Title: Motivational Interviewing and Neuroimaging with Adolescents (MINA)
Document type: Study Protocol and Statistical Analysis Plan
NCT: NCT03367858
Document date: 10/3/18 (approved concurrent with consent)
(disregard "Template" footer; that is for the IRB document template)

Minimal Risk Protocol Template

1) Protocol Title

Motivational Interviewing and Neuroimaging with Adolescents (MINA)

2) Objectives

Alcohol is the most abused substance by adolescents (CDC 2012). The majority of American youth (79%) have consumed at least one drink by age 19. Approximately one third of American youth engage in binge drinking, a high-risk pattern of consumption directly implicated in the incidence of accidents and unintentional injuries, the leading cause of mortality for American youth (Blum & Quershi 2011).

In the minority-majority state of New Mexico (>60% racial/ethnic minority), rates of youth binge drinking surpass national averages (CDC 2012). This is particularly concerning because most youth do not seek, receive (e.g., Garland et al 2005), or complete indicated alcohol treatment (Alegria et al 2011). Thus, we need to find brief, effective interventions if we are to prevent youth from continuing on a trajectory of alcohol use and related consequences into adulthood (e.g., Grant & Dawson 1997).

Many widely-used, brief alcohol treatments, including motivational interviewing (MI; Miller & Rollnick 2013), have gained empirical support for reducing alcohol use (Hettema et al 2005, Lundahl et al 2010). MI has some of the strongest outcomes for adolescent substance use more broadly (Dennis et al 2004), as well as within the youth alcohol treatment more specifically (Cronce & Larimer 2011). While MI shows quite a bit of promise, effect sizes with adolescents suggest that there is still some room for improvement (Jensen et al 2011).

In order to strengthen treatment response for this age group, **NIAAA PAR-14-051** is encouraging "*…translational research [to] identify potential neurobiological …processes that….mediate the direct link between specific 'active ingredients' and alcohol use treatment outcomes."* Following this call, translational studies integrating brain-based and behavioral components are emerging (Feldstein Ewing & Chung 2013). However, only a handful of teams, including our own, has the hands-on experience and expertise to examine this synergistic relationship. Notably, PI Feldstein Ewing is the one of the leading experts in this line of work.

This proposal directly builds upon her innovative line of theoretical and empirical studies evaluating within-session factors, neurobiological responses, and subsequent behavior change (Feldstein Ewing et al 2011a, Feldstein Ewing et al 2011b, Feldstein Ewing et al 2013c, Feldstein Ewing et al 2012a, Feldstein Ewing et al under review-c). Responding to NIAAA PAR-14-051, we will use functional magnetic resonance imaging (fMRI) to evaluate how neural (BOLD) response mediates the link between salient within session active ingredients (therapist behaviors) and adolescents' treatment outcomes (problem drinking).

This study will catalyze movement in the field of adolescent alcohol treatment in several ways. First, it will establish how salient active ingredients within an empirically-supported alcohol treatment initiates neurocognitive changes. Second, it will determine how that neurocognitive response relates to both proximal and distal behavior change. Third, and most importantly, this study will form critical groundwork to pave the way for new translational studies in adolescent addiction.

To achieve these aims, we will enroll **243** adolescent binge drinkers (ages 14-19) in this alcohol treatment (2 x 1-hour sessions of MI). We will examine youths' brain response (BOLD response) to salient within-session active ingredients (therapist language), and examine how that BOLD response predicts proximal (3- and 6-month) and distal (12- month) behavior change (problem drinking). These data will facilitate our examination of how brain-based factors (BOLD response) mediate youth treatment outcomes. These data are critical to guiding and improving behavioral treatment programming for binge-drinking adolescents.

Aim 1: Evaluate how therapist language is associated with youth brain-based and behavior changes.

● Hypothesis 1: Based on our preliminary data, we hypothesize that MI-consistent therapist behaviors (e.g., reflections) will be associated with greater BOLD response in the medial frontal gyrus (MFG), inferior frontal gyrus (IFG), and insula, as compared with MI-inconsistent therapist behaviors (e.g., confront).

● Hypothesis 2: Greater BOLD response (MFG, IFG, insula) will be associated with greater proximal (3-month, 6-month) and distal (12-month) reductions in adolescent problem drinking (frequency of binge drinking, alcohol related problems).

Aim 2: Evaluate whether brain activity mediates therapist language and youth behavior change.

● Hypothesis 3: BOLD response (MFG, IFG, insula) will mediate the relationship between MI-consistent therapist behaviors (e.g., reflections) and proximal and distal reductions in adolescent problem drinking.

3) Background

Adolescence is a unique developmental period. Within the United States (U.S.), adolescents are encouraged to begin taking responsibility for more "adult" decisions (e.g., driving, dating, unsupervised social events, which often include alcohol). Yet, the brain regions responsible for weighing consequences, judging costs and benefits, and self-regulating, are still very much in development during this period (Luna et al 2010). This matters because recent human and animal studies suggest that alcohol use during adolescence may be neurotoxic (Feldstein Ewing et al under review-b, Jacobus & Tapert 2013, Spear 2013). Meaning drinking, particularly in high-risk patterns like binge drinking, may negatively influence youths' neurodevelopmental trajectory, subsequently placing youth at greater risk for sustained patterns of alcohol use and related problems as they transition into adulthood (e.g., Luciana et al 2013, Squeglia et al 2012).

What makes the problem especially challenging. Not only do youth exhibit high levels of binge drinking (CDC 2012), binge drinking youth are unlikely to seek, receive, or complete indicated alcohol treatment (Alegria et al 2011, SAMSHA 2011). Thus, improving the effectiveness, particularly for brief, behavioral alcohol treatments is integral to decreasing binge drinking and related harms for this age group. While existing alcohol treatments (including MI) show promise (e.g., Deas 2008, Larimer & Cronce 2007), they are not universally effective. Furthermore, despite being one of the stronger evidence-based alcohol treatments for this age group (SAMHSA; http://www.nrepp.samhsa.gov/), effect sizes for MI with adolescents suggests that there is still some room for improvement, particularly with respect to how MI might influence long-term (distal, >6 month) youth treatment outcomes (Jensen et al 2011, Larimer & Cronce 2007).

One reason for the slightly lower adolescent MI effect sizes may be due to inherent differences in adolescent and adult neural functioning. To that end, the adolescent brain appears to have unique structure and function during this developmental period (Blakemore & Choudhury 2006, Giedd 2004, Spear 2000). Our own work supports this, as we found evidence for distinctly different patterns of neural response underlying MI response between adolescent and adult substance users (Feldstein Ewing et al 2011b, Feldstein Ewing et al 2013b). However, we have only begun this line of research. Critical work needs to be done to truly understand the adolescent brain, and how it may respond in the context of indicated psychosocial alcohol interventions.

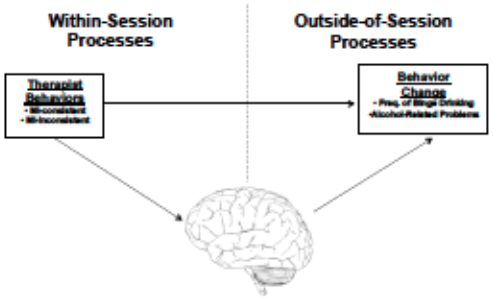

Figure 1: Working Theoretical Model

How this approach challenges the standard paradigm. NIAAA is dedicated to understanding salient mechanisms of change and using that data to guide improvements in adolescent alcohol treatment. One avenue that has been underexplored

is the integration of biology and behavior (NIAAA 2008). While research has supported the bidirectional relationship between biology and behavior in the development, progression, and maintenance of substance use (Bechara 2005, Volkow & Li 2004), few behavioral researchers have evaluated the role of basic biological factors (i.e., brain response) in psychosocial treatment efficacy. In addition, basic biological investigators tend to focus exclusively on biological factors rather than evaluate how psychosocial interventions may precipitate biological changes. Ultimately, innovative translational studies are vital to elucidating how neurobiological and behavioral factors interact to catalyze the initiation and maintenance of behavior change. However, few teams have tested these translational questions (Feldstein Ewing & Chung 2013). Consistent with **NIAAA PAR-14-051**, we believe that the key to developing more successful treatments for binge drinking adolescents is through applying a translational perspective to understand basic brain factors that influence youths' treatment response.

