Cognitive Recovery With Cannabis Abstinence Among
High School-Aged Adolescents
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PARTNERS HUMAN RESEARCH COMMITTEE

DETAILED PROTOCOL: Cognition and Adolescent Health
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I. BACKGROUND AND SIGNIFICANCE

A. Access to cannabis among children and adolescents is escalating. Cannabis is currently the most commonly used illicit substance among adolescents in the United States and is one of the only substances with steadily increasing prevalence estimates. In fact, rates of use now surpass those of cigarettes[1] and are approaching those of alcohol among adolescents.[2] Recent estimates suggest that 52.2% of 18 to 25 year olds have ever tried cannabis,[2] with the rates of experimental use significantly increasing over the course of middle and high school (10.3% of middle schoolers[3], 30.1% of 9th graders, 48.6% of 12th graders[1]). In addition, it is estimated that approximately 1.7% of middle schoolers and 6.8% of high schoolers have tried cannabis for the first time before age 11 and 13, respectively, demonstrating that early exposure to cannabis is common.[3] Patterns of regular use are also prevalent among youth, with 6.5% of high school students reporting daily use and 27.7% reporting monthly use.[1-2] Cannabis use among children and adolescents is likely to increase further with legalization and subsequent increased availability.

These increasing prevalence estimates may be, in part, due to the cultural context in which adolescent cannabis use occurs. There has been an overall decrease in perceived harm of cannabis use,[1] which has likely contributed to an increase in social and legal permissiveness for recreational use as well as increased acceptability and application of medicinal cannabis.[4] Further, there has been an increase in the availability of more potent cannabis strains, which are nearly 25 times stronger than varieties available previously.[5-6]

The more prevalent usage of a more potent drug in an era of swelling cannabis acceptance is a significant public health concern, to the extent that there are adverse sequelae from chronic cannabis exposure. A growing body of research supports the notion that cannabis may be addictive. The lifetime risk for cannabis dependence is approximately 9% and nearly 17% when use is initiated during teenage years.[7] Although these cumulative dependence estimates are lower for cannabis than for other substances of abuse, the rate of transition from non-problematic to problematic cannabis use may occur faster than for drugs such as nicotine and alcohol.[7] Therefore, it is not surprising that use of cannabis during adolescence is associated with several short- and long-term problems. For instance, cannabis intoxication has been associated with an increased risk for motor vehicle accidents.[8-9] Additionally, use between the ages of 14 and 21 years is associated with later difficulties in the domains of education, employment, income as well as relationship and life satisfaction.[10-11]

B. The developing brain is most vulnerable to harmful effects from cannabis. The potential contraindications of cannabis use are particularly important to consider during adolescence given that this represents a developmentally vulnerable period of profound and dynamic changes throughout the brain, involving changes to micro- and macrostructure particularly in the prefrontal cortex, limbic system and white matter association fibers as well as neurochemical alterations. Significant dendritic pruning and increased myelination occurring during this time improves efficiency of processing and supports higher-order cognitive functions (e.g., complex attention, working memory, reward processing, and inhibitory control).[12-16] Additionally, given that the endocannabinoid system plays a central role in overall neuromaturation[17-18] and is also undergoing substantial development during adolescence (e.g., dramatic pruning of receptor density levels in subcortical and frontal regions[19-20]), it is not surprising that the developing brain is particularly susceptible to insults from exogenous cannabinoids.[12]

C. More research is needed on the relationships between neuropsychological functioning and cannabis use. Available reports have shown that adolescence may be a unique developmental window during which cannabis exerts its most profound impact on neurocognitive functioning. Even after taking into account multiple potential confounds, those who initiate before 18 years tend to show more pronounced impairments in visual

attention,[21] visual search efficiency,[22] episodic memory,[23-24] and executive functioning[25-28] as well as possible declines in intellectual functioning.[29] For example, only early age of initiation (before age 16) was predictive of impaired reaction times on a visual scanning task, above and beyond the effects of current age, THC plasma levels and cumulative lifetime cannabis exposure as compared to late onset users who were not different from controls.[21] Similarly, Solowij and colleagues[24] found that earlier age of cannabis onset was associated with poorer learning, retention and retrieval of novel verbal information even after adjusting for the frequency and amount of cannabis exposure. Further, the relationship between early cannabis use and neurocognitive concerns may also be accompanied by unique patterns of brain activity: earlier onset chronic cannabis users made more errors on a behavioral inhibition task and showed more focal activation of the middle anterior cingulate cortex than late onset chronic users.[26] These apparent neuropsychological differences among individuals with earlier cannabis debut may yield important functional implications as early age of initiation is also associated with up to a four-fold greater risk of cannabis dependence within the first two years of use.[30]

Preliminary reports of lasting cognitive decrements with adolescent cannabis use need to be replicated and extended in order to understand the time course of early cognitive changes associated with intoxication and elucidate which cognitive impairments may be persistent.[31-33] While disproportionate risk for cognitive decline when cannabis use is initiated in adolescence may be due to profound brain maturational changes during this period, **the literature on cognitive compromise from cannabis use is mixed and interpretation of findings is obscured by methodological limitations.** This proposal is responsive to a NIH-NIDA RFA to define the time course for cognitive recovery in adolescent cannabis users. We propose to examine cognitive performance longitudinally, with rigorous assessment techniques that are robust to serial test administration in a representative adolescent sample who use cannabis at least weekly, a sample that represents 40% percent of high school students, compared to non-users. Further, this proposed study offers an important opportunity to pilot a contingency management (CM) strategy for feasibility, acceptability and efficacy at reducing cannabis use in adolescents regardless of their desire to quit. This information will be critical to planning a larger intervention for a K23 application.

D. Rationale for Proposed Research. These data are necessary to fill important gaps in the extant literature. The proposed project addresses critically important clinical questions of the impact of cannabis use, and particularly the potential beneficial effect of short term cannabis abstinence, on learning and cognitive performance in children and adolescents. That is, to understand whether, in children and adolescents who use cannabis regularly, 4 days or 30 days of abstinence results in an improvement in cognitive performance compared to those who do not stop cannabis use. This is a highly relevant question, as the perception among children and adolescents and often their parents, is that cannabis use 'on the weekend' does not impact their ability to learn and perform in school a few days later. It has the potential to have profound impact on our understanding of the clinical effect of cannabis on cognition in young people as well on policy, given the rapidly shifting political landscape on cannabis use in the US that will no doubt have a strong impact on prevalence and frequency of child and adolescent cannabis use, regardless of age restrictions on purchase. Additionally, this study is critical to establishing feasibility and efficacy of contingency management interventions among cannabis-using children and adolescents. Current data of this type is limited and virtually no data exists on the feasibility of contingency management interventions in a school-based setting or in non-treatment seekers. Together, this study is critically important first-of-its-kind investigation of the longitudinal relationships between child and adolescent cognition and cannabis use, as well as the potential utility of contingency management for cannabis use, questions of high and growing public health significance given children's and adolescents' increased access to cannabis with legalization.

II. SPECIFIC AIMS

Aim 1: To provide updated information on prevalence and frequency of cannabis use in relation to other forms of substance use in a representative sample of school-aged children and adolescents.

Aim 2: To evaluate the effect of contingency management on initial 30-day verified cannabis abstinence in children and adolescents and older adolescents who use cannabis at least weekly and are not seeking treatment.

Aim 3: To determine whether there is cognitive dysfunction in cannabis use that persists in the short term (4 days) after use but resolves with extended abstinence (30 days) compared to cannabis users who do not quit and non-using controls.

Aim 4: To estimate the rate of cognitive improvement with cannabis abstinence as a function of time since last use and concentration of detectable cannabis metabolites in urine.

Aim 5: To assess the neural correlates of cannabis abstinence using structural and functional brain imaging measures.

Aim 6: To explore the effects of cannabis abstinence on objective and subjective measures of sleep quality.

