PROTOCOL APPROVED OCTOBER 19, 2018

Phase II of the project (*22.5* months) will include a pilot RCT comparing combined CBSST-CCT to goal-focused supportive contact (SC), an active control group. 64 participants (16 from each of 4 community locations) will be recruited, and the interventions will be delivered in a group format on-site by masters-level research therapists. The locations will include a large board and care facility, a clubhouse, and two psychosocial rehabilitation centers (see letters of support). Participants with schizophrenia and moderate-to-severe negative symptoms will be randomized to condition after completing baseline assessments, and will then be treated for *4.5* months and followed longitudinally for *6* months after treatment. Assessments will be administered at baseline, midway through treatment, post-intervention, and *6* month follow-up. The *6*-month follow-up recognizes the need to determine enduring effects, as well as findings that differences between CBT and control conditions are often greater at follow-up than at post-treatment (Sensky et al., 2000; Granholm et al., 2007b; Gould et al., 2001). The last-enrolled participants will finish their *6*-month follow-up assessments during quarter 2 of year 3. During the last 2 quarters of the project, we will (1) conduct our data analyses, (2) write manuscripts, and (3) prepare an R01 application for a larger scale study of CBSST-CCT.

Figure 3. Timeline of the proposed study

Year 1				*Year 2*				*Year 3*			
Q1	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*
-Hire and train staff -Focus groups (patients, family members, clinicians) -Develop combined CBSST-CCT manual -Practice group (4.5 mos)			*Recruit, enroll, randomize, and deliver intervention to first 16 participants (4.5 months tx + 6 months f/u)*								
				Recruit, enroll, randomize, and deliver intervention to second 16 participants (4.5 months tx + 6 months f/u)							
					Recruit, enroll, randomize, and deliver intervention to third 16 participants (4.5 months tx + 6 months f/u)						
						Recruit, enroll, randomize, and deliver intervention to fourth 16 participants (4.5 months tx + 6 months f/u)		*-Data analysis -Manuscript writing -R01 preparation*			

3.3. Participants. Inclusion/exclusion criteria were designed to select 64 participants with schizophrenia with moderate-to-severe negative symptoms (Buchanan, 2007), enriched for predominantly primary negative symptoms but allowing for untreated secondary negative symptoms. Selecting for moderate-to-severe negative symptoms will minimize the likelihood that negative symptom improvement is secondary to improvement in positive symptoms or depression, and will capture those negative symptoms that lead to functional disability and are currently an unmet treatment need (Buchanan, 2007). The NIMH-MATRICS Consensus Statement on Negative Symptoms (Kirkpatrick et al., 2006) has recommended this approach. **Inclusion criteria**: (1) Voluntary informed consent to participate; (2) Age 18 to *65*; (3) DSM-IV diagnosis of schizophrenia or schizoaffective disorder based on MINI/SCID; (4) Moderate-to-severe negative symptoms on the Clinical Assessment Interview for Negative Symptoms (CAINS total score >19); (5) ≥ 6th grade reading level on the Wide Range Achievement Test-4 Reading subtest (needed for reading treatment manual); *(6) Stable on medications; no changes within 3 months prior to enrollment.* **Exclusion criteria:** (1) Prior CBT, SST, or CCT in the past 5 years; (2) Severe positive symptoms on the Positive and Negative Syndrome Scale (PANSS Delusions, Disorganization, Hallucinations, or Suspiciousness >5); (3) Severe depression on the Calgary Depression Scale for Schizophrenia (CDSS >8); (4) Ocular damage/disease/surgery/medications that affect pupil dilation; (5) DSM-IV alcohol or substance dependence diagnosis in past 6 months based on the MINI or SCID; (6) Level of care required interferes with outpatient therapy (e.g., hospitalized; severe medical illness).

3.4. Feasibility of recruitment and retention. Subjects will be recruited from a large board and care facility (Broadway Home), a clubhouse (The Meeting Place), and two psychosocial rehabilitation and recovery programs in San Diego (Project Enable and Areta Crowell). All four locations have the numbers of service users needed to recruit a group of 16 individuals, and all have the space to run groups on-site (please see letters of support). (We also have a back-up location, the Psychosocial Rehabilitation and Recovery Center, directed by Dr. Granholm at the VA San Diego Healthcare System.) In our prior CBSST trials, we achieved a 79% consent rate of patients with schizophrenia. In two ongoing trials, we have enrolled 242 patients with schizophrenia from the proposed recruitment locations and 42% had at least moderate-to-severe negative symptoms at baseline, demonstrating that we can enroll patients with negative symptoms into psychosocial intervention studies. In addition, we will enhance feasibility by providing all interventions on-site, particularly important with negative symptom cohorts. Monetary incentives (only for assessments, not therapy sessions) will also facilitate enrollment and retention, and we have found that a strong intervention focus on real-world

