



Neurobiological studies of trauma-related psychopathology: a public health perspective

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ABSTRACT

The societal burden of psychiatric disorders that result after exposure to psychological trauma is enormous. The study of trauma-related disorders using neurobiological and public health approaches is often disjointed. It is critical to emphasize the translational potential of neurobiological work and its relevance to the public health burden of psychological trauma. Applying a public health model to traumatology that includes primary, secondary, and tertiary levels, we highlight ways in which advancing the field of neurobiology can pave the way for scalable interventions that can improve outcomes and help to address the public health problem.

Estudios neurobiológicos de la psicopatología relacionada con el trauma: una perspectiva de salud pública

La carga social de los trastornos psiquiátricos que resultan después de la exposición al trauma psicológico es enorme. El estudio de los trastornos relacionados con el trauma que utilizan enfoques neurobiológicos y de salud pública a menudo es inconexo. Es fundamental enfatizar el potencial de traslación del trabajo neurobiológico y su relevancia para la carga en la salud pública del trauma psicológico. Aplicando un modelo de salud pública al trauma psicológico que incluye niveles primario, secundario y terciario, destacamos formas en las que avanzar en el campo de la neurobiología puede allanar el camino para intervenciones escalonadas que puedan mejorar los resultados y ayudar a abordar el problema de salud pública.

创伤精神病理学的神经生物学研究：公共卫生观点

暴露于心理创伤后导致的精神疾病带来巨大的社会负担。使用神经生物学和公共卫生方法对创伤相关疾病的研究通常是脱节的。强调神经生物学工作的转化潜力及其与心理创伤的公共卫生负担的相关性至关重要。使用公共卫生模型应用于包括初级、二级和三级水平的创伤学，我们强调了推进神经生物学领域可以为扩展干预措施铺平道路，这些干预措施可以改善结果并帮助解决公共卫生问题。

ARTICLE HISTORY

Received 23 October 2018

Revised 23 November 2018

Accepted 28 November 2018

KEYWORDS

Trauma; post-traumatic stress disorder (PTSD); neurobiology; translational neuroscience; neuroimaging; public health; intervention

PALABRAS CLAVE

trauma; trastorno de estrés postraumático (TEPT); neurobiología; neurociencia traslacional; neuroimagen; salud pública; intervención

关键词

创伤创伤后应激障碍 (PTSD); 神经生物学; 转化神经科学; 神经影像学
公共卫生干预



HIGHLIGHTS

- The societal burden of trauma- and stress-related psychiatric disorders is enormous.
- Our knowledge of the neurobiology of psychiatric disorders is gradually increasing.
- We highlight the translational potential of neurobiological work and its relevance to the public health burden.
- Improved understanding of the neurobiology may lead to interventions with better treatment outcomes.

Exposure to traumatic events can lead to the development of psychiatric conditions, including post-traumatic stress disorder (PTSD), major depressive disorder (MDD), substance use disorders, and suicide (Thomas et al., 2010). The individual and societal burden of these disorders is enormous. Worldwide, the burden of PTSD alone is estimated at 78 lifetime person-years per 100 individuals in the population (Kessler et al., 2017). These figures are even more pronounced in certain groups, such as refugees, where trauma and

chronic stress exposure are much higher (Knaevelsrud, Stammel, & Olf, 2017). In 2012 alone, the US Department of Veterans Affairs (VA) and Department of Defense (DoD) spent over \$3 billion on the treatment of PTSD in service members and veterans (Institute of Medicine, 2014). However, despite the critical need for effective therapy, treatment options and access remain limited (Akiki & Abdallah, 2018a).

A better understanding of the neurobiology of trauma-related disorders may be key to advancing

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effective interventions (Ross et al., 2017). Significant resources are being advanced by various funding agencies to enable research in the field. More than ever, it is critical to highlight the potential benefit from such investments. Translational research focusing on the neurobiology of stress-related psychopathology should be framed in the context of the public health burden. While the translational neuroscience and the public health approaches have often been treated as separate subjects (e.g. Akiki, Averill, & Abdallah, 2017; Fragkaki, Thomaes, & Sijbrandij, 2016; Frewen, Schmahl, & Olf, 2018; Lanius & Olf, 2017; Magruder, Kassam-Adams, Thoresen, & Olf, 2016; Magruder, McLaughlin, & Elmore Borbon, 2017), it is vital to integrate both approaches. Applying a three-tiered prevention model to traumatology (Magruder et al., 2016), we highlight ways in which translational neuroscience can pave the way for public health-focused interventions at various levels.

Primary prevention, in this context, refers to interventions that target risk factors to mitigate the development of stress- or trauma-related psychopathology. As such, a prerequisite for primary prevention efforts is being able to effectively identify individuals with vulnerability in at-risk subpopulations – such as first responders and members of the armed forces – or even in the population at large (when low-cost and effective screening tools become more accessible). Markers of biological risk factors (neural, endocrine, genetic, molecular, etc.) hold significant promise for use in risk stratification, and are likely to complement the more readily measured psychological and social risk factors (Kalisch et al., 2017). After identifying individuals who are at increased risk, primary preventive interventions can be implemented either to minimize the risk of trauma exposure in vulnerable individuals (e.g. by limiting workplace-related exposure) or to enhance their resilience to prevent the development of pathology should they be exposed to psychotrauma. While no known biological interventions currently exist in mainstream practice, there are several promising preclinical investigations under way. For example, pretreatment with the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine was shown to foster resilience in mice when given 1 week before exposure to models of chronic stress (Brachman et al., 2016). While the feasibility and safety of this specific example may not be optimal, such studies are crucial proofs of concept.

