




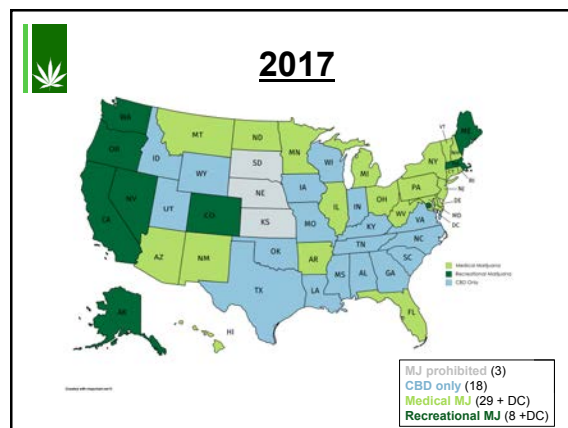
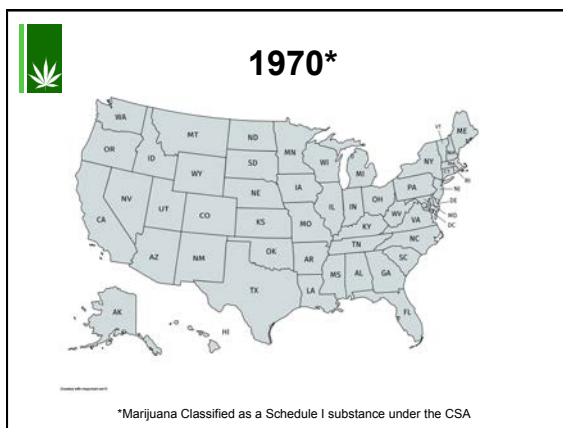
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MARIJUANA: CLEARING THE SMOKE




Marijuana (MJ) has been around seemingly forever...

*We hold these truths to be self-evident
 that not all cannabis is created equal*



Not all marijuana is "the same"

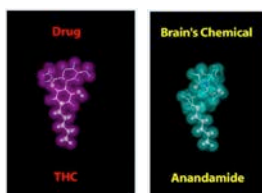


Marijuana (MJ) is a term used to describe the plant *Cannabis Sativa* L.

- Two main species:
 - Sativa
 - Indica
- There are also many strains of cannabis which are a hybrid of the two plants
- There are over 400 known chemical constituents in MJ
- MJ contains 100 or more **phytocannabinoids**:
 - "Plant-derived natural product capable of either directly interacting with cannabinoid receptors or sharing chemical similarity with cannabinoids or both" (Gertsch et al. 2010)
- Most common phytocannabinoids:
 - Δ9-tetrahydrocannabinol (THC)**, the primary psychoactive constituent of cannabis
 - Cannabidiol (CBD)**, the primary non-intoxicating constituent of cannabis

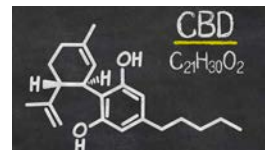
Δ^9 -tetrahydrocannabinol (THC)

- THC is the primary **psychoactive** constituent in MJ
 - In other words, THC is what makes users feel high
- THC is similar to a natural chemical found in the brain: anandamide



Cannabidiol (CBD)

- CBD is one of the primary, **non-intoxicating** constituents in MJ
- Evidence suggests that CBD may mitigate the effects of THC
- As CBD has shown some potential medicinal value, there is great interest in studying it for medical applications
- CBD may have therapeutic potential for numerous indications such as:
 - Anxiety
 - Epilepsy
 - Cancer
 - Pain
 - Movement Disorders
 - Mood
 - Countless other indications...



Individuals may also be differentially affected by MJ use based on age:

- The human brain was once believed to be developed by the onset of puberty
- Data acquisition continues into adulthood

Given this critical period of neurodevelopment, adolescents are likely to be more vulnerable to the adverse effects of MJ relative to adults.



