



Neuropsychological Functioning in Adolescent Marijuana Users

Krista Lisdahl Medina, Ph.D.
University of Cincinnati



Susan Tapert, Ph.D.
University of California, San Diego



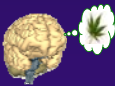
Disclosures

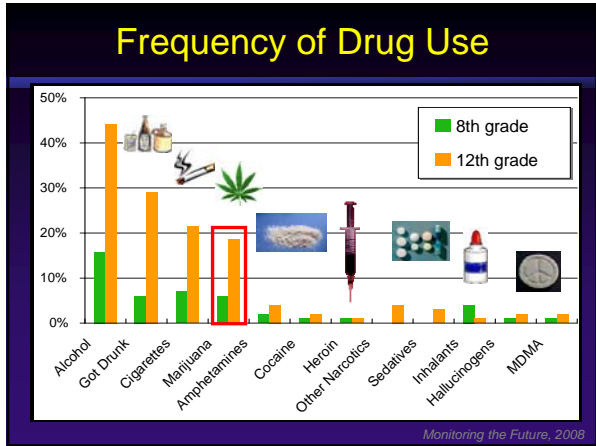
Faculty Disclosure Information
I have had NO financial relationships with manufacturer(s) of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity.

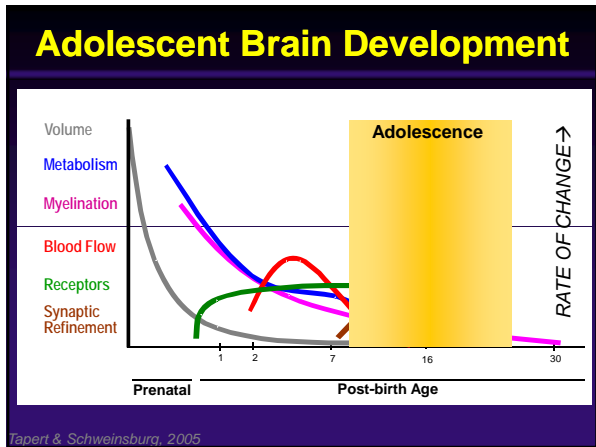
I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

