Study Protocol and Statistical Analysis Plan

Study Title: Prevention of Adolescent Risky Behaviors: Neural Markers of Intervention Effects

Clinical Trials ID: NCT03370393

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I. INTRODUCTION TO RESUBMISSION APPLICATION (1 R01 DA040966-01A1)

We thank the reviewers for their valuable comments on the previous application. We combined the concerns in resume/summary (*"S"*) and critiques (*"C"*) and grouped them in sections. Changes in the proposal are bracketed.

Significance: 1. *Practical utility of fMRI (C2).* We agree that fMRI is currently fiscally impractical, but believe that will change rapidly. In the interim, fMRI has significant contributions to make, as the reviewer acknowledges: "mechanistic knowledge may guide interventions… by identifying critical circuits and associated psychological functions...." This study will offer insights on how to merge neuroscience methods and prevention science as this tool becomes more integrated in the direct assessment of programmatic effects, and offer guidance on how to personalize prevention program exposure, addressing continuing concerns about specificity and dosage (**III B**).

Investigators: 1. *Delay in start-up (C3).* We do not anticipate undue delay in the start-up of this project because of personnel issues. Dr. Rao's center has staff members on board who are experienced in coordinating various types of studies and research activities related to behavioral and mental health. The center has had continuous NIH funding since its inception 28 years ago. The research staff transition from one study to the next based on the funding cycles of the research projects in the center. In addition, the center has decades of experience in successfully recruiting and training personnel for research projects. We have access to a large pool of qualified candidates to attract to these positions, given that we have five local universities along with two medical centers.

2. *Collaboration history (S, C3).* In addition to acquiring pilot data, the team has worked collaboratively on other projects and grant proposals (**IIIC.2; Rao Biosketch**). As cited in the resume/summary (*S*), Dr. Rao has an established record of successfully completing collaborative, multi-disciplinary studies and publishing their results.

Innovation: We very much appreciate all the positive comments. No weaknesses were identified in this section.

Approach: 1. *Analysis of multiple measures (S, C1).* PAAS is a family intervention. Data from PAAS and SAAF indicated that the intervention has both direct and indirect effects. Positive parenting improves self-regulation in offspring around pubertal transition which, in turn, protects these youth against behaviors associated with HIV/ AIDS and substance abuse risk as they progress through middle and late adolescence (**IIIC.3b, Figure 2**). Here, we will examine the effects of parenting on youth's neurobiological changes in exploratory analyses (**II**, **IIIC.7d.3**).

2. *How fMRI tasks reflect PAAS' effects on regulation processes (S, C1).* The primary fMRI task is a decision-making task in the context of risk/reward opportunities, and this task targets both socio-emotional and cognitive-control neural substrates (**IIIC.3c, Fig 3**). Behavioral performance on this task is related to reward-seeking traits and risky behaviors in real life. PAAS targets developmental vulnerabilities and exploits sensitivity to rewards by incentivizing cognitive-control functioning by enhancing youth's resistance efficacy skills and raising awareness of the association between risk engagement and compromised future goals (**IIIC.3b, Fig 2; IIIC.4f.6,Table 2**). To ensure risky decision-making is not confounded by poor impulse control, we included a control task (**IIIC.1**).

3. *Handling confounds (S, C1).* Youth on medications affecting the brain, with behavioral/emotional problems at a clinical level, or those using alcohol/drugs three days prior to the fMRI scans will be excluded (**IIIC.4c**). We proposed standardized assessments and urine drug screens to evaluate these factors (**IIIC.4f.3, Table 1**).

4. *Wait-list control (C2).* The intervention's efficacy was proven in randomized, controlled trials and psychological "active ingredients" were identified. The focus of this proposal is on their underlying neurobiological substrates. The wait-list control does not account for "general" (attention) effects. PAAS-tech does not involve a therapist, so this is not an issue. This control provides greater statistical power to detect group differences in addition to the benefit of a proven intervention for the control group after completing the experimental phase (**Fig6; IIIC.10c**).

5. *Quality control imaging data (C2).* The pilot data were in 9-12 or 12-18 year-olds, which cover the age range (i.e. 11-13 years) in the proposed study (**IIIC.3**). Our neuroimaging studies have included youth as young as 6 years, with reliable data in 93%-97% of the samples (**IIIC.4f.2b.2**). We implement many reliable data collection methods (**IIIC.4f.2b.1, 2b.2**). We also institute established methods to reduce dropout rates (**IIIC.10a**). So, the estimated 20% dropout rate is easily attainable. Should this not prove to be the case, we agree with the reviewer: "this concern is mitigated by the robust recruitment mechanisms in place which could supply additional subjects."

6. *Motion artifacts (C2).* We propose several methods to address motion artifact at individual level. These metrics can be summarized to a single number and then compared between groups or used as covariates (**IIIC.4f.2b.6**).

7. Power analysis (C2). To avoid biased estimates from small sample sizes, we used *minimum detectable effect size* (ES) at a clinically meaningful level. ES from pilot data (.3-.5) are consistent with the power analysis (**IIIC.7e**).

8. *fMRI tasks not novel (C3).* We deliberately selected theoretically-based, well-established tasks in this novel study on neural basis of a prevention program. Untested tasks could lead to confounds in interpreting the results.

9. *Miscellaneous.* IQ should be ≥80 (*C3*). We will provide laptops to those who don't own them (*C3;* **IIIC.4f.6**).

II. SPECIFIC AIMS

African-American (AA) youth are disproportionately affected by the high morbidity and mortality associated with risky behaviors, including human immunodeficiency virus (HIV) infection, acquired immune deficiency syndrome (AIDS), and other sexually-transmitted infections (STIs).[1-6] Adolescence is characterized as a time of increased experimentation and exploration. Although such behaviors aid in the progression towards autonomy, this comes at a great cost. For example, motor vehicle accidents, suicide and violence rise dramatically during adolescence, [7-13] largely due to problems with behavioral and emotional self-regulation, commonly associated with short- and long-term consequences of alcohol and addictive drugs.[14-16] Recent advances in neuroscience suggest that a temporal disassociation in the maturation of the brain's "socio-emotional" (reward) system, which develops early, and the "cognitive-control" (self-regulation) system, which occurs later, creates a period of poor decision-making and heightened vulnerability to risk-taking (reward-seeking) behavior with the onset of pubertal maturation.[17-24] However, we know little about how our knowledge of changes in neural circuitry governing adolescent decision-making can be used to improve intervention programs seeking to reduce the onset and escalation of alcohol and drug use in co-occurrence with risky sexual practices among AA youth or those from other ethnic/racial groups.

Reasons for the cross-racial HIV/AIDS disparities are not clear, but extant data suggest that cumulative exposure to stress associated with poverty, family disruption, discrimination and neighborhood segregation exacts a toll on AA families. These stressors may not only compromise parenting practices and increase youth exposure to troubled peers but also influence early brain development with sustaining effects, and as explanatory causes for race crossover drug use among AAs as they transition into young adulthood. Our team has developed and tested a family-based intervention program designed to deter and avert HIV-risk vulnerability in AA youth, **Pathways for African Americans' Success** (**PAAS**). In randomized controlled trials (RCTs), PASS was effective in deterring substance use and early sexual activity by influencing both parenting practices and youth psychological protective factors (i.e. cognitive as well as emotional self-regulation) (**IIIC.3b; Fig 2**).[25-36] Our *long-term goal* is to develop implementation strategies that maximize the effectiveness of this intervention for high-risk AA youth.

We address a crucial question -- which neurobiological mechanisms are involved in the process of intervention-induced changes in youth protective factors that evoke behavioral change. This information is necessary to: 1) refine the program by focusing on the components that are most effective in changing both behavioral and neural circuitry; and 2) guide the development of personalized behavioral interventions by identifying individuals who are most likely to benefit from the program. The *objective of the study* is to identify the effects of PAAS on the risk-taking/self-regulation neural circuits and assess whether changes in these circuits correlate with changes in youth protective factors (improving self-regulation) in 128, 11-13 year-old AA youth (**Fig 1**), which we hypothesize will dissuade behaviors that place youth at risk for HIV/AIDs, as they transition into middle and late adolescence. **Our overarching hypothesis is that the balance in the activation of reward and cognitive-control systems correlates with youth self-regulation, and that PAAS shifts this balance in the positive direction.**

Specific Aim 1: Assess the effect of PAAS on reward-drive and cognitive-control neural circuitry.
Method 1: Youth will be randomized to a 6-week PAAS intervention or a wait-list condition. Functional magnetic resonance imaging (fMRI) scans will be acquired at rest and in response to a task involving the balance between reward-drive and cognitive-control circuits pre- and post-intervention to assess functional connectivity changes.
Hypothesis 1: PAAS will produce a greater balance in reward-drive and cognitive-control systems (by increasing functional connectivity between these two components of the neural circuitry) compared to the wait-list condition.

