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Enhancing Efficacy of PTSD Treatment: Role of Circuits, Genetics and Optimal Timing

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Enhancing Efficacy of PTSD Treatment: Role of Circuits, Genetics and Optimal Timing

Current treatment approaches for posttraumatic stress disorder (PTSD) include the use of medications, psychotherapy, or a combination of both, but they are limited in their effectiveness as only some have access to, or are able to tolerate exposure therapy, and pharmacotherapy is largely nonspecific, and only partially effective. As PTSD incurs substantial cost both to individuals (e.g., disruptions in daily life functioning, health status, and well-being), and to society (with elevated rates of substance use, hospitalization and suicidal behavior), the development of more effective pharmacological treatments is critical, and requires a better understanding of the neurobiological mechanisms implicated in the pathogenesis of PTSD. Kelmendi, Adams, Southwick, Abdallah, and Krystal (2017) provide a comprehensive review of neurotransmitter systems implicated in PTSD, and highlight that the understanding of neurotransmitters and the modulatory systems involved is essential for sophisticated use of pharmacotherapy in PTSD. It is important, however, to take into consideration that neurotransmitter "abnormalities" occur within an anatomical/functional context, i.e., within specific neural circuits, that perform specific functions, and thus lead to specific symptoms. For example, exaggerated norepinephrine (NE) in the amygdala might lead to one symptom, but exaggerated NE secretion in the hippocampus or prefrontal cortex might lead to a different set of symptoms. Thus, understanding the role of neural circuits involved in different intermediate phenotypes and disorder subtypes (Liberzon & Abelson, 2016) will be critical for designing more specific treatment approaches. Further, the fact that dysfunction in neurotransmitter systems can be affected by an individual's genetic factors has been gaining increased attention, and related concepts have led to the development of "personalized medicine" in other fields, such as cancer therapy. Certain genotypes, or epigenetic processes, such as DNA methylation, or histone acetylation, can not only constitute risk or resilience factors for PTSD development, but may also serve as the biomarkers of outcomes of specific treatments. Kelmendi et al. (2017) briefly mention the role of individual genetic profiles, in the context of limited efficacy and lack of specificity of available PTSD treatments, but we believe these important topics deserve further attention, as they have critical implications for clinical practice. We also mention another important factor that was not directly addressed in the review by Kelmendi et al., but we believe should be considered in developing effective treatment approach, which is the timing of an intervention, within the dynamics of PTSD development.

Neurocircuitry-Based Models of PTSD: Representing Altered Brain Functions and Different Intermediate Phenotypes

As noted by Kelmendi et al. (2017), dysregulations on anatomical level lie within distinct neural systems. Advances in affective neuroscience in the last decade have unveiled specific neural systems (neurocircuits) implicated in PTSD development, as well as some of the underlying molecular/cellular mechanisms involved. These include fear learning (FL), threat detection (TD), emotion regulation (ER) and context processing (CP) systems. These dedicated systems/circuits serve distinct brain functions, and are associated with subsets of biological abnormalities that are likely to explain different aspects of PTSD. Liberzon and Abelson (2016) also suggested that FL, TD, ER and CP might correspond to specific PTSD subtypes if PTSD indeed represents a collection of somewhat distinct neurobiological entities. Understanding of neurocircuits, and underlying mechanisms involved in them, may be useful for developing a more specific and personalized treatment approach; a specific treatment (e.g., medication, therapy, or a combination of both) can be chosen based on the dominant phenotype in a given patient, which will in turn enhance the effectiveness of the chosen treatment.

Neural Circuits: Brain Regions and Functions.

Among these, FL circuitry governs fear acquisition, fear extinction, and fear generalization. PTSD is characterized by a diminished ability to learn that something once dangerous is now safe (i.e., altered fear extinction), and to discriminate between dangerous and safe cues (i.e., overgeneralization pattern). More specifically, these processes involve the basolateral complex of the amygdala (BLC), which receives sensory information (input) from the thalamus, and is where fear/safety learning takes place. The amygdala and BLC sub-networks are interconnected with ventral medial prefrontal cortex (vmPFC) and the hippocampus, and in work in conjunction to regulate fear/extinction learning. Indeed, impaired extinction recall in PTSD is manifested in hyperactivation of amygdala and hypoactivation of mPFC, raising the possibility that the fear learning deficit in PTSD might stem from extra amygdala regulatory regions (Liberzon & Abelson, 2016).

TD circuitry governs the more general ability to detect salient cues in the environment, whether positive or negative, and TD abnormalities could lead to hypervigilance, preferential processing of trauma cues, and more. Insula/operculum, dorsal Anterior Cingulate (dACC) and amygdala are key structures in TD circuitry, with dACC participating in error and conflict

detection, while insula is linked to anticipation and monitoring the internal states. Together these highly interconnected regions constitute a Salience Network (SN), a circuit that is responsible for detecting and orienting to salient stimuli. Indeed, PTSD is associated with attentional bias toward threat, and with increased connectivity within SN, and is also associated with hyperactivation of insula, amygdala, and dACC on various tasks.

