The Evidence Supporting CBD Use in Rare Neurologic Behavioral Disorders

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Disclosures

- Dr. Carney has no disclosures to report.

Learning Objective 1

Review of rare epileptic encephalopathies and the historical use of cannabis-based therapies for epilepsy.

Learning Objective 2

Review contemporary research about cannabis-based therapies for pediatric epilepsy.

Learning Objective 3

Describe the considerations in choice of cannabis product for the management of seizure disorders in children.

Epileptic Encephalopathy

- The epileptic encephalopathies are age dependent refractory epilepsies of childhood
- Characterized by frequent brief seizures resistant to medication and progressive brain dysfunction
- Associated with loss of developmental skills
- Occur during period of cerebral development, therefore associated with residual permanent mental handicap

Epileptic Encephalopathy

- Catastrophic epilepsies of early infancy
  - Ohtahara syndrome
  - Early myoclonic encephalopathy
  - Infantile spasms/West syndrome
- Early childhood and older
  - Severe myoclonic epilepsy of infancy (Dravet syndrome)
  - Lennox-Gastaut syndrome
  - Angelman syndrome
  - Landau-Kleffner syndrome

Dravet Syndrome

- Onset usually in the first year of life
- Typically presents with febrile status epilepticus
- As child gets older, other seizure types emerge including seizures without fever
- Developmental stagnation or regression seen by 1-4 years of age
- Usually very resistant to treatment
- 70% secondary to mutation in SCN1A gene

SCN1A = sodium voltage-gated channel alpha subunit 1.

Shabarou R, Mikati MA. *Semin Pediatr Neurol*. 2016;23(2):134-142.

Renewed Interest in Cannabis to Treat Epilepsy

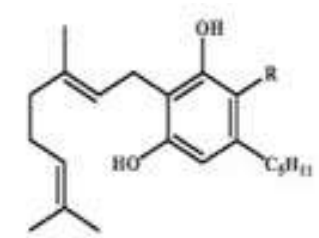
- Interest in cannabis ended with development of new medications and passing of the Marihuana Tax Act in 1937
- From 1970-1980 several case reports of patients having reduction in seizure frequency when smoking cannabis
- Smoking cannabis also seemed to have a protective effect against first unprovoked seizure
- Cannabis during this time period had much lower concentrations of Δ9-THC and higher concentrations of CBD
- Interest in cannabis resumed only in last 2 decades
- Initially focused on Δ9-THC and other CB1R agonists

CBD = cannabidiol; CB1R = cannabinoid 1 receptor; THC = tetrahydrocannabinol.

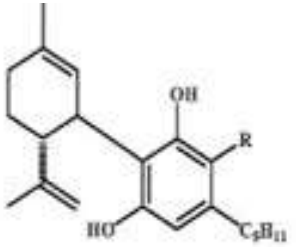
Brust JC, et al. *Trans Am Clin Climatol Assoc*.1992;103:176-s81.

Cannabinoids

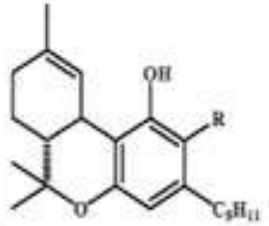
- Over 140 cannabinoids produced by C. sativa
- Referred to as phytocannabinoids
- Have a C21 structure with aromatic core and with terpenyl and pentyl side chains
- Divided into 6 main categories



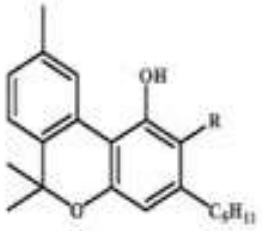
R = H, cannabigerol (CBG)
R = COOH, cannabigerolic acid (CBGA)



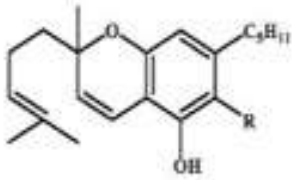
R = H, cannabidiol (CBD)
R = COOH, cannabidiolic acid (CBDA)



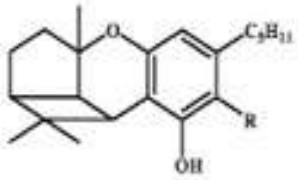
Δ^9-tetrahydrocannabinol (Δ^9-THC)
Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA)



R = H, cannabinol (CBN)
R = COOH, cannabinolic acid (CBNA)



R = H, cannabichromene (CBC)
R = COOH, cannabichromenic acid (CBCA)

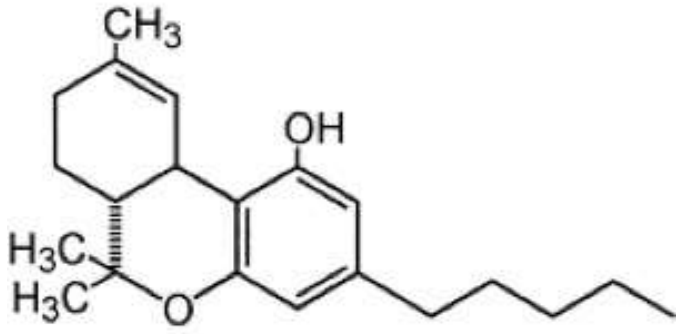


R = H, cannabicyclol (CBL)
R = COOH cannabicyclolic acid (CBLA)

C = cannabis.

Δ9-THC in Animal Models of Epilepsy

- Most abundant cannabinoid in cannabis
- Anticonvulsant properties felt to be through activation of neuronal CB1 receptors
- CB1R activation affects neuronal activity via several pathways
- Has anticonvulsant properties in several *in vitro* and *in vivo* models of epilepsy
- Potentiates the effect of several anticonvulsants
- Toxicity and psychotropic side effects limit use as an anticonvulsant agent



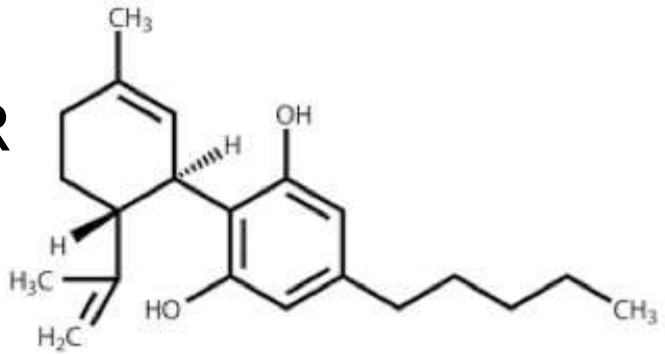
Δ-9-tetrahydrocannabinol (THC)

CH_3 = methenium; O = oxygen; OH = hydroxide.

Reddy DS, Golub VM. *J Pharmacol Exp Ther*. 2016;357(1):45-55.; Turkanis SA, Karler R. *Neuropharmacology*. 1982;21(1):7-13.

CBD in Animal Models of Epilepsy

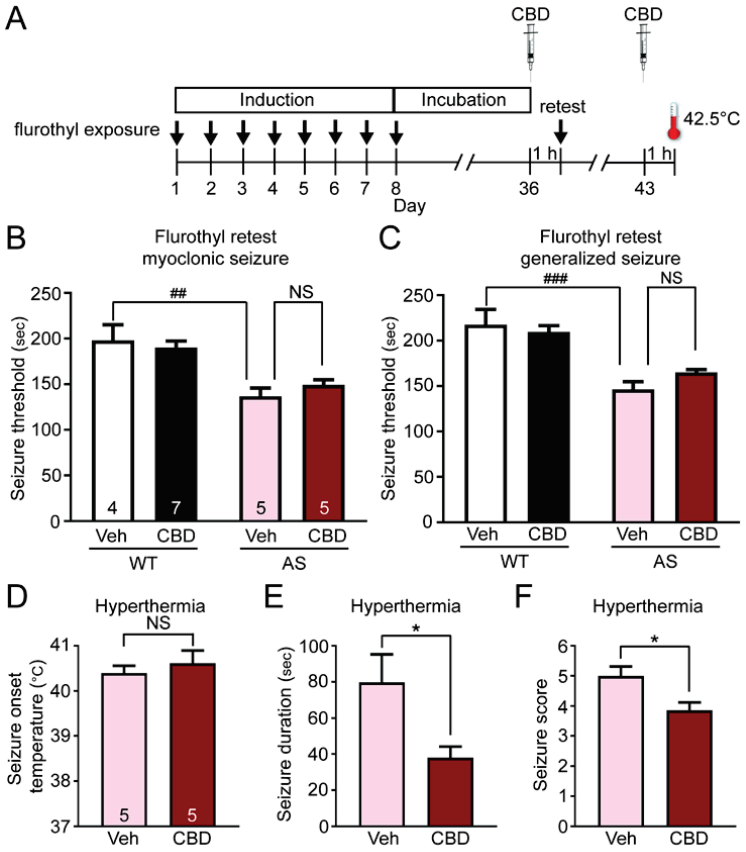
- Showed anti-convulsant effects in several animal models
- Blocked the pro-convulsant effects of Δ9-THC
- Negative allosteric modulator of CB1R
- Anti-convulsant effects independent of CB1R
- Increases neuronal adenosine and $5HT_{1-2A}$ activity and binds to TVPR1 receptors
- Rats given high doses of CBD (200 mg/kg) showed no motor impairment
- Suggests that CBD would be an ideal potential anti-convulsant for children