Specific Aim 2: Evaluate if the post-intervention neural changes mediate PAAS' effects on youth self-regulation.
Method 2: Direct and indirect (i.e. functional connectivity) effects of PAAS on youth cognitive and emotional self-regulation measured three months post-intervention will be assessed to identify which neural changes mediate PAAS' effects on these self-regulation measures.
Hypothesis 2: PAAS-induced changes in self-regulation will be mediated by PAAS' effects on the neural circuitry.

Exploratory Analyses: We will identify subgroups of youth who benefit more from PAAS intervention effects on self-regulation defined by demographic, neurobiological and social-contextual factors (e.g. individual differences in baseline functional connectivity may predict who benefits most from the intervention [**IIIC.3c, Fig 3**]).

The *expected outcomes* of Aims 1 and 2 will contribute to an integration of our understanding of neural circuitry governing adolescent decision-making and of the effectiveness of an intervention shown to reduce HIV-related risky behaviors among AA youth.[37-39] These outcomes will *positively impact* efforts to improve interventions that target high-risk behavior in youth from other ethnic/racial groups by linking biological mechanisms, psychological processes, social-contextual factors and behavioral outcomes associated with these interventions.[21,37,40-44]

III. RESEARCH STRATEGY
III A. SIGNIFICANCE

IIIA.1. Individual Differences in Adolescent Risk-taking Behavior: Despite evidence of an overall increase in risky behaviors in adolescence compared to childhood, it is important to recognize the substantial individual differences. Evidence from longitudinal studies suggests that a significant amount of the problematic behavior observed in adolescents is clustered in a small proportion of youth.[45-48] It is likely that underlying differences in brain function play a role in the dramatic differences in decision-making in these two sub-groups. Thus, we need a better understanding of how individual differences in brain function that underlie the more problematic risk-taking behaviors can be used to address numerous ethnic/racial disparities that continue to plague our society.

IIIA.2. Neural Substrates of Risk-taking Behavior during Adolescence: Some developmental neuroscientists postulate that risky behavior during adolescence is the product of the interaction between changes in two distinct neurobiological systems: a reward system, localized in the limbic and paralimbic areas of the brain including the amygdala, ventral striatum, medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC); and a cognitive-control system, consisting mainly of lateral prefrontal and parietal cortices (including dorsolateral prefrontal cortex [DLPFC]) and their connections to the anterior cingulate cortex (ACC).[17,24] According to this model, there is a dramatic increase in dopaminergic activity within the reward system around puberty, which increases reward-seeking behavior.[18,49,50] This increase in reward-seeking precedes the maturation of the cognitive-control system. Connections between cognitive-control and reward systems gradually unfold during adolescence and lead to better self-regulation and impulse control.[19,24,51-57] The temporal disassociation between the maturation of reward and cognitive-control systems creates a period of heightened vulnerability to risky behaviors.[17-24]

IIIA.3. Efficacy of PAAS in Reducing HIV-Risk Behaviors in Youth: PAAS, recently tested in TN, and its earlier iterations, the **Strong African American Families (SAAF) and SAAF-T** (teens) programs, tested in GA, were effective in delaying/preventing a cluster of behaviors associated with HIV/AIDS, including substance use disorders (SUD), risky sexual behaviors (early onset of sexual activity, unprotected sex) and conduct problems through induced positive changes in executive and emotional functioning in AA youth (**IIIC.3b; Fig 2**).[25-36]

[IIIA.4. Scientific Premise: Despite significant advances in understanding the developmental changes in neural circuitry associated with risky behavior during adolescence, little is known regarding individual differences in the functional connectivity between reward-seeking and cognitive-control systems and their maturational course — factors which may heighten or lower vulnerability for engaging in behaviors that place youth at risk for HIV/AIDS and SUD. Similarly, while several prevention programs aimed at curbing high-risk behaviors have been tested, they typically did not seek to ameliorate malleable mechanisms, raising concerns about specificity and dosage of the interventions that have shown efficacy.[41] The development of interventions to avert/delay risky behaviors has progressed independently of the neuroscience on neural circuitry governing adolescent decision-making. Practicing behavioral/cognitive skills induces structural and functional brain changes,[43,58-62] particularly during a time of high neuroplasticity.[63-65] The proposed study will advance the benefits of PAAS and other evidence-based programs by improving our understanding of the ways in which neurobiological mechanisms affect intervention-induced psychological and behavioral changes, and subsequently influencing the modification of programs to be maximally effective and efficient in preventing SUD and HIV-risk behaviors in youth.[37,40,43,44]**]**

III B. INNOVATION

The combination of fMRI technology and a theoretically-driven, empirically-tested program that is designed to foster skills/capacities to avert/delay HIV-risk behaviors, offers promise for identifying the mechanisms through which the intervention affects self-regulatory and decision-making skills to yield positive behavioral outcomes. The findings have the potential of advancing ways to translate models of personalized medicine to behavioral preventive interventions (*e.g. a behavioral vaccine*).[66,67] For example, if the study shows that a subgroup of youth who have preferential recruitment of reward-seeking brain regions/circuits relative to cognitive-control structures when processing probabilistic rewards don't show significant improvement in response to PAAS, the intervention can be modified/supplemented to take advantage of their reward-seeking tendency by providing incentives, or booster sessions, for engaging the cognitive-control functions to shift the functional equilibrium between these two circuits, as has been shown previously,[44,68-70] and thereby accelerate the maturation of self-regulatory skills.

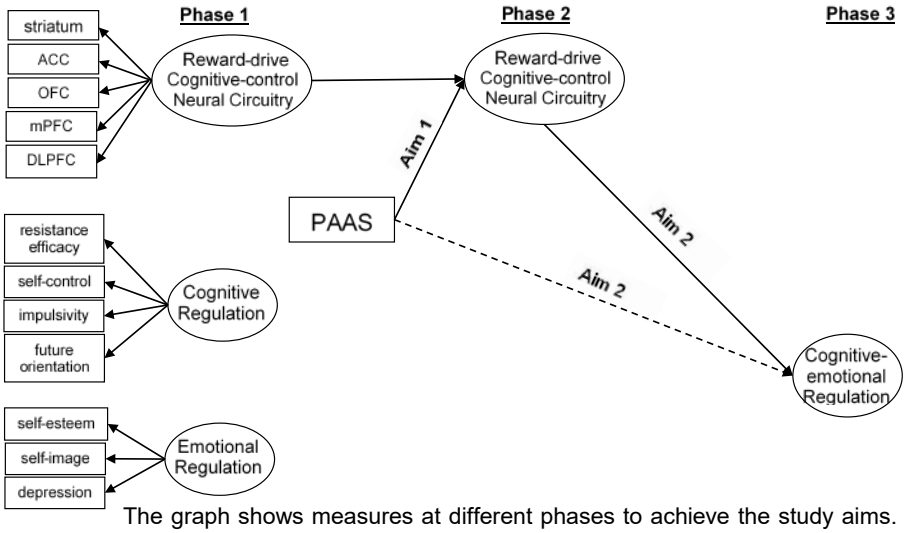
Although neuroimaging is expensive and may not have practical utility in large-scale prevention and intervention programs at the present time, given the extant knowledge on developmental neuroscience of risky behaviors [17,19,21,24] and the modest effects of current interventions,[41] we believe that it is time to incorporate this technology into prevention science to better understand ways to target malleable neural mechanisms to explore methods to advance the implementation of successful evidence-based interventions,[37,40,43,44] and offer insights on ways to

enhance cultural-tailoring strategies often undertaken to improve acceptability and responsiveness to preventive interventions. These methods may include, for example, the development of biopsychosocial profiles which can be used efficiently to focus intervention efforts. In addition, recent technological advances such as mobile MRI scanners and real-time fMRI (rtfMRI) will likely reduce the cost and make this technology more practical, as has been shown for genetic testing. Investigators have begun to use fMRI or rtfMRI to examine the neural basis of therapeutic techniques to reduce drug cravings as well as cognitive-behavior therapy (CBT), cognitive training, mindfulness therapy and neurofeedback for various psychiatric disorders.[43,44,71-77] This work informs current and future studies that seek to integrate neuroimaging and prevention science to address health disparities, including HIV/AIDS and SUD. Another promising avenue is to use neurobiological information to better understand why some youth don't respond to preventive interventions so that the programs can be modified and/or personalized, at least at the subgroup level (e.g. reward/sensation seekers, deficits in inhibitory control).

