2004; Pena et al. 2014; Eghbal-Ahmadi et al. 1999; Suchecki et al. 1993). Most studies have manipulated the *quantity* of maternal care using well-established models of maternal separation (Stanton and Levine 1990; Aisa et al. 2007; Colorado et al. 2006; Hill et al. 2014; Kundakovic et al. 2013; Matthews et al. 1996; Michaels and Holtzman 2006, 2007). Reduced quantity of maternal care has often led in the offspring to measures of depressive-like behavior in the forced swim test (Stanton and Levine 1990; Aisa et al. 2007; Shalev and Kafkafi 2002; Dimatelis et al. 2012; Lee et al. 2007) as well as to anxiety-like behaviors (Shalev and Kafkafi 2002; Lee et al. 2007). However, the development of anhedonia does not seem to depend on quantity of care: Reduced quantity of maternal care through intermittent deprivation has been reported to increase (Hill et al. 2014; Kundakovic et al. 2013; Matthews et al. 1996; Michaels and Holtzman 2006), reduce (Stanton and Levine 1990), or not change sucrose preference, a measure of anhedonia.

To develop a robust and reproducible model of early life adversity, the Baram Laboratory developed a model of simulated poverty, which involves normal quantity of maternal care but *changes the patterns of care.* Specifically, limiting bedding and nesting material in the cages induces fragmented and unpredictable patterns of maternal care. This paradigm, adopted widely around the world (Walker et al. 2017), provokes profound anhedonia in adolescent male rats (Molet et al. 2016a; Bolton et al. 2017, 2018; Der-Avakian and Markou 2012). Anhedonia is manifest as both reduced preference for sucrose (a highly rewarding stimulus in rodents) and reduced social play without effecting other social behaviors. More recently, rats exposed to early life fragmentation also exhibit reduced pleasure from sweet rich foods and reduced response to cocaine have been established (Molet et al. 2016a). These data suggest that some types of early life adversity, specifically those associated with disruption of maternal care patterns (e.g., chaotic household, evictions, and change of caretakers) might predispose to pathology specifically in reward response.

5 Anhedonia Reflects Aberrant Brain Circuits Subsequent to Early Life Adversity in Rodents

Cognitive and emotional brain functions involve coordinated activities of brain circuits that integrate molecular, cellular, synaptic, and network signaling (Khazipov et al. 2004; Caspi et al. 2003). And as previously noted, mental disorders may arise from dysfunction (failure) of crucial brain circuits originating from genetic risk and environmental influences, particularly during sensitive developmental periods (Khazipov et al. 2004; Caspi et al. 2003; Heim and Binder 2012). Environment-derived sensory signals clearly influence development of brain circuits (Khazipov et al. 2004; Espinosa and Stryker 2012; Dulac et al. 2014) and, in some cases, may drive aberrant circuit maturation that can promote mental and cognitive problems.

Specifically, we found that a type of early life adversity characterized by unpredictable sensory input early in life reduced sucrose preference and social play during adolescence (Molet et al. 2016a). Both of these behaviors depend on an intact dopaminergic pleasure/reward circuitry (Dym et al. 2009; Kraft et al. 2015; Muscat and Willner 1989; Siviy et al. 2011; Siviy and Panksepp 2011; Trezza et al. 2010; Vanderschuren et al. 1997). The dopaminergic pleasure/reward system is not fully mature until the third postnatal week in rodents (Voorn et al. 1988) and is sensitive to the influence of early life experiences (Pena et al. 2014; Ventura et al. 2013). It has been reported that predictable sequences of events engage and shape the reward system (Berns et al. 2001; Rutledge et al. 2014). These observations lead us to speculate that predictable patterns of maternal care provide crucial cues for maturation of the pleasure/reward system (Pena et al. 2014; Khazipov et al. 2004; Berns et al. 2001). In the absence of such input, the ability to experience reward from pleasurable sensations including the sweetness of sucrose or the joy of play with peers might be (Pena et al. 2014; Ventura et al. 2013) generating anhedonia (Romer Thomsen et al. 2015). Indeed, recent data demonstrate aberrant interactions of reward and fear/anxiety circuits after early life FRAG (Der-Avakian and Markou 2012; Glenn et al. 2017).

