

**Study Protocol For**  
**R21DA041531 - Rescuing Cognitive and Emotional Regulatory**  
**Processes to Aid Smoking Prevention**  
**Version Date: June 15, 2015**

## SIGNIFICANCE

Despite declines in cigarette use during the past several decades, smoking remains highly prevalent (19.3%) among U.S. adults, resulting in an estimated 443,000 premature deaths annually. Moreover, adolescents from low socio-economic status (SES) families have higher rates of smoking than their higher SES peers,<sup>25,26</sup> and have greater increases in smoking over time.<sup>27</sup> Individuals from low SES also have been found to benefit less from standard informational smoking prevention,<sup>1,9</sup> exacerbating health disparities across SES levels. One possible explanation for this may be that cumulative stressors associated with low SES disrupt cognitive and emotion regulatory processes, which may increase the likelihood of smoking initiation and undermine the efficacy of prevention programs.

### Adolescence and Smoking

Adolescence is characterized by heightened exposure to life stressors and negative affect,<sup>28</sup> as well as experimentation, novelty and sensation seeking,<sup>29</sup> which all increase the likelihood of smoking initiation. In 2010, most *new smokers* were younger than 18 when they first smoked (CDC, 2012). Around 70% of *current smokers* begin smoking before the age of 18 years; of those who do not begin to smoking by this age, few are likely to become smokers as adults.<sup>2</sup> Moreover, research shows that performance of adolescents on tasks including inhibitory control,<sup>30,31</sup> working memory (WM) and decision-making improve during adolescence.<sup>32,33</sup> These marked changes in self-regulatory capacity make this developmental period a time both of vulnerability and opportunity for training and intervention.<sup>34</sup>

### Poverty, Working Memory Capacity, and Smoking

Stress negatively influences executive functioning, including working memory.<sup>35-36</sup> Recent research has linked WM capacity to a wide range of health behaviors, including drug use.<sup>17</sup> Specifically, greater WM capacity is hypothesized to allow for greater use of strategies to resist maladaptive urges. As argued by Grenard et al.<sup>37</sup>: “For those higher in WM capacity, more top-down, goal-directed attentional resources are available to (a) suppress the influence of associative tendencies when they interfere with other active goal-states, (b) maintain conflicting goals in active memory, (c) draw on more knowledge concerning potential short vs. long-term outcomes, and (d) apply one of several cognitive processing strategies to resolve the goal conflict.” WM capacity has been found to be a strong predictor of the resumption of smoking in untreated individuals, and efficacious interventions for smoking modify this risk.<sup>38,39</sup> WM has also been linked to smoking initiation among adolescents<sup>15</sup> and is further linked with addiction potential through strong associations with delay discounting.<sup>40,41</sup> Indeed, WM training in addicted individuals improves delay discounting.<sup>42</sup> The validity of WM capacity as a treatment target in adolescents is supported by findings of reliable improvements in WM from a number of verbal and non-verbal training tasks ( $N = 40$ , 9–11 years of age; 10 sessions of training).<sup>43-45</sup> Although transfer of training effects to other cognitive tasks or academic performance can be small,<sup>46-48</sup> this is not an issue for the current protocol, in which improved WM capacity and associated delay discounting level are the targeted acute outcomes for training. Because poverty has been shown to correlate with lower executive function abilities,<sup>35</sup> adolescents from disadvantaged backgrounds, in particular, may benefit from these interventions.