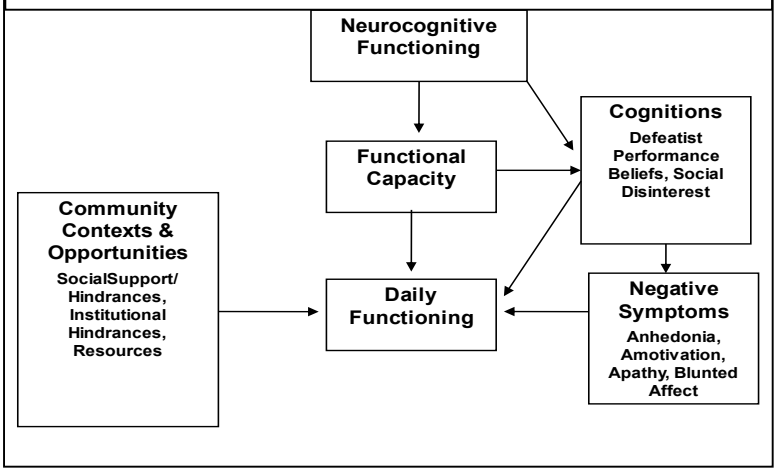
goals (e.g., relationships, independence, finances, work/school) promotes enrollment and retention. We will optimize follow-up with regular patient contact in treatment, mailings to confirm whereabouts (e.g., birthday and holiday cards), and consent to contact at least one person likely to know subject whereabouts. These methods have resulted in low drop-out rates in prior trials (<10% drop-out at 4.5 months, 20% drop-out at 18 months).

3.5. Procedures and Design Considerations. To ensure that participants meet study criteria, we will use the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) or Structured Clinical Interview for DSM-IV (SCID; First et al., 1997), followed by a consensus diagnosis with an experienced clinician, using all available records and the structured interview. To reduce participant burden, participants who have undergone a SCID or MINI interview by a trained, reliable interviewer as part of other research participation within the past year will not have to repeat the interview. We will also obtain demographic data, medical/pharmacologic history, and alcohol/substance history. We will use the Schedule for the Deficit Syndrome (Kirkpatrick et al., 1989) to characterize the sample into deficit and nondeficit groups for exploratory analyses. Following informed consent and baseline assessment, randomization via computer-generated randomization scheme (www.randomization.com) will be used to assign participants to one of the two conditions. Assessors will be blind to randomization status. Assessments will be administered at baseline, midway through treatment (*2.25* months), post-treatment (*4.5* months), and *6-month follow-up (10.5 months)*. Thus, participants will be enrolled in the study for *10.5 months*. Participants will not be compensated for their time receiving therapy, but they will be compensated for their time at all four assessments. Participants will be paid $30 for participating in each (~3 hr) assessment, plus a $20 bonus for completing all four assessments. Two masters-level therapists will provide both interventions at two locations each so as not to confound therapist effects with location effects. All participants will continue to receive their current treatments, including pharmacotherapy, with their current providers throughout the study. We will ensure that patients enrolled in either treatment condition in this project do not receive other CBT, SST, or cognitive remediation/training interventions during study participation, but will not restrict any other types of services or medications. We will not try to influence pharmacotherapy, but will track medications at each assessment and these data will be used to explore differences in outcomes. We will attempt to obtain follow-up data on all participants, regardless of whether or not they complete treatment.

Design Considerations. The main strengths of the proposed study are its importance, innovation, design, and feasibility. The study design will answer the questions of interest with adequate power and will be **feasible to complete** (n=16 needed at each location), given the ample number of potential participants available at each location (see letters of support). Importantly, the four locations are all part of the San Diego County mental health system, and all assessors, therapists, and study staff will be the same across the four locations, therefore, this is not a multi-site trial with the potential for site effects. We are **intentionally selecting participants with a high negative symptom burden** and identified treatment locations enriched for lower-functioning patients with more severe negative symptoms. **For the control condition,** we considered using "treatment as usual," but opted for an active comparison condition that wouldn't confound specific with nonspecific therapeutic factors. We also considered comparing CBSST-CCT with standard CBSST or CCT, but concluded that this design would not be appropriate for a pilot project, in which the central question is, "does the bundled intervention work?" Multiple treatment arms (CBSST-CCT vs. CBSST vs. CCT vs. SC) would not be feasible in a pilot study and we have already established the efficacy of CCT and CBSST relative to control groups. This is not a dismantling study, and at this stage we believe it is less important to determine whether one of the components of CBSST-CCT is more effective. The bundling of CBT, SST, and CCT components that target the multiple deficits linked to negative symptoms and poor functioning in schizophrenia (e.g., defeatist attitudes; social competence; problem solving; cognitive impairments) is potentially more effective. We will be able to compare the effects of CBSST-CCT to historical effects of CBSST and CCT alone, which have been studied in >250 people with schizophrenia. We elected to have **two masters-level therapists deliver both interventions at each location**, which will equate treatment conditions and locations for nonspecific therapist characteristics, a common procedure in psychosocial clinical trials. With this procedure, it will be important to actively monitor the nature of clinician interactions with consumers to ensure CBSST-CCT interventions are not delivered in SC. We are confident that we can prevent treatment contamination because CBSST-CCT will be manual-driven and rated for fidelity, and we will record sessions in both conditions to carefully monitor and address any contamination that might arise. We have experience with this approach to monitoring fidelity to different interventions from our prior CBSST and CCT trials. Finally, we chose masters-level therapists, because few doctoral-level therapists are available in community mental health systems.

