Targeting Stress Reactivity in Schizophrenia: Integrated Coping Awareness Therapy

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Clinical Protocol

Targeting Stress Reactivity in Schizophrenia: Integrated Coping Awareness Therapy

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
CBT	Cognitive Behavioral Therapy
DSI	Daily Stress Inventory
FDA	U.S. Food and Drug Administration
FESFS	First Episode Social Functioning Scale
FFMQ	Five Facets of Mindfulness Questionnaire
HRV	Heart Rate Variability
I-CAT	Integrated Coping Awareness Therapy
IRB	Institutional Review Board
mDES	Modified Differential Emotions Scale
NIMH	National Institute of Mental Health
OASIS	Outreach and Support Intervention Services Clinic
PANSS	Positive and Negative Syndrome Scale
PSS	Perceived Stress Scale
PWB	Perceived Well Being Scale
QLS	Abbreviated Quality of Life Scale
RCT	Randomized controlled trial
RSA	Resting/Baseline Heart Rate Variability
SAE	Serious Adverse Event
SCS	Self-Compassion Scale
SSD	Schizophrenia spectrum disorder
TAU	Treatment as usual
UNC	University of North Carolina at Chapel Hill
WASI	Wechsler Abbreviated Scale of Intelligence

PROTOCOL SYNOPSIS

Study Title	Targeting Stress Reactivity in Schizophrenia: Integrated Coping Awareness Therapy (I-CAT)
Funder	National Institutes of Health
Clinical Phase	Phase I
Study Rationale	The purpose of the I-CAT trial is to test the feasibility of a psychosocial intervention that combines mindfulness, positive psychology, and determine the effectiveness of this intervention on the physical and mental health for individuals with schizophrenia spectrum disorders.
Study Objective(s)	1. Feasibility- Can I-CAT be delivered within this treatment setting? 2. Tolerability- How well is I-CAT accepted by the subjects? 3. Intervention adherence 4. Evaluation of I-CAT
Test Article(s) *(If Applicable)*	FirstBeat HR Bodyguard 2 devices, will be utilized to monitor heart-rate variability at rest and while engaging in mindfulness activities.
Study Design	This is a two arm, randomized controlled trial with 40 subjects (20 assigned to I-CAT and 20 assigned to TAU).
Subject Population key criteria for Inclusion and Exclusion:	<u>Inclusion Criteria</u> 1. DSM-V diagnosis of a SSD (Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Schizophreniform Disorder, and Unspecified Schizophrenia Spectrum and Other Psychotic Disorder) 2. Less than 8 years of antipsychotic and/or psychological treatment for psychosis 3. Between the ages of 18-35, both genders, and any ancestry 4. IQ>80. IQ will be assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) 5. Does not meet current substance dependence criteria 6. No hospitalizations for psychiatric reasons in the last 3 months 7. Not actively practicing meditation (not taking a workshop or practicing meditation in the past year) 8. Clinically stable (no psychiatric medication changes within the past month and on medication regimen not anticipated to change during the next 6 months) 9. Willing and able to provide informed consent.
Number of Subjects	40 individuals with schizophrenia spectrum disorders

Study Duration	Each subject's participation will last 12 months, 9 months of intervention and a 3-month follow-up
Study Phases **Screening** **Study Treatment** **Follow-Up**	Pre- Screening- Will be completed prior to the first in-person visit via a telephone screen for study eligibility. Screening- Subjects who are deemed eligible will be brought on site to obtain consent and complete the screening assessments (Demographics, Wechsler Abbreviated Scale of Intelligence [WASI], Perceived Stress Scale [PSS]). Baseline - Subjects will complete the Daily Stress Inventory (DSI), Five Facets of Mindfulness (FFMQ), modified Differential Emotions Scale (mDES), Perceived Well Being (PWB), short Self Compassion Scale (short SCS), First Episode Social Functioning Scale (FESFS), Positive and Negative Syndrome Scale (PANSS), abbreviated Quality of Life Scale (QLS). Subjects will also provide saliva samples every half hour over 2.5 hours for the measurement of cortisol. Additionally, subjects will wear the FirstBeat device to provide heart rate variability while resting and during a mindfulness activity. Mid-Treatment - Subjects will complete the FFMQ, mDES, PWB, short SCS, FESFS, PSS, PANSS, and the QLS). Post-Treatment – Subjects will complete the DSI, FFMQ, mDES, PWB, short SCS, FESFS, PSS, PANSS, QLS. Subjects will also provide saliva samples every half hour over 2.5 hours for the measurement of cortisol. Additionally, subjects will wear the FirstBeat Bodyguard 2 device to provide heart rate variability while resting and during a mindfulness activity. At the conclusion of the trial, investigators will administer a brief questionnaire to the subjects regarding satisfaction and acceptability. 3-Month Follow-up – Subjects will complete the FFMQ, mDES, PWB, short SCS, FESFS, PSS, PANSS, and QLS. Study Treatment- Subjects will participate in individual therapy sessions (I-CAT or TAU) weekly or bi-weekly for 60 minutes.
Efficacy Evaluations	Primary outcome – Psychological - Least means change from baseline scores at mid-treatment, post-treatment, and follow-up on positive emotions (mDES), role functioning (QLS, FESFS), and stress reactivity (PSS, DSI). Primary outcomes – Biological - Least means change from baseline to post-treatment on salivary cortisol. Secondary outcomes- Psychological- Least means change from baseline scores at mid-treatment, post-treatment, and follow-up on psychiatric symptoms (PANSS), mindfulness (FFMQ, short SCS), and well-being (PWB).

