Science of Behavior Change (SOBC)

Applying Novel Technologies and Methods to Inform the Ontology of Self-Regulation

Aim 4 Stanford Study Protocol

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Introduction

Health risk behavior, including poor diet, physical inactivity, tobacco and other substance use, causes as much as 40% of the illness, suffering, and early death related to chronic diseases. Non-adherence to medical regimens is an important exemplar of the challenges in changing health behavior and its associated impact on health outcomes. Although an array of interventions has been shown to be effective in promoting initiation and maintenance of health behavior change, the mechanisms by which they actually work are infrequently systematically examined. One promising domain of mechanisms to be examined across many populations and types of health behavior is self-regulation. Self-regulation involves identifying one's goals, and maintaining goal-directed behavior. A large scientific literature has identified the role of self-regulation as a potential causal mechanism in promoting health behavior.

Advances in digital technologies have created unprecedented opportunities to assess and modify self-regulation and health behavior. In this project, we plan to use a systematic, empirical process to integrate concepts across the divergent self-regulation literatures to identify putative mechanisms of behavior change to develop an overarching "ontology" of self-regulatory processes.

This multi-year, multi-institution project aims to identify an array of putative psychological and behavioral targets within the self-regulation domain implicated in medical regimen adherence and health behavior. This is in service of developing an "ontology" of self-regulation that will provide structure and integrate concepts across diverse literatures. We aim to examine the relationship between various constructs within the self-regulation domain, the relationship among measures and constructs across multiple levels of analysis, and the extent to which these patterns transcend population and context. The project consists of four primary aims across two phases of funding (UH2 and UH3 phases). Note that Aims 1–3 were conducted under our prior UH2 phase, and we herein include the protocol for Aim 4 to be conducted in the UH3 phase:

Aim 1. Identify an array of putative targets within the self-regulation domain implicated in medical regimen adherence and health behavior across these 3 levels of analysis. We will build on Multiple PI Poldrack's pioneering "Cognitive Atlas" ontology to integrate concepts across divergent literatures to develop an "ontology" of self-regulatory processes. Our expert team will catalog

tasks in the self-regulation literature, implement tasks via online testing (Mechanical Turk) to rapidly obtain large datasets of self-regulatory function, assess the initial ontology via confirmatory factor analysis and structural equation modeling, and assess and revise the resulting ontology according to neural similarity patterns across tasks (to identify tasks for Aim 2).

Aim 2. Evaluate the extent to which we can engage and manipulate putative targets within the self-regulation domain both within and outside of laboratory settings. 50 smokers and 50 overweight/obese persons with binge eating disorder will participate in a lab study (led by Poldrack) to complete the tasks identified under Aim 1. We will experimentally modulate engagement of targets (e.g., stimulus set of highly palatable foods images or tobacco-related images as well as self-regulation interventions). A comparable sampling of 100 persons will participate in a non-lab study (led by Multiple PI Marsch) in which we will leverage our novel mobile-based behavioral assessment/intervention platform to modulate target engagement and collect data in real-world conditions.

Aim 3. Identify or develop measures and methods to permit verification of target engagement within the self-regulation domain. Led by Co-I MacKinnon, we will examine cross-assay validity and cross-context and cross-sample reliability of assays. We will employ discriminant and divergent validation methods and Bayesian modeling to refine an empirically-based ontology of self-regulatory targets (to be used in Aim 4).

Aim 4. We will evaluate the degree to which engaging targets produces a desired change in medical regimen adherence (across 4-week interventions) and health behavior among smokers (n=50 each at Dartmouth and Stanford) and overweight/obese persons with binge eating disorder (n=50 each at Dartmouth and Stanford) (objectively measured smoking in the former sample and physical activity in the latter sample). We will employ our novel mobile behavioral assessment/intervention platform to engage targets in these samples, given that (1) it offers self-regulation assessment and behavior change tools via an integrated platform to a wide array of populations, and (2) content within the platform can be quickly modified as needed to better impact targets. The proposed project is designed to identify valid and replicable assays of mechanisms of self-regulation across populations to inform an ontology of self-regulation that can ultimately inform development of health behavior interventions of maximal efficacy and potency.

This protocol details the Aim 4 study at Stanford led by Multiple PI Poldrack.

Objective

We will evaluate the degree to which engaging targets produces a desired change in medical regimen adherence (across 4-week interventions) and health behavior among smokers (n=50) and overweight/obese persons with binge eating disorder (n=50) (objectively measured smoking in the former sample and physical activity in the latter sample). We will employ our novel mobile behavioral assessment/intervention platform to engage targets in these samples, given that (1) it offers self-regulation assessment and behavior change tools via an integrated platform to a wide array of populations, and (2) content within the platform can be quickly modified as needed to better impact targets.

Study Design

This phase of the study takes what we learned about self-regulation in the first three phases and applies it in two samples that are exemplary for "lapses" in self-regulation: individuals who smoke and overweight/obese individuals with binge eating disorder. We learned in Aim 2 that many real-world conditions (e.g., temptation, negative affect) may decrease self-regulation, whereas training through the mobile intervention described below may increase self-regulation. The primary purpose of this Aim 4 study is to target self-regulation to impact health behaviors.

