Mueller *et al.* also highlight intersubject variability as a crucial factor in the critical discussion of group means [1], which are often presented in task-based functional neuroimaging studies. Because the statistical maps of such studies are based on group means, brain regions with low variability in spatial localization and extent, as well as functional activity, reach with higher probability the cut-off for significance than regions with higher intersubject variability. This finding has important implications for the interpretation of group means, because the non-uniformly distributed variability of structural and functional features throughout the brain can lead to false positive and false negative results, and shows a regional and functional system-specific bias.

In summary, the analysis of intersubject variability provides an important perspective for understanding functional/structural relationships in the human brain. Intersubject variability is not noise – it counts!

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The slippery slope of fear

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'Fear' is used scientifically in two ways, which causes confusion: it refers to conscious feelings and to behavioral and physiological responses. Restricting the use of 'fear' to denote feelings and using 'threat-induced defensive reactions' for the responses would help avoid misunderstandings about the brain mechanisms involved.

The Janus-faced nature the word 'fear' has long been a source of confusion in scientific investigations of this emotional state. 'Fear' most commonly refers to the conscious experience that one has when in the presence of a threat to well-being. However, fear is also used to refer to the behavioral and physiological responses that are elicited by threats. These two kinds of consequences of threats often occur together in people, which leads to the assumption that they are intertwined products of the same brain circuit and also to the assumption that, because similar circuits also control behavioral/physiological responses to threats in other animals, the circuits give these creatures experiences like fear that are akin to what humans feel when in danger. Both of these assumptions are problematic.

A recent study flirts with, and can be used to illustrate, the slippery slope of 'fear'. Feinstein *et al.* examined the effects of CO_2 inhalation in people with amygdala damage [1]. In the introduction of the paper, the authors argue that, because amygdala detection of CO_2 elicits fear behavior in mice, patients with amygdala damage, unlike some healthy people, should not feel fear when inhaling CO_2. As a result, the authors were surprised to find that amygdala-damaged patients felt fearful under these conditions. The study makes important empirical contributions, but also contributes to the ongoing confusion about what fear is.

As the authors rightly note, much research shows that the amygdala is involved in responding (often by expressing innate defensive behaviors) to innate and learned threats in animals and humans [2]. Nonetheless, a qualification is needed. The amygdala is not necessarily involved in controlling responses to all possible kinds of threats. For example, when threatening experiences are well-learned, the amygdala is not involved in controlling the responses [3]. Also, when threats are unpredictable, the key circuitry involves the bed nucleus of the stria terminalis, rather than the amygdala [4]. It is unclear whether other more cognitively based threats, such as challenges to self-esteem or the thought that death is certain, involve the amygdala circuits that control innate defense responses. Finally, even when the amygdala is involved, there are multiple different kinds of circuits for different kinds of threats [5]. Threat processing is far more complex than is often implied in the literature.

However, the key issue is whether one should seamlessly transition from the involvement of the amygdala in some forms of threat processing to the conclusion that the

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amygdala is the well-spring of fearful feelings that those same threats evoke. The authors are partly justified in assuming this, because other studies found that threats not only failed to elicit threat-based responses, but also failed to elicit feelings of fear in patients with amygdala damage [5]. However, contrary to popular belief, the brain damage in these patients is not restricted to the amygdala [5]. Nevertheless, for the sake of argument, let us assume that this is not a problem and ask why amygdala-damaged patients might not feel fear.

Here are two possible answers. One follows from the common assumption that the amygdala is the neural mechanism of fearful feelings, a mechanism that humans inherit from their animal ancestors. I strongly oppose the view that humans have inherited circuits that create feelings [5]. A second possibility is that amygdala activation elicits fear responses in the body and brain that, in turn, help create a state that enters conscious awareness as a feeling of fear [6]. This is, I believe, is closer to the way things are. However, I take issue with the use of the term 'fear responses' to describe these amygdala-mediated consequences of threat detection [5], even though I have previously used this terminology myself (e.g., in [2]). This language implies that the defense responses go hand in hand with the feeling of fear. However, all organisms, from simple bacterial cells to incredibly complex animals, such as humans, must detect and respond to threats, regardless of whether they can experience fear. Calling these 'fear responses' puts the evolutionary cart before the horse. I prefer calling these 'threat-elicited defense responses' and this is not a mere semantic preference.

When a circuit in a starfish, ant, fish, mouse, or human detects a threat, defense responses are mobilized to help promote survival. In many complex animals, this results in the monopolization of brain and body resources, creating a motivationally specific global organimsic state [5]. Fear is only experienced if the organism is capable of consciously experiencing this state [7]. People obviously are. Whether other animals are also capable of such conscious experience is unknowable.

'Threat-triggered defense responses' and fearful feelings can be separated in the brain. For example, people can respond to learned threats without being conscious of the stimulus and without any particular feeling of fear [8] and can freeze or jump back from danger before feeling afraid. The brain systems that generate responses to threats are not one and the same as the circuits that allow us to experience fear. To understand 'fear' we need to understand consciousness [7].

Further complicating the idea that circuits that detect and respond to threats also generate the feeling of fear is the fact that there are far too many kinds of fearful feelings for fear to be simply encoded in a single subcortical brain circuit [9]. There are more than three-dozen words in English alone for variants of fear and anxiety [10].

As long as the term 'fear' is used interchangeably to describe both feelings and brain/bodily responses elicited by threats, confusion will continue. Restricting the scientific use of the term 'fear' to its common meaning and using the less-loaded term, 'threat-elicited defense responses', for the brain/body responses yields a language that more accurately reflects the way the brain evolved and works, and allows the exploration of processes in animal brains that are relevant to human behavior and psychiatric disorders without assuming that the complex constellation of states that humans refer to by the term fear are also consciously experienced by other animals. This is not a denial of animal consciousness, but a call for researchers not to invoke animal consciousness to explain things that do not involve consciousness in humans.

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