III. SUBJECT SELECTION

Inclusion Criteria for School-Aged Study Component

General:

1. Male and female children and adolescents from the Boston area who are between the ages of 10 and 19 (inclusive);
2. Have a parent or legal guardian who is able and willing to provide written informed consent for the active study phase (if under the age of 18);
3. Competent and willing to provide written informed assent for the active study phase (if under the age of 18);
4. Competent and able to provide written informed consent (if age 18 or older)
5. Able to communicate in English language
6. Able to commit to 9 study visits in approximately 60 days
7. No severe developmental delays (including, but not limited to, Autism Spectrum Disorder, Intellectual Disability, and Down Syndrome.
8. Able to safely participate in the protocol and appropriate for outpatient level of care, in the opinion of the investigator

Cannabis-Using Group:

1. Use of cannabis at least once per week on most weeks
2. Cannabis use reported within 7 days of both baseline visits.
3. No immediate plan to discontinue cannabis use.

Non-Using Group:

1. Use of cannabis less than 5 times in lifetime
2. No cannabis use in the past year
3. No cannabis use before age 16

Exclusion Criteria (The Epiphany School and Cohasset, Maynard, Northshore, Needham, Millis, Medford, Walpole, Westford, and Cambridge Public Schools)

1. Passive consent for initial school-wide assessment withdrawn by parent or legal guardian

Exclusion Criteria (Waltham Public School)

1. Written parental consent not provided prior to screening

Inclusion Criteria for College-Aged Study Component

General:

1. Male and female children and adolescents who are between the ages of 18 and 25 (inclusive) who report regular cannabis use
2. Competent and willing to provide written informed consent
3. Able to communicate in English Language
4. Cannabis use reported within 7 days of second baseline visit.

Additional Enrollment Criteria for Participants to Undergo MRI Scanning

Inclusion:

1. Meets all cannabis-use criteria as outlined above

2. Written permission granted to undergo MRI scanning by parent/legal guardian (for those under the age of 18) on informed consent form
3. Written assent provided to undergo MRI scanning by participant (for those under the age of 18) on informed consent form
4. Written consent provided to undergo MRI scanning by participant (for those 18 years of age or older) on informed consent form

Exclusion:

1. Known claustrophobia
2. Presence of electrically, magnetically, or mechanically activate implants (such as cardiac pacemakers) or intracerebral vascular clips
3. History of working with metal (e.g. shavings or fragments could be lodged in scalp or eye)
4. Pregnancy (a pregnancy test will be conducted prior to each MRI scan)
5. In the opinion of the investigator, not able to safely participate in this study

Additional Enrollment Criteria for Participants to use Fitbits

Inclusion:

1. Meets all cannabis-use criteria as outlined above
2. Written permission granted to undergo Fitbit monitoring by parent/legal guardian (for those under the age of 18) on informed consent form
3. Written assent provided to undergo Fitbit monitoring by participant (for those under the age of 18) on informed consent form
4. Written consent provided to undergo Fitbit monitoring by participant (for those 18 years of age or older) on informed consent form

Exclusion:

1. Inability to wear Fitbit device

IV. SUBJECT ENROLLMENT

Given the community-based nature of this protocol, specific enrollment procedures are tailored to the request of administrators from each individual school-district. For example, Westford administrators prefer that all students be initially screened under passive parental consent, prior to parents being contacted for full study consent. Our study-wide enrollment target is 500, with 100 older adolescent participants from the college-aged component and 400 school-aged children and adolescents from the school-aged component.

School-Aged Study Component (The Epiphany School and Cohasset, Maynard, Northshore, Needham, Millis, Medford, Walpole, Westford, Cambridge, and Waltham Public Schools; Community):

We aim to enroll 400 school-aged children and adolescents into the proposed protocol, including approximately 300 cannabis users and 100 non-using controls.

Screening

- **Children and Adolescents Recruited and Enrolled from The Epiphany School and Cohasset, Maynard, Northshore, Needham, Millis, Medford, Walpole, Westford, and Cambridge Public Schools: Passive Consent for School-Wide Screening.** The proposed project will begin with a school-wide assessment in order to characterize the demographics and general behavioral profile of the schools attended by the participants. **This survey will occur through a parent screening protocol (#2021P001873).** Briefly, participants will be recruited by MGH study staff from the MGH Center for Addiction Medicine and not by any district and/or school personnel. Recruitment will occur at Westford Academy, Cambridge Rindge and Latin School, Lloyd G. Blanchard Middle School, Stony Brook Middle School, Walpole High School, Medford High School, Andrews Middle School, John J. McGlynn Middle School, Millis Middle School, Millis High School, The Epiphany School, Cohasset High School, Pollard Middle School, Needham High School, Northshore Recovery High School, and Maynard High School, through an opt-out procedure conducted solely by MGH staff. Specifically, at the request of MGH staff, the participating school will contact all parents/guardians of 5th through 12th grade students in the school's preferred method (e.g., through reverse 9-11 calls, emails, mass mailings) indicating that MGH study staff will be distributing and collecting a very brief and de-identified questionnaire during a designated time at school. Parents and guardians will be told that they can freely withdraw their child from participating in the school-wide assessment phase without any penalty or

consequence to the child, including any impact on school or educational activities and that parental written consent must be provided to MGH staff for active phase study participation. Parents and legal guardians will be informed that this is not a study or program of the respective school district, including a program of the specific school. School personnel will not be involved in administrating or operating the study in any capacity, including answering student and/or parent or legal guardian inquiries regarding the study. Parents and legal guardians will be free to contact the principal investigator of this study at MGH directly at any time if they have questions about the school-wide assessment or the specific items included on the questionnaire. Given the history of low response rate of studies requiring students to return parent permission forms (which limits the number of students who can be involved in the project and threatens the ability to generalize the results, thus limiting the usefulness of our research results), we propose conducting this study for those enrolled directly from local schools with passive parental consent for school-wide screening, a waiver of parental consent for telephone screening (to confirm interest, eligibility, and parent contact information) and active student assent and parent consent for the active study phase.

- **Children and Adolescents Recruited and Enrolled from Waltham High School: Written Parental Consent for Active Study Phase Required Prior to Telephone Screening.** Participants will be recruited by MGH study staff from the MGH Center for Addiction Medicine and not by any district and/or school personnel. Recruitment will begin through mailed envelopes from Waltham High School to all parents/guardians of 9th through 12th grade students. These envelopes will include a consent form cover letter that briefly explains the nature and purpose of the study, instructions for signing and returning consent forms, a contact sheet for parents to provide their child's and their own contact information, and a self-addressed, stamped envelope to return the forms to the MGH Center for Addiction Medicine. Consent forms in English, Spanish, and Haitian-Creole will be included in the envelopes for parents to sign if they would like to give permission for their child to be contacted by MGH study staff. Parents and guardians will be told that they can refrain from signing the consent form without any penalty or consequence to the child, including any impact on school or educational activities and that parental written consent must be provided to MGH staff for active phase study participation. Within the consent form is a description of collection of saliva samples for genetic analysis; parents can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is a description of MRI procedures; parents can decline consent for scanning without penalty on participation for the rest of the project. Parents and legal guardians will be informed that this is not a study or program of the respective school district, including a program of the specific school. School personnel will not be involved in administrating or operating the study in any capacity, including answering student and/or parent or legal guardian inquiries regarding the study. Parents and legal guardians will be free to contact the principal investigator of this study at MGH directly at any time if they have questions about the school-wide assessment or the specific items included on the questionnaire. Students whose parents signed the consent form and completed the contact sheet will then be contacted by MGH study staff, at which time students will be told about the study and, if interested in participating, will be screened for eligibility criteria over the phone.
- **Children and Adolescents Recruited and Enrolled from the Community: Waived Parental Consent for Telephone Screening.** School-aged participants recruited through online advertisements and flyers posted throughout the community (see recruitment materials) will complete a brief telephone screener to determine eligibility and interest in the study protocol (see telephone script). Among participants that are eligible, under the age of 18, and interested in participating in the study, parent/legal guardian contact information will be collected in order to obtain informed consent for the active study phase. No active study procedures will be conducted with potential participants under the age of 18 prior to obtaining written parent/guardian informed consent.
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This request for a waiver of written consent for telephone screening only(for adolescents recruited through schools or the community) is justified given the following:

- **The proposed research involves no more than minimal risk to participants.** During screening, we will provide details about the study and ask potential participants if they have any questions or concerns about the study protocol. We will also ask participants basic demographic

information as well as brief questions related to frequency and recency of cannabis use to determine eligibility. These questions are indistinguishable from questions asked during standard school substance use assessments. This screener is anticipated to take no more than five minutes and participants are free to refuse to answer any questions. They will be told that all information will be kept strictly confidential and answers to screening questions will be stored separately from any identifying information. If participants are interested in the study and are eligible, we will collect parent/guardian contact information so that we can obtain written parental consent for study enrollment. No study procedures will occur before written parental consent is obtained. We will also obtain written child/adolescent assent at the baseline visit, prior to the initiation of any study procedures, during which time we will review the study in detail.

