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Preface

The Tenth Annual Amygdala, Stress, and PTSD Conference: “The Amygdala: Dysfunction, Hyperfunction, and Connectivity”

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The *Amygdala, Stress, and Posttraumatic Stress Disorder (PTSD) Conference*, often referred to simply as *The Amygdala Conference*, is a continuing education conference held each April at the Uniformed Services University (USU) and sponsored by The Center for the Study of Traumatic Stress in collaboration with the USU Department of Psychiatry, USU Neuroscience Program, USU Department of Family Medicine, and The Walter Reed National Military Medical Center Department of Psychiatry. Free and open to the public, this conference brings together nationally and internationally recognized scientists and clinicians to help support the translation of high-quality science into excellent clinical care.

Dedicating an entire conference to the amygdala stems from its neurobiological importance. The amygdala, a pair of almond-shaped clusters of nuclei located medially and deep in the temporal lobe, is a complex structure with variable processes and connections. Adding an additional level of complexity is its internal physiology, which varies between nuclei (Sah et al., 2003). The alterations in these processes as well as the internal physiology are fundamentally important to understanding a range of disorders, which can cause substantial suffering, including increased morbidity and mortality among a wide range of individuals, as well as having substantial impact on families and their communities.

The amygdaloid complex comprises approximately 13 nuclei, including the basolateral complex, medial nucleus, cortical nucleus, central nucleus, and intercalated cell clusters (Krettek and Price, 1978; Lang and Pare,

1998). Each nucleus receives inputs from multiple, yet distinct, brain regions but also has extensive intranuclear and internuclear connectivity. Efferent projections from the amygdala are widespread and include both cortical and subcortical regions (McDonald, 1998; Pitkanen, 2000). The amygdala as a whole comprises primarily glutamatergic pyramidal neurons and, to a lesser extent, GABAergic inhibitory interneurons. However, as in the case of the basolateral complex, GABAergic activity

SIGNIFICANCE

The amygdala is an intensely studied brain structure that plays an essential role in emotional processing and mental illness. Recent investigations have revealed the amygdala's involvement in many disorders beyond anxiety and fear-related disorders, including epilepsy, autism, fragile X disorder, schizophrenia, Urbach-Wiethe disease, and psychopathy. The *Amygdala, Stress, and PTSD Conference*, an annual conference held at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, highlights the amygdala and serves as an ongoing effort to resolve the biological basis of stress, fear, and PTSD. In this inaugural Special Issue, we bring together a collection of articles from past speakers at the *Amygdala, Stress, and PTSD Conference*, as well as from scientists studying the amygdala, to emphasize its role in a variety of disorders. Our goal is to highlight the importance of the amygdala and its regulation in ameliorating symptoms associated with a variety of neurological and neuropsychiatric disorders.

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predominates, leading to extremely low levels of spontaneous activity (McDonald, 1992; Pare et al., 1995; Pare and Gaudreau, 1996; Mahanty and Sah, 1998; Pare and Smith, 1998).

The amygdala plays a pivotal role in emotional memory processing and, in particular, the processing of fear-provoking experiences (Duvarci and Pare, 2014; Janak and Tye, 2015). Recent evidence, however, has revealed a more essential role for the amygdala than was previously thought. Indeed, excess acetylcholine (ACh) in the amygdala, resulting from the loss of acetylcholinesterase, the catalyzing enzyme for ACh, results in seizure generation after exposure to the nerve agent soman (Prager et al., 2013). Furthermore, excessive activation of the amygdala may contribute to the cluster of PTSD symptoms, including hypervigilance, intrusive memories, and impaired sleep (Diamond and Zoladz, 2016). Alternatively, a failure of the amygdala to function properly may be central to the development of Urbach-Wiethe disease, which impairs fear responses and emotional memory processing (Koen et al., 2016).

