UC San Diego
UC San Diego Previously Published Works

Title

Functional MRI of inhibitory processing in abstinent adolescent marijuana users

Permalink

Journal

Psychopharmacology, 194(2)

ISSN

0033-3158

Authors

Tapert, Susan F
Schweinsburg, Alecia D
Drummond, Sean P A
et al.

Publication Date

2007-10-01

Peer reviewed

Functional MRI of Inhibitory Processing in Abstinent Adolescent Marijuana Users

Susan F. Tapert, Ph.D. [a b *]

Alecia D. Schweinsburg, Ph.D. [c]

Sean P.A. Drummond, Ph.D. [a b]

Martin P. Paulus, M.D. [a b]

Sandra A. Brown, Ph.D. [a b c]

Tony T. Yang, M.D., Ph.D. [b]

Lawrence R. Frank, Ph.D. [a d]

[a] VA San Diego Healthcare System, 3350 La Jolla Village Dr. 116B, San Diego, CA 92161
[b] University of California San Diego Department of Psychiatry, 9500 Gilman Dr., La Jolla, CA 92093-0603
[c] University of California San Diego Department of Psychology, 9500 Gilman Dr., La Jolla, CA 92093-0109
[d] University of California San Diego Department of Radiology, 9500 Gilman Dr., La Jolla, CA 92093-0677

* Corresponding author: Susan Tapert, Ph.D., University of California San Diego, Department of Psychiatry, 3350 La Jolla Village Drive (116B), San Diego, CA 92161, (858) 552-8585 x2599, (858) 624-6474 fax, stapert@ucsd.edu.

Number of words in abstract: 230
Number of words in text: 5043
Number of tables: 3
Number of figures: 2
Supplementary material: 0

Abstract

Background: Marijuana intoxication appears to impair response inhibition, but it is unclear if impaired inhibition and associated brain abnormalities persist after prolonged abstinence among adolescent users. We hypothesized that brain activation during a go/no-go task would show persistent abnormalities in adolescent marijuana users after 28 days of abstinence.

Methods: Adolescents with (n=16) and without (n=17) histories of marijuana use were compared on blood oxygen level dependent (BOLD) response to a go/no-go task during functional magnetic resonance imaging (FMRI) after 28 days of monitored abstinence. Participants had no neurological problems or Axis I diagnoses other than cannabis abuse/dependence.

Results: Marijuana users did not differ from non-users on task performance, but showed more BOLD response than non-users during inhibition trials in right dorsolateral prefrontal, bilateral medial frontal, bilateral inferior and superior parietal lobules, and right occipital gyri, as well as during "go" trials in right prefrontal, insular, and parietal cortices (p<.05, clusters >943 µl). Differences remained significant even after controlling for lifetime and recent alcohol use.

Conclusions: Adolescent marijuana users relative to non-users showed increased brain processing effort during an inhibition task in the presence of similar task performance, even after 28 days of abstinence. Thus, increased brain processing effort to achieve inhibition may predate the onset of regular use or result from it. Future investigations will need to determine whether increased brain processing effort is associated with risk to use.

Introduction

Many individuals first experiment with alcohol and drugs during adolescence (SAMHSA, 2003), and marijuana is the most commonly used illicit substance among teenagers (Johnston, O'Malley, Bachman, & Schulenberg, 2005). Nearly half of 12th graders have tried marijuana, and 6% disclose daily use (Johnston et al., 2005). Adolescence is also a period of continued neurodevelopment, including frontal lobe myelination and synaptic pruning that subserve improved executive functioning (Gogtay et al., 2004; Sowell, Trauner, Gamst, & Jernigan, 2002), including abilities such as decision making, inhibitory processing, and impulse control. The influence of marijuana use on these maturational processes is unknown, although executive dysfunction may affect the development and maintenance of substance use and problems during adolescence (Tapert, Baratta, Abrantes, & Brown, 2002).

Adults with heavy marijuana use histories have demonstrated abnormalities in executive functioning (Fletcher et al., 1996; Pope & Yurgelun Todd, 1996; Solowij et al., 2002) and indices of frontal lobe operation (Block et al., 2000; Kanayama, Rogowska, Pope, Gruber, & Yurgelun Todd, 2004; Lundqvist, Jonsson, & Warkentin, 2001; Solowij, Michie, & Fox, 1991, 1995; Struve, Patrick, Straumanis, Fitz-Gerald, & Manno, 1998). To determine if cognitive deficits in marijuana users are transient or persistent, Pope and colleagues (Pope, Gruber, Hudson, Huestis, & Yurgelun Todd, 2001) tested 63 current marijuana users (>5000 lifetime uses), 45 former users (>5000 lifetime uses), and 72 normal controls (1-50 lifetime uses), all ages 30-55. Participants were abstinent for 28 days, verified by urine drug screens, and given neuropsychological tests on days 0, 1, 7, and 28 of abstinence. Current users showed some deficits relative to controls on days 0, 1, and 7, but groups did not differ on any test by day 28. In contrast, a study (Bolla, Brown, Eldreth, Tate, & Cadet, 2002) that hospitalized 22 marijuana

using adults (>2 years of marijuana use) for 28 days to assure abstinence found greater marijuana intake linked to poorer performance on tests of inhibition, problem solving, learning, and reaction time.

Disinhibition, i.e. the impaired ability to inhibit a potentially inappropriate response, is a common feature of substance misuse (Chen et al., 2007; Kamarajan et al., 2006; Kirisci, Tarter, Reynolds, & Vanyukov, 2006; Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006). Neuroimaging studies have reported both prefrontal and posterior parietal cortical involvement during inhibitory processing in healthy volunteers (Liu, Banich, Jacobson, & Tanabe, 2004) which may be over-active in populations with impulse control problems (Schulz et al., 2004).

Few studies have examined inhibitory processing in marijuana users. Functional magnetic resonance imaging (FMRI) characterized the neural correlates of inhibition during a Stroop task, in which heavy marijuana using adults and nonusers were asked to inhibit the automatic process of reading words and, instead, name the colors of words printed in incongruent ink (Gruber & Yurgelun-Todd, 2005). Marijuana users not only showed greater mid-cingulate and reduced anterior cingulate blood oxygen level dependent (BOLD) response, but also more widespread bilateral dorsolateral prefrontal activation during inhibition relative to color naming trials. The investigators speculated that the altered activation pattern in marijuana users reflects compensation and use of alternate strategies. The same investigators had shown in a previous fMRI study using a working memory task before and after a 28-day abstinence period (Yurgelun-Todd et al., 1998) that adult users demonstrated less prefrontal and more anterior cingulate response than controls after just 24 hours of non-use. Although users showed some normalization of prefrontal functioning after 28 days of abstinence, they still showed anterior cingulate dysfunction, which is supportive of persisting neural processing abnormalities. These

results support the hypothesis that adult marijuana users show abnormal neural inhibitory processing, compensatory hyper-activity, and altered neural processing differences in the absence of the intoxicating agent.

