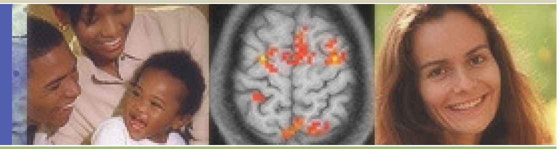

Science Update
May 6, 2008

Imaging Identifies Brain Regions and Chemicals Underlying Mood Disorders; May Lead to Better Treatments

WASHINGTON, DC, May 6 — Recently developed imaging techniques allow the mapping of the brain circuits and chemical systems believed responsible for a range of mood abnormalities including depression and bipolar disorder, and hold promise for improved treatments, scientists say.

They spoke today at a press conference involving presenters from symposia sponsored by the National Institute of Mental Health (NIMH), a part of the National Institutes of Health, during the American Psychiatric Association Annual Meeting here.

"These studies contribute new information about how the brain malfunctions in depression and bipolar disorder, what goes wrong with brain chemicals, and where in the brain the problems arise," says Ellen Leibenluft, MD, of NIMH. "We find that the brain systems involved and the exact nature of the difficulties, differs among patients, even when those patients have similar symptoms. Eventually, data like these will allow us to develop more individualized and targeted treatments for these illnesses."

Charting Brain Systems for Major Depression

Major depressive disorder (MDD) is an illness with high prevalence in the population, yet its underlying biological mechanisms are complex, with genetic and environmental factors influencing each other and leading to varying levels of vulnerability and resiliency.

New studies of two brain chemical systems thought to be involved in the modulation and response to stressful events finds that both are altered in untreated patients with MDD. "Dysregulation of these systems is present in patients diagnosed with MDD and we are studying their relationship with specific characteristics of the illness, such as severity and treatment response," says Jon-Kar Zubieta, MD, PhD, of the University of Michigan.

Using molecular imaging with positron emission tomography, Zubieta and his colleagues traced levels of the receptors for the brain chemicals serotonin and endogenous opioids, or naturally-occurring pain killers. Receptors are specific protein molecules on nerve cells where brain chemicals exert their effect. In a study of 17 untreated patients, the researchers found an overall reduction in the concentration of serotonin 1A receptors in the hippocampus, compared with 19 matched healthy subjects. The hippocampus is a brain region critically involved in memory formation, but also in the regulation of stress, among other functions.

"The reductions in these receptors were correlated with the functional impairment of the patients in work and with their families, with greater impairment being associated with lower receptor concentrations in this region," Zubieta says. Patients responded

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to treatment with the antidepressant citalopram.

In another study, the scientists examined a subtype of opioid receptor in a separate sample of 18 unmedicated MDD patients. They found that the concentration of "mu" opioid receptors was decreased in the thalamus of these patients, an area implicated in emotion regulation, compared with 19 matched healthy controls. The mu receptors are key molecular switches in regulating mood and triggering brain reward systems.

These reductions in receptors were further correlated with a greater concentration of stress hormones, such as cortisol, in the blood of the patients, which may reflect an exaggeration of biological stress responses in these patients, say the researchers. They found that patients who failed to respond to the antidepressant fluoxetine (Prozac) had lower concentrations of these specific receptors in the anterior cingulate, a brain area involved in the processing of emotional states.

This information highlights the biological diversity of MD, Zubieta says. In addition, alterations in brain chemical systems and brain circuitry involved in stress and responses to environmental events can disrupt an individual's work, social, and family life, and response to typical antidepressant treatment. Improved understanding of the sources of this biological diversity, including genetic and environmental influences, will help define subtypes of the illness and their implications for diagnosis and treatment.

"For example, the study on the mu opioid system suggests that a profound dysregulation of central stress-responsive systems may identify a subgroup of patients less likely to respond to first-line, standard antidepressant treatments," Zubieta says. "Further delineation of these processes would lead to the development of tests that may orient treatment decisions. Of course, there are a number of neurotransmitter systems that may be disregulated in MDD, this being the topic of ongoing research and tool development."

Abnormal Reward Patterns Found in Depression

In other studies, researchers are using PET and functional magnetic resonance imaging (fMRI) to determine the brain mechanisms underlying one of the symptoms of depression — anhedonia, or the inability to experience pleasure. "The identification of brain systems and circuits whose activity can be correlated with specific symptoms is a first step toward the development of more targeted and effective treatments for depression and other disorders of the brain," says Wayne Drevets, MD, of NIMH. Drevets' review of five studies — involving about 120 patients and as many controls — reveals abnormal patterns of neural activity and brain chemical function in specific circuits in depressed people as they perform reward processing tasks. The series of neuroimaging studies from the NIMH show how abnormalities in their brain reactions during the act of winning money could be turning normal pleasures into unimportant or even uncomfortable events.

In the brain, feelings of pleasure coincide with the release of the chemical dopamine, which is then taken up by proteins called receptors designed to receive it. The network of areas in the brain devoted to processing pleasurable experiences interacts with dopamine to form a "reward-learning pathway," including the amygdala and hippocampus. This network participates more generally in controlling emotional behavior and organizing activities designed to achieve goals, and storing memories.

To test the idea that depressed people's impaired ability to feel and react may be caused by different patterns of responding within the reward-learning pathway, scientists using PET and fMRI looked for differences in brain blood flow, dopamine release, change in mood, and performance by participants given a chance to win money. These activities are known to turn on the brain's reward pathway. Tasks ranged in difficulty and level of reward. Half were done without reward; half included a screen after each response telling subjects whether or not they had answered correctly and how much they had won or lost.

