

Brain Volume Changes Seen in Opioid Users

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OAK BROOK, Ill. — Researchers at the Yale School of Medicine found structural and functional alterations in specific brain regions of individuals with opioid use disorder. The study's results were published today in *Radiology*, a journal of the Radiological Society of North America (RSNA).

Opioids are a class of drugs that include synthetic opioids such as fentanyl, prescription pain relievers like oxycodone, and illegal narcotics, including heroin. Opioids have a high potential for misuse, and opioid use is a major contributor to drug overdoses in the U.S.

According to the National Institute on Drug Abuse, in 2021, approximately 2.5 million adults in the U.S. had opioid use disorder. Provisional data from Centers for Disease Control and Prevention's National Center for Health Statistics indicate there were an estimated 81,083 overdose deaths involving opioids in the U.S. during 2023.

"We are in the midst of an opioid epidemic, with millions affected worldwide and more than 80,000 deaths related to opioid overdoses in the U.S. last year alone," said Saloni Mehta, M.B.B.S., postdoctoral associate in the Department of Radiology and Biomedical Imaging at the Yale School of Medicine. "We need to get a better understanding of the system-level neural alterations associated with opioid use disorder."

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Saloni Mehta, M.B.B.S.

In the study, Dr. Mehta and colleagues conducted a secondary analysis of data from the National Institutes of Health-funded Collaboration Linking Opioid Use Disorder and Sleep Study (CLOUDS), comparing participants with opioid use disorder on methadone treatment and healthy controls. The data included structural MRI and functional MRI (fMRI) exams performed between February 2021 and May 2023.

Resting state fMRI allows researchers to measure brain activity by detecting changes in blood flow. With resting state fMRI, the connectivity between neural regions—known as resting state networks—can be observed while the brain is at rest.

Researchers analyzed CLOUDS structural MRI data for 103 individuals with opioid use disorder and 105 individuals from the control group. They also analyzed the resting state fMRI data on 74 participants with opioid use disorder and 100 controls. The individuals with opioid use disorder were all recently stabilized with medication for the disorder (less than 24 weeks). The median age in the group with opioid use disorder was 37 years, and 40% were women. In the control group, the median age was 27 years, and 55% were women.

"Previous studies have been performed on small sample sizes, many of which included no women," Dr. Mehta said. "Ours is a moderate sample size, approximately half of which is female."

Whole-brain analysis revealed structural and functional alterations in opioid receptor-dense regions in the opioid use disorder group compared to healthy controls. In individuals with opioid use disorder, the thalamus and right medial temporal lobe of the brain were smaller in volume, while the cerebellum and brainstem were larger in volume than in controls. In the individuals with opioid use disorder, all these brain regions also had increased functional connectivity compared to controls.

"We observed widespread increases in global connectivity in individuals with opioid use disorder," Dr. Mehta said. "Our goal is to understand better what could have caused these alterations to inform new treatment targets."

The results also revealed that women in the group with opioid use disorder had smaller medial prefrontal cortex volume, compared to males in the same group.

"We found that alteration patterns in the medial prefrontal cortex—a core region involved in many mental health conditions—were different between men and women in the group with opioid use disorder," Dr. Mehta said. "This highlights the importance of assessing sex differences in opioid use disorder neuroimaging studies."

Dr. Mehta said the study builds a foundation for future research to investigate potential behavioral implications of these brain differences and whether they are permanent.

"Our eventual goal is to examine how brain alterations in individuals with opioid use disorder may be linked to outcome measures," she said.

"Alterations in Volume and Intrinsic Resting-State Functional Connectivity Detected at Brain MRI in Individuals with Opioid Use Disorder." Collaborating with Dr. Mehta were Hannah Peterson, B.S., Jean Ye, B.A., Ahmad Ibrahim, M.B.B.S., Gul Saeed, M.B.B.S., Sarah Linsky, M.P.H., Iouri Kreinin, C.C.R.P., C.C.R.C., Sui Tsang, M.S., Uzoji Nwanaji-Enwerem, Ph.D., F.N.P.-B.C., Anthony Raso, M.H.S., Jagriti Arora, M.S., Fuyuze Tokoglu, M.S., Sarah W. Yip, Ph.D., C. Alice Hahn, B.A., Cheryl Lacadie, B.S., Abigail S. Green, M.D., Ph.D., Sangchoon Jeon, Ph.D., R. Todd Constable, Ph.D., Declan T. Barry, Ph.D., Nancy S. Redeker, R.N., M.S.N., Ph.D., Henry Yaggi, M.D., M.P.H., and Dustin Scheinost, Ph.D.

