

Lost in translation?

Perdidos na tradução?

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No one with a background in literary theory would dare to say that translation is a trivial matter. It is a science as much as an art, and seminal translations have been as important as original literary material in many cultural scenes. It is also hard work: a recent translation of the first third of Joyce's *Finnegans Wake* has recently come out in China after 8 years of labor by its author.¹ Still, hardly anyone would consider the difficulty of translation as a reason to abolish linguistic diversity and establish a universal language. Although we evidently need communication between different societies, much of our cultural richness comes precisely from diversity, and many people dedicate their lives to making sure that the uniqueness of a particular language is preserved from globalization.²

These facts may seem distant from psychiatric research, but the connection is not that far-fetched. The concept of translational science has invaded the biomedical field over the last two decades, starting out in cancer research in the early 1990s³ and rapidly progressing to guide a number of initiatives around the world, including the 2003 NIH Road Map,⁴ the 2004 FDA Critical Path Initiative,⁵ and the 2005 NIH Clinical and Translational Science Awards Program.⁶ Brazil is no exception to the rule, with the creation of National Institutes of Science and Technology for Translational Neuroscience, Translational Medicine, and Molecular Medicine in 2008.⁷ The rationale behind the demand for translational research is simple: scientists must be more efficient in translating advances in basic sciences to clinical practice (or, as the much-

repeated motto states, in bringing knowledge "from the bench to the bedside"), in order for patients to benefit from scientific progress.

However, at least in psychiatry (and arguably in most medical specialties), one is forced to admit that the translational concept has not yet lived up to this promise. Examples in which neuroscience has actually suggested new treatment approaches (such as deep brain stimulation for depression,⁸ or pharmacological augmentation of exposure-based therapy for anxiety disorders⁹) are few and at an experimental stage, and most new treatments are still developed on the basis of existing therapeutic strategies – which, in turn, were derived from chance and empirical pharmacology, rather than by an understanding of the neurobiology of mental illness. We still lack good pathophysiological models for most psychiatric syndromes, at both the molecular and systemic level. And diagnostic categories in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)¹⁰ basically follow the same structure as former ones, developed decades ago, much to the disappointment of those who expected to see neuroscience play a bigger role in psychiatric nosology.¹¹

Of course, it could be just a matter of time before translation from basic neuroscience starts yielding its fruits in psychiatry. But after two decades of translational research causing more headlines than changes in psychiatric practice, perhaps it should be time to ask ourselves whether we are aiming our translational efforts in the right direction.

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There is “translation” in “translational”

The term translational obviously implies translation, which means “the process of translating words or text from one language into another.”¹² This concept not only assumes but actually requires the existence of two different languages to start with; however, this fact seems to have been frequently forgotten in the approximation between psychiatry and neuroscience. On the contrary, the rise of translational research has led to a great effort by both sides in trying to speak the same language – as well as in trying to use similar paradigms, diagnostic classifications, and terminology. Over a relatively short period, clinical psychiatrists began to speak naturally of serotonin, mirror neurons, or the prefrontal cortex, even though those terms are still largely dispensable in their everyday practice. At the same time, many neuroscientists started adding a “translational” twist to their projects, presenting research on basic topics (e.g., fear or attention) as “preclinical models” for conditions such as post-traumatic stress disorder (PTSD) or attention deficit/hyperactivity disorder (ADHD), often in order to attract more interest and funding.

Is there a downside in this convergence of languages? Perhaps. If on the one hand it has facilitated approximation between psychiatry and neuroscience, it also has the potential to impoverish our capability of describing things. Different fields of study use different languages for good reasons: studying the brain/mind at different levels of complexity (e.g., molecular, cellular, systemic, mental), each with its own set of methods (e.g., biochemical studies, imaging techniques, patient reports), will necessarily require different paradigms, classifications, and definitions; no single language or set of concepts will be efficient or useful at every one of these levels. Nevertheless, in these times of translational frenzy, it is not uncommon for researchers to inadvertently assume that concepts used to describe one level of research should naturally be applicable to other levels as well. This holds particularly true for DSM-V categories, a set of symptom-based constructs which have been “reified” (i.e., turned into natural entities) to the point that many unconsciously hold it as a given that they should correlate to specific molecular, cellular, or imaging alterations in patients, or even in animal models.¹³

It is not particularly hard to see that this is not the case. Even though concepts such as schizophrenia, attention deficit disorder, or social anxiety have proven useful in classifying patients with similar symptoms into categories (and thus have allowed clinical research in psychiatry to flourish), there is hardly a way to model such complex sets of dysfunctions in other species, or, even worse, in *in vitro* preparations. And although this

fact is generally acknowledged,¹⁴ this has not prevented many neuroscientists from taking existing fields of study in basic neuroscience (e.g., fear conditioning in rodents) and starting to brand them as models for something essentially human (i.e., PTSD), often without thinking about the simplifications involved. In this case, the “translational” effort not only does not add anything new to science (as it basically consists of building a new discourse for the same research¹⁵), but might actually take something away from it, as one is left to wonder how many subtleties are lost in the translation process, and how many senseless conclusions and overstatements can be reached when those subtleties are forgotten.

