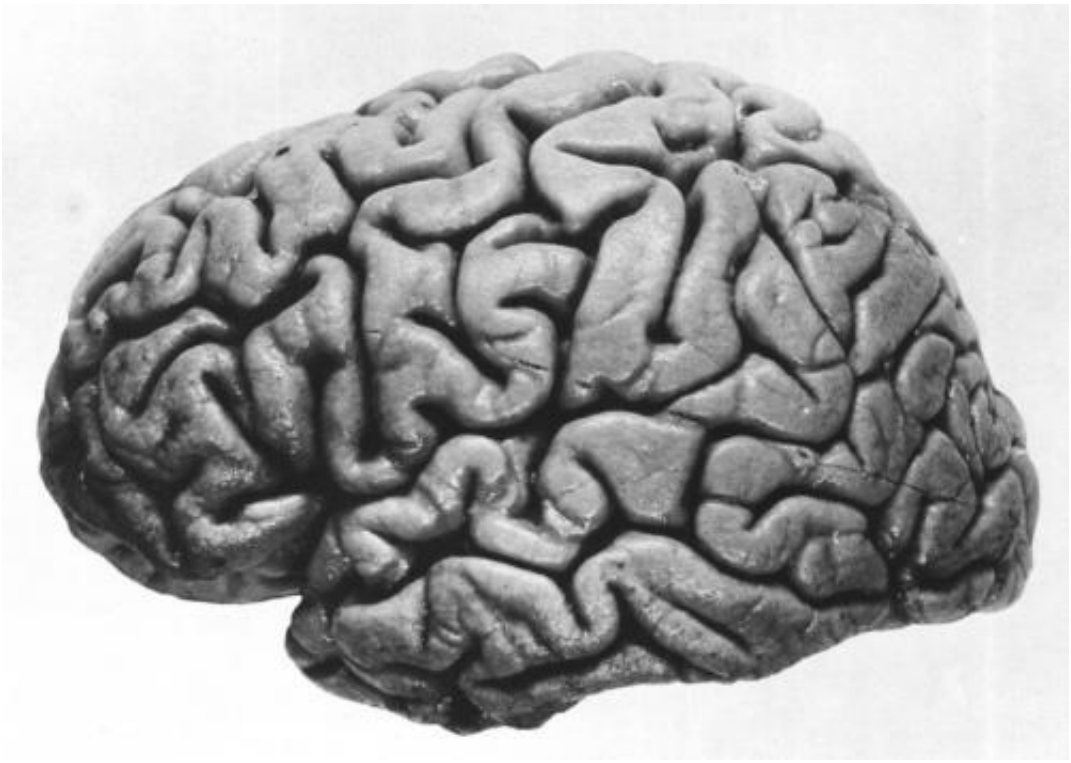
Researchers identify brain areas activated by itch-relieving drug

September 24 2014



Left hemisphere of J. Piłsudski's brain, lateral view. Credit: public domain

Areas of the brain that respond to reward and pleasure are linked to the ability of a drug known as butorphanol to relieve itch, according to new research led by Gil Yosipovitch, MD, Professor and Chairman of the Department of Dermatology at Temple University School of Medicine (TUSM), and Director of the Temple Itch Center. The findings point to

the involvement of the brain's opioid receptors—widely known for their roles in pain, reward, and addiction—in itch relief, potentially opening up new avenues to the development of treatments for chronic itch.

The article, published online September 11, in the *Journal of Investigative Dermatology*, is the first to show precisely where in the brain butorphanol works to relieve itch. In identifying those areas, the study helps to explain why butorphanol works better for chronic itching mediated by histamine, a small molecule involved in allergic reactions, than for nonhistamine-related types of itch.

"The research allows us to assess butorphanol's effects," Yosipovitch said. "We can now identify better targets in the brain that drugs can work on to relieve itch."

The research marks an important step toward the development of itch-specific agents. As Yosipovitch explained, chronic itching, which affects roughly 12 percent of the population, comprises not just one disease, but many—ranging from atopic eczema and psoriasis to systemic diseases such as lymphoma and chronic liver failure. Biochemically, each of those diseases induces itching via one of two main pathways: one that is mediated by histamine and one that is not. Most pathological itching originates along nonhistaminergic pathways.

Working with Dr. Alexandru D. P. Papoiu, MD, PhD, at Wake Forest University School of Medicine, Yosipovitch experimentally induced itch in human volunteers using either histamine or cowhage, which incites nonhistaminergic itching. Study volunteers were then treated with either butorphanol or a placebo and subjected to functional magnetic resonance imaging (fMRI) to analyze brain activity and assess the effects of butorphanol (or placebo). When volunteers returned seven days later, they received the other treatment and again underwent fMRI.

Butorphanol suppressed histamine itching in all cases and reduced cowhage itching in 35 percent of subjects. The drug's suppression of histamine itching was associated specifically with the activation of brain areas known as the nucleus accumbens and septal nuclei—areas located deep at the base of the forebrain. The regions are notably rich in so-called kappa (κ)-opioid receptors, on which butorphanol acts. By contrast, the relief of cowhage itch by butorphanol was linked to effects in other brain areas.

The findings suggest that butorphanol works primarily on κ-opioid receptors to suppress the itch sensation induced by histamine. But the drug also has important effects on an itch pathway that does not involve histamine, where the demand for new treatments is greatest.

How nonhistaminergic itching is reduced through the involvement of opioid receptors remains unclear. Opioid receptors modulate the transmission of information about itch in the brain and occur in high levels in the areas of the brain that house neural pathways associated with reward. Reward pathways are known particularly for their response to pleasurable stimuli. Yosipovitch and Papoiu have shown in previous work that the activation of reward circuits is correlated with pleasurability and the degree of itch relief derived from self-scratching.

The new study, which Yosipovitch carried out at Wake Forest University prior to joining the TUSM faculty in 2013, further illustrates the power of applying imaging technologies to basic questions in itch research. At Temple's Itch Center, Yosipovitch is continuing to explore those applications.

"We are in a position now to better understand the itch-scratch cycle," he said. "To break the cycle from the top down, knowing where to target receptors in the brain, would be a major achievement."