Few studies have examined neurocognitive effects of marijuana use among adolescents, but some reports identified decrements in attention (Tapert, Granholm, Leedy, & Brown, 2002), and learning and memory (Millsaps, Azrin, & Mittenberg, 1994; Schwartz, Gruenewald, Klitzner, & Fedio, 1989) associated with early marijuana use. We previously demonstrated increased dorsolateral prefrontal and decreased inferior frontal FMRI response during a spatial working memory task among teens with comorbid alcohol and marijuana use disorders compared to those with alcohol use disorders alone and to non-using controls, suggesting a marijuana use-related increase in dorsolateral prefrontal effort (Schweinsburg et al., 2005b). However, most studies of adolescent marijuana users were conducted after several days of abstinence, so effects could be transitory. Jacobsen and colleagues (Jacobsen, Mencl, Westerveld, & Pugh, 2004) addressed this concern by evaluating 7 adolescent marijuana users, 7 demographically similar tobacco smokers, and 7 non-users with a working memory task during FMRI acquisition after about a month of abstinence. Marijuana users were less accurate on the task, and showed increased BOLD response in the right hippocampus relative to other groups. The authors suggested that marijuana users might have failed to inhibit hippocampal activity during the task, perhaps due to cannabis-induced changes in inhibitory neurotransmission or apoptosis in the hippocampus. These researchers then compared 15 adolescents with and 18 without histories of cannabis use during nicotine withdrawal. Cannabis users, but not non-users, showed nicotine withdrawal-precipitated increases in parietal activation and disruptions in fronto-parietal connectivity during a verbal working memory task (Jacobsen, Pugh, Constable, Westerveld, &

Mencl, 2006). Collectively, existing data indicate some executive impairment and neural

dysfunction associated with adolescent marijuana use, although the neural substrates specific to

inhibitory processing have not yet been examined in teenage marijuana users.

In the current study, we performed BOLD FMRI during a go/no-go task to characterize

response inhibition among adolescent marijuana users and non-using controls. Because studies of

marijuana using adults have suggested improvements in cognitive and neural functioning after 28

days of abstinence (Pope et al., 2001), we required participants to complete 28 days of monitored

abstinence before scanning to ensure that any group differences were not due to recent use. The

go/no-go task (Anderson, Schweinsburg, Paulus, Brown, & Tapert, 2005; Schweinsburg et al.,

2004b) was designed to assess inhibitory processing by asking participants to withhold a

response to an infrequently occurring stimulus. Previous studies have observed activation in

dorsolateral prefrontal, inferior frontal, anterior cingulate, and posterior parietal regions among

adolescents using this task (Anderson et al., 2005; Schweinsburg et al., 2004a) and similar

inhibition paradigms (Adleman et al., 2002; Luna et al., 2001; Tamm, Menon, & Reiss, 2002).

Based on findings of response inhibition among teenagers and marijuana using adults, we

predicted that abstinent marijuana using adolescents would demonstrate increased prefrontal and

decreased cingulate response compared to non-using controls during inhibition trials.

Methods and Materials

Participants

Participants were 16- to 18-year-olds enrolled in an ongoing study of adolescents

recruited from local high schools and colleges (Lisdahl Medina, Nagel, Park, McQueeny, &

Tapert, in press; Lisdahl Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, in press; Nagel

et al., 2006; Schweinsburg, Nagel, & Tapert, 2005a). Sixteen adolescents were marijuana users

(MJ) with at least 60 lifetime episodes of cannabis use and limited histories of other drug use, and 17 adolescents were demographically similar non-using controls (see Table 1 for demographic characteristics) with less than 5 lifetime episodes of cannabis use. Written assent and consent were obtained from adolescents and their parent/legal guardians in accordance with the University of California San Diego Human Research Protections Program. Eligibility was ascertained through separate, private telephone screening interviews with the youth and the parent. Exclusionary criteria included left handedness; history of head injury with loss of consciousness >2 minutes, learning disabilities, medical or neurological problem, DSM-IV (APA, 1994) Axis I psychiatric disorder (i.e., mood, anxiety, psychotic, attention, and conduct disorders) as assessed by the computerized NIMH Diagnostic Interview Schedule for Children Predictive Scales (DISC-PS-4.32b; (Lucas et al., 2001; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) Youth and Parent versions, and use of any psychotropic medication; significant maternal drinking (>2 drinks on an occasion or > 4 drinks in a week) or other drug use during pregnancy; family history of bipolar I or psychotic disorders determined by the Family History Assessment Module (Rice et al., 1995); and MRI contraindications.

MJ youth disclosed using marijuana an average of ~500 times in their lives (see Table 1), and three control youth had experience with marijuana (<5 times). MJ youth used marijuana every other day on average, before being asked to remain abstinent for the 28 days prior to scanning. Most MJ youth were current users, as all but three used in the month prior to monitored abstinence. MJ users typically consumed 35 drinks per month, one cigarette per day, and had used alcohol roughly 100 times and other drugs approximately 7 times (range 0 to 25 times; primarily misuse of pain medications) in their lives. Users and controls did not differ on

age, household income, general intellect, externalizing and internalizing behaviors, and other

demographic variables (see Table 1).

Measures

Substance use assessment. Substance involvement was ascertained using the Customary

Drinking and Drug Use Record (Brown et al., 1998), an interview that obtains information on

lifetime and past three-month use of marijuana, alcohol, nicotine, other illicit drugs, and misuse

of prescription and over-the-counter medications, and negative consequences associated with

substance use. Strong internal consistency, test-retest, and inter-rater reliability have been

demonstrated with adolescents (Brown et al., 1998; Stewart & Brown, 1995). The Fagerstrom

Test for Nicotine Dependence (FTND; (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991)

indicated that no participant was dependent on nicotine. The Timeline Followback (Sobell &

Sobell, 1992) collected details on substance use patterns for the month prior to and during the

28-day abstinence period.

Mood. The Beck Depression Inventory (BDI; (Beck, 1978) and state scale of the

Spielberger State Trait Anxiety Inventory (STAI; (Spielberger, Gorsuch, & Lushene, 1970)

assessed mood 30 minutes before scanning.

Psychopathological Syndromes. Continuous indices of level of internalizing and

externalizing psychopathological syndromes were assessed by the 113-item Child Behavior

Checklist (CBCL; (Achenbach & Rescorla, 2001), administered to parents (typically biological

mothers) covering youth behaviors in the past 6 months. Eight factor *T*-scores (Rule-Breaking

Behavior, Aggressive Behavior, Withdrawn/Depressed, Anxious/Depressed, Somatic

Complaints, Attention Problems, Social Problems, and Thought Problems) and summary *T*-

scores (Externalizing, Internalizing) are provided.

Personality. Disinhibition and substance use may relate to personality traits. Thus, all participants completed the NEO Five-Factor Inventory (NEO-FFI; (Costa & McCrae, 1992), a 60-item self-report personality questionnaire that assesses five domains of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness. This factor structure has been replicated in adolescent samples (Fruyt, Mervielde, Hoekstra, & Rolland, 2000).

