

# Assessing the Effectiveness of Cannabidiol for Reducing Brain Inflammation and Improving Cognitive Function in Multiple Sclerosis Using Neuroimaging Markers: A Systematic Review

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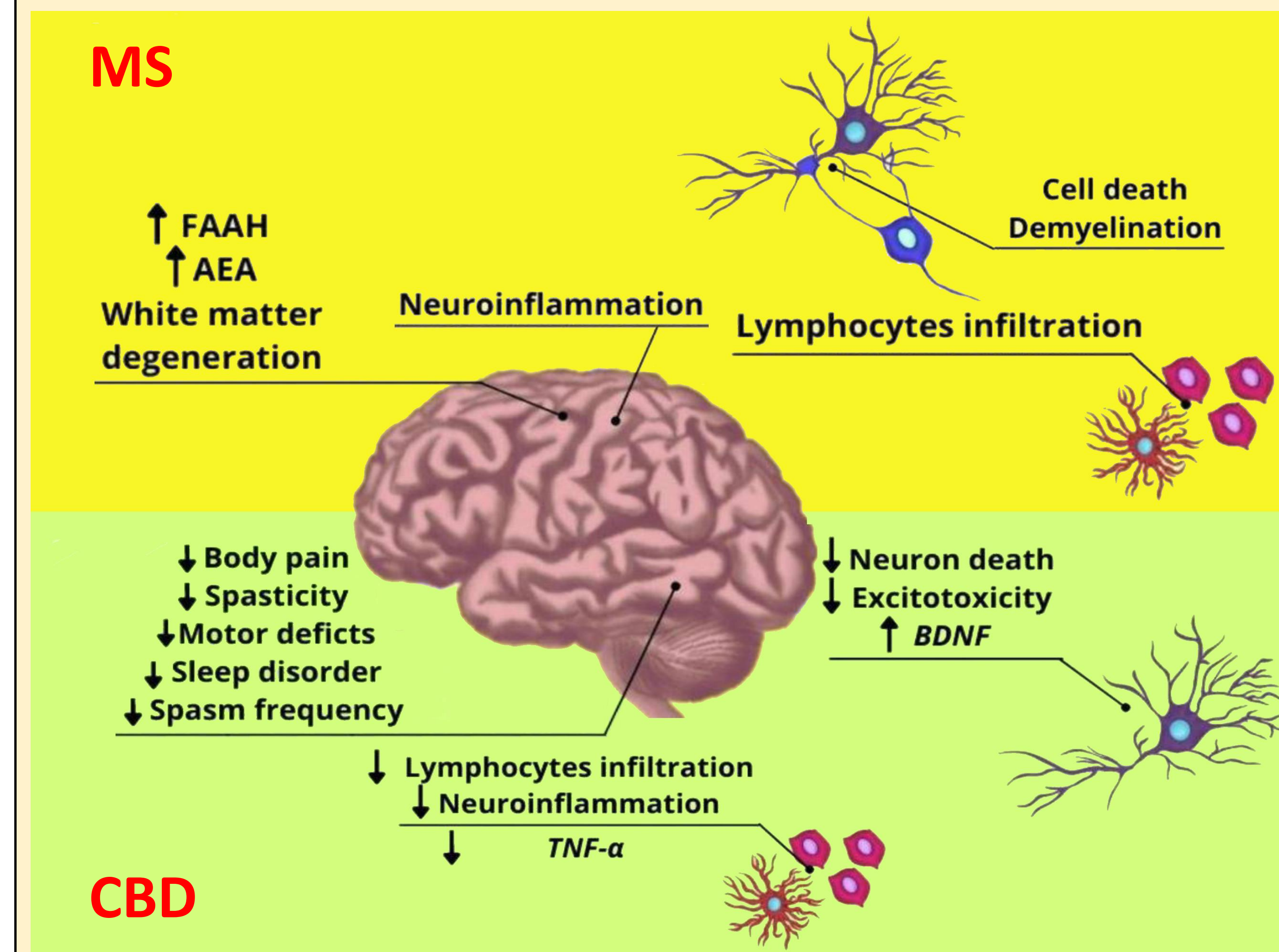
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## Introduction