III C. APPROACH

IIIC.1 Overview: The conceptual model guiding our study is presented in **Fig 1**. Aim 1 will assess the effects of PAAS on the magnitude of Phase 2 functional connectivity between reward-drive and cognitive-control neural circuitry at rest and during a decision-making task after controlling for pre-intervention (Phase 1) levels. Aim 2 will evaluate if Phase 2 post-treatment neural circuitry changes mediate PAAS' effects on psychological processes (i.e. cognitive and emotional self-regulation) at the 3-month follow-up (Phase 3) after controlling for Phase 1 values. Our overarching hypothesis is that the functional connectivity between reward and cognitive-control networks correlates with self-regulation, and that PAAS increases the magnitude of functional connectivity between these neural networks. In addition to these hypotheses, we will identify characteristics (demographic, neurobiological, psychological, behavioral and social-contextual factors) that moderate PAAS' effects on the relationship between functional brain changes and cognitive-emotional self-regulation in exploratory analyses (**IIIC.3b; Fig 2**).[29,32,34-36]

Fig 1. Conceptual Model of Associations among Primary Measures



The graph shows measures at different phases to achieve the study aims. Rectangles represent observed variables for the primary variables (circles).

A total of 128 AA volunteers (ages 11-13 years, 50% male and female) and 128 parents (primary caretakers) will be recruited. Youth and parents will complete assessments on intervention targets (i.e. parenting processes, youth psychological protective factors and cognitions/behaviors associated with HIV and SUD vulnerability). fMRI scans will be acquired in the youth to assess functional connectivity between reward-drive and cognitive-control neural circuitry during rest and while performing a decision-making task involving probabilistic monetary rewards. A second task that assesses general impulsivity/motor response inhibition (in contrast to reward-drive) will be included as a supplementary measure. Following assessments, the families will be randomized to either PAAS or a wait-list control condition for 6 weeks. fMRI scans will be repeated after 6 weeks to measure functional brain changes from pre-to-post intervention. They will repeat the intervention-targeted assessments 3 months later, after which the wait-list controls will be offered PAAS as a benefit for participation in the study (**IIIC.4f.1; Fig 6**).

IIIC.2. Qualifications of the Research Team: The multi-disciplinary team has the required expertise to achieve the stated specific aims and to translate the knowledge gained into new interventions that will benefit vulnerable youth. Dr. Rao has expertise in developmental psychopathology of addictive and mood disorders in adolescents, neurobiology (including ethnic influences), translational intervention studies and longitudinal study designs.[78-88] She has led several successful research projects on translational neuroscience. Dr. Benningfield's research is focused on the neural substrates of impulsivity/risk-taking as they relate to risk for developing SUD in youth.[89-97] Dr. Murry brings expertise in family systems and socio-cultural processes, and has two decades of experience with AA youth and their families employing longitudinal designs.[47,98-106] She played a key role in the development, design, implementation and testing of PAAS and SAAF (an earlier iteration) programs.[25,27-36,103-110] Dr. Rogers' background is in medical physics and neuroimaging. He has expertise in neural functional connectivity, including both resting-state and task-based connectivity, in various psychiatric disorders across the life span.[111-122] Dr. Green has expertise in behavioral/mental health, applied statistics and multivariate statistical models.[123-133]

Dr. Brown has expertise in prevention implementation methodology for risky behaviors in youth including SUD and HIV-risk.[134-147] Dr. Ernst has expertise in the neural substrates of adolescent risk-taking behavior.[52,58,148-160] She has developed and tested many tasks for fMRI study designs, including the task in the proposed study.

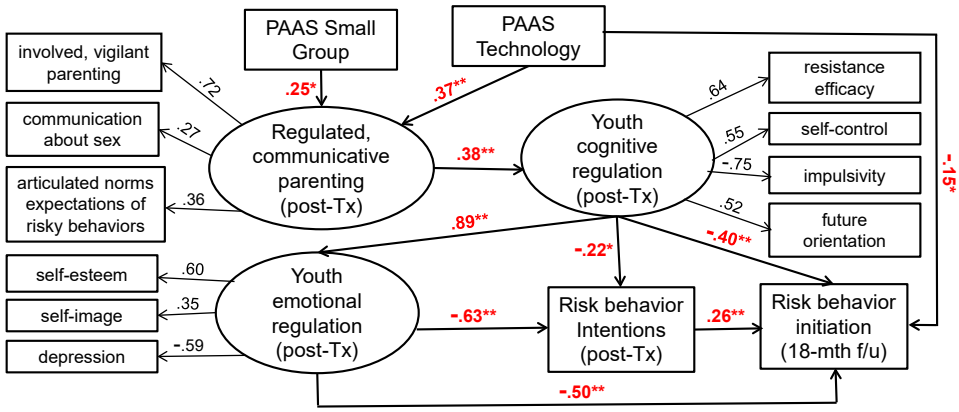
[Dr. Rao has well-established connections with the Vanderbilt team. She has advised and collaborated with Dr. Benningfield since 2010. Both collaborated with Dr. Rogers, and together with Dr. Murry, conducted a pilot study focusing on neural substrates of risky behavior and SAAF. Also, Dr. Rao has a joint appointment at Vanderbilt since 2011 and has access to all the resources required by the study. Drs. Ernst and Rao have a long history of collaboration (25 years). Drs. Brown and Murry collaborated for many years. Given the history of collaboration, we are confident that the team will work cohesively in the execution of the project and the resulting publications.**]**

IIIC.3. Preliminary Studies

IIIC.3a. Overview: We will describe data on the effects of PAAS on youth self-regulation and HIV-risk behaviors followed by data that support the proposed methods for studying the underlying neurobiological mechanisms.

IIIC.3b. PAAS Effects on Parenting Practices, Youth Self-Regulation and HIV-Risk Behavior: In a 6-week RCT of PAAS in 412 AA 7th grade students in Middle/West TN, Dr. Murry compared the efficacy of three delivery modalities in delaying/deterring risky behaviors among AA youth: PAAS small-group (n = 137), PAAS-technology (n = 138) and risk-prevention information home-mailing (n = 137). PAAS involves weekly separate but concurrent sessions with parents and youth followed by parent-child sessions. Both PAAS modalities were more effective in improving regulated, communicative parenting, which was associated with increased cognitive and emotional regulation in youth (**Fig 2**). These factors impacted youth intentions to engage in HIV-risk behaviors (in opposite direction) post-treatment as well as in dissuading engagement in risky behaviors (alcohol/drug use, sexual behaviors) at 18-month follow-up. PAAS-tech showed more robust effects compared to PASS small-group (p = .05). PAAS had a direct effect in preventing risky behaviors at 18 months. The results replicate the SAAF findings (earlier iteration of the small-group), <u>with sustained effects on alcohol and drug use and sexual risk behavior at least for up to 65 months,[25-36] thereby reducing HIV risk in highly vulnerable youth</u>.

Fig 2. PAAS Effects on Parenting and Youth Processes and Risky Behavior

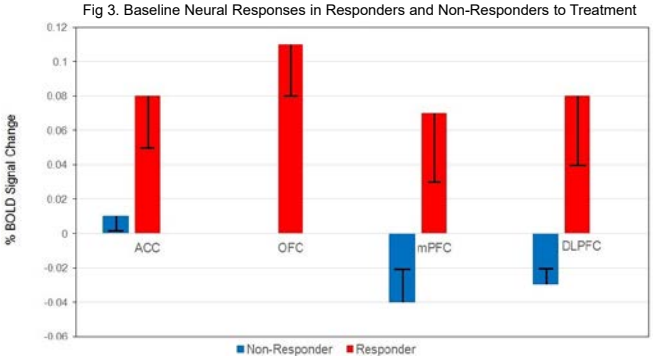


SEM model (N = 249): 436.90; p <.01; CFI = .87; RMSEA = .05 . *p < .05; **p < .01 (one-tailed).
<--- Stability of the construct. All measures were controlled for pre-test scores.

Parenting practices that include warmth and consistent, inductive discipline protect youth against risky behaviors.[161,162] Such parenting practices may have an even greater effect in AAs than NHWs.[163-167] These data suggest that positive parenting improves self-regulation in the offspring around pubertal transition which, in turn, protects these youth against behaviors associated with HIV/AIDS and SUD risk as they progress through middle and late adolescence. The current proposal plans to explore the neural underpinnings of changes in youth self-regulatory processes in response to PAAS with particular interest in youth's neural responses to risk (reward) opportunities.

IIIC.3c. Neural Responses to Risky Choices and Relation to Treatment Effects: Rao et al. administered the Wheel of Fortune (WOF), a two-choice decision-making task involving probabilistic monetary outcomes, to 19 adolescents who then received CBT for smoking cessation. **Fig 3** shows blood-oxygen-level-dependent (BOLD) signal changes during high-risk choice compared to the low-risk choice in responders (**red bars**) and non-responders (**blue bars**) to the CBT program. Responders had greater changes in the PFC (ACC: p = .05, OFC: p = .03, mPFC: p = .03, and DLPFC: p = .04) compared to non-responders. Utilizing this task, Ernst et al. reported neural changes in response to the CBT in adult depressed patients.[58] These findings suggest that the WOF is useful for probing decision-making/reward processes (see the next paragraph), and that these neural circuits may be sensitive to the acute effects of psychosocial interventions, such as CBT and PAAS.