Neurocognition. Executive processing was assessed using the Delis-Kaplan Executive Function System (D-KEFS; (Delis & Kaplan, 2001) Trail Making, Towers, and Verbal Fluency subtests. Premorbid IQ was assessed with the Wide Range Achievement Test-3 (WRAT3; (Wilkinson, 1993) Reading subtest and Wechsler Abbreviated Scale of Intelligence (WASI; (Wechsler, 1999) Vocabulary subtest.

Go/no-go task. Participants performed a go/no-go task during FMRI scanning (Anderson et al., 2005; Schweinsburg et al., 2004b). The task alternated between active blocks and resting blocks. During resting blocks, participants viewed a "+" in the center of the screen. During active blocks, a large square, small square, large circle, and small circle were presented one at a time for 200 ms every 1500 ms. Participants were instructed to press a button as fast as possible every time they saw a shape (go stimuli) *except* for the small square (no-go stimulus), thus requiring response inhibition. The task lasted 6 min 24 sec. Participants additionally performed the entire task before scanning to ensure adequate comprehension of instructions and to resolve potential practice effects (Drummond, Paulus, & Tapert, 2006).

Procedures

To confirm that participants did not use substances in the 4 weeks prior to scanning, all participants (controls and marijuana users) provided at least nine urine toxicology screens (two to three times per week) during these 28 days. Urine toxicology procedures can reliably detect

evidence of marijuana use four to 25 days after last use (Fraser, Coffin, & Worth, 2002; Huestis & Cone, 1998), sometimes longer (Lafolie et al., 1991), depending on pattern of use, body lipid content, and metabolic features. Each urine sample was evaluated for metabolites indicating recent use of cannabis, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, codeine, morphine, phencyclidine, and ethanol using cloned enzyme donor immunoassay (CEDIA DAU, Microgenics, Fremont, CA). Observed urine sample collection procedures reduced the possibility of participant tampering. THC values were monitored over the 28-day period to ensure that levels decreased. Initial samples testing positive for THC metabolites were assumed to reflect residual use if values decreased with each subsequent sample collected. If levels increased or a positive screen was obtained following a negative screen, the participant was given the option to restart the 28-day screening process or be dropped from the study. Breathalyzers (AlcoSensor IV, Intoximeter, St. Louis, MO) were conducted at each visit. To confirm urine results, a hair sample collected on the scan day was analyzed for THC and other drug metabolites suggestive of past month use (Psychemedics, Culver City, CA). Seven users, not described in this paper, were unable to complete the 28-day abstinence protocol.

In preparation for scanning, each participant lay on the scanner bed. Foam pads were arranged around the head to minimize motion. A mirror above the participant's eyes enabled viewing of a screen at the foot of the scanner bed, on which the task was rear-projected from a laptop. Behavioral responses during the task were collected through a fiber-optic button box (LumiTouch, Vancouver, BC). Imaging data were acquired on a 1.5 Tesla Signa LX (General Electric, Madison, WI) system. A structural image was collected in the sagittal plane using an inversion recovery prepared T1-weighted 3D spiral fast spin echo sequence (repetition time 2000 ms, echo time 16 ms, field of view 240 mm, 128 continuous slices, resolution $0.9375 \times 0.9375 \times$

1.328 mm, acquisition time 8:36)(Wong, Luh, Buxton, & Frank, 2000). During the go/no-go

task, functional imaging was acquired in the axial plane using T2*-weighted spiral gradient

recall echo imaging (repetition time 3000 ms, echo time 40 ms, flip angle 90°, field of view 240

mm, 20 slices covering the whole brain, slice thickness 7 mm, in-plane resolution 1.875 x1.875

mm, 128 repetitions, acquisition time 6:24).

Data Analyses

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI;

afni.nimh.nih.gov)(Cox, 1996). First, an automated motion correction algorithm was applied to

the time series datasets (Cox & Jesmanowicz, 1999). Two raters examined the time series data

and removed repetitions containing residual visible head motions. If >18% of repetitions were

removed, the participant was not included (*n*=3 not described in this paper). Groups did not

differ in the number of repetitions removed (*p*=.87) or absolute mean rotational or translational

adjustments applied. Average rotational (roll, pitch, and yaw) and translational (superior, left,

and posterior) movement, respectively, was 0.04˚, 0.11˚, 0.05˚, 0.07 mm, 0.04 mm, and 0.04 mm

for MJ users, and 0.06˚, 0.12˚, 0.06˚, 0.10 mm, 0.04 mm, and 0.06 mm for controls. No

significant differences between groups were found for task-correlated motion (*r*s for the

correlation between the task reference function and each motion parameter were -.08, -.10, -.02, -

.11, -.07, and -.07 for MJ users and -.04, -.06, -.04, -.10, -.08, and -.06 for controls).

Next, time series datasets were deconvolved with a reference function representing the

timing of go, no-go, and rest stimuli presentation over the course of the task (Ward, 2002), while

accounting for hemodynamic delays (Bandettini, Jesmanowicz, Wong, & Hyde, 1993; Boynton,

Engel, Glover, & Heeger, 1996) and covarying for motion adjustments applied and linear trends.

This yielded fit coefficients representing the BOLD response for (1) inhibition (no-go) trials

relative to baseline and (2) go trials relative to baseline in each voxel of the brain for each

subject. Data were transformed to standard space (Lancaster et al., 2000; Talairach & Tournoux,

1988), resampled into isotropic 3.5 mm voxels, and spatially smoothed with a Gaussian filter

(3.5 mm full width half maximum) to account for anatomic variability between subjects.

We determined regions of significant BOLD response differences between MJ and

control adolescents using independent samples *t*-tests in each voxel of the brain, performed

separately on the BOLD response contrast for no-go and for go trials. To control for Type I error,

we used a combination of *t*-statistic magnitude and cluster volume thresholding (Forman et al.,

1995; Ward, 1997) by only interpreting clusters comprised of at least 22 contiguously activated

voxels at $a<.05$ ($\geq$943 µl in volume). Anatomic localization was confirmed using the Talairach

Daemon (Lancaster et al., 2000; Ward, 1997) and AFNI (Ward, 1997).

Normality of distribution was evaluated for key variables (Tabachnick & Fidell, 2007).

No outliers or non-normal distributions were found for BOLD response contrast in clusters

showing group differences. However, five variables (marijuana hits per month, lifetime other

drug use, cigarettes smoked per month, FTND total, and BDI total) were positively skewed and

kurtotic, so were inverse transformed (i.e., $1/(1 +$ the skewed variable)) (Tabachnick & Fidell,

2007). Group comparison results were further examined in ANCOVAs that controlled for

potential confound variables that differed between groups. Follow-up regression analyses were

conducting among the MJ users (*n*=16) to examine BOLD response contrast to no-go trials,

averaged across the cluster, in the regions that continued to differentiate users from controls in

the above ANCOVAs. BOLD response contrast to no-go trials was the dependent variable, and

variables indexing marijuana use, other substance use, and risk factors for substance involvement

were the predictors. Behavioral data were compared between groups in one-way ANOVAs (a = .05).