RSNA is an association of radiologists, radiation oncologists, medical physicists and related scientists promoting excellence in patient care and health care delivery through education, research and technologic innovation. The Society is based in Oak Brook, Illinois. ([RSNA.org](https://www.rsna.org))

For patient-friendly information on brain MRI, visit [RadiologyInfo.org](https://www.rsna.org/radiologyinfo).

Images (JPG, TIF):

Participants with OUD

n=186 individuals with OUD enrolled in the CLOUDS study from February 2021-February 2023

- Excluded from imaging:
- out of contact (n=45)
 - contraindications to MRI (n=21)
 - attempted a scan but no usable data (n=10)
 - did not come for scheduled scan (n=2)
 - excluded for history of neurological abnormality (n=2)
 - did not want to get scanned (n=1)
 - dropped out of study (n=1)
 - deceased (n=1)

n=103 included

- Excluded from rs-fMRI:
- had only structural imaging (n=16)
 - average framewise displacement >0.2mm for quality control (n=13)

n=103 T1-weighted images

n=74 rs-fMRI

Healthy controls

n=277 unique adults completed MRI for separate transdiagnostic study from February 2018-May 2023

n=107 met criteria for healthy controls

- Excluded:
- scanned on a Siemens Vida scanner (n=2)

n=105 included

- Excluded from rs-fMRI:
- average framewise displacement >0.2mm for quality control (n=5)

n=105 T1-weighted images

n=100 rs-fMRI

Figure 1. Flowchart of study inclusion and exclusion. Participants with opioid use disorder (OUD) were recruited for the Collaboration Linking Opioid Use Disorder and Sleep (CLOUDS) study, and data from healthy control participants were collected as part of a separate transdiagnostic study. rsfMRI = resting-state functional MRI.

[High-res \(TIF\) version](#)