Based on information provided in the study ads, interested individuals will be directed to an eligibility screening questionnaire through Stanford's Research Electronic Data Capture (REDCap) system and may call or email our study staff with questions. Those who meet the eligibility criteria for the study based on the online screening will be scheduled for an in-person introductory session at our research center. The study staff will determine whether possible participants are willing to consent to the study, and participants who consent will sign a consent form (electronic through REDCap via a checkbox or "agree" button) and be offered an electronic or paper copy. Consenting participants will complete baseline tasks and questionnaires, as described in the assessments below. We expect this introductory session to take 30 minutes of participants' time. Participants will then undergo a 90-minute neuroimaging session on a separate date. The tasks will be administered in the scanner. The first neuroimaging session

is expected to take 2.5 hours (approximately 1.5 hours of scanning and one hour of practice, setup, and assessments outside the scanner).

During the study period (the details of which are below), participants will complete a series of questions related to self-regulation and contexts. The questions, including the momentary self-regulation questionnaire, were used in Aim 2. Participants will be asked to complete items in response to queries using mobile ecological momentary assessment (EMA); i.e., questions/questionnaires asked at a given time point outside of a laboratory setting via a mobile device. We will assess antecedent conditions prior to health risk behavior: smoking or binge eating among our smoking and binge eating samples, respectively. These antecedent conditions include mood, companionship, location, and temptation. We will offer the resources of Laddr® (a science-based behavior change intervention delivered via an interactive, self-directed mobile platform) to individuals and assess the effect of this mobile intervention system on putative targets of self-regulatory function. Laddr will also be used to deliver the EMAs to participants. Participants will use their own smartphones.

We will ask participants to respond to EMAs and to engage with the mobile intervention for 28 consecutive days. We will prompt them four times daily to inquire about health risk behavior and ask them to complete measures of self-regulation and potentially important contexts. We will send the four prompts at random times within time windows (e.g., 8–11:30 AM, 11:30 AM–3 PM, 3–6:30 PM, 6:30–10 PM). The time windows may vary based on participants' waking hours, and we will program through the software at least an hour between prompts (e.g., if a participant receives a prompt at 11 AM, he/she cannot receive another prompt until 12 PM). We will ask them to use Laddr daily to, at a minimum, update progress toward goals and complete various activities on the application that we expect will improve their self-regulation. Participants will be recommended priority therapy guides (binge eating for the binge eating sample; smoking for the smoking sample) and can also choose to engage with other guides, such as depression, anxiety, and substance use.

Participants will also be asked to use devices that allow for objective measuring of behaviors of interest. We will ask participants in the smoking sample to provide carbon monoxide (CO) samples via a breath CO meter (iCO™ Smokerlyzer®, Bedfont® Scientific Ltd.). The monitor measures breath CO in parts per million

(ppm) based on the conversion of CO to CO_2 over a catalytically active electrode. We will ask smoking participants to provide one CO sample in the same time window each day. Smoking participants will have a goal of smoking abstinence by the end of the study, as evidenced by a CO reading of less than 4 ppm. We will ask participants in the binge eating sample to wear a physical activity tracking device (Fitbit Flex 2™), which tracks steps, distance, calories burned, active minutes, hourly activity, stationary time, and sleep. Objective measures of eating are in a nascent phase, and all participants in the binge eating sample are overweight or obese, making physical activity a suitable behavior to measure. We will ask binge eating participants to wear the activity tracker for at least 12 hours per day. We will encourage participants to use a changing criterion design to set stepped goals, in which participants set a 7-day activity criterion goal and are encouraged to increase their criterion goals in each subsequent 7-day block if they achieve the goal on at least 4 of the 7 days.

Participants in the smoking sample may use nicotine replacement medications, and we will track which participants use these medications. Potential participants taking medications for psychiatric reasons will be excluded from both samples.

All participants will be asked to complete a battery of follow-up tasks and surveys at the end of their four-week study period. Participants will be asked to return in person to the research center to undergo a 90-minute neuroimaging session. The tasks and some of the questionnaires will be administered in the scanner. Like the baseline visit, the follow-up visit is expected to take 2.5 hours (approximately 1.5 hours of scanning and one hour of practice, setup, and assessments outside the scanner). Participants will be compensated in full at the end of their study period.

Samples

This study consists of samples from two target populations: (1) persons who smoke, and (2) overweight/obese persons with binge eating disorder. The specific eligibility criteria are as follows:

Inclusion criteria:

- Age 18–50 years
- Understand English sufficiently to provide informed consent
- Use a smartphone operating system compatible with Laddr (Android

version 5.1 or higher or iOS version 10 or higher)
- Right-handed
- Normal or corrected-to-normal vision and no color blindness
- Interest in participating in an intervention to change behavior

- **Additional inclusion criteria for binge eating sample:**
  - $27 \leq BMI \leq 45$ kg/m^2
  - Weight limit of 350 lbs
  - Have binge eating disorder according to DSM-5 criteria
  - Non-smoking (defined as no cigarettes in past 12 months—this includes former and never smokers)
  - Confirmed interest in a physical activity intervention
  - Use a smartphone compatible with Fitbit

- **Additional inclusion criteria for smoking sample:**
  - Smoke 5 or more tobacco cigarettes/day for past year
  - $17 \leq BMI < 27$ kg/m^2
  - Confirmed interest in a smoking quit attempt
  - Use a smartphone compatible with the iCO Smokerlyzer

Exclusion criteria:

- Enrolled in Aim 2 study
- Significant medical illness
  - Have had heart attack (MI), stroke, coronary heart disease, congestive heart failure, or angina
  - Have had coronary artery bypass surgery or cardiac catheterization such as percutaneous transluminal coronary angioplasty (PTCA), cath or stent placement
  - Have moderate to severe asthma, or chronic obstructive pulmonary disorder (also called emphysema or chronic bronchitis)
  - Had cancer within the past 5 years (except non-melanoma skin cancer)
  - Currently under medical care for digestive issues, gastrointestinal distress, abdominal pain, or diarrhea
  - Had an organ transplant
  - Have an immunodeficiency disorder
- History of head trauma with loss of consciousness, cerebrovascular

accident, seizures, neurosurgical intervention, or brain tumor

- Current use of any medication for psychiatric reasons (including stimulants and mood stabilizers)
- Any additional contraindication for MRI (including body metal [non-removable piercings, braces])
    - https://cni.stanford.edu/cniwiki/images/5/59/CNI_Screening_form.pdf
- Any current substance use disorder
    - Will not exclude based on use of substances
- Currently pregnant or plans to become pregnant in next 3 months
- Lifetime history of mental disorder due to a medical condition
- Lifetime history of major psychotic disorders (including schizophrenia and bipolar disorder)
- Current use of prescription pain medications (e.g., Vicodin, oxycodone)
- Current use of any medication for smoking (e.g., Wellbutrin, varenicline)
    - Exceptions: will not screen out for nicotine replacement therapy (e.g., patch, gum, lozenge, nasal spray, inhaler)
- Current use of any medication for weight loss
- Current
- Have undergone weight-loss surgery (e.g., gastric bypass, lap band)
- Current nighttime shift work or obstructive sleep apnea
- NOTE: We will not exclude based on e-cigarette use.

- **Additional exclusion criteria for binge eating sample:**
    - Compensatory behavior (e.g., purging, excessive exercise, fasting)
        - Already excluded as part of the DSM-5 binge eating disorder criteria
    - Lost weight in recent past (>10 pounds in past 6 months)
    - Currently in a weight-loss program (e.g., Weight Watchers, Jenny Craig)
        - Will ask about, but won't exclude on, online/mobile app weight-loss programs as part of the screener
    - Currently on a special diet for a serious health condition
    - Current engagement in psychotherapy for binge eating disorder

- **Additional exclusion criteria for smoking sample:**
    - Binge eating behavior according to QEWP-5 ("yes" to questions 8 and

9 and for question 10, at least one episode per week for three months).

- QEWP-5 #8: During the past three months, did you ever eat in a short period of time (for example, a two-hour period) what most people would think was an unusually large amount of food? [yes or no]
- QEWP-5 #9: During the times when you ate an unusually large amount of food, did you ever feel you could not stop eating or control what or how much you were eating? [yes or no]
- QEWP-5 #10: During the past three months, how often, on average, did you have episodes like this? That is, eating large amounts of food plus the feeling that your eating was out of control? (There may have been some weeks when this did not happen. Just average those in.) [less than one episode per week, five response options for 1 or more episodes per week]

- Current engagement in psychotherapy for smoking behavior

Recruitment

Study advertisements will be posted online (e.g., Craigslist, Facebook, Google AdWords) and in the community (e.g., local newspapers, flyers at community centers). Additional participants may be identified from co-investigators' participant records at Stanford (Drs. Bohon and Prochaska). Our team has had great success with similar recruitment strategies in previous research studies, including in Aim 2 of this project. We expect the samples to include approximately 50% women, 39% non-White race, and 26% Hispanic/Latino ethnicity.

Compensation

Compensating participants for active study participation will help ensure exposure to the intervention intended to manipulate targets.

Participants will be compensated up to $350 per participant for all baseline tasks, surveys, and neuroimaging (required to complete full battery of tasks, surveys, and neuroimaging to receive $350). This full compensation schedule breaks down as follows:

$20 for completion of a 30-minute introductory session with baseline surveys and consent form signing

$50 for completion of the first neuroimaging session

Up to $230 (see below for detail) for completion of the four-week EMA period:

*$1 per EMA * 4 EMAs per day * 28 days = up to $112*

*$2 per day for Laddr activities (at least 5 minutes of engagement) * 28 days = up to $56*

*$2 per day for wearing the wrist sensor for a minimum of 12 hours per day and inputting activity data into Laddr (binge eating sample) or using the CO monitor daily and inputting CO reading into Laddr (smoking sample) * 28 days = up to $56*

$6 for data plan reimbursement (required to complete minimum of 12 EMAs)

$50 for completion of the second neuroimaging session

Note that these schedules are based on the maximum compensation possible. Participants may receive partial compensation for certain activities. Participants will be compensated with their full payment at the end of their study period after completing the follow-up tasks, surveys, and neuroimaging session (and for binge eating participants, after returning the wrist sensor). The research team may deduct up to $50 from a binge eating participant's compensation for failure to return, or for damage to, the wrist sensor. Smoking participants are able to keep the carbon monoxide monitor as this device is intended for use by a single person.

Study Assessments

At baseline and follow-up we will use the highest-loading subscale for each of the 12 factors identified in the survey factor analytic space from prior aims of the project. We will also include the additional surveys listed below. Some of the

additional surveys have been well defined in the self-regulation literature, and others apply specifically to smoking or eating behavior.

All tasks and surveys/subscales below were used in Aim 2 of this project at Dartmouth and/or Stanford. The numbers in parentheses indicate the number of items included.

We will also include a limited number of tasks; namely, the same 3 putative self-regulation tasks used in the Aim 2 imaging study: (1) two stop-signal tasks that involve responding to imperative go stimuli except when a subsequent stop signal occurs, and which maps onto four of the factors related to the drift-diffusion model that emerged in our task factor space in previous aims of our project, and (2) a delay discounting task that requires choosing between hypothetical smaller-sooner or larger-later monetary rewards, which mapped onto the fifth and final factor in the task factor space from prior project work.