Results

Behavioral Measures

Groups did not differ significantly on mood state measures (see Table 1), but MJ users showed a trend for higher BDI scores (p=.08). Groups were similar and in the normal range on all CBCL factor *T*-scores, except the MJ group was higher on Rule-Breaking Behavior (53.00±8.23 MJ, 45.21±5.19 controls, p<.005). On the NEO-FFI, MJ youth demonstrated greater scores on Openness (44.25±3.11 MJ, 41.18±4.88 controls, p<.05), but were statistically equivalent on other personality scores. MJ youth committed more errors than controls on several cognitive tests: more sequencing errors across all DKEFS Trails conditions (p<.01), more intrusion errors on a word list learning task (p<.05), and more repetition errors on DKEFS Verbal Fluency (p<.05).

Task performance data were available for 15 MJ and 15 control adolescents. No group differences or group by condition interactions were found. As expected, participants responded more accurately (p<.001) to go trials (98.97±1.88% MJ, 98.70±1.62% controls) than no-go trials (82.92±9.57% MJ, 81.64±10.73% controls). Groups were equivalent on reaction time to go trials (588.11±40.44 MJ, 606.13±74.35 controls, p=.38). D', a signal detection index that considers the probability of correct and incorrect responses (i.e., the ability to separate go stimuli from the no-go stimulus), was also similar between groups (3.30±0.49 MJ, 3.04±0.84 controls, p=.54). Exit interview data showed that groups were equivalent on task effort, motivation, and perceived errors, but MJ users indicated use of more perceptual strategies (e.g., "look for the small square

to show up"), while controls tended to endorse cognitive strategies ("remember to hold off when I see that shape" or "concentrate").

FMRI Response

Whole brain analyses showed that during inhibitory trials relative to baseline, control adolescents showed significantly increased activation in superior medial frontal cortex and the left parahippocampal gyrus, and decreased activation in bilateral posterior parietal and inferior frontal regions. MJ users also showed increased inhibition-related activation in superior frontal areas, as well as in additional regions compared to controls, including numerous left and medial prefrontal clusters, left posterior parietal cortex, and multiple bilateral cerebellar regions. MJ users showed decreased BOLD response during no-go trials relative to baseline in right posterior parietal, inferior frontal, and middle temporal cortices.

Between group comparisons revealed several clusters in which MJ users showed significantly more BOLD response during inhibition trials than controls: right anterior superior and middle frontal gyri (BA 10,46), right superior middle frontal gyrus extending down to the anterior insula (BA 6, 13), left anterior middle and superior frontal gyri (BA 10), medial prefrontal cortex (BA 6), right and left posterior parietal cortex (BA 7, 40), and right lingual gyrus (BA 18) (see Table 2 and Figure 1). There were no clusters in which MJ users showed significantly less inhibitory brain response than controls.

For go trials relative to baseline, controls showed significant BOLD response in the bilateral ventral prefrontal cortex, bilateral medial posterior parietal cortex and cuneus, anterior cingulate, precentral gyrus, right anterior insula, and medial cerebellum. MJ users had multiple clusters of significant response to go trials relative to baseline, including increased activation in substantial portions of bilateral ventral prefrontal cortex, bilateral medial superior frontal cortex,

right posterior parietal cortex, bilateral temporal cortex, anterior cingulate, precentral gyrus, left insula, and bilateral cerebellum.

Between group comparisons indicated that MJ users had significantly more BOLD response during go trials relative to baseline than did controls in the right inferior frontal gyrus and anterior insula (BA 44, 13), right superior frontal gyrus (BA 9, 10), right superior parietal lobule (BA 7), right inferior parietal lobule (BA 40), and medial precuneus (BA 7) (see Table 3). There were no clusters in which MJ users had significantly less go response than controls.

To determine whether the group differences reported above were due to differences in other substance use or factors that could predate marijuana use, secondary analyses using ANCOVAs separately (due to limited power) controlled for lifetime alcohol consumption, days since last drink, drinks per month, years of regular drinking, time since last cigarette, past week cigarettes per smoking day, cigarettes per month, FTND total, number of lifetime other drug use episodes, family history of substance use disorders, family history of psychiatric disorders, each NEO-FFI score, and BDI total. For all analyses, groups continued to differ on BOLD response in all clusters (*p* range: .001 to .0001).

To determine whether differences between groups were due to duration and intensity of exposure to THC or related to the recency of marijuana use, we conducted a series of exploratory regression analyses among MJ users (*n*=16). Duration of regular marijuana use was *negatively* related to no-go brain response in the right anterior superior frontal gyrus (BA 10; $\beta = -.73$, *p*<.001; plotted in Figure 2), right superior middle frontal gyrus (BA 6; $\beta = -.58$, *p*<.025), and left anterior superior frontal gyrus (BA 10; $\beta = -.58$, *p*<.025), suggesting that youth with *longer* durations of marijuana involvement had *less* no-go brain response. Similarly, *early* age of onset of regular marijuana use ($\beta = .66$, *p*<.01) and *more* lifetime marijuana use episodes ($\beta = -.62$,

p<.025) related to *less* inhibitory response in the right anterior superior frontal gyrus (BA 10).

Typical number of marijuana hits per month also was *negatively* related to brain response in the

right anterior superior frontal gyrus (BA 10; *ß* = -.73, *p*<.005), right superior middle frontal

gyrus (BA 6; *ß* = -.71, *p*<.005), left anterior superior frontal gyrus (BA 10; *ß* = -.68, *p*<.01), and

left posterior parietal cortex (BA 40; *ß* = -.62, *p*<.025). Days since last marijuana use (range 28

to 240), age, and neuropsychological test performance were not associated with brain response in

any region demonstrating a group difference. Number of lifetime other drug use episodes

(primarily pain medications) was *positively* associated with BOLD response contrast to no-go

trials in the right anterior superior frontal gyrus (BA 10; *ß* = .57, *p*<.025) and right middle frontal

gyrus (BA 6, *ß* = .56, *p*<.025). All analyses were re-run controlling for lifetime other drug use

and remained unchanged except that hits per month no longer significantly predicted BOLD

response.

Discussion

In this study, marijuana using adolescents showed increased BOLD response during both

inhibitory and non-inhibitory trials of a go/no-go task, even after a 28-day washout period of

abstinence from cannabis, as compared to control adolescents with limited substance use

histories. Differences were prominent in dorsolateral prefrontal and parietal areas. Our findings

with adolescent marijuana users extend those of others (Gruber & Yurgelun-Todd, 2005), who

showed that adult marijuana users exhibited increased prefrontal response during inhibition

tasks. The present results thus suggest that the effects of cannabis use on brain function in

adolescents may persist after a period of abstinence. A pattern of increased activation yet

comparable performance is consistent with functional compensation and dedifferentiation (Rajah

& D'Esposito, 2005) which supposes that loci of functional activity are spread to more and larger

regions. Therefore, adolescent marijuana users appear to recruit more neural tissue in executive control areas to adequately perform the task, which is consistent with other studies showing increased dorsolateral prefrontal activation in MJ users during inhibition (Gruber & Yurgelun Todd, 2005) and other (Schweinsburg et al., 2005b) cognitive tasks. Repeated cannabinoid use may alter neuromaturation in regions with high CB1 densities, such as prefrontal cortex (Eggan & Lewis, 2006). Synaptic pruning and gray matter sculpting occurs late in some of the regions showing increased BOLD signal among users, such as bilateral dorsolateral prefrontal cortex, where cortical thickness peaks at age 11.5 on average (Gogtay et al., 2004; Sowell, 2003). If prefrontal synaptic pruning is slowed by adolescent marijuana use, greater activation may reflect excess neural firing caused by a larger number of synaptic links.