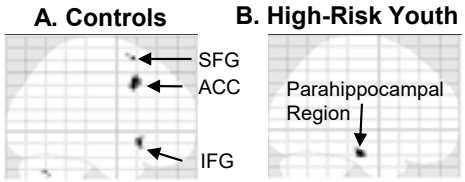
Fig 3. Baseline Neural Responses in Responders and Non-Responders to Treatment



We administered the WOF to 33 normal adolescent volunteers.[160] High-risk choice was associated with greater activation in the striatum compared to the low-risk choice (p = .05). A higher frequency of the high-risk choice was associated with lower activation in the PFC (ACC: r = -.60, p = .0008; OFC: r = -.58, p = .001; and mPFC: r = -.40, p = .04), as well as reward-seeking traits and risky behaviors in real life.[88] Ernst et al. used this task with a risk-avoidance component (passing the bet; **IIC.4f.2b.3, Fig 7**) in both adolescents and adults; similar to the above findings, neural responses to the task were associated with risky vs. risk-averse behaviors in real life.[158,168]

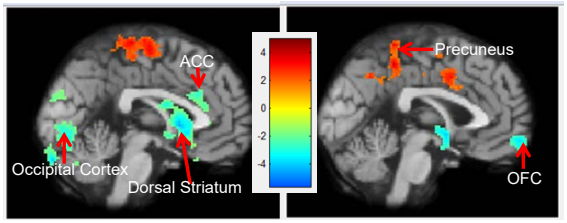
IIIC.3d. Neural Responses to Behavioral Inhibition Task in High-Risk Adolescents: Rao et al. administered the Go/No-Go Task[169,170] to 10 normal controls and 11 healthy adolescents at familial risk for SUD and studied their neural responses. Controls had greater activation in ACC (p = .0002), inferior frontal gyrus (IFG; p = .0002) and superior frontal gyrus (SFG; p = .0004) than the high-risk group during successful No-Go (inhibition) trials (**Fig 4A**). In contrast, the high-risk youth had significantly greater activation in the parahippocampal region (p = .0002) (**Fig 4B**). These data suggest that the task engaged brain regions involved in cognitive control more actively in the controls, whereas an area involved in emotional processes was engaged more actively in high-risk youth, suggesting poorer inhibitory control over negative emotions.[171-173]

Figure 4. Activation During Inhibition



IIIC.3e. Association between Risk-taking Traits and Functional Connectivity at Rest: Benningfield et al. examined the relationship of impulsivity, or sensation-seeking, with resting-state functional connectivity (RSFC) between ventral striatum and other brain regions in 25 children. Impulsivity (**Fig 5**; **left panel)** was negatively correlated with ventral striatum's RSFC with the ACC, dorsal striatum as well as the occipital cortex (**blue**). Sensation-seeking (**right panel**) was positively correlated with ventral striatum's RSFC with the precuneus (**red**; involved in self-referential processes) but negatively correlated with OFC (**blue)**.

Fig 5. RSFC and Impulsivity (L) or Sensation-seeking (R)



IIIC.3f. Integration of Pilot Data: Together, these pilot data demonstrate two aspects relevant to the proposed study: (1) feasibility: we can recruit and conduct prevention trials and functional neuroimaging studies in youth; and (2) support for the proposed hypotheses: PAAS is effective in improving cognitive-emotional self-regulation around puberty which serves as a deterring agent for risky behaviors as AA youth progress through adolescence. The reward-processing (decision-making) task is ecologically valid for assessing risky behaviors in youth, and the neural circuits tapped by this task have a predictive power in determining differential clinical response and sensitivity to the effects of psychosocial interventions. The proposed study will pair these validated paradigms to examine neural changes in response to PAAS and will examine whether the neural changes (a balance between reward-drive and cognitive-control/self-regulation circuitry) mediate the intervention's effects on cognitive and emotional self-regulatory processes. Risky behaviors in AA youth are a source of considerable morbidity and mortality. A better understanding of the moderating and mediating factors associated with the intervention effects to reduce HIV-risk behaviors will facilitate the development of personalized programs for high-risk youth.

IIIC.4. Research Design and Methods

IIIC.4a. Program Sites and Participants: Participants will be recruited from pediatric primary care programs in Vanderbilt University Medical Center (VUMC), behavioral and mental health programs at Centerstone and VUMC School-based Mental Health Program of Metropolitan Nashville Public Schools. Over 1,000 adolescent patients (41% AA) were seen in the General Pediatrics Division at VUMC in the previous 12 months **(see letter from Dr. Patterson**). In the Adolescent and Young Adult Clinic at VUMC, more than 2,000 adolescent patients (40% AA) visited the clinic in the previous 12 months (**letter from Dr. Walker**). Most of the patients in these primary care clinics are seen for routine physical examinations or minor acute illnesses, such as the flu, and are free from chronic medical and psychiatric conditions. Centerstone offered behavioral and mental health services to 10,000 youth (37% AA) in the past year (**letter from Dr. Rhea**). The clientele at VUMC and Centerstone is representative of the local census, and the clinics offer care at subsidized rates to low-income families. The VUMC School-based Mental Health Program operates in nine middle schools; 88% of students are AA (**letter from Mr. Majors)**. Dr. Benningfield is the Medical Director of this program. Drs. Benningfield and Rao have secondary appointments in the Department of Pediatrics at VUMC. Dr. Rao works closely with Drs. Patterson, Rhea and Walker, and she has previously utilized these resources for her research (R01 MH068391, U54 MD007593 and G12 MD007586).

Based on these substantial resources and our previous successes in recruiting for such studies, recruiting 128 youth is very feasible. We will recruit participants from the full range of socioeconomic status (SES). As the state capital with employment opportunities in government and home to three Historically-Black Colleges/Universities

(HBCUs; namely, Meharry Medical College, Fisk University and Tennessee State University), Nashville offers the opportunity to recruit racial-minority groups representing the full range of SES. In the 2010 Census, some racial-minority neighborhoods comprising of AAs reported an average income of $75,000 or higher, while other neighborhoods having a large number of the same racial-minority residents consisted of low-income families.[174]

IIIC.4b. Inclusion Criteria: Participants will be between 11 years 0 months and 13 years 11 months of age and of AA racial status (self-reported). They will speak and read English. The youth and a parent/legal guardian must agree to participate in the 6-week PAAS program and complete the assessments.

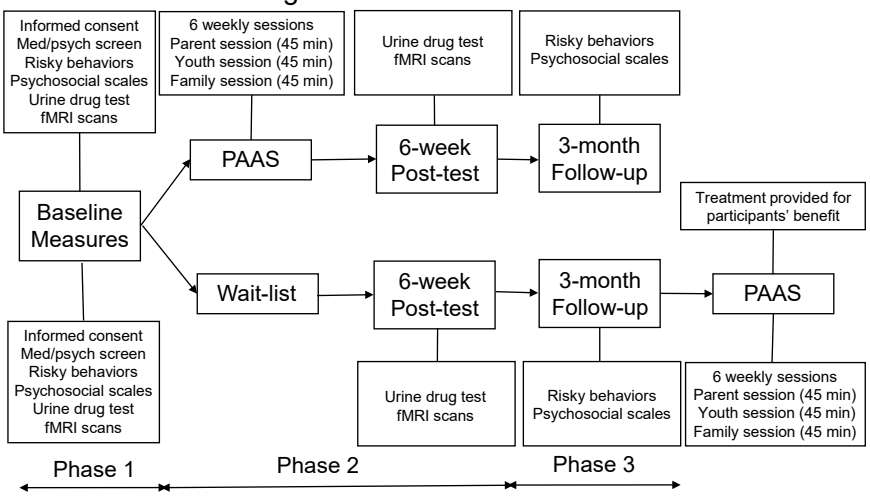
IIIC.4c. Exclusion Criteria: Youth with major medical problems (e.g. neurological disorders) or on medications that affect the central nervous system will be excluded. Persons with behavioral/emotional problems at a clinical level (by parent and/or youth report) will be excluded because psychiatric disorders can affect neural responses. Pregnant females, or those of suspected of being pregnant, will be excluded. Individuals with color-blindness, claustrophobia or metallic implants will be excluded. Persons using alcohol and/or drugs in the three days prior to neuroimaging studies (based on history and/or urine drug screen) will be excluded.

IIIC.4d. Rationale for the Restricted Age Range: We selected 11-13 year-olds because most youth at this developmental stage do not abuse alcohol or drugs and are not sexually active, but they are typically beginning to experience social pressures and pubertal changes that increase their vulnerability to these behaviors; in our previous samples of AAs, about 20% had ever used alcohol/drugs and 10% had sexual debut. Second, we have found the PAAS intervention to be more salient for youth at this age (**IIIC.3b**).[25,28,32,34] Third, sensation-seeking traits and the brain regions that respond to rewards (specifically the striatum) are more active around this period, with heightened vulnerability to risky behaviors in the context of an immature cognitive-control system.[23,57,175,176]

IIIC.4e. Rationale for Excluding Other Ethnic/Racial Groups: AA youth are selected because of the high rates of risky behaviors and associated negative consequences (e.g. HIV/AIDS, violence) compared to other groups (**see II**). PAAS was designed specifically for AAs. Although it contains elements that are generalizable, some components of the program are specific to AA (e.g. adaptive racial socialization, and managing stress associated with racial discrimination). If neurobiological mediators of this program are identified, future investigations will be able to test these effects in other ethnic/racial groups, by modifying ethnic-specific elements of the intervention.