We will also use a movie-watching task that includes embedded food and smoking stimuli to evaluate more naturalistic responses to these stimuli. Finally, we will include a manipulation task in the scanner that includes now and later cues to food [binge eating sample], smoking [smoking sample], and neutral stimuli. This will assess the degree to which subjects can modulate their cravings in response to external cues.

Subscales at baseline and follow-up representing the 12 factors identified in the survey factor analytic space:

1. Reward sensitivity – BIS/BAS: BAS Fun Seeking (4)
2. Sensation seeking – Zuckerman Sensation Seeking Scale: Thrill and Adventure Seeking (10)
3. Financial risk-taking – DOSPERT Risk-taking Survey: Financial (6)
4. Social risk-taking – DOSPERT Risk-taking Survey: Social (6)
5. Ethical risk-taking – DOSPERT Expected Benefits Survey: Ethical (6)
6. Eating control – Three-Factor Eating Questionnaire-R18: Uncontrolled Eating (9)
7. Impulsivity – UPPS+P Impulsivity Survey: Lack of Premeditation (11)
8. Emotional control – Ten-Item Personality Inventory: Emotional Stability (2)
9. Mindfulness – Five Facet Mindfulness Questionnaire: Act with Awareness (8)

10. Goal directedness – Selection-Optimization-Compensation: Loss-based Selection (12)
11. Agreeableness – Ten-Item Personality Inventory: Agreeableness (2)
12. Risk perception – DOSPERT Risk Perceptions Survey: Health Safety (6)

Additional surveys at baseline and follow-up:

- Brief Self-Control Scale (13)
- Ten-Item Personality Inventory (6 [10 minus 4 above])
- Three-Factor Eating Questionnaire–R18 (9 [18 minus 9 above])
- Reward-based Eating Drive Scale (RED-13) (13)
- Stanford Leisure-Time Activity Categorical Item (L-Cat 2.2) (1)
- Alcohol, smoking, and drug questionnaire from Aim 1 (36)
- Demographic questionnaire from Aim 1 (24 [28 minus 4 at screening])
    - Baseline only

- Additional for eating sample:
    - QEWP-5 (11)
        - At screening in addition to baseline and follow-up (but baseline and follow-up will ask about past month instead of past 3 months)

- Additional for smoking sample:
    - Select set of smoking questions, including from the PROMIS Smoking Initiative (6)
    - Fagerström Test for Nicotine Dependence (5 [6 minus 1 already included in alcohol, smoking, and drug questionnaire])

Tasks at baseline and follow-up:

- Stop Signal Task
- Stimulus Selective Stop Signal Task
- Delay Discounting Titration Task
- Movie-watching Task
- Manipulation Task (with now and later cues to food [binge eating sample], smoking [smoking sample], and neutral stimuli)

Ecological momentary assessment (EMA) during study period:

- Momentary self-regulation questionnaire

- Self-reported behavior of interest (binge eating for the binge eating sample; smoking for the smoking sample)
- Questions assessing daily intents and barriers
- Questions assessing contexts

The proposed baseline battery of surveys includes approximately 200 items, and the proposed follow-up battery includes approximately 175 items. The Aim 2 baseline battery included 165 items and took roughly 20 minutes to complete. We expect the Aim 4 baseline and follow-up survey batteries to take no more than 30 minutes each. The proposed baseline and follow-up tasks are estimated to take approximately 30 minutes. The tasks will be completed within the scanner and take 60-90 minutes.

Each EMA is designed to be completed in less than five minutes. The average EMA completion time in Aim 2 at Dartmouth was less than five minutes, and we plan to administer the same EMAs in Aim 4.

Data Monitoring

The research assistant plans to monitor data quality on a daily basis and report any issues to the project manager. Our study team will use an initiation application for Laddr, developed by the same team that developed Laddr, to initiate participants into the EMA portion of the study. The team will download password-protected raw data files from a website created by the Laddr developers to monitor EMA completion and Laddr usage. These files will also allow the study team to track compensation amounts for each participant. Data are uploaded to the server when the smartphone is connected to the Internet (either via cellular or WiFi). If participants do not have access to a connection, the data are stored locally on the smartphone and uploaded to the server once a connection is established.

For the overweight/obese participants with binge eating disorder, our study team will use Fitabase, a data management platform designed specifically for Fitbit data. As long as participants maintain a wireless connection (either cellular or WiFi), the sensor data are uploaded to the Fitabase server up to every 15 minutes, allowing for monitoring throughout the day. If participants do not have access to a connection, the data are stored locally on the smartphone and uploaded to the

server once a connection is established. Fitabase allows for near-real-time data monitoring.

For the smoking participants, our study team will be able to monitor whether participants have input their daily CO readings into Laddr via the same password-protected raw data files noted above regarding EMA completion and Laddr usage.

Poor compliance regarding any data source will first be addressed through reminders sent to the participant's smartphone (text message or app notification) or email address. If poor study compliance persists, the participant may be withdrawn from the study, and an additional participant will be enrolled.

Sample Size

We propose a sample size of up to 154 participants (77 individuals who smoke and 77 overweight/obese individuals with binge eating disorder) recruited from the United States, including U.S. districts and territories.

We propose the sample sizes above to reach 50 participants in each sample with at least 10% EMA response percentage over the duration of the four-week study (at least 12/112 EMAs). We calculated the percentage of participants who completed at least 10% of their EMAs in Aim 2 at Dartmouth. We then estimated a target sample size to reach at least 50 participants in each sample with adequate EMA participation (at least 10% completion). The proposed sample sizes account for participants who sign consent but participate minimally, and the target sample sizes of 50 for each sample with at least 10% EMA completion were determined through power calculations in Aim 2.

