

Response from Dr Ray Greek to an open letter from Joaquín M. Fuster, MD, PhD, and Professor at UCLA School of Medicine.

The following letter, originally to me, was published as an [open letter](#) by [Speaking of Research](#) on August 24, 2009. The letter is from Joaquín M. Fuster, MD, PhD, and Professor at UCLA School of Medicine. I reproduce it here in order to address the issues raised.

Fuster:

This is a copy of a letter written to Dr. Greek long ago (July 2003) in response to his request for a written contribution from me. Everything I say in this letter is the honest truth of what I think now, as I did then, with regard to cognitive neuroscience in the non-human primate. At the foot of the letter I add a glossary of terms unfamiliar to other readers.

In 2003, I wrote to several researchers asking if they would contribute a chapter to a book Niall Shanks and I were working on. That book eventually became [Animal Models in Light of Evolution](#). We originally wanted to write a point-counterpoint book but were unable to find enough researchers willing to debate the issue in print so published a traditional book instead.

Fuster:

Dear Dr. Greek,
Thank you for your letter of July 8 inviting me to contribute a chapter to your new book on the scientific evaluation of the animal model in science and medicine. It seems a highly worthwhile and timely project. Unfortunately, because of my—deserved or undeserved—reputation, to which you kindly refer, I am unable to contribute the chapter that you solicit. I have a very active research program, a splendid group of graduate and undergraduate students to teach, and an apparently never-ending list of meetings and writing commitments. In a word, I'm swamped.

I believe Dr Fuster but considering this was the response I received from numerous researchers, I am forced to conclude that despite their protestations to the contrary, a vast majority of researchers simply do not want to engage in a debate, in print or otherwise, on this issue. Currently, society agrees with them when they say that animals are vital for medical advances to continue so the researchers really have little to gain by educating society.

Fuster:

However, because I think the issue is legitimate and important, and you are interested in hearing both sides of the controversy, I cannot refrain from addressing it here with a few words, although only sketchily. Of

course, I presume you see me, correctly, on the side of those who believe that the animal model is extremely useful, at least for some aspects of neuroscience. Indeed, I firmly believe that, with regard to the cerebral cortex, there is no adequate substitute for the non-human primate model (no set of algorithms, no computer simulations, no inferences from human imaging or scalp electrophysiology). The value of the primate model, in what pertains to cognitive functions and the role of the cortex in the human, rests in the homology between the cortex of the non-human primate and that of the human.

Fuster is here making the usual *animals are useful* argument. This raises the question, what does *useful* mean? In *Animal Models in Light of Evolution* Shanks and I state:

Animals play roles in basic biomedical research aimed at uncovering fundamental biological knowledge, as well as applied research intended to have more or less immediate human clinical and/or medical relevance. The two contexts are not the same. Experiments on animals that expand the basic fund of biological knowledge may or may not be relevant to human medicine. Relevance cannot simply be assumed without evidence. After all, animal subjects, useful in the context of basic research, may nevertheless be causally disanalogous to the human target population that is the focus of applied research. Experiments, valuable in one context, may not be valuable in another.

When one considers the usefulness of animal models one must ask: Useful for whom? Useful for what? When Fuster compares the animal model to human neuroanatomy and physiology he is making the claim that animal models can and do predict human response. This claim is falsifiable and we have falsified it in *Animal Models in Light of Evolution*. We agree that computer models and in vitro studies cannot predict human neuropathology vis-à-vis Alzheimer's disease or human response to medications acting on the brain either, but that does not make animal models preferable. The animal model fails at prediction regardless of what else is or is not available.

Fuster:

That homology is structural as well as functional. As you probably know, the cytoarchitectonic structures of the two cortices are very similar, almost indistinguishable from each other. Functionally, the homology is just as striking. Here I am referring to the physiological mechanisms and principles of operation of the principal cognitive functions (perception, attention, memory, intelligence); not language, of course, which is exclusive patrimony of our species.

This language is telling. Fuster is essentially saying we are similar except for where we are different. The same can be said about any carbon-based life form. As we point out in *Animal Models in Light of Evolution*, the very small differences between species and even between individuals of the same species are why a drug will cure one person but kill another and why a disease may be fatal in humans but of no consequence in animals.

Fuster

Certainly, human cognition is immensely richer than monkey cognition, but the same essential network structure and dynamics can be recognized in the cortex of the two species. I do not need to explain to you the implications of the similarities in cortical structure and function for the pathogenesis, etiology, diagnosis, and treatment of certain nervous and mental disorders, even though some of those implications may not be direct or immediate (“lifesaving”).

Similarity does not imply predictability. Granted monkeys and humans are very similar; except where they are different.

