

The anxious mind and brain: challenging current approaches in understanding anxiety

Dr Joseph LeDoux is a neuroscientist at the Center for Neural Science at New York University (NYU), and is Director of the Emotional Brain Institute. He researches the biological basis of emotion and memory. By understanding our responses to threat, he hopes to be able to help develop novel, more effective treatment options for patients suffering from fear and anxiety disorders.

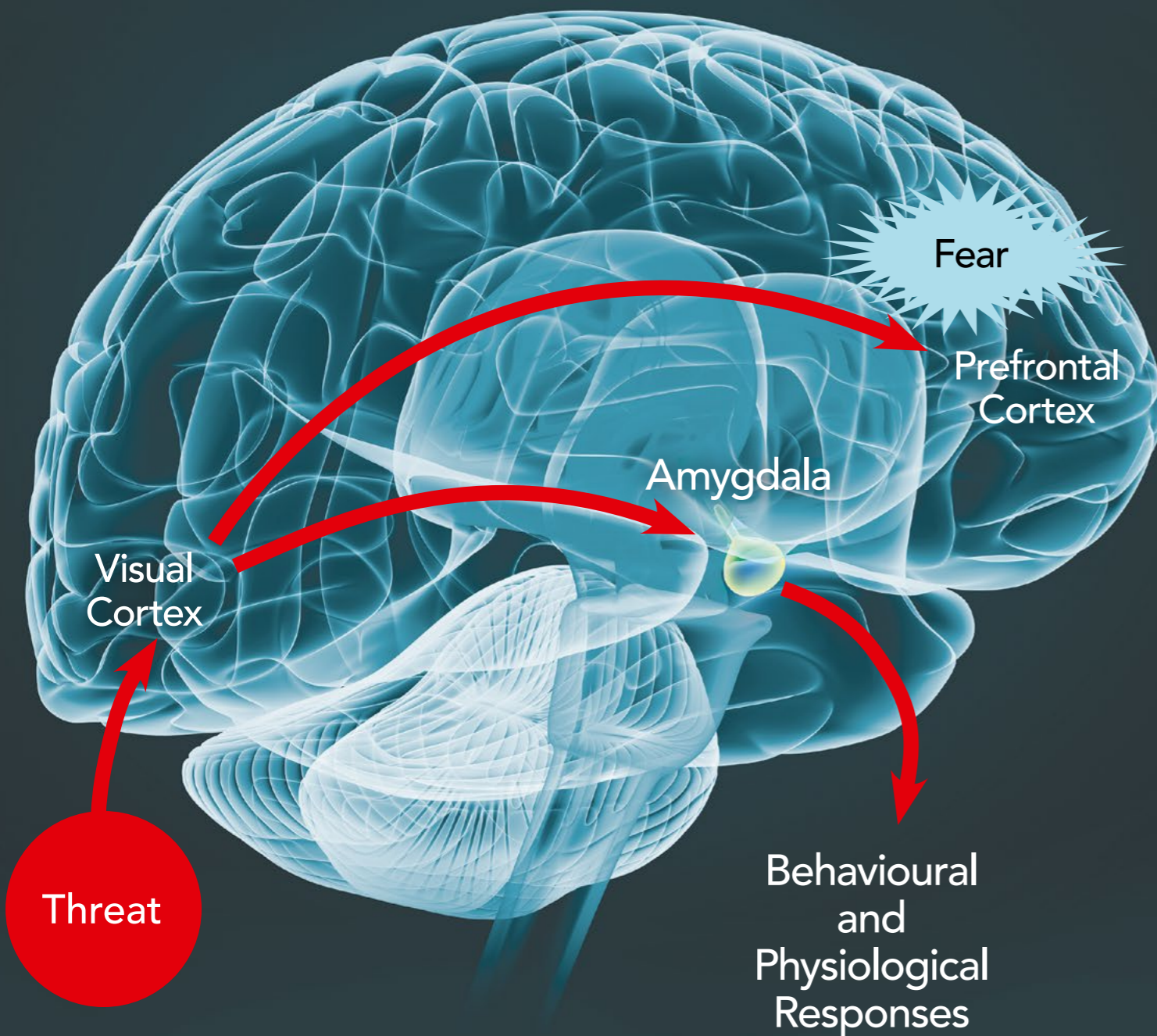
behavioural and physiological responses to threats.

