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2015 ADAA SCIENTIFIC RESEARCH SYMPOSIUM

Psychobiology of the intersection and divergence of depression and anxiety

Mounting evidence highlights substantial genetic, neurobiological, and symptomatic overlap between depression and anxiety disorders, suggesting that current classification systems do not "carve nature at its joints." Stemming from this is a notable lack of precision in treatment selection, and frontline treatments for depression and anxiety disorders fail to relieve symptoms in many patients. For example, up to 50% of individuals with major depression failed to respond to antidepressant treatments, and only one in three patients achieved remission (full recovery) within the nationally representative Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Trivedi et al., 2006). Response rates for psychotherapy (e.g., cognitive or behavioral therapies) show similar patterns, with about 50% of individuals with major depression (Cuijpers et al., 2014) or anxiety (Loerinc et al., 2015) displaying a beneficial response. As outlined in a series of recent reviews (e.g., Hyman, 2010; Insel et al., 2010; Pizzagalli, 2014), there are several reasons for the modest success in treating these prevalent and debilitating disorders. These include a high degree of comorbidity (reaching to up 75% in clinical samples [e.g., Sørensen, Nissen, Mors, & Thomsen, 2005]), the considerable heterogeneity of diagnostic syndromes as conceptualized by current classification systems (e.g., Diagnostic Statistical Manual, International Classification of Diseases), and an incomplete understanding of the pathophysiology and etiology of depression and anxiety disorders. Together, these constitute a formidable barrier to treatment development and implementation.

To address these challenges and also highlight exciting new developments, the Scientific Research Symposium held during the 2015 Annual Meeting of the Anxiety and Depression Association of America (ADAA) was centered on the psychobiology of the intersection and divergence of depression and anxiety. The goal of this symposium was to feature and integrate recent advances in our understanding of the pathophysiology, manifestation, course, and treatment of depression and anxiety disorders. In particular, through a "bench to bedside approach" that emphasized cross-species convergence, integration of different levels of analysis (e.g., molecules, brain circuitry, behavior, self-report), consideration of developmental trajectories, and a focus on well-characterized phenotypes that cut across diagnostic boundaries (e.g., reward and threat sensitivity, fear extinction), this symposium aimed to highlight major advances that are illuminating shared and unique features of depression and anxiety and identifying novel targets for treatments. All symposium speakers submitted review or empirical papers for the current special issue. In this editorial, I provide a brief synopsis of each contribution, highlight areas of intersection and synergies, and underscore unanswered questions that should be addressed in future research.

1 | KAPPA OPIOID ANTAGONISTS AND STRESS-INDUCED NEUROADAPTATION

Incomplete understanding of the pathophysiology of depression and anxiety disorders has represented a major challenge along the path toward discovering new therapeutics, and serendipity has often played a key role in drug development. Half a century ago, a number of compounds developed for certain medical conditions, such as the antitubercular agent isoniazid, were found to have antidepressant effects. Further studies on the pharmacological effects of these drugs gave rise to monoaminergic theories of depression, which have dominated theories and treatments for depression for decades. As summarized by Carlezon and Krystal, growing interest in kappa opioid receptors (KOR) antagonists for depression and anxiety disorders arose *after* elucidating their effects on molecular pathways critically implicated in stress-induced neuroadaptation (rather than after establishing their clinical efficacy in humans). Specifically, elegant preclinical studies have produced convincing evidence that stress induces an increase in CREB (cAMP response element binding protein), which in turn elevates the expression of the opioid peptide dynorphin in the nucleus accumbens. As KOR are expressed on ventral tegmental area neurons, KOR activation by dynorphin inhibits dopamine release, inducing depression- and anxiety-like symptoms. Blockage of KOR has been found to block dynorphin action, restore dopamine function, and produce antidepressant and anxiolytic effects. Although more research is needed, evidence from preclinical models suggests that the efficacy of KOR antagonists on both anxiety and depressive behaviors may be explained by their ability to reduce or even block the effects of stress. If the stress-mitigating effects found in preclinical models extend to humans, this would afford an enticing opportunity to deploy preventive treatments in individuals at risk for stress-related disorders (e.g., PTSD in soldiers or first responders). Moreover, KOR antagonists' ability to restore mesolimbic function (thereby counteracting anhedonia-like behaviors) and mitigate the effects of stress, makes it an especially promising candidate for the treatment of stress-mediated syndromes. In line with this notion, an ongoing multisite study funded by the National Institute of Mental Health (Fast-Fail Trials in Mood and Anxiety Spectrum Disorders, FAST-MAS) is using a Proof of Concept approach to test the hypothesis that a KOR antagonist will reduce anhedonia and normalize reward-related mesolimbic abnormalities across the mood and anxiety spectrum disorders.

