Brain signature of depressed mood unveiled in new study

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Neurosurgeon Edward Chang, MD (right), talks with psychiatrist Vikaas Sohal, MD, PhD, in the Sandler Neurosciences Building at UCSF’s Mission Bay campus. [Photo by Steve Babuljak]

Most of us have had moments when we’re feeling down—maybe we can’t stop thinking about our worst mistakes, or our most embarrassing memories—but for some, these poor mood states can be relentless and even debilitating. Now, new research from UC San Francisco has identified a common pattern of brain activity that may be behind those feelings of low mood, particularly in people who have a tendency towards anxiety. The newly discovered network is a significant advance in research on the neurobiology of mood, and could serve as a biomarker to help scientists developing new therapies to help people with mood disorders such as depression.

Most human brain research on mood disorders has relied on studies in which participants lie in an fMRI scanner and look at upsetting images or listen to sad stories. These studies have helped scientists identify brain areas associated with emotion in healthy and depressed individuals, but they don’t reveal much about the natural mood fluctuations that people experience over the course of a day or provide insight into the actual mechanisms of brain activity underlying mood.

Newly published research by UCSF Health neurosurgeon and neuroscientist Edward Chang, MD [2], and psychiatrist and neuroscientist Vikaas Sohal, MD, PhD [3]—both members of the UCSF Weill Institute for Neurosciences [4] and the recently launched UCSF Dolby Family Center for Mood Disorders [5]—has begun to fill these gaps in our understanding of the neuroscience of mood by continuously recording brain activity for a week or more in human volunteers and linking their day-to-day mood swings to specific patterns of brain activity.

The new study—appearing online in Cell [6] on November 8, 2018—was funded by the Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program of the Defense Advanced Research Projects Agency (DARPA). Launched in 2014 [7] under the auspices of the White House BRAIN Initiative, this multi-institutional collaborative project seeks to enhance understanding of the brain circuitry underlying neuropsychiatric conditions such as depression and anxiety, and to develop novel technology to treat these disabling brain disorders.

“It is remarkable that we are able to see the actual neural substrates of human mood directly from the brain,” Chang said. “The findings have scientific implications for our understanding of how specific brain regions contribute to mood disorders, but also practical implications for identifying biomarkers that could be used for new technology designed to treat these disorders, which is a major priority of our SUBNETS effort.”

**Direct recordings of human brain activity link memory, emotion, and anxiety during bouts of low mood**

The researchers recruited 21 patient volunteers with epilepsy who had had 40 to 70 electrodes implanted on the brain’s surface and in deeper structures of the brain as part of standard preparation for surgery to remove seizure-causing brain tissue. The researchers recorded a wide range of brain activity in these patients over the course of seven to 10 days, particularly focusing on certain deep brain structures that have been previously implicated in...
mood regulation. Meanwhile, the patients regularly logged their mood throughout the day with tablet-based software.

The researchers then used computational algorithms to match patterns of brain activity to changes in the patients? reported mood. These new algorithms were developed by the lead author, Lowry Kirkby, PhD [8], a postdoctoral researcher in the Sohal lab, and Francisco Luongo, PhD, a recent alumnus of UCSF?s Neuroscience Graduate Program [9].

To avoid biasing their analysis at the onset, the team did not look at the mood surveys right away. Instead, they first analyzed the long-term recordings of brain activity in each participant to identify so-called intrinsic coherence networks (ICNs). ICNs are groups of brain regions whose activity patterns regularly fluctuate together at a common frequency (like members of a college band, marching in lockstep). This synchronization was used as a clue about brain regions that communicate with one another in potentially important ways.

Then, to compare results across the unique brains and distinct electrode placements of all 21 research participants, the researchers mapped each subject?s ICNs onto neural connectivity diagrams. Comparing these standardized records of network activity across subjects revealed several ?cliques? ? groups of brain regions that repeatedly became synchronized at specific frequencies, and were therefore likely to represent functional brain networks.

One such clique was highly active and coordinated in 13 research participants, all of whom had also scored high on a psychological assessment of baseline anxiety conducted prior to the start of the study. In these same individuals, changes in the activity of this brain network were also highly correlated with day-to-day bouts of low or depressed mood. This mood-related network was characterized by so-called beta waves ? synchronized oscillations between 13 and 30 cycles per second ? in the hippocampus and amygdala, two deep brain regions which have long been linked, respectively, to memory and to negative emotion.

Sohal said the research team was at first taken aback by the clarity of the finding. ?We were quite surprised to identify a single signal that almost completely accounted for bouts of depressed mood in such a large set of people,? said Sohal. ?Finding such a powerfully informative biomarker was more than we?d expected at this stage of the project.?

Surprisingly, this powerful link between of mood-associated beta waves in the amygdala and hippocampus was entirely absent from eight other research participants, all of whom had comparatively low preexisting anxiety, suggesting new questions about how the brains of people prone to anxiety may differ from others in how they process emotional situations.