CONSCIOUSNESS OF FEAR

Dr LeDoux argues that though the amygdala detects and responds to danger, it is not, as commonly assumed, a “fear centre,” as it is not itself responsible for the conscious feeling of fear. His conclusion is supported by research showing that while damage to the amygdala in humans eliminates the responses to threats, it does not prevent the people from feeling afraid. Subjective experiences of fear and other emotions, such as anxiety, LeDoux argues, are processed by higher-order brain circuits mostly involving the prefrontal cortices. These circuits underlie cognitive processes such as attention, working memory, and decision making. Neural connections within these networks allow you to make sense of a threat in light of memories, including memories about what emotions are (emotion schema) and who you are (self schema), label the state in words, and have the conscious experience of fear, the feeling that your well-being is in jeopardy.

FROM SURVIVAL THREAT TO MODERN-DAY WORRIES

Though surviving necessitates an innate and immediate response to threat, modern society has introduced new challenges, which require an active monitoring of potential harm. We are less likely to fall prey to predators on a daily basis, but instead worry about financial security, job satisfaction, politics, and the meaning of life. Worries can manifest as anxiety disorders or obsessive-compulsive behaviours toward selected objects or other people. Symptoms of panic disorders include an excessive anticipation of disaster, but also bodily signals such as trembling, sweating and muscle tension generated nonconsciously. In line with Dr LeDoux’s conclusions, it is the complex interplay between such conscious and nonconscious factors that make anxiety disorders difficult to treat.



Anxiety disorders are now a leading form of mental illness worldwide, affecting 40 million adults at a cost of \$42 billion a year in the US alone (National Institute of Mental Health). In trying to identify the neurobiological foundations of fear and anxiety, animal studies have demonstrated the existence of an innate brain system that detects and responds to threats to well-being. This system is often called a “fear system” and is assumed to underlie conscious feelings of fear as well as behavioural and physiological responses that accompany such feelings. However, research based on the “fear system” assumption has not been as helpful as had been hoped in aiding the discovery of successful clinical treatments in humans.

Dr LeDoux proposes that a conceptual reframing that distinguishes the neural circuits that control behavioural and physiological responses to threat from conscious states of fear and anxiety is required for a deeper understanding of what fear and anxiety are and how they might be more effectively treated.

THE AMYGDALA IS NOT THE SOURCE OF FEAR

Experiences with danger can result in an almost automatic physical response. Mammals, including humans, freeze in the presence of a sudden danger, such as an attacker. Dr LeDoux has led the way in discovering how external threats initiate such defensive responses. Using a variety of technologies and techniques – including behavioural approaches, such as Pavlovian conditioning, as well as tract tracing, electron microscopy, cellular physiology, pharmacology, and molecular manipulations – his work has implicated the amygdala in processing threats and controlling defensive responses.

The amygdala is a paired structure, one on each side, located below the neocortex, the outer covering of the brain that underlies thinking, planning and even consciousness. The amygdala is traditionally said to be the hub of the “fear” circuit of the brain, and helps to ensure survival in the presence of harmful threats. This brain region is so important that animals or humans with amygdala damage fail to produce

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WHY TREATMENTS AREN'T MORE SUCCESSFUL