	Secondary outcomes- Biological- Least means change from baseline to post-treatment on resting/baseline heart rate variability (RSA).
Safety Evaluations	A safety plan for the intervention sessions will be developed prior to the initiation of the study with Drs. Penn and Perkins, as well as the study clinicians.
Statistical and Analytic Plan	Analyses will focus on average change over time (i.e., change from baseline scores) on primary outcomes (positive emotions, role functioning, stress reactivity, salivary cortisol) and secondary outcomes (psychiatric symptoms, mindfulness, well-being, heart rate variability). Analyses will utilize hierarchical linear models with random intercepts for each subject that will estimate the average change from baseline (i.e., least means change) for each treatment group (TAU, I-CAT) at mid-treatment, post-treatment, and follow-up timepoints.
DATA AND SAFETY MONITORING PLAN	Dr. Diana Perkins will function as the Project Medical Officer. An independent physician will serve as the Medical Monitor (Dr. Karen Graham, from the Department of Psychiatry).

1 BACKGROUND AND RATIONALE

Affecting one out of every one hundred people, schizophrenia is a common and all-too-often devastating disorder (Perkins, 2011). Florid psychotic symptoms respond well to available antipsychotic medication. People can recover in the early stages of illness; however with repeated relapse, persons with schizophrenia typically develop residual deficits that interfere with the ability to achieve a sustained, full recovery such that less than 20%, of those affected avoid disability (Lambert et al., 2006; Robinson et al., 2004). Residual impairments include negative symptoms, such as low motivation and drive, social withdrawal, and reduced hedonic capacity, as well as social and cognitive deficits. We add to the list of residual impairments a dysregulated stress response, as indexed by endocrine (Walker et al., 2008), autonomic (Castro et al., 2008; Chang et al., 2009; Lee et al., 2006; Sarosi, 2006), and immune (Miller et al., 2011) parameters. The costs of residual impairments and psychotic relapse are enormous—schizophrenia ranks as the third leading cause of disability-adjusted life years lost for young persons under the age of 24 (Gore et al., 2011). The cost of direct treatments for persons with schizophrenia is almost 3% of total health care expenditures driven by relapse, re-hospitalization, and residential treatment costs (Knapp et al., 2004).

Epidemiological studies clearly establish that stressful life events precede the onset of the first episode and occurrence of psychotic relapse (van Os et al., 2005; van Os et al., 2010; Broome et al., 2005; Brown et al., 2011; Nuechterlein et al., 1984; Thompson et al., 2007; McEwen et al., 2000) Observational studies consistently find alterations in autonomic (Sarosi et al., 2006; Castro et al., 2008), endocrine (Walker et al., 2008), and immune system (Miller et al., 2011) function in persons with schizophrenia and their first degree relatives, consistent with a dysregulated stress response. In agreement with these studies, we find that persons with first episode schizophrenia have elevated afternoon basal cortisol and a blunted cortisol response to a mental arithmetic stressor (Figure 1a). Similarly, we find a dysregulated cardiovascular response to the same stressor (Figure 1b-c). Persons who develop schizophrenia may suffer allostatic overload, defined as the physiological consequences or “wear and tear” on the body in response to repeated stressful situations (McEwen, 2000), for several possible reasons. They have a greater likelihood of exposure to stressful events such as childhood trauma, which corresponds to an increased sensitivity to stress and difficulties regulating the stress response (Lardinois et al., 2011; van Winkel et al., 2008). In addition, consequences of acute psychosis (e.g., disrupted social relationships) are significant stressors. There also is evidence that persons with schizophrenia may have an innate low capacity to respond to stressors (Ventura et al., 1989; Zubin et al., 1977), and thus even daily hassles and routine stressors may lead to allostatic overload.

We theorize that allostatic overload in persons with schizophrenia contributes to the severity of neurocognitive and social cognitive deficits that are most strongly associated with impaired function. Furthermore, we propose that impaired stress reactivity underlies the observed relationship of stressful life events and psychotic relapse. We further theorize that, as with healthy individuals under chronic stress, impaired stress reactivity contributes to the medical morbidity associated with schizophrenia, including high risks of cardiovascular disease and premature death. Despite the compelling evidence of dysregulated stress reactivity in persons with schizophrenia, translational studies investigating mechanisms and intervention studies targeting stress reactivity are lacking. Thus, we hypothesize that an intervention to ameliorate and improve impaired stress reactivity will change the trajectory of schizophrenia and reduce the likelihood of chronic disability and the associated medical morbidity.

Although the importance of stress in the etiology of schizophrenia has been well established (Walker et al., 2008; Corcoran et al., 2003), there is a critical lack of approaches that specifically target the dysregulated stress response in treatment. Pharmacological treatments target psychotic symptoms but do not prevent disability. Psychosocial treatments for schizophrenia such as illness self-management approaches, cognitive

behavioral therapy (CBT), and cognitive remediation are aimed at improving the proximal deficits surrounding symptoms, relapse, and cognitive impairments, but these treatments often have only small to moderate effects on long-term functional recovery (Dixon et al., 2010). None of these interventions directly address impaired stress reactivity that we theorize is an underlying deficit strongly associated with relapse risk and impaired functional recovery. There is thus a critical need for a shift in the design and application of treatments for schizophrenia to more adequately address the lack of functional recovery and high relapse risk. The research proposed in this application is innovative because it represents a departure from the status quo of the current array of treatments and targets functional recovery and relapse prevention through an intervention aimed at improving resilience to stress. There are a number of proximal measures associated with stress reactivity including autonomic, endocrine, and immune system function measures that will be key indicators of treatment change in this paradigm shift. We propose to test this theory targeting stress reactivity by developing an intervention aimed at altering the stress response through mindfulness, as well as buffering against the negative effects of stress through meaningful coping strategies and positive affect. This should restore allostatic load and result in functional recovery (Bower et al., 2008; Hamilton et al, 2006; Mauss et al., 2011).