Our work builds upon the strong legacy of mechanisms of change research in MI (Miller & Rose 2010). Within this work, Dr. Theresa Moyers and Co-I Houck pioneered the examination of MI active ingredients by deconstructing within-session client and therapist verbalizations. A number of studies, including their own, found that within-session client statements (e.g., client statements in favor of change; or "change talk"; CT; "*I've been blacking out more when I've been drinking*"), and/or aspects of CT, predicted post-treatment behavior change (reductions in substance use) (e.g., Amrhein et al 2003, Baer et al 2008, Gaume et al 2013). While many studies have focused on the client side of this relationship, therapist behaviors are clearly also critically important (Barnett et al in press). This makes sense, as MI ideally involves a dynamic exchange between client and therapist. Indeed, behavioral studies have found that client verbalizations are contingent on therapist statements. Following the seminal work of Patterson and Forgatch (1985), Glynn and Moyers (2010) found that when therapists utilized MI-consistent behaviors (e.g., reflections *"You're worried about your drinking."*) young substance users provided significantly more CT, contrasted with when therapists utilized non-MI consistent statements. Ultimately, these studies suggest a strong relationship (a causal chain) between MI-consistent therapist behaviors (e.g., reflections), subsequent client speech (client CT), and distal (up to 15 month) substance use reductions (Morgenstern et al 2012, Moyers & Martin 2006, Moyers et al 2007).

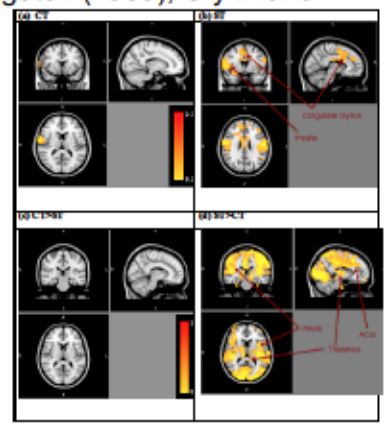

Figure 2: BOLD Activation during CT and ST with Adults with Alcohol Dependence

Forming the foundation for the PI's working theoretical model (Feldstein Ewing et al 2011a) (**see Figure 1**), our lab's data show a brain-based relationship between within-session client language and post-treatment behavior change. As the first step in this line of research, the PI extracted client's within-session statements from an individual MI for adults with alcohol use disorders (AUDs; see Week 1 MI). Specifically, we pulled 5 unique within-session client verbalizations in favor of change (CT), and 5 unique within-session client verbalizations in favor of maintaining the status quo (Sustain Talk; ST; *"Drinking is fun."*). We then represented those statements back to the clients (by sight and sound) within an fMRI paradigm (see fMRI task). In line with the behavioral research, we found brain-based support for the salience of client language. Specifically, we found significant activation of striatal (reward) areas when adults were presented with their within-session ST, but no activation when they were presented with their within-session CT (2011b) (see **Figure 2**).

The PI then evaluated the neural substrates of client CT with cannabis-abusing adolescents (Feldstein Ewing et al 2013b). With the same MI intervention proposed for this study, adolescent cannabis users significantly changed their cannabis use [proximal (1-month) reductions]. However, in contrast to the adults, youth showed a different pattern of neural activation, with greater BOLD response during CT rather than ST, and in areas important to self-awareness (e.g., insula, medial frontal gyrus; MFG) rather than reward (Feldstein Ewing et al 2013b). These data support the efficacy of this brief, MI intervention to catalyze youth behavior change, and suggest that a unique pattern of neural responses may subserve MI response within this developmental period.

The next logical question was to for us to understand what features of CT make it relevant for brain response. We were curious whether repeating (even parroting) language that "sounds like" change language would activate relevant neural substrates, or whether change language needed to

be spontaneously generated by the client, within a true, therapeutic context (e.g., during an MI session) to catalyze neural response. Investigating this question, the PI found that young binge drinkers who naturally generated their change language in the context of an MI session showed significantly greater brain response than youth who repeated an ecologically-valid, but pre-provided script of change language (see Preliminary Studies). These data indicate the importance of engaging in a true therapeutic exchange; parallel levels of neural activation were not observed in the absence of this therapeutic interchange.

Despite this foundational work, we still do not know how within-session mechanisms may meditate treatment response for adolescent binge drinkers. This is particularly important, given their potential neurodevelopmentally-specific response. Thus, we will employ a highly-innovative, neurobiological perspective to understand what happens to adolescents' brains during MI, and how that neural response may mediate the relationship between salient active ingredients (therapist language) and proximal (short-term) and distal (long-term) real-world adolescent drinking behavior after they leave the therapist's office.

Significance.

Why testing this hypothesis or solving this problem is important. Despite the critical role of therapists within the MI relationship, only a handful of published studies have investigated the role of therapist factors in adolescent treatment outcome (e.g., Feldstein & Forcehimes 2007, Resko et al 2012, Smith et al 2009). Even fewer published studies have evaluated youths' within-session brain response in the context of psychosocial addictions treatment (Feldstein Ewing & Chung 2013). This is critical because behavioral-only studies may be unable to detect subtle, but highly important clinical changes (Hutchison 2010).

Thus, if we can use a distinctly sensitive method (neuroimaging) to detect salient brain-based responses that are likely to escape other methods of detection, we can use that information to guide improvements in adolescent alcohol treatment development. For example, if we find that youth BOLD response in the insula mediates the relationship between therapist behaviors and proximal (6-month) and distal (12-month) youth drinking outcomes, then we know the following. First, we know which treatment mechanisms need to be strengthened to bolster behavior change. More concretely, following our prior work in MI treatment development (Feldstein Ewing et al 2012b), based on these data, we would modify our adolescent MI treatment protocol to dedicate more time to working with youth on skills associated with insular response (e.g., self-reflection and decision making skills; such as through "what if" scenarios) (Feldstein Ewing et al 2008), which the PI would also share with the adolescent treatment community via published report and conference presentations (see Biosketch). Second, with these data, we would know which youth brain systems should be targeted as mechanisms of change with both the adolescent addictions neuroscience and treatment literatures (Feldstein Ewing et al 2011a). This is particularly important, given the emergent, but still relatively sparse literature on how binge drinking affects the adolescent brain (Feldstein Ewing et al under review-b). Third, we suggest that it would be impractical to use neuroimaging in real-world treatment contexts; thus, we do not suggest that all youth should be imaged before receiving outpatient treatment. Rather, in line with the **NIAAA PAR-14-051**, at this time, this field needs a creative and innovative approach to accelerate discovery; it is precisely the inclusion of the neurocognitive component that makes this study responsive to NIAAA's PAR-14-051. If we can better understand how the adolescent brain responds to therapist language, and how that activation mediates treatment outcomes, this would represent an enormous scientific leap. As evidenced by years of incremental gains (Feldstein Ewing & Chung 2013), this type of giant stride simply has not been (and arguably may not be) accomplished in behavior-only investigations. Understanding these mechanisms among youth is important not only for binge drinking interventions, but is *highly* applicable to other studies, as the neural mechanisms of risk behavior appear to be consistent across substances of abuse (Bechara 2005).

Innovation.

Why this Approach is Novel and Important. (1) Clinical alcohol treatment. Despite the prevalence of adolescent binge drinking (79%) (CDC 2012), we still do not know what clinical steps maximize youth behavior change (e.g., "*How can we get you to drink less when you're at a party?*"). Adolescent binge drinking is difficult to treat, and youth alcohol counselors often request clinical directives to guide their work. Concretely, when the PI presented how adolescent cannabis users'

client language (CT) influenced the brain and subsequent treatment outcomes (Feldstein Ewing et al 2013b) (American/Canadian Academies of Child and Adolescent Psychiatry; 2011), the audience of child/adolescent psychiatrists rated the PI's talk to be the most practically useful presentation, as her data showed that clinical time focused on eliciting youth CT was time well spent; these data are particularly important in clinical contexts where providers may only have a brief time with their young patients. **(2)** The developmental neuroscience. At this time, the neural substrates of alcohol treatment response in youth are unknown. This study will directly address this gap by determining which brain areas are critical in youths' response (therapist language), and how they mediate treatment outcomes (e.g., *Is it a pattern of mesocorticolimbic activation, as observed in adult addiction? Is it more insular, as observed across other brain-based evaluations of MI? Or does it parallel the emotion regulation literature?)* Uniquely, our study will directly link developmental neuroscience with real-world behavior by addressing the strength and endurance of BOLD response to youths' actual, real-world drinking after they leave our therapists' office. **(3)** The fMRI task. Some of our colleagues argue that the most novel aspect of this project is the task itself. Looking at how therapist's language influences neurocognitive processes is innovative. Also, using within-session, rather than generic, therapist language is not only unique, but directly controls for the impact of individual variability. **(4)** Ultimately, this program of research is directly in line with NIMH's RDoC, which aims to "*translate rapid progress in basic neurobiological and behavioral research to an improved integrative understanding…and… development of new and/or optimally matched treatments...*"