- **The waiver of consent for screening will not adversely affect the rights and welfare of subjects.** The waiver of parental consent for screening only will not adversely impact a child's or adolescent's access to or the nature of any ongoing health services or primary care in any way nor adversely affect his/her rights or welfare. The study will be detailed to potential participants before any screening questions are asked of them, giving them a chance to decline screening if they are not interested in the study. They are also free to refuse to answer any screening questions that make them feel uncomfortable. They will be clearly told that written parental consent and child/adolescent assent will be required for enrollment in the active study phase and that answers to phone-based questions are for screening purposes only.
- **The research could not practicably be carried out with the waiver or alteration.** This study could not be practicably carried out without a waiver of consent for phone screening for community-based school-aged children and adolescents under the age of 18 due to the burden that would be imposed on parents of potential participants that are not yet even known to be eligible and interested in study participation. This study utilizes a brief, de-identified telephone screen to assess whether the potential participant is interested and eligible for the study. Screening questions are similar to questions asked in standard school substance use assessments. In our experience, the consent process generally takes approximately 30 minutes, while the brief screener should only take about 5 minutes or less for most participants. Requiring consent for screening would thus dramatically increase parent burden, and in many cases, this imposed burden would be unnecessary because it is not guaranteed that their child is interested or eligible for the study. Due to this increased parent burden, we expect that requiring consent for screening would greatly reduce enrollment and compromise the representativeness of the sample. Therefore, we are proposing to seek written consent only for potential participants who we know are interested and eligible in the study. It is for these reasons that our study requires a waiver of consent for participant screening for community-based school-aged children and adolescents under the age of 18.
- **Participants and parents will be provided with additional pertinent information after participation.** Prior to the first study visit, written parental consent will be obtained and parents will be provided with copies of the consent form which will fully detail the study protocol as well as any associated risks and benefits. They will be given contact information of key study staff if they would like more information. Similarly, study participants will be given a copy of the signed parental consent/study assent form.
- **The research involves no more than minimal risk to the privacy of the participants.** This research involves no more than minimal risk to the privacy of participants. During the screening, only basic demographics and information to determine eligibility will be collected. The protocol fully details our plan to protect any identifying information from improper use and disclosure.

Active Study Phase

- **Children and Adolescents Recruited and Enrolled from The Epiphany School and Cohasset, Maynard, Northshore, Needham, Millis, Medford, Walpole, Westford, and Cambridge Public Schools: Written Parental Consent and Student Assent.** Students who expressed interest in participating in the active study phase will be contacted via telephone and/or email by MGH study staff directly to describe the study, and discuss their interest in and understanding of the proposed protocol.

MGH staff will send home an informed consent form containing our contact information for their parent or legal guardian, to read, consider and sign. Parents can electronically sign the consent form and send the document back to study staff if they would prefer. This option will only be available if this is preferred by parents; the opportunity to meet with study staff in person or over the phone will be made available to all parents. Parents may reach out to MGH study staff with any questions or concerns. The initial study visit will be coordinated with the student over the phone and/or via email and he/she will be told that the signed parental consent form must be received from his/her parent/guardian prior to the first visit or the student must bring the signed parental consent form to the first visit. The active phase study procedures will not begin for any participant under the age of 18 until the parental consent form is obtained. Within the consent form is a description of collection of saliva samples for genetic analysis; parents can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is also a description of MRI, Fitbit, and ActiGraph GTX-9 procedures; parents can decline consent for scanning,use of Fitbits, and use of ActiGraph GTX-9 without penalty on participation for the rest of the project. During the initial study visit, informed assent will be obtained from the student by a trained member of the study staff prior to administering any study procedures. The students may also have the option to sign electronically. As in the parental consent form, students will indicate on the assent form whether they permit collection and analysis of genetic samples as well as neuroimaging. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the assent process. Contact information of key MGH study staff will be provided and participants (and parents/guardians) will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All participants as well as their parents/guardians (if from the school-based study component) will be provided with a copy of their signed parental consent and student assent forms.

Students who are interested in participating and are over 18 years old will be contacted by a member of study staff, who will coordinate the initial study visit. At the time of such visit, informed consent will be obtained by a trained member of the study staff prior to administering any study procedures. Informed consent may be obtained electronically. Within the consent form is a description of collection of saliva samples for genetic analysis; participants can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is a description of MRI, Fitbit, and ActiGraph GTX-9 procedures; participants can decline consent for scanning, use of Fitbits, and ActiGraph GTX-9 without penalty on participation for the rest of the project. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff during the consent process. Contact information of key study staff will be provided and participants will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All eligible participants will be provided with a copy of their signed consent form.

Cannabis users will be randomized to either a monitoring condition where they will not be asked to stop using cannabis (but may freely do so if they wish) or a contingency management intervention during which they will be asked to discontinue cannabis use for 30 days. Cannabis users (regardless of the group to which they are randomized) and non-users will complete identical study procedures.

- **Children and Adolescents Recruited and Enrolled from Waltham High School: Written Parental Consent and Student Assent.** Students whose parents mailed back the signed consent form and completed contact sheet will be contacted via telephone and/or email by MGH study staff directly to describe the study, and discuss their interest in and understanding of the proposed protocol. Students who are interested in participating and are deemed eligible via telephone will be scheduled for their study visits. The active phase study procedures will not begin for any participant under the age of 18 until the parental consent form is obtained. During the initial study visit, informed assent will be obtained from the student by a trained member of the study staff prior to administering any study procedures. As in the parental consent form, students will indicate on the assent form whether they permit collection and analysis of genetic samples as well as neuroimaging. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the assent process. Contact information of key MGH study staff will be provided and participants (and parents/guardians) will be

informed that the co-investigators are available to answer any questions or concerns they may have about the study. All participants as well as their parents/guardians (if from the school-based study component) will be provided with a copy of their signed parental consent and student assent forms.

Students who are interested in participating and are over 18 years old will be contacted by a member of study staff, who will coordinate the initial study visit. At the time of such visit, informed consent will be obtained by a trained member of the study staff prior to administering any study procedures. Within the consent form is a description of collection of saliva samples for genetic analysis; participants can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is a description of MRI, Fitbit, and ActiGraph GTX-9 procedures; participants can decline consent for scanning, use of Fitbits, and use of ActiGraph GTX-9 without penalty on participation for the rest of the project. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff during the consent process. Contact information of key study staff will be provided and participants will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All eligible participants will be provided with a copy of their signed consent form.

Cannabis users will be randomized to either a monitoring condition where they will not be asked to stop using cannabis (but may freely do so if they wish) or a contingency management intervention during which they will be asked to discontinue cannabis use for 30 days. Cannabis users (regardless of the group to which they are randomized) and non-users will complete identical study procedures.

- **Children and Adolescents Recruited and Enrolled from the Community: Written Parental Consent and Student Assent.** Parent/guardian contact information will be collected from students who expressed interest in participating in the active study phase, who were found to be eligible on the telephone screen, and who are under the age of 18. Parents/guardians will be contacted directly by MGH staff. MGH staff will send home an informed consent form containing our contact information for their parent or legal guardian, to read, consider and sign. Parents can electronically sign the consent form and send the document back to study staff if they would prefer. This option will only be available if this is preferred by parents; the opportunity to meet with study staff in person or over the phone will be made available to all parents. Parents may reach out to MGH study staff with any questions or concerns. The initial study visit will be coordinated with the student over the phone and/or via email and he/she will be told that the signed parental consent form must be received from his/her parent/guardian prior to the first visit or the student must bring the signed parental consent form to the first visit. The active phase study procedures will not begin for any participant under the age of 18 until the parental consent form is obtained. Within the consent form is a description of collection of saliva samples for genetic analysis; parents can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is a description MRI, Fitbit, and ActiGraph GTX-9 procedures; parents can decline consent for scanning, use of Fitbits, and use of ActiGraph GTX-9 without penalty on participation for the rest of the project. During the initial study visit, informed assent will be obtained from the student by a trained member of the study staff prior to administering any study procedures. The students may also have the option to sign electronically. As in the parental consent form, students will indicate on the assent form whether they permit collection and analysis of genetic samples as well as neuroimaging. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the assent process. Contact information of key MGH study staff will be provided and participants (and parents/guardians) will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All participants as well as their parents/guardians will be provided with a copy of their signed parental consent and student assent forms.