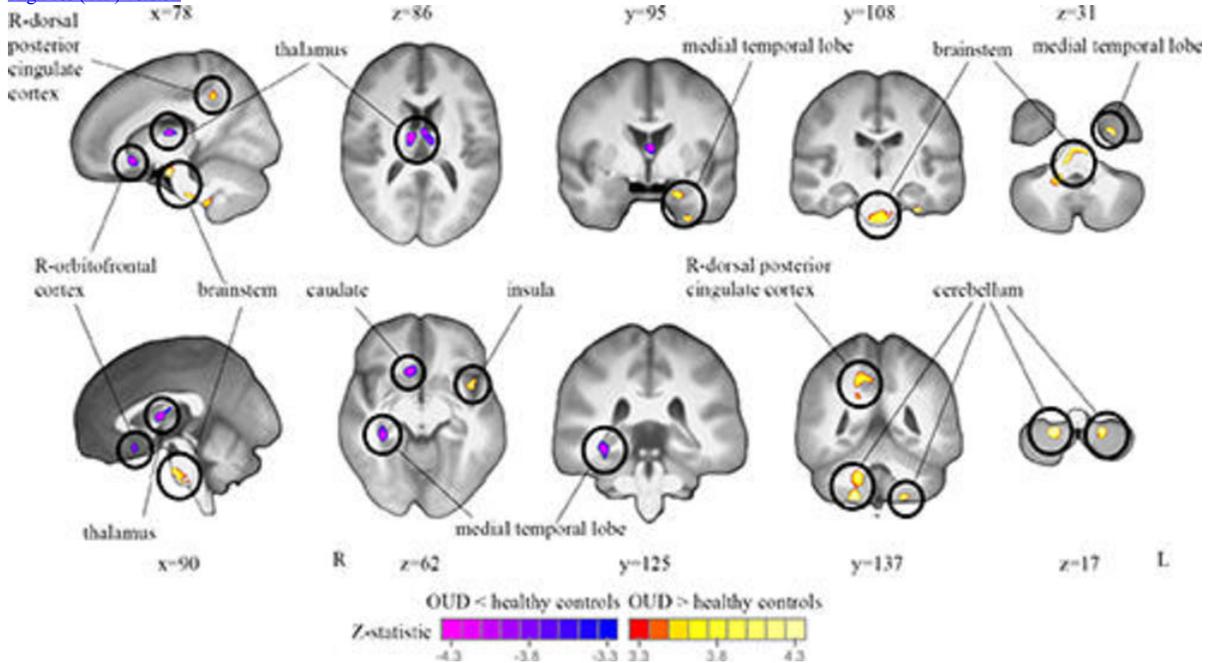


Figure 2. Tensor-based morphometry (TBM) analysis of T1-weighted MRI scans shows a comparison of brain volumes in participants with opioid use disorder (OUD) and healthy control participants. Widespread volume differences are observed between participants with OUD and healthy controls when accounting for total brain volume. Specifically, the bilateral thalamus, right caudate and orbitofrontal cortex, and right medial temporal lobe show lower volume in participants with OUD compared with healthy controls. The left medial temporal lobe, brainstem, bilateral cerebellum, left insula, and right dorsal posterior cingulate cortex show greater volume in those with OUD compared with healthy controls. All results are shown at $P < .05$, corrected for multiple comparisons. The color scale indicates the Z statistic, whereby blue to pink represents smaller volumes in the OUD group compared with healthy controls, and red to yellow represents larger volumes in the OUD group compared with healthy controls. L=left, R=right.

[High-res \(TIF\) version](#)

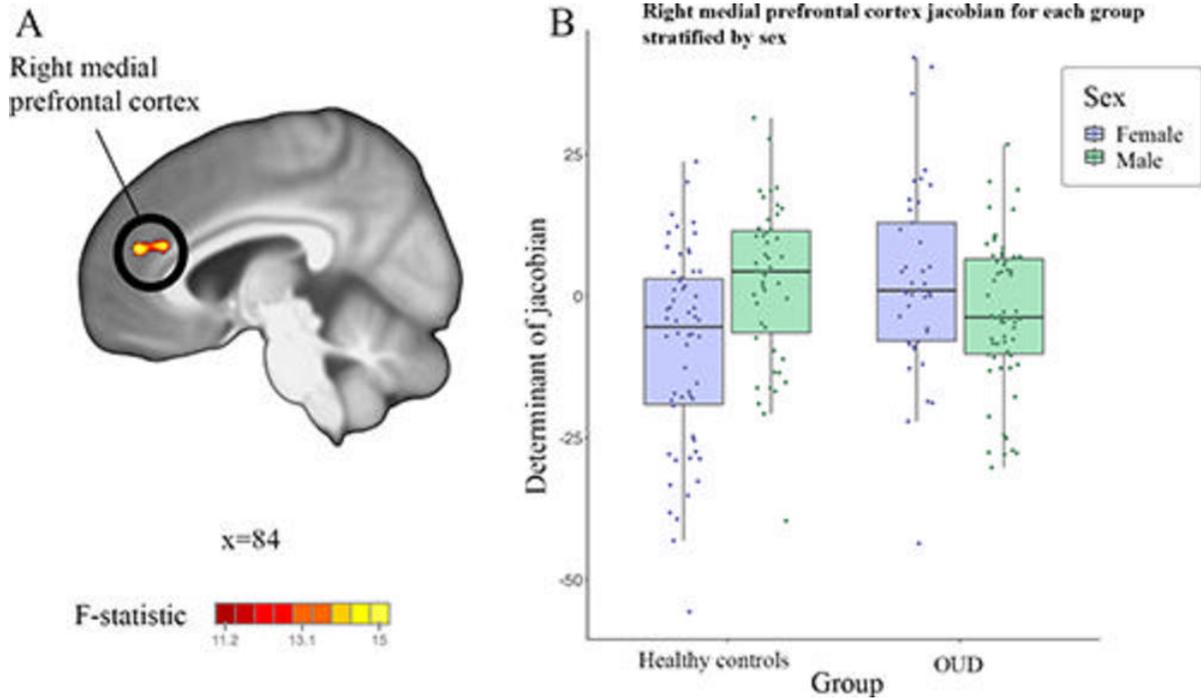


Figure 3. (A) Tensor-based morphometry analysis of a T1-weighted MRI scan shows an interaction between sex and group for brain volume in the right medial prefrontal cortex when accounting for total brain volume ($P < .05$, corrected for multiple comparisons). (B) Post hoc box plot shows the average determinant of Jacobian values from the medial prefrontal cortex cluster for each group stratified according to sex. In the healthy control group, male participants had greater volume in the medial prefrontal cortex. In the opioid use disorder (OUD) group, this pattern was reversed. The solid line in the middle of each box represents the median, and the box represents the IQR.