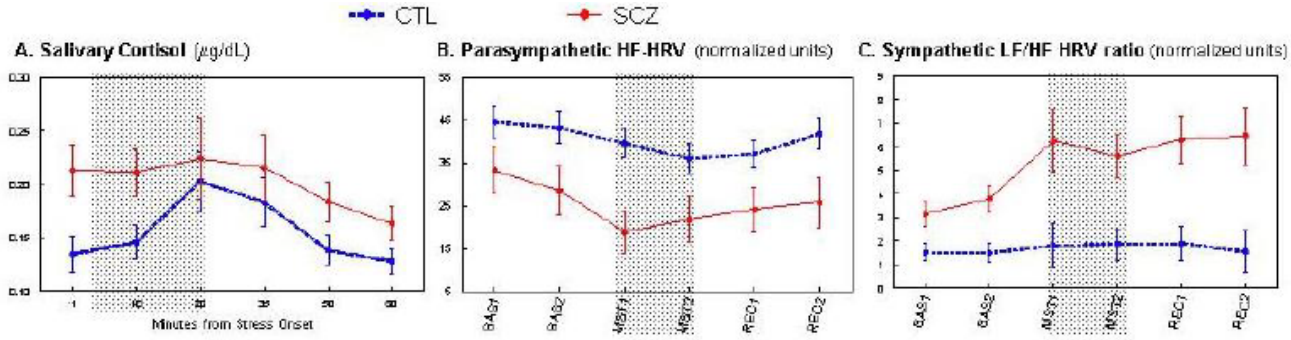

Figure 1. A pilot study of 10 schizophrenia (SCZ) probands, and 17 controls (CTL), aged 19.4 ± 3.5, using the Montreal Imaging Stress Task (MIST) was done in a laboratory setting (not in the scanner). Compared to CTLs, SCZ probands had abnormal reactivity to the 20-minute stressor (shaded area). CTLs showed the expected rise and fall of cortisol, decreased parasympathetic activity, and minimally increased sympathetic activity, with complete recovery following stressor termination. Patients showed blunted cortisol and parasympathetic responses and elevated, prolonged sympathetic reactivity.

2 RESEARCH DESIGN AND METHODS

2.1 OVERVIEW

To test the feasibility of a clinical trial implementing I-CAT for people with first-episode schizophrenia, a small RCT with 40 individuals (20 assigned to I-CAT and 20 to TAU) will be conducted. The objective of this small RCT is to conduct a feasibility trial of the I-CAT approach in anticipation of a larger scale trial. To complete this object, we will conduct a study using a small RCT comparing I-CAT to TAU (i.e., supportive therapy). This will allow us to evaluate the feasibility of recruitment, randomization, retention, assessment procedures, and the training and implementation of the revised I-CAT manual in a real-world setting. Successful completion of this stage of treatment development will provide preliminary information on the possible impact of I-CAT on stress reactivity.

Justification and Feasibility - The proposed study will evaluate the outcomes of the I-CAT intervention in a real-world clinical setting to estimate effect sizes in preparation for a larger clinical trial. We will begin standardizing the intervention, refine the clinician training protocol, and a measure of fidelity. The goal is to establish estimates of effect size before moving forward with a large-scale RCT. We are confident that comparing I-CAT to an active treatment will establish an accurate estimate of effect size from our key outcome domains.

Sample Size Justification - We have chosen to collect data from a sample size of 40 subjects with 20 in

each group. Currently, OASIS has a census of 140 people and admits approximately 3-5 people per month. With approximately 2 years to recruit 40 subjects, we will have to recruit approximately two subjects per month. In a previous randomized treatment trial at OASIS, we recruited 45 people with schizophrenia in approximately 30 months, suggesting these recruitment goals are realistic. 48 We conducted a power analysis using the Optimal Design power software developed by Raudenbush. The results suggest that, with 20 subjects per group, alpha=.05, and covariates that account for 40% of the variance, the study should have reasonable power (B = .70) to reliably detect treatment effect sizes of .65 or larger (although in this proposal, we have not designed the study with the anticipation that we will see effect sizes of this magnitude). We will compute effect sizes from these analyses and regard them as clinically meaningful if they exceed .20 for more distal outcomes and .30 for more proximal outcomes.

Research Design - We will randomly assign 40 subjects to either I-CAT or (*n*=20) or TAU (*n*=20) for up to nine-months of individual therapy sessions. Blinded raters will assess subjects at mid-treatment, post-treatment, and follow-up. A computer program, held by the data manager, will determine randomization; randomization sequences will not be known by anyone in advance. The data manager will then do the randomization. Subjects will be instructed not to discuss the type of therapy they are receiving with the blinded research assistants. Any violations to treatment blinding will be noted in the study log and possibly addressed in subsequent data analyses.

Biological Specimen Analyses - Our primary outcome measure is cortisol. Our preferred method of analyzing cortisol will be collecting saliva at 5 times points over 2.5 hours and performing analyses with the Salimetrics High Sensitivityassay.