The same holds true for clinical researchers, who frequently assume that, just because a syndrome can be observed consistently enough to be included in the DSM, this implies that specific neurobiological abnormalities should exist to explain it at any level of analysis, and that we should thus be able to find diagnostic markers for it at the molecular level. However, there is enough distance between the molecular and the mental (with all kinds of causal loops in-between¹⁶) for the mapping between these levels to be potentially very frail, and thus a clear possibility that genetic or molecular markers might be an oxymoron for many (or most) psychiatric disorders.¹⁷ Not surprisingly, genome-wide association studies have largely failed to find specific genes for most common disorders, not only in psychiatry but in most clinical fields, raising the question of whether the expectation that genes and molecules would soon become the basis of diagnosis in medicine may have been overplayed.

There are many steps from bench to bedside

The main point in understanding the difficulties involved in translational research is that there are many levels at which the brain (or mind) can be studied, and that each of them should be approached with its own particularities. We can describe phenomena at molecular, cellular, network, systemic, behavioral, or clinical levels, and none of them is a better descriptor of reality than the others – the reductionist idea that replacing symptoms with genes will lead to more solid knowledge is misguided, in the same way that understanding transistors and wires will not make someone a better software programmer.¹⁶ Thus, there is no sense in trying to “replace symptoms with molecules” in psychiatry, as has been frequently advocated¹⁸: they represent complementary ways of looking at the same phenomena and cannot be substituted for one another. Conversely, there is also no point in trying to use DSM-V clinical constructs to

guide research in basic neuroscience, which needs to propose its own paradigms, rather than blindly accepting established diagnostic models, in order to have a real impact on psychiatry. And even though new classification proposals such as the Research Domain Criteria (RDoC), based on basic behavioral dimensions rather than clinical syndromes,¹⁹ might represent a way forward in bridging these different levels, they will also ultimately fail if used as a universal paradigm for all kinds of research in psychopathology.

This should not mean, of course, that we should refrain from translational efforts. But we must acknowledge that there is a myriad of translation steps from molecules to mental suffering. In this sense, it might be foolish to expect that most clinical psychiatrists will have a deep enough grasp of basic neuroscience to use it fruitfully – or, as stated by current NIMH director Thomas Insel, that psychiatry will eventually become a “clinical neuroscience discipline.”²⁰ Psychiatry is not clinical neuroscience, in the same way that medicine is not clinical biology – they are much more than that and should remain that way. At the same time, neuroscience is also much more than a set of models for clinical disorders, and should be free to build solid knowledge on its own terms, without having to invent a clinical application for every finding. Failure to understand this will lead to oversimplification, exaggerated claims, and wastes of time and money in translational endeavors built on a precarious common language.

So how should we foster translation? Just as in literature, we need to stimulate linguistic diversity as well as the existence of translators. It is insane to expect that every basic scientist can provide a translational perspective on his work, or that every psychiatrist should have a solid background in molecular neurobiology. One can be a very good neuroscientist without understanding clinical syndromes, or a very good clinical psychiatrist without being able to tell an excitatory from an inhibitory synapse. Of course, we do need some scientists who have a grasp of both sides in order to translate knowledge from one field to another, but they do not have to be everybody – and in fact, they will probably not be the leading scientists in any particular field, as one who is pursuing top-end research in basic science might be too focused in his own language to become proficient in clinical science and vice-versa.

Fostering translational science means training these scientists who understand basic and clinical research, and promoting their interaction with researchers on both sides; it does not mean trying to merge both fields into one. More than requiring every research project to be translational, or forcing basic and clinical scientists to speak the same language, we should stimulate linguistic diversity between fields – while at the same time

acknowledging the difficulty of translation and ensuring that those responsible for it are skilled enough to face it with the necessary care. This seems to be a given in literature, where no one seems to be arguing that translators are taking too long to bring *Finnegans Wake* to Chinese. And if we cannot concede that the mind is a lot more complex than a James Joyce novel, and respect the large gaps between basic neuroscience and psychiatry – or between molecules and mental illness –, we are likely to remain lost in translation for a long time.

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