Recreational Marijuana

MJ & Cognition: Recent Research Findings

- Nearly **ALL** of what we know about the impact of MJ use comes from studies of recreational MJ users - often difficult to characterize
- Results have been somewhat mixed when assessing the impact of MJ on the brain – this may be due to a number of factors including **frequency and amount of MJ used, product type, duration of use, and age of onset of MJ use**
- Overall, however, reviews of the non-acute effects of MJ report that:
 - Executive functioning, attention and memory** are most strongly affected by regular (weekly or more often) MJ use
 - Processing speed** may also be adversely impacted in regularly users
 - However, findings are more variable with regard to IQ

(Broyd et al., 2016; Crean et al., 2011; Ganzer et al., 2016; Solowij & Battisti, 2008)



Study Aim

- Given that adolescence is a time of neurodevelopmental vulnerability, MJ may have a different (more pronounced) impact on young consumers
- While previous investigations reported alterations in both brain structure and function which are associated with marijuana use, *few have directly compared early and late onset MJ smokers*.
- Study Aim:** to examine the potential impact of age of onset of MJ use on both performance of neurocognitive tasks & brain function and structure in chronic, heavy recreational MJ smokers.
- Hypothesis:** We hypothesized that cognitive decrements and alterations in brain structure and function would **primarily be attributable to early onset users**.

Early MJ onset:
regular MJ use
prior to age 16



Late MJ onset:
regular MJ use
after age 16

Early vs Late Onset MJ Smokers: MJ Use Patterns

Compared to those who started smoking after age 16, early onset marijuana smokers:

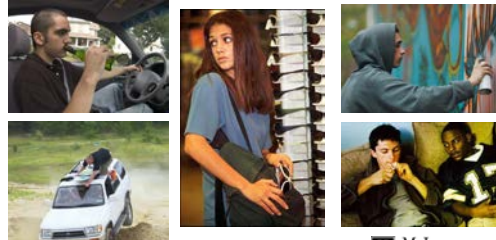
- Smoked **nearly twice as often** and...
- Smoked **over 2.5 times as much** MJ (in grams) as their later smoking counterparts



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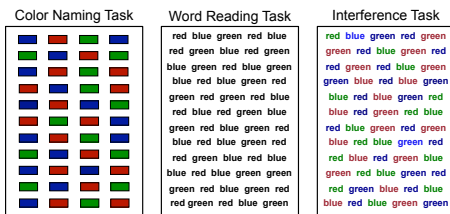
Executive Function

Controlled by the frontal part of the brain, these involve monitoring and changing behavior as needed, decision-making, abstract thinking, rule acquisition and **inhibiting inappropriate actions**



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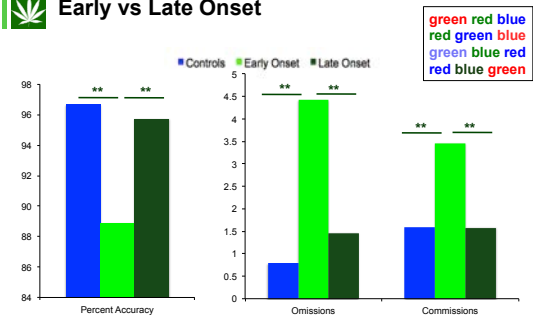
Stroop Color Word Task



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Stroop Interference Performance: Early vs Late Onset

Sagar et al. 2015



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Neurocognitive Function: 3-Group ANOVA Controls vs Early vs Late MJ Users

Variable	HC (N=44)	Early MJ (N=28)	Late MJ (N=34)	3-group ANOVA F	p (p ²)	Dunnett t HC v E	HC v L
Stroop Color Word Test							
Color Naming Commission						NS	NS
Color Naming Accuracy						NS	NS
Word Reading Commission					.03	.03	
Word Reading Accuracy					NS	NS	
Interference Commission					.02	NS	
Interference Accuracy					.01	NS	
WCST							
Total Categories					.02	NS	
Total Perseverations					.01	NS	
Total Losses of Set					.01	NS	
Trail Making Test							
A Time (sec)					.05	NS	
A Errors					.05	NS	
B Time (sec)					.02	NS	
B Errors					.01	NS	

Early onset MJ users perform significantly more poorly than both healthy controls and late onset users.