Cardiovascular Measures - Cardiovascular monitoring will include measurement heart rate variability (HRV). At the baseline and post-treatment visits, HRV will be measured over a 5 minutes rest period (watching a 5-minute nature video) to obtain resting state HRV data, then over 5 minutes of paced breathing, and finally over an additional 5 minute rest period (watching a 5-minute nature video). HRV data will be collected using a FirstBeat Bodyguard 2 device, a wearable IBI monitoring and recording device. CardioEdit/CardioBatch Plus, and Kubios HRV Standard will be used to prepare, edit and analyze vagal activity, 99,100 in 5-minute epochs, indexed by respiratory sinus arrythmia.

2.2 SUBJECTS

Study subjects will be primarily drawn from the OASIS clinic at UNC Hospitals. Once a person is referred to the study (or self refers), a study clinician will meet with the individual (and any other individuals that she/he indicates, such as a family member) and describe the study protocol, expectations of study participation and potential study risks and benefits. The study clinician will evaluate the subject's understanding, and will not proceed with consent unless the individual understands these elements. All study subjects will sign a written informed consent document approved by the UNC Institutional Review Board. To obtain an estimate of IQ and to rule out any individuals with possible mental retardation, we will administer the WASI, which is comprised of Matrix Reasoning, Vocabulary, Similarities, and the Block Design subtests. Additional demographic and clinical information that will be collected as self-report for possible use as covariates includes: age, sex, ancestry, education, parent education, substance use, current medications, duration of outpatient treatment, and date of initial SSD diagnosis.

2.2.1 INCLUSION CRITERIA

1. DSM-V diagnosis of a SSD (Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Schizophreniform Disorder, and Unspecified Schizophrenia Spectrum and Other Psychotic Disorder)

2. Less than 8 years of antipsychotic and/or psychological treatment for psychosis
3. Between the ages of 18-35, both genders, and any ancestry
4. IQ>80. IQ will be assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)
5. Does not meet current substance dependence criteria
6. No hospitalizations for psychiatric reasons in the last 3 months
7. Not actively practicing meditation (not taking a workshop or practicing meditation in the past year)
8. Clinically stable (no psychiatric medication changes within the past month and on medication regimen not anticipated to change during the next 6 months
9. Willing and able to provide informed consent.

3 ASSESSMENT OF DATA

At this stage of treatment development, specific outcomes include:

1. Feasibility- Can I-CAT be delivered within this treatment setting?
    a. Attrition rates
2. Tolerability- How well is I-CAT accepted by the subjects?
    a. I-CAT feedback survey outcomes
3. Intervention adherence
    a. Attendance rates, session fidelity ratings
4. Evaluation of I-CAT
    a. Primary and secondary outcomes will be compared between I-CAT and TAU

3.1 OUTCOMES

The central hypothesis is that I-CAT will increases positive emotions, increase role functioning, and decrease stress reactivity as measured by self-report measures and salivary cortisol. Secondary hypotheses are that I-CAT will decrease psychiatric symptoms, increase mindfulness, and increase well-being as measured by self-report, clinical interview measures, and heart rate variability. Guided by strong preliminary data, this hypothesis will be tested via four specific aims:

1. To examine the feasibility of implementing I-CAT at a community mental health clinic
2. To examine the tolerability of I-CAT at a community mental health clinic
3. To examine I-CAT adherence through attrition and attendance rates
4. We will also examine the impact of I-CAT on primary outcomes (positive emotions, role functioning, stress reactivity), and secondary outcomes (psychiatric symptoms, mindfulness, well-being) compared with TAU.

We hypothesize that I-CAT will be associated with:

- Improved primary outcomes including increased positive emotions, increased role functioning, and decreased stress reactivity at mid-point, post-test, and three-month follow-up.

- Improved secondary outcomes including decreased psychiatric symptoms, increased mindfulness, and increased well-being at mid-point, post-test, and three-month follow-up.

4 STUDY DESIGN

During this phase of the trial, 40 subjects will be assigned to one of two interventions (i.e., I-CAT or TAU) of 20 subjects each. Intervention will last for approximately 9 months. Subjects will be asked to complete a total of five in-person assessments at screening, baseline, mid-point, post-test, and three-month follow-up.

4.1 INTERVENTION

After subjects are randomized to treatment intervention (i.e., I-CAT or TAU), subjects will meet weekly for individual therapy sessions with master's level clinicians or advanced graduate students with at least a master's degree. Clinicians will be monitored by three experienced clinicians/ instructors with over 15 years of experience in the field (Penn, Meyer, and Gaylord). Clinicians will also have weekly supervision. Sessions will be recorded and assessed with the fidelity scale.

4.1.1 I-CAT

I-CAT is a manual-based intervention (manual available upon request). Sessions include collaborative agenda setting, practice of skills, refining and problem-solving obstacles, and collaborative homework assignments.

Part I of I-CAT includes psychoeducation on stress reactivity and mindfulness and assessment of stressors. Part II of I-CAT integrates practice of mindfulness (e.g., sitting meditation, body scan) and positive coping strategies (e.g., identification of personal strengths, setting positive goals, active/constructive responding). Sessions focus on a new strategy broken down into small steps demonstrated and practiced in session. Handouts are provided to increase integration of new skills in daily routines and track practice of skills between sessions. Part III of I-CAT focuses on 1) development of an individualized daily routine integrating mindfulness and meaningful coping skills, and 2) development of positive and personally meaningful goals (e.g., return to school). Handouts are also utilized in Part III to break goals into small steps, track progress, and identify barriers to goal achievement.