3.5.1. Experimental condition: CBSST-CCT. Our combined intervention will be a seamless integration of CBSST and CCT, each described here. **Please see Appendix 1 and 2 for copies of the CBSST and CCT manuals.**

Figure 4. Empirically-driven model of functional outcome.



CBSST (Granholm et al., 2002; 2005; McQuaid et al., 2000) integrates CBT and SST to target the different factors contributing to negative symptoms and poor functioning in our model of functional outcome (Figure 4). The CBSST manual includes a patient workbook describing the skills and homework assignments. The CBT components are based on established CBT techniques (Beck et al., 1979; Beck, 1995) and techniques developed specifically for patients with schizophrenia (Kingdon & Turkington, 1994; Beck & Rector, 2000). The SST components are based partly on an SST intervention available from Psychiatric Rehabilitation Consultants (Liberman, 1991) and Bellack, Muser et al. (2004). Cognitive therapy is combined with role-play practice of communication skills and problem-solving training. CBSST, therefore, targets the multidimensional deficits that contribute to negative symptoms and disability in patients with schizophrenia. CBSST is a group therapy intervention delivered in three, 6-session modules (see Table 1) for a total of 18 group therapy sessions, but participants cycle through the sequence of three modules twice, for a total of 36 sessions *(we have successfully delivered CBSST both weekly for 9 months and twice-weekly for 4.5 months).* Repeating the modules in this way provides skills practice consistent with behavioral learning principles to compensate for cognitive impairment. This is not simply rote repetition, as skills are applied to different thoughts, problems, and social situations in patients' lives during repetition of the modules, and repetition promotes mastery and self-efficacy. Each group therapy session is two hours, with a lunch or snack break mid-way. **CBSST will be modified to strengthen its impact on negative symptoms for the proposed project in several ways:** (1) Most importantly, all modules will focus more extensively on challenging defeatist performance beliefs hypothesized to be associated with negative symptoms (see Table 1); (2) Therapy will be provided on-site and motivational interviewing techniques (e.g., four squares discussion of what is good and not so good about coming to group or working on goals) are added to the initial session of each module to promote treatment engagement; (3) Affect expression and recognition is targeted more extensively in behavioral role plays in the social skills training module; (4) Behavioral activation activities (e.g., scheduling pleasant activities; behavioral day scheduling) are added to the problem solving module.

CCT (Twamley, 2008, 2011, 2012) is a 12-week, manualized, low-tech, group-based compensatory cognitive training intervention designed to target 4 cognitive domains: (1) prospective memory, (2) attention and vigilance, (3) learning and memory, and (4) executive functioning. These domains were selected based on their degree of impairment in schizophrenia-spectrum disorders, relevance for psychosocial functioning, and potential modifiability (Green et al., 2000; McGurk & Meltzer, 2000; Spaulding et al., 1999). Our goal was to take advantage of intact abilities in schizophrenia, such as habit learning (Clare et al., 1993; Keri et al., 2005) and imagery (Thakkar & Park, 2012) to bolster impaired functions. Because habit learning is also highly resistant to forgetting (Bayley et al., 2005), we aimed to help participants form new habits in attention, learning, and problem-solving to automate tasks and reduce the active cognitive effort usually demanded for effective performance. CCT does not use computers, and strategies taught do not "train to the test" or use any of the outcome measures during training. Selected strategies taught in each domain are presented in Table 2. The CCT treatment manual has been distributed to over 250 clinicians and has been used with first episode schizophrenia participants, clients in supported employment and supported education settings, and has been adapted for other disease populations (brain injury, mild cognitive impairment, multiple sclerosis, Parkinson's disease, compulsive hoarding, and substance use disorders). CCT improves negative symptoms and can also enhance CBSST by enhancing attention to CBSST content, learning of content, and memory for content.