  Students who are interested in participating and are over 18 years old will work directly with MGH staff following completion of the telephone screen to coordinate the initial study visit. At the time of such visit, informed consent will be obtained by a trained member of the study staff prior to administering any study procedures. Informed consent may be obtained electronically. Within the consent form is a

description of collection of saliva samples for genetic analysis; participants can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is a description of MRI, Fitbit, and ActiGraph GTX-9 procedures; participants can decline consent for scanning, use of Fitbits, and use of ActiGraph GTX-9 without penalty on participation for the rest of the project. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff during the consent process. Contact information of key study staff will be provided and participants will be informed that the co-investigators are available to answer any questions or concerns they may have about the study. All eligible participants will be provided with a copy of their signed consent form.

Cannabis users will be randomized to either a monitoring condition where they will not be asked to stop using cannabis (but may freely do so if they wish) or a contingency management intervention during which they will be asked to discontinue cannabis use for 30 days. Cannabis users (regardless of the group to which they are randomized) and non-users will complete identical study procedures.

Participant Withdrawal (All School-Aged Cohorts)
Participation is completely voluntary and participants may stop being in the study at any time or decide not to join the study. Similarly, parents/guardians of students older than 18 may withdraw their child from the study at any time or decide not to allow their child to participate in the school-wide assessment phase and/or active study phase. If a participant or parent/guardian decides not to participate, they will not be penalized in any way, and will not lose any benefits to which they are otherwise entitled.

Confidentiality (All School-Aged Cohorts)
All phases and aspects of this project will be conducted according to the Declaration of Helsinki and will comply with HIPAA regulations. The sponsors of this research will be the only individuals who will have access to data on individuals that are stripped of all unique identifiers according to HIPAA guidelines. School staff and personnel, including Westford Academy, Cambridge Rindge and Latin, Lloyd G. Blanchard Middle School, Stony Brook Middle School, Walpole High School, Medford High School, Andrews Middle School, John J. McGlynn Middle School, Pollard Middle School , Needham High School, Northshore Recovery High School, Maynard High School, Millis Middle School, Millis High School, The Epiphany School, Cohasset High School, and Waltham High School staff will not have access to or receive any individual data. A Certificate of Confidentiality from the National Institutes of Health has also been obtained for this study.

College-Aged Study Component:
We aim to recruit approximately 100 older adolescent regular cannabis users who are between the ages of 18 and 25. We will preferentially recruit participants who have previously been screened and/or enrolled into a similar protocol in our laboratory (Protocol #: 2012D002985) and who have expressed interest in being re-contacted for other studies and who reported regular cannabis use on the telephone screener of Protocol #: 2012D002985 (approximate n = 100). We will describe this new study and determine their interest in participating (see telephone script). We will supplement if necessary with older adolescents from the community and will use online advertisements and flyers for recruitment (see recruitment materials).

Written Participant Consent
Participants who are deemed eligible (i.e., report regular cannabis use and are between the ages of 18-25 years) and who are interested in participating will be asked to come in to the laboratory for a study visit. At the time of such visit, informed consent will be obtained by a trained member of the study staff prior to administering any study procedures. Within the consent form is a description of collection of saliva samples for genetic analysis; participants can decline consent for DNA without penalty on participation for the rest of the project. Within the consent form is also a description of MRI, Fitbit, and ActiGraph GTX-9 procedures; participants can decline consent for scanning, use of Fitbits, and use of ActiGraph GTX-9 without penalty on participation for the rest of the project. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff during the consent process. Contact information of key study staff will be provided and participants will be informed that the co-investigators are available to answer any questions or

concerns they may have about the study. All eligible participants will be provided with a copy of their signed consent form.

Participant Withdrawal
Participation is completely voluntary and participants may stop being in the study at any time or decide not to join the study. If a participant decides not to participate, he/she will not be penalized in any way.

Confidentiality
All phases and aspects of this project will be conducted according to the Declaration of Helsinki and will comply with HIPAA regulations. The sponsors of this research will be the only individuals who will have access to data on individuals that are stripped of all unique identifiers according to HIPAA guidelines. A Certificate of Confidentiality from the National Institutes of Health has also been obtained for this study.

V. STUDY PROCEDURES

School-Aged Study Component (The Epiphany School and Cohasset, Maynard, Northshore, Needham, Millis, Medford, Walpole, Westford, Cambridge, and Waltham Public Schools; Community):

Screening

- **Children and Adolescents Recruited and Enrolled from Westford Academy, Cambridge Rindge and Latin School, Lloyd G. Blanchard Middle School, Stony Brook Middle School, Walpole High School, Medford High School, Andrews Middle School, John J. McGlynn Middle School, Millis Middle School, Millis High School, The Epiphany School, Cohasset High School, Pollard Middle School, Needham High School, Northshore Recovery High School, and Maynard High School: Passive Consent for School-Wide Screening (Phase I).** The purpose of the school-wide assessment is to tabulate basic demographic characteristics as well as quantify average rates of substance use in the school. The school-wide assessment phase will begin several days after contact is made to all parents/guardians to ensure that they have adequate time to discuss questions with MGH study staff and/or withdraw their children from the school-wide assessment should that be their preference. During the time of the school-wide assessment, MGH study staff will distribute a brief questionnaire to all students who were not opted-out by their parents/guardians in the method requested by the school principal (either electronically or in person). This questionnaire will include general demographic items as well as basic questions related to health behavior such as frequency and recency of cannabis and alcohol use. All students who are not withdrawn from this study phase by their parents/guardians and who wish to complete the questionnaire will also complete a separate form where they indicate their interest in being contacted for the active study phase and provide their contact information. MGH study staff will collect all school-wide questionnaires and contact information forms as well as the incomplete forms from uninterested students. The contact information form and the brief questionnaire will be immediately separated to protect individual confidentiality. Questionnaires will then be reviewed only by MGH study staff and classified into two groups (cannabis users and non-users) based on their responses of frequency and recency of cannabis use, yet all students who indicated a willingness to be contacted will be considered potentially eligible for the active study phase, pending receipt of written parental consent and student assent (see below). A screening log that includes a non-identifying subject ID, the date of screening, whether eligible as a cannabis user or non-user, and enrollment decision or status (see below) will be kept for all individuals screened.

- **Children and Adolescents Recruited and Enrolled from Waltham High School: Written Parental Consent for Active Study Phase Required Prior to Telephone Screening:** Students whose parents mailed back the signed consent form and completed contact sheet will be contacted via telephone and/or email by MGH study staff directly to describe the study and complete a brief telephone questionnaire that will include general demographic items as well as basic questions related to health behavior such as frequency and recency of cannabis and alcohol use. Eligible and interested participants will schedule their initial study visit with MGH staff and informed consent will be obtained directly from these students at their baseline visit. The active phase study procedures will not begin for

any participant under the age of 18 until the parental consent form is obtained. A screening log that includes a non-identifying subject ID, the date of screening, whether eligible as a cannabis user or non-user, and enrollment decision or status (see below) will be kept for all individuals screened.

- **Children and Adolescents Recruited and Enrolled from the Community: Waived Parental Consent for Telephone Screening.** In response to community advertisements, students will call the laboratory to inquire about details of the study and complete a brief telephone questionnaire that will include general demographic items as well as basic questions related to health behavior such as frequency and recency of cannabis and alcohol use. Eligible and interested participants under the age of 18 will be asked for parent/guardian contact information to coordinate obtaining written parental informed consent. Eligible and interested participants age 18 and older will schedule their initial study visit with MGH staff and informed consent will be obtained directly from these students at their baseline visit. A screening log that includes a non-identifying subject ID, the date of screening, whether eligible as a cannabis user or non-user, and enrollment decision or status (see below) will be kept for all individuals screened.