In contrast, very few differences are observed between late onset MJ users and healthy controls.

MJ & Brain Function: Recent Research Findings

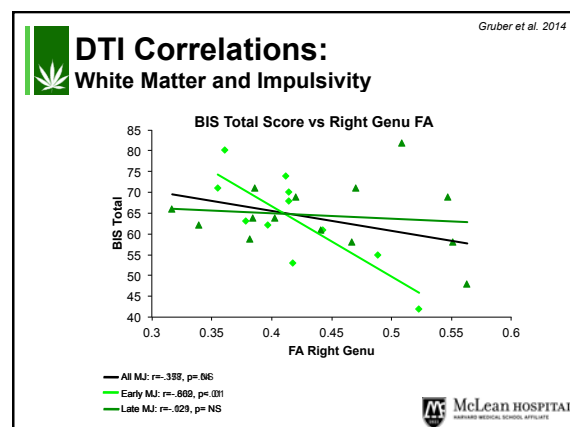
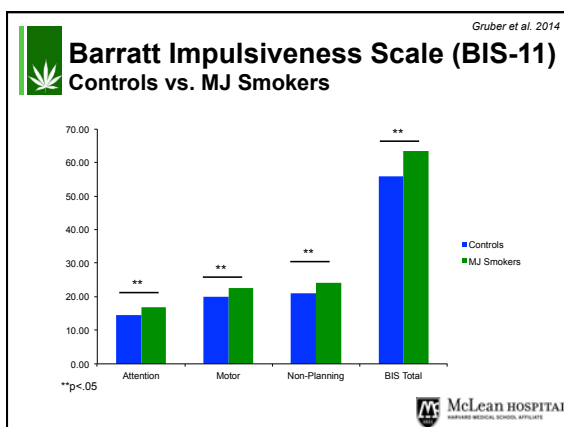
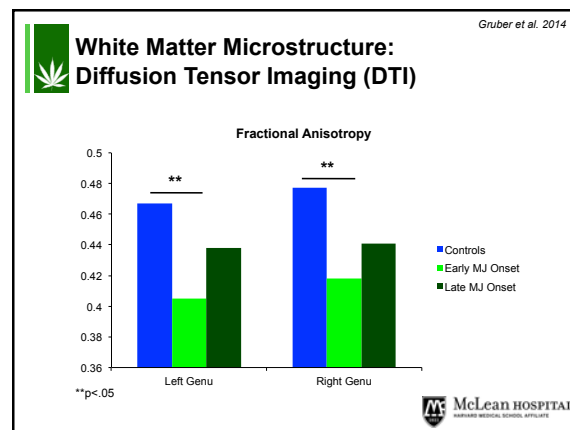
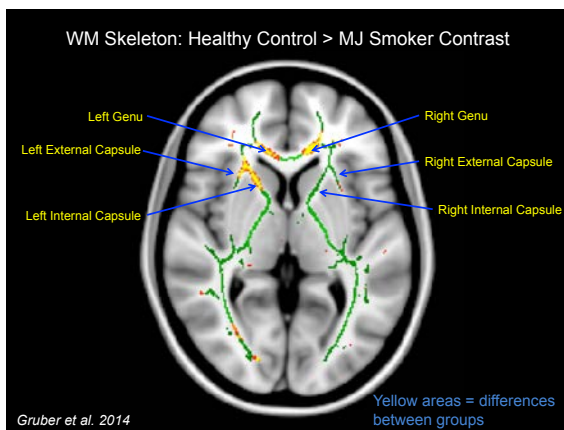
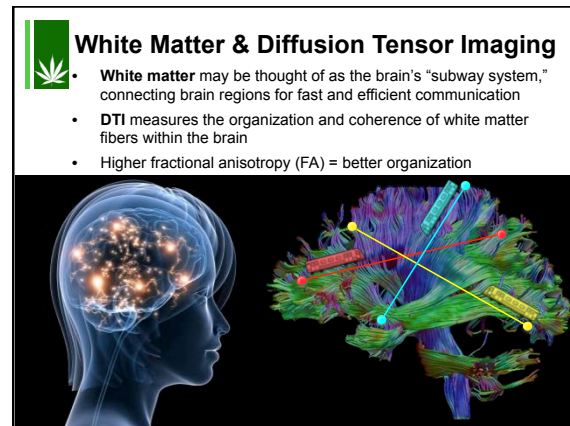
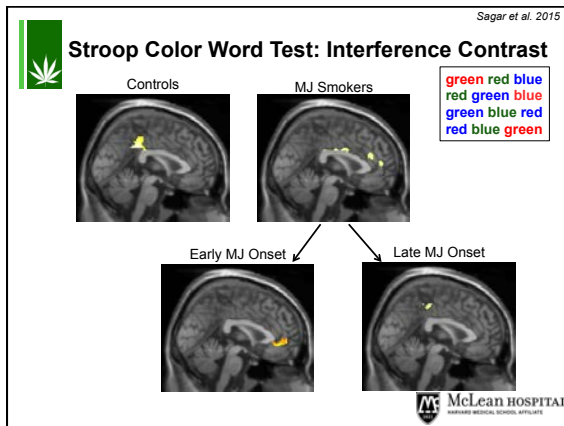
- Functional magnetic resonance imaging (fMRI) studies have reported **different patterns of brain activation in MJ users** during tasks involving:

- Attentional Control
- Memory/Working Memory
- Reward processing
- Executive functioning

- Structural imaging studies examining brain's gray matter and white matter (i.e., volume, density, organization) have shown that **MJ users exhibit alterations in brain structure** as well

- Earlier onset of use is generally related to greater alterations

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Summary of Findings

- Studies of recreational MJ use have reported cognitive impairments, particularly in those who initiate use during adolescence:
 - MJ-smoking youth experience deficits in a variety of domains, including processing speed, attention, memory, and executive function
 - MJ smokers report higher levels of impulsivity than non-MJ smokers
- Early MJ use is associated with alterations in brain structure and function relative to late onset smokers and non-MJ smokers:
 - Alterations are more pronounced in those who begin using MJ earlier
 - In early onset smokers specifically, lower white matter integrity is associated with higher levels of impulsivity
- Early onset smokers used MJ nearly twice as often per week and smoked more than 2.5 times as much MJ as late onset MJ smokers
 - This may represent a trait characteristic of early onset smokers



“Just say no” didn’t work...

“JUST NOT YET”
may be a more easily adopted and appropriate message for youth



High Potency MJ & Concentrates



Rising Potency of Cannabis Flower



Average Cannabinoid Concentration	1995	2014	Percent Increase
Δ-9 THC	3.96%	11.85%	199%
CBD	0.28%	0.15%	-46%

- Potency of cannabis (% THC) has increased over the past few decades,
- In contrast, CBD (which may mitigate negative effects of THC) has decreased
- It is now estimated that the average THC:CBD ratio has gone from 14:1 to 80:1
- Newly popular concentrates (dabs, shatter, budder, wax) deliver even higher levels of THC (up to 80% or higher)
- These rising levels of THC could potentially increase negative/undesirable side effects in recreational consumers as well as MMJ patients who choose high THC products

