Study Protocol

Evaluating Two Types of Cognitive Training in Veterans with Schizophrenia

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Background and Significance

One of the most exciting developments in the treatment of schizophrenia in the past decade has been the rise of cognitive remediation (CR). CR is a "behavioral training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition, or metacognition) with the goal of durability and generalization" [1]. This collection of interventions aims to restore cognitive functioning by targeting different levels of cognition from basic perceptual processes (e.g., auditory or visual processing) to the more molar and complex cognitive skills (e.g., memory, problem solving). CR has been used in disorders other than schizophrenia, such as stroke, TBI, PTSD, and ADHD. Yet, its popularity in schizophrenia has grown because cognitive impairments are a core feature of the illness and remain unsuccessfully treated with the available antipsychotic medications. Schizophrenia is a disorder that affects both higher-level neurocognitive operations and lower-level perceptual processes. These deficits contribute to the poor community outcome and high levels of functional disability seen in patients [2]. Therefore, treatment of the cognitive dysfunction associated with this illness is important to achieve improvements in daily functioning. Numerous evidence-based approaches to CR have been developed to treat the cognitive deficits in schizophrenia. In general, improvements in cognition have been found with both cognition-enhancing approaches that attempt to restore neuronal and neurocognitive functioning, as well as compensatory approaches that seek to circumvent cognitive impairments to improve broader aspects of function [3]. Recent meta-analytic studies on cognitive training in schizophrenia [4, 5] report that cognitive training has a moderate effect-size impact on cognitive functioning (0.45) and a lower impact on daily functioning (0.36) and clinical symptomatology (0.28). Based on these studies, 2104 inpatients and outpatients with schizophrenia (with a mean age of 36 years old and a high school education) have participated in randomized controlled trials (RCTs) of cognitive interventions. They were typically exposed to 17 weeks of treatment, receiving about 32 hours at a dosage of 2 to 3 times a week. The interventions in these RCTs consisted of drill-and-practice training, as well as strategy-based learning.

CR has been shown to produce changes in the brain. In a recent study, patients who received CR demonstrated a reduced loss in the hippocampus, and in some cases, an increase in gray matter volume in the amygdala [6]. CR is considered to be a learning activity and as such, it relies on neuroplasticity and occurs when neurons adjust their activity and organization in response to new situations or to changes in the environment. CR is designed to leverage the brain's plasticity to create additional processing capacity by exposing subjects to cognitive exercises that challenge their attention and memory. According to principles of systems neuroscience, the brain adapts to training by representing the relevant sensory stimuli and action outputs with disproportionately larger and more coordinated populations of neurons [7]. This principle implies that all brains are capable of adaptive plastic change, even if there is underlying neuropathology.

At this point, it is unclear whether training lower-level perceptual processes (bringing in sensory data into the brain) or higher-order cognition (strategies, problem-solving, ability to make more complex inferences about the world) will most benefit patients with schizophrenia. Most training interventions for schizophrenia have only targeted higher-order cognitive processes [8]. However, patients with schizophrenia also have deficits in basic visual processing, such as visual motion perception [9] and backward masking [10], as well as deficits in preattentive auditory processing, such as automatic sensory discrimination [11] and gating [12]. The abnormal signal detection at these early stages of processing combined with the impaired coordination of neuronal responses throughout the cortex [13] are thought to lead to abnormal higher-level cognition in schizophrenia.

A few recent interventions in schizophrenia have targeted basic perceptual processing and these studies have shown that auditory [14] and visual [15] perceptual abilities can be trained and improved in patients with schizophrenia, suggesting that perceptual plasticity is intact in schizophrenia.

Improvements associated with lower-level perceptual training programs can extend beyond perceptual measures to include improvements in neural responses and higher-order cognition. For instance, visual perception training led to changes in electroencephalographic (EEG) indices of early visual processing (N100), and these changes were correlated with working memory improvements in a non-clinical sample of older adults [16]. Moreover, intensive auditory training in patients with schizophrenia improved verbal memory and auditory neural responses (M100) assessed with magnetoencephalography (MEG) [17, 18]. These training-induced gains were associated with improvements in community functioning 6 months later [19]. This series of studies was conducted by Dr. Vinogradov's research team and suggests that a bottom-up auditory training results in improved cognitive performance and restoration of neural correlates of both elemental and complex operations. These studies compared the experimental approach to a control condition consisting of commercial computer games. A vital question that remains is whether a neuroplasticity-based, bottom-up intervention is more effective than an intervention that targets top-down functions like attention, working memory, and executive functioning. Only one study [20] made this direct comparison and found that a bottom-up treatment targeting basic auditory processing normalized sensory gating (measured with MEG by the M50), and improved cognitive performance more than a top-down treatment targeting a broad range of higher-order cognitive functions. Unfortunately, this study had a relatively small sample of 39 patients total between both groups.