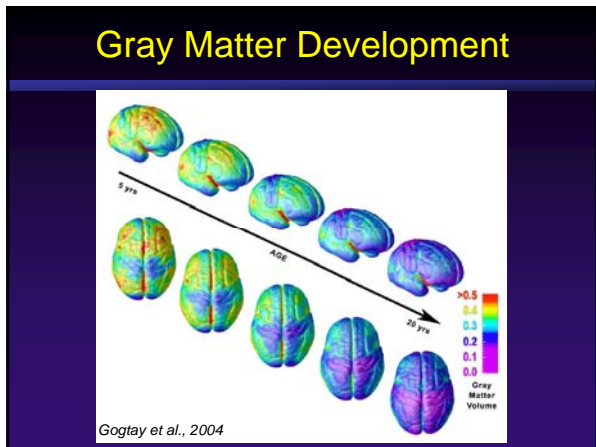
Adolescent Marijuana Use

- Research rationale**
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions

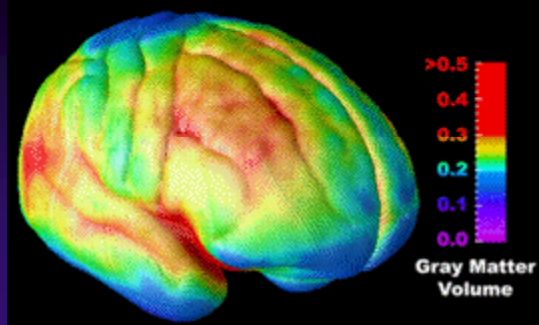






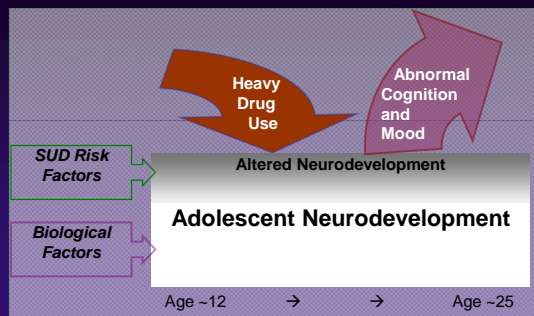


Adolescent Brain Development



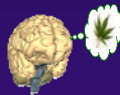
Gogtay, Giedd et al., 2004

Theoretical Model



Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions



Studies Overview: Participants

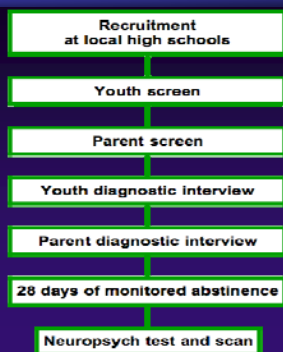
- 16.0 - 18.9 years old
- Parent/Guardian Permission
- Fluent English Speakers
- Marijuana Users
 - Used marijuana >200 times
 - Never met Cahalan criteria for Heavy Drinker
 - Haven't used other drugs >25 times
- Controls
 - Used marijuana <5 times
 - Never met criteria for Heavy Drinker
 - Never used other illicit drugs

Exclusion Criteria

- MRI contraindication
- Axis I psychiatric disorder
- Psychiatric medications
- Family hx bipolar or psychosis
- Complicated/premature birth
- Prenatal alcohol/drug exposure
- Neurologic illness or injury



Marijuana Study Procedure



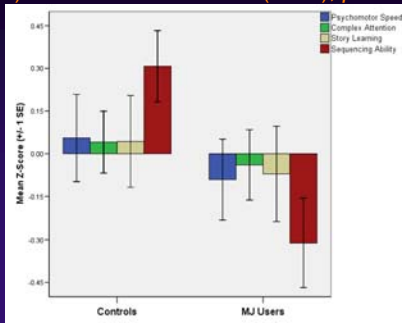
Staying Abstinent

- 2-3x/wk urine samples
- 2/3 stay abstinent 1 month
- Non-abstainers:
 - Heavier users



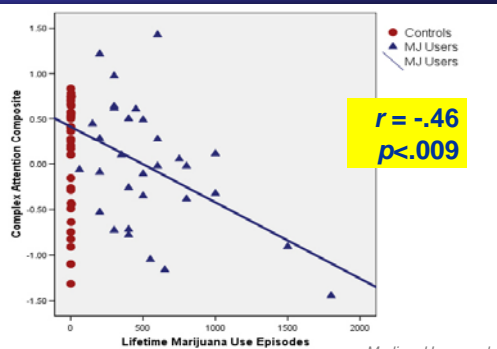
MJ & Cognition

- MJ users (n=31) different than Controls (n=34), $p < .05$
- After 1 month abstinence



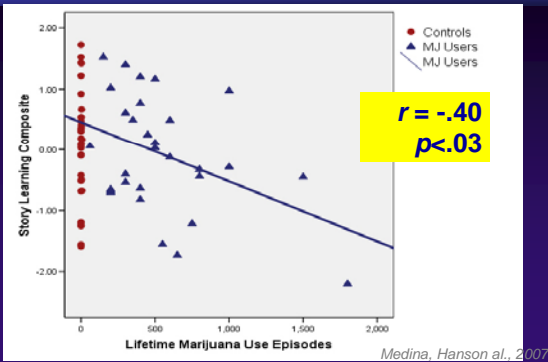
Medina, et al., 2007

MJ & Cognition



Medina, Hanson et al., 2007

MJ & Cognition



MJ Use & Emerging Adulthood

- Controls (n=42), MJ (n=21)
- Ages 18-25
- Neuropsychological battery
- Axis I psychiatric disorder
- Psychiatric medications
- Family hx bipolar or psychosis
- Neurologic illness
- Major medical illness
- Minimum 1 week abstinence