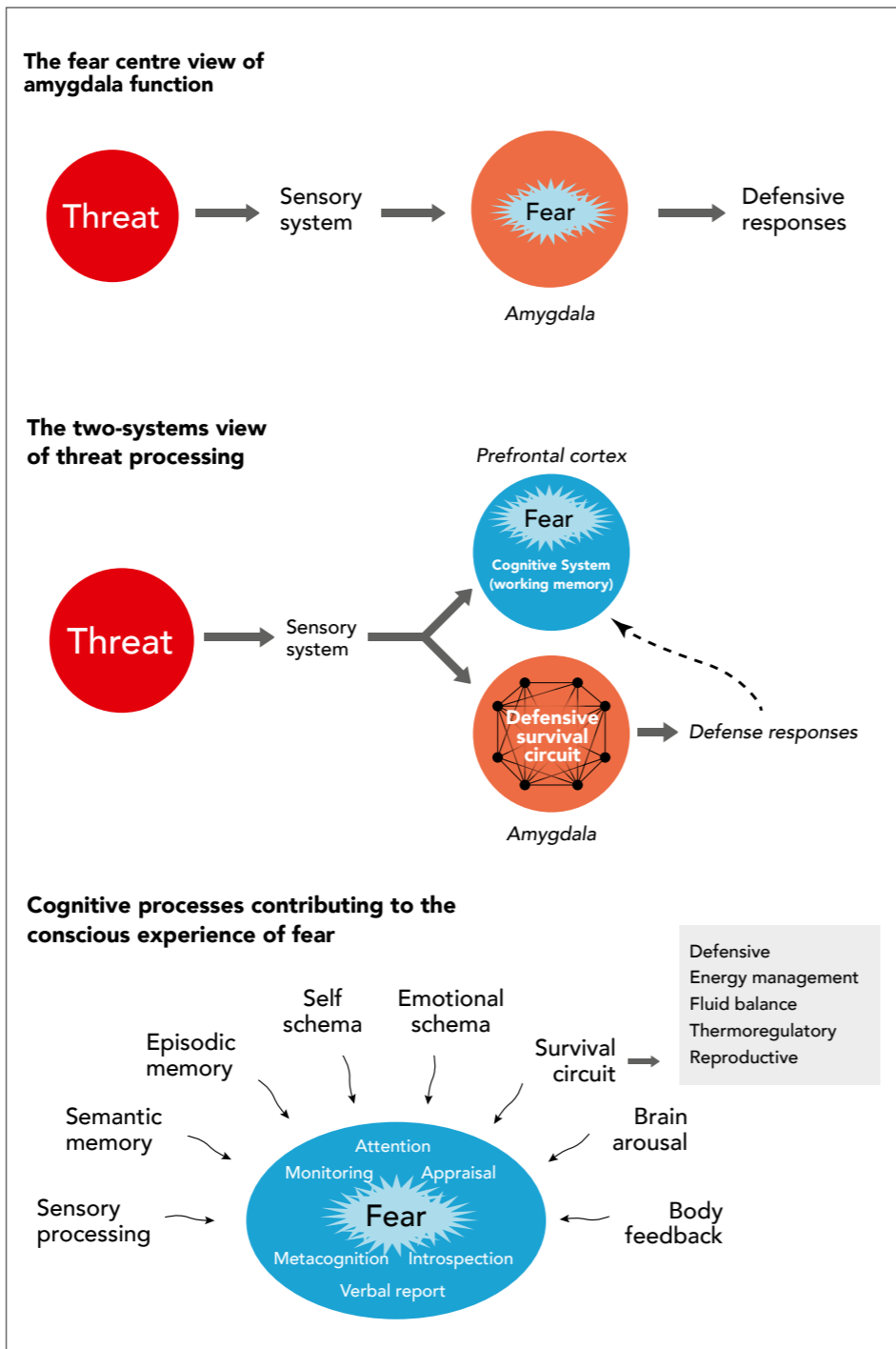
Progress to provide effective therapeutic and clinical options for patients suffering from anxiety disorders has been slow. The over-reliance on animal research has resulted in an under-appreciation of the contribution of cortical networks to biological underpinnings of fear and anxiety – important when seeking new treatments. Though mice and men may share the same underlying biology facilitating a fast behavioural and physiological response to danger, the neural circuits that underlie conscious experience of fear in humans are poorly developed in rodents. Emotions like fear, LeDoux argues, are not behavioural and physiological responses that can be studied equally in humans and other animals but instead are conscious experiences that can only be known directly through introspection. This does not mean that animal research has no place. Medications developed through behavioural studies of animals will by necessity be more likely to affect pathological behaviours, such as avoidance, than pathological feelings of fear or anxiety.

A TWO-SYSTEM FRAMEWORK FOR BETTER TREATMENT OPTIONS

In a recent article, Dr LeDoux and psychiatrist Daniel Pine have suggested a conceptual reframing of the current approach to fear and anxiety using what they term a two-systems framework. This revolutionary approach advocates a distinction between subjective feelings and defensive behaviours. If a medication treats the physiological symptoms of a panic attack, it does not necessarily mean the person feels less anxious. Symptoms such as sweating or heavy breathing may be diminished, but the subjective experience may be unchanged (or not sufficiently changed for the patient to feel better). Indeed, clinical research has shown, time and again, that anxiety medications, while helpful in some cases, are not meeting the expectations of many patients.