One index of neural functioning that is of particular interest for understanding outcome in schizophrenia is mismatch negativity (MMN). MMN is an event-related potential (ERP) that is elicited in response to infrequent, physically deviant tones interspersed in the repeated presentation of a standard tone [21]. MMN is thought to index automatic, preattentive information processing, as it can be elicited without directing attention to stimuli [22]. MMN has shown stable, large deficits in schizophrenia [23] that have downstream effects on more complex cognitive operations, such as verbal learning [24], social cognition [25] and social functioning [26]. MMN is often followed by P3a, another ERP component that is assumed to reflect the covert shift in attention [27]. Similar to MMN, reductions in P3a amplitude have been documented in schizophrenia [28]. MMN has never been studied within a non-pharmacological RCT. It has been studied in pharmacotherapy trials with mixed results. Some reports found that MMN is partially normalized by second-generation antipsychotic medications [29], and others did not [30]. Given the robust MMN abnormality in schizophrenia and its relationship to higher-order cognition and real-world functioning, it will be useful to ascertain whether MMN is an appropriate treatment target and can be influenced by CR.

The proposed study aims to contrast a bottom-up intervention targeting auditory processes and a top-down intervention targeting higher-order cognitive functions, compared with a control condition, in Veteran and non-Veteran patients with schizophrenia. These interventions will be assessed by their effects on representative measures from three outcome domains: neurocognition, EEG (MMN), and functional capacity. We will also assess the effects of these interventions on social cognition and community functioning as part of our exploratory analyses. This proposal extends the study by Popov et al. by: 1) including a much larger sample size, 2) adding a control treatment condition to the bottom-up and top-down conditions, 3) investigating a different neural measure of auditory processing that is more closely associated with daily functioning, 4) using a broader and well-normed neurocognitive test battery, and 5) including measures of functional capacity/community functioning to evaluate whether the effects of treatment generalize to a more distal outcome. We will study a neuroplasticity-based training focused on auditory rather than visual systems given that verbal learning/memory tends to be the most impaired cognitive domain in schizophrenia [31] and a strong predictor of work performance and functional outcome. We will utilize EEG techniques, ERPs in particular, because they allow us to examine early perceptual processes with a high level of precision and temporal resolution [32].

This proposal will determine which training approach leads to the largest magnitude of improvement in neurocognition, functional capacity, and neural functioning measured with EEG. Moreover, it will shed light on the underlying mechanism of action associated with the observed improvements in cognition. Based on the neuroscience-guided theoretical framework described above, we expect that the effects of the bottom-up training 1) will result in robust changes in higher-order cognitive operations, 2) will be evident at the earliest stages of auditory processing (normalization of MMN), and 3) will generalize to functional capacity. We also expect that the bottom-up training will lead to superior effects on the primary and secondary outcomes relative to the top-down training. The proposed study will help to decide how best to implement CR interventions to improve the cognitive and social functioning of patients with schizophrenia. Subsequent studies could consider additional research questions, such as whether the benefits of training are maintained over time. Depending on the results of this study, treatment providers at the VAGLAHS will be able to decide which version of CR will lead to more substantial gains. Our prediction is that it will be the neuroplasticity-based intervention. However, this study will provide a clinically meaningful answer, even if our hypothesis is incorrect.

Preliminary Studies

Previous Work on Neurocognition in Schizophrenia

During the first part of my doctoral training, I worked under the supervision of Dr. Kristin Cadenhead at the UCSD Cognitive Assessment and Risk Evaluation (CARE) program. My first publication from this laboratory [33] examined the course of neurocognitive functioning in the prodrome and first episode of schizophrenia. This study demonstrates my skills in neurocognitive assessment and familiarity with the challenges of assessing change in neurocognitive functions across repeated testing in a clinical sample. I learned how to analyze longitudinal data while statistically accounting for problems such as practice effects and regression to the mean. The study included 48 subjects at risk for psychosis (AR), 20 patients in their first episode of schizophrenia (FE), and 29 normal comparison subjects (NC) who were assessed on a neurocognitive battery at baseline and 6-month follow-up. We found that the AR group's overall baseline performance (global neurocognitive index mean score) fell between the NC and FE groups' performance. There were significant group differences across all cognitive domains, significant time effects for executive functioning, processing speed, verbal learning, and general intelligence, as well as a significant group by time interaction for verbal learning. Whereas the NC and AR groups remained stable over time in their verbal learning performance, the FE group demonstrated a significant improvement in verbal learning over the test-retest interval (see Figure 1).