Multiple sclerosis (MS) is an auto-immune disorder that disrupts neural communication in the central nervous system (CNS). **People with multiple sclerosis (pwMS) consume cannabis-based products for alleviating symptoms such as spasticity, pain, and sleep difficulties.** Multiple studies and clinical trials have demonstrated the benefits of  $\Delta^9$ -tetrahydrocannabinol (THC) for relieving these symptoms in PWMS. However, less attention has been given to cannabidiol (CBD) which, unlike the psychoactive THC, **provides several benefits due to its anti-inflammatory, anti-oxidative, and neuroprotective properties** making it a strong add-on therapeutic option for better clinical management of MS.<sup>1</sup>



## Objective

To perform a systematic literature review to summarize **the effects of CBD and other cannabis products on the CNS in pwMS**, using neuroimaging methods.



## Methods

A literature search was performed in the PubMed library for articles containing the terms “multiple sclerosis” combined with “cannabidiol”, “cannabinoid”, “cannabis”, or “marijuana” and with “MRI” or “PET”.

## Results

The literature search resulted in **only 9 articles related to the use of THC or CBD and brain changes using neuroimaging in pwMS**, eight of those using MRI and one using PET imaging.

## MRI Studies

**Five articles** examined cognitive changes in **pwMS who smoked cannabis**, showing cognitive deficits correlating with tissue volume reduction on structural MRI and less efficient activation on functional MRI.<sup>2-6</sup>

One of these studies also showed recovery in some cognitive functions after a 28-day abstinence from cannabis.

**Two articles** examined **pwMS treated with nabiximols (THC:CBD)**, showing reduced spasticity and changes in brain functional connectivity, but no microstructural improvements based on diffusion MRI.<sup>7-8</sup>

**One article** from the CUPID study found that **dronabinol (THC)** had no effect on brain lesion volumes in pwMS compared to other cannabis compounds.<sup>9</sup>

**None of the articles that used MRI examined the effect of CBD alone on the brains of pwMS.**

## PET Studies

**One PET study** showed the **differential effects of THC and CBD** on brain metabolism in **pwMS**, with those taking THC showed hypermetabolism of cerebral fluorodeoxyglucose while those taking CBD had hypometabolism.<sup>10</sup>

To the best of our knowledge, this is **the only study investigating the effect of CBD, without THC, on the brain.** Furthermore, no advanced MRI techniques, such as MR spectroscopy, diffusion kurtosis imaging, and neuromelanin MRI, and no cannabinoid-receptor specific PET ligands were used in the articles we found.