Table 1. CBSST Module Goals and Corresponding Manual Content

CBSST Thought Challenging Module Goals	Session/Homework Content
Address symptoms and challenge defeatist beliefs that interfere with real-world skills execution	Thought challenging skills to challenge defeatist performance beliefs, including expectancies ("It won't be fun"), self-efficacy beliefs ("I always fail"), and atypical beliefs ("Spirits will harm me")

	Planning to engage in effortful goal-directed behaviors and use the skills they have
Introduce the general concepts of CBT, including the relationship between thoughts, actions and feelings, automatic thoughts, thought challenging by examining evidence for beliefs, and mistakes in thinking	Discussion, thought records, and homework involving identifying (a) thoughts, (b) relationships between thoughts, feelings and behaviors, and (c) mistakes in thinking (e.g., jumping to conclusions; mind reading; all-or-none thinking)
	Behavioral experiments to gather evidence to evaluate beliefs
	CBT techniques to help patients examine the logic of beliefs and generate more adaptive alternatives to mistakes in thinking
Help participants learn and remember to use their CBT skills	Mnemonic aids are provided (e.g., wallet cards describing skills). Example: to foster thought challenging, we use the acronym, "**3C's**: **C**atch it, **C**heck it, **C**hange it," where "it" is a maladaptive thought
CBSST Social Skills Training Module Goals	**Session/Homework Content**
Improve communication skills and psychosocial interactions (e.g., asking someone for support) via behavioral role plays	Role plays focused on interacting with roommates, friends and family, making new friends, and effectively interacting with case managers, other service providers, and support persons
Improve expression of positive and negative feelings, making requests, comfortable sharing of feelings, and communicating assertively	Role plays emphasize non-verbal affect expression and recognition of affect in others (e.g., group members are asked to change facial expressions and label and comment on affect expression in others performing role plays)
	Improving everyday activities and psychosocial functioning are common role play topics (e.g., asking a roommate to change their behavior; asking someone to go to the movies; assertive interactions)
Improve self-efficacy and defeatist performance beliefs	Self-efficacy and performance beliefs are elicited before and after role plays (0-10 ratings of how successful you think you will be/were) to challenge defeatist beliefs about communication abilities
CBSST Solving Problems Module Goals	**Session/Homework Content**
Improve basic problem-solving skills	Skills are taught using the acronym, SCALE – **S**pecify the problem, **C**onsider all possible solutions, **A**ssess the best solution, **L**ay out a plan, and **E**xecute and **E**valuate the outcome
Help participants develop plans to solve real-world problems and improve illness self-management	Use skills to address living situations, finances, use of public transportation, finding a job, enrolling in school, coping with symptoms and stress, remembering to take medications, and hygiene/health
Improve negative symptoms	Planning and scheduling pleasant activities; behavioral activation techniques
Develop confidence in effective problem-solving	Challenge defeatist beliefs by eliciting ratings of expected success or failure before executing a plan and review evidence about success after executing a plan

Table 2. Cognitive Domains Targeted in CCT and Corresponding Manual Content

Cognitive Domain	**Strategies taught and practiced to improve cognition and functioning**
Prospective Memory	Calendar use; to-do lists; prioritizing tasks; linking tasks by using planned cues; automatic places; using routines to automate tasks
Attention/Vigilance	Eye contact, paraphrasing, asking questions during conversations; self-talk during tasks; taking breaks to refocus
Learning/Memory	Taking notes; association; chunking; categorization; acronyms; visual imagery; overlearning
Executive Functioning	Six step problem solving method; self-talk and self-monitoring while solving problems; hypothesis testing using pro and con evidence; set shifting; set maintenance

Defeatist Beliefs and Rationale for the Combined Treatment Approach. It is well-known that neurocognitive deficits are associated with poor functional outcome in schizophrenia (Green, 1996; Green et al., 2004; Milev et al., 2005; Kurtz et al., 2005), but this relationship is at least partially mediated by several factors, including negative symptoms. Neurocognitive abilities and learning opportunities determine functional skill capacity on performance-based measures, but several personal factors determine whether skills are actually performed (e.g., attitudes/expectations, motivation, anhedonia, moods, insight; Bowie et al., 2006; Grant & Beck, 2009; Horan et al., 2010; Wiersma et al., 2000; Robinson et al., 2004; Twamley et al., 2002). In particular, the premise that **expectations and performance beliefs** can influence symptoms and functional outcome is a key component of the cognitive model that guides CBT interventions for schizophrenia. Several researchers (Avery et al., 2009; Grant & Beck; 2009; Horan et al., 2010; Rector et al., 2005) have found that defeatist beliefs (e.g., "Why bother, I always fail," "It's not worth the effort") and effort contribute to negative symptoms and poor functioning in schizophrenia. Rector et al. (2005) proposed that dysfunctional attitudes about the personal costs of applying energy can lead to passivity and avoidance of activities that require effort, as a defense against anticipated failure and negative evaluations by others. This avoidance and lack of effort manifests as diminished motivation (avolition-apathy), loss of pleasure (anhedonia-asociality), impoverished speech (alogia), and blunted affect. Defeatist beliefs and low expectations for success are associated with neurocognitive impairment (Grant & Beck, 2009), possibly because neurocognitive impairment can lead to discouraging failure experiences that lead to low success expectancies. Pathophysiological processes associated with cognitive impairment in schizophrenia can also lead to impaired striatum-mediated reward