In their study of heavy marijuana using adults, Gruber and colleagues (Gruber & Yurgelun Todd, 2005) reported that heavy users had increased prefrontal response to an inhibition task, as seen in this study of adolescents, but also showed reduced anterior cingulate response, which we did not observe here. One possible explanation for this difference is the duration of marijuana use in our cohort. It may take a longer period of use to evidence such changes in cingulate responding. The increased parietal activation among marijuana using adolescents is consistent with findings from Jacobsen and colleagues (2006) of heightened parietal response in marijuana-involved youth during a verbal working memory task while undergoing nicotine withdrawal, although here, nicotine use rates were relatively low. As right dorsolateral prefrontal and parietal regions have been implicated in sustained attention (Drummond et al., 2005), perhaps users had a greater cognitive load associated with attending to the stimuli in general and in identifying the no-go stimulus in particular. Both go and no-go trials

require sustained attention, and overlap was observed for the right prefrontal/insular and parietal regions where users showed greater BOLD response than controls for both conditions.

Adolescents with later onsets (age 16-18) and briefer durations (1-2 years) of regular marijuana use showed the greatest divergence from normal controls in BOLD response to the inhibition trials. Similarly, Chang and colleagues (Chang, Yakupov, Cloak, & Ernst, 2006) reported that adults who started marijuana use in late adolescence had more frontal activation during a visual attention task than adults who started in early adolescence. Although our data do not address the molecular mechanism of this difference, we can speculate about the nature of this finding. For example, increased prefrontal activation during an inhibitory task in adolescent users with a more recent onset may reflect a stage of neural and behavioral compensation. This compensatory response may occur within the first few years of regular adolescent marijuana use and may later be followed by neuroadaptation or other processes, possibly related to downregulation of cannabinoid (CB1) receptors. Therefore, an inverted U-shaped response pattern may emerge over time, which eventually results in brain activation patterns that are indistinguishable from non-users (suggested in Figure 2).

BOLD response is influenced by cerebral blood flow, often abnormal in marijuana users acutely and subacutely. Up to 36 hours since last use, THC intake is associated with increased cerebral blood flow (Mathew et al., 2002) and volume (Sneider et al., 2006) in frontal, insular, anterior cingulate, cerebellum, temporal, and paralimbic regions; reductions in auditory and visual cortex, parietal lobe, and thalamus; and no change in nucleus accumbens, basal ganglia, or the hippocampus (O'Leary et al., 2002). Although increases in blood flow velocity and cerebrovascular resistance dissipate from 3 to 28 days of abstinence in adults with marijuana use levels consistent with this sample (i.e., 15.9 days per month), very heavy users remained

abnormally elevated (Herning, Better, Tate, & Cadet, 2005). Thus, increased BOLD response in

adolescent marijuana users could reflect residual cerebrovasculature abnormalities, although

increased blood flow or volume would likely yield *lower* BOLD response (Brown et al., 2003),

not greater, as seen here.

This study had several limitations. While groups were equivalent on many demographic

variables, intelligence, and task performance, marijuana users had greater alcohol and other

substance histories and a trend for more depressed symptomatology. Although activation patterns

remained after controlling for these factors, substance and affective differences pose the

possibility of synergistic effects, and we have previously found adolescent heavy drinking to be

related to abnormal activation patterns on a spatial working memory task (Caldwell et al., 2005;

Schweinsburg et al., 2005b; Tapert et al., 2001; Tapert et al., 2004). Reduced educational

engagement or altered sleep quality related to marijuana use might account for differences.

Critically, the current data cannot ascertain if marijuana use during adolescence produces the

observed differences or if abnormalities existed prior to the onset of regular use. Groups did not

differ on proportion with a family history of substance use disorder, and youths with psychiatric

diagnosis (e.g., conduct disorder, attention-deficit/hyperactivity disorder) were excluded from

study. Groups were similar with regard to most personality and psychopathological syndrome

dimensions, but did differ on openness to new experiences and parent report of delinquent

behaviors, which also may predate or result from adolescent marijuana use, but did not account

for group differences in brain response.

On the other hand, the adolescents who diverged most from normal controls may simply

differ on unmeasured risk factors related to the initiation and escalation of substance use. Altered

inhibitory processing may make adolescents vulnerable to substance use initiation and escalation.

The indication of extra neural effort required to inhibit responses has important implications for adolescent development and future substance involvement. Demands for inhibitory control increases substantially over the course of late adolescence, particularly in school and work environments as well as social and intimate relationships. Consequently, youth required to exert extra neurocognitive effort may be disadvantaged or become less successful in maneuvering the normal transitions of adolescence and young adulthood. Additionally, it may be harder for these youth to inhibit the use of substances, particularly in situations where cognitive demands are strained due to conflicting goals, distractions, peers, substance-relevant cues, or low mood states. Longitudinal studies are needed to see if changes in marijuana use among youth are associated with corresponding changes in brain functions shown abnormal in adolescent marijuana users.

Acknowledgements

Table 1: Demographic and substance use characteristics of participants

	Marijuana Users (*n*=16) M (SD) or %	Controls (*n*=17) M (SD) or %
Age (range: 16.0 – 18.9)	18.1 (0.7)	17.9 (1.0)
Grades completed in school	11.4 (0.8)	11.2 (1.1)
% Female	25%	29%
% Caucasian	75%	59%
% Family history negative for substance use disorder [a]	63%	76%
Parent annual salary ($ thousands)	131.4 (88.9)	131.7 (65.3)
Grade point average	3.3 (0.4)	3.1 (0.6)
WRAT3 Reading standard score	106.9 (6.4)	105.8 (8.3)
WASI Vocabulary *T*-score	54.9 (9.1)	55.8 (7.6)
Child Behavior Checklist Externalizing *T*-score	48.1 (6.0)	44.9 (7.1)
Child Behavior Checklist Internalizing *T*-score	47.6 (7.3)	46.8 (9.0)
Spielberger State Trait Anxiety *T*-score	39.2 (8.1)	39.7 (9.8)
Beck Depression Inventory total	4.6 (7.0)	1.2 (2.0)
Age of first marijuana use	14.0 (1.6)	14.7 (0.6) [b]
Age of first weekly marijuana use	15.4 (1.7)	-
Lifetime marijuana use episodes**	475.6 (268.5)	0.5 (1.3)
Marijuana use days per month before abstinence**	14.3 (11.6)	0.0 (0.0)
Days between scan and last marijuana use**	58.4 (52.8)	608.0 (210.7) [b]
Lifetime total drinks **	194.50 (136.81)	15.06 (38.81)
Drinks per month before monitored abstinence**	34.8 (21.5)	2.7 (9.4)
Alcohol hangover symptoms, past 3 months	0.4 (1.2)	0.0 (0.0)
Cigarettes per smoking day	1.4 (2.7)	0.2 (0.0)
Fagerstrom Test for Nicotine Dependence score	0.3 (0.8)	0.1 (0.2)
Lifetime other drug use episodes*	6.9 (8.6)	0.0 (0.0)