I-CAT can be flexibly administered with a minimum of 14 sessions recommended to cover all skills and participate in the individualized plan, or up to 24 sessions based on client needs over a nine-month period. Subjects in the I-CAT condition will also complete coordinated specialty care appointments (e.g., medication management, family therapy, supported employment, peer support).

4.1.2 TAU

Subjects randomized to TAU participated in weekly or bi-weekly therapy sessions and coordinated specialty care appointments. Therapists conducting TAU sessions were instructed to conduct sessions as usual and to refrain from introducing I-CAT elements (e.g., mindfulness and positive psychology). The frequency and duration of TAU will be the same as I-CAT with subjects encouraged to complete at least 14 sessions over nine months.

4.2 STUDY PROCEDURES AND MEASUREMENTS

4.2.1 SCREENING VISIT

The following measures will be examined at screening:

- Demographics- We will collect information on age, sex, ancestry, education, parent education, smoking, substance use, current medications, duration of outpatient treatment, and date of initial SSD diagnosis.
- Intelligence- In adherence with our inclusion criteria that subjects must have an IQ greater than 80, the Wechsler Abbreviated Scale of Intelligence (WASI) will be administered.
- Diagnosis-The Structured Clinical Interview for the DSM-V (SCID) will be utilized to assess symptoms. The SCID is a semi-structured interview that assesses for DSM diagnoses. The SCID will be used to verify that subjects have a schizophrenia spectrum diagnosis before they are enrolled in the study. Raters will be trained to conduct the SCID to a gold standard of reliability (i.e., intraclass correlation > .80).

4.2.2 Baseline and Post-Treatment Visits

The following measures will be examined at the baseline and post-treatment visits:

- Daily Stress Inventory (DSI) - The Daily Stress Inventory (DSI; Brantley et al., 1987) is a 58-item self-report measure assessing the frequency and intensity of stressful events within the past 24-hours. If an event is endorsed, participants rate the amount of stress the event caused (0 = *did not occur*, 1 = *occurred but was not stressful* to 7 = *occurred and caused me to panic*). The DSI yields three scores: frequency (number of events endorsed as occurred; range 0 - 58), sum (sum of the total impact rating of endorsed events; range 0 - 406), average impact rating (AIR; average impact of ratings given items endorsed [sum/frequency]).
- Five Facets of Mindfulness (FFMQ) - The Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006) is a 39-item self-report measure assessing facets of being mindful in daily life (i.e., observing, describing, acting with awareness, non-reactivity to inner experience, and non-judging of inner experience). Items are endorsed on a five-point scale (1 = *never or rarely true* to 5 = *very often or always true*) and averaged for a total score and five subscale scores for each facet of mindfulness (range 1-5).
- Modified Differential Emotions Scale (mDES) - The modified self-report Differential Emotion Scale (mDES; Fredrickson et al., 2003) assessed the frequency of experiencing discrete emotions from the previous week. Items are endorsed on a five-point scale (0 = *not at all*, 4 = *most of the time*) and averaged to yield positive and negative emotion subscales (range for both 0-4).
- Perceived Well Being (PWB) - The Psychological Well-Being Scale (PWB; Ryff, 1989) is a 54-item self-report measure with items endorsed on a seven-point scale (1 = *strongly disagree* to 6 = *strongly agree*). Items are summed for a total score (range 54 - 324) and six subscale scores (i.e., autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, self-acceptance; range 9 - 54).
- Short Self Compassion Scale (short SCS) - The Self-Compassion Scale Short Form (SCS; Raes et al., 2011) is a 12-item self-report measure of self-compassion. SCS items are endorsed on a five-point scale (1 = *almost never* to 5 = *almost always*) and are summed for a total score (range 12 – 60) and six subscales (i.e., self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identified; range 2 – 10).

- First Episode Social Functioning Scale (FESFS) - The First Episode Social Functioning Scale (FESFS; Lecomte et al., 2014) is a 42-item self-report measure assessing social functioning in early SSD. The FESFS includes a total score and eight subscales assessing: independent living skills, interacting with people in different contexts, social activities, intimacy, friendships, family relations, work, and school. Domain scores are averaged with higher scores reflecting better perceived functioning (range 0-4).
- Perceived Stress Scale (PSS) - The Perceived Stress Scale (PSS; Cohen et al., 1983) is a ten-item self-report measure of the degree to which daily situations from the past week are perceived as stressful, unpredictable, uncontrollable, as well as how "overloaded" individuals feel (0 = *never,* 4 = *very often*). Items are summed for a total score (range 0 – 40) with higher scores indicating more perceived stress.
- Positive and Negative Syndrome Scale (PANSS) - The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) assessed current symptoms. PANSS items are rated on a seven-point scale with higher scores reflecting more severe symptoms (ICCs for study assessors >.90). Items are summed for a total score (range 30 – 210). Items were also averaged according to the five-factor structure with the most consensus across studies (Wallwork et al., 2012) to yield five subscales (range 1-7) assessing negative, positive, depression, excited, and disorganization symptoms.
- Abbreviated Quality of Life Scale (QLS) - The abbreviated Quality of Life Scale (QLS; Bilker et al., 2003) is a seven-item semi-structured interview assessing domains of functioning (i.e., intrapsychic foundation, interpersonal relationships, instrumental role, and engagement in community). Items are rated on a six-point scale yielding a sum total score (range 0 - 42) with higher ratings reflecting better functioning.
- Subjects will also provide saliva samples every half hour over 2.5 hours for collection of salivary cortisol
- Subjects will wear the FirstBeat Bodyguard 2 device to provide heart rate variability while resting and during a paced breathing activity.