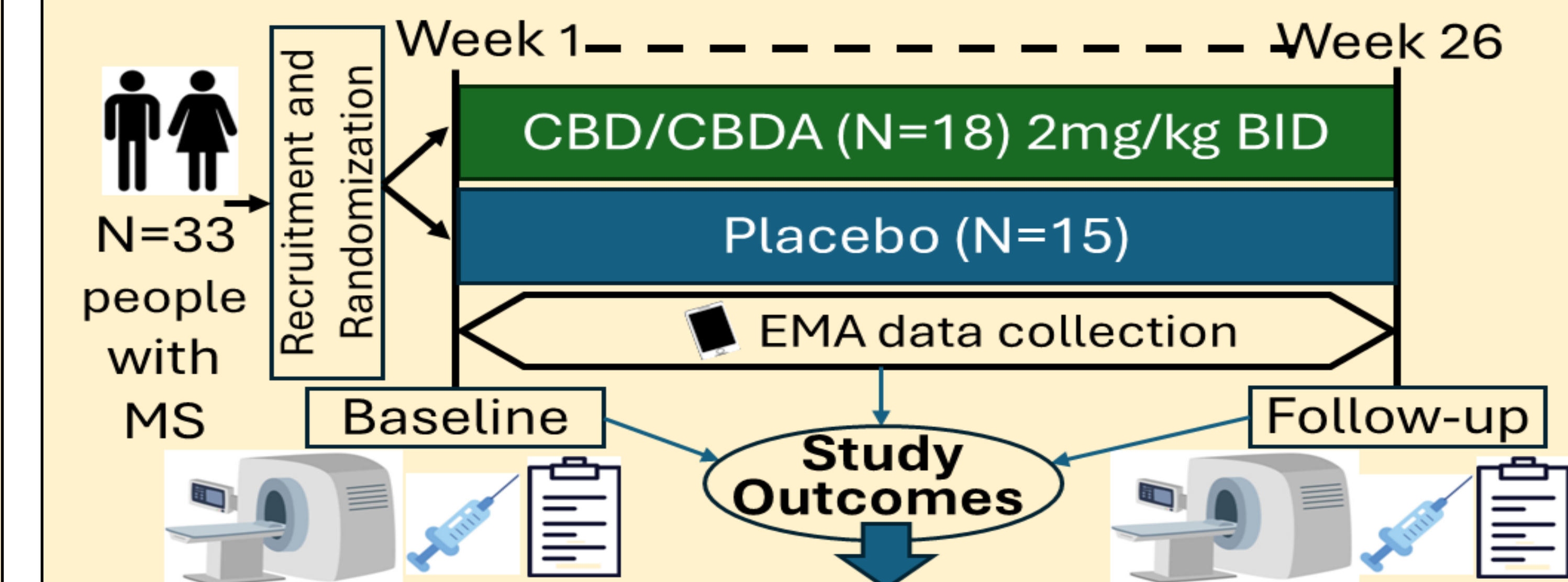
## Current Proposal

In a recently submitted proposal to the Consortium for Medical Marijuana Clinical Outcomes Research (MMJCOR), we proposed **to evaluate the efficacy of a 26-week long CBD + cannabidiolic acid (CBDA) intervention in pwMS** (18-40 y.o.; CBD group n=18; placebo group n=15).

The CBD group will be given CBD+CBDA-rich hemp extract (1:1 ratio; 2mg/kg, BID). Procedures will include: **MRI brain scan, a blood draw, and assessments of cognition, physical/mental health, and quality of life** at 2 time-points.

We propose to use advanced MRI techniques: whole-brain **MR spectroscopic imaging (MRSI), diffusion tensor/kurtosis imaging (DTI/DKI) with free-water elimination (FWE), neuromelanin (NM)-MRI, and myelin water imaging (MWI).**

Biomarkers obtained from these methods can evaluate changes in neuro-inflammation and -immune activation, neuronal integrity, structural integrity, and neurotransmitters.