The full breadth and magnitude of the project's potential impact on science and/or health. Given the emerging work suggesting that therapist language (MI-consistent language) is integral in driving positive MI outcomes (Gaume et al 2010, Gaume et al 2008, Moyers et al 2009), the missing data on how therapist language impacts youth outcomes, along with distal (>6 month) behavior change in youth has impeded an in-depth understanding of MI with binge-drinking youth (Jensen et al 2011, Larimer & Cronce 2007). Based on our prior work (Feldstein Ewing et al 2013b), the next critical step involves using a highly-sensitive, developmental neuroscience approach to evaluate the neural substrates of this therapeutic mechanism with youth, and determining how that brain response mediates behavior change. These data are critical to strengthening clinical intervention approaches and treatment outcomes for binge-drinking youth.

Any of these goals might be innovative enough to stand alone as an R01 proposal. The further innovation is their integration; we have the resources and experience to successfully evaluate developmental neuroscience factors (brain-based activity) in the context of adolescent alcohol treatment. There are few places with the facilities, equipment, and personnel to conduct this type of translational work. The established relationships between the investigative team facilitates this effort. To that end, the accessibility of the 3T MRI suite at the OHSU, in combination with our working relationship with the public allows us to assess neurocognitive function with real world (rather than self-selected) adolescent binge drinkers, providing a highly representative group of youth. Importantly, this is a population that is normally very difficult to reach and to involve in basic neuroscience work. Furthermore, the synergy and complementary experience of this collaborative team, offers expertise across translational evaluations of MI with adolescents (PI Feldstein Ewing), examinations of client language (Co-I Houck), brain-based substrates of alcohol use disorders (Co-I Claus), and cutting-edge approaches in addictions neuroscience (Co-I Filbey); this team has published together extensively, providing support for this project's success (see Biosketches).

4) Study Design

5) Study Population

a) Number of Subjects

We will need 243 binge drinking adolescents to successfully complete all study procedures. In our other studies, we have had to screen and enroll twice that number in order to reach a

sample of eligible youth. Thus, we anticipate screening/enrolling a potential **500 youth** to generate the 243 youth who complete research procedures.

b) Inclusion and Exclusion Criteria

Participants. We anticipate screening 500 unique binge drinking youth. The approach for this study follows Dr. Feldstein Ewing's prior NIH-funded work with the target population and is purposefully broad to maximize generalizability of study outcomes. Following our successful prior work in recruiting from community samples of substance-users, we will recruit adolescent binge drinkers via community based general media outlets (e.g., print, radio, internet) in the greater Portland metropolitan area. Examples of community based recruitment include advertising the study participation opportunity on undergraduate college and university "human subjects pool" websites (e.g., the University of Portland's SONA system), speaking with high school and college classes about the brain and related research participation opportunities, and recruiting at the OMSI Brain Fair.

We will also recruit adolescent binge drinkers through local juvenile justice departments (e.g., the Multnomah County Department of Community Justice (DCJ), Washington County Juvenile Department). These community-based youth may or may not be on probation and/or receiving services (e.g., family counseling). However, none of them will be incarcerated, detained, or otherwise mandated to reside in a residential facility. Individuals in a mandated residential setting, on parole, and/or participating in an electronic monitoring program (e.g., wearing an ankle bracelet) will not be eligible to participate. If any of the participants from community or justice department recruitment become incarcerated, on parole, or part of an electronic monitoring program during the duration of the study, then their participation in the study will be discontinued. We will recruit from the justice departments by disseminating information about study participation opportunities through flyers and brochures, which may in turn be disseminated by justice department staff. The justice departments will also provide sign-up sheets to youth who express interest in study participation to our research group, at which point we will follow up with interested youth as detailed below.

Phone Screen. Interested youth will call into our program line, and will be evaluated by our trained research assistant (RA) over the phone using our established phone screen. Youth referred by other research or community groups (such as the justice departments) will be contacted by an RA to receive more information about participation opportunities and to complete the phone screen if interested. During screening, potential participants will be informed of the general procedures for the study, and if interested, will answer several questions to establish potential eligibility.

For inclusion, youth must : **(1)** be aged 14-19, and complete the entire study before turning 21 **(2)** have not participated in any of the PI's prior or current studies, **(3)** be currently binge drinking (defined as 3+ drinks per drinking occasion for girls, and 4+ drinks per drinking occasion for boys; with a minimum of 1 binge drinking event during the past two months, with enrollment priority going to those who are heavier drinkers, e.g., $\geq$3 binge drinking events in the past month) (Feldstein Ewing et al 2013a), (**4**) have breath alcohol level of 0 before participating in all study components, **(5)** have not used recreational drugs, including prescription medications used without a prescription and/or used in a way counter to the intended dose/use, more than 3 times (total; doesn't have to be more than three uses of a single substance) in the past month (exceptions are marijuana, tobacco, and e-cigarette products, which are permitted due to high comorbidity with alcohol use) **(6)** agree to be contacted to participate for 3-, 6-, and 12-month follow-ups, **(7)** for youth ages $\leq$17 years: informed consent of a parent or legal guardian; and **(8)** all youth: personal informed assent/consent.

With respect to the fMRI component, we have attempted to maintain tight control over factors that may increase error variability and that maximize protection for our participants. Thus, our exclusion criteria are: **(1)** history of brain injury or neurological diagnoses (including loss of consciousness >2 minutes), **(2)** currently taking psychotropic medications (e.g., neuroleptics, anticonvulsants), **(3)** current psychotic disorder, **(4)** neurodevelopmental disorder, **(5)** pregnancy (as self-reported or tested immediately prior to scans), **(6)** fMRI contra-indications (e.g., non-removable metal implants, braces, claustrophobia), and **(7)** left-handedness.

c) Vulnerable Populations

Minors. Minors are considered a special population because their age may restrict their ability to give independent informed consent. To minimize the possibility of coercion or undue influence, we will take several precautions. Minors will be given the opportunity to ask questions and discuss enrollment with staff members and their family. We will obtain informed consent from legal guardians, but will also describe the study to both legal guardians and minors. We will also require informed assent from the minors. Signing the assent will indicate that the youth is willing to participate in the study. Minors will not participate if they do not assent to participate, even if a legal guardian has consented.

d) Setting

Once the consent has been obtained, youth will be scheduled to participate in the next available session. As with the PI's prior studies, adolescents with documented assent and consent will organize their own transport to and from OHSU for Session 1 (1-2 weeks following eligibility screening), Session 2 (1 week after the first session), and the 3-month follow up (3 months after the second session). Research staff may provide assistance with transportation in the form of bus fare or similar methods to minimize the transportation burden on participants.

Consistent with the PI's current NIH-funded research, 6- and 12-month follow-ups can be completed at a location convenient for youth (e.g., OHSU, local community center) if the youth does not have reliable access to the internet, but will otherwise be offered as a combination phone and REDCap questionnaire battery for participant convenience.

e) Recruitment Methods

The recruitment approach for this study follows Dr. Feldstein Ewing's prior NIH-funded work with the target population and is purposefully broad to maximize generalizability of study outcomes. Following our successful prior work in recruiting from community and justice-involved samples of substance users, we will recruit adolescent binge drinkers via community-based general media outlets (e.g., print, internet) in the greater Portland metropolitan area and through flyer and brochure dissemination and interest-based referrals through the justice departments. Ads will be submitted to the IRB prior to use.