ER circuitry encompasses one's ability to modulate emotions (responses to stimuli) by engaging higher cognitive/executive function (EF), like redirecting attention away from emotional stimuli, or deploying different strategies such as cognitive reappraisal, distancing, or suppression of emotion. ER circuitry includes prefrontal cortical regions: dorsolateral, ventrolateral, lateral orbifrontal, dorsomedial PFC as well as dACC. PTSD is characterized by exaggerated emotional responses, heightened impulsivity, and irritability that can arise if ER circuitry is dysfunctional. Indeed, PTSD has been associated with diminished ability for cognitive reappraisal and has been linked to decreased activation of dorsolateral and dorsomedial PFC. Specific cellular and molecular mechanisms that might lead to deficits in TD and ER circuits need to be identified in order to better understand their contribution to PTSD symptoms, and to facilitate approaches to treatment.

CP circuitry is responsible for representation and retrieval of more general information in the environment, and modulates our responses to a particular cue to best fit the current situation. CP also "supports" fear conditioning and fear extinction by guiding our responses to the cue, based on the context within which cue occurs. In PTSD, deficits in CP could lead to dominance of fear over safety memories, or hypervigilance. The hippocampus is a key structure implicated in CP, and is thought to be responsible for context encoding. The hippocampus is connected with mPFC, which also plays a significant role in the context processing (and consequently, in fear learning, extinction and memory consolidation). More specifically, mPFC is responsible for learning associations between context and corresponding adaptive responses, particularly emotional responses. PTSD is associated with hypoactivity of vmPFC and hippocampus, as well as diminished connectivity between the regions. Glucocorticoid signaling in the hippocampus as well as glutamatergic transmission in prefrontal regions might be involved in context processing deficits.

Understanding of the aforementioned neural circuits and mechanisms involved creates an opportunity to develop treatments that targets these circuits. For example abnormalities in FL

circuity can be targeted by combining exposure therapy and cannabinoids. Exposure therapy enhances the process of fear extinction, while cannabinoids can facilitate extinction memory formation. CP circuitry deficits (specifically, hypoactivation of mPFC) could be amenable to glutamatergic transmission modulation (for instance, ketamine administration) in combination with contextual processing "retraining". Disruption in hippocampal function, which impairs contextual processing, might be responsive to neuro- or synaptogenesis enhancing agents or behaviors (novelty/exercise). Dysfunction within ER circuity might be treated by psychotherapeutic approaches that practice emotional regulation strategies, or by agents such as paroxetine, which has been shown to increase recruitment of prefrontal regions. Thus, while we agree with the authors that identification of "subtypes" of PTSD can improve treatment approaches, a more granular understanding of neural circuits involved will be required for the development of "personalized" treatment, which targets a dominant phenotype and altered neural circuitry, in an individual patient.

Genetic Factors and PTSD Treatment.

The genetic risks factors for PTSD development are still unknown, (although major international collaboration is underway to uncover genetic architecture of PTSD) and current treatment approaches to PTSD are yet to include genotype-based precision medicine, currently used in other medical specialties. The statement by Kelmendi et al. (2017) that "limited efficacy of SSRIs in the treatment of PTSD must be understood in terms of variable individual genetic profile" (p.) is appropriate, and we argue that genetic aspects in PTSD treatment deserve further elaboration. If we are to learn from our colleagues in medical sub-specialties, an understanding of an individual's genotypes has the potential to significantly treatment selection and can therefore enhance the effectiveness of an intervention. As genotyping becomes more affordable, our field can rapidly capitalize on this progress, and we can use genotyping in clinical trials.

Genetics and Treatment Response

Some specific examples of genetic factors in PTSD pharmacotherapy involve genetic variants in: 1) 5-HTTLPR - serotonin-transporter-linked polymorphic region, which is involved in serotonin secretion and linked to amygdala activation, 2) BDNF (brain-derived neurotrophic factor), involved in hippocampal neurogenesis, synaptic plasticity, and thus, memory consolidation and learning, and 3) FKBP5 glucocorticoid receptor chaperon protein that together with hear shock proteins participates in glucocorticoid receptor transport to the nucleus, and thus,