**Brain MRI:** Neuro-inflammation and immune activation, neuronal integrity, neurotransmitters, volumetrics.

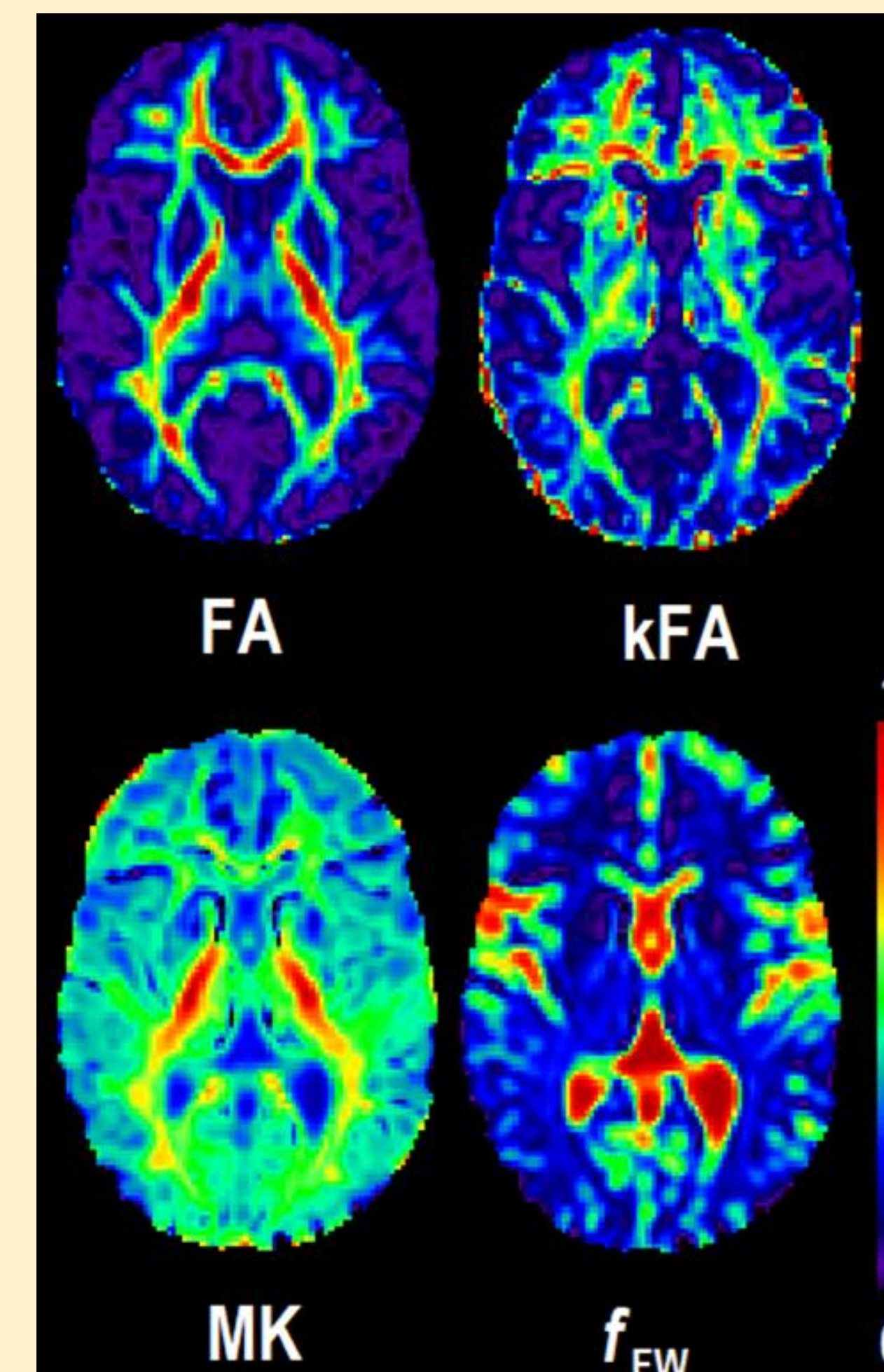
**Blood samples:** Inflammation, immune activation, neuronal injury, CBD/CBDA metabolites.

**Physical/mental health:** pain, sleep, QoL, anxiety, depression.

## Data from Ongoing MMJCOR-funded Study

In an ongoing study funded by MMJCOR (PI: Govind), we utilized the above proposed MRI techniques to **investigate the effects of HIV infection and marijuana use in the brain of people with HIV infection (PWH).** We enrolled n=11 subjects with n=14 additional subjects to be enrolled within the next 2 weeks.

**Sample whole-brain FWE-DTI/DKI data** obtained from a subject are shown here to demonstrate the feasibility of the MRI protocol in the proposed study on MS.



## Conclusion

Despite MS being a qualifying condition for receiving medical marijuana, **evidence-based knowledge on the effects of cannabinoids, in particular CBD, on the CNS in pwMS is still lacking.** Comprehensive brain imaging studies using advanced MRI techniques are warranted for evaluating neuro-inflammation, neuro-immune activation, neuronal function, and neurotransmitters in pwMS who are taking cannabis products.

Our current proposal seeks to fill this knowledge gap by investigating the role of CBD+CBDA intervention in pwMS.

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