Phone Screen. Interested individuals will call into our program line, and will be evaluated by our trained research assistant (RA) over the phone using our established phone screen. Youth referred by other research or community groups will be contacted by an RA to receive more information about participation opportunities and to complete the phone screen if interested. During screening, potential participants will be informed of the general procedures for the study, and will answer several questions regarding alcohol and other substance use (e.g., how often do you use alcohol?), contra-indications for participating in an MRI study (e.g., do you have any medical implants?, have you ever welded?), and head injury history (e.g., have you ever lost consciousness?). Individuals will be informed that university researchers are developing

intervention programs, and thus a number of individual difference measures including brain imaging and genetic samples in the form of saliva will be collected. Individuals are told that this program discusses sensitive topics such as alcohol use and other risky health behaviors. All procedures will be carefully explained to potential participants. Eligible participants are invited in for the first available appointment.

Participant Incentives. Consistent with our prior NIH-approved work with youth, we will compensate youth in cash for their participation for in-person visits, and with gift cards for phone/REDCap visits (so that study staff do not need to mail cash). Youth will receive $30 for Session 1, $35 for Session 2, $40 for the 3-month, $45 for 6-month, and $55 for the 12-month follow-up. The participant or their parent will be provided an additional $15 for each of the first three sessions to offset transportation costs for a possible total of $250. Youth who do not complete the study will receive compensation for the sessions they completed, and will receive full session compensation for any partially completed session (for example, if participant was unable to complete a scan for some reason, the participant would still receive full payment for that scan visit).

f) Consent Process

Prior to beginning any study procedures (both during the phone screen and reiterated in person), the trained RAs will inform adolescents (and for youth age 17 and under, also their parents/guardians) that researchers at OHSU are trying to improve our understanding of adolescent health behavior and related consequences, and that their participation will help us develop better programs to help teenagers like them stay healthy. Adolescents will be told that some of the questionnaires will ask questions about sensitive topics, such as about alcohol use behaviors (which is illegal for everyone under the age of 21) and sexual activity. They will also be informed that the researchers are interested in understanding how health behaviors affect the body and the brain, thus, a number of measures, including brain imaging, saliva, their thoughts on alcohol use, and other health risk and related behavior, will be collected. All procedures will be fully explained. The staff member will be explicit that participation is completely voluntary, meaning that youth can decide to opt out of the research protocol at any time they wish without repercussion, and that opting out does not affect their involvement with any community or justice programs in which they may be involved.

Adolescent and parent consent will be obtained, but adolescents will have the opportunity to speak with study staff about the study details without a parent present before signing the consent form. This is to diminish discomfort that adolescents might feel in being asked to participate when their parents are present, as asking them to agree to participate in front of their parents might not allow them to ask important questions about the study without violating their privacy.

If the adolescent agrees to participate, the RAs will seek OHSU-approved informed (written) assent from the adolescents, as well as informed telephone consent from parents/guardians (for youth ages 17 and under) prior to their commencement of Session 1. Minors will not participate if they do not assent to participate, even if a legal guardian has consented. If a minor turns 18 during the course of the study, then they will be asked to consent for themselves by re-signing the consent form as an adult.

Once a young person (under age 18) expresses interest and signs the informed assent, the research staff will contact the parent/guardian by phone, explain all aspects of the study, read the consent form verbatim, obtain verbal consent over the phone, and answer any questions that the parent or guardian has. Following previously successful procedures to verify the parents' identity over the phone, we first ask if the "parent or guardian of (insert adolescent's name) is home." Once that person is brought to the phone or if that person identifies him/herself

as the parent/guardian, we ask them to please state their full name. If the name given is not the same as that given to us by the adolescent, we thank them for their time and do not proceed with the consent. These conversations will be tape-recorded, logged, and kept for proof of consent. A copy of the consent form signed by the child will then be mailed to the parent or guardian for their records. We place the highest priority on parents/guardians being completely informed about what their child is being asked to do, and on making sure that we are indeed getting consent from a parent or legal guardian. We have tried other methods of obtaining consent (e.g., mailing consent forms home) and have either not received any response, or more importantly, have received consents of questionable validity. Further, mailing of consent information does not allow parents/guardians to ask detailed questions that they may have about the research prior to consenting. In the 10 years that the PI and colleagues have conducted research with adolescents, we have found phone consent to be the most reliable way to assure that we obtain fully informed consent with parents/guardians. During these 10 years of using phone consent, we have never had an adverse event related to consent. In fact, we have found that these conversations allow us to open the lines of communication between research staff and parents/guardians.

Of note: we have found in our prior work, phone consent has been demonstrated to be an ethical solution to the dilemma of acquiring consent from parents of high-risk adolescents. Phone consent facilitates the opportunity for adolescents, who may not otherwise be able, to participate in behavioral risk interventions (e.g., Schmiege et al., 2009). This study will not proceed without documented (written) assent from adolescents and documented (audio-recorded) telephone consent from parents/guardians. Informed written and phone consents will be stored apart from the raw data.

As an alternative to consenting by phone, research staff will offer youth and their parent/guardian the opportunity to review and complete the assent/consent forms through email via REDCap. This option is offered to increase the accessibility of the assent/consent process. Electronic versions of assent/consent forms will have the exact same text as the written versions mailed to the parent/guardian and reviewed with prospective participants and parent/guardians over the phone. Once the electronic versions have been received by the youth and parent/guardian, a phone call will be made by study staff to carefully review the content of the forms like the audio recorded consenting procedure described previously. If the youth and/or parent/guardian chooses to sign the electronic consents, they will have the option to opt out of the phone consultation. Research staff will note whether informed assent/consent was obtained in person, by phone, or electronically, and will include the opt-out form if applicable. If the youth and parent/guardian assent/consent to participate using the REDCap electronic forms, the assent/consent forms can be returned to study staff electronically through the secure REDCap system.

For parent/guardians requesting to consent through email but unable or unwilling to navigate the REDCap system, staff will send a PDF of the full consent form to the parent/guardian's preferred email address. The email will describe how to complete the form, and request that the parent/guardian call lab staff upon receipt with questions and concerns. The email will explicitly state that it the parent/guardian's right to receive a consent review by phone to ensure they understand the key points. Parent/guardians will have the option to return the completed signature page by email, or to send it with their child to their child's first study visit, if the parent is not accompanying the youth to OHSU. See the **Parent Consent Email Template** for exact wording of the email.

If a parent is accompanying their child to the first study visit, the parent can consent in person before the youth begins Session 1.

At each point of data collection, research staff will reiterate the voluntary nature of all aspects of the study (behavioral, neuroimaging, saliva sampling), and participants' right to refuse to answer any questions, and cease participation in any aspect of the study at any time without any type of recrimination.

6) Procedures

Session 1 components.
Behavioral Assessment. To improve accessibility, all Session 1 components will be delivered at OHSU in a confidential room dedicated to our team for this purpose. The trained RA will conduct the behavioral assessment using Audio Computer-Assisted Self-Interviewing (ACASI) on an individual laptop. ACASI has proven to be a reliable way to obtain survey data assessing health risk behaviors (Williams et al 2000). ACASI technology allows survey questions to be displayed on a laptop computer screen while respondents hear the spoken text over headphones. A saliva sample will be collected during this time for DNA banking.