IIIC.4f. Methods

Fig 6. Protocol Outline



IIIC.4f.1. Overview: A description of the protocol/procedures is provided (**IIIC.4f.2 - IIIC.4f.6; Fig 6,Table 1**). Eleven-to-thirteen year-old AA youth and their parents will complete information on demographic and health status as part of their clinic visits. Families selected randomly from the eligible pool will be invited to participate, while at the clinic or later via mail (**IVA.2a, Human Subjects**). Research is an integral part of these participating clinical programs and processes are in place for a smooth transition from clinical care to research that follows the Institutional Review Board and Health Insurance Portability and Accountability Act (HIPAA) guidelines. When contact is made, they will be provided information about the study, with an overview of the time commitment and assessments. Interested families will be screened further to determine eligibility by obtaining medical, psychiatric and treatment history.

Phase 1 (Pre-intervention Assessments): Information on psychiatric symptoms, psychosocial factors and risky behaviors will be completed. Those who meet eligibility criteria will have a blood draw for gonadal hormones and receive training on the fMRI tasks and have a mock scan. A urine sample will be obtained to test for alcohol/drug use and pregnancy. They then will complete baseline fMRI studies. Phase 2 (Intervention Phase): The families will be randomized using procedures described in **IIIC.4f.5** to PAAS or wait-list condition (1:1 ratio) for the 6-week intervention period. PAAS consists of 6 web- or DVD-based weekly sessions, 90 minutes per session; the first half includes individual, concurrent curricula for caregivers and youth, and the second half is a family-joint session designed for practicing the skills learned in the individual sessions. At the end of the 6-week intervention period, the urine drug test and fMRI studies will be repeated in both groups. Phase 3 (Follow-up Phase): Three months after the intervention phase, both psychosocial and risky-behavior assessments will be repeated. The wait-list group then will be offered the PAAS intervention as a benefit for participation in the study.

IIIC.4f.2. Measures for Primary Hypothesis Testing

IIIC.4f.2a. Youth Psychological Protective Processes: This index consists of seven measures (**Appendix 1**).

IIIC.4f.2a.1. Resistance Efficacy: Participants respond to three versions of a scenario to report the actions they believe they would take if presented with the chance to drink alcohol, smoke cigarettes or use marijuana.[30,177]

IIIC.4f.2a.2. Self-control: The 25-item Self-Control Inventory includes items of good self-control (e.g. delay of gratification, planning, problem-solving, dependability, and soothability) and poor self-control (e.g. impulsivity, immediate gratification, distractibility, and low frustration tolerance).[178]

IIIC.4f.2a.3. Future Orientation: The Time Perspective Inventory consists of the future, present/hedonistic, and present/fatalistic subscales.[179] The future subscale reflects formulation of goals and plans to achieve them.

IIIC.4f.2a.4. Emotion Regulation: On the Coping Processes Inventory,[180] respondents are provided definitions of various coping behaviors and asked how often they use each approach for dealing with problems concerning school, parents, health and sadness.

IIIC.4f.2a.5. Self-image: Body Image subscale from the Sexual Self-concept Inventory consists of eight items that index the youth's evaluation of his/her own physical appearance.[181]

IIIC.4f.2a.6. Self-esteem: Rosenberg Self-esteem Scale includes a 5-item general positive self-esteem subscale and a 5-item general negative self-esteem subscale.[182]

IIIC.4f.2a.7. Impulsivity: Eysenck Impulsiveness Scale includes 13 items that assess personality traits related to impulsivity and venturesomeness.[183]

Table 1. Assessment Schedule

	Informant		Duration	Screen	Phase 1		Phase 2 - Intervention						Phase 3
Phase Window	**Parent**	**Youth**	**Minutes**		**5-10 Days**		**Starts within 14 Days of Screen**						**3 Mth**
Visit					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Intervention Week							**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	
Clinic/Telephone Screen	X	X	15-30	X									
Informed Consent/Assent	X	X	45-60		X								
Demographic Information	X		10-20		X								
Psychiatric Diagnstic Screen	X	X	30-60		X								
Youth Beh/Emotional Problems	X	X	20-30		X								
Reward-drive Traits		X	15-20		X								
Risky Behaviors		X	15-20		X								X
Resistance Efficacy		X	10-15		X								X
Self-control		X	15-20		X								X
Future Orientation		X	10-15		X								X
Emotion Regulation		X	5-10		X								X
Self-image		X	5-10		X								X
Self-esteem		X	5-10		X								X
Impulsivity		X	5-10		X								X
Involved-vigilant Parenting	X	X	10-15		X								X
Risk-behavior Communication	X	X	10-15		X								X
Adaptive Racial Socialization	X	X	10-15		X								
MRI Safety Screen	X	X	5-10		X							X	
Handedness Scale		X	5-10		X								
Tanner Stages		X	5-10		X								
Serum Gonadal Steriods		X	10-15		X								
Urine Alcohol/Drug Test		X	10-15			X						X	
Urine Pregnancy Test		X	0			X						X	
Task Practice/Mock Scanner		X	60-90			X							
Resting and Task-based fMRI		X	90-120			X						X	
PAAS Intervention	X	X	90-100				X	X	X	X	X	X	

IIIC.4f.2b. Neuroimaging Protocol

IIIC.4f.2b.1. Mock MRI Scan: At the baseline assessment, participants will be provided take-home information that will help to prepare them for MRI scanning. They will complete a mock scan to practice staying still in the scanner, get used to the noise and practice the fMRI tasks. This also will allow us to assess for claustrophobia.

IIIC.4f.2b.2. Data Acquisition: Neuroimaging data will be acquired on a 3 Tesla Philips Achieva MRI scanner with a 32-channel head coil located at Vanderbilt University Institute of Imaging Science (VUIIS; **letter from Dr. Smith**). Padding behind the head and neck will be used to increase comfort, and the forehead will be strapped to prevent head motion. A 20-25 minute break will be provided between resting and task-based scans to reduce motion artifacts and impaired performance on the task. To correct for the confounding effect of overlapping physiological signals, pulse and respiration will be measured with MRI-compatible non-invasive equipment. In our multi-modal imaging protocols lasting 60-90 minutes, we had reliable data in 93%-97% of the samples.

A high-resolution T1-weighted scan (1 mm isotropic resolution; 6.5 min) will provide anatomical information to serve as a basis for cortical parcellation and a template for registering the functional imaging data. This will be followed by a B0 mapping sequence (1 min) to correct image distortions due to magnetic field errors. Next, resting-state (rs-fMRI) scans will be obtained to measure intrinsic functional connectivity. T2* weighted BOLD images with a voxel size of 3mm isotropic and a volume acquisition time of 2 sec will be acquired using a 2D gradient echoplanar imaging (EPI) sequence over 12 min (360 image volumes) to obtain more reliable data. Participants will be instructed to relax with their eyes open and to look at a fixation cross. They will be monitored with eye-tracking equipment to ensure that they do not fall asleep. For task-based fMRI scans (45 min), stimulus presentation will occur with E-Prime, with the images projected onto an overhead LCD panel. A 5-button box will be used for recording behavioral data. Functional images will be acquired with a gradient-echo, EPI sequence: 34 oblique axial slices (3 mm thick, 0 mm gap), oriented to the AC-PC line and encompassing the entire cerebrum

and most of the cerebellum (TR/TE = 2000/25 msec, FOV = 24 cm, matrix = 64 × 64). This sequence was designed to preserve the signal in the striatum and ventral PFC, areas which are susceptible to signal drop-out. An automated higher-order shim procedure will be applied to minimize potential magnetic field inhomogeneities.

IIIC.4f.2b.3. The WOF Task: This task allows for the analysis of both risk-seeking and risk-avoidance (**Fig 7**).[158] During each trial, the participants will be shown a wheel on which the probabilities of winning and losing points are shown as pink and yellow sections, respectively. The number of points that can be won or lost is printed on the wheel sections. The words "Bet" and "Pass" are displayed each time, prompting participants to select one or the other. For the present study, this "decision phase" is the period of interest. After 3 seconds, the wheel spins for a variable, randomly jittered period (1, 3, 5, or 7 sec), and the final result is displayed for 1 sec. If participants choose to bet, and the wheel lands on the pink section, they win the points indicated. Conversely, if the wheel lands on the yellow section they lose the number of points shown. These amounts will be added (or subtracted) to a running total that is not revealed until the end of the task. If participants choose to pass, they still see the outcome but no points will be added or deducted.