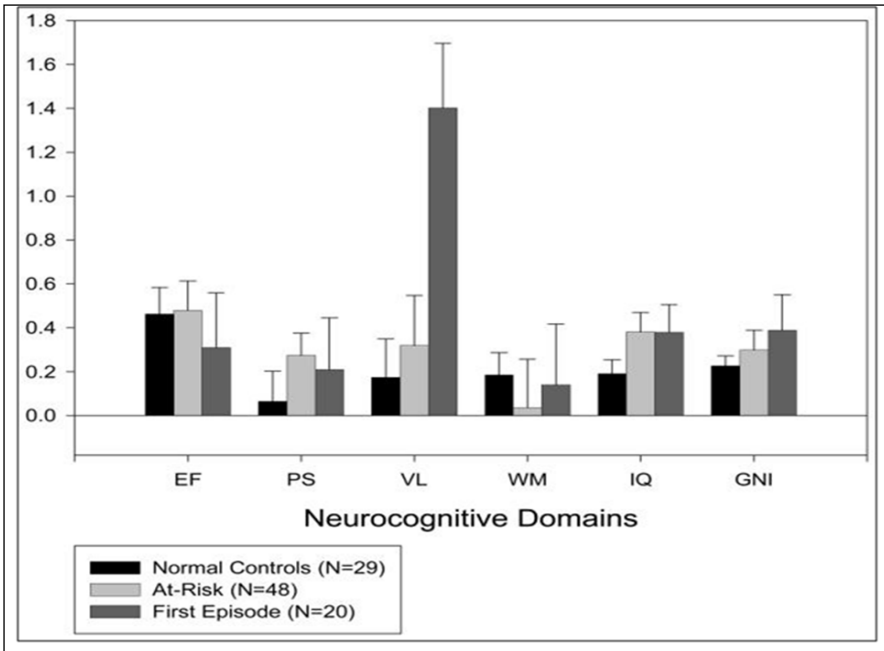

Figure 1. Mean z-score differences (follow-up – baseline) and standard errors for each group. Higher is better. EF = executive functioning; PS = processing speed; VL = verbal learning; WM = working memory; IQ = general intelligence; GNI = global neurocognitive index.

We also examined the pattern of change in neurocognitive performance over time at the individual level. For each subject, we determined whether the observed fluctuations represented meaningful changes or normal variability in performance using a regression-based approach that controls for practice effects and regression to the mean. We found that a high proportion of FE subjects showed an improvement in verbal learning, and a significant number of AR subjects improved in general intelligence. Moreover, a higher than expected percentage of FE subjects, as well as AR subjects who later converted to psychosis, showed deterioration in working memory and processing speed. Our results suggest that cognitive functions do not follow a unidimensional trajectory in schizophrenia, but rather vary by cognitive domain and phase of the illness. Unlike the neurocognitive deficits in chronic schizophrenia, which tend to be fairly stable [34], there may be more changes during the prodromal period and right after the illness sets in.

Previous Work on Electrophysiology in Schizophrenia

After studying the course of cognitive deficits in the early stages of schizophrenia using behavioral-based measures, I developed an interest in the neural mechanisms of these disturbances. During the second part of my doctoral training, I joined the laboratory of Dr. Gregory Light to learn how to apply EEG techniques. For my dissertation [35], I assessed three ERPs of automatic, preattentive information processing in 26 individuals at risk for psychosis, 31 recent-onset and 33 chronic schizophrenia patients, as well as 28 healthy control subjects. The primary aim of the study was to examine mismatch negativity (MMN), P3a, and RON (reorienting negativity) in these three patient samples. As described in the previous section, MMN is an index of automatic change detection. It is largest at central midline scalp sites and typically peaks between 160 to 220 ms after the onset of the deviant stimulus. P3a is a positive going wave that follows MMN and measures the orienting of attention. It is frontally maximal and peaks between 250 and 300 ms post-stimulus. RON is thought to measure the automatic preparation for detecting subsequent stimulus changes. This attentional reorienting is reflected in a negative going wave that follows the P3a, peaks between 400 and 600 ms, and is centered on frontocentral electrodes [36].