Primary individual difference measures (reference the Measures.list document for additional detail as to when each measure is administered). We will utilize the interviewer-administered **Time-Line Follow-Back** (TLFB; Sobell & Sobell 1992), a calendar-based measure which provides quantity and frequency of all substance use during the past 30 days (including our target, number of binge drinking days). This measure will also provide rates of co-occurring tobacco, marijuana, and other drug use, and co-occurring sexual behaviors. Our problem drinking measures follow the PI's prior NIAAA-funded work in this area and is comprised of two variables: past month binge drinking days and past month alcohol-related problems. Our **Demographic** questionnaire collects information regarding age, gender, race/ethnicity, pubertal status, education and occupation/income, and parent education/family income. The **Big Five Inventory** (John et al., 2009) will be used to assess personality. The **Childhood Trauma Questionnaire** (Bernstein et al., 1997) will be used to assess trauma history. As a measure of baseline psychopathology and related symptomatology, we will utilize the **Diagnostic Interview Schedule for Children** (DISC) **Predictive Scales (DPS)**. We capture additional information regarding risky behaviors that often co-occur with substance use using the **Arrest and Recidivism History Questionnaire** (modified from a previous study). Substance use within the family, including parents, guardians, and siblings will be obtained using the **Family Substance Use** measure (generated for previous study). We will assess parental monitoring and sources of parental knowledge with the **Parental Monitoring Questionnaire** (Kerr and Stattin, 2000). We will measure pubertal status with the **Pubertal Development Scale** (Peterson et al., 1988). The second component of our problem drinking variable is alcohol-related problems, which will be assessed with the **Rutgers Alcohol Problems Index** (RAPI; White & Labouvie 1989). We will also evaluate hazardous symptoms with the **Alcohol Use Disorder Identification Test** (AUDIT; Babor 2006), **Self-Reported Effects of Alcohol** (SRE; Schuckit et al., 1997), **DSM-5 Alcohol Use Disorder Criteria** (APA 2013), **Cannabis Use Disorder Identification Test** (CUDIT; Adamson et al., 2003), **DSM-5 Cannabis Use Disorder Criteria** (APA 2013), and **Cannabis Problems Questionnaire** (Martin et al., 2006) to evaluate both overall AUD criteria as well as youth's response to the craving criterion (Chung et al 2012). We will administer select questions from the Centers for Disease Control and Prevention **Youth Risk Behavior Surveillance System** (YRBSS; http://www. cdc.gov/HealthyYouth/ yrbs/index.htm) to evaluate co-occurring problem behaviors. The **Substance Use History** questionnaire (generated for a previous study) is a comprehensive survey of participant substance use that captures behaviors outside of the TLFB 30-day window, and the **Sexual Behavior Questionnaire** (generated for a previous study) serves the same purpose but for risky sexual behaviors. We will assess **Perceptions of Peer Substance Use** and **Peer Use** via the Tucker et al. 2003 and Bryan et al 2005 questionnaires, and the participant's **Resistance to Peer Influence** using the Steinberg and Monahan (2007) scale. **Substance Use Readiness Rulers** (CASAA instrument) will be used to assess behavior with regards to alcohol, cannabis, and tobacco. We will assess motivation to change using the **Change Questionnaire** (importance, readiness, and ability to change; taking steps) (Miller & Johnson 2008), and **Substance Use Intentions** measure (Bryan et al, 2005), and self-efficacy to change via the **Drink Refusal Self-Efficacy Questionnaire** (DRSEQ) (Young et al., 1991). We will assess

participants' future goals and attitudes using the **Future Orientation Scale** (Steinberg et al., 2009), and the **Goal Orientation Scale** (Child Trends). **Counselor Measures** (Feldstein et al., 2012) to gather the counselor's subjective assessment of the MI and BAM interventions. We will administer the **Wechsler Abbreviated Scale of Intelligence** (WASI; Wechsler 1999) Vocabulary and Matrix Reasoning subtests and an fMRI **Theory of Mind** task (cartoon stories) (Sebastian et al., 2012) to evaluate basic cognitive skills. We will query youth's level of agreement with each presented counselor statement (Feldstein Ewing under review), presented in their individualized fMRI paradigm via likert scale immediately after their fMRI session in the **Scanner Exit Questionnaire**. We will assess client sleepiness during the scan with the Karolinska **Sleep Scale** (Akerstedt & Gillberg, 1990). Finally, we will administer the **Working Alliance Inventory** (Tracey & Kokotovic 1989) to all counselors and youth at the end of each session to assess youth and counselor perspectives of therapeutic alliance, along with the **Counselor and You** scale (Aron et al., 1992), client and counselor ratings of the **Most Important In-Session Clinical Moment** (Walsh 2004) and client and counselor ratings of the **Therapist's Level of Empathy and Warmth** (Miller & Moyers, 2013). Following Session 1, the counselor will select the 20 most relevant BAM or MI statements using the **BAM** or **MI Counselor Statement Selections** worksheet, which allows the NILE fMRI to be catered to individual participants.

Intervention Session 1:
Experimental Condition: Half of the enrolled youth will receive 2 60-minute MI sessions which explicitly target reducing problem drinking. All sessions will be conducted by a postdoctoral fellow or graduate-level counselor and will proceed according to our established adolescent MI manual (Feldstein Ewing et al 2008). The first session is focused on an open-ended exploration of youth's problem drinking behavior. This session is audio-recorded to facilitate the transfer of within-session statements to the fMRI task (see Session 1 MI).

Control Condition: Half of the enrolled youth will be randomized to a control condition to help researchers isolate the mechanisms of MI that relate to behavior change. The control condition will receive 2 60-minute Brief Adolescent Mindfulness (BAM) sessions. The first session is focused on the normalization of the experience of intrusive thoughts, particularly worry and rumination; and an overview of mindfulness concepts including maintaining a nonjudgmental and present-focused mental state and engendering greater awareness of one's thoughts, feelings, reactions, environment and stressors.

Session 2 components.
Neuroimaging Session. We conduct the neuroimaging session during the second visit in order to have sufficient time to cater the counselor statements to the participant's in-session change talk statements, and to integrate their thematic content into each youth's individualized fMRI Neural In-Session Language Examination (NILE) task. Session 2 takes place at OHSU's Advanced Imaging Research Center (AIRC). Consistent with the PI's prior work (Feldstein Ewing under review), participants will be required to abstain from alcohol 24 hours prior to the scan as verified before the scan by breathalyzer, and will also complete a urinalysis to corroborate self-report as a measure of drug use and a voluntary test for pregnancy in females. Upon arrival to OHSU, youth will be screened to assure the absence of fMRI contraindications (no metal in body; not pregnant; breath alcohol = 0). Only approved youth will be scanned. We will use the 3T Siemens Prisma that includes 32 RF channels × 102 coil elements, multi-nuclear support, clinical features (extremity coil, shoulder array coil, spectrus injector), and additional software (e.g., BLADE). fMRI scans will be collected with single-shot full k-space echo-planar imaging (EPI) with ramp sampling correction using the intercommissural line (AC-PC) as a reference (TR: 2.0s, TE: 27ms, α: 70°, matrix size: 64×64, field of view: 24x24, 33 slices, voxel size: 3.75×3.75×4.5 mm). Image-based higher order automatic shimming will be employed. fMRI data will be acquired with the 32-channel phased array-coil. Automated analysis of scanner instability with the Weiskoff method will be carried out using a software tool provided by the MGH. A tilting acquisition will be used to improve the signal dropout and warping in the orbitofrontal cortex (Deichmann et al 2003) similar to our previous published studies (Feldstein Ewing et al 2013b). The subjects will complete a high-resolution structural scan collected for image registration and normalization, followed by the experimental procedure. The

tasks will be presented using a rear projection to a mirror system the subject views while in the head coil. Responses will be recorded using a fiber-optic pad that has four response buttons. Stimulus presentation will be delivered using Presentation. The timing of the stimulus presentation will be synchronized with trigger pulses from the magnet to ensure precise temporal integration of stimulus presentation and fMRI data acquisition.

NILE fMRI Task. PI Feldstein Ewing and Co-I Filbey have pioneered the examination of within-session factors (client language; therapist language) in the brain. For this study, we will expand upon a task that we have developed and published on, which has empirically shown how salient within-session factors influence the brain and subsequent treatment outcomes (Feldstein Ewing et al 2011b, Feldstein Ewing et al under review-a, Feldstein Ewing et al 2013b, Feldstein Ewing under review). Based on our work with client language (change talk; CT; sustain talk; ST), our fMRI procedure assesses the effects of within-session counselor language on adolescent BOLD response. Consistent with our pilot work, to enhance external validity and provide context for counselor utterances, we will present youth with clinical exchanges directly inspired by their Week 1 MI or BAM session. Specifically, 5 client change talk statements (CT; e.g., "*I've been blacking out lately")* will be generated during the Week 1 MI or BAM session. Using the themes of these CT statements as a guide (e.g., references to getting in trouble, feeling hungover), the PI and study counselors will select pre-recorded (from the NILE pilot portion) MI-consistent statements (empathically inflected complex reflection; e.g., *"It is scary to see your drinking is starting to get out of control."*), BAM-consistent statements (e.g., *"You're noticing that your drinking is starting to change*"), and BAM- and MI-inconsistent statements (e.g., "Your drinking is starting to get out of control*)*. All counselor statements will be audio-recorded by the participant's study counselor for presentation within the NILE fMRI paradigm. In line with our successful pilot work (Feldstein Ewing et al under review-a), we will assess the strength of counselor language on youth's BOLD response. All participants receive one ~13 minute run of the NILE task, with order counterbalanced across participants. Each run will include 20 counselor statements of each type, for a total of 60 statements per NILE task version. Each run will consist of 60×12.5-second trials. Each trial will consist of one 500ms "listen" cue, one 4 second audio clip and visual text presentation of the counselor statement, and a 4-10 second fixation jitter necessary for modeling the BOLD response during analysis.