2 | BRAIN-DERIVED NEUROTROPHIC FACTOR AND FEAR LEARNING

Even more well-established than the role of abnormal reward processing in anhedonia, is the critical role that abnormal fear learning

plays in theoretical accounts of anxiety (e.g., Milad & Quirk, 2012). For decades we have known that brain-derived neurotrophic factor (BDNF) is pivotally implicated in the regulation of neural differentiation and synaptic plasticity, and ultimately, learning and memory. Building on recent findings from their laboratory, which focus on a human genetic BDNF SNP (Val66Met) knock-in mouse model, Dincheva, Lee and colleagues summarize an innovative body of work showing that BDNF shapes fear learning and fear circuitry in a developmentally fine-tuned fashion during the transition from childhood to adolescence. In particular, these and other studies reveal that in both humans and rodents, fear extinction learning and retention are attenuated during adolescence relative to childhood and adulthood. In rodents, poorer fear extinction during adolescence has been linked to reduced plasticity within the infralimbic cortex, which is critical for the suppression of conditioned fear responses. This temporal specificity is particularly interesting when considering epidemiological data indicating that human anxiety and related disorders peak during childhood and adolescence (Kessler et al., 2005). Collectively, these findings indicate that adolescence—a developmental period characterized by a surge in rates of anxiety and depression—is associated with reduced synaptic plasticity in the prefrontal cortex and diminished regulation of fear extinction.

The potential implications of this work are manifold. First, identification of sensitive periods may open a window of opportunity to normalize fear-related behaviors, which might boost treatment efficacy. Second, these data highlight limitations of current therapeutic interventions, since treatments are often developed and evaluated in adult subjects and then adapted to younger samples. A disregard for development trajectories of fear learning and circuitry might greatly diminish clinical outcomes among youth struggling with anxiety and related disorders. Third, in light of the fact that BDNF can be profoundly blunted by environmental and physiological stressors, future studies should investigate across species how early adversity that occurs during particular sensitive periods might drive abnormal BDNF-mediated plasticity in regions that play a pivotal role in anxiety and fear responses, such as the amygdala, hippocampus, and prefrontal cortex. Notably, a recent functional neuroimaging study showed that early adversity (being institutionalized and exposed to maternal deprivation) was associated with negative coupling between the amygdala and medial prefrontal cortex (PFC), a pattern opposite from the positive amygdala–medial PFC coupling observed in youth not exposed to early adversity (Gee et al., 2013).

3 | AMYGDALA–PFC CONNECTIVITY IN ANXIETY

Extending similar themes to humans, and building on a large body of preclinical and imaging literature emphasizing an amygdala–ventromedial prefrontal cortex (vmPFC) circuit in the acquisition, expression, and extinction of fear (Milad & Quirk, 2012), Gold, Pine and colleagues used functional magnetic resonance imaging (fMRI) to investigate anxiety- and development-related abnormalities in amygdala–PFC connectivity across three different task conditions. The study tested four groups—anxious youth, healthy youth, anxious adults, healthy adults—and involved two separate sessions. In the first, participants underwent a fear acquisition phase, followed by fear extinction. Approximately 20 days later, the same participants performed an extinction recall task, where they were asked to make threat–safety discriminations related to the CS+ and CS−. Critically, discrimination decisions were made under three attention conditions: threat appraisal (probing subjective fear), explicit threat memory (probing memories for the CS), and physical discrimination (probing physical characteristics of the stimuli). When using the left amygdala as a seed for psychophysiological interaction (PPI) analyses, Gold and colleagues found two clusters in the vmPFC characterized by anxiety-, task-, and development-specific effects. Follow-up analyses showed that relative to the physical discrimination condition, the threat appraisal and explicit threat memory conditions elicited opposite patterns of amygdala–vmPFC connectivity in anxious youth (negative connectivity) versus anxious adults (positive connectivity). Taken together, these data suggest that across youth and adults, the same phenotype (clinical anxiety) is characterized by opposite patterns of functional connectivity between two key nodes implicated in fear acquisition and extinction, highlighting important developmental trajectories.