4.2.3 Mid-Treatment and Three-Month Follow-up Visits

The following measures will be examined at the mid-treatment and three-month follow-up visits:

- Daily Stress Inventory (DSI)
- Five Facets of Mindfulness (FFMQ)
- Modified Differential Emotions Scale (mDES)
- Perceived Well Being (PWB)
- Short Self Compassion Scale (short SCS)
- First Episode Social Functioning Scale (FESFS)
- Perceived Stress Scale (PSS)
- Positive and Negative Syndrome Scale (PANSS)
- Abbreviated Quality of Life Scale (QLS)

5 STATISTICAL ANALYSES

5.1 DATA ANALYTIC PLAN

Feasibility will be defined by our ability to meet our recruitment targets (40 people), frequency of engagement in the intervention by participants (session attendance and attrition rates), and feedback on the intervention from I-CAT participants.

Differences between group demographics to check effectiveness of randomization will utilize independent samples t-tests (continuous variables) or Pearson chi-square tests (categorical variables). Little's Missing Completely at Random test will be performed to establish whether data is missing at random and to determine if data imputation will be needed for subsequent analyses.

To test whether intervention groups differ in their amount of change on treatment outcomes over time, data will be analyzed according to the intent-to-treat principle, in which all subjects randomized will be included in the analysis. To examine intervention effects on primary and secondary outcomes, linear mixed-effects models will be utilized with restricted maximum likelihood estimation where missing data will be handled via full information maximum likelihood. The linear mixed-effects models will include effects of time (i.e., baseline, mid-treatment, post-treatment, and follow-up), intervention group, and a group by intervention interaction with random intercepts to account for baseline differences on outcome variables. Observations classified as outliers (i.e., residual values less than or greater than 1% of all observations) will be excluded. Changes from baseline will be estimated using least-squares means for each intervention group.

5.2 POWER ANALYSIS

We conducted a power analysis using the Optimal Design power software developed by Raudenbush. The results suggest that, with 20 subjects per group, alpha=.05, and covariates that account for 40% of the variance, the study should have reasonable power (B = .70) to reliably detect treatment effect sizes of .65 or larger (although in this proposal, we have not designed the study with the anticipation that we will see effect sizes of this magnitude). We will compute effect sizes from these analyses and regard them as clinically meaningful if they exceed .20 for more distal outcomes and .30 for more proximal outcomes.

5.3 DATA MANAGEMENT

All data will be entered by trained research assistants using Qualtrics software. Double data entry will be required for information not directly entered by the participants. Double data entry will also be entered by trained research assistants using Qualtrics software. All data analysis will be conducted by statistician, Oscar Gonzalez.

6 RISKS AND BENEFITS

Risks associated with collection of clinical assessments include anxiety or embarrassment due to revealing personal information. In addition, persons are asked to reveal information about use of illegal drug; information that could impact work or school status. There is a risk that confidential personal information would be disclosed to others outside of research staff. Risks associated with participation in the I-CAT intervention include anxiety related to discussing stressors. The risks associated with routine venipuncture include bleeding, bruising, infection, and fainting.

6.1 Monitoring Risks

To address subject anxiety or embarrassment due to revealing person information, we have trained research staff who are experienced in working with individuals with schizophrenia spectrum disorders. They have been trained to put subjects at ease, let them take their time, and to conduct interviews in private rooms.

To address the issue of accidental disclosure of personal information to others outside of the research staff, we will obtain a NIH Certificate of Confidentiality for the study. In addition, identifying research subjects by study number on all research documents minimizes the risk of breach of confidentiality. Study documents that must contain personal information, including the informed consent document, and the document that links study ID number to personal identifying information (necessary due to the longitudinal nature of the open trial and RCT) are kept in locked filing cabinets in locked rooms. Research data will be kept on password-protected drives, and our computer systems are HIPAA compliant. All study staff participate in annual human subject training that includes education about responsibilities to minimize risk that confidentiality may be breached.

Should any subject experience any problems during the study, our research team has trained staff that will be able to provide immediate care on-site. Subjects will be referred for additional care to the appropriate providers on campus, such as Campus Health Services or the UNC Hospitals Emergency Department, if necessary.

6.2 NON-SIGNIFICANT RISK DOCUMENTATION

Pregnant women will be excluded because pregnancy alters autonomic, endocrine, and immune stress responsivity.

6.3 POTENTIAL BENEFITS OF THE RESEARCH TO SUBJECTS AND OTHERS

The subjects who receive the I-CAT treatment may receive benefits that could be associated with decreases in stress and symptoms and improvements in social and/or occupational functioning. Society will benefit from the new knowledge about stress reactivity in schizophrenia. Ultimately, this information will improve our knowledge about treatment targeting stress reactivity in schizophrenia.

6.4 CONFIDENTIALITY OF DATA

Risks regarding confidentiality will be minimized by using code numbers instead of names on study data. The code and the data will be stored in separate locked files at Howell Hall on UNC's campus. Similar subject records are scrutinized regularly and our procedure will add an extra level of protection because the research case numbers will be different from subject numbers (random numbers not associated with date of birth) and the code will be unavailable to anyone outside of the research team. Audio recordings of weekly group sessions will be saved on our secure lab server and on OneDrive so that offsite investigators may review and provide feedback to the clinicians conducting the sessions.