Intervention Session 2**.** Immediately after the scan, youth will meet with their study counselor in a private visit room within OHSU. The second MI session focuses on providing youth personalized feedback regarding their alcohol use (from their baseline data), working with youth to identifying high-risk drinking situations, and determining avenues to help reduce their problem drinking (see Session 2 MI). The BAM group receives mindfulness problem-solving strategies to practice in daily life and in addition, the counselor will discuss the connection between anxiety, stress, and worry with alcohol use, and will reiterate mindfulness concepts. The second intervention sessions for both groups with be audiotaped, but there will be no videotaping as the fMRI stimuli comes from Intervention Session 1 and thus verification is only required for the first session.

Follow-Up Procedures. Given that the impact of MI on youth distal behavior change (>6 month) is not well understood (Jensen et al 2011, Larimer & Cronce 2007), we will evaluate youth over a 12-month period using a near-identical behavioral measurement package administered at baseline (specifically, at 3-, 6-, and 12-months) to obtain an understanding of the nature and duration of brain-based factors in youths' alcohol treatment response. Certain questionnaires will only be administered at Session 1 because they capture a "past year" period (DPS, CTQ) or do not require readministration throughout the entire study (Arrest and Recidivism History, Family Substance Use). The PDS will only be administered at scan visits (Session 2 and the 3 month follow up). See Measures List for additional details. At each in-person visit, we will have the participant complete a breathalyzer and urinalysis to corroborate self-report of drug and alcohol use. For the 3-month follow up, in addition to the follow up procedures described above, participants will return to OHSU for a final MRI scan identical to the one completed in Session 2, and complete the **TLFB 3 Day Use Short Form** before scanning to check for recent substance use. Consistent with our prior NIH- and IRB-approved protocols, 6- and 12-month follow-ups can be completed in-person at a location convienient for youth (e.g., community centers; OHSU), but will be offered to participants as a combination phone (for the TLFB interview) and REDCap (for the remaining measures)

questionnaire battery to eliminate the need for participants to travel to complete the visits. In cases where follow ups are conducted by phone/REDCap, no biological screening will occur (UA, breathalyzer, saliva). For participants who are unable to come to the OHSU campus for the 3-month follow up and corresponding MRI scan, phone/REDCap measures will be offered instead to minimize missing data.

Rationale for Choice of Intervention Approach and Study Duration.
We chose MI as the target behavioral alcohol treatment for this age group for several reasons. First, MI is recognized as an evidenced-based substance abuse treatment for youth (SAMHSA; http://www.nrepp. samhsa.gov/). At the same time, MI has also been identified as a treatment that warrants further investigation in the mechanisms of behavior change research (PAR-14-051). Second, important to this study, the theoretical mediators of MI are well-specified. MI seeks to promote behavior change through the use of specific therapist behaviors (e.g., MI-consistent statements) to elicit client speech in favor of change, constructs that can and have been objectively measured across both behavioral (Moyers & Martin 2006, Moyers et al 2007) and neuroimaging studies (Feldstein Ewing et al 2011b, Feldstein Ewing et al 2013b, Feldstein Ewing et al under review-c). Third, MI is one of the most widely-disseminated interventions, utilized across primary care through addictions treatment centers (Burke et al 2003, Jensen et al 2011). Thus, findings on brain based factors underlying MI response has a high potential for clinical and scientific impact (Feldstein Ewing & Chung 2013). Fourth, application of adult brain-based models to adolescents have not been supported; thus, evaluating youths' neurodevelopmentally-specific response to MI is critically important (Feldstein Ewing et al 2013b). And, we could find no published studies examining the impact of therapist behaviors on the adolescent brain. The unique contributions and ultimate effectiveness of MI cannot be evaluated without a comparison condition. For example, if the youth in the mindfulness condition show greater change in neurocircuitry related to cognitive control which corresponds to behavior change during follow up, as compared to the MI condition, then we know more about what components of the different interventions may or may not be having a positive impact on participants.

Intervention Overview. Following PI Feldstein Ewing's work in developing and evaluating MI interventions for youth problem drinking (Feldstein Ewing et al 2008), half of all enrolled youth will receive two individual 60-minute MI sessions – one within the same week as the baseline visit (Session 1) and a second one week later (Session 2), while the other half of enrolled youth will receive a mindfulness control intervention (BAM). All intervention sessions will take place in a confidential room at OHSU. All sessions will be conducted by a postdoctoral fellow or a graduate student in clinical psychology. All MI interventions will be conducted in an MI-consistent manner, meaning, they will be open, strength-based, affirming, non-judgmental, and empathic, with a goal of reducing resistance and highlighting ambivalence around problem drinking to foster and support youths' intrinsic motivation for behavior change.

Assurance of Intervention Fidelity. To ensure intervention integrity and fidelity, all MI sessions will follow our adolescent MI intervention manual (Feldstein Ewing et al 2008). This MI intervention was developed based on the PI's clinical work with substance-using youth and continues to be updated in line with seminal publications in MI (Miller & Rollnick 2013). The PI is a recognized expert in training and conducting MI with youth. All mindfulness training is based on the mindfulness based stress reduction (MBSR) instructor training guidelines, including a personal mindfulness practice (with ≥1 month of Mind practice required), multiple didactic training sessions, directed readings, experiential exercises in meditation, role plays, test cases and ongoing support and supervision. Consistent with her training/supervisory role on her own NIH-funded work and other investigators' NIH-funded R01s (PI's: Bryan, Hutchison, Kong), she will train each study therapist using the following 5 steps. The therapist will (1) receive didactic training on the theories behind the relevant intervention, (2) be required to read the appropriate study manual, (3) pass a knowledge test to evaluate their grasp of the concepts within and behind MI or mindfulness (e.g., with a pass rate of at least 80% on the fidelity checklist and 100% adherence to essential therapeutic elements), (4) watch the PI conduct each session with a pilot participant and discuss the details of the session, and (5) conduct two pilots of each session, which will be observed by the PI who will assess the therapist's

proficiency in the manualized MI or mindfulness intervention. All sessions will be audio-recorded for the purposes of systematic supervision, allowing PI Feldstein Ewing to ensure fidelity and prevent therapist drift. In addition, consistent with his expertise in training and evaluating process research (NIDA R03, PI: Houck), Co-I Houck will oversee the evaluation of 25% of the audio-recordings by an independent third party (e.g., highly trained undergraduate research assistants). Consistent with his prior work, Co-I Houck will ensure that the audio-recordings are coded to determine the presence of essential elements of the MI intervention (e.g., reflections, open-ended questions). If a therapist is found to have lower levels of intervention integrity or significant drift by the PI or Co-I Houck, the PI will provide the therapist with detailed feedback and training until that person is back on track.

Session 1 MI. Following the PI's prior work (Feldstein Ewing et al 2008, Feldstein Ewing et al 2013a, Feldstein Ewing et al 2013b), the study counselor will open the first MI session by eliciting the youth's story about their alcohol use. Following this open-ended exploration, the counselor will guide youth through a values clarification task (Miller et al 2001). Our prior work has firmly demonstrated that all participants generate at least 5 unique statements in favor of change (change talk; CT) These statements will be directly extracted from the recorded MI session and used for thematic inspiration for the individualization of the NILE fMRI task. The counselor will close Session 1 with a summary of the session and a broad and non-judgmental query of where the youth are in terms of their drinking (e.g., "*Tell me how you would like your drinking to look in the next week*.")

Session 1 Brief Adolescent Mindfulness (BAM): Like the first MI session, the study counselor will begin the session by eliciting the youth's story about their alcohol use. Following this, the counselor will introduce the concepts of mindfulness and discuss how mindfulness meditation techniques can be used to cope with negative affect. The counselor will walk the participant through a mindfulness experiential exercise to illustrate these techniques. Like the MI session, statements from the session will be extracted for use in individualizing the NILE fMRI task.