[a] No first-degree biological relative with alcohol or drug abuse or dependence
[b] Figure includes only the 3 controls a with history of use
* *p*<.05   ** *p*<.001

Table 2

Inhibition ("no-go") trial differences in BOLD response contrast between marijuana using and

non-using adolescents

Anatomic Region	Brodmann Area	Volume (μl)	Talairach Coordinates [a]			Effect Size Cohen's *d*
			x	y	z	
Marijuana Users > Controls [b]						
R superior & middle frontal gyri	10, 46	2015	37R	48A	14S	2.84
R middle frontal gyrus & insula	6, 13	2358	44R	3A	42S	2.33
L middle & superior frontal gyri	10	1200	33L	55A	3S	3.03
Bilateral medial frontal cortex	6	1544	2L	3A	52S	3.00
R inferior & superior parietal lobules	40, 7	1372	40R	57P	45S	2.16
L inferior & superior parietal lobules	40, 7	3473	40L	54P	52S	2.35
R lingual & middle occipital gyri	18	1929	23R	89P	3S	1.99

[a] Talairach coordinates refer to maximum signal intensity group difference within the cluster;

R, right; L, left; A, anterior; P, posterior; S superior; I, inferior

[b] Marijuana users did not show less BOLD response contrast than controls in any region.

Table 3

"Go" trial differences in BOLD response contrast between marijuana using and non-using

adolescents

Anatomic Region	Brodmann Area	Volume (μl)	Talairach Coordinates [a]			Effect Size Cohen's *d*
			x	y	z	
Marijuana Users > Controls [b]						
R inferior frontal gyrus, insula	44, 13	4588	54R	13A	14S	2.58
R superior & middle frontal gyrus	9, 10	1715	23R	52A	31S	2.55
R superior parietal lobule	7	1544	30R	57P	56S	3.11
R inferior parietal lobule	40	1372	47R	43P	49S	2.92
R medial precuneus	7	1243	5R	64P	59S	3.47

[a] Talairach coordinates refer to maximum signal intensity group difference within the cluster;

  R, right; L, left; A, anterior; P, posterior; S superior; I, inferior

[b] Marijuana users did not show less BOLD response contrast than controls in any region.

Figure Legends

<u>Figure 1</u>. Inhibition trial differences in BOLD response contrast between marijuana using (*n*=16) and non-using (*n*=17) adolescents after 28 days of monitored abstinence. Blue areas show where users had more significantly BOLD response during inhibition (no-go) trials relative to baseline than non-users ($p<.05$, clusters >943 µl); no clusters in which users showed significantly less activation than controls were found (see Table 2).

<u>Figure 2</u>. Marijuana using adolescents (*n*=16) show more BOLD response (y-axis displays fit coefficients) during inhibition trials relative to baseline than control adolescents (*n*=17) in right dorsolateral prefrontal cortex, largely accounted for by users with one to three years of regular (weekly) marijuana use.

References

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Adleman, N. E., Menon, V., Blasey, C. M., White, C. D., Warsofsky, I. S., Glover, G. H., & Reiss, A. L. (2002). A developmental fMRI study of the Stroop color-word task. *Neuroimage, 16*(1), 61-75.

Anderson, K. G., Schweinsburg, A. D., Paulus, M. P., Brown, S. A., & Tapert, S. F. (2005). Examining personality and alcohol expectancies using fMRI with adolescents. *Journal of Studies on Alcohol, 66*(3), 323 - 331.

APA. (1994). *Diagnostic and statistical manual of mental disorders (4th ed.).* American Psychiatric Association, Washington, DC.

Bandettini, P. A., Jesmanowicz, A., Wong, E. C., & Hyde, J. S. (1993). Processing strategies for time-course data sets in functional MRI of the human brain. *Magnetic Resonance in Medicine, 30*, 161-173.

Beck, A. T. (1978). *Beck Depression Inventory (BDI)*. San Antonio, TX: Psychological Corp.

Block, R. I., O'Leary, D. S., Hichwa, R. D., Augustinack, J. C., Ponto, L. L., Ghoneim, M. M., Arndt, S., Ehrhardt, J. C., Hurtig, R. R., Watkins, G. L., Hall, J. A., Nathan, P. E., & Andreasen, N. C. (2000). Cerebellar hypoactivity in frequent marijuana users. *NeuroReport, 11*(4), 749-753.

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., & Cadet, J. L. (2002). Dose related neurocognitive effects of marijuana use. *Neurology, 59*(9), 1337-1343.

Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *J Neurosci, 16*(13), 4207-4221.

Brown, G. G., Eyler Zorrilla, L. T., Georgy, B., Kindermann, S. S., Wong, E. C., & Buxton, R. B. (2003). BOLD and perfusion response to finger-thumb apposition after acetazolamide administration: Differential relationship to global perfusion *J Cereb Blood Flow Metab, 23*, 829-837.

Brown, S. A., Myers, M. G., Lippke, L., Tapert, S. F., Stewart, D. G., & Vik, P. W. (1998). Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): A measure of adolescent alcohol and drug involvement. *Journal of Studies on Alcohol, 59*, 427-438.

Caldwell, L. C., Schweinsburg, A. D., Nagel, B. J., Barlett, V. C., Brown, S. A., & Tapert, S. F. (2005). Gender and adolescent alcohol use disorders on BOLD (blood oxygen level dependent) response to spatial working memory. *Alcohol & Alcoholism, 40*, 194-200.

Chang, L., Yakupov, R., Cloak, C., & Ernst, T. (2006). Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. *Brain, 129*(Pt 5), 1096-1112.

Chen, A. C., Porjesz, B., Rangaswamy, M., Kamarajan, C., Tang, Y., Jones, K. A., Chorlian, D. B., Stimus, A. T., & Begleiter, H. (2007). Reduced frontal lobe activity in subjects with high impulsivity and alcoholism. *Alcohol Clin Exp Res, 31*(1), 156-165.

Costa, P. T. J., & McCrae, R. R. (1992). *Professional Manual: Revised NEO Personality Inventory (NEO PI-R) and NEO Five-Factor Inventory (NEO-FFI)*. Lutz, FL: Psychological Assessment Resources.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *29*, 162-173.

Cox, R. W., & Jesmanowicz, A. (1999). Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine, 42*, 1014-1018.

