Axiety 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 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.

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.
WHY TREATMENTS AIN’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 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 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 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.