### Poverty, Distress Tolerance, and Smoking

Adolescents who experience affective distress appear to be at a heightened risk to take up smoking and progress to nicotine dependence.<sup>49,50</sup> Furthermore, negative affectivity has been linked to maladaptive coping<sup>51</sup> and greater smoking dependency specifically among low-income African American smokers.<sup>52</sup> Other work suggests negative affect (in the form of anhedonia) among adolescents who had never had a single puff of a cigarette is related to greater curiosity about trying smoking.<sup>53</sup> Moreover, teens with higher anhedonia reported greater expectancies that smoking causes pleasure, despite never smoking a cigarette, suggesting that anticipated effects of smoking in nicotine-naïve anhedonic youths may confer initiation risk.<sup>53</sup> Another body of work indicates that low distress tolerance (DT), a perceived or behavioral tendency to not tolerate affective and physical distress, is related to both negative mood vulnerability and smoking.<sup>54</sup> Additionally, our work has demonstrated that poverty is associated with decreased DT, as measured by task persistence.<sup>55</sup> More generally, an abundance of evidence indicates that it is *not just negative affect* that drives maladaptive or impulsive behavior, *but the relative intolerance of this affect*. Specifically, the degree of DT is an effective predictor of maladaptive coping across a wide range of disorders and health-related behaviors. For example, our group has shown that anxiety sensitivity (one effective measure of DT)<sup>56,57</sup> predicts the degree of eating in response to negative affective episodes,<sup>58</sup> negative affect during and avoidance of exercise,<sup>58,59</sup> illicit drug use patterns,<sup>60,61</sup> treatment dropout among inner city drug users,<sup>62</sup> and impulsive behavior more generally.<sup>63</sup> DT has been linked to the duration of abstinence from smoking in a variety of studies,<sup>64-68</sup> and treatment that

includes efforts to facilitate DT capacity produce better smoking cessation outcomes.<sup>69-71</sup> Adolescents from disadvantaged backgrounds, in particular, may benefit from preventive interventions targeting low distress tolerance, because poverty is associated with the use of negative health behaviors to regulate stress,<sup>72</sup> and negative affect/stress is a partial mediator of the effects of low SES on difficulties with smoking cessation.<sup>74</sup>

### **Why Target Negative Affectivity and DT with a Mindfulness-Based Intervention?**

Mindfulness-based cognitive therapy interventions improve emotional regulation and reduce both depression and anxiety symptoms in clinical samples, and lower the likelihood of relapse of depressive symptoms, while also offering executive function benefits.<sup>75,76</sup> Furthermore, mindfulness and DT are positively associated<sup>77,78</sup> and mindfulness training improves DT to a variety of stimuli (e.g., with pain).<sup>79,80</sup> As one would expect, emotional regulation interventions (including mindfulness interventions) have shown initial successes for other substance use and impulse control disorders.<sup>79,81</sup> The degree of DT appears to moderate the effects of mindfulness interventions on drug use disorders, with mindfulness having a greater benefit among those with lower DT.<sup>77</sup> Mindfulness is also significantly associated with lower levels of nicotine dependence in smoking adults,<sup>82</sup> and mindfulness interventions have shown specific success in reducing smoking.<sup>83-85</sup> Relevant to the potential for larger scale prevention projects, short-term mindfulness training can be offered online, with documented benefits for reductions in stress, anxiety, and depressive symptoms.<sup>86,87</sup> Overall, the available evidence suggests that mindfulness-based cognitive therapy is an excellent candidate for offering preventive effects against the risks for smoking conferred by negative affectivity, DT, and other self-control challenges.

## **INNOVATION**

Given converging evidence from developmental studies, psychopathology studies, intervention studies, and basic research on self-control abilities, we have identified WMC and DT as transdiagnostic, malleable risk variables in the fight against smoking initiation. Research provides overwhelming evidence that low-SES youth are at an increased risk for smoking,<sup>88,89</sup> and this project is designed to address an existing intervention failure (informational smoking prevention approaches) for this particularly high-risk population. In addition to the novel targets for intervention matched to existing risk factors, this project utilizes novel methodologies, including both implicit and explicit propensities-to-smoke measures. This project has the potential to shift current paradigms for smoking prevention, attending to the rescuing of cognitive/affective self-regulation deficits to provide at-risk adolescents a greater capacity to utilize smoking prevention messaging and resist smoking urges and self-control lapses more generally. Delivery of interventions at school and community center settings is relevant to ultimate dissemination in prevention intervention applications. Our analytic model examines crucial covariates (see below: parental smoking, peer smoking, and sensation seeking) of particular relevance to the study cohort in order to provide more precise estimates of the influence of the experimental variables, and to more fully characterize variables of influence for the population under study. The effects of the interventions are studied against a backdrop of a standard antismoking informational intervention, exactly the sort of intervention that has shown less success with low SES adolescents.

