

*The highlight for May, 2010 is by Dr. Fernando Torrealba who is at the Department of Physiological Sciences in the Faculty of Biological Sciences of the Pontificia Universidad Católica de Chile. Dr. Torrealba has had an interesting path leading to his work in perceptual states. Having initially traced sensory projections of visual information (working with Dr. Vincente Montero and Dr. R.W. Guillery), he turned to the visceral system where he identified and examined primary projections to the nucleus of the solitary tract to the thalamus and then to the insular cortex. It is this latter projection area that he and his colleagues have examined in relation to malaise and drug craving. In a seminal paper with Drs. M. Contreras and F. Ceric (Science 315:2007; 531-534), Dr. Torrealba identified an area in the insular cortex that apparently receives and projects sensory information about the body state (in response to amphetamine and LiCl). Such information is used to identify reward and aversion states in the body and to act on these states. What is most interesting about this assessment (of reward and aversion) is the fact that the identification of such pathways and their implications for motivated behaviors did not come out of a learning and memory background. His work argues nicely that parallel approaches to common issues can generate preparations and paradigms that provide important and complementary findings. Dr. Torrealba's highlight describes his interest in sensory systems and their mediation of behavior. His work has important implications for all of us in food avoidance and drug abuse research.*

My interest in brain research was directly related to the reason to study medicine: to understand multiple sclerosis, the disease that killed my maternal grandfather. Such an extremely specific drive was slowly replaced along my medical studies by a more general interest in understanding brain function as it relates to neurological diseases first and human behavior or psychiatry in a distant second place.

At that time in Chile, after finishing high school, it took seven years of study in medical school to become a general physician. A small fraction of we medical students were interested enough in basic science so as to work in some of the research laboratories at the Universidad de Chile School of Medicine. After a year in the laboratory in the Department of Neuroanatomy, where not much frontier research was conducted, I moved, during my fifth year as a medical student (*ca.* 1970), to one of the laboratories conducting electrophysiological studies on the visual system. This move marked the beginning of my distancing from medical practice. Another important contributing factor was the realization, while I took the introductory Neurology or Psychiatry courses for medical students, that as opposed to what Internal Medicine could offer to their patients in terms not only of diagnosis but, more importantly, in terms of evidence-based treatments (an old concept that crystallized later on), the two medical branches dealing with brain and its pathologies did not have much to offer patients.

I worked on the rat visual cortex and, with Dr. Vicente Montero and his colleague Arístides Rojas, we published the first mapping of the visual cortex that showed the existence of multiple distinct visual areas in the posterior cortex of the rat (Montero et al., 1973). It was amazing to realize that I could contribute to understanding the brain better, and at that time, in the early seventies, the visual system was (and it still is) the

paradigmatic brain system where many key questions could be posed and answered!

And, best of all, understanding in depth one sensory system (the visual), one could hope that perhaps other brain functions and systems could also be understood. In 1978, I was invited to work as a postdoctoral fellow in Professor R. W. Guillery's laboratory at The University of Chicago (at that time, an M.D. like myself could be a postdoctoral fellow without having a Ph.D. degree).

My 3 years stay in Chicago was a turning point in my career as a neuroscientist, because it was there that I learned the craft of designing experiments to address a significant question and writing a paper. Further, the intellectual environment in Guillery's laboratory was quite unparalleled and extremely exciting. Whatever grasp I had of brain structure, development and function was greatly enriched there. In addition, in Guillery's lab at that time the central structure to be understood was the visual thalamus, which nicely complemented my initial work on the visual cortices. In 1981, I went back to Chile and quickly decided that while in Chile I could not compete in vision research. At that time, it seemed that the relevant research in vision could only be made on primates, something impossible at that time in my country. So, I decided to try to understand a much less studied sensory system: that originating from the internal organs. From the start, I had always in mind making a comparison between the visual system and the visceral sensory system.