COMBINED AND TAILORED TREATMENT APPROACHES

Pharmaceutical treatment in combination with cognitive therapy has in some studies shown greater rates of improvement, possibly because medications target the subcortical behavioural control system more, and cognitive therapy affects the cortical subjective experience system to a greater degree: both must be treated. More



Dr LeDoux’s two-systems approach advocates a distinction between subjective feelings and defensive behaviours. If a medication treats the physiological symptoms of a panic attack, it does not necessarily mean the person feels less anxious

Q&A

What inspired you to start researching emotions?

I was a graduate student in the 1970s. One of my professors gave me a good suggestion. He told me to find something that wasn’t being studied to death. The cognitive revolution had taken over psychology and neuroscience, and it seemed that emotions were being ignored. Emotion seemed to be wide open.

What are your plans for future research within this area?

We have learned a lot about how the brain detects threats and responds to danger with innate responses like freezing. Less is known about how we produce more complex actions (like avoidance). Also, the topic of conscious emotional experience, which is what emotion is all about, is, for me, the most important thing to figure out.

Has the two-system framework been implemented for testing yet? And if so what were the results?

The two-system framework accounts for a great deal of existing data much better than past approaches. While we

don’t have new data on this yet, we are starting to do research now. So stay tuned.

Do you think that by educating patients on the conscious aspects of their anxiety disorders, they are more empowered to consider therapy?

I think patients need to have a better sense that their problems involve both conscious and non-conscious aspects of brain function. For example, if you expect that a medication will make you feel less anxious in a social situation, you will be disappointed if you don’t feel less anxious. But if you know that the medication is going to affect non-conscious systems that make it easier for you to get yourself to the party, in spite of not making you less anxious there, you can use the situation to your advantage. Instead of being disappointed that you still feel anxious, you can expose yourself to the stressful situation in small doses and try to weaken the responses controlled by the non-conscious systems. It’s really all about having realistic expectations about what any kind of treatment can actually accomplish.



BIO

Dr Joseph E LeDoux is the Henry and Lucy Moses Professor of Science at NYU in the Center for Neural Science, as well as directing the Emotional Brain Institute, both at NYU and at the Nathan Kline Institute. He is also a professor of Psychiatry and of Child and Adolescent Psychiatry at NYU Langone Medical School. He is a member of the National Academy of Sciences, and has won numerous awards throughout his career, including the 2016 William James Book award for his book *Anxious*. Away from science, he is the lead singer and songwriter of a rock band called The Amygdaloids, and the acoustic duo, So We Are.

Detail

RESEARCH OBJECTIVES

Dr LeDoux is a neuroscientist whose research aims to understand the neural pathways through which the brain detects and responds to threats, and how these circuits contribute to fear and anxiety disorders. His work looks to further understand the neural mechanisms underlying how humans respond to fear and challenges, to improve treatment options for sufferers of fear and anxiety disorders.

FUNDING

Dr LeDoux’s work has traditionally been funded by the National Institutes of Health, including NIMH and NIDA, but more recently he is turning to private philanthropy and industry support.

COLLABORATORS

For many years, he has collaborated with Elizabeth Phelps, also of NYU. Phelps, among other things, studies human analogues of LeDoux’s animal research.

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CONTACT

Dr Joseph LeDoux
Center for Neural Science
New York University
4 Washington Place
New York, NY 10003
USA

E: ledoux@cns.nyu.edu

T: +1 212 998 3937

W: www.joseph-ledoux.com

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experimental treatment options (including new biological or behavioural approaches) may target certain circuits separately to observe a change in one before pursuing the other. In addition, neuroimaging methods may in the future offer more advanced insights and viable biomarkers to advance the development of more precise treatment options. However, individual differences between patients are still one of the biggest hurdles in finding optimal solutions. Dr LeDoux’s two-systems approach proposes a rationale for a brain-informed therapy plan

in which treatments target symptoms that are products of different systems, hopefully providing a better match to the patient’s individual needs.

Dr LeDoux’s latest book *Anxious: Using the Brain to Understand and Treat Fear and Anxiety* discusses this topic further and provides solutions to how we should think about anxiety to evaluate the treatment that may best suit the sufferer.