## **APPROACH**

### **Design Overview and Considerations**

We are targeting a high-risk (low SES adolescents) population at a highly relevant period (high school) for smoking onset. The study design calls for block randomization of 150 non-smoking adolescents to one of three intervention conditions: (1) a control condition offering health education combined with a smoking prevention informational intervention (C+SPII), (2) a WM intervention delivered prior to a smoking prevention informational intervention (WM+SPII), (3) a DT training intervention delivered prior to a smoking prevention informational intervention (DI+SPII). Smoking risk proximal outcomes are assessed by smoking propensity self-report, delay discounting, and implicit associations to smoking; Smoking behavior is assessed at one-month follow-up.

- **Why Utilize a SPII as a component common to all randomized conditions?** Meta-analytic review indicates that smoking prevention informational interventions can offer benefits,<sup>1</sup> but there is also evidence these benefits are limited for low-SES participants.<sup>1,9</sup> Our interventions are designed to enhance the ability of individuals to utilize standard SPIIs (by enhancing cognitive and affective self-control skills), and hence, are designed to rescue prevention outcomes for these at-risk individuals.
- **Why block randomize by parental smoking?** Parental smoking is associated with smoking attitudes among children and confers a significantly higher risk of smoking initiation.<sup>90-92</sup> Crucially, research indicates that parental smoking is one significant mechanism by which low SES translates into youth smoking.<sup>93</sup> Ensuring balance of parental smoking status across the intervention conditions allows evaluation of potential

moderating effects of this factor on interventions and outcomes.

- **Why covary parental smoking, peer smoking, and sensation seeking?** As noted, we will ensure equal representation of parental smoking in the randomized conditions. Peer smoking<sup>94</sup> and sensation seeking<sup>95</sup> are risk factors for smoking onset, that, at least in some studies,<sup>95</sup> appear to be separate from each other and the independent variables under study. For example, in a longitudinal study of college students, high sensation seekers were more likely to initiate smoking and still identify themselves as smokers 20 years later.<sup>95</sup> Statistical control of these variables should allow enhanced precision of independent variable effects.
- **Why focus on DT modification rather than affect itself in predictive models?** As detailed above, DT has functioned as a transdiagnostic predictor of maladaptive coping responses. Affect is also a powerful predictor, but affective content and intensity may vary widely between assessment periods, and unlike smoking cessation/relapse studies, there is no specific several-week period where more intensive monitoring of affect would be expected to be useful for capturing new onset smoking under naturalistic conditions. For this reason, in data analysis we focus on the potentially powerful prediction offered by the more-stable DT measure. Nonetheless, negative affect at the assessment periods, and DT by affect interactions, will be the focus of exploratory analyses.
- **Why Utilize Proximal-- susceptibility to smoking, smoking IAT, delay discounting--Smoking Risk Outcomes?** Proximal smoking risk outcomes are needed to allow testing of risk models outside a full longitudinal prevention study. We have selected three smoking risk outcome measures that include both well-established self-report measures as well as measures that do not rely on self-report about intentions. First, susceptibility to smoking (defined as not being able to rule out the idea of smoking) is a well-established self-report measure that has repeatedly proven itself to be valuable in large scale (N > 4000) studies of smoking onset in adolescents.<sup>96-98</sup> Second, the Implicit Association Test (IAT) has been successfully used to assess implicit associations toward smoking in children. This smoking IAT has shown itself to be valuable in identifying more favorable implicit attitudes in children from households with smoking parents.<sup>99</sup> Also, among smokers, IAT responses are linked with measures of smoking motivation and dependence,<sup>100</sup> and are predictive of smoking cessation outcomes.<sup>101</sup> Third, concerning delay discounting, Bickel and associates<sup>102</sup> have proposed that delay discounting may function as a behavioral marker of addiction potential by 1) identifying individuals who are drug-dependent, 2) identifying those at risk of developing drug dependence, 3) acting as a gauge of addiction severity, 4) correlating with all stages of addiction development, and 5) changing with effective treatment. Indeed, higher delay discounting rates are linked to smoking status<sup>103-106</sup> and poorer response to smoking cessation treatment, specifically in low-SES<sup>107</sup> and adolescent samples.<sup>108</sup> Delay discounting is also a mediator of the link between stress and cigarette smoking in adolescents,<sup>109</sup> and in a large longitudinal study of adolescents across ages 15 to 21 found that delay discounting predicted both new-onset smoking and increased smoking rates.<sup>110</sup> Similar relationships exist outside of smoking, where delay discounting predicts a wide range of substance use disorders, consistent with the notion that delay discounting represents a trans-disease process placing individuals at risk for initial or continued substance use.<sup>40</sup>