ElSohly et al. 2016



Effects of High Potency/ High Dose MJ



- Overall, some “real world” studies suggest that MJ users titrate intake based on potency of product (i.e. higher THC level = less MJ used) (Freeman et al., 2014; Van der Pol et al., 2014)
- **Cognitive function:**
 - Administration of high potency MJ (13% THC) has been shown to be related to decrements on measures of executive function and motor control, which were dose-dependent (placebo, 250mcg/kg, 500 mcg/kg) in recreational users (Ramakers et al. 2006).
 - Users with higher levels of THC (measured by hair samples) demonstrated worse performance on prose memory tasks; the presence of CBD resulted in better recognition memory regardless of THC level (Morgan et al., 2012).
 - Administration of high dose MJ (22mg vaporized THC) was related to impaired divergent thinking and creativity relative to low THC (5.5 mg) and placebo (Kowal et al., 2015).
- **Physiological/Psychological effects:**
 - Administration of high dose THC (69mg) MJ cigarettes resulted in more sedation and longer duration of sedation than lower dose THC (29 mg) MJ cigarettes (Hunault et al., 2014) (actually spill preparations; 700 mg CAN, 300 mg tobacco/joint).
 - Paranoia and anxiety have been observed in those administered high doses of THC in lab-based settings (Bhattacharyya et al., 2010; Fusar-Poli et al., 2009; Winton-Brown et al., 2011)
- **Brain alterations:**
 - Rigucci and colleagues (2016) found that frequent use of self-reported “high potency” products is associated with alterations in corpus callosum microstructure in both healthy controls and patients with psychosis.




MJ Concentrates and “Dabs”




- Novel products (concentrates) are made by extracting THC to make a concentrated product
- MJ concentrates are highly potent and contain THC levels generally between 25-85% or higher
- “Dabbing” is considered the act of vaporizing a ‘dab’ of MJ concentrate with a “rig” and blow torch (to heat the dab) – consumers get a large bolus of THC at once by design
- Dabbing may be more dangerous due to solvent-based extraction processes (i.e., butane, hexane, ethanol) often used to make dabs, and the potential for inhaling residual solvents



MJ Concentrates



- Reasons for using concentrates (Loflin & Earleywine 2014):
 - Different kind of high
 - Stronger intoxicating effect
 - Fewer hits necessary to achieve desired effects
- Survey/tweet studies have shown concentrate use **may be** related to:
 - Negative experiences** (coughing, nausea/vomiting, loss of bodily control; Cavazos-Rehg, 2016) – Tweets related to dabbing were assessed
 - Higher levels of **physical dependence** (Meier, 2017) - psychopathology in sample surveyed not reported
 - Individuals with lifetime history of **depression** and **anxiety** (Chan et al., 2017)
 - Limitations:** survey studies are limited with regard to information on potency, type, mode, and duration of use/effects
- However, **no studies to date** have directly assessed concentrate users vs conventional flower users



Medical Marijuana

Medical MJ ≠ Recreational MJ

- Derived from the same plant, recreational and medical MJ may seem to be "the same," but important differences distinguish the two:

	Recreational MJ	Medical MJ
Common modes of use	smoke, vaporize, edibles, concentrates	smoke, vaporize, edibles, tinctures
Goal of use	To feel high, euphoric, altered	To alleviate symptoms
Age of onset	Typically during adolescence	Typically over the age of 25
Constituent profile	Prized for high THC levels, virtually undetectable CBD	May be high in THC and/or CBD and likely to contain other cannabinoids


Review of Medical Marijuana (MMJ) Research

The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (NASEM, 2017)

- There is "conclusive or substantial evidence" that cannabis or cannabinoids are effective:
 - For the treatment of **chronic pain** in adults
 - As anti-emetics in the treatment of **chemotherapy-induced nausea and vomiting**
 - For improving patient-reported **multiple sclerosis spasticity** symptoms
 - Since the NASEM report was published, there is now emerging evidence that MMJ is "also useful in reducing some forms of **very severe child seizure disorders**" – Marie McCormick
- In addition, there is "moderate" or "limited" evidence for a range of other conditions, suggesting that additional research is **desperately needed**
- No studies thus far have looked specifically at the effects of MMJ on cognitive performance**
 - Some studies have looked at cognition as a secondary variable in the context of the illness/disorder, but by no means has this been exhaustive