The first anatomical difference between the two sensory systems we found was the much higher degree of overlap in the projection of visceral primary afferents to the nucleus of the solitary tract, where the second neuron in the visceral sensory system resides (Claps and Torrealba, 1988; Torrealba and Claps, 1988). Primary sensory

afferents and/or the first central neuron of a sensory pathway are known to initiate an ascending sensory pathway and to participate in local reflexes. While in the visual system emphasis is usually placed on the projection to the visual thalamus and visual cortices, that is, the branch of the visual system that underlies conscious perceptions of visual objects or the perception of components of visual objects, in the visceral sensory system the emphasis has been placed on its reflex, non-perceptual branch. We then showed that indeed there existed perceptual (ascending) and reflex (descending) parallel visceral streams of processing arising from different neurons from the nucleus of the solitary tract (AcunaGoycolea et al., 2000). We made the point that each of these processing streams could be differentially modulated by descending glutamatergic projections from the insular (Torrealba and Müller, 1996) and the infralimbic (Torrealba and Muller, 1999) cortices.

The next step was to show that the sensory visceral thalamus, located in the parvicellular ventroposterolateral nucleus, is connected with a particular sector of the GABAergic thalamic reticular nucleus in the same way as other, better known, sensory thalamic nuclei like the visual, gustatory or the classic somatosensory thalamus. This finding is important because it revealed an attentional mechanism common to visceral and exteroceptive sensory systems. Such a mechanism may explain how we direct our attention to visceral sensory information (Accarino et al., 1997). In addition, and as important to the idea of a visceral sensory thalamus, there was the realization that there might be a primary (or first order) visceral sensory cortex in the posterior insula and a secondary (or higher order) visceral sensory cortex in the anterior insula of the rat (Stehberg et al., 2001), something similar perhaps to what had been postulated for the human insula (Craig, 2002). Importantly, Craig showed that the lamina I interoceptive

pathway, which carries information from thermal, pain, itch, limbic touch, muscle fatigue among others, converged with the visceral sensory pathway at least in the insular cortex and may be in a common thalamic region, forming a single Interoceptive Sensory System in charge (at least) of continuously monitoring the physiological state of the body.

We had been trying to figure out an answer to a chronic question we had been asking ourselves: if the viscerosensory system has a very robust ascending pathway that projects to the insular cortex, what conscious perceptions are the results of insular cortex activity? Around that time I read the thought provoking book by Antonio Damasio (Damasio, 1994) “Descartes error”, where he updated and much extended William James ideas on emotions and their possible relation to bodily states. That was for me an eye-opener in the sense that now I could imagine many conscious perceptions that could be affected by insular cortical activities.

We therefore began to set up experiments to better reveal the role of the posterior (primary) insular cortex in the perception of bodily states and used two examples of bodily states that were amply studied and so quite acceptable as models: malaise and drug craving (Contreras et al., 2007). We first induced the state of gastrointestinal malaise that is widely used as the unconditioned stimulus in conditioned taste aversion (CTA) learning, i.e., a single i.p. injection of LiCl. We assessed malaise by evaluating latency to (and time spent) lying on the belly, as well as other typical signs, and found that the reversible inactivation of the primary interoceptive insular cortex with a bilateral microinjection of 1  $\mu$ l/side of lidocaine, a sodium channel blocker, completely abolished the signs of malaise. The effect lasted 15-20 min, which is the time lidocaine

is able to inactivate a small cortical region. It was amazing to see the rats just injected with LiCl show normal ambulatory behavior with no obvious signs of illness. In contrast, the intact rats showed not only the behavioral signs of malaise, but an increased Fos-ir expression in subregions of the granular insular cortex.

The second experiment concerned drug craving, and here we evaluated craving by measuring place preference in amphetamine-experienced rats. About half of the rats treated with amphetamine changed their place preference to the place in which they had received systemic amphetamine injections. The rats whose primary interoceptive cortex (in the posterior insula) had been reversibly inactivated with lidocaine returned to their default preference for a black compartment, while rats microinjected with vehicle in the insula or microinjected lidocaine in the primary somatosensory cortex maintained their preference for the place associated with amphetamine.

We interpreted these findings as a clear indication that the reversible inactivation of the posterior insular cortex makes rats blind for a while to their bodily states, and perhaps bodily needs, so that the absence of interoceptive information from the insula to the rest of the brain is equivalent to a state of well being (or at least “no problems from the body front”). We believe that many more experimental studies in animals, in addition to the more correlational studies in humans, are needed to better understand the relationship between insular cortices activities and motivated, including emotional, behavior (Damasio). In my laboratory, my students and I are exploring the role of the insular cortices in homeostatic behaviors, like drinking and feeding, and its role in emotional responses, inspired by James and Damasio’s ideas relating bodily responses to emotions

with the idea of getting a more comprehensive understanding of normal and pathologic feelings and emotions.

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