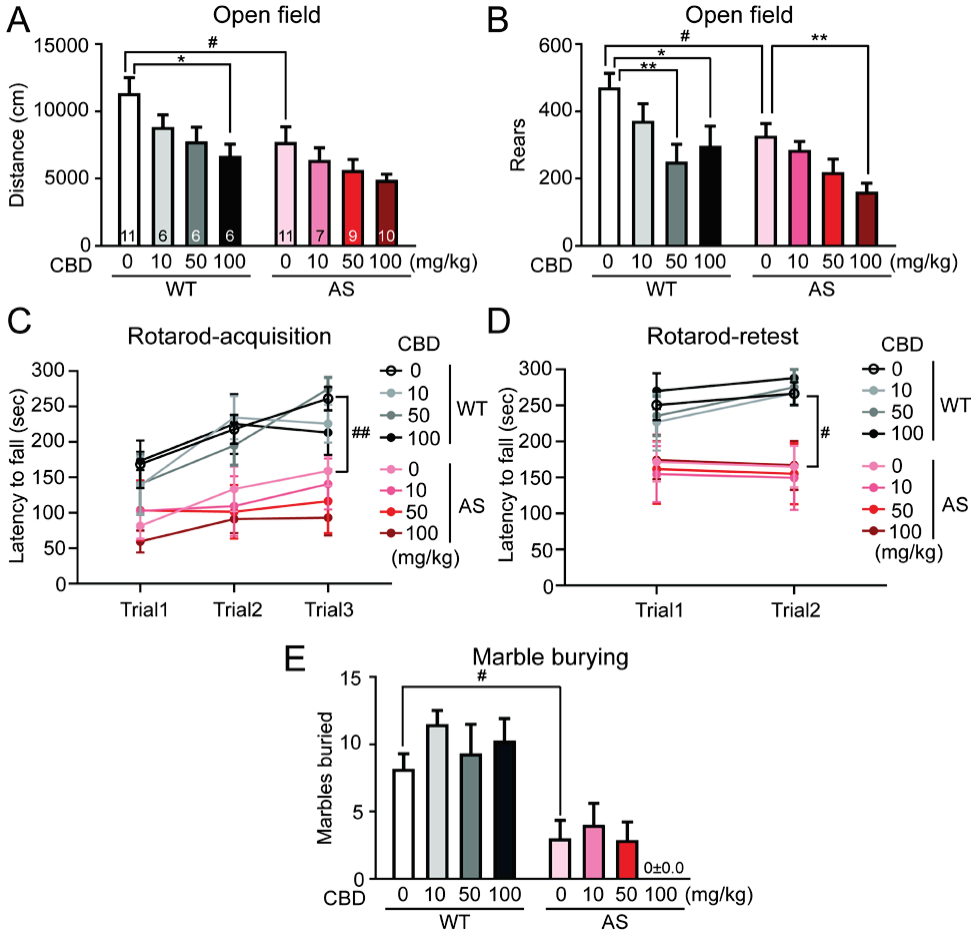


5HT = 5-hydroxytryptamine; TVPR1 = transient receptor potential cation channel subfamily V member 1.

Jones NA, et al. *J Pharmacol Exp Ther*. 2010;332(2):569-577.; Reddy DS, Golub VM. *J Pharmacol Exp Ther*. 2016;357(1):45-55.

Animal Studies of Cannabinoids and Epilepsy





AS = angelman syndrome; Veh = vehicle; WT = wild type.
Gu B, et al. *J Clin Invest*. 2019;129(12):5462-5467.

Human Studies of Cannabinoids in Epilepsy

- Human trials to assess efficacy of CBD enriched cannabis
- First human epilepsy trials by Mechoulam and Carlini (1978), and Cunha (1980). Both had significant design and reporting flaws[1,2]
- No human studies for over 2 decades
  - Largely in part because of legal restrictions on cannabis possession and research
- Surge of interest following reports of Charlotte Figi who became seizure free taking a cannabis preparation called “Charlotte’s Web”

1. Mechoulam R, Carlini EA. *Naturwissenschaften*. 1978;65(4):174-179.; 2. Cunha JM, et al. *Pharmacology*. 1980;21(3):175-185.

The Cannabidiol Studies (2016)

- Open label study including children and adolescents with refractory epilepsy[1]
- Overall 36.5% reduction in seizures[1]
- Significant variability in daily dosage (up to 25 mg/kg/day)[1]
- Adverse events included somnolence, diarrhea, and fatigue[1]
- Rosenberg (2016) performed a post-study analysis of QOLCE surveys in 20 patients enrolled[2]
- Significant improvements in global scores and sub-scores[2]

QOLCE = Quality of life childhood epilepsy

1. Devinsky OE, et al. *Lancet Neurol*. 2016;15(3):270-278.; 2. Rosenberg EC, et al. *Epilepsia*. 2017;58(8):e96-e100.

The Cannabidiol Studies (2017)

- 120 patients with Dravet syndrome randomized to receive cannabidiol 20 mg/kg/day or placebo
- Median seizure frequency decreased from 12.4 to 5.9 in cannabidiol group vs 14.9 to 14.1 in the control group
- While difference in convulsive seizures between the CBD and control groups reached clinical significance there was no significant change in the number who became seizure free or had > 50% seizure reduction
- Most common side effects in cannabidiol group were diarrhea, vomiting, somnolence and increased liver enzymes

Devinsky O, et al. *N Engl J Med*. 2017;376(21):2011-2020.

The Cannabidiol Studies (2018)

- 171 patients with LGS randomized to receive CBD or placebo
- 2-week dose escalation to 20 mg/kg/day CBD then 12 weeks maintenance
- Monthly atonic seizures decreased 43.9% in CBD vs. 21.8% in placebo group
- Difference between groups ~19.45 during 12-week maintenance phase (p = .0096)
- 44% of patients in CBD group had a ≥50% reduction in atonic seizures
- Monthly total seizures decreased 41.2% in CBD vs.13.7% in placebo group
- Difference between groups ~23.3% during 12-week maintenance phase (p = .0004)
- Common adverse events in the CBD group included diarrhea, somnolence and decreased appetite

LGS = Lennox-Gastaut syndrome.
Thiele EA, et al. *Lancet*. 2018;391(10125):1085-1096.

Cannabis Oil Preparations Containing Δ9-THC

- Open label study in 74 children with refractory epilepsy given escalating doses of CBD enriched Cannabis herbal extract
- Dose of CBD variable. Divided into two groups: < 10 mg/kg/day and > 10 mg/kg/day
- 52% of participants had > 50% reduction in seizures
- Those with Lennox Gastaut syndrome responded better that those with Dravet syndrome
- 7% withdrew due to side effects

Tzadok M, et al. *Seizure*. 2016;35:41-44.

Questions That Remain

- Based on available data CBD appears to have a favorable efficacy and side effect profile compared to other anticonvulsants
- Difficult to interpret results as different doses of CBD and preparations used
- Many questions remain:
  - Why do some children seem to respond better than others?
  - What is appropriate dose of CBD?
  - Pediatric pharmacokinetics?
  - Is there benefit in adding a small amount of Δ9-THC and how much?
  - What about other cannabinoids?
  - Does response correlate better to dose or therapeutic level?