The complexity of the amygdala has understandably resulted in an impressive array of invaluable research with strong clinical implications. The 2014 and 2015 *Amygdala Conference* themes were from “Bench to Bedside” and “Of Mice and Man,” respectively. The significance of these 2 years, in particular, was the emphasis of translational research and clinical application. In 2014, Joshua Corbin, Alexander Crawford, and Israel Liberzon were among the speakers. Their talks emphasized animal models as well as translational implications in understanding specific disorders. For example, Dr. Corbin spoke about the role of the amygdala in fragile X syndrome, a neurodevelopmental disorder, and Dr. Crawford’s talk emphasized the use of zebrafish as a model for exploring the role of the amygdala in emotional memory and motivational behavior. Dr. Liberzon spoke about contextual processing in PTSD in animal models and in humans.

In 2015, a more clinical and holistic approach to understanding the role of the amygdala in health and disease was highlighted. Dr. Jacek Debiec provided strong evidence that offspring learn adaptive and maladaptive behaviors, such as anxiety, from their parents and that this may lead to significant increases in amygdala activity. Dr. Abigail Marsh reviewed various theories concerning the role of the amygdala in perceiving fearful expressions and explained how dysfunction in the amygdala may be associated with an inability to recognize others’ fear, while Dr. Daniel Stein spoke of trauma and PTSD in South Africa. Dr. Harvey Pollard reviewed how the amygdala might act as a network hub and explained what changes in this network reveal about normal and pathological conditions.

After concluding last year’s *Amygdala Conference*, we realized that, to facilitate the translation of high-quality science into excellent clinical care, we had to reach an audience beyond the conference attendees. Therefore, as part of the tenth anniversary of the *Amygdala Conference*, we collaborated with the *Journal of Neuroscience Research* to

create this Special Issue entitled “The Amygdala: Dysfunction, Hyperfunction, and Connectivity.”

In compiling this Special Issue, we asked prior conference speakers, along with other top-notch scientists studying the amygdala, to submit articles for consideration. The positive response that we received to this and to our call for content shows the high value placed on this topic by the community. The result is an outstanding collection of scholarship centered on the topic of the amygdala.

We begin by covering a question that is the heart of the title of this issue: is the amygdala hyperfunctional or dysfunctional in different diseases? Diamond and Zoladz (2016) argue that speaking of the amygdala as dysfunctional may be inappropriate for some disorders, including PTSD. Rather than the amygdala being impaired, the authors address whether the symptoms of PTSD represent a sensitized (hyperfunctional) status. Indeed, they suggest that the amygdala is functioning optimally if the goal is to ensure a person’s survival but that the cost of a hyperfunctional amygdala may be PTSD.

To understand better the role of the amygdala and its biological processes in different diseases, it is important to use animal models. Perathoner et al. (2016) provide an excellent review discussing the potential of zebrafish as a model for exploring the role of the amygdala in emotional memory and motivational behavior. This model of emotional memory and motivational behavior may have relevance to understanding trauma-related disorders such as PTSD. Cota et al. (2016) discuss how electrical stimulation of the amygdala may be a novel means to treat medically refractory epilepsy. In particular, they review evidence demonstrating that temporally unstructured electrical stimulation of the amygdala is capable of suppressing both acute and chronic spontaneous seizures. This may be of great clinical significance. Controlling seizures is essential and, as Yilmazer-Hanke et al. (2016) discuss, without proper treatment the structural and functional changes that occur within the amygdala may contribute to comorbid anxiety, depression, and other psychiatric symptoms experienced in the interictal phase, especially in pharmacoresistant epilepsy.

The important use of animal models in understanding human disease states is further highlighted by Koen et al. (2016). Comparing data from rodent models with human cases, Koen et al. review investigations undertaken on subjects with Urbach-Wiethe disease and find that the lesions occurring in the human amygdala are consistent with and support rodent models of selective basolateral amygdala lesions. The comparisons between human and rodent data indicate that the basolateral complex is integral to processing sensory stimuli and exhibits inhibitory regulation of responses to unconditioned innate fear stimuli. The amygdala also plays a critical role in both generating and responding to experiences of fear. In her review, Dr. Abigail Marsh (2016) critically examines amygdala responsiveness to fearful expression. She details how subjects with psychopathic traits, which typically emerge

during development, are more likely to have a hypoactive amygdala as a result of damage or dysfunction.