Secondary prevention strategies, in the classical sense, target individuals exhibiting early signs of illness. In the context of trauma-related disorders, the definition can be adapted to include individuals who have been exposed to trauma, regardless of symptomatology. This group is usually (although not always) easy to target, given the often identifiable timepoint of the index trauma. Secondary preventive interventions could therefore be

implemented as part of a post-traumatic prophylaxis framework to target individuals in this acute phase to prevent the development of chronic pathology. Several pharmacotherapies have been proposed and investigated, including classical agents such as beta-adrenergic blockers, corticosteroids, and benzodiazepines (see Abdallah et al., 2018a, for a recent review). Although there certainly have been early promising works, no consistent beneficial effect has been demonstrated (Akiki & Abdallah, 2018a). Nevertheless, several novel investigational approaches have yielded encouraging results. For example, a recent randomized controlled trial of oxytocin revealed benefit in a subgroup with severe (but not mild) PTSD symptoms when administered in the acute phase post-trauma, an effect that was sustained at the 6 month follow-up assessment (van Zuiden et al., 2017). The application of brain stimulation approaches in traumatology is still in its infancy, but non-invasive interventions [e.g. transcranial magnetic stimulation (TMS)] may hold substantial promise in terms of fostering the robustness of vulnerable neural circuits (Lanius, Frewen, Tursich, Jetly, & McKinnon, 2015).

Tertiary prevention targets patients with an established psychiatric disorder, with the goal of achieving and maintaining remission, preventing deterioration, enhancing their functional status, and in this context of trauma-related pathology, minimizing the toxic effects of chronic stress. It is the level at which the vast majority of therapeutic interventions are currently being administered, and it is likely to remain an important target point. Current interventions – psychotherapy and pharmacotherapy – are limited in their efficacy (Akiki & Abdallah, 2018a), which contributes to the public health burden. Ongoing investigations involving rapid-acting antidepressants – most notably ketamine – have shown significant promise in robustly and rapidly reducing PTSD and depressive symptoms (Abdallah, Averill, & Krystal, 2015; Feder et al., 2014). Likewise, preliminary studies of drug-augmented psychotherapy with 3,4-methylenedioxymethamphetamine (MDMA) and oxytocin have yielded promising results (Flanagan, Sippel, Wahlquist, Moran-Santa Maria, & Back, 2018; Mithoefer et al., 2018). Neurobiological studies can serve an important role in facilitating the development of rational therapeutics by mapping the mechanistic basis of the disorder (e.g. understanding the neural circuit dysfunction) and developing biomarkers for target validation (Akiki et al., 2018c; Morey, Haswell, Hooper, & De Bellis, 2015). Our recent pharmacoinaging work has found putative *in vivo* neural signatures for response to rapid-acting antidepressants (Abdallah et al., 2018b). Similarly, neuroimaging work with oxytocin has also yielded important mechanistic findings (Frijling et al., 2016). Even from a public health perspective, where non-selective interventions with potential for broad

dissemination are desirable, it is becoming increasingly clear that there is no escape from precision medicine to effectively achieve treatment goals. Identifying neurophysiological subtypes of trauma-related psychopathology may allow for the tailoring of treatments based on specific brain abnormalities that may not be discernible at a phenotypic-behavioural level. The mechanisms underlying the response to brain stimulation approaches such as TMS are only now beginning to be understood (Philip et al., 2018). Neuroimaging approaches that respect individual differences in neural circuitry will probably need to be emphasized (Akiki & Abdallah, 2018b; Nahas, 2010). Perhaps the most obvious example at present comes from the field of deep brain stimulation, where subject-specific (Riva-Posse et al., 2018) – but not non-selective (Holtzheimer et al., 2017) – electrode placement was associated with MDD treatment response.



Finally, as we learn more from translational neuroscience, it is important to focus on implementing the findings into policy, and cultural and social norms. For example, if supported by future evidence, policies requiring regular screenings, and limiting the exposures in those at risk can be implemented in first responders. It may also be useful to tackle factors such as exercise, environmental enrichment, and support networks, through social interventions, as they are all known to affect the brain's stress circuitry (Krystal et al., 2017). Cultural destigmatization of promising controlled substances (e.g. ketamine and MDMA) will facilitate both access to treatment and research into their potential.

In summary, work on the neurobiology of trauma-related disorders is not only relevant from the point of view of burden on individual patients, but also extremely important and timely from a public health perspective. Improving our understanding of the neurobiology of post-traumatic disorders may be crucial in ushering in an era of improved outcomes for trauma survivors.

Disclosure statement

TJA and LAA declare no conflicts of interest. CGA has served as a consultant or on advisory boards for Genentech, Janssen, and FSV7, serves as editor for the journal *Chronic Stress*, published by SAGE Publications, Inc., and has filed a patent for using mTOR inhibitors to augment the effects of antidepressants (filed on 20 August 2018).

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