Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Biol Psychiatry. 2016 September 1; 80(5): 343–344. doi:10.1016/j.biopsych.2016.07.003.

Gain in Translation: Is It Time for Thigmotaxis Studies in Humans?

Christian Grillon and **Monique Ernst**

Section on the Neurobiology of Fear & Anxiety, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

Animal models have long been used to explore neurobiological substrates of behaviors and to develop treatment for mental illnesses. Although these models have considerably contributed to our understanding of neurobiological processes, they have been overwhelmingly disappointing to date for the drug discovery process, as preclinical models are poor predictors of clinical efficacy. It is largely agreed that many animal models lack cross-species translational validity, and that improvement will depend on maximizing the similarity of the measures of responses across species. Thus, paradigms yielding comparable observed phenomena in both preclinical animal models and human behavior are an important first step in this direction.

This commentary addresses the promises of a new translational behavioral paradigm for use in the study of agoraphobia, and, perhaps more generally, anxiety in humans. In this issue of *Biological Psychiatry*, Walz *et al*. (1) present results of a human analog paradigm to the rodent open field test (OFT) (2) to quantitatively measure the proclivity for avoidance of open spaces, the core symptom of agoraphobia.

Specifically, this study comprised 2 experiments. First, patients with agoraphobia and individuals with high anxiety sensitivity, a vulnerability marker for agoraphobia, and their respective healthy control groups were followed with a global positioning system during a 15-minute walk on a soccer field surrounded by wall-like vegetation. Second, only patients with agoraphobia and controls were asked to walk in a city with an open market square on their path. Strikingly, the agoraphobic patients and the individuals high in anxiety sensitivity exhibited thigmotaxis, similarly to rodents in the OFT. They showed a propensity to walk near the border of the stadium and away from the center of the field. In addition, during the city walk, the agoraphobic patients showed greater avoidance of the market square compared with the controls, suggesting that thigmotaxis can capture the core symptom of agoraphobia directly probed by the market square avoidance.

The work by Walz *et al*. (1) is an exciting step toward developing a translational model to identify cross-species mechanisms implicated in anxiety. This is especially relevant given the recent developments with the DSM-5, which has reinstated agoraphobia as a stand-alone

Address correspondence to Christian Grillon, Ph.D., NIMH/MAP, 15K North Drive, Building 15K, Room 203, MSC 2670, Bethesda, MD 20892-2670; christian.grillon@nih.gov.

Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

diagnosis in addition to agoraphobia with panic disorder (3). Psychiatric disorders involve psychological, physiological, and behavioral components. Clinical diagnoses are routinely based on self-reports and clinical observations, which are inherently subjective. The study of Walz *et al*. (1) may provide a first step toward a reconsideration of clinical assessment in terms of objective measurements, one objective of the National Institute of Mental Health Research Domain Criteria (4). The introduction of small computers and comfortable wearable biosensors has created new opportunities for monitoring the human body over long periods of time. An obvious development is to combine these biosensors and global positioning system in the human OFT to better characterize the agoraphobic phenotype.

At this juncture, however, questions emerge regarding the value of this translational paradigm for neuroscience research in humans, which will be addressed below. We will conclude by considering the next steps in the development of this human OFT.

Before addressing the model itself, we briefly recapitulate the features of the rodent OFT. The rodent OFT is a traditional conflict-avoidance task to study anxiety (2). It consists of measuring behavior elicited by placing the animal in an open space, from which escape is prevented by a surrounding wall. It takes advantage of the natural tendency of rodents to avoid exploring open, novel, and bright spaces, where they are vulnerable to predators. This natural tendency, termed thigmotaxis (i.e., tendency to stay close to the outer wall), is understood as an innate measure of anxiety in response to a perceived danger.

To what extent does thigmotaxis map onto agoraphobia? Here, the agoraphobic patients exhibited both thigmotaxis in the stadium and avoidance of the market square. However, it is unclear whether these behaviors were correlated (i.e., whether those patients with the highest levels of thigmotaxis were also those who avoided the market square). Similarly, whether elevated thigmotaxis in the participants with high anxiety sensitivity is also associated with avoidance of the market-square would inform the specificity of OFT sensitivity.