Cannabidiol in Children with Refractory Epileptic Encephalopathy Study

- A pilot study run by Department of Pediatrics, University of Florida
- Funded by the Florida Department of Health (Senate Bill 1030)
- Open label dosage escalation design
- Attempts to answer questions about most appropriate dose of CBD for seizure control, safety, and behavioral changes

5EP01. Effects of cannabidiol use on the developing brain in medically refractory childhood epilepsy. Agency: Florida Department of Health. Available at https://facts.fldfs.com/Search/ContractDetail.aspx?AgencyId=640000&ContractId=5EP01. Accessed February 23, 2020.

Cannabidiol in Children with Refractory Epileptic Encephalopathy (Florida Epilepsy Network) Study

- 50 children with epileptic encephalopathy enrolled across 4 Florida sites
  - 36 visits spaced one month apart over 3 years
  - Brief survey regarding parental perception of cannabis use in children
  - Seizure log to measure baseline seizure status
  - Parents instructed not to change medications or anticonvulsant therapies
  - Suicidal screen at baseline and every visit
  - ADOS and measures of behavior at baseline and every 4 months x 8
  - Laboratory: routine, AED levels, U/A

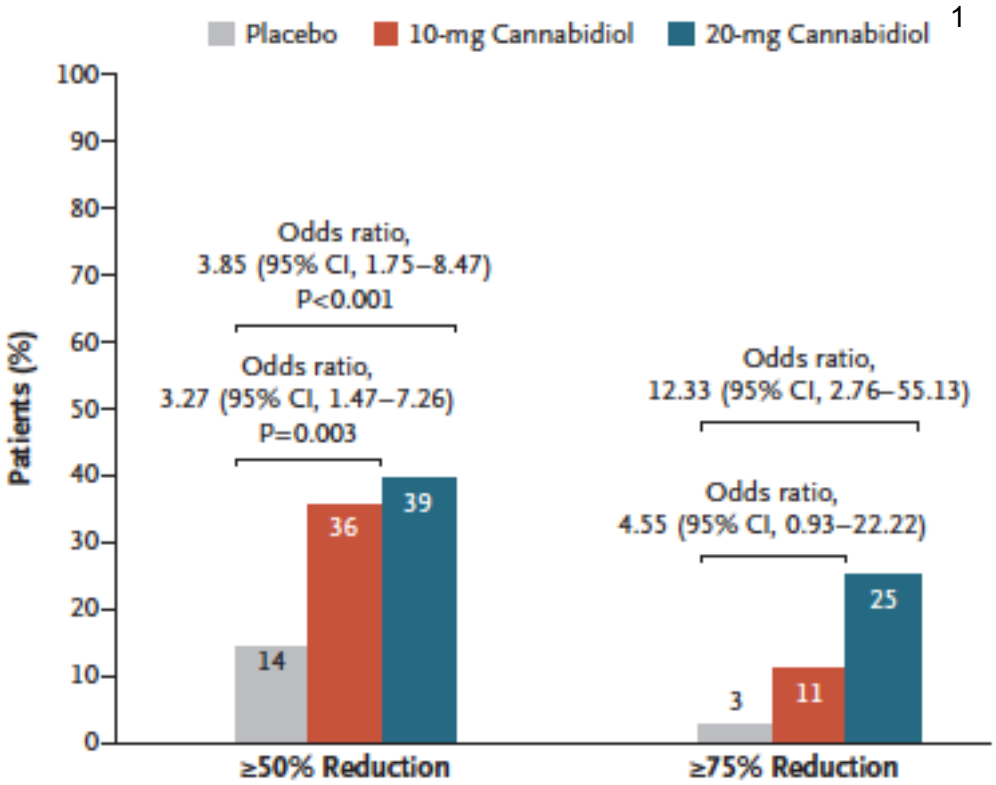
ADOS = Autism Diagnostic Observation Schedule; AED = antiepileptic drug; U/A = urinalysis.
Anderson CL, et al. *J Pediatr Neurol* 2017;15(4):143-150.

Florida Epilepsy Network Study Findings

- Study included pre-dose plasma concentrations of THC, CBD, and anticonvulsants
- Observations:
  - Dose reduction of a benzodiazepine in several children
  - Linear dose-concentration relationship
  - 12/50 participants became seizure free
  - 38/50 participants had >50% reduction in seizures with 67% reduction in drop (atonic) seizures
  - 2 children who became seizure free of Seminole ethnicity suggesting a possible pharmacogenomics relationship
  - No participants withdrawn due to side effects
  - Differences in effect at different doses - one dose size does not fit all

Anderson CL, et al. *J Pediatr Neurol* 2017;15(4):143-150.

Florida Department of Health Florida Epilepsy Network Study Findings



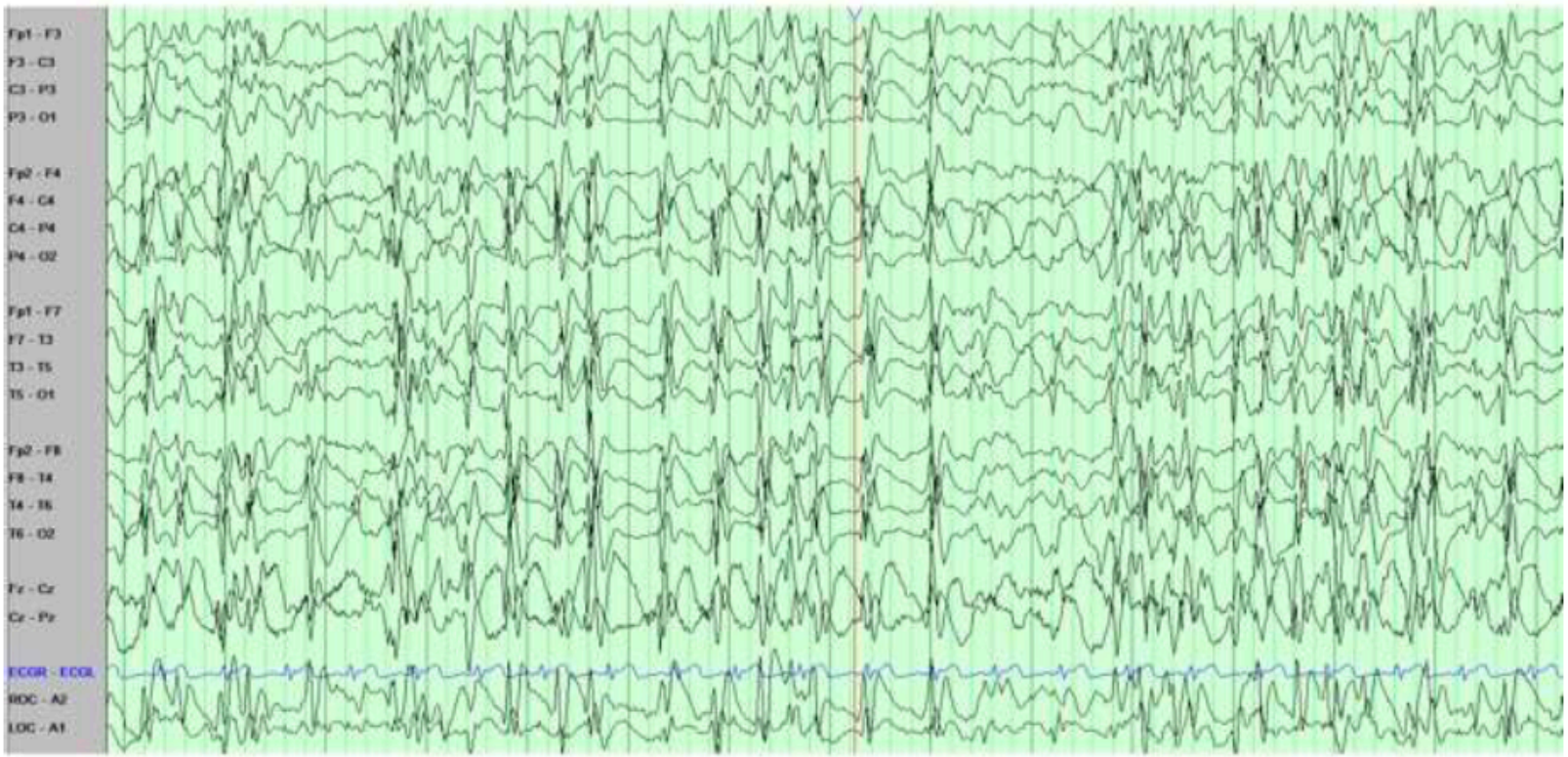
[1]

Positive/Negative Side Effects [2]	n = 33
Seizure Severity Decrease	22 (67%)
Better Mood	14 (42%)
Increased Alertness	11 (33%)
Better Focus	13 (39%)
Improved Social Interaction	15 (45%)
Better Sleep	3 (9%)
Improved Appetite	5 (15%)
Negative Side Effects	n = 33
Drowsiness	11 (33%)
Fatigue	4 (12%)
Diarrhea	4 (12%)
Negative Mood	3 (9%)
Decreased Appetite	2 (6%)

CI = confidence interval.

