Imaging a Brighter Future

The first functional magnetic resonance imaging (fMRI) study of a psychiatric illness appeared in The American Journal of Psychiatry nearly two decades ago and began with the following statement: “Functional echo planar magnetic resonance imaging (MRI) probably will be of importance in assessing brain abnormalities in psychiatric disorders” (1). The ability to observe the physiology of the living brain has been an intriguing tool for psychiatry since the development of the EEG in the early 20th century, but the value of what has actually been learned has often seemed elusive. Certainly, there is as yet little, if any, clinical use for any form of functional brain imaging. Studies typically do not generate insight into how abnormal brain function determines patients’ thoughts and actions. Clinical readers have every reason to skip over yet one more set of brain images, and research colleagues from other disciplines may wonder whether anything has been learned to warrant all of the efforts put into these studies over 17 years.

What may not be appreciated is the emergence of a different perspective on how imaging informs understanding of mechanisms in psychiatric illness, a development illustrated by two articles in this issue of the Journal, by Shin et al. (2) and Etkin and Schatzberg (3). These two studies demonstrate functional alterations in the cingulate gyrus within the medial prefrontal cortex in posttraumatic stress disorder (PTSD), generalized anxiety disorder, and major depression. Psychiatry has long struggled with the limitation of our investigative tools. We cannot biopsy the brain or otherwise directly observe the function of its nerve cells, except as they are revealed indirectly through patients’ words and actions. We do not have animal models for most illnesses, unlike other medical specialties for which animal models are keys to therapeutic advances. Of course, this is because of mental illnesses’ complex features, features not easily modeled outside the clinic: laboratory animals cannot tell us of their moods and anxieties.

The Shin et al. and Etkin and Schatzberg articles—not uniquely but certainly in an exemplary way—bridge the gap separating studies in people and animals. They do so by suggesting that the medial prefrontal cortex neurons mediating an animal’s response to danger are also dysfunctional in human PTSD, anxiety, and depression. Psychiatry has long struggled with the limitation of our investigative tools. We cannot biopsy the brain or otherwise directly observe the function of its nerve cells, except as they are revealed indirectly through patients’ words and actions. We do not have animal models for most illnesses, unlike other medical specialties for which animal models are keys to therapeutic advances. Of course, this is because of mental illnesses’ complex features, features not easily modeled outside the clinic: laboratory animals cannot tell us of their moods and anxieties.

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Shin et al. examined the neural correlates of genetic risk. They found that combat veterans with PTSD had increased reaction time slowing when they responded to targets that seemed out of position. Relative to other targets, these out-of-position targets also produced increased activation of the dorsal cingulate cortex in veterans with PTSD compared with veterans without PTSD. Similar increases in reaction time and brain activation were seen in comparisons of two groups of monozygotic twins, with neither group exposed to combat. However, one but not the other of these two groups had a twin with PTSD. These findings suggest that cingulate dysfunction is a genetically determined risk factor for PTSD.

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Etkin and Schatzberg examined specificity in the neural correlates of anxiety and depression. Their task presented research participants with conflict by using stimuli that create competing emotional responses (e.g., happy faces with the word “FEAR” written over them or fearful faces with the word “HAPPY”). They found that reaction time slowing decreased as subjects adapted to the conflict. This occurred in healthy subjects and in subjects with major depression but not in those with generalized anxiety disorder. Moreover, while depressed patients resembled healthy subjects in terms of their behavioral slowing, they resembled anxious patients in terms of their cingulate function. Thus, in terms of their neural responses, both anxious and depressed patients showed less adaptation than healthy subjects to the conflicting stimuli, based on levels of engagement in the ventral cingulate cortex. Moreover, the depressed patients’ ability to perform normally on this task, despite the presence of abnormal cingulate function, appeared to result from their ability to compensate for a cingulate-based deficit by engaging other prefrontal cortex areas.

What is remarkable, and perhaps unstated, when considering both studies is that their findings now show how researchers can conclude with increasing precision that human anxiety and depression share a common neuronal substrate with experimental models of animal stress and fear. When rodents hear a tone followed by a mild electrical foot shock, they quickly develop a startle response to the tone. If the tone is presented repeatedly without the shock, rodents gradually lose or extinguish their startle responses. They have not forgotten that the tone and foot shock were paired. We know this because the startle reaction often reappears when the tone is presented on a later day in a different setting. Instead, rodents have learned that some tones exhibit significant but relatively weak associations with foot shocks, unlike other tones, which exhibit either very strong or no associations whatsoever with these shocks.

This research shows that a relatively subtle, clinically relevant form of learning can be mastered by the rodent. This form of learning depends on the rodent’s ability to activate specific neurons in their frontal cortex, including the rodent analogue of the primate cingulate cortex. Moreover, this ability influences the rodent’s capability to respond to other circumstances. Animals that appear fearful in various settings are less able than fearless animals to activate these neurons and less able to overcome their fear by mastering this subtle form of learning. Nonhuman primate models extend the role of the prefrontal cortex to even more complex, conflict-laden situations, such as the situations modeled by Shin et al. and by Etkin and Schatzberg. Studies like the two in this issue show that we can now examine the same neurophysiological mechanisms in animal models and human mental illnesses.

Thus, basic animal models for human anxiety, depression, and PTSD can now emerge to facilitate the piloting of new treatments. Medication and nonmedication development are both possible outcomes. Current psychotherapies focus on teaching patients new information processing strategies by talking about perceptions and emotions. But brain imaging studies suggest that the dysfunctions in anxiety, depression, and PTSD also involve relatively rapid, nonlinguistic processes about which our patients cannot tell us. Such findings might encourage attempts to use procedures, such as stimulus-response conditioning, to alter sublinguistic information processing dysfunctions and monitor the effect on emotions and behavior.

Whether considering psychopharmacology or psychotherapy or both, researchers can now begin to model new treatments in animals with some confidence that the effects on brain function in these animals operate similarly in affected patients. Moreover, functional neuroimaging allows researchers to examine effects of these treatments directly on dysfunctional brain-based processes in patients. This facilitates the evaluation of therapeutic effects at an earlier stage of treatment development than is currently possible. Such a process of examining the effects of a treatment on underlying organ system dysfunction raises hopes for novel treatment discovery. This is because it brings.
the treatment-discovery process in psychiatry more closely in line with the processes used successfully in other medical specialties. With this approach, researchers can first examine treatments’ biological effects in animals and people before they expect effects to become evident in people’s quality of life or survival.

References


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