Social stress messes up the hippocampus

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How do you feel when you are stuck in a traffic jam for hours? Or when you are late for a flight? Or when you are waiting at the university hall to pass an exam? Obviously, you feel stressed, which might endanger your hippocampus according to a research paper recently published in *PLOS One* by Stankiewicz and colleagues.

Stress is an alerting signal for the brain

The idea that stress may be hazardous for the brain is not new; indeed, discoveries continue to strengthen this concept. A large body of research has clearly shown that stress, especially when repeated and unpredictable, is capable of modifying the structure and the activity of neuronal circuits. In fact, stress is a risk factor for many mood-related disorders such as depression, anxiety and schizophrenia. Adaptive and maladaptive modifications take place in our brain to counteract stressors and these modifications could lead to severe mental pathologies. One of the most vulnerable structures of the brain is the hippocampus, a brain region greatly involved in learning and memory functions.

Social stress modifies the hippocampal transcriptome

Stankiewicz and colleagues decided to evaluate the impact of acute and chronic stress in the hippocampal transcriptome (set of transcribed genes) using a behavioral protocol of social stress. This paradigm relies on the ability to induce stress-like responses based on social aggression. In order to induce agonistic behaviors characteristic of stressful social encounters in mice such as upright postures, aggressive grooming, fights, and escape, single-housed mice were exposed to group-housed mice several times per day. The authors then used transcriptomic approaches to identify gene clusters differentially regulated in acutely or chronically stressed mice compared to control animals. General genome-wide analyses revealed that acute and chronic stress (13 consecutive days of social stress) were able to modify the expression of dozens of genes. Interestingly, while a general downregulation of some genes was observed in acutely stressed mice, a robust upregulation of the same genes was detected in chronically stressed animals.

This intriguing phenomenon indicates that the same stressful event has dramatic impacts, which are differentially characterized depending on the duration and frequency of exposure.

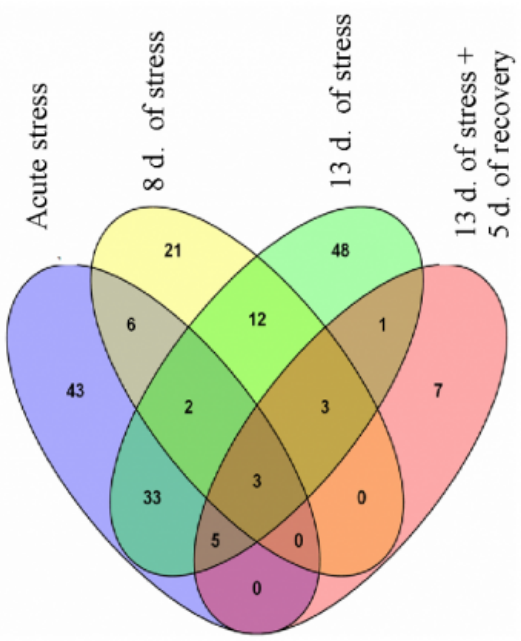
Stress and inflammatory functions

Stress responses have been correlated with altered inflammatory functions; for example, infiltration of leukocytes in the brain of socially defeated mice has been reported. As such, Stankiewicz and colleagues searched for potential modifications in expression of brain-inflammation markers in hippocampi from stressed mice. Two functionally related genes, S100a8 and S100a9, that participate in the regulation of immune cell transmigration (neutrophils) during inflammation were overexpressed in chronically stressed mice, thus supporting the notion that social stress may result in an inflammatory response in the hippocampus. Amongst the rest of the clusters of genes differentially regulated, the authors also report increased expression of genes coding for hemoglobin (Hbb-b1, Hba-a1, Hba-a2), which may result from modifications of the vascular system in stressed mice. This seemingly surprising result is in accordance with other research efforts exploring different areas of the brain, such as the nucleus accumbens, the ventral tegmentum and the prefrontal cortex, all of which are implicated in mood disorders. Furthermore, the hypothesis of the presence of a possible vascular injury that may correlate with pro-neuroinflammatory events is strengthened by the overexpression of other genes (Isg20, Spp1, Lcn2, etc) known to have a key role in the inflammation processes.

A

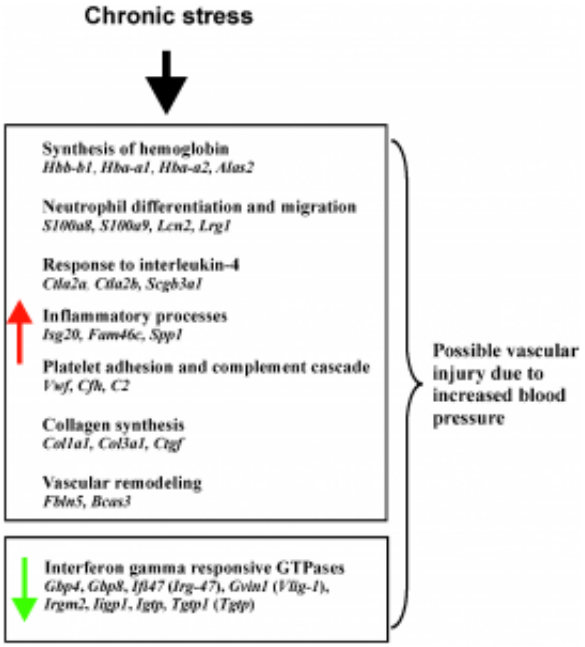
	Acute stress	8 d. of stress	13 d. of stress	13 d. of stress + 5 d. of recovery
Up-regulated	4	36	95	13
Down-regulated	88	11	12	6
Total	92	47	107	19

B



Stankiewicz and colleagues have previously reported similar changes in the patterns of expression of gene related to inflammation in the prefrontal cortex, another brain region highly sensitive to stress (Stankiewicz et al., 2014). The fact that both the hippocampus and the prefrontal cortex of stressed mice exhibit such resemblances, led the researchers to believe that chronic stress may impact the whole brain. Therefore, even though a clear causal relationship between the transcriptomic changes and the altered phenotype is somehow missing, Stankiewicz and colleagues put forward the idea that "the regulation of genes involved in the function of vascular system, injury and inflammation suggest that the vascular system may constitute a link between stress and stress-induced brain pathology."

Reversible or irreversible modifications?



Thankfully, good news also came out from this study. We all have experienced the pleasant effects of rest following stressful periods; in fact, Stankiewicz and colleagues found that after 5 days of recovery from a protocol of chronic stress most of the altered genes had returned to basal levels, suggesting that maladaptive modifications are indeed reversible. This finding reinforces the idea that our brain is able to adapt to any circumstances, healthy or unhealthy, and that our life style could sometimes be the best cure to our messed up brains.

In conclusion, understanding and unraveling the mechanisms underlying stress-induced brain dysfunctions may ultimately lead to improved therapeutic approaches, as well as to possible preventive strategies to decrease the incidence of mood disorders.

More information: Adrian M. Stankiewicz et al. The Effect of Acute

and Chronic Social Stress on the Hippocampal Transcriptome in Mice, *PLOS ONE* (2015). DOI: 10.1371/journal.pone.0142195

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Krishman V, Han MH, Graham DL, Berton O et al., (2007). Molecular Adaptations Underlying Susceptibility and Resistance to Social Defeat in Brain Reward Regions. *Cell*. 131(2):391-404.