Animal models have also been used to understand early developmental and intergenerational mechanisms. Debiec and Sullivan (2014) have previously shown that rodents acquire maternal fear through social learning at birth via an amygdala-dependent mechanism. In this Special Issue, Chang and Debiec (2016) show that the mother-to-infant transmission of fear in preweaning rats is also associated with a significant increase of activity in multiple subcortical brain regions beyond the amygdala. Although it is also known that stress throughout childhood is associated with structural changes in the brain, Evans et al. (2016) provide new translational evidence from human subjects that exposure to chronic stress via cumulative risk exposures during childhood leads to larger amygdala volumes and elevated amygdala reactivity in adulthood. However, structural changes do not occur only as a result of chronic stress. In a Letter to the Editor, Williams et al. (2016) find clear neuroarchitectural changes in the basolateral amygdala but not the centromedial amygdala of schizophrenic patients.

Although a substantial portion of the issue is devoted to translational research, this issue also provides a series of studies and reviews examining how different diseases lead to changes in synaptic transmission and the importance of animal models in the development of novel therapies. Prager et al. (2016) provide an overview of the GABAergic inhibitory system within the amygdala in health and disease. The authors discuss mechanisms that modulate inhibitory synaptic transmission within the basolateral complex and how different deficits in inhibitory synaptic transmission contribute to various disorders. One such disorder that is discussed is fragile X. Studies have found pathological changes in GABAergic neurotransmission in this neurodevelopmental disorder, leading to alterations in the excitatory/inhibitory balance in local circuits, including the amygdala (Paluszkiwicz et al., 2011). In an original research article, Martin et al. (2016) target tonic inhibitory transmission to treat neurophysiological symptoms such as anxiety in a fragile X model. They find that application of a novel agonist targeting extrasynaptic GABA_A receptors rescues inhibitory neurotransmission in the amygdala and improves the excitatory/inhibitory balance. Changes in excitatory neurotransmission are also discussed. In another original research article, Klein et al. (2016) find that, after a mild traumatic brain injury (TBI), excitatory synaptic transmission is increased. Exposing animals to stress prior to TBI was found to lead to a significant decrease in excitatory synaptic transmission after TBI.

In an excellent summary article, Mears and Pollard (2016) discuss the complex network that is the brain and the role of the amygdala as a hub in health and disease. Their article explains how graph theory has been applied to study structural and functional networks in the brain. Some brain networks are highly connected hubs, which play an essential role in information processing because of their high connectivity and centrality. The amygdala may

be considered a network hub because it is considered one of the most highly connected regions of the brain. Changes in the nodal properties of the amygdala are present in depression but may also be present in other neurological diseases. The authors rightfully conclude this inaugural issue by suggesting that focusing operational attention on the amygdala network and its associated functional and anatomical systems will contribute to the development of new tools to predict, diagnose, and design individualized treatment strategies for a broad range of neurological and psychiatric disorders.

This Special Issue, rather than representing a culmination of 10 years of conferences, is the beginning of further efforts to communicate this excellent science to other researchers and clinicians. Moving forward, we are excited about our next conference, the 11th annual *Amygdala, Stress, and PTSD Conference: The Effects of Stress and Loss* (www.amygdalaPTSDconference.org). We will hear presentations from five esteemed scientists, including Stephen Suomi, Patrizia Casaccia, Naomi Simon, Michael Fanselow, and David Krantz, each of whom will speak about different biological mechanisms underlying stress, loss, fear, and downstream effects of PTSD. We will take this opportunity to continue our collaboration with *The Journal of Neuroscience Research* through the In Focus Section, which is a collection of articles that focuses on updating a particular subject within neuroscience.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

ROLE OF AUTHORS

All authors take responsibility for the integrity and accuracy of this article. Drafting of the manuscript and critical revisions of the article: EMP, GHW, RJU.

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