Active Study Phase (Phase II; The Epiphany School and Cohasset, Maynard, Northshore, Needham, Millis, Medford, Walpole, Westford, Cambridge, and Waltham Public Schools; Community)
Interested students under the age of 18 who provide informed assent and have a parent/guardian who provides informed consent, and students over the age of 18 who provide informed consent, will be enrolled in the active phase of the study. All participants, regardless of substance use history and group assignment (i.e., non-users; cannabis users, monitoring; cannabis users, contingency management), will complete identical study procedures. The only distinguishing factor will be the remuneration schedule, which will be detailed below.

After the school-wide assessment (for participants recruited directly at schools) conducted by MGH study staff or telephone screener (for participants recruited from the community), all participants will complete nine study visits, which will be spaced across approximately two months and, for the convenience of MGH study staff and participants, will be conducted confidentially at Westford Academy, Cambridge Rindge and Latin School, Lloyd G. Blanchard Middle School, Stony Brook Middle School, Walpole High School, Medford High School, Andrews Middle School, John J. McGlynn Middle School, Millis Middle School, Millis High School, The Epiphany School, Waltham High School, Cohasset High School, Pollard Middle School, Needham High School, Northshore Recovery High School, Maynard High School, or in the laboratory at MGH. In rare circumstances (eg. shortage of available rooms on school campus), we may request that study visits be conducted in a private space in the near-by public library. Parents of students under the age of 18 who are recruited from one of the participating schools will be notified ahead of time for any visits not conducted on school grounds. Assessments will be conducted at baseline (part I and II), and approximately 3, 4, 5, 14, 21, 28, and 56 days following the second baseline. Participants will complete cognitive tests at the second baseline and at visits approximately 5, 14, 21, 28, and 56 days following the second baseline. Urine drug tests will be completed at visits 2 through 9. Self-report questionnaires, as well as semi-structured assessments of mood and substance use will be completed at all study visits. Cannabis abstinence will be indexed by self-reported non-use and, given cannabis' long half-life, by progressively decreasing quantitative levels of 11-nor-delta-9-THC-9-carboxylic acid (THCCOOH), the primary cannabis metabolite, in urine. A cutoff level of 50 ng/ml for THCCOOH will be used to determine cannabis abstinence at 30 days.[39-42] Laboratory processing of cannabis metabolites will be conducted at Dominion Diagnostics.

At the first and second baseline visits, all cannabis using participants will be using cannabis as usual. At the end of the second baseline, half of the cannabis using participants (n=150) will be randomly assigned to 30 days of monitoring and half of the cannabis users will be randomly assigned to 30 days of contingency management (n=150). Cannabis using participants assigned to the monitoring condition will not be asked to abstain from cannabis use (but may freely do so if they wish) and will be compensated with vouchers for session attendance as will non-users. Cannabis using participants assigned to contingency management will be asked to abstain from cannabis use for one month after the second baseline and will complete a behavioral contract[43] that lists behaviors to be monitored, schedule of monitoring and contingencies to be imposed.

Contingency management participants will be reimbursed using a two-track incentive system: they will receive vouchers of progressively escalating values for both session attendance and cannabis abstinence (indexed by self-reported non-use and progressively decreasing quantitative levels of urine THCCOOH). The schedule of reimbursement for session attendance and abstinence has been reported effective in similar populations.[42] Participants are reset to the starting level when abstinence is not demonstrated. Cannabis using participants in the monitoring condition will receive vouchers of progressively escalating values for session attendance only. Non-using participants (n=100) will be assessed using identical study procedures (with the exception of being asked to change cannabis use) and will be compensated for session attendance similar to those in the cannabis monitoring condition. All compensation will be distributed between study visits. All participants will engage in a brief end-of-study debriefing visit.

A subset of cannabis using participants who meet scanning eligibility criteria (up to 10, with at least one participant selected from the monitoring and contingency management conditions), have parental consent to participate in this aspect of the protocol (if under the age of 18) or provide consent for this aspect of the protocol (if over the age of 18), will undergo an optional two-session scanning protocol which will be conducted at the Martinos Center for Biomedical Imaging. MRI visits will be conducted between baseline (part I and II; before the initiation of abstinence) and at approximately 28 days following the second baseline (prior to the removal of abstinence contingencies).

In addition, all remaining participants will be given the option to participate in an optional study component that collects sleep and activity data via a Fitbit Charge 3,a Fitbit Inspire 2, or an ActiGraph GTX-9. Participants who agree to participate will wear the watch after enrollment at Visit 1 through the final 4-week follow-up at Visit 9 (approximately 56 days after Baseline Part II). If participants demonstrate low compliance during the study period, they may be asked to participate in an extended portion of the study which uses an ActiGraph GTX-9 device. The extended period of data collection will run for two additional weeks after the final 4-week follow-up at Visit 9 (approximately 70 days after Baseline Part II).

Assessment Techniques
The order of measures will be counterbalanced across subjects to prevent test order effects or systematic effects of fatigue.

Child and Adolescent Questionnaires (N = 400): The child and adolescent questionnaire is an extensive survey on psychological, social, and behavioral factors. Construct areas include: demographics; cannabis use behavior and history of cannabis use; cannabis dependence; cannabis motives and expectancies; cannabis withdrawal; current and past use of other substance of abuse (e.g., tobacco, alcohol); family rules about substance use; parental messages about substance use; quality of family communication; peer support; social integration; exposure to risky peer networks; self-esteem; coping; depressive and anxiety symptoms; delinquent behaviors; temperament. The questionnaire is designed to be completed during the protocol visits and is estimated to take approximately 1 hour to complete. Students will be asked to complete this survey in its entirety at the baseline visit. Additionally, certain composite measures that may be sensitive to fluctuations over a 30 day period will also be completed at the remaining seven protocol visits. Such questionnaires may include items relevant to cannabis withdrawal and craving and mood. Questionnaires completed at visits occurring approximately 3, 4, 5, 14, 21, 28, and 56 days following the second baseline will take approximately 20 minutes to complete. If the student prefers, some surveys may be sent electronically via secure REDCap survey links to complete outside of study visits to reduce the length of visits. Participants will have the option to complete all surveys during visits if they choose. Participants will enter data directly into REDCap electronically and will initial and date at the end of each survey to indicate that they inputted this information. In special warranted cirumstances, participants will complete questionnaires using pen and paper and study staff will enter the data into REDCap on their behalf.

Child and Adolescent Interviews (N = 400): At the first baseline visit, participants will complete a semi-structured interview to assess for current and past psychiatric and substance use disorder diagnoses. At the first baseline, they will also participate in a 20-minute semi-structured time-line follow-back interview. The purpose of this interview is to create retrospectively a calendar of cannabis episodes as well as other

substances of abuse over the previous 90 days. To complete the calendar, MGH staff will work with children and adolescents to identify both the days when they used substances and the substances used on each day. To gather this information, staff will use a modified version of the timeline follow-back procedure that has been successfully used in other studies with child and adolescent substance users. This includes identifying important dates or events that stand out to the participant (e.g., start/end of school, family vacations, parties, dances, etc.). At the second baseline visit as well as visits occurring approximately 3, 4, 5, 14, 21, 28, and 56 days following the second baseline, students will complete this timeline follow-back interview but substance use will only be assessed in the time interval since their previous visit. For children and adolescents who do not use substances and in visits following baseline, this interview will be extremely brief.

Cognitive Testing (N = 400): We will focus on changes in verbal learning/memory, attention, working memory, and complex decision-making as some studies show differences in these domains between cannabis users and non-users.[44-45] Additionally, the neurobiological substrates typically implicated in performance on these tasks (e.g., prefrontal cortex, fronto-subcortical circuitry) undergo the most protracted development during adolescence and may therefore be most susceptible to insults from exogenous cannabinoids. We are proposing to do much of the cognitive testing with the Cambridge Neuropsychological Test Automated Battery (CANTAB). We specifically selected the CANTAB, which is a "state-of-the-art" cognitive battery, based on several criteria to address practical and methodological concerns that may arise from a longitudinal, non-laboratory study. First, the CANTAB has been validated in many populations (including substance using adolescents[46]) and normative data are available. The CANTAB is also administered on a small computerized touch screen tablet, which allows for easy portability, efficient testing of many people (essential for study feasibility), and standardized administration. Third, tests have been adapted from animal model paradigms to increase translatability of findings and tests can be analyzed based on their cognitive components to more readily define impaired and spared cognitive capacities. Next, neuroimaging studies are available that show reliance on neural circuitry implicated in cognitive functioning and addiction. Finally, the CANTAB has been validated longitudinally and offers the unique advantage of parallel forms for retest. The cognitive battery will be administered at the second baseline and visits that are approximately 5, 14, 21, 28, and 56 days following the second baseline.