Delis, D., & Kaplan, E. (2001). *Manual for the Delis-Kaplan Executive Function System*. San Antonio: Psychological Corporation.

Drummond, S. P. A., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, C. M., & Meloy, M. J. (2005). The neural basis of the Psychomotor Vigilance Task. . *Sleep, 28*, 1059-1068.

Drummond, S. P. A., Paulus, M. P., & Tapert, S. F. (2006). Effects of 2 Nights Sleep Deprivation and 2 Nights Recovery Sleep on Response Inhibition. *Journal of Sleep Research, 15*, 261-265.

Eggan, S. M., & Lewis, D. A. (2006). Immunocytochemical Distribution of the Cannabinoid CB1 Receptor in the Primate Neocortex: A Regional and Laminar Analysis. *Cereb Cortex*.

Fletcher, J. M., Page, J. B., Francis, D. J., Copeland, K., Naus, M. J., Davis, C. M., Morris, R., Krauskopf, D., & Satz, P. (1996). Cognitive correlates of long-term cannabis use in Costa Rican men. *Arch Gen Psychiatry, 53*(11), 1051-1057.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33*(5), 636-647.

Fraser, A. D., Coffin, L., & Worth, D. (2002). Drug and chemical metabolites in clinical toxicology investigations: the importance of ethylene glycol, methanol and cannabinoid metabolite analyses. *Clinical Biochemistry, 35*(7), 501-511.

Fruyt, F. D., Mervielde, I., Hoekstra, H. A., & Rolland, J.-P. (2000). Assessing adolescents' personality with the NEO-PI-R. *Assessment, 7*, 329-345.

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., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci, 101*(21), 8174-8179.

Gruber, S. A., & Yurgelun Todd, D. A. (2005). Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Brain Res Cogn Brain Res, 23*(1), 107-118.

Gruber, S. A., & Yurgelun-Todd, D. A. (2005). Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Cognitive Brain Research, 23*(1), 107-118.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionaire. *Br J Addict, 86*(9), 1119-1127.

Herning, R. I., Better, W. E., Tate, K., & Cadet, J. L. (2005). Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. *Neurology, 64*(3), 488-493.

Huestis, M. A., & Cone, E. J. (1998). Differentiating new marijuana use from residual drug excretion in occasional marijuana users. *J Anal Toxicol, 22*(6), 445-454.

Jacobsen, L. K., Mencl, W. E., Westerveld, M., & Pugh, K. R. (2004). Impact of cannabis use on brain function in adolescents. *Annals of the New York Academy of Sciences, 1021*, 384-390.

Jacobsen, L. K., Pugh, K. R., Constable, R. T., Westerveld, M., & Mencl, W. E. (2006).

Functional Correlates of Verbal Memory Deficits Emerging During Nicotine Withdrawal in Abstinent Adolescent Cannabis Users. *Biol Psychiatry*.

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2005). *Monitoring the Future national results on adolescent drug use, 1975-2004: Volume 1, Secondary school students (NIH Publication No. 05-5727)*. Bethesda, MD: National Institute on Drug Abuse.

Kamarajan, C., Porjesz, B., Jones, K., Chorlian, D., Padmanabhapillai, A., Rangaswamy, M., Stimus, A., & Begleiter, H. (2006). Event-related oscillations in offspring of alcoholics: neurocognitive disinhibition as a risk for alcoholism. *Biol Psychiatry, 59*(7), 625-634.

Kanayama, G., Rogowska, J., Pope, H. G., Gruber, S. A., & Yurgelun Todd, D. A. (2004). Spatial working memory in heavy cannabis users: A functional magnetic resonance imaging study. *Psychopharmacology, 176*(3-4), 239-247.

Kirisci, L., Tarter, R. E., Reynolds, M., & Vanyukov, M. (2006). Individual differences in childhood neurobehavior disinhibition predict decision to desist substance use during adolescence and substance use disorder in young adulthood: a prospective study. *Addict Behav, 31*(4), 686-696.

Lafolie, P., Beck, O., Blennow, G., Boreus, L., Borg, S., Elwin, C. E., Karlsson, L., Odelius, G., & Hjemdahl, P. (1991). Importance of creatinine analyses of urine when screening for abused drugs. *Clin Chem, 37*(11), 1927-1931.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., Kochunov, P. V., Nickerson, D., Mikiten, S. A., & Fox, P. T. (2000). Automated

Talairach atlas labels for functional brain mapping. *Human Brain Mapping, 10*(3), 120-131.

Lisdahl Medina, K., Nagel, B. J., Park, A., McQueeny, T., & Tapert, S. F. (in press). Depressive symptoms in adolescents: Associations with white matter volume and marijuana use. *Journal of Child Psychology and Psychiatry*.

Lisdahl Medina, K., Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J., & Tapert, S. F. (in press). Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicology & Teratology*.

Liu, X., Banich, M. T., Jacobson, B. L., & Tanabe, J. L. (2004). Common and distinct neural substrates of attentional control in an integrated Simon and spatial Stroop task as assessed by event-related fMRI. *Neuroimage, 22*(3), 1097-1106.

Lucas, C. P., Zhang, H., Fisher, P. W., Shaffer, D., Regier, D. A., Narrow, W. E., Bourdon, K., Dulcan, M. K., Canino, G., Rubio Stipec, M., Lahey, B. B., & Friman, P. (2001). The DISC Predictive Scales (DPS): Efficiently screening for diagnoses. *J Am Acad Child Adolesc Psychiatry, 40*(4), 443-449.

Luna, B., Thulborn, K. R., Munoz, D. P., Merriam, E. P., Garver, K. E., Minshew, N. J., Keshavan, M. S., Genovese, C. R., Eddy, W. F., & Sweeney, J. A. (2001). Maturation of widely distributed brain function subserves cognitive development. *Neuroimage, 13*(5), 786-793.

Lundqvist, T., Jonsson, S., & Warkentin, S. (2001). Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicol Teratol, 23*(5), 437-443.

Mathew, R. J., Wilson, W. H., Turkington, T. G., Hawk, T. C., Coleman, R. E., DeGrado, T. R., & Provenzale, J. (2002). Time course of tetrahydrocannabinol induced changes in

regional cerebral blood flow measured with positron emission tomography. *Psychiatry Res, 116*(3), 173-185.

Millsaps, C. L., Azrin, R. L., & Mittenberg, W. (1994). Neuropsychological effects of chronic cannabis use on the memory and intelligence of adolescents. *Journal of Child and Adolescent Substance Abuse, 3*(1), 47-55.

Nagel, B., Medina, K., Yoshii, J., Schweinsburg, A., Moadab, I., & Tapert, S. (2006). Age-related changes in prefrontal white matter volume across adolescence. *NeuroReport, 17*, 1427-1431.

O'Leary, D. S., Block, R. I., Koeppel, J. A., Flaum, M., Schultz, S. K., Andreasen, N. C., Ponto, L. B., Watkins, G. L., Hurtig, R. R., & Hichwa, R. D. (2002). Effects of smoking marijuana on brain perfusion and cognition. *Neuropsychopharmacology, 26*(6), 802-816.