In addition, the interpretation of thigmotaxis as a measure of agoraphobia may be inconsistent with rodent data. First, no claim has been made yet as to a specific relevance of the rodent OFT to agoraphobia. If anything, the rodent OFT is thought as a model of generalized anxiety disorder (2). To better understand the difference between generalized anxiety disorder and (agora)phobia, it is important to distinguish between anxiety and fear, the former operationalized as a response to uncertainty and the latter as a response to imminent threat. Second, thigmotaxis, as a model of a component of agoraphobia, should be sensitive to the anxiolytics that are effective in agoraphobia. The first line of treatment for agoraphobia is the group of selective serotonin reuptake inhibitors (SSRIs). Rodent studies have shown inconsistent evidence of SSRIs' effect on thigmotaxis. However, the rodent OFT is sensitive to benzodiazepines, which are the most effective short-acting anxiolytic compounds. It remains to be determined whether the human OFT is sensitive to SSRIs. Notably, a major issue with the rodent model is that it probes an adaptive behavior, as opposed to a pathological condition. If anxiolytic drugs correct only maladaptive responses, then animals that display pathological anxiety may be sensitive to SSRIs in the OFT. Such pathological anxiety can be found among strains of mice and rats or induced by environmental, neurochemical, or genetic manipulations.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Caution should be taken, however, in interpreting thigmotaxis as an unambiguous index of anxiety. Thigmotaxis only represents the propensity to remain close to the wall of the OFT. This propensity is multifactorial and can depend on several factors, such as approach motivation (exploration), avoidance of open spaces and search for safety (defensive responses), and locomotor activity (2). This has important implications for the interpretation of the data. For example, depression, which is highly comorbid with anxiety disorders, is associated with lack of motivation to explore. This could manifest as enhanced thigmotaxis as well.

Does the human OFT have implications for treatment development? With the increasing ability of the pharmaceutical industry to develop compounds with anxiolytic profiles in animal models, it has become critical to identify, at an early stage, those compounds with therapeutic promise. The human OFT could promote an experimental medicine approach (5) by testing human models of pathology before launching costly and time-consuming clinical trials. The human OFT would help demonstrate that the drug does what it is supposed to do. Thus, the human OFT could help bridge preclinical science and clinical treatment studies via proof-of-concept investigations.

Finally, the development of an OFT analog suitable for use in the laboratory and scanner is essential to fully address the potential of the human OFT as a research tool. Could a virtual reality task mimic the OFT and retain some ecological validity? With the present human OFT, a number of factors cannot be controlled, and, importantly, this paradigm does not lend itself to neuroimaging. Therefore, from a neuroscience perspective, the ecological validity of the test must be balanced with the requirements of a laboratory task. In fact, virtual reality has been used for many years in clinical psychology in the treatment of phobia (6). While the combined application of virtual reality and functional magnetic resonance imaging in phobia research remains to be developed, such a combination has been successfully implemented in other anxiety research, such as with fear conditioning (7). The present finding provides the impetus to adapt the OFT paradigm for neuroimaging.

Defensive responses in humans are partly inherited from evolutionary history. Because of the translational nature of the OFT, we can assume that the neural mechanisms underlying thigmotaxis are highly conserved across species. Thigmotaxis in the rodent OFT has been shown to involve the main structures of the anxiety network (i.e., amygdala, bed nucleus of the stria terminalis [BNST], and hippocampus). New techniques in basic neuroscience, such as optogenetics, are paving the way to the identification of pathways specific to discrete symptoms. Already, studies have begun to apply optogenetics to uncover pathways in anxiety. For example, projections from the anterodorsal BNST to the lateral hypothalamus are involved in avoidance behavior, whereas projections from the anterodorsal BNST to the parabrachial nucleus mediate autonomic symptoms of anxiety (8). In addition, connections between the ventral BNST and the ventral tegmental area regulate anxiety and reward-seeking behavior in anxiogenic open fields (9). It is with the development of translational models in humans that advances in animal work can be best exploited. Fear conditioning stands as a prototypical example of a successful translational model for probing the neurobiology of fear (10). Could the OFT model play a parallel role in anxiety research?

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Mental Health Grant No. MH002798.

References

1. Walz N, Mühlberger A, Pauli P. A human open field test reveals thigmotaxis related to agoraphobic fear. Biol Psychiatry. 2016; 80:390–397. [PubMed: 26876946]
2. Prut L, Belzung C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: A review. Eur J Pharmacol. 2003; 463:3–33. [PubMed: 12600700]
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; Washingron, DC: 2013.
4. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]
5. Littman BH, Williams SA. The ultimate model organism: Progress in experimental medicine. Nat Rev Drug Discov. 2005; 4:631–638. [PubMed: 16056389]
6. Pull CB. Recent trends in the study of specific phobias. Curr Opin Psychiatry. 2008; 21:43–50. [PubMed: 18281840]
7. Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C. Contextual fear conditioning in humans: Cortical-hippocampal and amygdala contributions. J Neurosci. 2008; 28:6211–6219. [PubMed: 18550763]
8. Kim S-Y, Adhikari A, Lee SY, Marshel JH, Kim CK, Mallory CS, et al. Diverging neural pathways assemble a behavioural state from separable features in anxiety. Nature. 2013; 496:219–223. [PubMed: 23515158]
9. Jennings JH, Sparta DR, Stamatakis AM, Ung RL, Pleil KE, Kash TL, et al. Distinct extended amygdala circuits for divergent motivational states. Nature. 2013; 496:224–228. [PubMed: 23515155]
10. Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: Ten years of progress. Annu Rev Psychol. 2012; 63:129–151. [PubMed: 22129456]