Trends in Neurosciences

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Opinion

Acute or Chronic? A Stressful Question

Laura Musazzi,[1] Paolo Tornese,[1] Nathalie Sala,[1] and Maurizio Popoli[1,*]

Stress is a primary risk factor for neuropsychiatric disorders; at times, even a single trauma can trigger psychopathology. Many rodent models of neuropsychiatric disorders use chronic stress, measuring readouts at the end of long protocols. In a way, traditional chronic models overlook a crucial question: how does the physiological response to stressor(s) turn into a maladaptive pathway that may verge towards psychopathology? Recent evidence suggests that studying the long-term consequences of acute stress would provide critical information on the role of stress in psychopathology. This new conceptual framework could enable us to understand the determinants of a pro-adaptive versus maladaptive trajectory of stress response, and also to study the mechanism of rapid-acting antidepressants, such as ketamine, that target the glutamate system directly.

Stress May Come in Different Forms: Acute versus Chronic

Most neuropsychiatric disorders, such as depression, mood, and anxiety disorders, are stress-related disorders; even diseases that have a stronger genetic component (e.g., schizophrenia and bipolar disorder) are based on the unfavorable interaction between the individual genetic background and different kinds of adverse event [1–3]. Several lines of investigation showed that repeated stress and adverse life events, particularly early in life or during prenatal life, are strong determinants of subsequent psychopathology in adult life [4,5]. Although neuropsychiatric disorders are all stress-related disorders, they are distinct nosological entities. For instance, depression and post-traumatic stress disorder (PTSD) show different symptomologies, different courses of pathology and require different kinds of therapy.

The stress response is a physiological reaction to environmental changes that can be positive and pro-adaptive (in most cases) or negative and maladaptive [6–10]. Everyone reacts differently: for some people, stress is an incentive to do better, and may enhance one's cognitive capability. Others, both for different genetic characteristics and for their personal story, may have trouble reaching the necessary adaptation to environmental changes. This negative response can become more frequent when an individual is exposed to particularly strong, or repeated stressful stimuli. Such is the case with maladaptive responses, which can favor the onset of different types of disease, not only mental, but also cardiovascular and metabolic [11]. Even a single exposure to traumatic stressors may trigger a neuropsychiatric disorder (Box 1).

Central Issues in Research on Stress-Related Neuropsychiatric Disorders

A central issue in research on the pathophysiology of stress-related neuropsychiatric disorders is the quest for determinants of resilient versus vulnerable stress responses. Resilience, which is dependent on genetic background as well as multiple factors related to environmental influence, can be conceived as an active process that implies pro-adaptive neuroplasticity, favoring structural and functional brain changes that allow a new equilibrium to be reached with the

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Stress and traumatic events are increasingly recognized as risk factors for mental disorders, in particular for depression, anxiety disorders, and post-traumatic stress disorder (PTSD). In the latter, a single trauma may determine the pathology. It is not clear how a single stressful event may induce a potentially life-long pathology.

Changes in neuroarchitecture in select brain areas have been consistently found in psychiatric patients, particularly in those with depression and/or PTSD. Rodent studies with chronic stress showed similar changes as in humans. It has been suggested that the pathology-related changes (dendritic atrophy) are subsequent to an enhancement of glutamate release and excitatory transmission induced by stress, but clear evidence is still needed.

Recent evidence has shown that rapid and sustained changes in neuroarchitecture are also induced by acute stress, and that the enhancement of glutamate release induced by acute stress is extended for up to at least 24 h.

These lines of evidence allow the formulation of a working hypothesis, using acute stress protocols to investigate the pathophysiology of stress-related mental illnesses and the action of rapid-acting antidepressants targeting the glutamate system.

[1]Laboratory of Neuropsychopharmacology and Functional Neurogenomics – Dipartimento di Scienze Farmacologiche e Biomolecolari and Center of Excellence on Neurodegenerative Diseases, Università di Milano, Milano, Italy

Box 1. Acute Traumatic Stress May Cause Post-Traumatic Stress Disorder

On April 6 2009, at 03:32 h, an earthquake of magnitude 6.3 on the Richter scale struck the city of L'Aquila, a town of 72 000 in central Italy, destroying buildings and causing the death of 309 people and the injury of over 1600. Ten months later, a sample of 900 earthquake survivors was administered the Trauma and Loss Spectrum-Self Report, a tool exploring symptoms of post-traumatic stress. The results showed that 372 subjects (41.3%) reported symptoms of PTSD, the most commonly studied and probably the most frequent and debilitating mental disorder that occurs after traumatic events and disasters [58]. PTSD is usually related to deep stress caused by a sudden incident, such as a natural disaster, a traffic accident, or an episode of violence, or is often linked to combat situation, such as in war veterans. The prevalence of PTSD varies widely across studies, due to different assessment methods being used. However, different studies agree that its prevalence is lower in the general population compared, for instance, with war veterans, suggesting that stressful events have a key role in its pathophysiology [59,60]. Although this is not always true, in many cases, a single exposure to a traumatic event (or even witnessing other people being exposed to a traumatic situation) may trigger the disorder. There is at present no clear answer to how a single stressful event can induce such a potentially lifelong pathology.

*Correspondence:
maurizio.popoli@unimi.it (M. Popoli).

environment. Likewise, vulnerability has its roots in the genetic background, and particularly in previous adverse life events, which, through epigenetic changes, may alter the shape of future stress response [8,12]. Although the study of determinants of vulnerability has been going on for some time, interest in resilience has increased more recently, pushed by the idea that understanding what makes individuals more resistant to the deleterious effects of stress could suggest new paths for the development of treatments for stress-related disorders. An attractive aspect is that this could be reached by inducing natural mechanisms of resilience that are perhaps different from the action of traditional drugs (e.g., antidepressants).

Much of what we know about the effects of stress and its relationship with neuropsychiatric disorders comes from animal models of stress, which, in many cases, reproduce distinct features of human pathology, although there is no single model that can reproduce entirely depression or other disorders. Animal models of chronic or repeated stress are more commonly used than acute models for most disorders, and there is a large body of evidence illustrating structural and functional brain changes induced by chronic stress. In general, we tend to distinguish the effects of acute stress from those of chronic stress, but recent lines of evidence suggest that the outcome is not so different and that acute stress also has long-term consequences (see below).

Another central issue in the field is represented by the investigation of rapid-acting antidepressants (e.g., the noncompetitive NMDA receptor antagonist ketamine and related glutamatergic drugs), which have been shown to restore the maladaptive changes induced by chronic stress in a matter of hours [13]. Interestingly, the ketamine paradigm is now used not only to provide an approach for rapid and more efficient antidepressant treatment, but also to understand the basic neurobiological underpinnings of stress-related psychopathology [14]. However, in human studies, ketamine has been given to treatment-resistant patients (i.e., subjects who did not respond to treatment with traditional antidepressants), whereas, in rodent studies, the drug has been administered to all stressed animals, without distinguishing stress-vulnerable from stress-resilient animals. Therefore, investigating the effects of ketamine in stress-vulnerable versus stress-resilient animals may add further insight into the pathophysiology of stress.

Neuroarchitecture Is Altered in Stress-Related Neuropsychiatric Disorders and in Animal Models of Stress

It has been shown by several studies that the neuroarchitecture of select brain areas [hippocampus (HPC) and prefrontal cortex (PFC)] is altered in humans affected by some mental disorders, such as depression and PTSD [15–17]. The volume of these areas is smaller in patients and, in several studies, a reduced density of dendrites and synaptic spines has also