can affect glucocorticoid sensitivity. Bryant and colleagues (2010) reported that LL carriers of 5-HTTLPR respond more favorably to sertraline treatment and to CBT compared to S allele carriers. If, as suggested, the 5-HTTLPR S allele is associated with reduced efficiency of the serotonin transporter protein and hyperactivation of amygdala, S carriers might have more difficulty implementing adaptive fear-related processing necessary for treatment. Similarly, it was reported that the Met allele carries (Met/Met and Val/Met genotypes) of the BDNF gene, respond less favorably to CBT than the Val allele carriers, potentially due to differential BDNF secretion in the hippocampus. Finally, the T-allele carriers of the FKBP5 genotype, which has been linked to increased glucocorticoid receptor sensitivity and lower cortisol responses, respond less favorably to Narrative Exposure Therapy (NET) (Wilker et al., 2014). As NET involves trauma memory exposure, shortened cortisol response might alter fear extinction efficacy. Here the differences in therapy outcomes were noted after 10 months, but not immediately post-treatment, highlighting the importance of the time-dependent dynamics in this process. Finally, initial evidence of epigenetic effects on PTSD treatment has been emerging with Yehuda et al. (2013) reporting that higher pre-treatment glucocorticoid receptor (GR) promoter exon 1F promoter methylation predicts positive treatment response to prolonged exposure psychotherapy. Although these all are preliminary findings in small samples that require replication, we believe they herald the arrival of genotype-based precision medicine to psychiatry in general and PTSD in particular, in the near future.

Optimal Timing and Temporal Dynamics of PTSD Development

In addition to identifying and targeting intermediate phenotypes, or to implementing genotype-based treatment selection procedures, it might also be useful to consider both the temporal dynamics of PTSD development, as well as optimal timing for a particular treatment. With respect to PTSD development, several stages can be identified: (1) preexisting vulnerability stage (genetic or environmental risks), when prevention strategies that limit trauma exposure for vulnerable individuals, or resilience enhancement can take place; (2) early post-trauma exposure, when fear learning/safety consolidation take place, which allows for an opportunity for secondary prevention, and (3) disorder stage, when the full PTSD phenotype is expressed, and treatment of PTSD-specific pathophysiology can occur. Treatment efficacy will depend on the match between the drug's mechanism of action and the specific pathophysiologic process taking place at the time of administration. Thus, effective treatment approaches to these various stages

will likely differ, with pharmacotherapy relevant mainly to the two later stages. Temporal aspects might be even important within a particular stage – for example, the use of the beta blocker (adrenoreceptor beta) propranolol to weaken consolidation of trauma memories, which involves a time window of 6 hours following trauma exposure for administration to take place. Although the use of propranolol is still debated and under investigation, these examples highlight the potential importance of considering temporal dynamics in pharmacotherapeutic approaches to PTSD. Due to limited efficacy of current treatment practices and the high individual and societal costs of PTSD, designing more effective treatment approaches is crucial. The review by Kelmendi et al. (2017) provides an analysis of neurotransmitter systems, and the alterations found in these systems in PTSD, which is essential for the development of effective pharmacological agents. In this commentary, we discuss three additional considerations that are likely to improve current treatment practices. These involve the consideration of neural circuits that can shape specific subtypes of PTSD or highlight involvement of specific systems in a given patient, the consideration of known genetic factors that will likely improve treatment selection in the near future, and lastly, consideration of temporal aspects of both the pathophysiology and the treatment administration.

References

Bryant, R. A., Felmingham, K. L., Falconer, E. M., Benito, L. P., Dobson-Stone, C., Pierce, K.D.,
    & Schofield, P. R. (2010). Preliminary evidence of the short allele of the serotonin
    transport gene predicting poor response to cognitive behavior therapy in posttraumatic
    stress disorder. *Biological Psychiatry*, 67(12), 1217-1219.
    doi:10.1016/j.biopsych.2010.03.016

Kelmendi, B., Adams, T.G., Abdallah, C.G., Southwick, S., & Krystal, J.H. (2017). Posttraumatic
    Stress Disorder: An integrated overview and neurobiological rationale for pharmacology.
    Clinical Psychology: Science and Practice, 24(1). This issue

Liberzon, I., & Abelson, J. L. (2016). Context processing and the neurobiology of post-traumatic
    stress disorder. *Neuron*, 92(1), 14-30. doi:10.1016/j.neuron.2016.09.039

Wilker, S., Pfeiffer, A., Kolassa, S., Elbert, T., Lingenfelder, B., Ovuga, E., … Kolassa, I. T.
    (2014). The role of FKBP5 genotype in moderating long-term effectiveness of exposure-
    based psychotherapy for posttraumatic stress disorder. *Translational Psychiatry*, 4(6), 1-7.
    doi:10.1038/tp.2014.49

Yehuda, R., Daskalakis, N. P., Desarnaud, F., Makotkine, I., Lehrner, A., Koch, E… Bierer, L. M.
    (2013). Epigenetic biomarkers as predictors and correlates of symptom improvement
    following psychotherapy in combat veterans with PTSD. *Frontiers in Psychiatry*, 4, 1-14.
    doi:10.3389/fpsyt.2013.00118