Statistical Analysis Plan

To evaluate the degree to which changing self-regulation is associated with changes in medical regimen adherence (measured as daily smoking abstinence in smokers and daily physical activity in overweight/obese individuals with binge eating behavior), we will fit several multilevel models (e.g., linear mixed-effects models) in addition to an overall model examining mechanistic effects. Details are provided in the following text. At the momentary level, there two relationships to be examined to understand the role of self-regulation in behavior change: the relationship between context and self-regulation, and the relationship between

self-regulation and medical regimen adherence. We will examine each relationship separately prior to examining the full mechanistic model. To examine whether context is associated with level of momentary self-regulation, we will fit several multilevel models with momentary context as a predictor of momentary self-regulation measure. In Aim 2, we have identified several challenging contexts associated with worse momentary self-regulation, and we will confirm these relationships in this treatment-seeking sample of participants. The multilevel models will include a random individual-level effect to account for the non-independence of repeated observations over the 28-day period within an individual. Additionally, the models will also include a fixed effect of time to account for changes in momentary self-regulation over the treatment period. We will also consider a random individual-level slope term if there is significant variability in this change over time between individuals. Such a change in self-regulation over time may be due to the cumulative effect of Laddr use over the treatment period. We will also test whether including an interaction between context and recent Laddr usage is significant indicating Laddr use affects the association between context and momentary self-regulation. These models will identify contextual factors associated with increased or decreased momentary self-regulation.

The next model will examine the relationship between level of momentary self-regulation and daily medical regimen adherence. One model for each subscale of the momentary self-regulation will be fit. In each model, momentary self-regulation will be the predictor and daily medical regimen adherence (smoking abstinence for smokers and daily physical activity for overweight/obese participants with binge eating disorder) will be the outcome. These models will identify the influence of momentary self-regulation on medical regimen adherence. Together with the previous set of models, the components of a mechanistic effect of momentary self-regulation on medical regimen adherence will be estimated. If each relationship is significant, we will fit a full multi-level structural equation model to examine the indirect effect of momentary context on medical regimen adherence as well as the direct effect of context on medical regiment adherence, independent of momentary self-regulation. Bootstrapping will be used in estimating the indirect effect in the mediation model. Bootstrapping involves taking numerous pseudo-replicate samples from the dataset and using the variability in the statistic from sample to sample to construct an interval estimate conveying the direction, magnitude, and precision

of an indirect effect. This mediation model will allow us to estimate the impact of self-regulation as a mechanism for decreased medical regimen adherence in challenging contexts.

At the individual level, we wish to examine whether Laddr can influence momentary self-regulation in a positive direction and, in turn, increase medical regimen adherence. To test this hypothesis, we will examine both the effect of time in the study on momentary self-regulation via multilevel models (e.g. linear mixed-effects models) as well as the effect of various Laddr engagement metrics on momentary self-regulation. Since Laddr use is offered as an intervention during the 28-day intervention period, time in study serves as a proxy for the cumulative effect of Laddr use. Since individuals will differ in their use of Laddr during the course of the intervention period, we will also examine Laddr engagement metrics (e.g., guides read, goals tracked) in addition to time. If Laddr usage appears to influence momentary self-regulation in a positive direction, we will again fit a multi-level structural equation model to examine both the indirect and direct effects of Laddr use on medical regimen adherence.

Additionally, we will evaluate whether Laddr influences task behavior in our four tasks as well as fMRI activity and connectivity by comparing the pre and post scan results.

Power and Sample Size Justification

With 77 participants in each sample with up to 4 EMA responses per day for 28 days, the maximum number of observations in the momentary dataset is 8,624. However, EMA response rates are not expected to be 100%, and some participants may withdraw from the study. With 10% study drop-out and 75% EMA completion rate, the number of observations in a momentary dataset may be closer to 5,821. Even with this sample size, there will be adequate power to detect momentary relationships between contextual factors and momentary self-regulation. For example, with intraclass correlations ranging from 0.3 to 0.6, and prevalence of contexts of interest (e.g., recent exposure to smoking cue, easy food access) between 10% and 30%, there would be at least 80% power to detect differences in momentary self-regulation measures between context between 0.05-0.10 times an SD. These are small effect sizes. In the pilot data, the average SD of a momentary self-regulation measure was between 0.5 and 0.9, and the stated standardized effect sizes are equivalent to detectable mean differences

between contexts of 0.03-0.09 points on the momentary self-regulation subscales, which range from 1 to 5. Well-developed formulae for determining power to detect indirect effects within a multilevel structural equation model of intensively collected data do not exist. However, simulation studies of the bootstrap approach at the individual-level indicate that with a sample size of 71, an indirect effect with medium-sized component effects (β = .39) can be detected with 80% power.[1]

[1]Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. Psychol Sci 2007. Mar; 18(3):233-239.

Protection of Human Participants

Potential Risks:

The potential risks associated with the data collected are low.

Risks from behavioral testing: The types of data we plan to collect (assessment, self-report questionnaires, cognitive tasks, behavioral testing) will not harm the participants' financial standing, employability, or reputation, or expose the participant to civil or criminal liability. The types of risk associated with the data collected include possible fatigue, frustration, or the discussion of sensitive or personal information. If participants do not wish to answer particular mobile surveys, they may elect not to do so, and may continue in the remainder of the study without penalty. (Participants must complete the entire baseline and follow-up task and survey batteries to continue in the study.) Additionally, participants may be concerned about confidentiality risk when using the Internet to access Laddr, even on secured, encrypted connections. They may also be worried about prompts they receive on a mobile device designed to remind them to complete Laddr activities, such as updating goals.