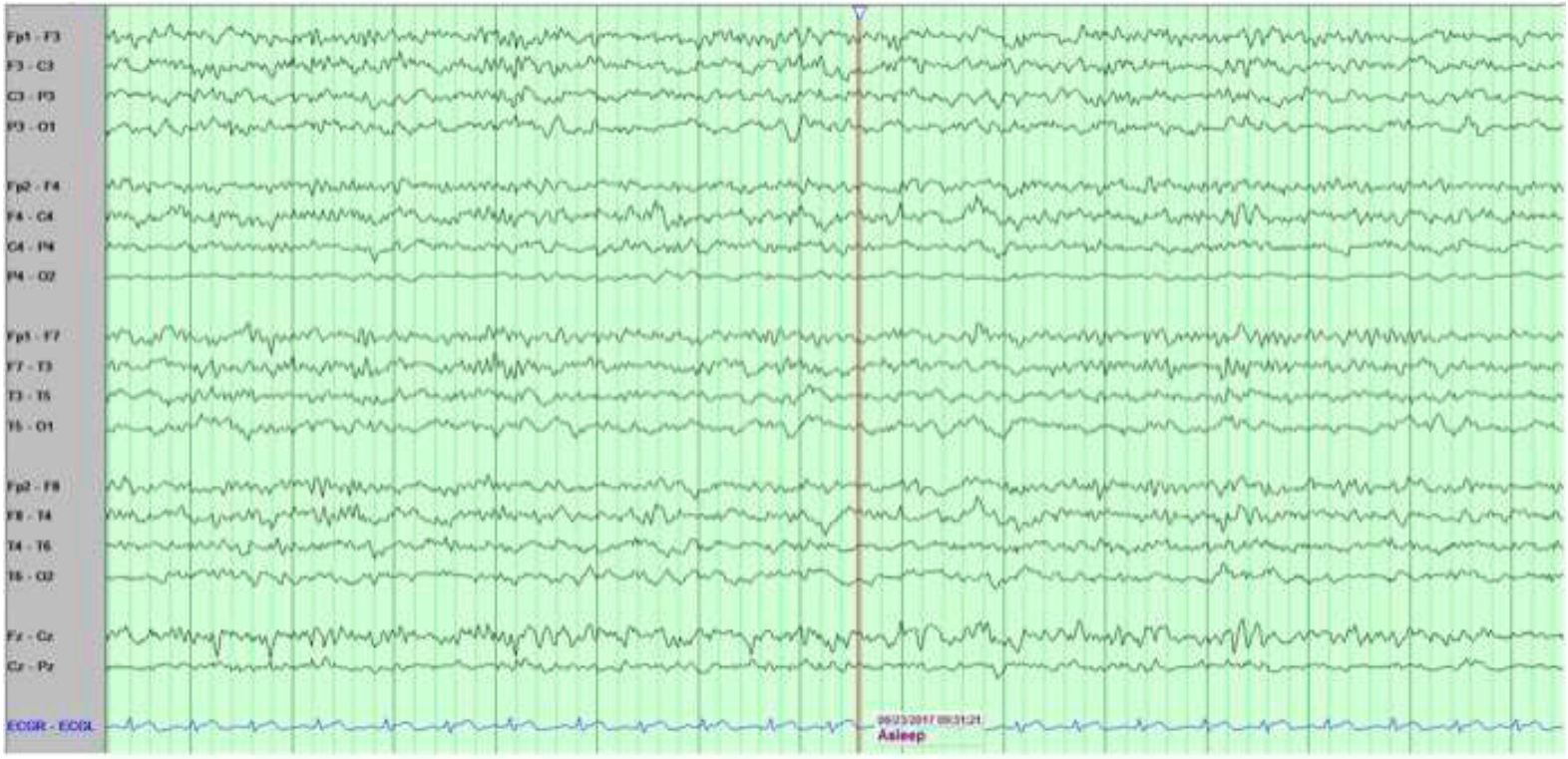
1. Anderson CL, et al. *J Pediatr Neurol* 2017;15(4):143-150.; 2. Carney PR, et al. American Epilepsy Society Annual Meeting 2017; December 2, 2017; Washington, DC. Abstract No. 1.048.

Baseline EEG (Asleep)



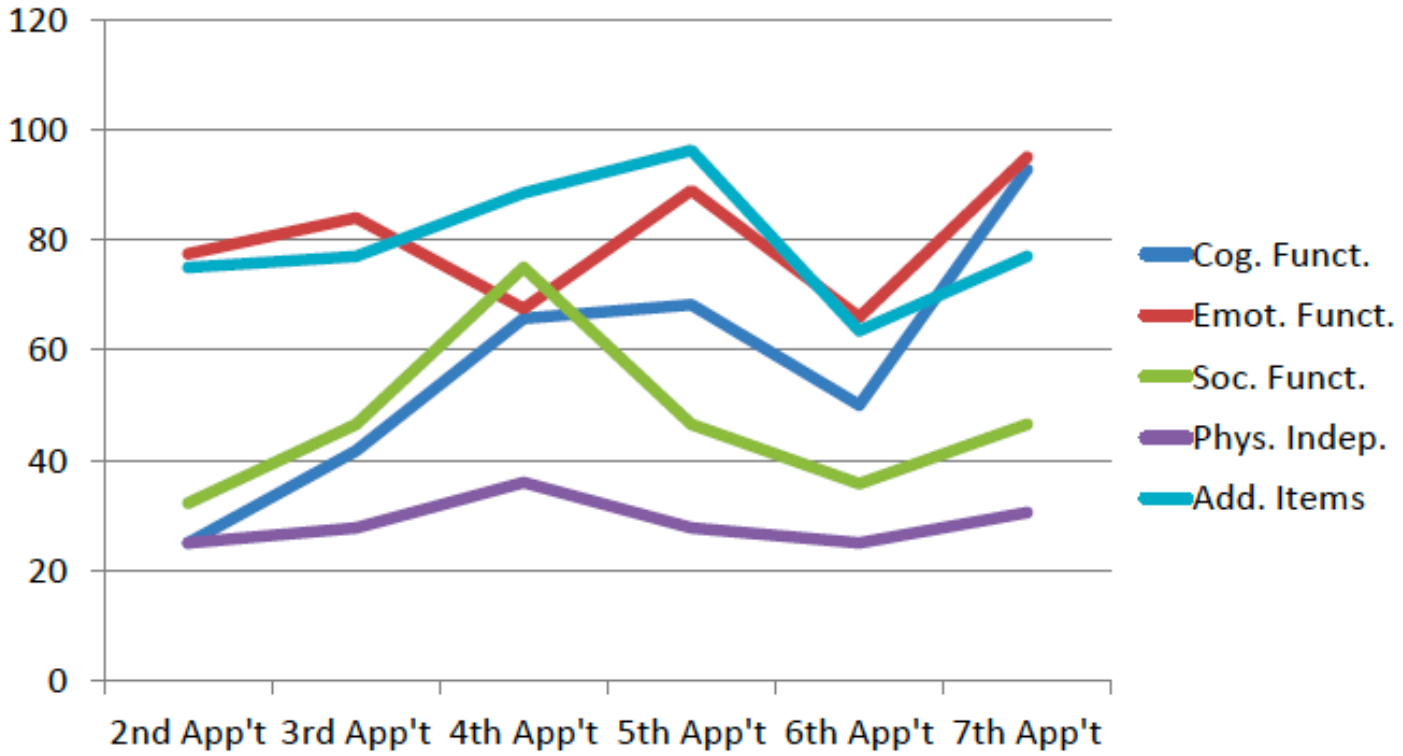
EEG = electroencephalography.
Anderson CL, et al. *J Pediatr Neurol* 2017;15(4):143-150.

