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Disrupted genetic clocks in schizophrenia-affected brains reveal clues to the disease

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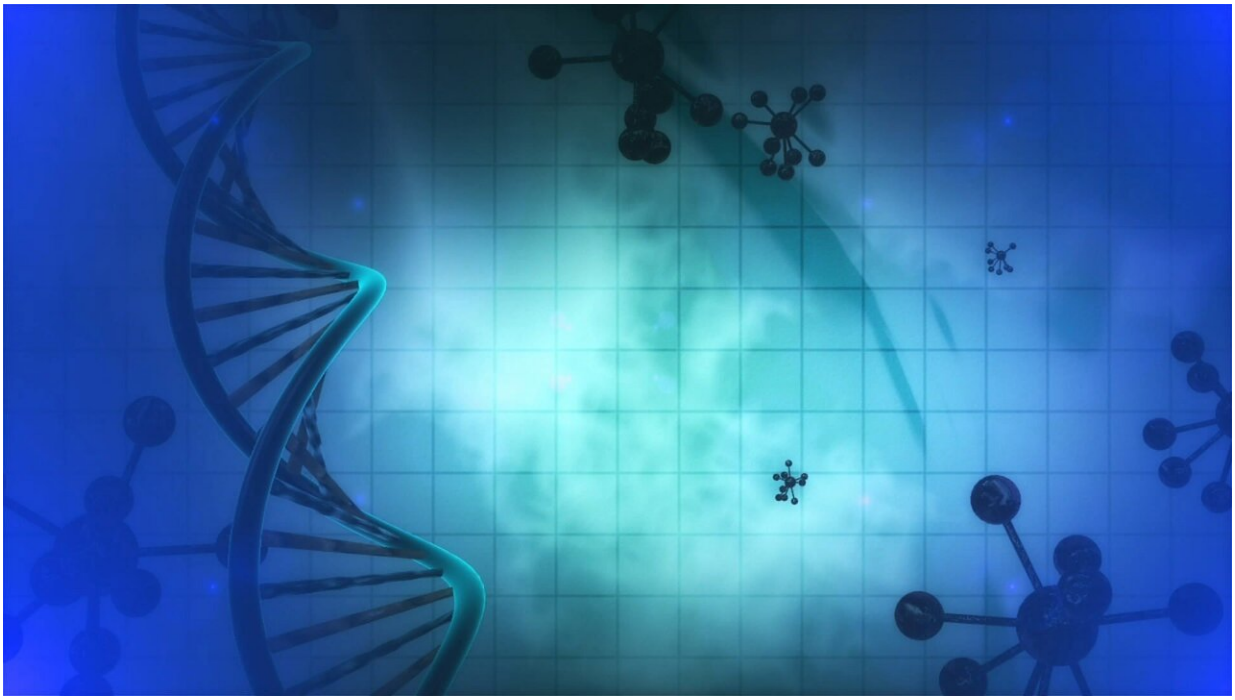

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Rhythms in gene expression in the brain are highly disrupted in people with schizophrenia, according to a new University of Pittsburgh-led study.

The findings, published today by researchers from the Pitt's School of Medicine in the journal *Nature Communications*, also suggest that

researchers studying schizophrenia-linked genes in the brain could have missed important clues that would help understand the disease.

"Our study shows for the first time that there are significant disruptions in the daily timing of when some genes are turned on or off, which has implications for how we understand the disease at a molecular level," said senior author Colleen McClung, Ph.D., professor of psychiatry at Pitt's School of Medicine.

Many bodily functions run on a 24-hour cycle, called a circadian rhythm, which extends to how genes are expressed within cells. Some genes turn on or off at certain times of the day or night.

In this study, McClung and colleagues analyzed gene expression data from the dorsolateral prefrontal cortex—a brain region responsible for cognition and memory—from 46 people with schizophrenia and 46 sex- and age-matched healthy subjects. The data was obtained from the CommonMind Consortium, a public-private partnership that has curated a rich brain tissue and data bank for studying neuropsychiatric disorders.

By knowing the time of death, the researchers were able to use a statistical method to determine changes in the rhythmicity of different genes, which revealed some interesting patterns.

McClung explained the findings by drawing an analogy of gene expression to electrical appliances in a house.

"In a normal house—like a healthy brain—let's say the lights are turned on at night, but the refrigerator needs to be on all the time. What we saw was that in a schizophrenia-affected brain, the lights are on all day and the refrigerator shuts off at night."

This is problematic, explains McClung, because it can affect how cells

function. In their samples, the genes that gained rhythmicity were involved in how mitochondria—the cell's powerhouse—functions, and those that lost rhythmicity were linked to inflammation.

The results also have implications for other researchers studying the genetics of schizophrenia, according to Marianne Seney, Ph.D., assistant professor of psychiatry at Pitt's School of Medicine and the study's first author. By not considering circadian rhythms, they could be missing out on important findings.

When Seney and McClung compared gene expression in brains from people who died during the day, the control and schizophrenia subjects were not different, but in those who died at night, there were major differences, since genes that had gained a rhythm had hit their low point during the night.

Seney alludes to the analogy of the house. "If we only looked to see if the refrigerator was on during the day we would see no difference, but at night, there would be one."

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