

New Theory Links Depression to Chronic Brain Inflammation

October 19, 2010

Scott LaFee

Chronic depression is an adaptive, reparative neurobiological process gone wrong, say two University of California, San Diego School of Medicine researchers, positing in a new theory that the debilitating mental state originates from more ancient mechanisms used by the body to deal with physical injury, such as pain, tissue repair and convalescent behavior.

In a paper published in the September online edition of *Neuroscience and Biobehavioral Review*, Athina Markou, PhD, professor of psychiatry, and Karen Wager-Smith, a post-doctoral researcher, integrate evidence from diverse clinical, biological and behavioral studies to create a novel theory they hope will lead to a shift in thinking about depression.

"In contrast to other biological theories of depression, we started with a slightly different question," said Wager-Smith. "Other theories address the question: 'What is *malfunctioning* in depression?' We took a step back and asked the question: 'What is the biology of the *proper* function of the depressive response?' Once we had a theoretical model for the biology of a well-functioning depressive response, it helped make sense of all the myriad differences between depressed and non-depressed subjects that the biomedical approach has painstakingly amassed."

According to the new theory, severe stress and adverse life events, such as losing a job or family member, prompt neurobiological processes that physically alter the brain. Neurons change shape and connections. Some die, but others sprout as the brain rewires itself. This neural remodeling employs basic wound-healing mechanisms, which means it can be painful and occasionally incapacitating, even when it's going well.

"It's necessary and normal so that an individual can adapt, change behavior and deal with altered circumstances," Markou said. Real problems occur only "when these restructuring processes go into overdrive, beyond what is necessary and adaptive, and for longer periods of time than needed. Then depression becomes pathological."

The theory extends findings made by other researchers that the neurobiological substrates of physical and emotional pain overlap. Just as the body's repair mechanisms for physical injury can sometimes result in chronic pain and inflammation, so too can the response to psychological trauma, resulting in chronic depression.

Markou and Wager-Smith argue that existing, conflicting views about depression actually describe different aspects of the same phenomenon. Psychoanalytic and sociological theories refer to the psychological transformation that occurs during a productive depressive episode. Biomedical theories relate to the neural remodeling that underlies this psychological change. And neurodegenerative theories account for remodeling malfunctions.

"The big question, of course, is why aren't all people affected the same way," said Markou. "Why do some people deal effectively with stress, but others perpetuate a pathological state? This is an interesting question for future research."

The researchers' findings may have clinical ramifications as well. If psychological and physical pain responses share similar biological mechanisms, then analgesic agents could be useful in treating at least some symptoms of depression. Similarly, if chronic depression is proven to be a neuroinflammatory condition, then anti-inflammatory treatments should also have some antidepressant effects. Several small trials with depressed patients have already been published that support this possibility, though Markou cautioned that much more specific research and larger clinical trials are required.

Funding for this work came from a National Institutes of Health National Research Service Award and a grant from the National Institute of Mental Health.

Media Contact: Scott LaFee, 619-543-6163, slafee@ucsd.edu

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