Session 2 MI. The second session will begin with an open-ended query of participant's experience during the scanning protocol. Next, the counselor will check in with the youth to see how their drinking went in the intervening week. The counselor will then provide personalized feedback (PF) of the youth's alcohol use and alcohol-related problems as derived from their baseline assessment data. Following this, the counselor will actively and collaboratively engage youth in the development of discrepancy (exploring how their drinking fits with youth's immediate and long-term goals), the identification of high-risk situations and triggers for drinking, and an exploration of strategies to manage those risks and triggers. Similar to the first MI session, the counselor will close Session 2 with a summary of the session and a broad and non-judgmental query of how the youth would like their alcohol use to be in the near future (e.g., "*Tell me how you would like your drinking to look when our team sees you again in 3 months.*")

Session 2 Brief Adolescent Mindfulness (BAM): Like the second MI session, the counselor will start with an open-ended query of the participant's experience during the scanning week. Next, the counselor will check in with the youth to see how their drinking went in the intervening week. The counselor will proceed by reviewing any instances of mindfulness utilized by the participant and discuss the connection between experiencing anxiety, worry, and/or stress and substance use. The counselor will help problem solve barriers to practicing mindfulness in the youth's life. In addition, the counselor will end the session with a review of mindfulness concepts and tools, and provide the participant with a handout outlining accessible mindfulness resources (e.g., free apps and websites with guided meditations).

Total length of participation. All youth will participate 5 times over the course of 12 months (Baseline Assessment/Intervention Session 1, fMRI/Intervention Session 2, 3-month follow-up with second fMRI, 6-month follow-up, 12-month follow-up).

Circumstances for withdrawing a subject without their consent. If a subject is disruptive, uncooperative, threatening or physically violent towards other subjects or research staff during a participation session, their participation will be terminated. If a subject chooses to stop participating

for any reason, the youth's participation will be terminated. If a parent chooses to have their adolescent stop participating for any reason, the youth's participation will be terminated.

Procedures for withdrawal, including partial withdrawal. If a youth withdraws from the research, we will continue to retain the data collected until that point, unless they specifically request removal of their data from the study. In this event, we will destroy all of their data. Subject identifying information and any video recordings will be destroyed following the final study participant's completion of his or her 12-month follow up; therefore, if a participant requests that his or her data be removed following the conclusion of the study, we may not be able to complete the request as the data will no longer be identifiable as coming from a particular research subject.

7) Data and Specimens

a) Sharing of Results with Subjects

Incidental findings from Imaging. The MRI scan is being done to answer research questions, not to examine individual brains for medical reasons. This MRI scan is not a substitute for a clinical scan (the type a doctor would order). The research scan may not show problems that may be picked up by a clinical MRI scan. If we find an abnormality that appears to require urgent follow-up after review by a neuroradiologist on the study team, we will contact the participant by phone to help answer questions, recommend that the participant contact their doctor to schedule a clinical scan, and assist in getting the right follow-up care for the individual. It is possible that the individual could be unnecessarily worried if a problem were suspected, but not actually found. Our research team is always available to answer any questions the individual may have about their scan.

Incidental findings from pregnancy testing. Parents or guardians of a child participating in this study may be told the results of the child's pregnancy test if the child is younger than 15. If the child is 15 or older the pregnancy test result will be released to the child. It will be up to her whether or not it is released to the parent or guardian. However, if the Principal Investigator believes that the child is not receiving adequate medical care for the pregnancy, she will refer the subject to a place where the participant can get the proper care.

Incidental findings from the questionnaires (CTQ, DPS). In the case that a participant's responses to any questionnaires, or spontaneous disclosure during a study visit, suggest that a participant may be having current thoughts of seriously hurting or killing him- or herself, or reports current physical or sexual abuse as a minor, the RA will elicit additional information as appropriate and call the Principal Investigator. If present, one of the study counselors may address these responses with the participant directly, calling the PI for additional support if needed. The PI may then initiate a conversation with the participant about his or her responses. If the investigator believes that the participant is a harm to him- or herself, at-risk for abuse as a minor, or that an abuser may be actively harming other minors, then the PI may voluntarily disclose this information to the appropriate parties (parent/guardian, Child Protective Services). In all cases, the RA will provide the participant with an updated resource sheet specific to the Portland area. To minimize "false alarms" and prevent unnecessary follow up, 4 short questions have been built into the computer questionnaires to filter out previously reported, historical incidents of possible child abuse. These questions immediately follow the Childhood Trauma Questionnaire so as not to appear abrupt or out of place in regard to subject matter.

b) Data and Specimen Banking

How and where data will be stored and the final disposition of the data/specimens. Standard institutional practices will be followed as described in the OHSU information security and resource data guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the

confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will only contain the subject code. Codes will not contain any part of the 18 HIPAA identifiers.

All data will be identified with a numeric code. Paper files will be stored in a locked cabinet separate from consent forms and confidential locator forms in restricted access offices at OHSU. Electronic data will be stored on encrypted computers and within restricted drives on the OHSU network. Access to all data/specimens will be restricted to study personnel.

Consistent with the PI's prior NIH funded work, all confidential locator forms will be destroyed upon participants' completion of the final follow-up.

Data released to other investigators will be labeled with only the code.

Follow up data from REDCap questionnaires will be stored upon collection in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system, then exported through REDCap to lab databases and stored as outlined above. Features of REDCap that protect participants' privacy and data security include:

- Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center, providing locked physical security
- Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.
- Controlled User Access: REDCap employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes "single click" ability to provide completely de-identified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

For future unspecified use. I intend to set up an approved repository to use de-identified data for future unspecified use (MRI scans; coded behavioral data, coded saliva samples). Please note: I will not be submitting anything into the repository until it is IRB approved. However, I would like to consent subjects now for those future uses. This will facilitate combining data from disparate subjects for the same subject, which may be needed.

8) Data Analysis

Power Analysis and Sample Size Requirements.

Sample size was selected to evaluate the primary research questions at a two-tailed alpha of .05 and power of .80. Estimates of effect size were conducted in G*Power 3 (Faul et al 2009, Faul et al 2007). For ***Hypothesis 1,*** the relationship between MI-consistent therapist statements and brain-based response, in our pilot evaluation, we found that MI-consistent behaviors (as contrasted with non-MI-consistent behaviors) showed a large effect size (z = 2.27, d = 1.31) within the IFG (Feldstein Ewing et al under review-a). Thus, this effect size requires a sample size of 22 subjects to power Hypothesis 1. In terms of ***Hypothesis 2***, that brain activity will correlate with reductions in proximal and distal problem drinking, our pilot study showed significant relationships between MI-consistent therapist behaviors and proximal (1-month) reductions in binge drinking days (right IFG z = 3.38, d = 1.95; insula z = 2.238, d = 1.29) (Feldstein Ewing et al under review-a); thus, for this analysis, we would need 22 subjects detect proximal behavior change. However, because no study to our knowledge has evaluated how BOLD response relates to youths' distal (12- month) behavior change, we suggest a more conservative (medium) effect size of d = .70 for this heretofore unexamined relationship. Together, this suggests the need for 68 youth to detect both proximal and distal behavior change for Hypothesis 2. For ***Hypothesis 3*** we refer to the work of Fritz and MacKinnon (2007) to determine sample size for our mediation hypothesis. For the A path, the relationship between therapist speech and adolescent BOLD response, our pilot evaluation suggests a large effect for MI-consistent therapist behaviors on BOLD activation. For the B path, the relationship between youth brain response and subsequent behavior change (proximal and distal treatment outcomes), we anticipate a medium effect size. For the indirect effect, that is, the effect of therapist speech upon problem drinking outcomes mediated by youth brain response, Fritz and Mackinnon indicate that with a large effect for the A path and a medium effect for the B path, we would need a sample of N = 204 to detect a mediated effect for Hypothesis 3 with power of .80 at an *a priori* alpha of .05.

The Impact of Attrition. In our prior NIAAA R01 with drinking youth (PI Feldstein Ewing), we have an established track-record of retaining ~84% of adolescents at our most distal (12 month) follow-up. Thus, we project losing 16% of the proposed sample, thus requiring **N = 243** youth to account for attrition.

Analysis Plan.
Analyses will be conducted to evaluate (1) the relationship between therapist behavior and youth brain response (BOLD), (2) the relationship of youth brain response (BOLD) to changes in youth problem drinking across proximal (3- and 6-month) and distal (12-month) follow-ups, and (3) and the mediational role of BOLD activation on the relationship between therapist behaviors and youth problem drinking outcomes. Measures will be derived from the baseline fMRI scan and behavioral data collected at baseline, 3-, 6- and 12-months.

fMRI preprocessing and single-subject analysis. The first three volumes of each run will be discarded to allow the MR signal to reach steady state. The remaining images in each youth's time series will be motion corrected (Jenkinson, Bannister, Brady, & Smith, 2002) using FSL's MCFLIRT module (FMRIB's Software Library). Images will be spatially smoothed with a 3D Gaussian kernel (FWHM = 8 mm^3), intensity normalized and temporally filtered with a 50 sec high pass filter FEAT (FMRIB's Easy Analysis Tool) (Smith et al., 2004).

