

Changing the future, not the past: a translational paradigm shift in treating anxiety

Jürgen Margraf & Armin Zlomuzica

Imagine that you have had a traumatic experience. Would you ask a therapist to change your memories or to help you to deal with your experience? Would you prefer temporary relief or lasting change? These questions are highly relevant given that emotional disorders such as anxiety, depression or post-traumatic stress disorder (PTSD) are now among the most frequent, chronic and burdensome health problems worldwide. Consequently, there is much interest in cost-efficient treatments with long-term efficacy for these conditions; indeed, a better understanding of the mechanisms of cognitive behavioral therapy (CBT) and the molecular basis of memory is beginning to yield new options for treating emotional disorders.

Many guidelines recommend CBT as the most effective and efficient treatment for anxiety disorders. Exposure therapy, the prototypical CBT method used to address past conditioning from the environment and other characteristics of emotional disorders, has been hailed as one of the biggest success stories in mental health. In sharp contrast to drug treatments, dozens of studies have shown that the positive effects of CBT and exposure therapy persist stably after the treatment ends.

CBT in general and exposure therapy specifically aim to modify the impact of past traumatic events on the ability of patients to cope with the present and future. They therefore strongly rely on learning and other memory-related processes, the understanding of which has made great progress in the past years. Among the latest findings, mice models have shown that a combination

of inhibitors of histone deacetylases with exposure-like interventions can persistently attenuate even remote aversive memories [1]. The results suggest that epigenetic factors play a crucial role in establishing memory at the molecular level, and that modifying epigenetic control of gene expression could ameliorate trauma derived from past experiences. What are the practical implications of this for human patients? The answer to this question may not be what we think.

For several decades, better treatments have been promised “in the near future” based on translating basic biological science into clinical practice. To put it bluntly, neuroscience has so far not led to measurably better outcomes for any of the anxiety disorders, nor for other emotional problems [2]. Although psychotropic drugs are by far the most often used treatment modality in industrialized countries, there is no compelling evidence for the long-term stability of their small to moderate results. The scant follow-up evidence points to high relapse rates once medication is withdrawn. Among the reasons for this failure is the use of a merely empirical approach, which has led to erroneous illness models and an overly simple additive model of combination treatments.

The thinking behind traditional drug approaches assumes pathophysiology of neurotransmitter systems. As such, drugs that target monoamines or gamma-aminobutyric acid (GABA) have been applied in rather chronic, non-specific ways. It is therefore not surprising that treatment effects vanish once drugs are withdrawn. More importantly, in order to qualify as a

causal factor, the assumed pathophysiology would have to have existed before the onset of the disorder. In contrast to various psychosocial risk factors, this has not been shown convincingly. Classic drug treatments thus rely on a shaky model of pathology to give patients relatively unspecific medications for prolonged periods of time while side effects, potential abuse and negative long-term effects further impede the cost–benefit ratio. Moreover, traditional approaches to combining pharmacological and psychological treatments have relied on a simple additive model: You put two things together and hope that the result gets better. Remarkably, this has not been the case in many studies. In fact, for several classes of drugs—such as benzodiazepines or tricyclics—the combination has been less successful than CBT alone.

Recently, however, we are seeing a true translational paradigm shift that recognizes learning, memory and neuronal plasticity as the basis for psychological treatments and for new drugs that specifically target some of these mechanisms as potential enhancers of CBT. This new approach is much more specific than earlier pharmacotherapy since it relies on a sound understanding of learning and memory, gives substances only briefly and aims at ameliorating processes which, at least in principle, should create lasting effects. Successful augmentation of exposure in human patients has been shown for agents such as DCS, methylene blue and cortisol. In addition, behavioral augmentation via physical exercise and sleep has also been demonstrated [3]. These interventions may work by enhancing the consolidation of

newly learned inhibitory memory connections, or by updating threat-related memories during reconsolidation.

In another exciting development, animal research has provided greater knowledge of the epigenetic mechanisms that regulate the expression of genes that are critical for memory formation. Enhancing gene transcription by increasing histone acetylation can indeed erase remote threat-related memories in mice [2]. This approach is especially relevant because it may generate persistent long-term memories that last beyond the duration of normal memories.