- The first program of its kind!**
- Dedicated to understanding the impact of medical marijuana (MMJ) on cognition, clinical state, quality of life, brain structure and function, and related measures
- Supports a number of projects designed to examine cannabinoid-based therapies for a range of indications and conditions
- Using longitudinal, observation, cross-sectional, survey, and clinical trial models



- Longitudinal, observational MMJ study (underway):**
 - Examines cognitive performance, mood, sleep, quality of life, brain structure and function measures **prior to beginning MMJ treatment**
 - Follows individuals for 3 or 4 visits over the course of 1 year of MMJ treatment – and beyond (18, 24 months)
 - Participants may use MMJ for multiple indications and use their choice of MMJ products, which is recorded throughout the study
 - Product samples are analyzed for cannabinoid constituent content by an outside laboratory
 - Patients must be MJ naive or have not regularly used MJ in the past several year; must be THC negative at baseline

frontiers
in Pharmacology

ORIGINAL RESEARCH
published: 17 October 2015
doi: 10.3389/fphar.2015.00055

Splendor in the Grass? A Pilot Study Assessing the Impact of Medical Marijuana on Executive Function*

Israel A. Gruber^{1,2*}, Kelly A. Sagar^{1,2}, Mary K. Deligdis^{1,2}, Megan T. Racine^{1,2}, Rosemary T. Smith^{1,2} and Scott E. Lukas^{1,2}

***Updated Analyses**

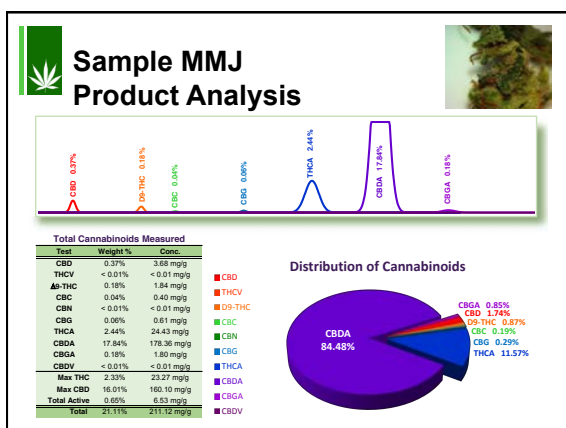
- n=40 participants have completed a baseline visit
- n=24 participants completed their first follow-up visit 3 months later
17 completed neuroimaging (n=15 analyzed thus far)
- Participant Information:** V1 + V2 sample analyzed thus far (n=22)
 - Average age: 50.64
 - 11 Males, 11 Females
 - 20 right-handed, 2 left-handed
 - Self-reported MMJ Indications:

Pain	Anxiety/PTSD	Mood	Sleep	Attention	Other
13	10	8	10	4	5

MMJ Use Information

MMJ Use	Mean (SD)
Days of MMJ Use/Week	5.21 (2.04)
Times/Day Used	1.78 (1.05)
Total MMJ Use Episodes/Week	9.88 (7.91)
Grams used/Week	1.62 (1.36)