A key unanswered question is whether this information could be harnessed to guide the development of new treatments or boost the efficacy of current treatments (in particular, exposure-based or cognitive behavior treatments). For example, would interventions aiming to normalize *negative* amygdala-vmPFC functional connectivity (e.g., through neurofeedback, transcranial magnetic stimulation, or cognitive training) have therapeutic effects among anxious youth but not anxious adults? And conversely, would anxious adults benefit from interventions that normalize *positive* amygdala–vmPFC functional connectivity? Given that many anxious youth do not become anxious adults (Pine, Cohen, Gurley, Brook, & Ma, 1998), developing novel ways for redirecting developmental trajectories toward well-being would be a major breakthrough. In addition, the specificity of these findings with respect to task conditions highlights the importance of engaging mechanisms that are immediately relevant to the clinical condition under investigation. Specifically, by asking participants to appraise or remember a previously learned threat—but not focus on basic physical characteristics of the stimuli—Gold and colleagues were able to uncover differences between anxious and psychiatrically healthy participants, and also between anxious youth and anxious adults. Finally, although the findings reported by Gold and colleagues highlight important development-specific dysregulation within the fear circuitry, it remains unknown whether such abnormalities are the cause or consequence of anxiety. Prospective studies in unaffected individuals at increased risk for anxiety disorders (e.g., young offspring of individuals with emotional disorders) will be needed to identify putative biomarkers associated with increased vulnerability to anxiety disorders.

4 | ADVANCING PREVENTION AND INTERVENTION STRATEGIES IN DEPRESSION AND ANXIETY

Another important issue that needs to be addressed is the lack of effective treatments available for symptoms of anhedonia. Current psychological and pharmacological interventions are generally focused on reducing negative affect rather than restoring positive affect and hedonic drive. However, low positive affect and anhedonia are known be an important symptom and risk marker for depression and anxiety disorders (Pizzagalli, 2014; Prenoveau et al., 2010), as well as a significant barrier to treatment engagement. In this context, Craske and colleagues make a case for developing novel treatments for anhedonia and introduce a new intervention (coined positive affect treatment [PAT]), which was specifically designed to target reward processing subcomponents (and associated neural circuitry) in a cross-diagnostic fashion. There are several noteworthy aspects of their argument. First, and consistent with conceptualizations of anhedonia emerging from the fields of affective and behavioral neuroscience (e.g., Der-Avakian & Markou, 2012; Pizzagalli, 2014; Treadway & Zald, 2013), these authors point out that anhedonia is not a unitary construct but can be decomposed into psychologically and neurobiologically distinct subcomponents, including reward anticipation, reward consumption, and reward learning. Critically, these subcomponents are supported by partially nonoverlapping neural circuitries and neurotransmitters, and have distinct behavioral and cognitive manifestations. Second, growing evidence indicates that these subcomponents of reward processing and their associated neural circuitry are dysregulated across a variety of disorders including depression, anxiety, schizophrenia, and substance abuse (e.g., Barch, Pagliaccio, & Luking, 2016; Koob, 2013; Whitton, Treadway, & Pizzagalli, 2015). A particularly attractive feature of PAT, which is nicely aligned with NIMH's experimental medicine approach, is that it lends itself to identification and verification of therapeutic targets. If the current version of PAT does not drive changes in self-report, behavioral, and/or neural markers of different reward processing subcomponents, revisions of the treatment will be needed. Refreshingly, these modifications can be implemented in the context of a rich psychological, behavioral neuroscience, and affective neuroscience literature, and thus can be rooted in empirical data. Initial findings, including significant increases in positive affect after PAT, especially in individuals with low baseline levels of positive affect, are promising (Craske et al., this issue).

