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Individual Differences Make a Marker in Fear Research

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Trauma- and stressor-related disorders, such as posttraumatic stress disorder (PTSD), cost billions of dollars in health care every year. Symptoms of these disorders vary dramatically among individuals, and many individuals that experience a traumatic event never develop PTSD (1). This suggests that individuals vary in their fear responses and propensity to develop PTSD. Despite this evidence, most research into the neurobiology of fear and the underlying mechanisms of PTSD combines individuals into group averages to improve analytical power. In contrast, some research, including the article in this issue by Graham *et al.* (2), identifies individual differences that play a key role in understanding fear responses and their underlying biology. These studies of individual differences in fear learning and memory hold promise to reduce the economic and personal burden of PTSD by developing better screening methods to identify individuals who are vulnerable to PTSD and transforming future translational research into therapies.

In research, the fear learning that leads to PTSD is often modeled using fear conditioning, a learning paradigm in which individual rodents or humans are presented with a neutral stimulus in combination with an aversive stimulus like a loud noise or a mild electric shock (3). After one or more pairings, individuals learn to express species-specific fear behaviors to the previously neutral stimulus. Their memory of this fear can then be observed later using a fear recall test. Graham *et al.* (2) used fear conditioning and recall to examine individual differences in fear responses in both rats and humans. Their primary focus was on correlations between fear responses during fear recall and the peripheral expression levels of fibroblast growth factor 2 (FGF2). FGF2 is downregulated in the postmortem brains of individuals diagnosed with major depressive disorder (4)—a disorder that is commonly comorbid with PTSD. In addition, Graham and Richardson have produced a body of work demonstrating that FGF2 can influence fear responses in rats (5). In their current work, Graham *et al.* (2) built on their previous work in rodents and expanded it to humans to demonstrate translational feasibility.

Graham *et al.* (2) first demonstrate that fear conditioning in rats elicits a range of individual fear responses (measured as freezing), and that these responses are negatively correlated with serum levels of FGF2: that is, rats with low levels of serum FGF2 have greater fear responses than animals with higher levels of FGF2. Graham *et al.* (2) also demonstrate that serum levels of FGF2 are correlated with hippocampal FGF2 levels in rats. These data

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extend the findings from their previous work using hippocampal FGF2 levels to serum, a relatively non-invasive measure and more comparable to one that could be used in humans.

Graham *et al.* (2) then extend their rodent findings to humans and show that salivary FGF2 levels after fear recall are also correlated with fear responses. Human individuals with low FGF2 show greater fear responses (measured by skin conductance responses), while individuals with higher FGF2 show lower fear responses. These novel results from Graham *et al.* (2) are exciting because they demonstrate a parallel between rodent and human peripheral markers of a major psychiatric illness. However, the human findings described in their article deserve a note of caution: the data display an unbalanced range, with most data points clustered together and a few outlier points likely near the limit of detection. As these outlier samples are likely to have high leverage, these data require replication with a more balanced range to confirm that the results are not being driven by a subset of the sample. Overall, these exciting results deserve replication so that we can build on them and learn whether FGF2 is predictive of fear responses across species.

These findings join a growing set of research into individual differences in fear responses. One study divided rats into high and low fear reactivity based on their responses to fear conditioning (6). This post hoc division of individuals is similar to the methods used by Graham *et al.* (2). My work has used animals selectively bred for specific behavioral phenotypes that demonstrate differences in FGF2 levels as well as fear behavior, allowing for prediction of which animals will be vulnerable to heightened fear responses before fear conditioning (7). Translational work on another growth factor, brain-derived neurotrophic factor, also demonstrated that in both humans and mice, genetic polymorphisms that lower brain-derived neurotrophic factor levels lead to reduced fear extinction or an inability to reduce fear (8). Together, these various lines of research demonstrate that both rodents and humans have variability in their responses to fear and that growth factors may modulate those responses. Additional investigation of the biological underpinnings of these individual differences may lead to new therapeutic options that might be used to screen individuals for vulnerability to PTSD.

The work by Graham *et al.* (2) is innovative in the use of a peripheral marker across species that correlates with differences in fear responses. This is the first time that FGF2 levels have been correlated between central nervous system and the periphery. A consistent pattern of expression between the brain and the periphery is crucial as researchers and clinicians consider the options for biomarkers or biological indicators of diseases such as PTSD. One outstanding question is where FGF2 levels should be measured in the brain when correlating with the periphery. Here, Graham *et al.* (2) correlated FGF2 levels of the hippocampus with serum FGF2 levels in rats. However, there are additional brain regions that would be interesting to test, such as brain areas known to be involved in the storage and retrieval of fear memories. The amygdala and hippocampus are involved in fear memory, as are areas of the prefrontal cortex (3). I hope that future studies will investigate the correlations between FGF2 levels in a variety of brain regions and peripheral FGF2 levels. In addition, it would be beneficial for future studies to present their FGF2 values in physiological units so that the data can be better interpreted and replicated. While the current study leaves many questions open for further research, the correlation between central and peripheral FGF2 is an

important step forward in the search for biomarkers of vulnerability to anxiety disorders such as PTSD.

The findings of Graham *et al.* (2) that individual differences in FGF2 values are correlated with individual differences in fear responses raise another question for future investigation: whether endogenous FGF2 levels as measured in serum or saliva are predictive of fear responses. Graham *et al.* (2) acknowledge this limitation of their data, suggesting that FGF2 be measured basally before fear conditioning in individuals to determine whether variance in FGF2 is caused by fear conditioning or is a pre-existing factor. In addition, it may be useful for future studies to apply linear regression to determine if FGF2 levels predict fear behavior in conditioned fear experiments. One caution mentioned above is that the human data in the current Graham *et al.* (2) article display an imbalanced range with strong central tendency. Additional research is needed to determine if the relationships described in this manuscript are robust and if they change from baseline. This is of particular importance to clinicians who could use peripheral levels of FGF2 in saliva as a screening tool to detect an individual's vulnerability to developing PTSD after trauma. Such screening tools could assist clinicians with applying therapies earlier or in a more targeted way for certain individuals.

Another interesting line of inquiry based on this new work by Graham *et al.* (2) is whether peripheral levels of FGF2 differ between healthy individuals and individuals with PTSD or other psychiatric disorders. FGF2 is known to be downregulated in the postmortem brains of patients with major depressive disorder (4). However, data from previous studies of peripheral FGF2 levels in individuals with depression have been inconsistent, perhaps because of disease state or variability in patient populations (9,10). If data from patient populations with depression or PTSD indicate that FGF2 levels are lower in those patients, then prospective studies can determine whether the FGF2 levels in rats and humans change with trauma or onset of depression. These insights would allow researchers and clinicians to better evaluate whether FGF2 levels can be used as a measure of vulnerability to PTSD or other mental health disorders.

The translational findings described by Graham *et al.* (2) in this issue are an important step forward in individual differences research in fear and anxiety. Similar evidence in both rats and humans associating lower peripheral FGF2 levels with greater fear responses provides an interesting basis for future research, opening up a variety of interesting questions regarding the role of FGF2 in fear responses and individual differences. Individual differences are key to understanding vulnerability to PTSD, and reducing the personal and economic burden that these diseases exact. Based on future studies, perhaps one day we will understand what factors underlie individual differences in fear responses in humans, and FGF2 might be one of them.

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