Medina, et. al., in progress

MJ Use & Emerging Adults

	Controls (n=42)	MJ Users (n=21)
Age	20.8±2.2	21.4±2.7
Education	13.8±1.7	13.4±2.2
% Female	52%	48%
% Caucasian	69%	62%
Reading	100.7±8.6	106.6±11.9
BDI-2*	4.0±3.8	9.5±8.4

Medina, et. al., in progress

*p<.001, Controls < MJ

MJ Use & Emerging Adults

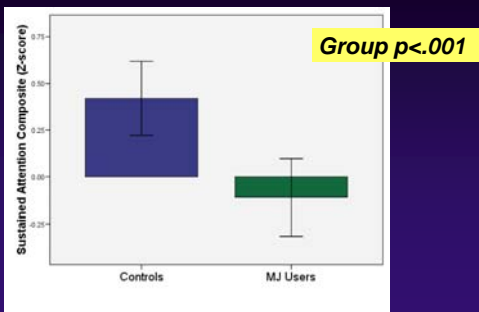
	Controls (n=42)	MJ Users (n=21)
Alcohol	105.8±172.3	261.6±326.5
Inhalants	0.0±0.0	0.0±0.0
Hallucinogens	0.2±0.9	1.9±4.2
*MJ	1.0±2.7	169.9±195.9
MDMA	0.0±0.0	0.0±0.0
Stimulants	0.1±0.5	1.6±4.5
Sedatives	0.2±1.1	0.0±0.6
Opioids	0.0±0.0	0.1±0.3

Medina, et al., in progress

*p<.001, Controls < MJ

MJ & Cognitive Function

... not related to verbal memory, inhibition, or fluency

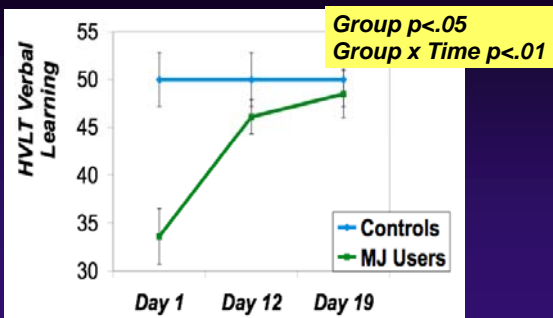


Medina et al., in preparation

MJ & Cognition: Summary

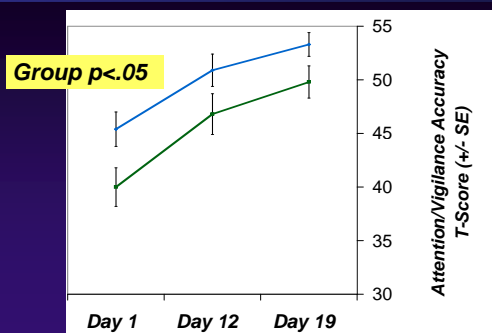
- After 7-30 days abstinence
 - Poorer psychomotor speed, sustained attention, verbal memory, and sequencing ability in adolescents
 - Poorer sustained attention in emerging adults
 - Increased symptoms depression, poorer grades, increased school problems
- MJ may interrupt neuromaturation
 - Hippocampus
 - PFC
 - Cerebellum
- Is there recovery of function in that first month?

MJ & Cognition Over Time



Hanson et al., in prep

MJ & Cognitive Function



Hanson et al., in prep

MJ & Cognition: Summary

- MJ use associated with poorer
 - Verbal list learning : significant improvements
 - Attention: continued deficits
- Some cognitive recovery may occur with abstinence, even after only a few days.
- Future studies needed to assess longer periods of abstinence