Owing to the high degree of comorbidity of depression and anxiety and their putatively shared etiology, Garber and colleagues present a timely meta-analysis investigating whether evidence-based psychological treatments developed to specifically treat or prevent depression *or* anxiety in children and adolescents might have cross-over effects (i.e., benefit also the other disorder). Several notable results emerged: for both randomized controlled trials (RCTs) for anxiety (18 studies) and depression (nine studies), significant beneficial effects were observed for both disorders, albeit stronger for the target disorder (e.g., depression in RCTs for depression), highlighting both cross-over effects and specificity. For anxiety prevention (14 studies), anxiety—but not depression—was ameliorated, highlighting no cross-over effects. For depression prevention (15 studies), no effects were seen for either disorder, although post hoc analyses revealed that the effects on depression (but not on anxiety) emerged for targeted (but not universal) samples.

These findings have several important implications for the development of trans-diagnostic interventions. Although none of the treatment protocols included in the Garber and colleagues' meta-analysis was developed to be trans-diagnostic, they showed beneficial effects on both disorders, possibly because they acted on shared mechanisms (e.g., negative maladaptive cognition). By improving our understanding of etiological and psychopathological mechanisms underlying shared risk for depression and anxiety (e.g., negative affectivity, behavioral avoidance), it is expected that truly trans-diagnostic interventions could be particularly efficacious. Further, prevention studies were largely ineffective in universal samples, whereas they showed promising findings in targeted (e.g., at-risk youth) samples. If replicated, these findings might be used to prioritize resources and thus, target individuals who would benefit most.

5 | CONCLUSION

Investigation, treatment, and prevention of depression and anxiety disorders remain a challenge. The current special issue highlights both substantial advances in our understanding of the potential causes of these prevalent disorders, as well as promising leads for the development of more effective interventions. In particular, by leveraging cross-species convergence and integrating different levels of analysis, considering developmental trajectories and potential sensitive periods, and focusing on well-characterized trans-diagnostic phenotypes, contributions in the current special issue pave the way for a fundamental improvement in our understanding of the etiology of depression and anxiety disorders. This represents a crucial step toward developing better treatment strategies, as well as highlighting new opportunities for the implementation of targeted and personalized intervention.

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REFERENCES

Barch, D. M., Pagliaccio, D., & Luking, K. (2016). Mechanisms underlying motivational deficits in psychopathology: Similarities and differences in depression and schizophrenia. *Current Topics in Behavioral Neurosciences*, *27*, 411–449.

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. *Journal of Affective Disorders*, *159*, 118–126.

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences*, *35*, 68–77.

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., Telzer, E. H., … Tottenham, N. (2013). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 15638–15643.

Hyman, S. E. (2010). The diagnosis of mental disorders: The problem of reification. *Annual Review of Clinical Psychology*, *6*, 155–179.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*, 748–751.

Kessler, R. C., Demler, O., Frank, R. G., Olfson, M., Pincus, H. A., Walters, E. E., … Zaslavsky, A. M. (2005). Prevalence and treatment of mental disorders, 1990 to 2003. *New England Journal of Medicine*, *352*, 2515–2523.

Koob, G. F. (2013). Theoretical frameworks and mechanistic aspects of alcohol addiction: Alcohol addiction as a reward deficit disorder. *Current Topics in Behavioral Neurosciences*, *13*, 3–30.

Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske, M. G. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clinical Psychology Review*, *42*, 72–82.

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology*, *63*, 129–151.

Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry*, *55*, 56–64.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393–423.

Prenoveau, J. M., Zinbarg, R. E., Craske, M. G., Mineka, S., Griffith, J. W., & Epstein, A. M. (2010). Testing a hierarchical model of anxiety and depression in adolescents: A tri-level model. *Journal of Anxiety Disorders*, *24*, 334–344.

Sørensen, M. J., Nissen, J. B., Mors, O., & Thomsen, P. H. (2005). Age and gender differences in depressive symptomatology and comorbidity: An incident sample of psychiatrically admitted children. *Journal of Affective Disorders*, *84*, 85–91.

Treadway, M. T., & Zald, D. H. (2013). Parsing anhedonia: Translational models of reward-processing deficits in psychopathology. *Current Directions in Psychological Science*, *22*, 244–249.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., … Fava, M. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *American Journal of Psychiatry*, *163*, 28–40.

Whitton, A. E., Treadway, M. T., & Pizzagalli, D. A. (2015). Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry*, *28*, 7–12.