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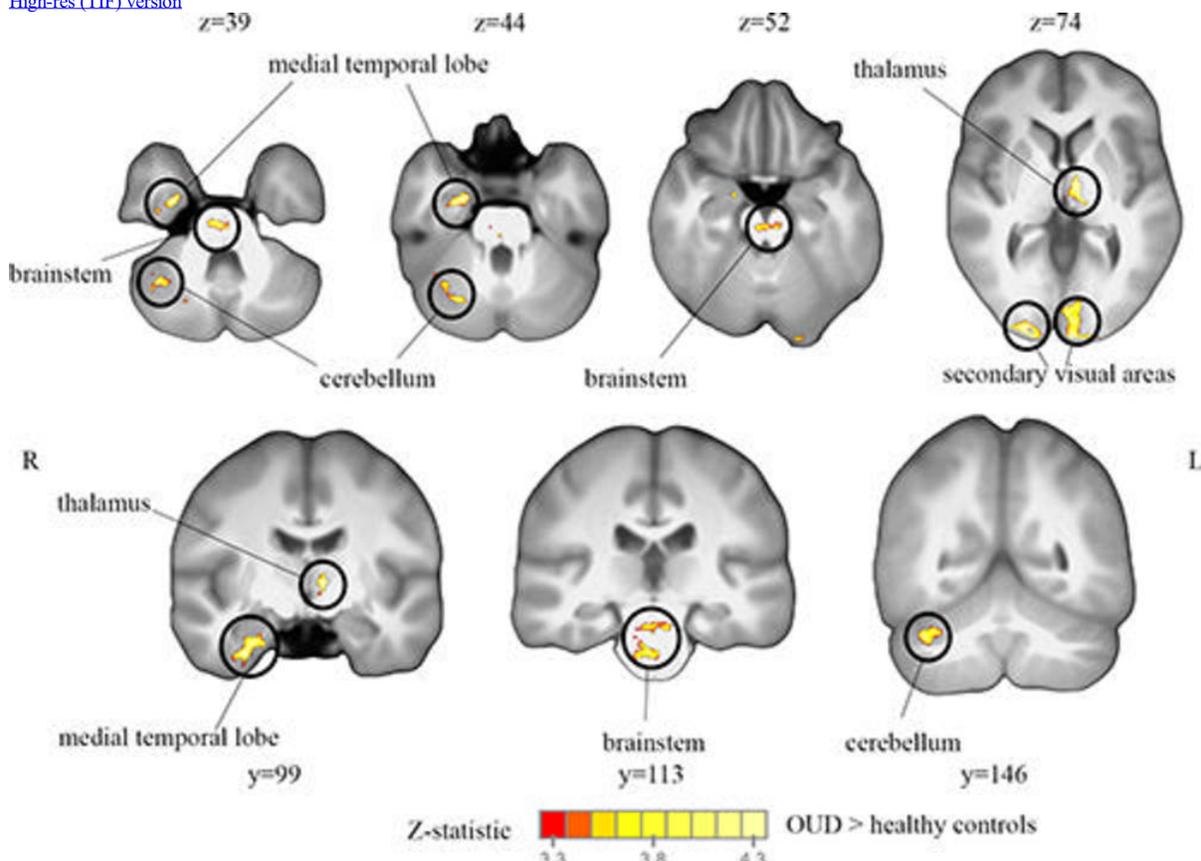


Figure 4. Intrinsic connectivity distribution analysis of resting-state functional MRI scans shows a comparison of global resting-state functional connectivity between participants with opioid use disorder (OUD) and healthy control participants. Color scale gradations of yellow indicate greater global connectivity in the bilateral secondary visual areas, left thalamus, right medial temporal lobe, right cerebellum, and brainstem in participants with OUD compared with healthy controls. No clusters of reduced connectivity were observed. All results are shown at $P < .05$, corrected for multiple comparisons.

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