prediction, which may reduce drive-motivated behavior by disrupting the process of generating accurate expectations of success (Barch & Dowd, 2010). In social learning and self-efficacy theories of motivation in healthy individuals (Bandura, 1986; 1997), self-competency beliefs are central to motivation to engage in goal-directed activities and willingness to expend effort when tasks become more difficult. People who expect to succeed are more willing to try new tasks, choose harder tasks, and expend more effort (Wingfield & Eccles, 2000; Bandura, 1997). Social learning theory and the CBT model applied to schizophrenia, therefore, suggest that defeatist beliefs may lead to disengagement from effortful social and community functioning activities as a defense against anticipated failure and negative evaluations by others, which manifests as negative symptoms and poor functioning. Table 3 shows how CBSST and CCT will be integrated in order to increase the focus on reduction of defeatist beliefs and negative symptoms, as well as increase attention, learning, memory, and executive functioning to reduce negative symptom severity and maximize benefit from CBSST.

Table 3. Proposed Integration of CBSST and CCT by Content Area

CBSST Thought Challenging Module	**Planned Integration of CCT Content**	
Address symptoms and challenge defeatist beliefs that interfere with real-world skills execution	All throughout: Use attention, learning, and memory strategies to aid in learning and retaining CBSST content	Use experiential exercises to prove to participants that when they try harder, they do better
Introduce the general concepts of CBT, including the relationship between thoughts, actions and feelings, automatic thoughts, thought challenging by examining evidence for beliefs, and mistakes in thinking		Introduce the types of cognitive problems that are common in mental illness
Help participants learn and remember to use their CBT skills		Teach and reinforce prospective memory skills to improve attendance, homework completion, and remembering to use skills
CBSST Social Skills Training Module		
Improve communication skills and psychosocial interactions (e.g., asking someone for support) via behavioral role plays		Teach and reinforce conversational attention skills (e.g., listening actively, eliminating distractions, asking questions, and paraphrasing [LEAP]) to improve cognitive aspects of communication and social communication
Improve expression of positive and negative feelings, making requests, comfortable sharing of feelings, and communicating assertively		
Improve self-efficacy and defeatist performance beliefs		
CBSST Solving Problems Module		
Improve basic problem-solving skills		Teach cognitive flexibility and planning strategies in addition to problem-solving (CBSST and CCT use a very similar problem-solving strategy already)
Help participants develop plans to solve real-world problems and improve illness self-management		Reinforce cognitive flexibility strategies to help participants realize when they should try a different strategy to achieve their goals
Behavioral activation to improve negative symptoms		Use planning skills to plan and execute pleasurable activities and social activities
Develop confidence in effective problem-solving		Use repetition and practice of executive skills to increase confidence

3.5.2. Control Condition: Goal-focused Supportive Contact (SC). We propose to use a robust control condition, SC, a group therapy intervention that provides the same frequency and amount of therapist and other group member contact as CBSST-CCT. Thirty-six *twice-weekly* SC sessions (*4.5* months) will be delivered, and each group therapy session is two hours, with a lunch or snack break mid-way. The SC intervention will have a primary focus on setting and achieving recovery goals (e.g., living, learning, working and socializing). As in the CBSST section above, focusing on personalized recovery goals is included to enhance motivation for treatment and reduce drop-out in this population with high negative symptoms. Sessions will be semi-structured and consist of check-in about symptoms and potential crisis management, followed by a flexible discussion about setting and working toward recovery goals. Sessions will typically include components of psychoeducation, empathy, and non-directive reinforcement of health, coping, and symptom management behaviors, that grow out of group discussions, with only minimal therapist guidance. Participants will be asked to think about how the discussions had bearing on their individual goals, and will be encouraged to ask for the advice of other participants in achieving specific goals, but no specific training will be provided in cognitive-behavioral coping strategies, social skills, problem solving, or cognitive strategies.

3.5.3 Treatment Fidelity. Recordings of CBSST-CCT sessions will be rated using items from the Cognitive Therapy Rating Scale for Psychosis (CTS-Psy; Haddock et al., 2001), the SST Fidelity scale (Bellack, Mueser et al., 2004), and the Cognitive Training Fidelity Scale (Twamley, unpublished). A random 20% of CBSST-CCT sessions will be rated by Dr. Dimitri Perivoliotis, who has delivered CBSST and CCT and will not be involved in participant assessments. Monthly fidelity ratings will be fed back to therapists during supervision to improve fidelity. SC sessions will also be rated to ensure that SC groups do not receive training in CBSST or CCT skills.