**Participants.** We propose to study 150 adolescents (expected mean age = 13) enrolled in high school as a freshman or sophomore. Reflecting the demographics of the community in which we are recruiting, we expect approximately 70% of the sample to be at or below the poverty level, balanced between males and females, with the majority from an ethnic minority background. Dr. Doan's previous work among adolescents suggests that at this age, smoking rates are very low.<sup>3</sup> Among a sample of 185 adolescents, only 3.8% reported smoking regularly and 87% reported having smoked once ever, or never at all. In sum, we do not believe that smoking status at this age is a problem, however, our targeted enrollment (N = 150) has accounted for the possibility of having to drop current smokers in the final analyses as well as attrition.

**Feasibility.** Dr. Doan has experience working with low-income youth, and we plan to engage the following recommended best practices to ensure sufficient recruitment and retention.<sup>111</sup> We attach letters of support from local high schools and community centers who serve individuals with characteristics suitable to our study. The headmasters of two local high schools have demonstrated enthusiasm for our study and plan to provide both institutional and social support in our endeavor. Additionally, we have budgeted for financial compensation for all components of the study (assessments and interventions), as well as snacks for the intervention sessions in order to improve enrollment and retention. The following projects and published studies demonstrate the productivity and preparedness of our research team for investigations in the impact of WM and mindfulness training on risk factors and smoking-related outcomes in at-risk youth. Dr. Doan is a developmental psychologist and expert in the acquisition and longitudinal study of low-income youth. Her work focuses on documentation of the effects of stress in this population. She has examined the impact of poverty on

adolescents' behavioral problems and self-regulatory ability,<sup>35</sup> as well as the impact of poverty on WM (Doan & Evans, 2012), and health outcomes including smoking,<sup>3</sup> and body mass index.<sup>112</sup> Dr. Otto has extensive experience with proof-of-concept intervention studies<sup>113,114</sup> and subsequent large-scale trials in specialty psychiatric as well as substance abusing populations,<sup>115,116</sup> including smokers (ongoing: <sup>128</sup>; ongoing R34 DA034658; recently completed R21 DA030808). Dr. Otto is also experience with conducting successful cognitive training interventions,<sup>117</sup> as well as neuropsychological assessment studies for specialty populations ranging from those with depression<sup>118</sup> to schizophrenia<sup>119</sup> and illicit substance abuse.<sup>120</sup> The co-PIs will also receive help from the consultant team (1) Dr. Zvolensky: leading expert in the study of negative affectivity and DT on smoking outcomes,<sup>121-123</sup> (2) Dr. Bickel, a foremost expert on the association between delay discounting, WM, WM training, and addictive behavior including smoking,<sup>40,105,107</sup> and Dr. Rosenfield, an expert statistician who has been a regular collaborator with both Drs. Otto and Zvolensky.

**Interventions.** Participants will be randomized to 1 of 3 study conditions according to two block randomization factors: sex and parental smoking status. Each intervention is to be delivered over eight consecutive weeks. Interventions are to be led by the Project Director, with ongoing supervision from Drs. Otto and Doan. Although online training is available for mindfulness, and provides an excellent potential for aiding dissemination in a subsequent prevention study, we are conducting in-person mindfulness training to help reduce the impact of differential computer skills on the uptake of skills. For WM training, a computer program is used, but the Project Director will be present to facilitate use of the computer and work through the module.