Repeat EEG (Asleep)

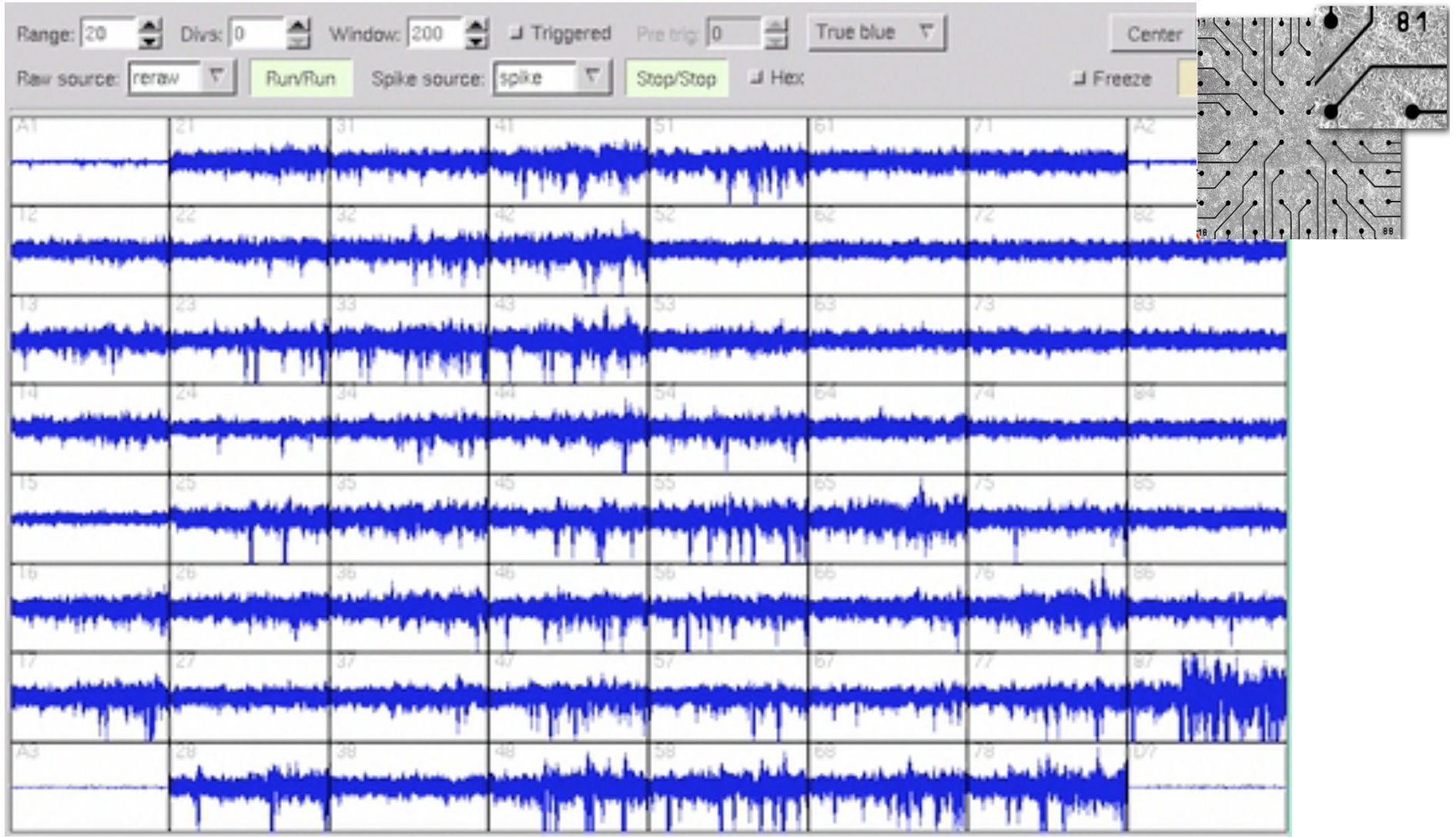


Anderson CL, et al. *J Pediatr Neurol.* 2017;15(4):143-150.

Subscale Results

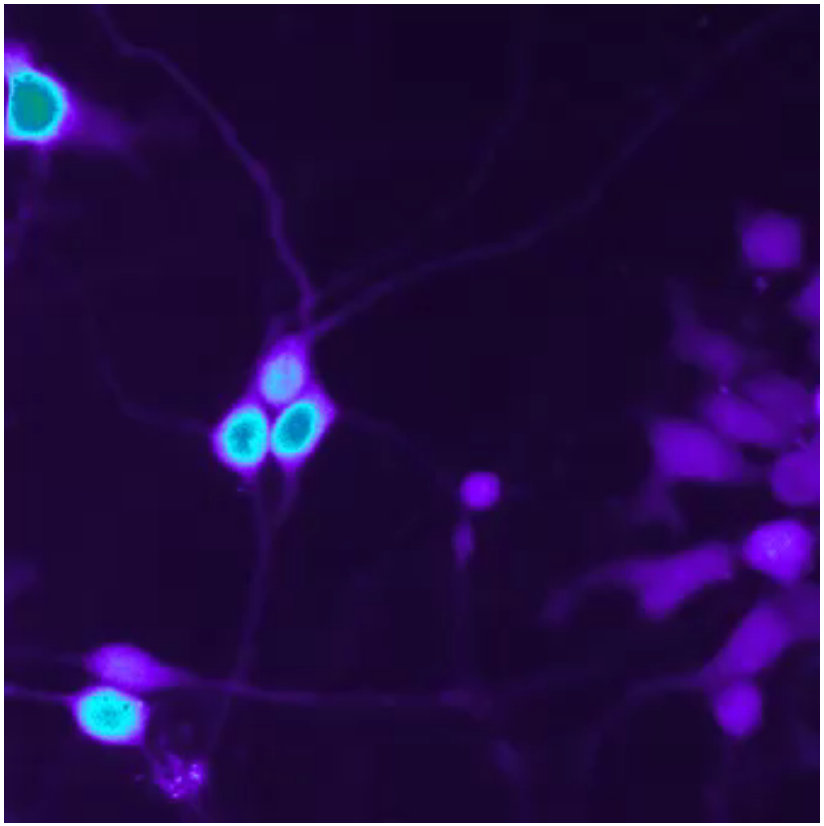


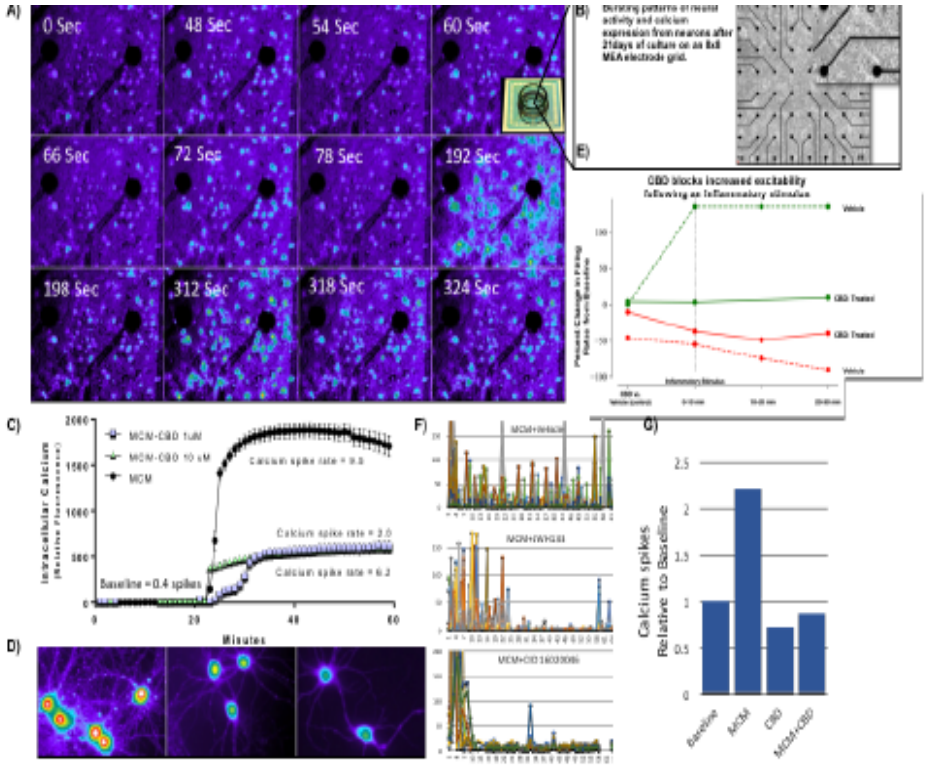
Anderson CL, et al. *J Pediatr Neurol.* 2017;15(4):143-150.



