In the early 1900s, German neurologist Korbinian Brodmann began to study the architecture of the human brain. He divvied up the cerebral cortex—the outer, convoluted brain region that plays a key role in higher functions, such as memory, attention, and consciousness—into 52 distinct regions.

One of these, a sliver of tissue buried deep inside, became known as Brodmann area 25. More colloquially, it’s known as the brain’s “sadness center.”

“When somebody is transiently sad for a reason, let’s say something happened to a family member or a friend, it’s normal to be sad, and this area lights up,” says neuroscientist Helen Barbas, a Sargent College professor of health sciences and a graduate program in neuroscience faculty member. “But in people who are depressed, this area stays active. It’s on all the time.”

Barbas, whose specialty is charting the pattern of circuits in the brain, and her student Mary Kate Joyce (MED’19) have created a new, finely detailed map of the neural pathways leading to and from area 25 in nonhuman primates. This work shows strong connections between area 25 and other regions involved in emotional regulation, memory, internal states, and stress response.

Barbas and Joyce also found a moderate connection between area 25 and frontopolar area 10, a part of the brain that helps regulate emotions and is smaller in humans with major depression. While these findings represent preliminary work in nonhuman primates, they suggest that strengthening the link between these two areas may offer a possible target for treating chronic depression.

“This is an area that people may look at for some kind of therapeutic intervention, and it doesn’t have to just be drugs. It could be activating the frontopolar area 10 noninvasively, maybe using transcranial magnetic stimulation,” says Barbas, whose work is funded by the National Institutes of Health. She notes that neurologists have used deep brain stimulation in area 25 to treat drug-resistant depression, and suggests that frontopolar area 10’s location closer to the brain’s surface may make it an easier target for such treatment.

Neurons from the “sadness center,” seen in green, terminate in an area associated with emotions.
To create their map, Barbas and Joyce injected four tracers of different colors and characteristics in primate area 25. The brain cells at the site of injection absorbed the tracers into their cell bodies, then sent them down their long axons to their branching endpoints in other areas. The brain cells absorbed other tracers backward, through axons at the injection site, into the parent cell bodies. The experiment allowed researchers to see which areas receive signals from area 25, which areas send signals to area 25, and which circuits looped both ways. The scientists then fed that information into computational analyses to measure the strength and patterns of the connections.

“The pattern of connection is very important,” says Barbas. Area 25 “acts like a feedback system” to most cortical areas, she says. However, it feeds signals forward to certain memory-related areas, like some near the hippocampus. “That means area 25 is probably triggering personal memories through those areas,” she says.

The moderate connection between area 25 and frontopolar area 10, a region best known for juggling complex working memory tasks, surprised the scientists. “We think that it may help modulate area 25, exercise some kind of control,” Barbas says. “So this is why it’s relevant.”

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