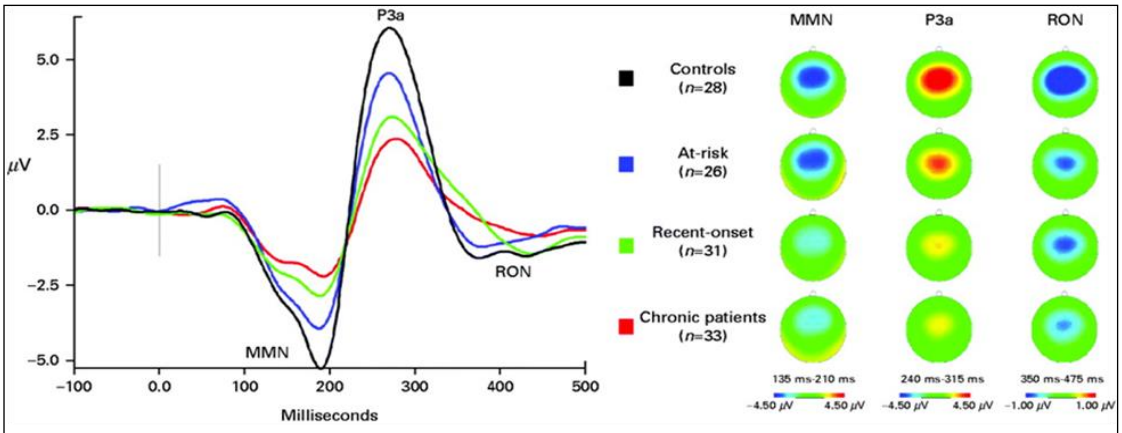

Figure 2. Grand average difference ERPs, at electrode FC1, and their corresponding scalp distributions, formed by subtracting the ERP elicited by standard tones from the ERP elicited by deviant tones, for each group. MMN, mismatch negativity; RON, reorienting negativity.

Our findings showed that robust frontocentral deficits in MMN and P3a were present in all patient groups. The at-risk group's MMN and P3a amplitudes were intermediate to those of the healthy control and recent-onset groups, with the chronic group having the most pronounced reductions (see Figure 2). The recent-onset and chronic patients, but not the at-risk subjects, showed significant RON amplitude reductions, relative to the healthy control subjects. Although this is a cross-sectional study, the findings suggest that MMN and P3a abnormalities precede the onset of psychosis while RON deficits do not emerge until after the full manifestation of the illness. These results support the continued examination of MMN and P3a as potential early biomarkers of schizophrenia and raise the possibility of progressive worsening in early auditory information processing with illness chronicity.

Since starting my postdoctoral training 1.5 years ago, I have continued to use EEG techniques and behavioral measures to study the cognitive and perceptual impairments in schizophrenia. I have been involved in several studies, including one that examined how early preattentive abnormalities in bipolar disorder compare to those found in schizophrenia. Our lab's research efforts have increasingly focused on understanding bipolar disorder because of the pathophysiological features it shares with schizophrenia, including genetic risk factors [37], high rates of functional disability, and notable cognitive impairment. In a recent paper [38], we assessed the MMN and P3a ERP components in 52 bipolar patients, 30 schizophrenia patients, and 27 healthy controls during a duration-deviant oddball paradigm. We found impairments in both MMN and P3a in bipolar disorder (see Figure 3). At the earlier stage of automatic sensory discrimination reflected by MMN, bipolar patients showed deficits that were similar to patients with schizophrenia, but to a lesser degree. This finding suggests that both groups of patients may have problems detecting changes in their auditory environment. At the slightly later stage of orienting to salient auditory stimuli reflected by P3a, bipolar patients showed pronounced deficits, and these impairments were non-significantly larger than those in schizophrenia. This proposal will use the same auditory oddball paradigm, which has been tested in a large number of patients and healthy controls in our lab, to measure MMN and P3a.