Fig 7. WOF Task

Win amounts are kept constant while probability and loss amounts are manipulated orthogonally resulting in 6 different wheels that represent 4 win/loss ratios (100/0, 60/40, 40/60, 0/100) and 2 levels of expected value (EV; +12 and −12). Participants are not explicitly told about the uniformity of expected values. The 0/100 wheel (100% chance of losing 12 points) and the 100/0 wheel (100% chance of winning 12 points) serve as no-risk control conditions and each is presented 8 times. Each 40/60 and 60/40 wheel (EV+ and EV−) is presented 22 times across 4 blocks. Behavioral outcomes include risk-seeking (percent of trials betted), risk-avoidance (percent of trials passed), and response times across conditions of varying probabilities and expected values. We found no practice effects with repeated tasks in at-risk adolescents during longitudinal follow-up (Rao, unpublished data).

IIIC.4f.2b.4. Go/No-Go Task: The task assesses behavioral responses, with the subjects selectively responding to target stimuli ("X" ~.80 probability) and inhibiting responses to infrequent non-target stimuli ("K"~.20 probability; **IIIC.3d**).[169,170] The task consists of two runs, with 245 trials per run (7 min) and a random inter-stimulus interval.

IIIC.4f.2b.5 Quality Assurance (QA): Weekly QA data will be collected using the American College of Radiology Phantom Test Guidance Manual. The Functional Biomedical Informatics Research Network QA protocol will be used so that changes in image characteristics over the study period can be monitored and corrected.

IIIC.4f.2b.6. fMRI Data Processing and Analysis: Each participant's functional images (rest and task) will be corrected for head motion and co-registered to a common atlas space, then smoothed with a 6 mm kernel. After initial pre-processing, the time series at each voxel will have white matter, cerebrospinal fluid and motion-related signals removed via regression,[184,185] and will be low-pass filtered at 0.1 Hz to retain low frequencies relevant for connectivity estimation. Head motion can still be a significant confound in fMRI connectivity studies, particularly in children.[186] Hence, we will identify volumes that show large displacement (>0.5mm) or large change in global signal (>0.5%) relative to the preceding volume, and remove them prior to connectivity analysis.[187] **[**The resulting 3 metrics can be summarized to a single number and then compared between groups or used as covariates.**]**

For the task-based data, event-related neural responses will be modeled with separate canonical hemodynamic response functions for each of the conditions (e.g. wheel types). For instance, BOLD responses to Risk vs. No-Risk trials will be compared, within/across probabilities and expected values. Group-level analysis will compare the trials during which the participants passed the trials (risk-avoidance) to trials where they bet. For the Go/No-Go task, successful Go trials will be compared to both successful and unsuccessful No-Go (inhibition) trials.

Resting-state functional connectivity will be calculated as the Z-transformed correlation coefficient between pre-processed time series, using the CONN toolbox.[188] Connectivity between seed region time series and each gray matter voxel will be calculated to create connectivity maps for each seed region. Task-based connectivity will be calculated using the gPPI toolbox.[189-191] For both types of connectivity, we will use seed-region approaches with the following seeds: inferior and superior parts of the ventral striatum,[192,193] ventral and dorsal parts of the ACC,[194] mPFC, OFC and DLPFC. Seed regions will be defined using probabilistic atlases derived from structural tracings. Connectivity maps for each seed region will be compared at each voxel among the groups, using a restricted maximum likelihood approach that accounts for heteroskedasticity (SPM8 software implementation).[195] The resulting T maps will be thresholded at $p<0.05$, correcting for the multiple voxel comparisons based on spatial smoothness using random field theory,[196-198] to identify brain regions where the groups differ in connectivity.

In addition to hypothesis-driven seed-based functional connectivity of fronto-striatal circuits, the Wager/Lindquist Multilevel Mediation and Moderation (M3) Toolbox[199] will be used in conjunction with SPM[195] and MATLAB[200] to conduct whole-brain mediation analysis.[201] This analysis allows voxels to be identified that make the strongest case for mediation or search for maps of each effect in the mediation.

IIIC.4f.3. Variables to Determine Eligibility or Supplementary/Exploratory Variables in Hypothesis Testing

IIIC.4f.3a. Demographic Information: Caregivers will report their education level, yearly income, per capita income, employment status, duration of unemployment in the past 2 years, hours worked per week, numbers and ages of children and adults in the household, and relations of all household members to one another.

IIIC.4f.3b. Psychiatric Diagnostic Screen: The Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL), a semi-structured interview, will be administered separately to the parent and youth to screen for present and lifetime history of psychiatric illness.[202,203]

IIIC.4f.3b. Behavioral/Emotional Problems: The Child Behavior Check-List (CBCL) is an instrument designed for parents to rate the child's problem behaviors (120 items) as well as competencies (20 items) in the past 6 months.[204] Youth rate the same items using the Youth Self-Report (YSR).[204]

IIIC.4f.3c. Reward-drive Traits: The Behavioral Inhibition System and the Behavioral Activation System (BIS/ BAS) is a 24-item self-report scale that assesses motivational systems.[205] The BIS is sensitive to the signals of punishment and non-reward, whereas the BAS taps into appetitive motivation and is sensitive to the signals of reward. The BAS correlated positively with the high-risk choice on the WOF task.[88] We will assess whether BAS score modulates neural and cognitive-emotional self-regulation changes in response to the PAAS intervention.

IIIC.4f.3d. Risky Behaviors: This construct consists of alcohol/drug use and sexual behavior, each with three separate constructs (willingness, intention, and actual behavior). Intention and willingness will be measured in addition to behaviors as the participants are young and will have limited opportunity to engage in risky behaviors within the short follow-up period despite manifesting some risky behaviors. Prior longitudinal research has shown that intention and willingness are good predictors of alcohol/drug use and sexual risk behavior (**IIIC.3b**).[34,206-209]

Behavior Willingness is assessed by asking participants to imagine themselves in different situations and then to think about how they might respond if they were in that situation (**Appendix 1**). Opportunities for access to risky situations and prototype peers also are assessed. It includes 32 items for alcohol/drug use and 23 items for sexual behavior. *Behavior Intention* is measured with four items on alcohol/drug use, and four items on sexual behavior. *Behavior* E*ngagement* consists of three items for alcohol/drug use (two concerning lifetime behavior and one concerning recent use) and three items to assess age of onset of sexual activity and unprotected sex.

IIIC.4f.3e. Regulated, Communicative Parenting: This index consists of three measures (**Appendix 1**).

IIIC.4f.3e.1. Involved-vigilant Parenting: The scale is composed of 19 items, rated on a 5-point Likert scale, that assesses parental involvement, inductive discipline, consistent discipline and monitoring.[30,210,211]

IIIC.4f.3e.2. Communication about Risky Behaviors: Articulated norms and expectations regarding risky behaviors consists of two scales. The first is a 6-item scale that assesses parents' communication of expectations regarding the use of alcohol and other substances on a 5-point Likert scale.[212] Another scale modified for communication patterns about sexual issues assesses whether parents ever talked to the child about topics such as reproduction/having babies, menstruation, sexually transmitted diseases and HIV/AIDS.[213]

IIIC.4f.3e.3. Adaptive Racial Socialization: The Racial Socialization Scale includes 15 items rated on a 3-point Likert scale[214] to assess whether parents transmit explicit messages to youth about strong work orientation, race relations, and coping with racism and discrimination in the workplace, educational institutions and community.[215]

IIIC.4f.3f. MRI Safety Screen: Screening for metallic objects/devices and claustrophobic symptoms will be done with a standardized instrument utilized by VUIIS.

IIIC.4f.3g. Handedness: Handedness will be verified using the modified version of the Edinburgh Handedness Test, with right-handedness defined by a score >20 out of possible 28.[216]

IIIC.4f.3h. Physical/Laboratory Measures: Participants will rate their pubertal status based on the illustrations of stages of pubertal development.[217,218] Blood will be drawn for serum gonadal steroids (estradiol, progesterone and testosterone).[219] In exploratory analyses, we will examine the effect of pubertal stage and gonadal hormones on neural responses, as there likely will be a greater variation in pubertal maturation at this age range (11-13 years). A urine test will provide qualitative and quantitative information on substance use (amphetamines, benzo-diazepines, cannabinoids, cocaine, ethanol, opiates, oxycodone, and phencyclidine). Sexually active females will have a urine test to rule out pregnancy for the MRI studies.