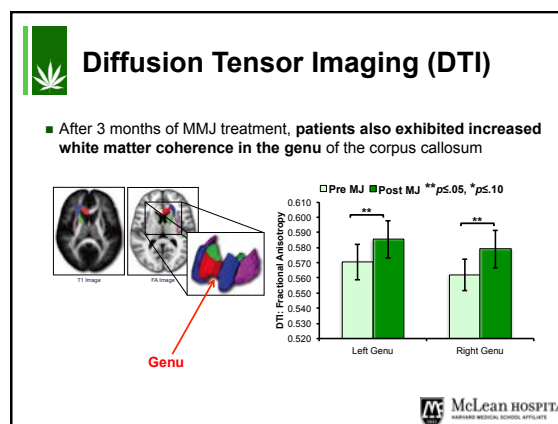
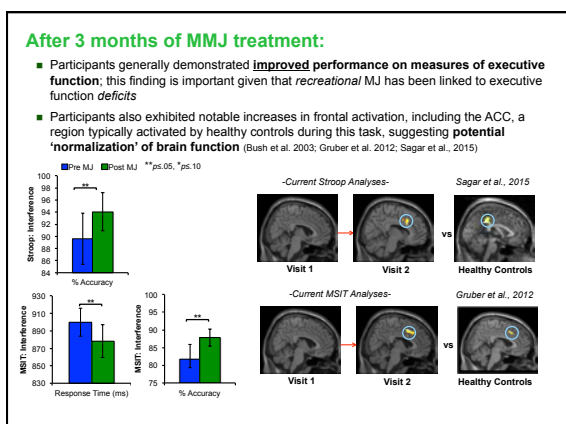
Mode of Use	# Participants
Smoke (flower product)	8
Vaporize (flower product)	9
Vaporize (oil/concentrates)	6
Oil/Concentrates	5
Tincture	6
Edibles	7
Topicals	2



Study 1 Data Summary

After 3 months of MMJ treatment:

- Participants generally demonstrated **improved performance on measures of executive function**; this finding is important given that *recreational MJ* use has been linked to executive function *deficits*
- Mood and quality of life self-report data also show areas of significant improvement** (sleep, depression, quality of life)
- Patients reported notable decreases in use of **opioids and benzodiazepines, each of which decreased by 47%** between baseline and Visit 2 assessment. **Use of antidepressants and mood stabilizers also decreased by 22% and 29%, respectively.**
- Participants exhibited potential '**normalization**' of brain activation during frontal/executive tasks accompanied by improved task performance
- DTI analyses revealed **increased white matter integrity** in frontal regions



Potential Reasons for Improvement?

- **Symptom alleviation**
 - "I feel better, so I can think more clearly"
- **MMJ Product Choice**
 - Unlike recreational MJ (typically chosen for high-THC content), other cannabinoids (i.e., CBD) may mitigate the negative effects of THC observed in recreational users
 - Certain cannabinoids may directly/indirectly affect cognitive performance
- **Reduction of use of conventional pharmaceuticals**
 - These medications can negatively impact cognitive function
- **Duration of use**
 - Will improvements be maintained/continue over longer periods of MMJ use?
- **Age of the consumer**
 - MMJ users in the current study (aged 28-74) are past adolescence/emerging adulthood; early onset recreational MJ users typically exhibit worse cognitive performance than late onset users
 - Recent preclinical data suggests THC may reverse age-related cognitive decline

...ALL TO BE EXPLORED WITH ONGOING RESEARCH!

MJ & Driving Research



MJ and Driving

- Recent MJ use and higher THC blood concentration are associated with impaired driving
- Acute MJ Intoxication is associated with
 - Increased lateral movement (lane weaving)
 - Slower reaction times
 - Impaired attention
 - Increased collision risk (~2 fold)
- Drivers often attempt to compensate for intoxication by driving slowly
- But what about the RESIDUAL impact of MJ use in chronic, heavy users?



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Driving Simulator

- "Real-world" driving skills in MJ users and non-users
- Participants not acutely intoxicated
 - Residual impact of MJ use
- Driving simulation was 4.2 miles long (~10 min)
 - Both rural and city conditions
 - Included stop signs, traffic lights, merges, turns, yielding to pedestrians and reacting to other vehicles



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Summary

- As hypothesized, MJ users (n=24) demonstrated **significantly worse** performance on the **driving simulator** relative to healthy controls (n=15):
 - **Accidents:** Increased number of pedestrians hit
 - **Rule-Following:** More missed stop signs & fewer stops at traffic lights
 - **Speed:** More speed exceedances & more time spent over the speed limit
 - **Lateral Movement:** More centerline crossings
- Further, when age of MJ onset was accounted for, impairment was driven by individuals who began using before age 16
 - Earlier age of MJ onset was associated with more severe impairment
 - Significant correlation between earlier age of onset and increased collisions as well as missed stop signs