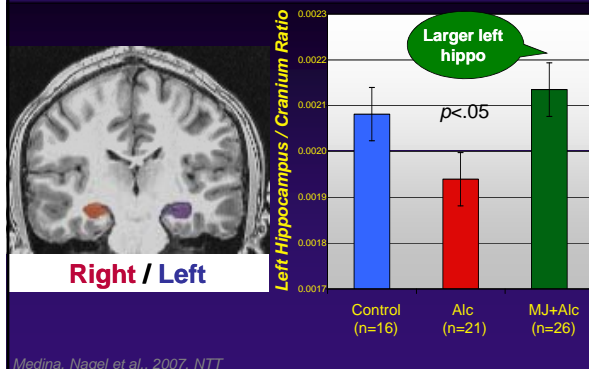


Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions

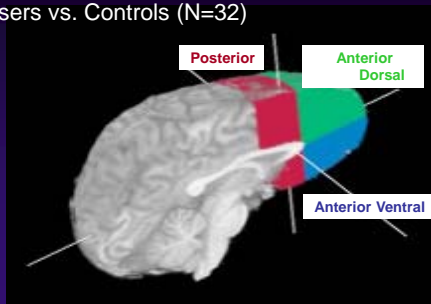


Hippocampal Volume



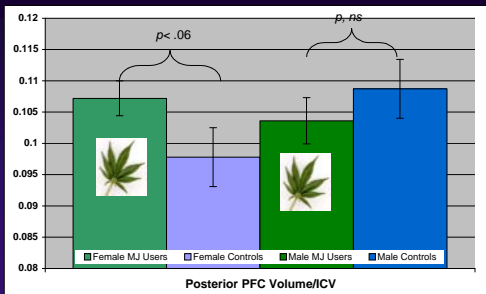
MJ & PFC Structure

Prefrontal Cortex ~ Executive Functioning
MJ users vs. Controls (N=32)



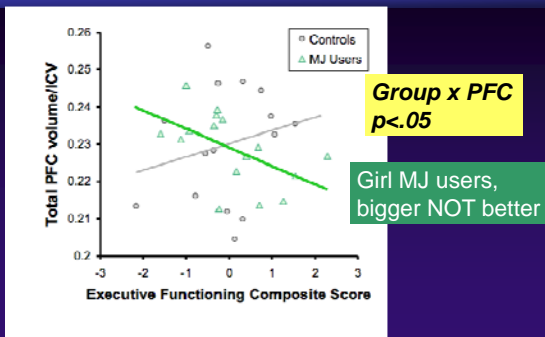
MJ & PFC Structure

Gender marginally moderated effects of MJ, $p < .09$



Medina, Nagel et al., In Press

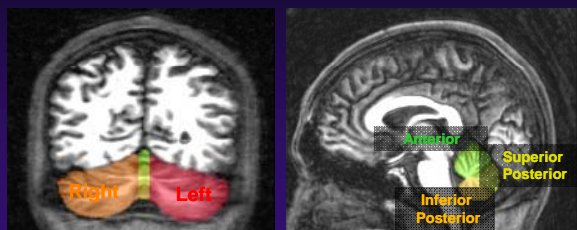
MJ & PFC Structure



Medina, Nagel et al., In Press

MJ & Cerebellar Structure

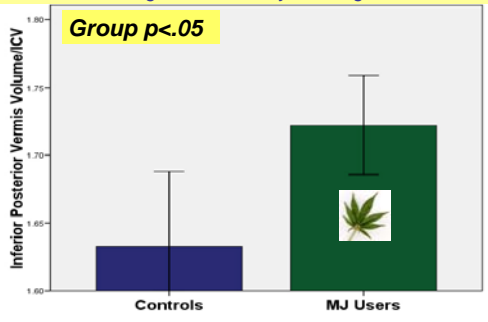
MJ users vs. Controls (N=32)



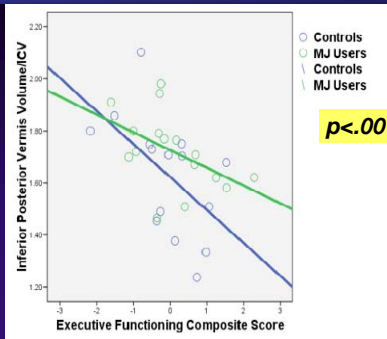
Medina, Nagel & Tapert, under review

MJ & Cerebellar Structure

... controlled alcohol, gender, ethnicity, reading level



MJ & Cerebellar Structure

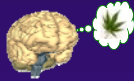


Brain Structure & MJ

- MJ use associated with increased hippocampal, PFC, and cerebellar volumes
 - Girls appear most affected
 - Pattern is consistent with cognitive deficits
- Bigger was NOT better!
- Interrupted gray matter pruning?

Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions

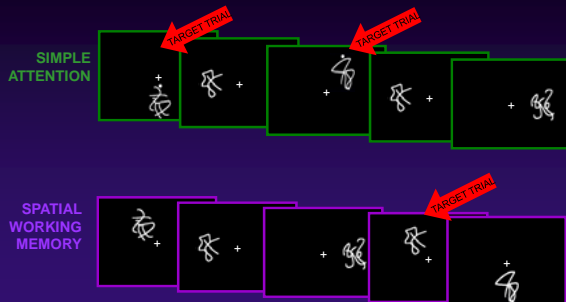


Brain Function & MJ Use

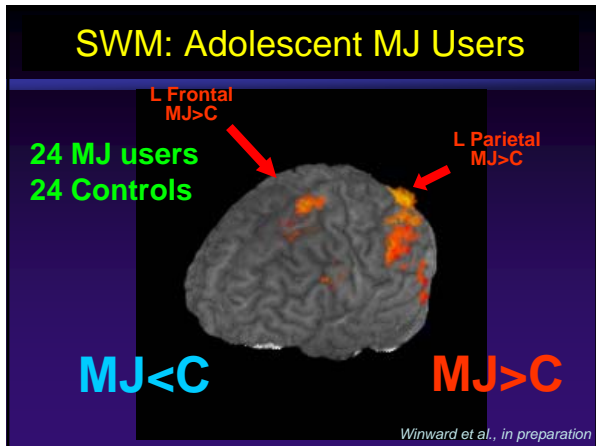
- FMRI Tasks
 - Spatial working memory
 - Verbal encoding
- UCSD 3T GE magnet
 - BOLD-weighted EPIs
- AFNI

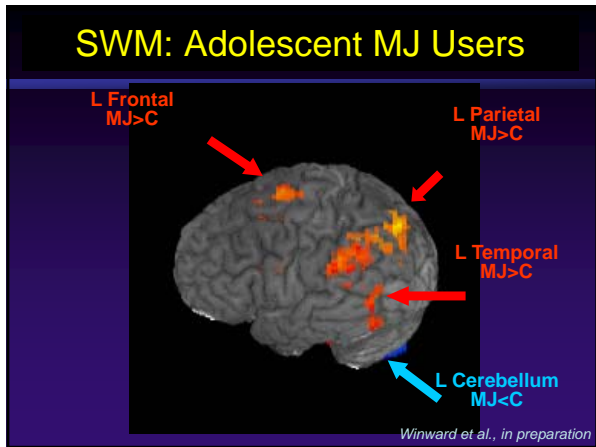


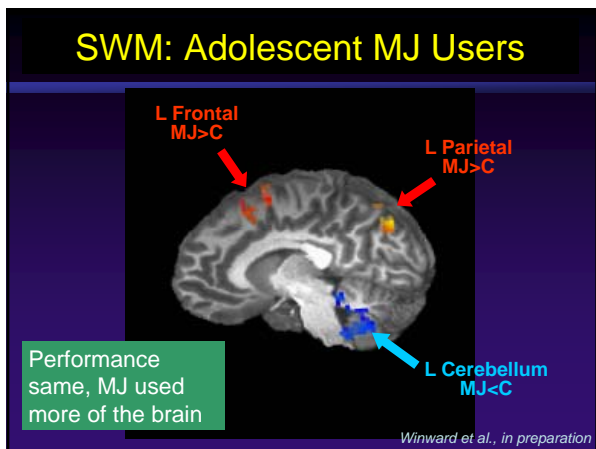
Spatial Working Memory Task



Tapert 2001, 2004; Schweinsburg 2005; Nagel 2005; Padula 2007; Schweinsburg 2008



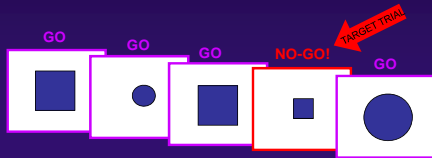




Go/No-Go Task

Instructions:

- Press the button as soon as you see a blue shape **EXCEPT** the **SMALL** blue square
- Respond as **FAST** as you can!