IIIC.4f.4. Data Collection Protocol: Trained staff members will conduct the assessments. They will have a minimum of 40 hours of training and supervised practice on how to obtain informed assent/consent, build rapport, interview, and assist participants on the computer-based data collection system and PAAS-technology program. Data collection will occur at clinical sites, the PI's lab, participants' homes or community settings, based on the participants' choices. Families will use the computer-based data system to complete assessments using audio computer-assisted self-interview (ACASI) procedures, which are integrated into the remote data management system (**IIIC.7a**). Each computer will have headphones, the computer screen will display one question at a time, and all information that appears on-screen also will be read to participants by the computer. Compared with face-to-face interviews and self-administered surveys, ACASI offers privacy and confidentiality that, in turn, elicits less social desirability bias,[220] and more accurate reports on questions about sensitive issues or negative behaviors. The use of ACASI in our previous studies reduced missing data, increased consistency and eliminated literacy requirements.[221] Psychiatric diagnostic interviews will be conducted by trained research assistants. Dr. Rao was involved in the development and testing of the K-SADS-PL. Prior to initiating the study, reliability will be assessed (requiring ≥85% agreement). In order to avoid reliability drift over time, reliability checks will be made annually. All interviews will be audio-taped, and a random selection of 15% of the interviews will be co-rated by Dr. Rao.

IIIC.4f.5. Randomization: A 2 (gender) x 2 (Tanner stage) x 2 (intervention) randomized, matched-pairs, block-design will be used to stratify participants based on gender and Tanner stage (I-II, III-V) comprising 4 blocks for 128 participants. Within each block, 16 pre-randomized (PAAS or wait-list) pairs based on order of intake will be prepared in advance. Randomization will proceed as follows: the first youth to enter the study in each block will be assigned to either PAAS or wait-list (based on pre-randomization for that pair) and the second will be assigned to the opposite condition. The third youth will be assigned to either PAAS or wait-list (based on pre-randomization for that pair) and the fourth will be assigned to the opposite condition. The randomization based on the order of entry will continue in this manner until all matched pairs within each of the 4 blocks are filled.

IIIC.4f.6. PAAS Protocol: PAAS is a 6-week, technology-delivered, family-based youth risk intervention program (**Table 2**). PAAS uses a set of six (one per week) DVDs or the web to deliver separate sessions for parents and youth, and joint sessions in which they both engage on the same computer to integrate and practice the skills they have just learned in their separate sessions. Each weekly session takes about 45 minutes to complete, for an average of 90 minutes per participant (45 minutes separate plus 45 minutes joint), and a total of 9 hours for the 6-week intervention. Each session includes a review, a virtual discussion, and observing and interacting with four parent and four youth Avatars that reflect phenotypes of AAs, with voice-overs by AA parents and youth. Videos portraying family interactions and intrapersonal processes are integrated into each session to convey key points of the intervention along with interactive activities to promote skill-building and to reinforce learning. PAAS also includes a technology tutorial and an introductory session. After receiving detailed instructions face-to-face, the program will be accessible through a website to participants who prefer using the Internet, or it will be downloaded onto laptop computers and delivered to them at their homes or other locations convenient to the participants, such as participating clinics or community settings (e.g. churches, community centers).

The PAAS curriculum will likely influence the neural pathways by: 1) providing opportunities for youth to negotiate novel situations in a safe environment until they gain better adaptive skills in self-control;[222,223] 2) fostering resistance-efficacy in high-risk situations, and reinforcing positive self-image and encouraging future orientation through goal-setting;[224-227] and 3) encouraging youth to think about the potential consequences of risky behaviors from their parents' perspective (**IIIC.3b; Table 2**). Each of these pathways has evidence to suggest that reward-drive and cognitive-control/self-regulation neural circuits are involved.[43,228-236] Parents play an important role in protecting youth against risky behaviors by providing warmth as well as consistent, inductive discipline.[161,162]

Data from the computer/web, which tracks time spent on the computer and the completion of activities, will be downloaded to a secure server. Participants also will complete questions pertinent to each intervention session to ensure that they grasped the main concepts. The computer-based program was selected for the following reasons. Families can experience a computer intervention when it is most convenient for them and at their own pace. It can be accessed at home or another convenient site where a computer is available. Computer literacy and familiarity, even among those from economically-disadvantaged households, is nearly universal now.[237] Our studies (**IIIC.3b**), as well as those of others, that included AA youth and adults have shown that computer-based prevention programs can be very engaging and motivating.[238,239] The privacy that computer-based interventions afford is particularly important in close-knit, ethnic-minority communities, in which participants typically know one another outside the intervention context and privacy is a key concern.[240,241]

Table 2. PAAS Curriculum: Program-Targeted Behaviors

Session	Parent Component	Parent-targeted Behavior	Youth Component	Youth-targeted Behavior	Family Component	Family-targeted Behavior
1	Supportive parenting	Importance of supportive parenting; normative dev. patterns of adolescence; parental expectations and goals; effective ways to support youth goals, dreams	Future orientation	Identify and visualize goals and dreams	Positive parent-child relationship	Build nurturing, supportive relationships; enhance parental involvement
2	Family rules and routines; nurturing, involved parenting	Understand the values of having specific house rules; appropriate and effective punishment for misbehavior	Self-discovery and autonomy	Identify positive self-qualities and capacities; clarification of values and social norms; association between responsibility and autonomy and privilege-granting by parents	Family values	Share family rules and chores; discuss family values; create a family shield of values
3	Adaptive racial socialization; encouraging racial pride	Identifying and managing racial discrimination; preparation for racial bias and promoting racial pride	Dealing with unfair situations	Identifying and clarifying reasons for differential treatment; active coping strategies to manage unfair & difficult situations	Encouraging racial pride	Learn strategies of handling difficult situations; identify special strengths of African-American families
4	Linking school and academic performance to goals and dreams to youths' future orientation	Understand the importance of success in school; learn ways to help youth succeed in school; learn effective ways to be an advocate for your child in school settings	Being cool and smart	Understanding the differences between passive, aggressive and assertive behaviors; adaptive responses that are smart and cool	Positive, affectionate family relations	Identify each other's stressors; reinforce ways to help each other to reach family goals and relieve stress
5	Protecting against dangerous behavior	Understand risk prevalence, overall and for your community; Importance of being an approachable parent	Peer pressure; parents' concerns about peer affiliation	Identify peer pressure; compare risk engagers from non-risk engagers; dealing with temptation; prosocial peer affiliation	Caregivers and youth working together to protect youth from risk behaviors	Develop family plan for handling peer pressure and temptation; share expectations and values about risk and friendship
6	Parental protections that reduce high risk behaviors	Learn how to effectively monitor youth; understand the prevalence of sexual activity in teens; establish expectations about sex	Dealing with sexual and substance use temptations	identifying and avoiding dangerous situations; connecting temptations, dreams, goals, school and future orientation	Our family plan and pledge for positive youth development	Share expectations, dreams, and hopes; discus/identify family strengths; establish a family creed of strength, growth and competence

IIIC.5. Primary Outcome Criteria: Primary outcome variables include fronto-striatal functional connectivity at rest and while performing the WOF task and youth psychological protective factors (cognitive and emotional self-regulation). Other neural measures/circuits, psychological/social-contextual and behavioral variables (**Appendix 1**) will be used either as supplementary measures or as potential covariates. By sharpening our focus to *a priori* specified neural circuits and psychological measures, we hope to increase statistical power and, in turn, our ability to identify important differences in the responses of these circuits according to youth protective factors.

IIIC.6. Sample Attrition: The team has experience with intensive longitudinal studies involving difficult-to-reach samples with retention rates exceeding 90% for short-term follow-up (**IIIC.10a**). Even with a liberal estimate of 20% attrition, we will have 102 participants, which will give us sufficient power to detect medium effects (**IIIC.7e**).

IIIC.7. Statistical Methods

IIIC.7a. Data Management: Data management will be done via remote electronic data capture (*REDCap*).[242] REDCAP was developed at VUMC to insure data integrity and completeness, including compliance with HIPAA (over 300,000 users). Data will be entered immediately after testing on data entry screens designed to duplicate the data collection forms (ACASI; **IIIC.4f.4**). Reports can be generated to track all contacts with the participants.

IIIC.7b. Procedures for Handling Missing Data: Missing data will be accounted for by including "missingness" as a covariate if the proportion of missing data is small,[243-246] or alternatively using multiple imputation methods if the proportion of missing data is large, e.g. >5%.[247]

IIIC.7c. Data Reduction: Each hypothesis will be examined using a primary variable, with supplemental information gained from analysis of other related measures (**see IIIC.5**).

IIIC.7d. Data Analysis: Descriptive statistics (e.g. means and standard deviations, frequencies and histograms) will be computed for all variables, along with 95% bootstrap confidence intervals. Significance tests will be two-tailed, with $p < 0.05$, controlling for multiple comparisons.[248-250] Pubertal stage/gonadal hormones, gender and SES will be included as concomitant variables in analyses where they are known to correlate with the outcome. These covariates, while not of primary interest, will reduce residual variance and increase the precision of effect estimates for improved statistical power.[251] Secondary analyses will determine if these covariates significantly affect the outcomes. Behavioral/emotional problem score (CBCL/YSR), lifetime history of substance use and dose of the intervention (number of completed sessions) will serve as additional potential covariates.