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Summary

Interestingly, driving impairment associated with residual MJ use is different from acute MJ intoxication

Additional research is needed to understand the impact of MJ on driving

- Acute Intoxication:**
- More Accidents
 - Slower Driving
 - Increased Lateral Movement

- Residual MJ:**
- More Accidents
 - Faster Driving
 - Reduced Rule-Following

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Barriers to Research

Regulatory Challenges: Current Situation



- In order to fully understand the potential benefit and possible risks associated with cannabis use, researchers must be able to **study actual cannabis products currently available to consumers** (for recreational and medical use):
- Current Limitations include:**
 - All individual constituents of the plant (phytocannabinoids) fall under Schedule I regulations regardless of diversion potential
 - Cannabis products must be obtained from a single federal source (NIDA)
 - Laboratory testing is limited to within-state facilities; labs with Schedule I licensure cannot test non-federal products
 - No current ability to assess commercially available hemp-derived products using clinical trial model
 - DEA regulations: State vs Federal considerations (issuance of Schedule I)



Scientific Challenges: How to measure MJ use

- Drug delivery system**
 - Smoking vs. vaporizing vs. dabbing vs oral vs. sublingual?
 - How comparable are methods of administration, time course (i.e. joint vs dabs vs edible)
 - Little research on benefits/downsides of these routes of administration for cannabinoids
 - Extraction methods and impact of solvent vs non-solvent based concentrates
- Assessment of cannabis exposure history**
 - No standardized queries for determining cannabis exposure (frequency, magnitude across product types), mode, potency, product choice
 - Limitations in self-report data
 - Biological samples have limited utility



Photo: Scott Storch/istockphoto.com

Testing MJ Products



Laboratory analyses are critical in order to:

- Obtain accurate levels of constituent composition
- Ensure no toxins are present:
 - Pesticides
 - Heavy metals
 - Contaminants
 - Aflatoxins
 - Mold
 - Yeast
- For concentrates, it is critical to ensure that concentrates are created using safe extraction methods and that no solvents remain



Future Directions



- Reality Check:**
 - MJ is here and likely to stay
 - Imperative to provide accurate information about MJ safety and effects, both positive and negative
- Need for high quality research:**
 - Expanded funding: state based initiatives are critical
 - Ecological validity: assess what people are actually using
 - Medical efficacy: clinical indications, dosage and product/strain assessment, etc.
 - Recreational use: public safety requires accurate information about potential harm/risks which requires additional research



More Research is Needed!



- Additional studies required to determine best practices:**
 - Explore possibility of harm reduction through varying constituents/ratios
 - Mode of use – smoking vs vaping vs edible etc – impact/effects?
 - Impact of concentrate/higher potency products vs conventional flower
 - Profiles and impact of individual cannabinoids vs whole plant materials
 - Recreational versus medical use – outcome/long term impact
 - Clinical indications for use: whole plant derived/purified/synthetic comparisons
 - Most efficacious strain(s) for specific indications, symptoms
 - Laboratory testing of currently available recreational and medical products
 - Development of appropriate laboratory test procedures per product type



Impact of Legalization & Adolescents



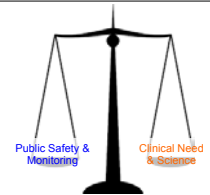
- As states have legalized MJ, several studies have attempted to determine whether **adolescent use rates** will be affected
 - Some studies have shown increased use
 - Others have shown no change or decreases in states with legalized MJ
- However, with increased access to MJ, it is critical to continue to assess the impact of MJ in adolescents and emerging adults



Future Directions

Imperative to balance:

Rigorous monitoring & public safety
WITH
Clinical need & scientific inquiry
AND
Consider growing numbers of consumers



...policy has outpaced science

Policy

Science



Research = Knowledge



Knowledge = POWER!



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