?Based on what we know about these brain structures, this suggests that interactions between the amygdala and hippocampus might be linked to recalling emotional memories, and that this pathway is particularly strong in people with high levels of anxiety, whose mood might then be heavily influenced by recalling emotion-laden memories,? Sohal said. ?We will need to investigate that hypothesis further, but as a psychiatrist it?s deeply satisfying to begin to be able to provide a conceptual framework to patients to help them understand what they are going through when they feel down.?

Both Chang and Sohal emphasized that support from both the Weill Institute and Dolby Center is critical to the future success of this project and to ongoing work needed to validate the findings and develop potential therapeutic applications.
The Dolby and Weill families have both recognized a special opportunity to break down walls between psychiatry, neurology, and neurosurgery in order to fill gaps in our knowledge about how mood is processed in the brain and to move towards new biologically driven therapies for mood disorders, Chang said.

**Authors:** Edward Chang, MD, and Vikaas Sohal, MD, PhD, are co-senior and corresponding authors on the study. Lowry Kirkby, PhD, a postdoctoral researcher in the Sohal lab, was the study’s lead author. Other authors were Francisco Luongo, PhD (formerly in the Sohal lab, now a postdoctoral researcher at Caltech), Morgan Lee (formerly in the Chang lab, now a medical student at the University of Southern California), Vikram Rao, MD, PhD [10], a neurologist with UCSF Health and assistant professor of neurology, and Heather Dawes, PhD [11], codirector and program manager of UCSF’s SUBNETS project; and Mor Nahum, PhD, and Thomas M. Van Vleet, PhD, of Posit Science, Inc.

Chang is a neurosurgeon with UCSF Health, professor of neurological surgery, Bowes Biomedical Investigator at UCSF, and co-director of the UCSF-UC Berkeley Center for Neural Engineering & Prostheses. Sohal is a psychiatrist with UCSF Health and associate professor of psychiatry at UCSF. Chang and Sohal are members of the UCSF Weill Institute for Neurosciences and the UCSF Dolby Family Center for Mood Disorders, of the Kavli Institute for Fundamental Neuroscience, and of the Sloan-Swartz Center for Theoretical Neurobiology at UCSF.

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**Disclosures:** Study authors Nahum, and Van Vleet are employees of Posit Science, Inc, which developed the mood surveys used in the study. The authors declare no competing interests.

**Read the research article**

- **Cell:** An Amygdala-Hippocampus Subnetwork That Encodes Variation in Human Mood [6]

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**About UCSF Psychiatry**

The UCSF Department of Psychiatry [12], UCSF Langley Porter Psychiatric Hospital and Clinics [13], and the Langley Porter Psychiatric Institute are among the nation’s foremost resources in the fields of child, adolescent, adult, and geriatric mental health. Together they constitute one of the largest departments in the UCSF School of Medicine and the UCSF Weill Institute for Neurosciences, with a mission focused on research (basic, translational, clinical), teaching, patient care, and public service.

UCSF Psychiatry conducts its clinical, educational and research efforts at a variety of locations in Northern California, including UCSF campuses at Parnassus Heights, Mission Bay and Laurel Heights, UCSF Medical Center, UCSF Benioff Children’s Hospitals, Zuckerberg San Francisco General Hospital and Trauma Center, the San Francisco VA
Health Care System, and UCSF Fresno.

**About the UCSF Weill Institute for Neurosciences**

The UCSF Weill Institute for Neurosciences [14], established by the extraordinary generosity of Joan and Sanford I. "Sandy" Weill, brings together world-class researchers with top-ranked physicians to solve some of the most complex challenges in the human brain.

The UCSF Weill Institute leverages UCSF’s unrivaled bench-to-bedside excellence in the neurosciences. It unites three UCSF departments?Neurology, Psychiatry, and Neurological Surgery?that are highly esteemed for both patient care and research, as well as the Neuroscience Graduate Program, a cross-disciplinary alliance of nearly 100 UCSF faculty members from 15 basic-science departments, as well as the UCSF Institute for Neurodegenerative Diseases, a multidisciplinary research center focused on finding effective treatments for Alzheimer’s disease, frontotemporal dementia, Parkinson’s disease, and other neurodegenerative disorders.

**About UCSF**

UC San Francisco (UCSF) [15] is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. It includes top-ranked graduate schools of dentistry, medicine, nursing and pharmacy; a graduate division with nationally renowned programs in basic, biomedical, translational and population sciences; and a preeminent biomedical research enterprise.

It also includes UCSF Health [16], which comprises three top-ranked hospitals ? UCSF Medical Center and UCSF Benioff Children’s Hospitals in San Francisco [17] and Oakland [18] ? as well as Langley Porter Psychiatric Hospital and Clinics, UCSF Benioff Children’s Physicians, and the UCSF Faculty Practice. UCSF Health has affiliations with hospitals and health organizations throughout the Bay Area. UCSF faculty also provide all physician care at the public Zuckerberg San Francisco General Hospital and Trauma Center, and the San Francisco VA Medical Center. The UCSF Fresno Medical Education Program is a major branch of the University of California, San Francisco’s School of Medicine.

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