We will utilize a regression approach (GLM - general linear model) to extract regularities with regard to temporal aspects (i.e., time series) of the data. Statistical analysis will be carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. We will create an explanatory variable (EV) for each trial type (MI-consistent, BAM-consistent, BAM- and MI-inconsistent). For each participant, we will use FILM to obtain a parameter estimate for each EV and create appropriate contrasts. Contrast maps of parameter estimates (PE) for each youth are transformed into a common stereotaxic space using the following 2-step registration prior to the group analyses. Statistical maps will be warped into the common MNI stereotaxic space (Jenkinson et al., 2002) before a random effect group analysis is performed. To do so, (1) the EPI image will be registered to the participant's high resolution T1 weighted image; (2) the T1-weighted high resolution image will be registered to the MNI 152 brain template image; and (3) statistical images

will be transformed to MNI space using the transformations matrices from step 2. Coordinates will be reported in MNI space. All registration will use FNIRT (FMRIB's Nonlinear Image Registration Tool).

To test ***Hypothesis 1***, that MI-consistent therapist behaviors will be associated with greater BOLD response (MFG, IFG, insula) than MI-inconsistent therapist behaviors, we will utilize the same procedure used in our pilot study (Feldstein Ewing et al under review-a). Group-level activations will be evaluated for MI-consistent vs. MI-inconsistent for change talk (CT) and sustain talk (ST) separately across the whole brain and thresholded using a false discovery rate (FDR) set to a false-positive $p<0.05$. Following our prior work (Feldstein Ewing et al under review-a, Feldstein Ewing et al 2013b), to test ***Hypothesis 2a*** *(from original submission)*, that BOLD response will be directly associated with proximal (3-, 6-month) and distal (12-month) behavior change (reductions in youth problem drinking), we will utilize an index of youth problem drinking (past month binge drinking days; derived from TLFB + past month alcohol-related problems; derived from RAPI). We will conduct linear regression analyses in FSL with baseline measures of alcohol use behavior and alcohol problems included as regressors to assess correlations between BOLD response and behavior change for youth problem drinking at each follow-up time point. To test ***Hypothesis 2***b of the Supplement, that greater BOLD response will be directly associated with proximal (3-, 6-month) and distal (12-month) behavior change (reductions in youth cannabis use), we will utilize an index of youth problem cannabis use (past month cannabis use days; derived from TLFB + past month cannabis related problems; derived from Cannabis Problems Questionnaire). We will conduct linear regression analyses in FSL with baseline measures of cannabis use behavior and cannabis problems included as regressors to assess correlations between BOLD response and behavior change for youth problem cannabis use at each follow-up time point.

To test ***Hypothesis 3***a (from original submission) and 3 b (from supplement) that BOLD response (MFG, IFG, insula) will mediate the relationship between therapist behaviors (MI-consistent) and proximal and distal reductions in youth problem substance use (drinking; cannabis use), we will use the product of coefficients method (Sobel 1982). Because the distribution of the product of coefficients is typically not normal, we will apply appropriate asymptotic confidence limits (MacKinnon et al 2007) following Co-I Houck's prior work examining causal chains in MI (Moyers et al 2009). Coefficients and standard errors for the A and B paths will be computed in FSL using the variables from Hypotheses 1 and 2 (i.e. signal change difference between MI-consistent and MI-inconsistent language, with (a) past month binge drinking/alcohol-related problems at 3-, 6- and 12-months; (b) past month cannabis use/cannabis-related problems at 3-, 6- and 12- months), and tested using the PRODCLIN macro (MacKinnon et al 2007). We will perform separate tests for proximal and distal drinking, each tested at $\alpha=.05$.

9) Privacy, Confidentiality and Data Security

First, prior to participation, participants are informed of all procedures, and both they and their parents/guardians must proceed through an informed consent process and provide assent or consent stating that they understand and agree to the procedures. Therefore, it is likely that any individual who would be made uncomfortable by answering questions about alcohol use and other health behaviors would decline to participate, as example questions are outlined in the consent form. **Second**, similar to the PI's prior NIH-funded work, and as done in other adolescent addiction studies (e.g., Chung et al., 2005; Schmiege et al., 2009), to ensure adolescent's confidentiality, all data will be identified with a numeric code and stored in a locked cabinet separate from consent forms and confidential locator forms. In addition, adolescents' data will be retained by the PI and maintained in a separate cabinet. Consistent with the PI's prior NIH funded work, the confidential locator forms will be destroyed upon participants' completion of the final follow-up. Like the locator forms, all videotapes used for paradigm verification will be destroyed when the final participant completes his/her final follow up. **Third,** our magnetic resonance (MR) technicians are highly experienced and have received specific training through OHSU's Advanced Imaging Research Center to prevent accidents in the fMRI scanner. Both the trained study staff

and the MR technician provide a rigorous screening to ensure that participants do not have any metal on or inside their bodies prior to entering into the scanner. This screening includes the use of a metal detection wand (similar to those used in airports) as a final check. In addition, access to the magnet is limited to prevent others from bringing in metallic objects. We also screen for claustrophobia and provide individuals with earplugs to reduce the amount of noise they experience. It is still possible that individuals may feel anxious in the scanner, but they are in constant communication with the experimenters (i.e., through headphones and an intercom system) and can stop the experiment (i.e., using an emergency squeeze bulb) and be removed at any time if they are feeling too anxious to continue. **Fourth**, we have not encountered any reticence by the youth to disclose their substance use and related risk behavior. Completion of the assessment measures has minimal risk and adolescents are notified that they may skip questions that are distressing for them to answer without it negatively impacting their compensation or status within the study. **Fifth**, our team is highly experienced at working with youth who are engaging in illegal behaviors, including substance use. We will continue to take exhaustive steps to protect youth's privacy in this study. Consistent with our prior work, we have obtained a federal Certificate of Confidentiality to serve as an additional layer of protection.

10) Risks and Benefits

a) Risks to Subjects

There are five potential risks associated with participation and every effort will be made to reduce potential discomfort. **First**, there is the potential discomfort involved in answering questions about sensitive topics, including alcohol use behavior. **Second**, there is the risk of breach of confidentiality of behavioral, neuroimaging, and/or genetic data. **Third**, while the fMRI procedures involve no pain or invasive techniques, individuals occasionally find the partially enclosed space and/or the noise of the scanner uncomfortable. Adverse events associated with fMRI can involve the action of the magnetic field on metallic objects. For example, metallic objects on or inside the body of participants or foreign metallic objects that are brought into the room with the magnet may injure participants. **Fourth**, standard risks for adolescent health risk behavior research often include discussions regarding illegal activities (e.g., discussions about drinking, as alcohol use under the age of 21 is illegal). **Fifth**, another standard risk includes the desire of parents/guardians to obtain data collected in this study regarding adolescents' health behavior and other activities. However, as has been done in the PI's prior research, this risk will be minimized through active efforts to protect the confidentiality of adolescents' data, including obtaining a Certificate of Confidentiality from NIH (which we have done), and the maintenance of data in locked cabinets and secure, encrypted servers at OHSU, which will only be accessible by the PI and trained research staff.

b) Potential Benefits to Subjects

This study is expected to add critical data that will add to the knowledge base to improve alcohol use treatment for binge drinking adolescents. Given the minimal risk to participants and the greater possibility of long-term benefit to the participant and the greater knowledge base, the risk/benefit ratio seems reasonable. As a part of this study, all participants will have the opportunity to examine their own alcohol use behavior in the context of completing measurement instruments, have the opportunity to work with a trained counselor, and receive a widely-used, empirically supported alcohol use treatment, which may help facilitate their efforts to reduce their problem drinking behavior. The costs associated with participating have been minimized via the consent procedures, procedures for maintaining confidentiality, and safeguards during the fMRI component. The minimal costs associated with participation in this research are reasonable in relation to the anticipated benefits to the participants themselves.