Identifiable data will only be shared with the clinicians of subjects in the study with the permission of the subjects (obtained during informed consent). Clinicians will be contacted if issues arise related to safety during the trial. As part of the informed consent process, all subjects will provide the name and contact info of a clinician that we may contact if we become concerned about their safety (e.g., physical and/or mental

health) during the course of the trial. We will not be sharing any confidential information with anybody outside of these clinicians.

Identifiable data will be maintained for 5 years following study completion. At that point, hard copies of identifiable data including consent forms and contact information will be shredded. Electronic data will be de-identified upon entry, with the exception of the subjects' birth dates for the purposes of calculating their exact age.

7 DATA SAFETY AND MONITORING PLAN

7.1 ADVERSE EVENTS

Dr. David Penn (Co-I) will function as the Project Medical Officer and will be available on pager and cell phone to all co-investigators to discuss any safety issue that emerges over the course of the study. All adverse events (AEs) occurring during the course of the study will be documented and reported to Dr. Penn. All Serious Adverse Events (SAEs) will also be reported to the IRB and NIMH. The occurrence of AEs will be assessed during the study and the investigators will follow all AEs to the point of satisfactory resolution. An independent physician will serve as Medical Monitor (Dr. Karen Graham, from the Department of Psychiatry). AEs will be tracked over the course of the study and will be reported at the midpoint and endpoint of each subject's course of intervention to the DSC. All SAEs will be reported to the DSC within 24 hours of learning of the event.

7.2 SERIOUS ADVERSE EVENTS

AEs will be assessed to determine if they meet criteria for a SAE. SAEs, as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE will be reported to the IRB and NIMH. The initial SAE report will be followed by submission of a completed SAE report to each institution. In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to SAE, the subject will have appropriate follow-up and/or stabilization. Follow-up will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study procedures, or results in death. Outcome of SAEs will be periodically reported to NIMH. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIMH.

The trial period is defined from the time that the informed consent document is signed until 30 days after the last study visit. All serious AE's occurring during the trial period (including death due to any cause) or within 30 days after the last study visit will be communicated within 1 day of the investigator becoming aware of the event to designated personnel, using the telephone or fax numbers provided in the Study Reference Manual. Any fatal or life-threatening AE's will be reported immediately, but no longer than 1 day from the time the investigator becomes aware of the event. A causality assessment will be provided for all SAEs. Critical follow-up information on SAEs will be provided as soon as it is available, but no longer than 1 day from the time the investigator became aware of the information. Other essential, but not critical, information may be reported within the following 5 days. An SAE, as defined by the FDA for use in clinical trials https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm), is an adverse event that satisfies any of the following criteria:

- Results in death.

- Is immediately life-threatening, including potentially life threatening suicidal behavior or suicidal behavior that results in hospitalization.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples would include allergic bronchospasm that requires treatment in an emergency department, or a seizure that does not result in hospitalization.

The causality of SAEs (i.e., their degree of relatedness to study treatment) will be assessed by the investigators.

7.3 DEATH

All deaths occurring within the trial period or within 30 days after the last day that the study intervention is administered will be reported within 1 day of the investigator becoming aware of the event. If an autopsy has been performed, results of the autopsy will be obtained and forwarded along with any available toxicology reports.

7.4 PREGNANCY

Pregnancy is an exclusion criterion and women who can become pregnant should use adequate methods of birth control as outlined in the inclusion criteria. Should a pregnancy occur it must be reported in accordance with the procedures described below. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an intervention may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. The Adverse Events/Side Affects form will be used for this purpose. All reports of congenital abnormalities/birth defects are SAE's. Spontaneous miscarriages should also be reported and handled as SAE's. All other outcomes of pregnancy must be reported on the Adverse Events/Side Effects form.

8 RECRUITMENT STRATEGY

Study subjects will be primarily drawn from the OASIS clinic at UNC Hospitals. Once a person is referred to the study (or self refers), a study clinician will meet with the individual (and any other individuals that she/he indicates, such as a family member) and describe the study protocol, expectations of study participation and potential study risks and benefits. The study clinician will evaluate the subject's understanding, and will not proceed with consent unless the individual understands these elements. All study subjects will sign a written informed consent document approved by the UNC Institutional Review Board.

9 CONSENT PROCESS

Research staff will obtain informed consent directly from each subject. Staff obtaining the consent will provide the subject with a written document explaining the testing procedures and risks, and will answer any

questions. We have several procedures in place to ensure that prospective participants fully understand the procedures, risks, and protections of the study. First, the consent form is written in easy to understand language. Second, the researcher reads the form to and with the potential subject, and invites questions after each section of the form. Third, the researcher asks the subject a series of questions about the study, such as what they are to do if they no longer want to participate, or what they would do if they experience any stress during the protocol (this is to be used as comprehension check before signing).

10 REFERENCES

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. *Assessment*, *13*, 27–45.

Bilker, W. B., Brensinger, C., Kurtz, M. M., Kohler, C., Gur, R. C., Siegel, S. J., & Gur, R. E. (2003). Development of an abbreviated schizophrenia quality of life scale using a new method. *Neuropsychopharmacology*, *28*, 773–777.

Bower, J. E., Low, C. A., Moskowitz, J. T., Sepah, S. & Epel, E. (2008). Benefit finding and physical health: Positive psychological changes and enhanced allostasis. *Social and Personality Psychology Compass 2*, 223-244.