Unpublished data from the lab of Paul Carney, MD.

CBD Suppresses Calcium Dysregulation and Reduces Hyperexcitability





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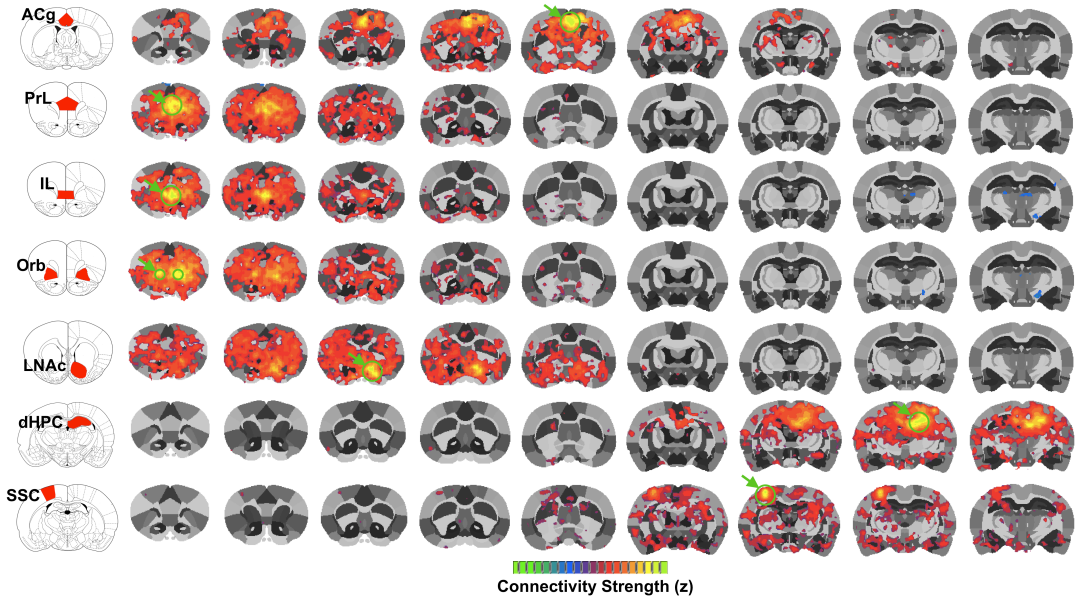
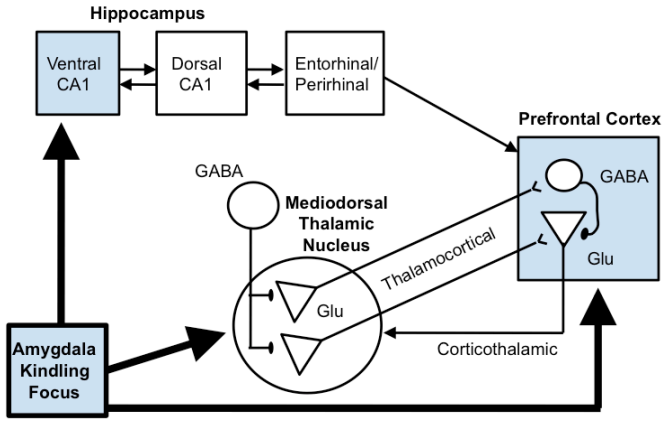
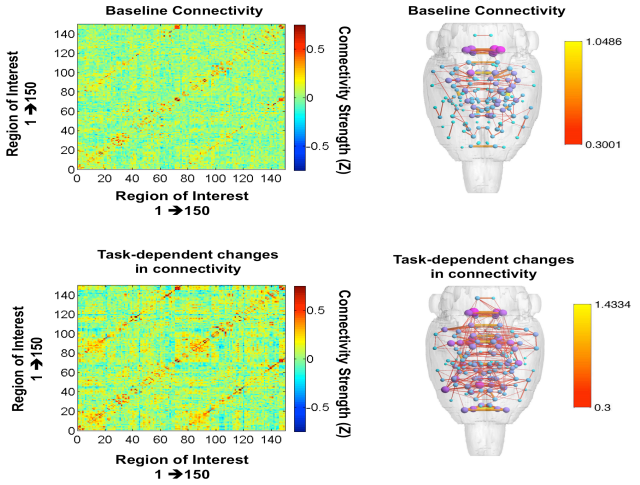
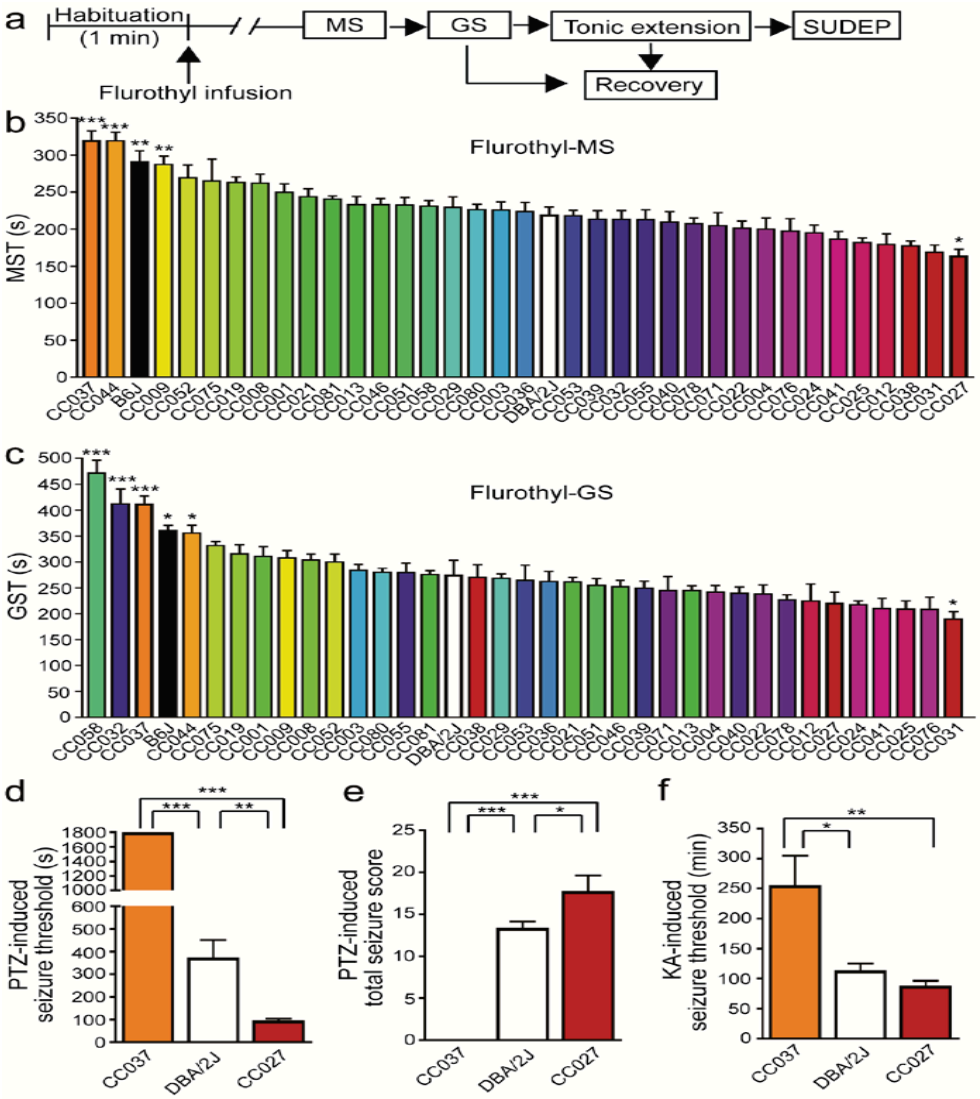