Drug Testing (N = 400): At all study visits, excluding the first baseline visit, participants will provide a urine sample, which will be used qualitatively screen for cannabis use as well as other substances of abuse and quantitatively screen for amount of THC metabolites in urine.

Due to the negative impact that recent outside drug or alcohol use could have on a subject's performance in the cognitive testing and responses to questionnaires/interviews, subjects in all groups will be asked to refrain from the use of any illicit drugs or the consumption of alcohol within 24 hours of study visits. This short-term abstinence will be assessed using subject self-report at each of the visits involving cognitive testing.

Passive parental consent		**Parental/student consent/assent** **Cannabis users in CM discontinue cannabis use**										
	V0		**BL Part I (V1)**	**BL Part II (V2)**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Opt. 2-week follow-up (Fitbit/ActiGraph GTX-9 Component only)**	**Opt. MRI Scan Visits**
Fitbit Charge 3/Inspire 2			X	X	X	X	X	X	X	X	X		
ActiGraph GTX-9												X	
Fitbit ActiGraph Survey											X	X	
Screener	X												
MRI Safety Screen			X										**X**
Background Questionnaire			X										

Psychopathology Questionnaires													
ADHD—Childhood Sx Checklist			X										
ADHD—Current Sx Checklist				X						X			
Prodromal Questionnaire – PQ-B				X									
MASQ				X			X	X	X	X	X		
Personality—TIPI			X										
Aggression—BP-AQ			X										
Depression Questionnaire—CES-DC (10-19 yrs, school cohort) – Will be administered at V2 & V8				X						X			
Anxiety Questionnaire—SCARED-R (10-19 yrs, school cohort) – Will be administered at V2 & V8				X						X			
Concise Health Risk Tracking Scale (CHRT)			X	X	X	X	X	X	X	X	X		
Family Psychiatric History			X										
APSS - Lifetime			X										
APSS - Current			X							X	X		
ERS			X										
Environment Questionnaires													
Family Risk/Protective Factors			X										
Cognition Questionnaires													
Executive Functioning—BRIEF (10-18yrs, school cohort)				X						X			
Executive Functioning—BRIEF (18-25yrs, older adolescent cohort)				X						X			
Delay Discounting--MCQ				X			X			X	X		
Peer Conformity—MISS			X							X			
Impulsivity—UPPS			X										
General SU Questionnaires													
Peer Substance Use/Tolerance			X										
COVID-19 Questions			X										
Alcohol Questionnaires													
Dependence—AUDIT				X									
Motives—DMQ			X										
Marijuana Questionnaires													
Expectancies—MEEQ				X						X			
Dependence—CUDIT-R				X									
Problems—MPS				X									
Craving—MCQ-SF				X	X	X	X	X	X	X	X		
Withdrawal—CWS				X	X	X	X	X	X	X	X		

Motives—MMM				X									
Tobacco Questionnaires													
Dependence—mFTQ				X						X			
Other Questionnaires													
Sexual History			X										
Exercise – GLTEQ				X			X	X	X	X	X		
Questions About Eating Behaviors				X			X	X	X	X	X		
School Engagement Questionnaire				X			X	X	X	X	X		
School History Questionnaire			X										
Sleep—PSQI				X			X	X	X	X	X		
Puberty History			X										
Puberty Stage – Tanner Scale			X										
COVID-19 Risk Perception and Coping Questions			X										
Interviews													
MINI 7.0 Adult, MINI 7.0 Kid			X										
TLFB			X	X	X	X	X	X	X	X	X		
Debriefing Interview										X			
Cognitive Tests													
CANTAB				X			X	X	X	X	X		
WTAR (18-25yrs, older adolescents)			X										
WASI (10-19 yrs, school cohort)			X										
MRI Tasks													X
Urinanalysis Tests													
Toxicology				X	X	X	X	X	X	X	X		X
Pregnancy													X

College-Aged Study Component:

All study procedures will be identical to those proposed for the school-aged cohorts. The only exceptions to this are that: 1) all older adolescent participants will be regular cannabis users, 2) all protocol procedures will be conducted at MGH, and 3) since this group is not comprised of minors, all participants will be able to give consent to participating (i.e. no parental consent is required).

DNA Collection and Analysis (Both Cohorts)

DNA Collection (Saliva): DNA samples will be collected using Oragene (OGR-500) saliva kits. Participants may be asked to provide a second sample if a re-collect is recommended after DNA extraction (i.e. there is very little DNA in the sample). Participants are not required to provide another sample if they do not wish to do so. Once extracted samples will be transferred to long term storage until genotyping. Samples will be stored with a unique participant ID.

GWAS Genotyping: The Broad Institute will perform molecular profiling (array-based) of subject samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the physiopathology of neurological and

psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Genetic Data Protection: In addition, steps will be taken to protect confidentiality of genetic data as outlined:

1) All MGH study staff are trained to make confidentiality the first priority.
2) No genetic research data will be entered into the medical record.
3) The results of the genetic analyses will not be shared with participants, their family members or unauthorized third parties.
4) Genetic data are encoded using coded identifiers. These codes, rather than personal identifiers, are used in any analytic datasets. The code key linking coded identifiers to personal identifiers are kept in an access-restricted, password protected electronic file and are not shared with the genetics laboratories.
5) Consent forms are stored in locked cabinets apart from demographic and diagnostic data.
6) Samples and genetic data stored in the laboratory will be identified only by the code numbers and laboratory personnel will not have access to personal identifiers.
7) The most serious risk would be identification of individuals in the publicly shared database. To prevent this, computerized data files provided to other investigators will not include any of the HIPPA-defined personal identifiers. Published material will not identify subjects.

Optional MRI Protocol (Both Cohorts): The purpose of the optional MRI portion of the study is to examine within-subject changes in neural correlates of abstinence among cannabis-using children and adolescents. Therefore, only participants randomized to the contingency management or monitoring groups will be given the option to undergo 3T MRI scanning. Participants will undergo MRI scanning between baseline part I and baseline part II before the initiation of abstinence (for those randomized to the contingency management group) and at approximately one month of continuous abstinence (if randomized to the contingency management group). Each scan session will last up to two hours during which structural and functional data will be collected. Participants will be positioned in the scanner and outfitted with audio and visual presentation and response indicator equipment. Visual images and auditory stimuli will be presented using MRI compatible presentation software and hardware. Participant responses are monitored using MRI-compatible keypads, and reaction times may be recorded for subsequent analysis of timing and accuracy of task performance. Participants may undergo the scans noted below:

1. Structural MRI

For the structural imaging sessions T1-weighted sequences may be acquired. Multiple anatomical imaging sequences may be run to assess specific image quality measures. The same anatomical scans will be repeated varying a limited range of pulse sequence parameters to assess their effect on the image contrast, image artifacts and signal to noise ratio. Parameters that will be varied may include the repetition time of the MR acquisition (TR), the echo time of the acquisition (TE), and the presence of pre-acquisition inversion pulses. The above parameters will also be evaluated in pulse sequences

which acquire parameters used in the reconstruction of the MR images. The software and hardware interlocks put in place by the scanner manufacturer ensures that the range of these parameters will be maintained within the FDA's non-significant risk criteria.

2. **Functional Magnetic Resonance (fMRI)**
The scanner is outfitted with audio and visual presentation and response indicator equipment. All tasks are programmed using presentation software that is synchronized with the video synch pulse of the computer running the task. The presentation software also collects the behavioral response information. The experimental paradigms will assess activation in brain regions underlying memory, attention, inhibitory control, and risk/reward. Participants may earn points for correct answers, and those points may be converted to monetary values. The experimental paradigm will take approximately 45 minutes to complete. We will also assess resting-state functional connectivity using standard FC-MRI sequences. The entire scan will last about one hour.