Sensory input early in life governs neuronal activity, which influences circuit maturation (Khazipov et al. 2004; Espinosa and Stryker 2012; Evans et al. 2005) as demonstrated in visual, tactile, and olfactory circuits. We propose that patterns of maternal-derived sensory input influence the maturation of both fear and pleasure–reward emotional systems within the developing brain. The pleasure/reward circuit in rodents is remarkably similar to that found in the human (Russo and Nestler 2013; Der-Avakian and Markou 2012; Nestler 2015), comprised of connectivity between the VTA, NAc, PFC, amygdala, and the hippocampus. The FRAG model appears to disrupt this circuit at a number of nodes, including the amygdala, hippocampus, frontal cortex, and NAc. First, we have recently reported that FRAG produces altered connectivity in adolescent rats between the medial PFC and amygdala as measured by diffusion tensor imaging (DTI) (Bolton et al. 2018). The anhedonia phenotype in the FRAG model is reversed by transcriptional suppression of corticotropin releasing hormone (CRH) signaling in the amygdala, suggesting that augmented CRH release from amygdala-centered cell bodies is required for anhedonia associated with FRAG exposure. Another group recently examined FRAG effects on resting

state fMRI of the reward circuit in adults, reporting reduced connectivity between the PFC and caudate putamen in FRAG exposed rats compared to controls (Yan et al. 2017). Finally, in the FRAG model of early life adversity, there is a significant loss of hippocampal dendritic arborization and volumes as well as increased fractional anisotropy (FA – a measure of structural integrity derived from DTI) in the hippocampus (Molet et al. 2016b). These hippocampal effects of FRAG also have real functional consequences. We have recently reported that FRAG across both humans and rodents, as measured by entropy of maternal interactions with offspring, is associated with poor performance in hippocampus-dependent memory tasks in later life (Davis et al. 2017; Molet et al. 2016b). Importantly, low hippocampal volume is a robust phenotype in PTSD, and both twin and prospective studies indicate that reductions in hippocampal function and structure are risk factors for development of PTSD [for review, see (Acheson et al. 2012; Logue et al. 2018; van Rooij et al. 2017)]. In rodents, high hippocampal FA correlates with susceptibility to chronic social defeat stress (Anacker et al. 2016), suggesting that across species, developmental effects on hippocampal circuits and functions may play a role in trauma susceptibility.

6 Conclusions and Future Research Directions

There is clear evidence for anhedonia and reward disruption in PTSD, but if these symptoms develop after trauma or contribute to pre-trauma risk is still very unclear. There are hints from the depression field and our own preliminary data in the MRS that adolescent anhedonia may be predictive of later risk for depression and PTSD. Childhood adversity is robustly linked to PTSD risk and anhedonia, but the specific early life experiences that contribute to this risk are not well understood. The FRAG model of early life adversity in both animals and humans suggests that anhedonia in adolescence/early adulthood can be a consequence of chaotic sensory and maternal signals during development. First, entropy of maternal mood during pregnancy influences mood and anxiety of her children at ages 10–13 (Glynn et al. 2017). In rodents, FRAG is robustly linked to increased anhedonia-like behaviors in adolescence with concurrent alterations in reward circuits (Bolton et al. 2018; Glenn et al. 2017). As discussed above, mood in adolescence is important an predictor of neuropsychiatric disorders in adulthood (Carlson and Pataki 2016; Hofstra et al. 2002; Copeland et al. 2014). Second, FRAG, as assessed by observing entropy of maternal interactions with infants in both rodents and humans, is associated with reductions in hippocampal function in later life (Davis et al. 2017). Hippocampal function has emerged as an important risk factor for the development of trauma disorders (Acheson et al. 2012; Glenn et al. 2017) and may provide an additional mechanism through which FRAG could contribute to PTSD risk. Clearly, research is required to understand the developmental trajectory of FRAG effects on circuit development, and most importantly, its contribution as an independent risk factor for trauma disorders. To begin to answer these questions, our group has developed novel measures in humans to operationalize FRAG: (1) in utero via entropy of maternal mood (Glynn et al. 2017), (2) in early life via observational studies of predictability of maternal care (Davis et al. 2017), and (3) in later life via a retrospective self-report instrument to document past FRAG exposure for use in adult populations such as in the MRS. These complementary measures of FRAG will support efforts to integrate studies across age groups and high-risk populations to identify the developmental trajectory

of FRAG effects on reward circuits and subsequent anhedonia, and their contribution to adult trauma disorders.

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