Brantley, P. J., Waggoner, C. D., Jones, G. N., & Rappaport, N. B. (1987). A daily stress inventory: Development, reliability, and validity. *Journal of Behavioral Medicine, 10*, 61–73.

Broome, M. R. et al. (2005). What causes the onset of psychosis? *Schizophrenia Research, 79*, 23- 34.

Brown, A. S. (2011) The environment and susceptibility to schizophrenia. *Progress in Neurobiology, 93*, 23-58.

Castro, M. N. et al. (2008). Heart rate variability response to mental arithmetic stress in patients with schizophrenia: Autonomic response to stress in schizophrenia. *Schizophrenia Research, 99*, 294-303.

Chang, J. S. et al. (2009). Differential pattern of heart rate variability in patients with schizophrenia. *Progress in Neuropsychopharmacol and Biological Psychiatry, 33*, 991-995.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*, 385–396.

Corcoran, C. et al. (2003). The stress cascade and schizophrenia: etiology and onset. *Schizophrenia Bulletin 29*, 671-692.

Dixon, L. B. et al. (2010). The 2009 Schizophrenia PORT Psychosocial Treatment Recommendations and Summary Statements. *Schizophrenia Bulletin 36*, 48-70.

Fredrickson, B. L., Tugade, M. M., Waugh, C. E., & Larkin, G. R. (2003). What good are positive emotions in crises? A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. *Journal of Personality and Social Psychology, 84*, 365–376.

Gore, F. M. et al. (2011). Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet, 377*, 2093-2102.

Hamilton, N. A., Kitzman, H. & Guyotte, S. (2006). Enhancing health and emotion: Mindfulness as a missing link between cognitive therapy and positive psychology. *Journal of Cognitive Psychotherapy 20*, 123-134.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*, 261–276.

Knapp, M., Mangalore, R. & Simon, J. (2004). The global costs of schizophrenia. *Schizophrenia Bulletin, 30*, 279-293.

Lambert, M. et al. (2006). Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. *The Journal of Clinical Psychiatry,* 67, 1690-1697.

Lardinois, M., Lataster, T., Mengelers, R., van Os, J. & Myin, I. (2011). Childhood trauma and increased stress sensitivity in psychosis. *Acta Psychiatrica Scandinavica, 123*, 28-35.

Lecomte, T., Corbière, M., Ehmann, T., Addington, J., Abdel-Baki, A., & MacEwan, B. (2014). Development and preliminary validation of the First Episode Social Functioning Scale for early psychosis. *Psychiatry Research*, *216*, 412–417.

Lee, K. H. et al. (2006). A functional magnetic resonance imaging study of social cognition in schizophrenia

during an acute episode and after recovery. *American Journal of Psychiatry, 163*, 1926-1933.

Mauss, I. B. et al. (2011). Don't hide your happiness! Positive emotion dissociation, social connectedness, and psychological functioning. *Journal of Personality and Social Psychology, 100*, 738-748.

McEwen, B. S. & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Arch Intern Med, 153*, 2093-2101.

McEwen, B. S. (2000). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research, 886*, 172-189.

Miller, B. J., Buckley, P. F., Seabolt, W., Mellor, A. & Kirkpatrick, B. (2011). Meta- analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biological Psychiatry.*

Nuechterlein, K. H. & Dawson, M. E. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin, 10*, 300-312.

Perkins, D. O. (2011). in *Essentials of Schizophrenia* (eds J.A. Lieberman, S. Stroup, & D.O. Perkins) Ch. 1, 1 10 (American Psychiatric Publishing, Inc).

Raes, F., Pommier, E., Neff, K. D., & Van Gucht, D. (2011). Construction and factorial validation of a short form of the Self-Compassion Scale. *Clinical Psychology and Psychotherapy, 18*, 250–255.

Robinson, D. G., Woerner, M. G., McMeniman, M., Mendelowitz, A. & Bilder, R. M. (2004). Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry, 161*, 473-479.

Ryff, C. D. (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *Journal of Personality and Social Psychology, 57*, 1069–1081.

Sarosi, A. (2006). Maintenance pharmacotherapy of schizophrenia: remission and the effectiveness of long-acting risperidone therapy. *Neuropsychopharmacology Hungarian, 8*, 179-187 (2006).

Thompson, K. N. et al. (2007). Stress and HPA-axis functioning in young people at ultra high risk for psychosis. *Journal of Psychiatric Research, 41*, 561-569.

van Os, J., Kenis, G. & Rutten, B. P. (2010). The environment and schizophrenia. *Nature, 468*, 203-212.

van Os, J., Krabbendam, L., Myin-Germeys, I. & Delespaul, P. (2005). The schizophrenia envirome. *Current Opinion in Psychiatry, 18*, 141-145.

van Winkel, R., Stefanis, N. C. & Myin-Germeys, I. (2008). Psychosocial factors and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophrenia Bulletin, 34*, 1095-1105.

Ventura, J., Nuechterlein, K. H., Lukoff, D. & Hardesty, J. P. (1989). A prospective study of stressful life events and schizophrenic relapse. *J Abnorm Psychol, 98*, 407-411.

Walker, E., Mittal, V. & Tessner, K. (2008). Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. *Annual Review of Clinical Psychology, 4,* 189-216 (2008).

Zubin, J. & Spring, B. (1977). Vulnerability--a new view of schizophrenia. *J Abnorm Psychol, 86*, 103 126.