**SPII: Smoking Prevention Informational Intervention.** This intervention *is common to all randomized conditions in the study*. We selected the intervention from brief primary-care based interventions (for a metaanalysis see<sup>1</sup>) which followed guidelines from the National Institute of Health the US Public Health Service Tobacco Use and Dependence Clinical Practice Guideline.<sup>124</sup> Youth will be provided with age-appropriate education on the norms and health consequences of smoking, affirmation of their non-smoking status, and help in developing a personalized strategy to maintain abstinence.<sup>125</sup> Additionally, we will incorporate a motivational interviewing component.<sup>126</sup> The SPII will be delivered during the last of the randomized intervention sessions described below.

**C: Control Condition Informational Interventions.** This control informational intervention has been used in our and other's previous studies.<sup>127,128</sup> In the current application, it will match the session time of the DT intervention and will omit a focus on smoking (that focus is specific to the SPII intervention provided across all interventions) and consists of discussions of a variety of healthy lifestyle topics, such as healthy eating, stress/time management, and recommended health screenings.

**WM: Working Memory Intervention.** For the working memory training, we will use the Cogmed RM program. Participants will be asked to use the program, while supervised twice a week, each time for an hour, for 8 weeks. Participants will also be asked to use the program on the other days for 25-35 minutes. For this additional use, a computer lab will be provided at the participating site to ensure all students have adequate access to the program. The CogMed Rm program has been shown to produce higher effect sizes than other programs including noncommercial programs developed by researchers for the purposes of their studies.<sup>129</sup> It resembles a video game, and comprises several different "games" that require visuo-spatial working memory (remembering the position of objects) and a combination of verbal and visual working memory (remembering phonemes, letters, and digits). The program adapts to the user's performance. If the trainee is doing well, the to-be-remembered list will increase by one item. If the trainee is struggling, the to-be-remembered list will decrease by one item. Accordingly, trainees are able to perform at the limit of their ability, stimulating WM capacity adaptation.<sup>130</sup>

**DT: Distress Tolerance (Mindfulness) Intervention.** To enhance DT, we will use a Mindfulness Based Stress Reduction (MBSR) program that has been adapted for use with adolescents.<sup>131</sup> This version of MBSR follows closely the original conceptualization developed by Kabat-Zinn.<sup>132</sup> The focus is on formal and informal mindfulness practices, which encourage participants to foster intention, attention and attitude.<sup>133</sup> We will make slight modifications to the delivery of the MBSR intervention to take into account the developmental period of our participants (e.g., their attention span) to encourage retention and increase relevancy. These changes will also allow us to match the duration with our WM intervention.

**Assessments.** See Table 1 for a summary of assessments; clinician-rated assessments will be completed by the Independent Evaluator.

**Parental and Peer smoking.** We will assess four categories of exposure to parent smoking: (1) both parents nonsmokers: (2) both parents former smokers or, one former smoker and one nonsmoker: (3) one parent a current smoker: the other a nonsmoker or a former smoker: (4) both parents current smokers.<sup>134</sup> Affiliation with peers who smoke is a strong psychosocial predictor of smoking initiation and current smoking,<sup>94</sup>

and will be measured by summing responses to three items asking whether the adolescent's best friend smokes and how many of his or her other four best male and four best female friends smoke (range 0 to 9 friends smoking).<sup>110,135</sup>

**Sensation Seeking (SS).** SS is positively associated with smoking onset,<sup>95</sup> as well as heavier smoking and poorer cessation adherence and success.<sup>136-138</sup> We will use the Sensation Seeking Scale,<sup>139</sup> as it has been used with acceptable reliability with low-income minority youth.<sup>140</sup>

**Smoking Susceptibility.** Consistent with previous work<sup>141</sup> we will measure smoking susceptibility with two items (e.g., "Have you ever been curious about smoking a cigarette: 0 = No, 1 = Yes") from the pan-Canadian Youth Smoking Survey, and three items repeatedly used in the literature (e.g., "If one of your best friends were to offer you a cigarette, would you smoke it: 0 = Definitely no, 3 = Definitely yes"; e.g.,)<sup>97,98</sup> to create a single composite score that is the sum of these five items providing a continuous score ranging from 0 (no susceptibility) to 11 (highest susceptibility).