Notwithstanding, it is important to realize several limitations. First, the observed augmentation effects are so far rather small. Second, the psychological treatments applied were often of “mild-to-moderate” intensity [4]. Thus, augmentation for full “gold standard” treatments remains yet to be shown. Third, at least some work seems to rely on misunderstandings about the nature and goals of psychological treatments for anxiety disorders: Exposure is more than extinction and extinction is not equivalent to erasure. Although extinction is a major candidate for explaining the effects of exposure, there are other relevant ingredients. These include corrective experience, disconfirmation of expectations, perceived control and self-efficacy. The goal of treatment is not zero anxiety, but realistic anxiety.

Consequently, therapy does not aim at erasing trauma or threat-related memories, but at changing their meaning by creating and enhancing new connections. It aims to change not only the meaning of past experiences, but also of future situations [5]. This applies even more to prospective memory or episodic future memory. Episodic memory is constructive rather than reproductive. In PTSD, appraisals of foreshortened future and permanent damage are associated with nonspecific and overgeneral past memories as well as reduced specificity in future episodic thinking. CBT not only addresses these aspects of memory, but typically also initiates behavior change in order to

ameliorate coping with future situations. Finally, learning to live with uncertainty is a developmental task. In a world of uncertainty in which about 90% of us will experience trauma at least once in our lives, it does not make sense to forget about it. As therapists, we should not underestimate how strong people are and should not make them underestimate themselves. Instead, we need to enhance our patients’ sense of self-efficacy and mastery of their lives. Therapy involves learning to cope with life.

Augmentation and mechanistic studies are relevant not only because of therapeutic gains for clinical practice, but primarily for advancing our knowledge about learning and memory. We should stop promising direct utility of basic findings and straw man arguments such as down-playing the efficacy of existing treatments. This is misleading because it distracts from the real potential of basic research: knowledge as an end in itself. As the example of astronomy shows, we are willing to pay for basic research even though the practical outcomes of cosmology or big bang theory are not immediately imminent. In the same vein, basic research into the mechanisms of psychological treatments should make it possible to overcome a central shortcoming of biological research into human anxiety disorders that equates correlation with causation.

Because much of this research has been correlative, the causal status of biological characteristics related to disorders remains unclear. For obvious ethical reasons, we cannot use experimental designs in humans and studies have thus relied on correlative designs or weak animal models that have limited validity and typically employ mild analogues. The classic psychological research on traumatic conditioning shows, however, that mild electric body shock in rats or memories of emotional pictures in humans are a far cry from the devastating and terrifying experiences of trauma as in PTSD or choking as in panic. Campbell *et al* [6] showed long ago that conditioned responses to respiratory paralysis do not extinguish even after a large series of

unreinforced trials. Differences in the complexity and contexts of human and animal behavior, as well as the differences between their respective cortical regions clearly call for human studies *in vivo*. This is where studying human treatments becomes relevant: Increasing health through treatment is ethically not only acceptable but actually imperative. Therapy can be conceived as an experimental manipulation of the assumed pathological processes that does not require recourse to laboratory analogues of dubious validity.

At a more general level, therapy is a prime example of the fact that humans are active, information-processing beings, able to change their world and their brains. Causal effects between the biological, psychological and social factors of health and disease do not represent a one-way street, but rather a two-way street with multiple dynamic interactions between local and distant neighbors, as well as systemic effects [7]. Epigenetics and gene–environment interactions as evidenced by the emerging field of therapy genetics are not among the least examples for this view. With the fascinating new methods available now, a major task for scientific research may be to remove barriers in thinking. Part of the ongoing translational paradigm shift could be to avoid focusing on small gains of limited practical progress and instead look for the big harvest of basic scientific knowledge about who we are and how we function.

References

1. Tsai LH, Gräff J (2014) *EMBO Rep* 5: 853–861
2. Gibertini M, Nations KR, Whitaker JA (2012) *Int Clin Psychopharmacol* 27: 100–106
3. Kleim B, Wilhelm FH, Temp L *et al* (2013) *Psychol Med* 43: 1–9
4. De Quervain D, Bentz D, Michael T *et al* (2011) *Proc Natl Acad Sci USA* 108: 6621–6625
5. Zlomuzica A, Dere D, Machulska A *et al* (2014) *Front Behav Neurosci* 8: 173–191
6. Campbell D, Sanderson RE, Lavery SG (1964) *J Abnorm Psychol* 68: 627–639
7. Margraf J (2015) *Psychol Rundsch* 65: 1–30