Optional Fitbit/ActiGraph GTX-9 Protocol (Both Cohorts): The purpose of the optional Fitbit/ActiGraph GTX-9 portion of the study is to assess the whether cannabis abstinence impacts objective measures of sleep in school-aged adolescents. At Baseline Part I, participants who consent to this optional portion of the study (and whose parent consents if <18 years of age) will receive either a Fitbit Charge 3 or Fitbit Inspire 2 that is paired with a premade, de-identified account or an ActiGraph GTX-9. At the first visit, participants will be instructed on how to use the device, including charging and syncing. Participants will then be instructed to wear the device at all times (except when charging the device), from Baseline Part I (Visit 1) through Visit 9 (approximately 56 days after Baseline Part II). Participants will be instructed to sync their device approximately every 3-4 days. At each visit, a member of study staff will also sync the Fitbit to the Fitbit app and upload the deidentified sleep and activity data to an MGH encrypted computer via a USB cable. If participants demonstrate low compliance during the study period, they may be asked to participate in an extended portion of the study which uses an ActiGraph GTX-9 device. Participants will wear this device for 2 weeks and can earn up to $25 based on their compliance (≥ 80%).

VI. BIOSTATISTICAL ANALYSES

We will use a proportional hazards model to evaluate time to relapse as the dependent variable and potential predictors (e.g., baseline cognitive function, demographics, substance use severity, mental health) as independent variables. We will use time to relapse instead of 30-day abstinence because differentiating between early and late relapsers may increase power.

To determine whether improvements in cognitive function with abstinence will be greater after 30 days than after 4 days among individuals who quit using cannabis compared to those who do not quit and non-users, repeated measures analysis of covariance will be conducted comparing groups on each cognitive measure across the testing sessions controlling for relevant covariates and using an unspecified covariance structure. We will test whether the difference in cognition after 4 and 30 days of abstinence among those who discontinue cannabis use will be greater than the same difference among children and adolescents who do not stop using cannabis and non-users.

For longitudinal analyses aimed at better understanding the time course of cognitive change with cannabis abstinence, we will conduct mixed-effects regression models with cognitive performance as the outcome variable. Models will include both fixed effects and random effects to account for repeated assessment over time. Random effects will include intercepts, allowing for individual differences in baseline cognitive performance, and slope, allowing for individual differences in the rate of change of cognitive function across assessments. Fixed effects will include group, time since last use, amount of detectable cannabis in urine, and relevant static and time-varying covariates. Two-way interactions between time since last use and group as well as amount of detectable cannabis and group will also be included as fixed effects in the model.

Power Analysis: Test-retest properties of the primary proposed cognitive instruments repeated 1 to 8 weeks apart ranged from 0.6 to 0.75.[47] We normalized the difference that we can detect by the population standard deviation of each test to calculate the detectable “effect size.” Which range from 0.51 to 0.65 with a two-sided

alpha of 0.05 and 80% power. Dropouts will be considered to be non-abstinent for Aim 1. These results will be used to generate effect estimates specific to non-treatment seeking child and adolescent cannabis users.

VII. RISKS AND DISCOMFORTS

There are a few potential risks to individuals participating in the study.

Psychosocial, Social and Legal risks: There are no uncommon psychological, social, or legal risks associated with participation in this study. There is a slight risk that the questionnaires and interviews may contribute to temporary discomfort when participants are asked about sensitive behaviors or personal feelings (e.g., cannabis use, smoking or moods), but in our experience with similar studies this risk is very minimal. To minimize these risks, all data will be coded with unique subject identifiers to help minimize concerns of confidentiality which may decrease comfort to respond to questions and interviews truthfully. Additionally, participants from school cohorts will be reminded by MGH study staff that they may omit any questions they do not wish to answer or discontinue their participation at any time. Participants will be told by MGH study staff on the assent form that if they feel distressed after participating and wish to discuss their concerns further, they may withdraw from the study immediately. Research staff will have information on counseling options for trusted treaters in the community available to distribute to students who request such information. Additionally, we will recommend consulting with a professional mental health worker to any student who meets criteria for a mental health diagnosis (this diagnostic interview will be conducted during the baseline visit). Given that we will be meeting with participants regularly and will be administering validated mood and substance use questionnaires during each visit, we are also uniquely positioned to monitor changes in endorsement of mental health symptoms. For any participant that experiences a worsening in symptoms during study enrollment, we will share these results with him/her and will suggest that he/she seeks professional support. For any School-Aged Study Cohort participant for whom we have concerns about emotional wellbeing, we will ask him/her if we can discuss this with his/her parents to help coordinate a plan for monitoring and treatment. Finally, on the unlikely event that a participant is emotionally distressed, MGH study staff is prepared to deal with such a situation should it occur. Our team is comprised of several investigators with significant expertise in mental health issues and is well prepared to handle emergency situations: our investigators are well-trained in psychotherapeutic interventions to help process and mitigate distress and have significant experience assessing for and addressing patient safety. Field staff who collect data will be trained by a licensed psychiatrist (A. Eden Evins, MD, MPH) and licensed clinical psychologist (Randi Schuster, PhD) on identifying and responding to emotional distress in a research participant. The study will be terminated if the clinician or the research team determine that their continued participation is unsafe or not in their best interest, e.g., in circumstances where there is deterioration in their mental or physical health judged to require a change in medication or hospitalization.

Additionally, some participants enrolled in participating schools may be concerned that participating in this protocol will disclose their cannabis-using habits, particularly to school personnel. However, the only people who will know a participant's group assignment are members of the MGH research team. No information about participants will be disclosed to others including their cannabis use history, including school personnel. We will be recruiting cannabis users and non-users and all participants will undergo the same study procedures, so involvement in this study in no way reveals their involvement with cannabis.

fMRI Risks: fMRI is a minimal risk procedure. Although fMRI scanning itself is painless, subjects may experience discomfort. Some may become claustrophobic inside the magnet. Subjects may also be bothered by the beeping and hammering sounds made when the scanner is collecting measurements, and/or experience peripheral stimulation, manifested as a gentle tap or sensation of mild electric shock. Because of the high magnetic field of the fMRI scanner, individuals with pacemakers, cosmetics, or certain metallic implants in their bodies must be excluded. Each potential subject must identify these and other possible contraindications prior to fMRI scanning. Because the scanner attracts certain metals, precautions must be taken to remove metallic objects from the MRI room.

Minimization: Since some subjects may be uncomfortable in the MRI, all subjects will be able to converse with the experimenter via a microphone and speaker system, and will be able to communicate an immediate need

to come out or stop the scan via a “panic squeezeball”. All efforts will be made to make the subjects as comfortable as possible while in the scanner. A member of the study staff will explain the procedure thoroughly to the subjects prior to scanning, allowing for maximal understanding and comfort. The MRI can be stopped at any time at the subjects’ request. In addition, the scanners are equipped with an emergency button that the subject can press if necessary. A qualified M.D. will always be on site or reachable by pager in the unlikely event that an adverse event occurs. If there are any concerns about a subject in need of clinical attention, the PI will be made aware of the issue immediately and will consult with appropriate medical personnel (co-investigator: A. Eden Evins, MD) to determine appropriate steps. If we do see something that looks like a medical problem, we will ask a radiologist to review the results. If the radiologist thinks there might be a problem, we will tell the participant and parent (if under the age of 18) and help them get follow-up care.

Fitbit/ActiGraph GTX-9 Risks: Fitbits and ActiGraph GTX-9 devices used for sleep and activity data pose minimal risk and do not alter the current level of risk for the main study. A small portion of people either find the device uncomfortable or have reactions to the device or band. Alternate material Fitbit/ActiGraph GTX-9 bands will be ordered as needed.

Confidentiality and Privacy: Another potential risk to participants is breach of confidentiality, but protecting the confidentiality and integrity of our research participants is a top priority for this MGH project. MGH’s careful consent and data confidentiality procedures should greatly minimize any potential risk to participants’ privacy. Only MGH project investigators and authorized study staff will have access to raw data. An individual’s data, including his/her cannabis use habits, will not released to anyone outside of MGH authorized project staff. Confidentiality is further assured by assigning a unique identifier to each participant. There will be a restricted access master list of names and other identifying information linked to the identification number. The master list will be kept in a locked cabinet and a password-protected computer file, separate from other data, along with other materials that have participant’s name (e.g., consent forms). No identifying information is listed on questionnaires or any other materials with data on them (e.g., cognitive tests, drug tests), with the exception of participant initials at the end of questionnaires to indicate that participants completed them directly. Participants will complete self-report questionnaires directly on REDCap using a Partners encrypted device, which greatly minimizes the likelihood of confidentiality breaches during transit. Only authorized MGH project members will be allowed access to this computer. Any raw data files in electronic format will be housed in our network server at the Center for Addiction Medicine at MGH and will be password protected so that only authorized project personnel have access to them. Data collected via Fitbit uploads will also be stored on MGH password protected computers. These files will not have participant names or identifying information attached to them and no information will appear in hospital medical records.