Pope, H. G., Jr., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun Todd, D. (2001). Neuropsychological performance in long term cannabis users. *Arch Gen Psychiatry, 58*(10), 909-915.

Pope, H. G. J., & Yurgelun Todd, D. (1996). The residual cognitive effects of heavy marijuana use in college students. *Jama, 275*(7), 521-527.

Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain, 128*(Pt 9), 1964-1983.

Rice, J. P., Reich, T., Bucholz, K. K., Neuman, R. J., Fishman, R., Rochberg, N., Hesselbrock, V. M., Nurnberger, J. I., Jr., Schuckit, M. A., & Begleiter, H. (1995). Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcoholism: Clinical and Experimental Research, 19*(4), 1018-1023.

SAMHSA. (2003). *Results from the 2002 National Survey on Drug Use and Health: National Findings* (No. DHHS Publication No. SMA 03–3836). Rockville, MD: Office of Applied Studies.

Schulz, K. P., Fan, J., Tang, C. Y., Newcorn, J. H., Buchsbaum, M. S., Cheung, A. M., & Halperin, J. M. (2004). Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event related FMRI study. *Am J Psychiatry, 161*(9), 1650-1657.

Schwartz, R. H., Gruenewald, P. J., Klitzner, M., & Fedio, P. (1989). Short-term memory impairment in cannabis-dependent adolescents. *American Journal of Diseases in Children, 143*(10), 1214-1219.

Schweinsburg, A. D., Nagel, B. J., Barlett, V. C., Killeen, L. A., Caldwell, L. C., Pulido, C. P., Brown, S. A., Paulus, M. P., & Tapert, S. F. (2004a). *fMRI of response inhibition across adolescent development.* Paper presented at the Annual Meeting of the International Neuropsychological Society, Baltimore, MD.

Schweinsburg, A. D., Nagel, B. J., & Tapert, S. F. (2005a). fMRI reveals alteration of spatial working memory networks across adolescence. *J Int Neuropsychol Soc, 11*(5), 631-644.

Schweinsburg, A. D., Paulus, M. P., Barlett, V. C., Killeen, L. A., Caldwell, L. C., Pulido, C. P., Brown, S. A., & Tapert, S. F. (2004b). An fMRI study of response inhibition in youths with a family history of alcoholism. *Annals of the New York Academy of Sciences, 1021*, 391 - 394.

Schweinsburg, A. D., Schweinsburg, B. C., Cheung, E. H., Brown, G. G., Brown, S. A., & Tapert, S. F. (2005b). fMRI response to spatial working memory in adolescents with comorbid marijuana and alcohol use disorders. *Drug Alcohol Depend, 79*(2), 201-210.

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(1), 28-38.

Sneider, J. T., Pope, H. G., Jr., Silveri, M. M., Simpson, N. S., Gruber, S. A., & Yurgelun-Todd, D. A. (2006). Altered regional blood volume in chronic cannabis smokers. *Exp Clin Psychopharmacol, 14*(4), 422-428.

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R. Z. Litten & J. P. Allen (Eds.), *Measuring alcohol consumption: Psychosocial and biochemical methods.* (pp. 41-72): Humana Press, Inc, Totowa, NJ, US.

Solowij, N., Michie, P. T., & Fox, A. M. (1991). Effects of long-term cannabis use on selective attention: an event-related potential study. *Pharmacology Biochemistry & Behavior, 40*(3), 683-688.

Solowij, N., Michie, P. T., & Fox, A. M. (1995). Differential impairments of selective attention due to frequency and duration of cannabis use. *Biological Psychiatry, 37*(10), 731-739.

Solowij, N., Stephens, R. S., Roffman, R. A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., & Vendetti, J. (2002). Cognitive functioning of long term heavy cannabis users seeking treatment. *JAMA, 287*(9), 1123-1131.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6*, 309-315.

Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine and Child Neurology, 44*(1), 4-16.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Stewart, D. G., & Brown, S. A. (1995). Withdrawal and dependency symptoms among adolescent alcohol and drug abusers. *Addiction, 90*, 627-635.

Struve, F. A., Patrick, G., Straumanis, J. J., Fitz-Gerald, M. J., & Manno, J. (1998). Possible EEG sequelae of very long duration marihuana use: pilot findings from topographic quantitative EEG analyses of subjects with 15 to 24 years of cumulative daily exposure to THC. *Clin Electroencephalogr, 29*(1), 31-36.

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics* (5th ed.). Boston: Pearson.

Talairach, J., & Tournoux, P. (1988). *Coplanar stereotaxic atlas of the human brain. Three-dimensional proportional system: An approach to cerebral imaging*. New York: Thieme.

Tamm, L., Menon, V., & Reiss, A. L. (2002). Maturation of brain function associated with response inhibition. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(10), 1231 - 1238.

Tapert, S. F., Baratta, M. V., Abrantes, A. M., & Brown, S. A. (2002). Attention dysfunction predicts substance involvement in community youths. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(6), 680-686.

Tapert, S. F., Brown, G. G., Kindermann, S., Cheung, E. H., Frank, L. R., & Brown, S. A. (2001). fMRI measurement of brain dysfunction in alcohol-dependent young women. *Alcoholism: Clinical and Experimental Research, 25*, 236-245.

Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: Neuropsychological functioning over 8 years in youth. *J Int Neuropsychol Soc, 8*(7), 873-883.

Tapert, S. F., Schweinsburg, A. D., Barlett, V. C., Brown, S. A., Frank, L. R., Brown, G. G., & Meloy, M. J. (2004). Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcohol Clin Exp Res, 28*(10), 1577-1586.

Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *J Int Neuropsychol Soc, 12*(3), 405-415.

Ward, B. D. (1997). *Simultaneous inference for FMRI data*. Milwaukee, WI: Biophysics Research Institute, Medical College of Wisconsin.

Ward, B. D. (2002). *Deconvolution analysis of FMRI time series data*. Milwaukee, WI: Biophysics Research Institute, Medical College of Wisconsin.

Wechsler, D. (1999). *Manual for the Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation.

Wilkinson, G. S. (1993). *The Wide Range Achievement Test-3 Administration Manual*. Wilmington, DE: Jastak Associates.

Wong, E. C., Luh, W. M., Buxton, R. B., & Frank, L. R. (2000). Single slab high resolution 3D whole brain imaging using spiral FSE. *Proceedings of the International Society for Magnetic Resonance in Medicine, 8*, 683.

Yurgelun-Todd, D., Gruber, A. J., Hanson, R. A., Baird, A. A., Renshaw, P. F., & Pope, H. G., Jr. (1998). Residual effects of marijuana use: An fMRI study. In L. S. Harris (Ed.), *Problems of Drug Dependence 1998: Proceedings of the 60th Annual Scientific Meeting, The College on Problems of Drug Dependence, NIDA Research Monograph 179* (pp. 78). Bethesda: MD: National Institute on Drug Abuse.