3.6. Measures. Assessments (see Table 4) will be administered at baseline, midway through treatment (*2.25* months), post-treatment, and *6*-month follow-up. Assessors will be blind to treatment condition. We have systematic procedures in place to counsel patients not to reveal their treatment assignment, which has maintained the blind in prior trials (Granholm et al., 2005). Assessors will receive extensive training using videotaped and practice interviews and will not complete assessments until achieving at least .80 inter-rater reliability. We will also check for rater drift every 90 days. We achieved high inter-rater reliability in other studies (e.g., ICC=.88 for PANSS total; .87 for positive symptoms; .83 for SANS total; .86 for MASC).

Table 4. Assessments and Timeline

Domain	Measure	Baseline	Midway	Post	*6*-mo f/u
Diagnostic assessment					
Diagnosis	SCID or MINI	X			
Deficit Syndrome	Schedule for the Deficit Syndrome	X			
Reading level	Wide Range Achievement Test-4 Reading	X			
Symptoms (primary outcome is negative symptoms)					
Negative symptoms	Clinical Assessment Interview for Negative Sx	X	X	X	X
Positive symptoms	PANSS positive subscale	X	X	X	X
Depressive symptoms	Calgary Depression Scale for Schizophrenia (CDSS)	X	X	X	X
Functioning					
Perf.-based functional capacity	UCSD Performance-Based Skills Assessment – Brief	X	X	X	X
Perf.-based social competence	Maryland Assessment of Social Competence	X	X	X	X
Rehabilitation goals/milestones	Psychosocial Rehabilitation (PSR) Toolkit	X	X	X	X
Self-reported living skills	Specific Levels of Functioning Scale (SLOF)	X	X	X	X
Neurocognition	MATRICS Consensus Cognitive Battery	X	X	X	X
CBSST-CCT Content Knowledge	Comprehensive Modules Test (CMT)	X	X	X	X
Defeatist Attitudes	Defeatist Performance Attitudes Scale (DPAS)	X	X	X	X
Effort Allocation – Pupillometry					
Pupil response, digit span recall	6^{th}-digit dilation amplitude	X	X	X	X
Pupil response to SOA task	10-letter array dilation amplitude	X	X	X	X

Diagnostic assessment (at baseline only) will ensure diagnosis and further characterize the participants. The Structured Clinical Interview for DSM-IV (SCID; First et al., 1997) or the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) will be used to establish diagnoses of schizophrenia or schizoaffective disorder. To reduce participant burden, participants who have undergone a SCID or MINI interview by a trained, reliable interviewer as part of other research participation within the past year will not have to repeat the interview. The Schedule for the Deficit Syndrome (SDS; Kirkpatrick et al., 1989) will characterize the participants as meeting/not meeting deficit syndrome criteria for potential moderator analyses. The Wide Range Achievement Test-4 (Wilkinson & Robertson, 2006) Reading subtest will ensure that participants have a reading level (6^{th} grade or higher) sufficient for reading the treatment manual, per the inclusion criteria.

Negative symptom severity will be measured with the Clinical Assessment Interview for Negative Symptoms (CAINS; Horan, Kring et al., 2011; Kring et al., 2013), a new, state-of-the-art instrument developed by an NIMH-funded consensus committee, addressing problems with previous measures (e.g., PANSS, SANS). We selected the CAINS because it was developed to better capture experiential deficits (e.g., motivation, interest, desire for social affiliation, anhedonia), which were the negative symptoms that changed most in our prior clinical trials, and experiential negative symptoms are most linked to defeatist attitudes (Grant & Beck, 2009; Green et al., 2012; Horan et al., 2010). The CAINS also relies less on behavioral or performance deficits to rate negative symptom severity, which minimizes overlap with functioning measures. The 13 CAINS items (9 interview items and 4 objectively rated items) are rated 0 (no impairment) to 4 (severe deficit) measuring Expression of emotions and speech and Motivation/Pleasure across social, vocational and recreational life domains. It has demonstrated good inter-rater reliability (ICCs=.77-.93), test-retest stability (r=.69), and convergent validity (with both negative symptom measures and real-world functioning), and discriminant validity. It is not confounded with depression, cognition, or medication side effects. The mean score in the standardization sample was 19, so we will use 19 as a cutoff score for study inclusion. **Positive symptom severity** will be measured with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) positive subscale, a gold-standard measure in the field. **Depressive symptom severity** will be assessed with the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1990), which was especially designed to capture depressive symptoms in schizophrenia without confounding cognitive, negative, and extrapyramidal symptoms. The CDSS is a 9-item scale derived from the Hamilton Depression Rating Scale and the Present

State Examination with demonstrated reliability (ICC=.89) and validity (Addington et al, 1992, 1994). A cut score of >9 best predicts a diagnosis of major depression in people with schizophrenia (Kim et al., 2006).