Risks from MRI: There are no known risks of the magnetic resonance imaging scanning procedures proposed in this application. Participants may experience increased anxiety before MRI scanning, just as for any interview or medical examination. The strong magnetic field can be dangerous if the participant has an implanted electronic device (such as a pacemaker), the participant has implanted metal in his/her body (such as an aneurysm clip), or the participant enters the field with magnetic objects on or in his/her body. Some participants may feel

claustrophobia inside the bore of the scanner, some participants who enter or exit the bore too quickly may feel dizzy or nauseous, and the scanner is noisy. Participants for whom it is not safe to enter the scanner, or who report claustrophobia, will not be included in the study.

Risks from mobile sensing of physical activity (binge eating participants only): This project does not involve any risks beyond those ordinarily encountered in daily life or the performance of routine tests. Participants may experience slight initial discomfort while wearing the wrist sensors, such as minor skin irritations. As with any electrical device, the sensors can theoretically cause electric shocks. Electrical shocks can be a health concern with certain health conditions (e.g., heart conditions that require a pacemaker). Additionally, participants could have privacy concerns regarding mobile sensing.

Risks from carbon monoxide monitor (smoking participants only): The carbon monoxide (CO) monitor requires participants to hold their breath for approximately 15 seconds and then to exhale for 15–20 seconds, which may cause slight discomfort for some participants. Additionally, the CO monitor carries the risk of spreading illnesses.

Risks from electronic databases: There may be risks to participants by virtue of their representation in electronic databases, principally involving the risk that privacy or confidentiality might be compromised if there were lapses in security of the information contained in these databases.

Risks from physical activity intervention (binge eating participants only): There may be physical health risks associated with increases in physical activity.

Risks from smoking quit attempts (smoking participants only): There may be psychological discomfort experienced as a result of making a smoking quit attempt.

Adequacy of Protection Against Risks

A. Informed Consent:

All descriptions in the informed consent form are written at the 8th-grade reading level. The consent document includes descriptions about: background of the

study, study procedures, risks and discomforts, benefits, payment for participation, voluntary nature of participation, privacy and confidentiality, and contact information for the research team. The consent form will be presented to prospective study participants online.

Individuals who wish to participate in the study will be asked to carefully read the consent form or to have the consent form read to them. If they have any questions about the study, they can ask the study staff before consenting and at any time afterward. Individuals who provide consent for participation in the study will be offered an electronic or paper copy of the form. Their screening information, agreement to participate, contact information, and baseline data will be saved in REDCap. Study participants will be informed that they can withdraw from the study for any reason at any time.

B. Protections Against Risk:

Protection against risks from behavioral testing: To protect against the possible risks associated with behavioral testing, which are fatigue and frustration, participants will receive EMA prompts four times daily and will not be asked to initiate use on their own. It will be made clear to participants during the informed consent process that they are free to discontinue their participation at any point without penalty. Any participant that experiences significant discomfort during the four-week period will be able to stop procedures immediately.

To protect against concerns that others may see when a participant receives a prompt from the Laddr system (the mobile behavior change intervention), the content of the prompts sent will be intentionally vague. While they will be designed to be meaningful to individual participants, they will not include specific references to study participation.

Protection against risks from MRI: There are no known risks of the magnetic resonance imaging scanning procedures proposed in this application. All scans will be conducted on an MRI system that is FDA approved, has been approved for research use, and uses sequences that are within FDA guidelines for relevant safety parameters. The risks associated with implanted electronic devices, implanted metal objects, and metallic objects being brought into the scanning room are minimized by an extensive set of safety procedures that are used to

screen participants for implants and ferromagnetic materials on or in their bodies prior to scanning, which include detailed questionnaires about medical/surgical and occupational histories. In addition, all participants are screened with a metal detector prior to scanning and security prevents unauthorized individuals from having access to the imaging suite. In addition, all users of the Center for Neurobiological Imaging at Stanford are highly trained in MRI safety and safety training is renewed annually.

To protect against the increased anxiety that is experienced prior to MRI scanning, participants receive information beforehand about what to expect, discuss with staff the methods for remaining still and feeling comfortable in the scanner, and receive training in the Simulator, all of which help to increase their familiarity with the scanning environment. Staff members are also highly experienced in the scan environment and help participants feel more comfortable in the scanner; however, if the discomfort cannot be reduced to an appropriate level, participants are told that they can discontinue the procedure at any time without penalty. To protect against risks associated with feeling uncomfortable in the scanner, and noise associated with the scanner, we use audio and video inputs, which decrease the feelings of being in an enclosed space for many participants. All participants will also be provided with earplugs and headphones to protect their hearing. Participants receive instructions before scanning about communicating with staff and scan operators, which can be done either by a squeeze bulb attached to the participant's headphone cord, or by voice through a microphone mounted inside the scanner. All participants will be told during consent and prior to the scan session that they can discontinue the procedure at any time without penalty.

Protection against risks from mobile sensing (binge eating participants only): Previous studies with wristband sensors have indicated that after a brief adjustment period, the majority of the participants adjusted to wearing the bands and did not find them to be intrusive or restraining. Although slight discomfort is possible from wearing the wrist sensors, Fitbit sensors have been used in over 600 studies. Therefore, we assess the severity of the discomfort and irritation of wearing the wrist sensors to be minimal. If irritation persists to a point where the participant no longer wishes to participate, any irritation is entirely reversible once the participant removes the wrist sensors.