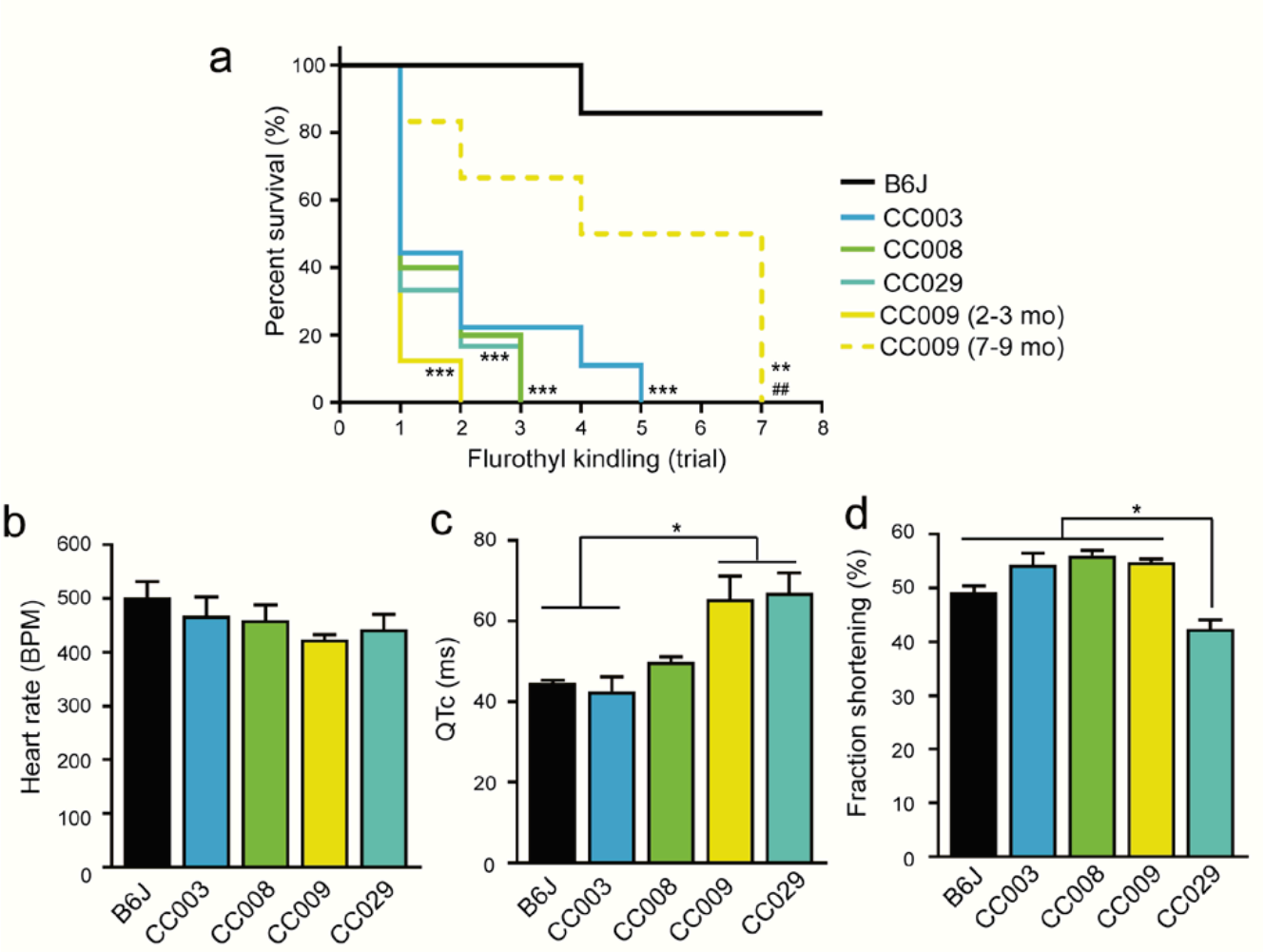
Unpublished data from the lab of Paul Carney, MD.

Response to Treatment is Highly Dependent On Background



CC = collaborative cross; GS = generalized seizure;
GST = GS threshold; MS = myoclonic seizure;
MST = MS threshold; PTZ = pentylenetetrazol;
s = second;
SUDEP = sudden unexpected death in epilepsy.
Gu B, et al. *bioRxiv.* 2019;690917. DOI: https://doi.org/10.1101/690917.

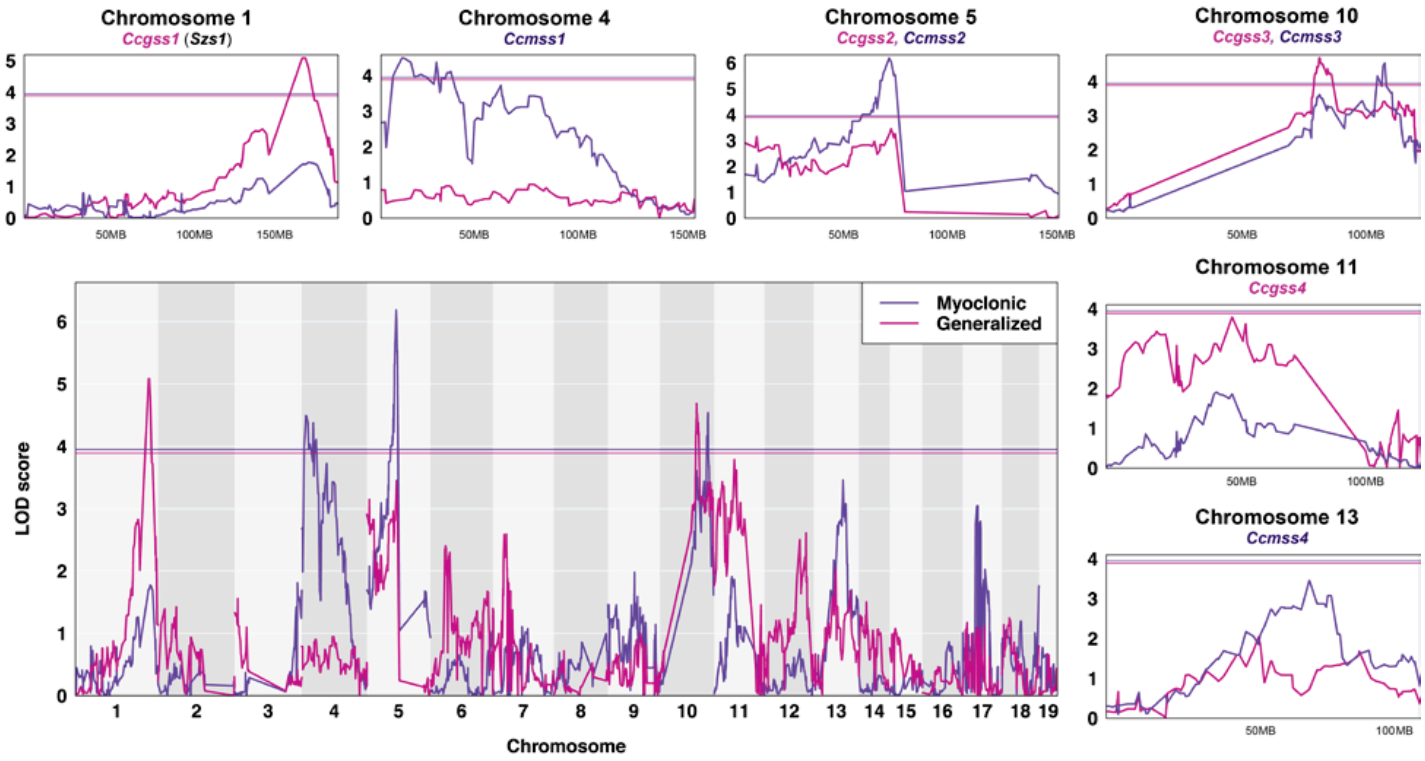
Response to Treatment is Highly Dependent on Background



BPM = beats per minute; ms = milliseconds.

Gu B, et al. *bioRxiv.* 2019;690917. DOI: https://doi.org/10.1101/690917.