IIIC.7d.1. Hypothesis 1: *PAAS will induce greater functional connectivity changes in the reward-drive and cognitive-control (fronto-striatal) circuitry compared to the wait-list condition.* Post-treatment neural connectivity

scores will be regressed on group assignment (PAAS vs. wait-list) as the independent variable and baseline (pre-treatment) neural connectivity score as a covariate. Two separate models will be run for resting-state and task-based fMRI connectivity measures. Other covariates (**IIIC.7d**) will be included if there are group differences.

IIIC.7d.2. Hypothesis 2: *PAAS-induced changes in youth self-regulation (cognitive and emotional regulation) at 3 months will be mediated by PAAS' effects on changes in neural circuitry.* A mediation process will be modeled using a sequential process of the associations between specified brain responses and self-regulation.[252] The Wager/Lindquist Mediation Toolbox (**IIIC.4f.2b.6)** will be deployed.[199,201] Mediation effects are estimated from the product of the regression coefficient (a) when a mediator of interest (e.g. neural response) is regressed on the intervention and regression coefficient (b) when the outcome criterion (self-regulation at 3 mon.) is regressed on the mediator, controlling for the intervention effect. The standard error of the mediated effect can be calculated in various ways, including the bootstrap method.[252,253] This method is referred to as the product-of-coefficients approach for testing mediation, and provides an efficient overall test of mediation processes.[252-254]

IIIC.7d.3. Exploratory Analyses: We will examine whether baseline characteristics moderate PAAS' effect (e.g. if reward-drive [BAS] score/ neural connectivity in the fronto-striatal circuit interacts with PAAS) on improvement in self-regulation. We will assess the association of neural changes (local/whole brain) with behavioral and social-contextual variables targeted by PAAS (i.e. risky behaviors and parenting behavior). Other functional connectivity changes (e.g. default-mode, cognitive and salience networks, and the fronto-limbic circuit) will be identified and the association between functional connectivity patterns at rest and during task performance will be evaluated.

IIIC.7e. Power Analysis: Statistical power was estimated with G power 3.1.9.2 software.[255] We used traditional criteria (alpha = .05 two-tailed, power = 80%) to estimate statistical power.[256] **[**Rather than base power estimates on modest pilot samples, we assessed power by *minimum detectable effect size* (*MDES*).[257]**]** For fMRI studies, Thirion et al. recommend sample sizes of 40 per group for reliable estimates of group differences.[258] Given the multiple variables of interest, we selected larger sample sizes. Randomized subjects will be compared in two conditions using a multiple regression model. With N = 102 participants (after accounting for attrition), a multiple regression would have adequate power to detect an effect size as low as r = .31 (R^2 = .10). Cohen[259] considers r ~ .10/.30/.50 to be small/medium/large effect sizes. Power will be sufficient to detect medium effects. Because we will use a repeated measures model with covariates, actual power should be somewhat better. A sample size of n = 102 is also sufficient to detect mediation in an analysis with medium-sized α and β paths.[260]

IIIC.8. Timeline: Table 3 shows the expected timeline of activities for the proposed research.

Table 3. Timeline of Research Activities

	Year 01				Year 02				Year 03				Year 04				Year 05			
Research Activities Per Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Train staff, set up database	x	x																		
Recruit subjects and conduct baseline assessments		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Implement PAAS intervention for the active group		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Post-intervention measures			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Follow-up assessments (3 months post-treatment)				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Implement PAAS for the wait-list group				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Data entry and management		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Data analysis																		x	x	x
Preparation of manuscripts																		x	x	x

IIIC.9. Expected Outcomes and Future Directions: The study is expected to contribute new knowledge in the following areas: (1) whether functional connectivity changes in decision-making (a balance between reward-drive and cognitive-control) neural circuitry occur in response to a preventive intervention (PAAS); (2) whether these functional connectivity changes mediate the improvement in youth self-regulation processes that are targeted by the intervention; (3) whether socio-demographic features, reward-drive traits and baseline functional connectivity can identify subgroups of youth who respond better to the intervention; and (4) if intervention-induced changes in functional connectivity and self-regulation are associated with a reduction in risky behaviors (willingness and intentions). The study will advance the benefits of PAAS and other evidence-based programs by improving our understanding of the ways in which neurobiological mechanisms affect intervention-induced behavioral changes.

If, indeed, brain changes in the decision-making circuitry mediate the intervention effects on self-regulation and risky behaviors, the intervention program can be tailored to individual youth to improve outcomes.[40,42,43] Novel pharmacological, psychosocial and neurofeedback treatments can be developed *to target specific neural circuits* as adjunctive interventions for reducing risky behaviors in this population.[71,73,76,261-266] Additionally, "personalized"

interventions can be developed for specific subgroups of at-risk youth to reduce risky behaviors and their long-term consequences. These methods may include, for example, the development of biopsychosocial profiles that can be used efficiently to focus intervention efforts. Recent studies in animals and humans have suggested that behavioral and psychological manipulations, including diet, exercise and CBT can induce neural changes.[267-270] The neural markers can be used to predict treatment outcome more effectively[79,263,271,272] and to index treatment response[71,73,76,261-263,266,273-276] in RCTs, which then can change clinical practice and public policy.

IIIC.10.Potential Problems and Alternative Strategies

IIIC.10a. Recruitment and Retention Issues: Recruitment and retention will be challenging. However, we are confident that we can manage these challenges because: (1) as previously described in **IIIC.4a**, we will have as our recruitment partners primary care and nonprofit service providers that see large numbers of youth and that Dr. Rao has successfully worked with on prior studies; and (2) we will employ retention procedures that we have used successfully with similar populations.

In previous studies, we have successfully recruited high-risk samples (low SES, mood and addictive disorders) and implemented intensive protocols (multi-dimensional clinical and biological measures with admissions for sleep/neuroendocrine studies lasting up to 3 consecutive days) that included much more lengthy longitudinal designs (follow-up assessments at 6-month intervals for up to 5 years). Also, Dr. Murry has more than 20 years of experience conducting community-based research, recruiting and retaining over 2,000 AA parents and youth in developmental and prevention studies. We had low attrition rates (10-20%) in these studies, and we will follow the same procedures, including evening/weekend appointments to accommodate participants, reminder calls the day before and on the appointment day, providing meals/snacks during visits, engaging local community partners and offering clinical and social service referrals to families when needed. We will provide reimbursement for travel and use a reimbursement protocol that is incentive-based (i.e. based on the number of visits attended). The PAAS intervention (tech version) also is feasible to implement at home at the participants' convenience.

IIIC.10b. Inherent Confounds in the Study Design: Even though invitations will be sent to randomly selected families, the participation will be based on their willingness and meeting subsequent stringent eligibility criteria. Hence, the findings might not generalize to the larger AA population. The participating clinics maintain electronic databases with demographic and clinical characteristics, and we will compare the sample with the remaining clinic population (and those who declined to participate or were excluded after the invitation) on these features. The other confounds related to restricted age range and race/ethnicity have been addressed (**IIIC.4d, IIIC.4e**).

IIIC.10c. Trial Design: We considered several alternative designs, including classic RCT with an active or non-treatment control group. **[**"Active ingredients" of the intervention were identified in previous RCTs (**IIIC.3b**).[25-36]**]** We opted for this design for following reasons: (1) a wait-list control group will provide greater power in detecting group differences than an active control group; and (2) from an ethical standpoint and to engage participants in the study, we are able to offer the control group an intervention that has been shown to be effective in prior RCTs after the wait-list control period. Since the control group also will be at high risk for HIV/AIDS and other negative consequences related to risky behaviors, this approach provides an opportunity to prevent such problems.

IIIC.10d. Accounting for Treatment Effects: The waitlist does not account for general treatment effects in the active condition. PAAS-tech program does not provide direct personal contact with "trained therapists", thereby minimizing therapeutic effects accounted for by therapist-participant interactions during intervention sessions. In the event we do not find the hypothesized changes in the fronto-striatal circuits in response to the intervention, we will perform whole-brain analysis to explore changes in other brain regions/circuits (**IIIC.4f.2b.6, IIIC.7d.3)**.

IIIC.10e. Intervention Effects in Rural Versus Urban Areas: The intervention was originally designed for rural AA families to address the problem of limited access to mental health services in the context of rising prevalence of HIV-risk behaviors in this population. However, the socio-cultural and risk factors for urban families are similar to rural families. The program was tested in small towns near urban areas (near Athens, GA, and Memphis, TN), where the population resembles patients from outlying areas of Nashville that are seen in the participating clinics. We examined site effects between rural and non-rural areas and found no differences in intervention effects.

IIIC.11. Scientific Rigor: As can be gleaned from the Research Design and Methods Section (**IIIC.4**), we have given careful consideration to the study design with respect to sample selection including biological and social factors, procedures to reduce attrition, alternative designs, randomization process, and pre-post-intervention assessments. We proposed quality control methods for data collection and processing to eliminate or minimize bias, *a priori* selected primary outcome criteria (**IIIC.5**) and controls for potential confounding variables in the data analysis (**IIIC.7d**). We considered anticipated problems and proposed ways to minimize them (**IIIC.10**).

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