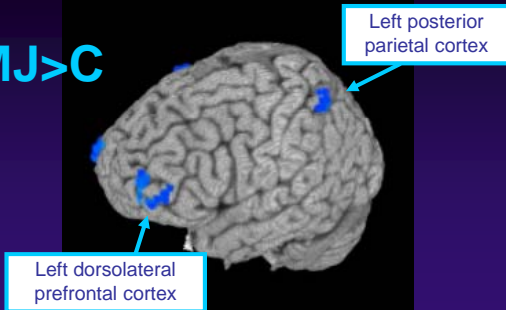


Schweinsburg et al., 2004; Anderson et al., 2005; Tapert et al., 2007

Inhibition: Adolescent MJ Users

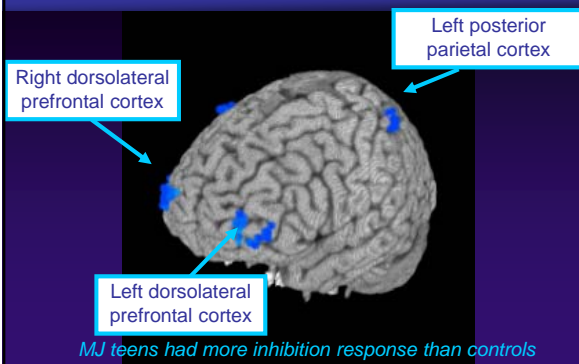
MJ teens (n=16) had more no-go response than controls (n=17)

MJ > C



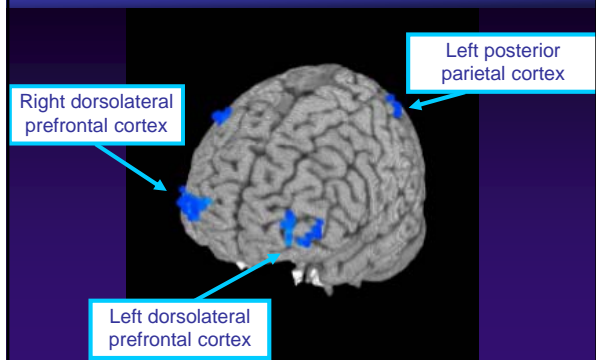
Tapert et al., 2007, Psychopharmacology

Inhibition: Adolescent MJ Users

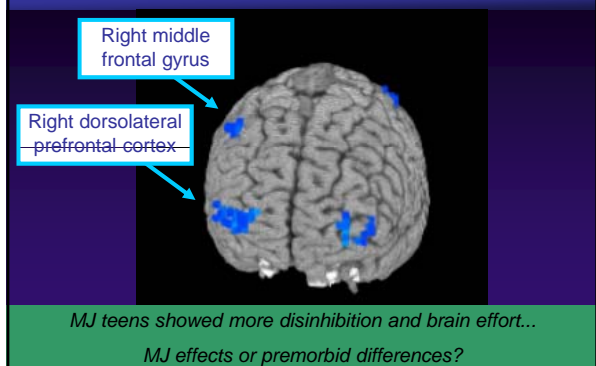


MJ teens had more inhibition response than controls

Inhibition: Adolescent MJ Users



Inhibition: Adolescent MJ Users



Adolescent Marijuana Use

- Research rationale
- Does adolescent MJ use adversely affect cognition?
- Does adolescent MJ use adversely affect brain structure?
- Does adolescent MJ use adversely affect brain function?
- Limitations & Future Directions**



Adolescent MJ Use: Summary

Marijuana	
Cognition	↓1st trial, speed, and attention <i>some recovery of function</i>
Volume	↑left hippo; Gender moderated PFC ↑inferior posterior vermis
SWM	= performance ↑parietal, PFC; ↓cerebellum
Go/No-go	↑errors; ↑parietal, PFC

