SPEAKER NOTES

New Research in Brain Imaging and Treatment of Bipolar Disorder

Summarized by Thomas T. Thomas

In honor of Bipolar Awareness Day in California, on January 22 our speaker was **Terence A. Ketter, MD,** who is Acting Associate Professor of Psychiatry and Behavioral Sciences, and Chief of the Bipolar Disorders Research Clinic at the Stanford University School of Medicine.

"There is a convergence of interests between biological research and groups like yours which are trying to destigmatize mental disorders," Dr. Ketter began. "Brain imaging is showing that most mental illness has the same physical basis as other diseases."

The doctor opened his presentation with an introduction to the brain and its component parts—or "subprocessors," as he called them—which regulate emotion and thought. These include the limbic system, the hippocampus, and the amygdala. He likened several of these structures to food items, which they look like and closely match in size: onion rings, dates, and almonds (although the hippocampus is named for the seahorse, which it also resembles).

He noted that the front parts of the brain, the frontal and temporal lobes, and the forward areas of each of these internal structures generally mediate emotions and moods. The back parts, especially the auditory and visual cortices, mediate memory and perception.

But the mind is much more complex than this. A sensation may recall an emotion, which evokes a memory of other feelings, which in turn may lead to other thoughts and mental images.

To help understand these relationships, Dr. Ketter distinguished between emotions, moods, and temperament, as follows:

- **Emotions** are acute and subject to rapid arousal. They are generally precipitated by sensory inputs and may last for only seconds or minutes. They often lead to direct action.
- **Moods** are of longer duration, often days or months, and usually arise from the action of hormones or brain chemicals. Moods often yield a chain of thought or understanding.
- **Temperament** seems to have a genetic component, as part of the individual's unique makeup, and endures for years or decades. Temperament renders us, in turn, susceptible to moods and emotions.

Individuals may be classified as hyperthymic, hypothymic, and cyclothymic. With "-thymic" simply meaning mood, such people are—respectively—actively involved in moods and emotions, subdued in their moods and emotions, or cycle between high and low states. The latter category includes bipolar patients.

Emotions occur deep inside the brain, while moods seem to be localized on the surface of the cortex. They form a feedback loop through the

"subprocessors," and the flow can be either positive or negative, depending on the shape of the loop.

Moods and emotions are regulated by two amino acids that saturate the brain: glutamate, which is excitatory; and gamma amino buteric acid, or GABA, which is inhibitory. Most modern brain drugs try to stabilize or hold back the actions of either glutamate or GABA.

Brain imaging looks at the brain and its structures and tries to determine which parts are active during particular brain functions like feeling a strong emotion or concentrating on a mental task. Brain imaging is performed in two steps:

- **PET scans** (short for "positron emission tomography") indicate which nerve cells are working by measuring their metabolic activity. This is shown by the radiation given off when the cell burns a radioactive sugar that has been injected into the cerebro-spinal fluid. The more active the cell or group of cells, the more radiation is emitted.
- **MRI scans** (short for "magnetic resonance imaging") use powerful magnets to align the hydrogen ions in the water that composes most of our body weight. A radio wave of a certain frequency is then sent through the brain, causing the ions in tissue of a specified density to respond with a return signal. This imaging system is like an x-ray but is more sensitive to soft tissues and less invasive.

Both of these scanning methods use powerful computers to create three-dimensional images of the brain, often in a series of color-coded "slices." By superimposing PET readings of metabolism upon MRI depictions of tissue, we can relate brain structures to brain function. This shows us the brain at work—a far superior picture to that given by picking through dead tissue at an autopsy.

By studying these combined images, psychiatrists are starting to build up a picture of "normative" brain function, which can be grouped by the ages of test subjects. Then people with suspected mood disorders can be compared with these base levels of data. Abnormally reduced brain activity, signified by lower metabolism, can be linked to depression; abnormally heightened brain activity is related to mania.

In this research, psychiatrists distinguish between primary mood disorders, which result directly from imbalances in brain metabolism, and secondary disorders in which some other process—a stroke, tumor, or injury—alters the metabolic activity.

For example, by blocking blood supply to parts of the brain responsible for emotion and mood, a stroke or tumor can create a depression. Interestingly, in one study, a stroke in the left frontal lobe resulted in emotional depression for 60 percent of patients, while a similar injury to the *right* frontal lobe almost never did. A stroke in the back quadrants of the brain had only a slight chance of creating depression.

In another study, test subjects received shots of procaine (the synthetic painkiller that dentists use) into their bloodstreams. Taken this way, the drug causes an extreme emotional response—either euphoria or distress—as well as the sensation of flashes of light and a ringing in the ears. Brain imaging reveals that

procaine causes activity in the amygdala which, so Dr. Ketter thinks, channels glutamate (the exciter molecule) back to the visual and auditory centers. People with mood disorders often have a suppressed reaction to procaine, suggesting an imbalance in their glutamate metabolism.

Superimposing PET scans on MRI images also reveals differing patterns of brain activity among bipolar patients. One group, identified as Bipolar 1, typically has "hot" temporal lobes—signifying a lot of activity—but only during the *depressed* part of their cycle. Bipolar 2's, on the other hand, have a "cooler" overall image but tend toward rapid cycling. These findings suggest that bipolar disorder may not be a uniform illness but instead represents a spectrum of related conditions.

The response of bipolar patients to various drugs appears to depend on their initial brain activity levels. A person with a very active or "hot" brain might be successfully brought down to more normal activity by a glutamate-inhibiting drug. But if he or she already starts at a depressed level, the drug may have little effect or worsen the symptoms.

"The drugs do something to everybody," Dr. Ketter said, "but where you start from is important."

Using brain imaging, psychiatrists are beginning to predict the response of an individual patient to any of the several drugs available to treat bipolar disorder.

Lithium, Tegretol, and Depakote—the top three choices so far—all work on GABA and have similar inhibitory effects. Interestingly, their basic molecular structure *looks* like that of GABA, too.

A number of the newer drugs, classed as anticonvulsants, work on glutamate. Among them is Felbamate, which started as a weight-loss drug but developed such side-effects in the general population that it is now restricted to use with juvenile epilepsy. Other new anticonvulsants are Gabapentin and Lamictal.

A second class of drugs for possible use with bipolar are the familiar antipsychotics—Clozaril, Risperdal, Zyprexa, and Serlect. These seem to function as mood stabilizers in treating bipolar disorder.

In closing, Dr. Ketter noted a similarity between the positive and negative symptoms of schizophrenia and the extremes of mood in bipolar disorder. Positive symptoms like delusion, hallucination, and loose association resemble mania. Negative symptoms like amotivation, anhedonia, and asociability tend to resemble depression. This again supports Dr. Ketter's suspicion that there is a spectrum of illnesses involved with what we call the mood disorders.