"In the end, healthy and depressed people won the same amounts of money, but people in the depressed group still felt bad," says Drevets. "They felt and did worse, in fact, when informed how they were doing. By contrast, such information had no affect on the mood or performance of healthy subjects. In addition, as the subjects received rewards, dopamine was released in the brains of healthy individuals, but not of depressed individuals."

Brain scans revealed that when depressed patients knew that their performance was being tracked and money was on the line, they did worse on the tasks and showed an increase in activity in the amygdala — a brain area known to control the expression of emotions, particularly fear. Activity also rose in the hippocampus and the insula on the left side of the brain. In depressed subjects, the prospect of winning appears to have generated enough anxiety to hamper their performance, especially on the harder tasks.

Brain reactions in the two groups also differed in areas of higher brain function, with depressed subjects showing less activity in the cerebral cortex than healthy subjects. "The relative lack of activity in the seat of reason may mean that depressed people do not apply as much thought as healthy ones to the evaluation of experiences when deciding if they are pleasant or unpleasant, stressful or fun," says Drevets. "Their brains rather seem to pass over the potential pleasure of winning money to focus on unpleasant emotions caused by the potential for failure."

Drevets notes that while much remains to be learned about the biology of depression, these studies contribute to understanding of how a specific symptom, anhedonia, produces abnormal patterns of activity in the brain.

Finding Brain Changes Early May Help Treatment

In other work, cutting-edge, specialized applications of MRI reveal differences in the brain circuitry of emotions in adults with bipolar disorder (BD), reports Hilary Blumberg, MD, of Yale School of Medicine.[*] MRI images show decreases in the volume of the brain's prefrontal cortex and its subcortical connections sites, including the amygdala in individuals with BD when compared with persons without BD. Functional neuroimaging studies of BD also have demonstrated abnormalities in the functioning of these brain structures, especially during the processing of emotional stimuli and during tasks that require the inhibition of impulsive responses.

The correspondence between the maturation of this circuitry and the emergence of prominent symptoms of BD in adolescence implicate abnormalities in the development of this circuitry during adolescence, says Blumberg. Recent findings of differences in the amygdala in teens with BD suggest brain changes in youth that may help in early detection and that might be targeted for early intervention. Other changes, such as those in prefrontal areas, may also be occurring during the teenage years.

Recent evidence also suggests that treatments may have the potential to reverse the circuitry abnormalities by restoring brain chemical functioning or by repairing circuitry structure through the effects of nerve growth factors. This raises the possibility to intervene early to prevent progression and improve prognosis.

"The findings provide important, new leads that may help in the development of new ways to detect the disorder earlier, to provide more effective treatments, and hopefully to someday prevent the disorder," Blumberg says.

In addition, new methods are being used to assess the integrity of the connections within this emotional brain circuit, such as diffusion tensor imaging and measures of functional connectivity. These have the potential to provide windows onto the connections within the circuitry disrupted in BD. Researchers are also combining genetic studies with imaging studies. "This is exciting as it may help us to identify new treatment strategies aimed at the molecular mechanisms associated with genes that affect brain circuitry," Blumberg says.

Separating ADHD From Bipolar Disorder

Scientists also are using fMRI to help determine whether children have severe irritability and ADHD as opposed to a form of bipolar disorder. This technique appears to separate youth with bipolar disorder from those with chronic irritability — suggesting a way that brain imaging may ultimately be helpful in clinical diagnosis.

"We're finding that these very irritable children with ADHD share some characteristics with children with bipolar disorder, but also have significant differences," says Leibenluft. Very irritable children with ADHD don't have the distinct episodes of mania that one sees in classic bipolar disorder, and they don't tend to have as much bipolar disorder in their family history. However, in a recent study she found that very irritable children with ADHD and those with bipolar disorder both frustrated more easily than controls, and they both had difficulty reading facial emotional cues; they shared deficits in social cognition.

"Yet what's happening in the brain during frustration differed between the two groups," says Leibenluft. "So these data indicate that, even when two groups of patients exhibit the same symptom, the brain mechanisms underlying that symptom can differ. Data like these indicate how, eventually, psychiatric diagnosis will be based on brain mechanisms, in addition to symptoms."

Leibenluft's study of frustration was performed using measures obtained on an electroencephalography machine. Her team is now extending the work by using magnetoencephalography (MEG), a new imaging technique that can detect electrical activity deep in the brain with excellent resolution in terms of both when and where activity takes place. Like MRI technologies, MEG does not involve any radiation or injections, so it is safe and comfortable for children. Using MEG technology, Brendan Rich, PhD, and other members of Leibenluft's team have identified some of the brain regions responsible for the difficulty that children with bipolar disorder have regulating their emotions when frustrated.

Specifically, the researchers found that the anterior cingulate, a region that directs attention to important signals in the environment, functions differently in children with bipolar disorder, compared with healthy children, when they are in frustrating situations. The anterior cingulate acts in concert with the prefrontal cortex, an area that organizes behavior — and here too the researchers found differences between the responses of patients and healthy children. Now, the researchers are conducting a similar study in children with severe irritability and ADHD, to see once again if the brain mechanisms involved in frustration differ between this group and children with bipolar disorder.

[*] Blumberg has consulted to Pfizer, Inc., and received speaker honoraria from Eli Lilly and Abbott.