While electrical devices do introduce the risk of electric shocks, the probability of a participant experiencing even minor electrical shocks is negligible. High impedance circuitry is used to limit current flow, even in the case of external events (e.g., through physical breaking of the sensor board or shorting of the battery leads). All sensors in the wristbands are commonly used in mobile phones and other activity monitors and pose minimal risk to participants. We expect that the wrist sensors, which have precedent of prior use in a research study or have otherwise been designed for everyday wear, will elicit similar acceptability among the participants in this study.

Regarding privacy concerns, participants' contact information will be linked to their study data via a code. The key to this code will be available only to the research staff at Stanford, and will be secured separately from the rest of the study data that is transmitted to Fitabase. Participants will be informed of their rights to terminate their participation in the study at any time. Participants will also be informed of their rights to remove the wrist sensors if they so choose, if they do not wish to be tracked. Participants will be given a summary of the incentive structure, and will be informed how their participation will affect their final incentive payment.

All personnel that will be present for the research activities will be essential personnel in the conduct of this research. All personnel who will interact with participants at Stanford are trained in human participants research. Moreover, all staff at Small Steps Labs LLC, which owns and operates Fitabase, will receive only coded data. No directly identifiable data will be provided to Small Steps Labs LLC staff, and the key linking participant codes to identifiers will not be shared under any circumstances.

Study participants will be informed that this research is conducted with the use of Fitabase and that coded data, which will not directly identify them, will be maintained in a database owned and operated by Small Steps Labs LLC.

Protection against risks from carbon monoxide monitor (smoking participants only): While slight discomfort may result from participants holding their breath and exhaling, these carbon monoxide monitors have been used in several previous studies. Most participants are able to provide readings without issue. Participants will be informed of their rights to terminate their participation in the

study at any time if they experience excessive discomfort related to holding their breath or exhaling.

To minimize the risk of any spread of illness from the use of the carbon monoxide monitors, participants will each be provided with their own CO monitor. The CO monitors will not be reused by subsequent participants who enroll in the studies.

Protection against risks from physical activity intervention (binge eating participants only): Participants will be encouraged to set physical activity goals in line with their current health and fitness status. Participants who have concerns about increasing their physical activity will be encouraged to contact a medical professional.

Protection against risks from smoking quit attempts (smoking participants only): While participants may experience psychological discomfort from making a smoking quit attempt, this discomfort is not beyond what participants would ordinarily encounter in daily life (e.g., cravings, disappointment from a lack of success). Laddr is designed to support participants through a smoking quit attempt. Participants experiencing psychological discomfort beyond that encountered in ordinary life will be withdrawn from the study and referred to the appropriate resources.

Protection against risks from electronic databases: To protect the privacy or confidentiality of participants' data stored in electronic databases, every effort will be made to safeguard the confidentiality of research records, using data files free of information enabling individual identification of participants, lock-and-key access to paper records, and computer data files maintained with encryption, password protection, and behind firewalls. We will remove individual identifying information from data representations so that security failures would not put individual privacy and confidentiality at risk. Individual identifying information will only be maintained in a separate encrypted database with passwords known only to the PIs and specific members of the research team.

Each of the following sources of data is explained in detail separately: (1) eligibility, baseline, and follow-up surveys; (2) baseline and follow-up tasks; (3) baseline and follow-up neuroimaging; (4) EMA and Laddr (mobile intervention); (5) mobile sensing of physical activity (binge eating participants only); and (6)

carbon monoxide monitor (smoking participants only).

(1) We plan for the eligibility, baseline, and follow-up survey batteries and resulting data to be available and coordinated through Stanford's Research Electronic Data Capture (REDCap) system. All eligibility, baseline, and follow-up survey data will be either acquired using REDCap forms or stored directly in REDCap upon acquisition.

(2) Baseline and follow-up task data will be acquired using The Experiment Factory, a platform for deploying behavioral experiments that our team created and implemented in Aim 1 of this project. All task data will be coded (i.e., a unique participant code will replace all other identifying information) and stored on the OAK storage system in Sherlock2, a supercomputing cluster at Stanford University. Only essential members of the research team will have access to a key linking each code to participant identifiers.

(3) Raw neuroimaging data will be stored on Flywheel, a state-of-the-art platform for storing neuroimaging data that reduces security risk. All raw imaging data will be promptly coded to eliminate privacy and confidentiality issues and stored on the OAK storage system in Sherlock2 alongside task and summary imaging data.

(4) All EMA and Laddr usage data provided by participants when using the web-based Laddr® intervention will be stored locally on the phone in an AES-256 encrypted database. Data are stored in a key-value store residing on AES-256 encrypted solid state drives (encrypted at rest). Data are sent to the server when the device is online over an encrypted connection using Secure Sockets Layer (SSL) over Hypertext Transfer Protocol Secure (HTTPS) and will not be accessible to anyone not affiliated with the research project. The server is located in a locked cabinet, in a card-key secured room, in a secure, monitored data center in Fremont, California. The server is behind multiple firewalls with intrusion detection systems in place. Security patches for system software are installed within days and most often within hours after their release. All data stored on this server will be coded by participant ID number.

Stanford research staff will use an application, developed by the

same team that developed Laddr, to initiate Laddr for each participant at the beginning of the participant's study period. Throughout the study the team will download password-protected raw data files from a website created by the Laddr developers to monitor EMA completion and Laddr usage. These files will also allow the study team to track compensation amounts for each participant. Exported data will be identified via participant code and stored on password-protected computers. We successfully used this application, file download process, and similar procedures in the prior Aim 2.