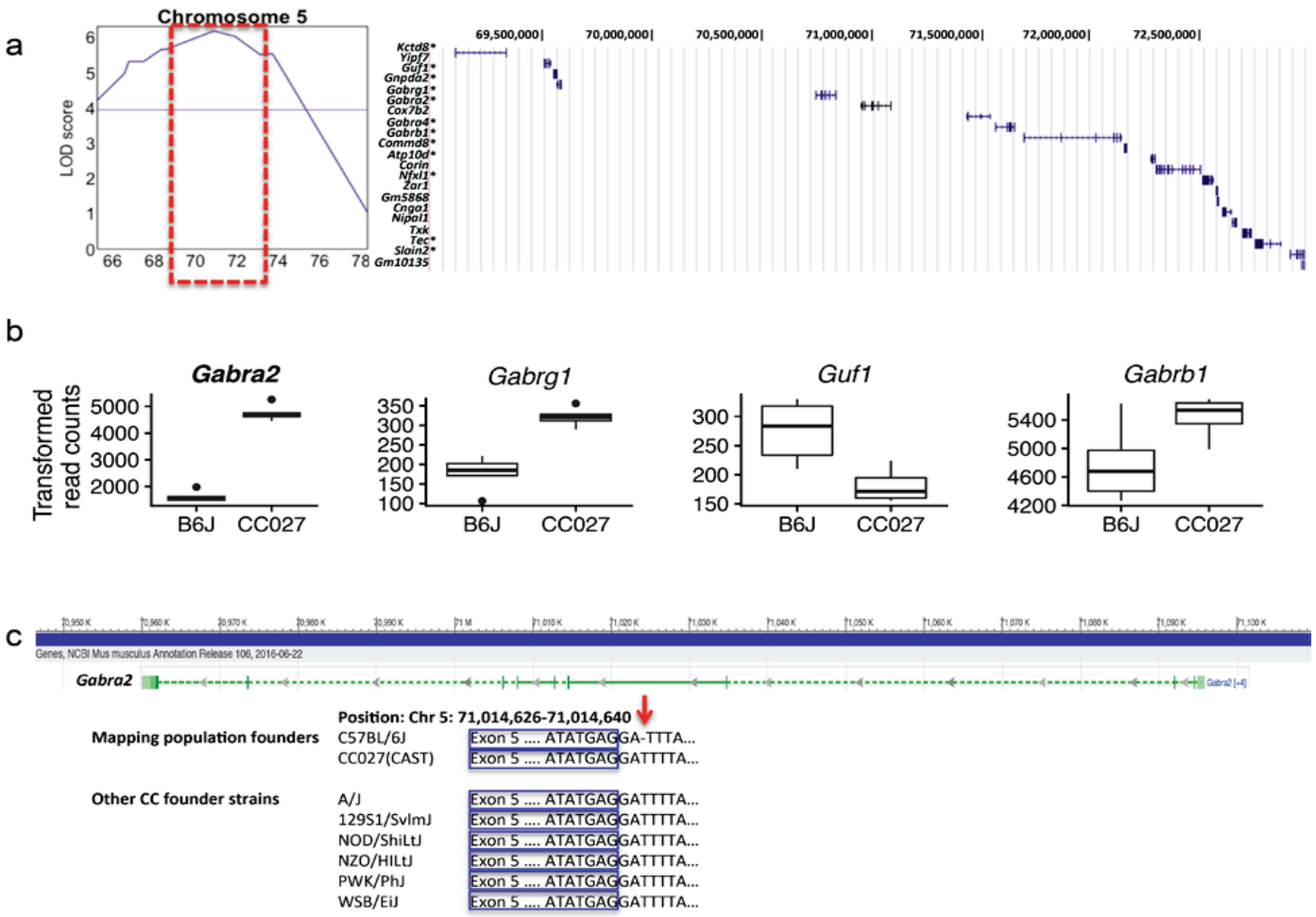
Response to Treatment is Highly Dependent on Background



LOD = logarithm of the odds; MB = megabase.

Xie Y, et al. 16th International Child Neurology Association Congress (ICNC), 49th Annual Child Neurology Society Meeting. 2020; San Diego, CA.

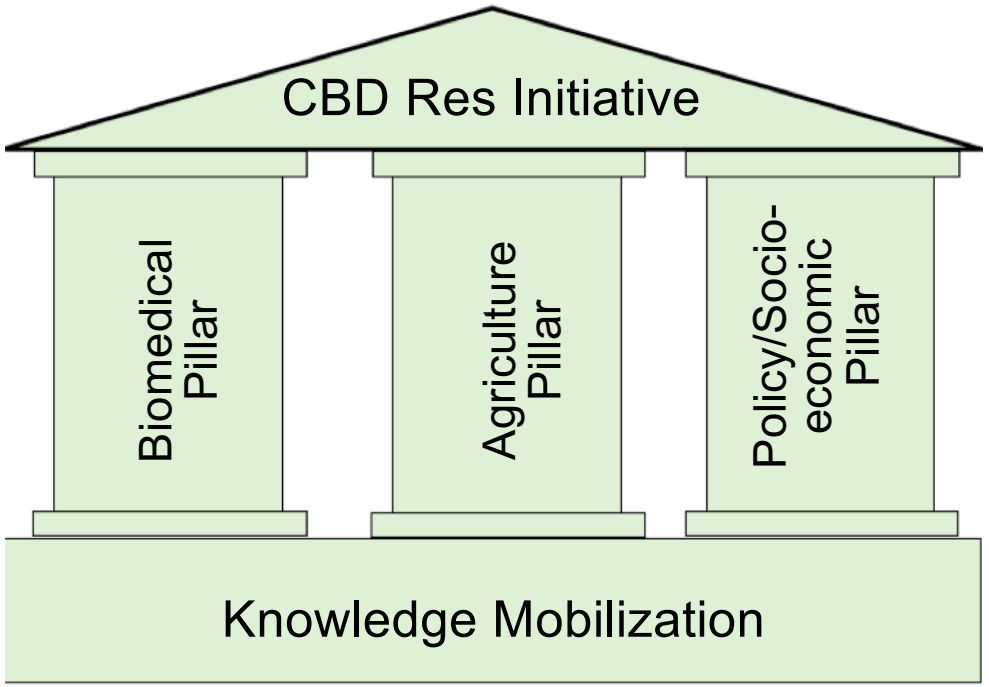
Response to Treatment is Highly Dependent on Background



Xie Y, et al. 16th International Child Neurology Association Congress (ICNC), 49th Annual Child Neurology Society Meeting. 2020; San Diego, CA.

Cannabinoid Research Initiative

- Biomedical Pillar
  - Scientific evidence about application of cannabinoids for health and disease in humans and animals
- Agricultural Pillar
  - Analysis of genomic and trait variation. To improve understanding of potential medicinal & agricultural uses
- Policy/Socioeconomics Pilar
  - Develop policy frameworks around economic development, health and safety, and public policy
- Knowledge Mobilization
  - To HQP, industry, and gov't stakeholders



HQP = Health Quality Partners.

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Utilize cannabidiol in appropriate patients with Dravet syndrome to achieve meaningful reduction in seizures
- Integrate genetic testing into the overall clinical evaluation of a patient with epilepsy

Acknowledgement

- Children and Families
- All University of Florida Institutional Review Boards (IRB) leadership and personnel
- University of Florida Clinical and Translational Science Institute (CTSI)
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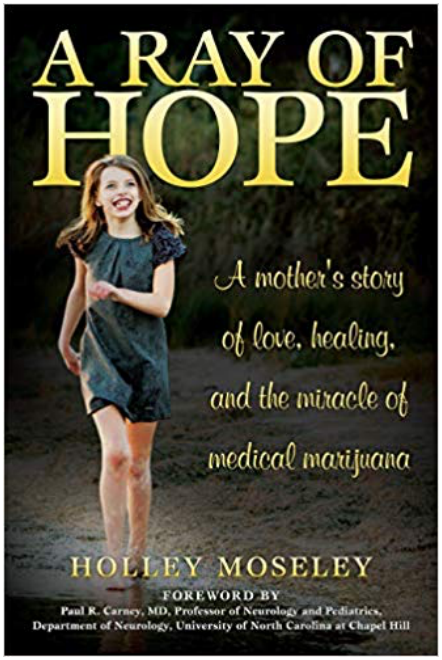
- Marcelo Febo, PhD


A RAY OF HOPE
A mother's story of love, healing, and the miracle of medical marijuana
HOLLEY MOSELEY
FOREWORD BY
Paul R. Carney, MD, Professor of Neurology and Pediatrics, Department of Neurology, University of North Carolina at Chapel Hill

Additional Abbreviations

ACg = anterior cingulate gyrus
dHPC = dorsal hippocampal lesion
GABA = gamma-aminobutyric acid
Glu = glucose
IL = infralimbic cortex
LNAc = left nucleus accumbens
NOD = non-obese diabetic
NZO = New Zealand Obese
Orb = rotated binary robust independent elementary
PrL = prolactin
WSB = Watkins Star Line B

#CBD2020

CBD2020 CONFERENCE

CME Outfitters

Exploring the Evidence for Medical Cannabis in Clinical Practice

February 26-27, 2020 | The LINQ | Las Vegas, Nevada

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