Stress may cause the brain to become disconnected

March 16 2009

Does stress damage the brain? In the March 1st issue of *Biological Psychiatry*, published by Elsevier, a paper by Tibor Hajszan and colleagues provides an important new chapter to this question.

This issue emerged in the 1990's as an important clinical question with the observation by J. Douglas Bremner and colleagues, then at the VA National Center for Posttraumatic Stress Disorder (PTSD), that hippocampal volume was reduced in combat veterans with PTSD. This finding was replicated by several, but not all, groups. In particular, it did not appear that this change was associated with acute PTSD. The importance of this finding was further called into question as a group associated with the Harvard Medical School found that reduced hippocampal volume predicted risk for PTSD among twins, rather than emerging as a consequence of PTSD.

Yet limitations of this twin study reduced the strength of this inference, as there were relatively high rates of early life trauma in the twins without combat-related PTSD, i.e., a potential environmental source for the reductions in hippocampal volume associated with later risk for PTSD. This group also showed that cortical volume reductions in other brain regions, such as the pregenual anterior cingulate cortex, were more clearly linked to trauma than were the hippocampal changes in these twins. "This collection of clinical findings highlights an important limitation of clinical neuroimaging studies. These studies have the ability to raise important questions about brain structure in a general sense, but we still rely on studies of postmortem human tissue and animal research

to determine the specific nature of neural changes," explains Dr. John Krystal, Editor of Biological Psychiatry and affiliated with both Yale University School of Medicine and the VA Connecticut Healthcare System.

This is where research conducted in animals has provided critical information. Initial data by investigators, such as Robert Sapolsky at Stanford University, suggested that stress might promote the death of neurons, suggesting that the volume reductions in patients with PTSD might reflect the loss of nerve cells. More recent research by Bruce McEwen and colleagues at Rockefeller University indicates that stress can cause neurons to shrink or retract their connections. This could be critically important to the ability of these neurons to work together in highly inter-connected networks. But what is the link between this type of "neural remodeling" and the behavioral changes that follow extreme stress exposure?

The new paper by Hajszan and colleagues at Yale University suggests that in learned helplessness, an animal model for depression and PTSD, stress-related reductions in synapses in the hippocampus are directly related to the emergence of depression-like behavior. These data help to make the case that stress-related changes in the structure of nerve cells may have important behavioral consequences, explains Dr. Hajszan. "The importance of our findings is derived from the well-known fact that synapses have a great potential for rapid changes, which may underlie sudden mood swings. More importantly, it is feasible to restore hippocampal synapses in a very short period of time (hours or even minutes), which opens up exciting new avenues for developing rapid-acting antidepressants that may provide immediate relief from depressive symptoms."

It cannot yet be said that reductions in cortical volumes in patients with PTSD reflect reductions in the number of synapses. However, these

findings underscore the potential importance of studying post-mortem human tissue to determine whether humans also show this pattern of neural changes. Dr. Krystal notes that "settling this issue could help us to better understand recent epidemiologic data suggesting that most of the adjustment problems of soldiers returning from Iraq and Afghanistan with mild traumatic brain injury (TBI) or post-concussive syndrome are attributable to PTSD." He adds, "We have tended to think of PTSD and mild TBI as unrelated at the neural level. However, with growing evidence from animal studies that PTSD may be associated with loss of neural connections, it may turn out that PTSD and mild TBI are two distinct, but interacting, ways that soldiers might be affected by their combat experience. " Research is ongoing in the authors' lab and in others as they continue to make progress in understanding how the brain is affected by depression and stress, and in developing targeted medications.

More information: "Remodeling of Hippocampal Spine Synapses in the Rat Learned Helplessness Model of Depression" by Tibor Hajszan, et al., Biological Psychiatry, Volume 65, Issue 5 (March 1, 2009)

Source: Elsevier