Limitations

- Do preexisting differences explain findings?
 - Risk factors for *using* marijuana explain this?
 - Subclinical conduct, attentional, mood problems
 - *Preexisting* executive functioning deficits
 - Family history and genetics
- Need...
 - larger sample of female users
 - marijuana users without comorbid alcohol use
 - more diverse samples (SES, ethnicity)
 - longitudinal studies of at-risk adolescents



Future Directions

- Targeting individual differences:
Do protective and/or risk factors exist?
 - Prenatal environment
 - Genetics
 - Gender
 - Hormone interactions?
 - Comorbid disorders
 - Sleep architecture
 - Stress



Future Directions

- Do combinations of drugs matter?
 - Independent and interactive effects of drugs, especially nicotine, alcohol and marijuana
- Do teens improve with abstinence?
- Are neurocognitive abnormalities related to treatment outcome?
- Interventions to treat adverse neural reactions?
 - Pharmacological
 - Enriched environments (e.g., exercise)



Acknowledgements

- **NIH Funding Institutes**
 - NIDA/NIH: R21 015228; R01 DA021182 (PI: Tapert); F32 DA020206 (PI: Medina); 2008 NIDA Travel funding (Medina)
 - Center for Environmental Genetics P30 ES06096 (PI: Medina)
- **UCSD Adolescent Brain Imaging Project (past & present)**
 - **Susan Tapert (PI)**, Bonnie Nagel (OHSU), Karen Hanson, Mairav Cohen-Zion, MJ Meloy, Sunita Bava, Alecia Schweinsburg (Yale), Carmen Pulido, Andrea Spadoni, Larry Frank, Gregory Brown, Sandra Brown, Martin Paulus, Marc Schuckit, Brian Schweinsburg (Yale),
- **UC Brain Imaging & Neuropsychology (Brain) Lab**
 - **Faculty collaborators:** Drs. Paula Shear, James Eliassen, Judith Strong.
Graduate/Undergraduate students: Jenessa Price, Tim McQueeny, Claudia Padula, Eric Harper, Patrick Logan, Dana Hamilton, Shana Vanderburgh, Alitta Barsch, Zach Graham, Brigitte Budion.

References

- Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., 3rd, Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L. and Thompson, P. M. (2004) Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America* 101, 11733-11737.
- Hanson, K. L., Winward, J. L., Schweinsburg, A., Medina, K. L., & Tapert, S. F. (in preparation). Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence.
- Medina, K.L., Hanson, K., Schweinsburg, A.D., Cohen-Zion, M., Nagel, B.J., & Tapert, S.F. (2007). Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after 30 days of abstinence. *Journal of the International Neuropsychological Society*, 13(5), 807-820.
- Medina, K.L., Nagel, B.J., McQueeny, T., Hanson, K.L., & Tapert, S.F. (in press). Prefrontal cortex morphometry in abstinent adolescent marijuana users. *Addiction Biology*.
- Medina, K.L., Nagel, B.J., & Tapert, S.F. (under review). Cerebellar morphometry in abstinent adolescent marijuana users.
- Medina, K.L., Price, J.P., & McQueeny, T.M. (in preparation). Neuropsychological consequences of marijuana use during emerging adulthood.
- Medina, K.L., Schweinsburg, A.D., Cohen-Zion, M., Nagel, B.J., & Tapert, S.F. (2007). Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal asymmetry. *Exposures During Adolescent Development: Are Neurotoxic Risks Increased?* *Neurotoxicology and Teratology*, 29, 141-152.
- Winward, J., Schweinsburg, A.D., Medina, K.L., McQueeny, T., Meloy, M.J., & Tapert, S.F. (in preparation). Effects of adolescent marijuana use on fMRI brain activation to spatial working memory.
- Tapert, S.F. & Schweinsburg, A.D. (2005). The human adolescent brain and alcohol use disorders. *Recent Dev Alcohol*, 17:177-97.
- Tapert, S.F., Schweinsburg, A.D., Drummond, S.P., Paulus, M.P., Brown, S.A., Yang, T.T. & Frank, L.R. (2007). Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology (Berl)*; 194(2):173-83.
