

BRAIN EFFECTS OF CANNABINOIDS



USING IMAGING TO VISUALIZE PERSONALIZED EFFECTS OF CBD AND THC ON INDIVIDUALS

Medical use of cannabinoids is permitted in 29 states and counting, yet critical unanswered questions remain

• How do cannabinoids such as THC and CBD influence brain networks?

• Why do CBD and THC have different effects for different individuals?

• How are effects of CBD and THC on the brain shaped by other cannabinoids and terpenes in whole plant preparations?

The answers to these questions will have a profound impact on how cannabinoids may best be used for medical treatments. To date, we do not understand many fundamental questions about cannabinoids such as which receptors in the brain they work through and how they cause changes in brain networks underlying attention, anxiety, pain, and mood. We do not know why there appear to be differences in effects for different cannabis strains. And we don't know how to personalize therapies for individual patients and medical conditions.

We have unique multidisciplinary expertise and technology at the University of Utah to answer these fundamental questions that can shape the developing field of cannabinoid therapy and focus medical research on personalized cannabinoid medicine. Using state-ofthe-art brain imaging, we can see how cannabinoids effect an individual's brain at a molecular level and how this results in changes across entire brain networks.



Expected areas of opioid and CB1 receptor binding in an individual participant



Functional imaging can identify changes in connections between thousands of brain regions in more than 20 networks



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- Identify across 40 different individuals personalized concentrations and binding of CBD and THC to CB1 and opioid receptors
- Measure changes in connectivity over brain networks related to attention, memory, and processing of novelty and change caused by CBD and THC preparations
- During molecular imaging we will use a stress and pain challenge to evaluate effects of cannabinoid modulation on stress regulatory mechanisms
 - Compare the molecular responses to cannabinoids to brain function to determine whether personalized effects arise from how many receptors of each type someone may have, individual differences in how cannabinoids bind to these receptors, or different effects of receptors on core brain networks

METHODOLOGY

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For each of 40 healthy young adults, we will measure at 3 timepoints opioid and CB1 receptor concentration and binding using positron emission tomography (PET) with dedicated molecular imaging agents synthesized at the University of Utah cyclotron, and with brain functional connectivity functional MRI at our flagship Prisma MRI scanner. Each individual will be characterized with neuropsychological testing, measurement of blood concentrations of CBD and THC, and hormones related to stress and pain response using a crossover, placebo-controlled design.



BUDGET

Imaging, Blood Testing, and Regulatory Costs	\$296,546
Personnel (Salary and Fringe)	\$352,730
Indirect Costs (University Administration)	\$316,598
TOTAL	\$965,874

EVALUATION AND TIMELINE



This study will not only answer important questions about how CBD and THC affect brain function, but will also provide critical experience, data, and infrastructure that will allow our team to continue to effectively compete for research funding from the National Institutes of Health and other funding agency to extend our findings into clinical trials and pursue new avenues of research opened up by these results.

TEAM

With combined expertise in neuroimaging, neuropsychology, biostatistics, imaging physics, and psychiatry, our team has unique resources to complete a landmark study on CBD and THC effects on the brain. Four co-investigators, two research coordinators, one graduate student and one research assistant will work over 24 months. The Clinical Trials Office will provide the support staff to conduct the study including FDA and DEA enrollment, consent, blood draws, and tracking.



JON-KAR ZUBIETA MD, PhD, Psychiatry

Dr. Zubieta is Professor and Chair of the Department of Psychiatry and Psychiatrist-in-Chief for the University Neuropsychiatric Institute, University of Utah. He will be responsible for the coordination of coinvestigators and staff, and will be directly involved in the performance and supervision of the studies, PET acquisitions, PET and MRI data processing and analysis.



JEFFREY ANDERSON MD, PhD, Radiology

Jeffrey Anderson is a neuroradiologist and neuroimaging scientist with primary expertise in brain network functional imaging analysis. He will be responsible for MRI image acquisition and functional image analysis, as well as statistical analysis and integration of PET and MRI results.



TIFFANY LOVE PhD, Psychiatry

Dr. Love is an Assistant Professor of Psychiatry at the University of Utah with expertise in neuroimaging, the opioid and cannabinoid systems. She will assist Dr. Zubieta in the setting-up of the study, data quality control, data analyses and publications and presentations in national conferences.



JARED NIELSEN PhD, Neuroscience

Dr. Nielsen is returning to the University of Utah from Harvard University as a world expert in functional and structural MRI analysis applied to individual patients, with responsibility for performing imaging exams, neuropsychological assessment, and coordination of regulatory submissions.



Expected Outcomes and Metrics:

While the medicinal use of cannabinoids has been growing, critical questions about effective treatment protocols remain. The initial study at the University of Utah was designed to answer three main questions:

1. How do cannabinoids such as THC and CBD influence brain networks?

2. Why do CBD and THC have different effects for different individuals?

3. How are effects of CBD and THC on the brain shaped by other cannabinoids and terpenes in whole plant preparations?

The expansion of the study will answer the same three questions with a specific focus on evaluating populations with previous opioid abuse or mental health issues. The resulting data will help health care professionals determine if CBD-rich therapeutics may be beneficial in treating opiod abuse or mental health issues.

Measurement Methods:

The expansion of the study will follow the same measurement protocols as the current study, which consists of four primary measurements:

1 Identify across 40 different individuals personalized concentrations and binding of CBD and THC to CB1 and opioid receptors.

2 Measure changes in connectivity over brain networks related to attention, memory, and processing of novelty and change caused by CBD and THC preparations.

3 During molecular imaging we will use a stress and pain challenge to evaluate effects of cannabinoid modulation on stress regulatory mechanisms.

4 Compare the molecular responses to cannabinoids to brain function to determine whether personalized effects arise from how many receptors of each type someone may have, individual differences in how cannabinoids bind to these receptors, or different effects of receptors on core brain networks.