Fuster:

To be sure, we have to be aware of the limits of the homology and of the important and undeniable inter-species differences. We have to also avoid the simplistic, indeed silly, assumption that homology is reducible to genetic identity. In the cortex, as in genetics, relationship is what really matters. Relationship—between cortical cell assemblies or between genes—is what ultimately defines the cognitive structure (percept, memory, etc.) or the phenotype. In the 21st century, as I see it, both cognitive neuroscience and genetics will finally make the much-needed Copernican shift from the sterile down-spiral of reductionism into molecules to the more holistic view of how biological systems operate (I recommend to you Hayek’s *Sensory Order*, U. Chicago, 1952 and my *Cortex and Mind*, Oxford, 2003, sorry I have no extra copy at hand to give you). For that crucial shift, the primate cortical network model is going to be pivotal.

Why? Merely stating something does mean it is true. In *Animal Models in Light of Evolution* we make our arguments from empirical evidence and the Theory of Evolution. Had Fuster agreed to have this discussion in a book, we could have explored why he maintains his position.

Fuster:

For many years, in my laboratory, we have been working on the neuronal foundation of memory and the role of the cortex, especially the prefrontal cortex, in it. It is difficult research, with its problems and limitations, like

any research in complex systems. It is also quite rewarding and productive. Again, to a person like you I do not have to explain, because you will readily understand, that we study neural activity at the cellular level because we are interested in cortical systems and networks and in the functional relationships between neurons and between cortical areas. Much of the knowledge we acquire in the monkey is undoubtedly transferable to the human. Some of it is not.

How does one know, prior to study in humans, which features in the monkeys will mimic humans and which will not? Until the human situation is known, we will not. Once again, the human data must be collected and analyzed at which there is no need for the monkey data, at least in terms of informing science about the human condition.

Fuster:

On the whole, our work is not only consistent with, but also supports, the network model of cortical function. Nowadays it gives me considerable satisfaction to see that model slowly but surely penetrating current thinking in cognitive neuroscience.

Acceptance in the animal-based research literature does not imply human relevance.

Fuster:

However, precisely because of the homology, indeed the unquestionable similarities, between human and monkey in cortex and cognition, we face some special problems. In your letter you state that you are not interested in ethical or philosophical questions. Yet, in our field, some of these questions are inextricable from scientific questions. In the first place, on scientific grounds alone, we cannot tolerate that our monkeys experience stress or pain. You know how detrimental both stress and pain can be for cognitive functions. Stress and pain, even minimal, can be serious obstacles to the attainment of our scientific aims, especially when we have to use behavioral tests for cognitive assessment. We have to avoid them in our monkeys at all costs. This is something that people in the animal rights movement do not seem—or want—to understand, even though I have no trouble understanding some of their ethical concerns. (In fact, years ago, when we had a miserable regulatory climate, I was gladly one of their best allies.)

I refer the reader to the numerous responses from the animal protection community that address the above paragraph.

Fuster:

Then, of course, there are the very legitimate ethical and philosophical questions of experimenting on animals that are very much like us but lack one of our cognitive functions, namely (no pun intended), language; they cannot tell us what pleases or displeases them, even though they are fully sentient. Fortunately, of course, they have emotional “language.” (I am sure you know it but, in case you don’t, I highly recommend to you Darwin’s wonderful book on emotional expression in man and animals, reedited by Eckman). Thus, by vocal, facial and bodily signs, monkeys can indeed tell us how they feel. (After almost half a century of working with macaques, I think I can proudly add “monkey language” to the list of the other six that I can understand reasonably well!)

So, the challenge in the study of primate cognitive neuroscience is to apply a judicious combination of scientific, ethical, and philosophical precepts. The ideal balance is difficult to achieve, but the basic principles are simple enough: (1) Impeccable scientific rationale toward practical and meaningful goals; (2) Minimum number of animals to attain those goals; (3) Exquisite care of the animals; and (4) Exhaustive analysis of the data to obtain maximum yield of information and to avoid duplication.

I again refer the reader to the numerous animal rights arguments that pertain to the above. AFMA and the book *Animal Models in Light of Evolution* do not address the ethical arguments but recognize that they are important to society and thus we suggest people read both sides and come to their own conclusions.

Fuster:

I’ll finish by going back to the scientific aspects, which are those that interest you. Right now, we are investigating the coupling, in higher cognitive functions, between neural activity—as reflected by neuronal discharge and local field potentials—and hemodynamic change, something that cannot be done in the human. The results of this exciting research, in my view, may have enormous implications for our understanding of the biophysics of functional imaging methods in the human and the dynamics of cortical networks.

This is exactly what we address in *Animal Models in Light of Evolution*. Fuster assumes animals are predictive for humans. They are not.

Although I cannot write the article that you graciously invited me to write (it almost seems that this long letter ought to do!), you are naturally welcome to visit my website, where you can find the details of my use of the monkey model in cognitive neuroscience. That would undoubtedly give you a better perspective of my views on the issue than I have been able to convey in these lines.

I wish you success with your book, which I look forward to reading after it appears in print. I hope you will, indeed, cover both sides of a very important controversy.

Yours sincerely,

Fuster's argument is typical for the basic research community. In the final analysis, almost everyone in the basic science community that uses animals attempts to justify this use by appealing to the predictive ability of animal models. Shanks and I refute this notion in *Animal Models in Light of Evolution* and I refer the reader there for more details.