Functioning will be measured with a combination of performance based measures, self-report measures, and objectively rated measures. Performance-based **functional capacity** will be assessed with the UCSD Performance-Based Skills Assessment – Brief (UPSA-B; Mausbach et al., 2007), comprised of Finance and Communication subscales, which has been shown to predict independent living status. For the communication subtest, participants take part in role plays using a telephone (e.g., to make an emergency call; calling to reschedule a doctor's appointment). For the finances subtest, participants count change, read a utility bill, and write a check to pay the bill. **Social competence** will be measured with the Maryland Assessment of Social Competence (MASC; Bellack et al., 1994), a role-play based measure of social skill and ability to resolve interpersonal problems through conversation. The MASC takes about 15-20 minutes to administer and consists of three 3-minute role-play communication scenarios (1 conversation initiation and 2 assertion), during which the participant interacts with a live confederate who plays a role (e.g., boss) in a problem-oriented situation (e.g., asking for a work shift change). The measure has three parallel sets of scenarios for multiple administrations. Videotaped role-plays are coded by blinded raters on dimensions of verbal content, nonverbal communication behavior, and an overall effectiveness score, which will be the primary MASC variable. **Functional status** (milestones) will be measured using the Psychosocial Rehabilitation (PSR) Toolkit (Arns et al., 2001), which assesses status and progress toward rehabilitation goals in the domains of work, education, finance, and residence. Objective information is collected on employment, educational activity, residential situation, and financial status. The measure requires no subject testing burden, because research staff complete the PSR Toolkit (with participant release of information). Participant status in each domain is rated on a progressive scale, ranging from the absence of meaningful functioning in the domain to fully independent functioning (e.g., Employment: 1=no employment, 2=non-paid work, 3=sheltered workshops…11=independent competitive employment). Finally, we will administer the Specific Levels of Functioning Scale (SLOF; Schneider and Struening, 1983), which was found to be the best rating scale in the recent NIMH-funded Validation of Everyday Real-World Outcomes (VALERO) study (Harvey et al., 2011).

Neurocognition will be assessed with the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008), an NIMH-funded consensus battery designed for multiple repeat testing of neurocognitive abilities relevant in schizophrenia. The MCCB was designed for use as an outcome measure in clinical trials and was developed through systematic selection and psychometric evaluation of the tests involved (Nuechterlein et al., 2008; Kern et al., 2008; Green et al., 2008). It measures speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. The specific tests in the battery include: Category Fluency, BACS Symbol Coding, Trail Making Test (Part A), Continuous Performance Test (Identical Pairs Version), University of Maryland Letter-Number Span, Wechsler Memory Scale-III Spatial Span, Hopkins Verbal Learning Test-Revised, Brief Visual Memory Test-Revised, NAB Mazes, and MSCEIT: Managing Emotions. In line with the suggestions of the MATRICS Neurocognition Committee and the MATRICS-NIMH advice to the FDA, we will use the composite score for the entire battery.

CBSST-CCT Content Knowledge will be measured with the Comprehensive Modules Test (CMT). The CMT was originally developed at UCLA for use with SST modules (Liberman, 1991) and was modified to assess skills trained in CBSST. Interviewers ask questions about content trained (e.g., "What are the 3C's?"), as well as the application of skills in vignettes. Questions with vignettes were developed to assess mastery of thought challenging, communication, and problem-solving skills. The CMT total score will be used.

Defeatist Performance Attitudes will be measured with the Defeatist Performance Attitudes Scale (DPAS), a 15-item self-report subscale derived from factor analysis of the commonly-used 40-item Dysfunctional Attitude scale (DAS; Cane et al., 1986; Weissman, 1978). The DPAS indexes defeatist beliefs about one's ability to perform goal-directed tasks (e.g., "If you cannot do something well, there is little point in doing it at all", "If I fail at my work, then I am a failure as a person," "People will probably think less of me if I make mistakes and fail") on a Likert scale. We have extensive experience with the DPAS: we (Quinlan, Granholm & Roesch, 2009), like others (Green et al., 2012; Horan et al., 2010) replicated the findings by Grant and Beck (2009) that defeatist performance beliefs mediate the relationship between neurocognitive impairment and negative symptoms in schizophrenia (see Figure 4), including both Diminished Expression (Affective Flattening+Alogia) and Diminished Motivation (Avolition+Asociality) factors.