A Certificate of Confidentiality from the National Institutes of Health has been obtained for this study. We can use this Certificate to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. We will use the Certificate to resist any demands for information that would identify participants, except in the instances of child abuse and neglect, or harm to self or others.

A. **Special Considerations for the School-Aged Cohort**: Parents and staff members at participating schools, including personnel of Westford Academy, Cambridge Rindge and Latin School, Lloyd G. Blanchard Middle School, Stony Brook Middle School, Walpole High School, Medford High School, Andrews Middle School, John J. McGlynn Middle School, Pollard Middle School, Needham High School, Northshore Recovery High School, Maynard High School, Millis Middle School, Millis High School, The Epiphany School, Cohasset High School, and Waltham High School will not be provided any information regarding study participants, including cannabis use habits, unless there is deemed risk to self or others. In the consent/assent forms, both parents and students are informed that only in emergency situations (in which an individual is at immediate risk for harm) would we release any information. Specifically, if a participant tells us that he/she has intent and/or a plan to cause harm self or other, we will tell the parents, guidance counselor (if enrolled from participating schools), and call 911. If the participant says that he/she has recurrent thoughts about harming him/herself or someone else but does not have intent or a plan to do so, we will notify the parents and other appropriate medical

or counseling personnel, including the guidance counselor (if enrolled from participating schools). Finally, if a participant discusses details about ongoing child abuse, we will report such abuse to the Department of Child and Families directly and will inform the guidance counselor (if enrolled from participating schools). If we learn about mood concerns or problematic substance use, we will provide the participant with local and trusted resources for follow-up consultation and we will ask him/her if this information can be disclosed to his/her parents to help coordinate and facilitate care. Additionally, schools that serve as research sites will not be identified and only minimal information about their characteristics will be released. Finally, when the results are published or discussed in conferences, no information will be included that would reveal an individual student's identity or the name of the school at which the research was conducted. All data will be analyzed on a group-level and not by individual participants.

We believe that staff training is one of the most important ways we can protect our participants from potential risks. Staff will participate in intensive training which will be lead by Drs. Evins (licensed psychiatrist) and Schuster (licensed clinical psychologist) before data collection begins with readings, lectures, role-playing, and group discussions. Staff members who collect data will meet with senior investigators on a weekly basis during assessment points to discuss any issues, review procedures, and conduct ongoing training on these important issues.

VIII. POTENTIAL BENEFITS

We believe that these collaborations will help engage students in meaningful and important research with immediate potential benefits to both the individual student and the larger community, provide for unique opportunities for education and outreach, and will yield valuable information that will allow schools to develop and integrate prevention programs that are custom-fit to their community needs.

Non-using participants will derive no direct benefit. Cannabis using participants may find that talking about cannabis use increases their awareness of any issues related to drug use. Additionally, this project may help several children and adolescents stop using cannabis even though they may not be seeking treatment. We will be assessing their willingness to quit throughout the study and will easily be able to connect them to resources, which will help promote longer-term abstinence. Finally, our experience with young adults participating in similar research is that they often enjoy the opportunity to interact with field staff, to engage in an interesting self-study, and to feel as if they are contributing to research on the lives of teenagers.

Information developed from this study may help researchers in the future. The expected scientific yield of the project is substantial. There is much to be learned from the project including: improved understanding of the impact of cannabis on cognitive functioning among children and adolescents, which represents a large and critical gap in the extant literature. Our aim is to quantify the time course of cognitive recovery in the early days of cannabis abstinence, which in turn, inform our understanding of cannabis' potential impact on academic functioning and will have measurable implications on policy, prevention and treatment efforts.

The greatest benefit will be to future cohorts of children and adolescents who will benefit from what is learned from this research project. Knowledge from this study is likely to directly inform development of prevention and cessation programs that are engaging and effective for children and adolescents.

IX. MONITORING QUALITY AND ASSURANCE

All participants will have direct contact information for the principal investigator and co-investigator if they have questions at any time. Drs. Evins and Schuster are responsible for the overall management of the study and will maintain regular communication with all the study staff. The principal investigator and co-investigators will meet weekly with all study investigators to review the details of data acquisition and analysis as well as any minor problems. In the event of any minor or significant adverse event, the principal investigator will be contacted immediately. The principal investigator is responsible for the generation of summary reports documenting this process and outcomes which will be included in the Continuing Review reports to the IRB.

Serious adverse events are not expected because of study procedures. Should one occur, it will be reported by telephone or email by the principal investigator to the Partners IRB per current PHRC Adverse Event Reporting Policy. All adverse events (if not serious) will be reported in writing to the Partners Human Research Committee. All information regarding experimental subjects will be kept in the offices of the principal or co-investigator. All data will be identified by a unique code number.

X. PARTICIPANT COMPENSATION

All participants will be paid by vouchers (e.g., iTunes, Amazon, local merchants) or reloadable cards between study visits for their participation. The level of compensation is deemed appropriate given the time commitment. Reloadable cards will be managed by CT (Clinical Trials) Payer. CT Payer is a secure web-based platform that facilitates “HIPAA & HITECH safe” clinical trial and study-related payments onto prepaid reloadable MasterCards. Unlike payment systems offered by banks and third-party payment providers, CT Payer does not collect any protected health information from research participants.

Voucher-based contingency management participants will be reimbursed using a two-track incentive system: they will receive vouchers of progressively escalating values for both session attendance and cannabis abstinence (indexed by self-reported non-use and progressively decreasing quantitative levels of urine THCCOOH). The schedule of reimbursement for session attendance and abstinence has been reported effective in similar populations. Participants are reset to the starting level when abstinence is not demonstrated. Cannabis using participants in the monitoring condition will receive vouchers of progressively escalating values for session attendance only. Non-using participants (n=100) will be assessed using identical study procedures (with the exception of being asked to change cannabis use) and will be compensated for session attendance similar to those in the cannabis monitoring condition. All compensation (monitoring: attendance vouchers; contingency management: attendance and abstinence vouchers; non-users: attendance vouchers) will be distributed between study visits. The table below details the maximum potential earnings; however, the total amount earned will depend on the number of sessions attended, and also for evidenced cannabis abstinence for those in the contingency management conditions.

		Non-Users	Cannabis Users					
			CM		Monitoring		Optional Study Components	
Visit Number		Attendance	Attendance	Abstinence	Attendance	Abstinence	Fitbit Compliance	MRI Scans
0	School-Wide Assessment/Screening	$0	$0	$0	$0	$0	$0	$0
1	Baseline Part I	$10	$10	--	$10		--	--
2	Baseline Part II	$15	$10	--	$15	N/A	$10	$40
3	3 days	$20	$10	$15	$20	N/A	--	--
4	4 days	$25	$10	$30	$25	N/A	--	--
5	1 week	$30	$10	$45	$30	N/A	$10	--
6	2 weeks	$35	$10	$60	$35	N/A	$10	--
7	3 weeks	$40	$10	$75	$40	N/A	$10	--
8	4 weeks	$45	$10	$90	$45	N/A	$10	$40
9	4-week follow-up	$50	$10 +$15 for completing	--	$50	N/A	$10	--
	Opt. 2-week follow-up (Fitbit/ActiGrap						$25	

h GTX-9 Component)							
Max Subtotal	$270	$105	$315	$270	N/A	$85	$80
Max Total	$270	$420		$270			

The subset of eligible cannabis-using participants who choose to undergo scanning procedures will be paid an additional $40 for each scan.

Participants will earn $10 for each of the six study intervals (weekly for visits 1-8, monthly for visits 8-9) during which they wear their Fitbit with 80% compliance. If participants demonstrate low compliance during the study period, they may be asked to participate in an extended portion of the study which uses an ActiGraph GTX-9 device. Participants will wear this device for 2 weeks and can earn up to $25 based on their compliance (≥ 80%). Payments will be made at the study completion. If a Fitbit device is lost or not returned, 20% of the total earned for this optional portion of the study will be deducted.

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