(5) (Binge eating participants only) Mobile sensing data will be used to infer physical activity among this sample. These data will first be aggregated from the wearable sensors and will be stored on the participants' smartphones. After participants configure the proper settings, aggregated wrist sensor data from the smartphone will be transmitted automatically to Fitabase, a data management platform designed specifically for Fitbit data. All study data will be sent via a Secure Sockets Layer (SSL) connection, which encrypts all transmitted data. Stanford research staff will link mobile sensing data to a participant code so that participant identifiers (except for a study-specific code) are not included in the participant's Fitbit.com account or Fitabase.

Data are stored and indexed in the Fitabase SQL Server database. These database servers are IP firewalled and whitelisted such that they refuse any connection from IP addresses not preprogrammed by Small Steps Labs LLC, which owns and operates Fitabase. Fitabase databases are stored on the Microsoft Azure platform, which uses geographically dispersed data centers that comply with industry standards, such as ISO/IEC 27001:2005, for security and reliability. Small Steps Labs LLC maintains snapshot archives of the databases, which are encrypted and password protected, for disaster recovery purposes.

Participants may also be asked to input their activity data directly into Laddr as part of tracking their goals and progress. Activity data in Laddr will then be protected and transferred based on the same methods detailed above in section 4 about Laddr.

(6) (Smoking participants only) The CO monitors connect directly to participants' smartphones via the headphone jack. The CO readings will be

stored locally on participants' smartphones in a mobile application designed for the CO reader. Participants will input their CO readings from the device app directly into Laddr. The CO data will then be protected and transferred based on the same methods detailed above in section 2 about Laddr.

At the PIs' discretion, with the approval of the relevant IRB, and while the study is ongoing, any coded data from this project may be shared with other research team members within the Marsch/Poldrack SOBC research team, and any de-identified data (i.e., stripped of all codes or other information that could be linked back to an individual participant) from this project may be shared with other researchers outside of the Marsch/Poldrack SOBC research team.

After completion of the study, a de-identified dataset (i.e., stripped of all codes or other information that could be linked back to an individual participant) will be generated and made available to the research community as a whole. Informed consent procedures will ensure that participants are aware that consenting to participate in the study means consenting to inclusion in this open dataset.

All information that is collected from the participants will be the minimum necessary, and de-identified to the maximum extent possible, to conduct the research. Study participants will be informed that research data collected about them will be stored at Stanford until they are no longer useful. It is estimated that the data will possibly be useful for 10 years, but the data may be useful and may continue to be retained indefinitely. Eligibility data from the screening questionnaires will be retained for those who participate but will be deleted at the end of study for those who screen out or choose not to participate. Data may be retained indefinitely for those who screen in and sign consent, regardless of further participation.

Potential Benefits of the Proposed Research to Human Subjects and Others

Participants may learn self-regulation skills through the Laddr mobile application, which may have a positive impact on their smoking (in the smoking sample) or binge eating behavior (in the binge eating sample). Additionally, the information to be gained from their participation may benefit others in the future.

Importance of the Knowledge to be Gained

The proposed activities are designed to identify valid and replicable assays of mechanisms of self-regulation across populations to inform an ontology of self-regulation that can ultimately inform the development/refinement of health behavior interventions of maximal efficacy and potency. Because the need to alter health-related behavior is ubiquitous across medicine, understanding the extent to which the principles of effective health behavior change, and the mechanisms by which they work, are similar or different across health conditions and settings is a critically important area of scientific inquiry. It may inform more efficient, cost-effective, and patient-centered care. This line of research may ultimately allow us to make great strides in crafting "precision medicine" approaches for a wide array of populations. Given the importance of the knowledge to be gained, the risks to the participants are reasonable, as the risks are minimal and plans for protection against these risks are in place.

Data and Safety Monitoring Plan

Consistent with best practices, the Principal Investigator (Dr. Poldrack) will oversee all data and safety monitoring functions (described above) to ensure the safety of participants in the proposed study and to ensure the validity and integrity of the data obtained in the study. The Principal Investigator will also regularly meet with the Project Manager, Research Assistants, and Co-Investigators to track study progress and review these monitoring procedures. The Principal Investigator will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, data management, and data analysis procedures, as well as regularly assess the risk/benefit ratio associated with participation in the study.

The Principal Investigator will train all project staff to recognize and report any adverse event immediately to them. Adverse events involving human participants include, for example, physical injuries, worsened physical or mental health, suicidal ideation, panic attacks, and depression. Other adverse events may also include the inadvertent disclosure by research staff of confidential research information to other persons and/or to staff of criminal justice or government agencies.

In the event that such adverse events are reported to the Principal Investigator, he will immediately inform the Chairperson of the appropriate Institutional

Review Board, who will make a decision about whether the reported event is a Serious Adverse Event (SAE) that must be reported to the National Institute on Drug Abuse (NIDA). If the Principal Investigator determines that there is sufficient evidence of an adverse event to necessitate suspension of data collection, further IRB review, modification of the protocol, or other changes, the Principal Investigator will immediately discuss this recommendation with the Chairperson of the IRB and reach a determination of whether to suspend data collection or to stop the study from proceeding. Resumption shall be based on the concurrence of the Principal Investigator, the Chairperson of the IRB, and any other relevant parties. NIDA will receive a written report within three days of any such suspension and/or resumption of data collection.

The Principal Investigator will provide an annual summary report of all adverse events to the IRB as part of the annual review and to NIDA as part of the annual Progress Report. If no adverse events have occurred, the report will state, "No adverse events affecting human participants have occurred during this project year."

Protocol Updates