Task Effort (Pupillometry). In the proposed project, pupil size will be recorded during performance of two cognitive tasks, a digit span recall task and a span of apprehension (SOA) task, because we have linked diminished pupillary responses (effort) on these tasks to more severe negative symptoms and defeatist

attitudes (Gallegos et al., 2009, Granholm et al., 2007a). On the **digit span recall task,** pupil responses will be recorded for up to 15 seconds on trials with fixed, randomly-determined spans of 3 (low load), 6 (moderate load), and 9 (high load) digits presented (four trials per span length) aurally at the rate of one digit per 1.5 seconds, while the subject views a gray dot on a white background. Pupillary response (average diameter for one second) at the last digit in the 6 digit condition showed the strongest relationships with both defeatist attitudes and negative symptoms in our prior study, so we will use this amplitude (change relative to baseline). On the **partial-report SOA task,** subjects will be told that either a "T" or an "F" will be presented on the computer screen in a group of other letters (70 msec exposure) and they must push one of two response buttons corresponding to the correct target. The target stimulus will be embedded in arrays containing either 2 (3-letter condition) or 9 (10-letter condition) distractor letterspace. 40 trials of each array-size condition will be presented in counterbalanced blocks. Peak dilation (change relative to baseline) in the 10-letter array condition, which was related to negative symptoms in our prior research, will be used as the primary dependent measure. Phasic change pupil responses are not affected by medications (Granholm et al., 1997, 2004, Ahern & Beatty, 1979). Dr. Granholm has published extensively on pupillary response (Granholm et al., 1997; 2004; 2007; 2009; Granholm & Steinhauer, 2004; Fish & Granholm, 2008), which has been used for over 80 years as an objective, reliable, and sensitive psychophysiological index of effortful processing resource allocation to tasks.

Blood collection and storage. Blood samples (10 mls) will be drawn and stored for future gene expression analysis to identify predictive markers of CBSST-CCT outcome. Collected blood will be prepared for RNA extraction by sequestering and preserving the peripheral blood mononuclear cells by passing the sample through a Leukolock™ filter (Ambion, Inc.) and then saturating the filter with RNA*later* (Ambion, Inc.). Saturated filters can be stored for extended periods of time for later analysis. Quality-assured total RNA samples will be stored at -80C for later microarray analysis in collaboration with our colleagues, Drs. Ming Tsuang, William Kremen, and Stephen Glatt. Drs. Tsuang and Kremen will donate blood drawing supplies, personnel, and freezer space for this project (see letter of support from Drs. Tsuang and Kremen).

3.7. General Statistical Approach. Data acquired in this project will be managed by a junior statistician, Peter Link, and analyzed with assistance from Dr. Shah Golshan. Primary analyses will be based on a linear mixed-effects model for continuous data (Hedeker et al., 1991; 1997; Laird, 1982) and will be performed using HLM 6.06. HLM is an intent-to-treat method that uses all available data, obviating the need for imputation of missing data. Our randomization procedure is expected to control patient and treatment variables that might be associated with outcome, but if there are any baseline differences between groups, we will control for them statistically. All hypothesis tests will be two-sided with alpha set at .05. We will control Type I error by reducing measures to one key variable or a total or composite score when possible and will use Bonferroni correction for secondary outcomes in a domain family and secondary analyses.

Hypothesis 1 (feasibility): 64 subjects at 4 community locations will be enrolled and retained (>80%) in a pilot RCT. (Inferential statistics not needed to determine whether enrollment and retention goals are met.)

Hypothesis 2 (efficacy): Compared to participants in SC, those in CBSST-CCT will show significantly greater reduction in negative symptom severity (primary outcome) and greater improvements in cognition and functioning (secondary outcomes) from baseline to post-treatment. Effect sizes for these outcomes will be greater than historical effect sizes (.42-.47) based on our previous studies of similar participants.

Hypothesis 2 will be tested with HLM. Baseline to follow-up effect sizes will also be computed The primary mixed-model analysis will include a random intercept, a random effect for assessment time (baseline, midway, post-treatment, *6*-month follow-up), with treatment group (CBSST-CCT vs. SC), and all interactions as predictors of the primary outcome measure, CAINS total. Model diagnostics will be used to determine the suitability of an autoregressive error component and nonlinear effects for assessment time. Using Bonferroni-correction within an outcome domain, secondary analyses will use the same mixed-model to examine the secondary outcome variables in the functioning domain and the other secondary outcome variables in Table 4, with the exception of the PSR ToolKit Global Indicator, which is not a continuous variable. A Chi square test will be used to determine if the treatment groups differ significantly in the proportion of participants who achieve improvements in objective indicators of real-life functioning goals on the PSR ToolKit indicator. Power analysis: The purpose of our pilot RCT is to examine feasibility and generate effect sizes to establish benchmarks for future studies, not to complete an adequately powered efficacy study. With a sample size of 64, we will have .50 power to detect an effect size of .5 and .80 power to detect an effect size of 1.0 and for negative symptoms (Spybrook et al., Optimal Design, 2011).