**Smoking IAT:** We will use a smoking-specific implicit association test (IAT)<sup>142</sup> that assesses implicit cognitive associations between smoking and negative vs. positive social consequences.<sup>101</sup> This version of the IAT successfully predicted odds of smoking abstinence over and above the effects of other relevant predictors.

**Delay Discounting.** Identical to methods employed by Reynolds & Fields<sup>143</sup> for adolescents experimenting with smoking, we will assess delay discounting by presenting participants with computer-based choices between \$10 available after a specified delay (i.e. 1, 2, 30, 180 or 365 days) and a smaller amount available immediately (e.g. 'would you rather have \$10 in 30 days or \$2 now?'). This computerized task uses an adjusting amount procedure (adjusting the immediate amount in increments of  $\pm \$0.50$ ) to derive indifference points. At the end of the session one question would be selected and honored—resulting in either immediate or delayed money.

**Smoking Status.** Self-reports of smoking status will be collected using time line follow-back methodology to determine the time frame of smoking initiation if it occurred. Self-reports of abstinence at each assessment visit will be verified by expired carbon monoxide (4 ppm cutoff).<sup>144</sup>

**WM Capacity.** WM assessment includes these three tasks plus a warm-up task, the sequence recall of digits—auditory (SRD-A). The Sequenced Recall Reversed Digits—Auditory (SRRD-A) program is identical to the SRD-A, except that participants are required to recall the digits in the reverse order of presentation. The Sequenced Recall of Words—Visual (SRW-V) task presents a list of four-letter words on a computer screen. The Verbal Memory—Categorizing (VM-C) presents participants with 20 words falling into four categories (e.g., colors, vegetables). The WM capacity data submitted for analysis will be the z-score (using BL means and SDs) average of the SRRD-A, SRW-V, and VM-C as specified below.

**Positive and Negative Affect Schedule (PANAS).** The

negative affective score will be used as additional exploratory predictor of smoking status alone and in interaction with DT.

**Distress Tolerance.** Because self-report and behavioral measures of DT are only partially correlated,<sup>56</sup> we will use both assessment strategies in the current study, with the variable submitted for analysis

<b>Measures</b>	Baseline	Intervention	1-Week Post-Intervention	1-Month Post Intervention
<b>Initial Assessment</b>				
Demographics	X			
<b>Additional Covariates</b>				
Parental Smoking	X			
Peer Smoking	X			
Sensation Seeking	X			
<b>Mediator Variables</b>				
Working Memory (WM)	X		X	
Distress Tolerance (DT)	X		X	
<b>Proximal Smoking Risk Outcomes</b>				
Smoking Susceptibility	X		X	X
Smoking IAT	X		X	X
Delay Discounting	X		X	X
<b>Actual Smoking Outcomes</b>				
Timeline Follow-Back	X			X
Carbon Monoxide	X			X
<b>Affect</b>				
PANAS	X		X	X
<b>Intervention Integrity/Acceptance</b>				
Participant Adherence		X		
Therapist Adherence		X		

representing the mean z-score (using the BL mean and SD) on the two assessment measures (follow-up analyses will consider the two measures individually). Perceived Distress Tolerance will be assessed with the 10-Item Distress Intolerance Index (DII).<sup>145</sup> Behavioral Distress Tolerance will be assessed with the computerized Mirror-Tracing Persistence Task (MTPT-C).<sup>146</sup>

**Participant Adherence.** The number of sessions attended will be used to assess patient adherence.

**Interventionist Adherence.** All mindfulness sessions will be audiotaped. Independent master-level raters (available to Dr. Otto) will rate 10% of sessions for therapist adherence.

### **Benchmarks**

This study is being conducted to validate specific cognitive-affective targets for use in larger prevention studies. As such, documenting a significant effect of interventions on delay discounting and distress tolerance represents a go/no go criterion for future study (Aim 2). Also, to encourage study of the modification of these targets in a larger scale (R01) environment, documentation of significant benefit on proximal measures of smoking risk/behavior is needed (Aim 3). Success with these benchmarks, in a design with adequate feasibility/acceptability would document the need for R01 study in a prevention trial with longitudinal follow-up.