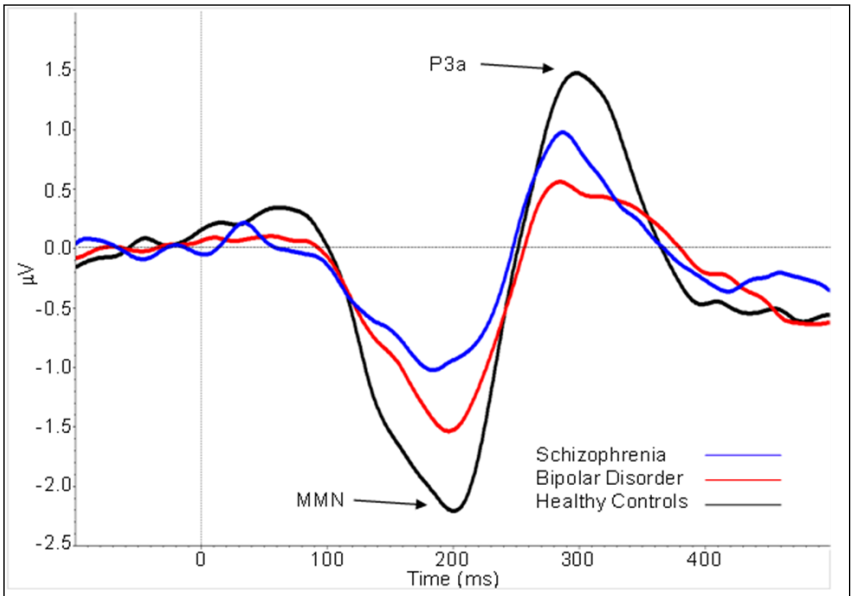

Figure 3. Grand average waveforms with MMN and P3a amplitudes at the midline region (average of electrodes Fpz, AFz, Fz, FCz, Cz).

Previous Work on Cognitive Remediation in Schizophrenia

I currently am lacking skills and experience in cognitive remediation with psychiatric patients, and I have identified this missing skill set as important to develop as part of my CDA training plan. Dr. Green's lab provides a conducive environment to filling that gap in my experience, given its long-standing research program focused on cognitive and social cognitive rehabilitation using both pharmacological and behavioral approaches. Moreover, the availability of local experts (Drs. Green, Kern, and Horan) in addition to the identified co-mentor (Dr. Vinogradov) will help me achieve my training goal.

Dr. Green's lab has had considerable success in applying compensatory and functionally-relevant remediation programs to Veterans and non-Veterans with schizophrenia. Previous studies have shown that the performance of schizophrenia patients on selected neurocognitive tests could be modified under carefully controlled training conditions [39], and that the durability of these training effects can be enhanced by using a compensatory approach, *errorless learning* [40]. Errorless learning is a remediation approach based on findings that learning is stronger and more durable if it occurs in the absence of errors. Errorless learning training methods can be applied to complex behaviors in patients with a psychotic diagnosis, as demonstrated in a study in which Veteran and non-Veteran patients assigned to an errorless learning group showed more improvements in social problem solving ability than those assigned to a symptom management group [41]. Ongoing efforts have examined the effects of errorless learning on vocational rehabilitation. In a recent publication [42], work performance, tenure, and personal well-being were compared with conventional job

training in a community mental health fellowship club that offered a 12-week time-limited work experience. Patients were randomly assigned to errorless learning or conventional instruction at a thrift-type clothing store. Errorless learning showed benefits on work quality compared with conventional instruction, and the group differences were relatively consistent over time. There were no group differences in personal well-being (self-esteem, job satisfaction, work stress) but for job tenure, results revealed a non-significant trend favoring errorless learning.

In addition to experience and publications on a compensatory remediation approach like errorless learning, Dr. Green's laboratory is familiar with direct training approaches relevant to the current proposal. Dr. Green previously served as a consultant for Posit Science (the software company for the training methods in the bottom-up arm of the proposal). His lab has collected data and published on one of their CR programs (the Aristotle package), that is focused on sustained attention, speed of processing, and response inhibition [43]. This training software is less established than the auditory-based Brain Fitness Program. The Horan et al.'s RCT evaluated the efficacy of social cognitive skills training for patients with schizophrenia using the Aristotle program as one of the treatment comparison conditions. We have no published data on Cogpack. Yet, we piloted this training program with schizophrenia patients (n = 11) to demonstrate its feasibility.

We piloted the Cogpack in two stages. Initially, we piloted with 5 patients who each completed a one-hour session that included a range of exercises (at least 4 different ones) and rated how much they liked the program on a Likert scale ranging from 1 (not at all) to 10 (very much). All patients were able to understand the tasks following instructions, and they rated the exercises as highly tolerable (average rating of 8.8). Following the session, all 5 patients commented that they found the tasks to be engaging. This first piloting stage established that the tasks were well tolerated in this patient group.

We then wanted to see if the Cogpack procedures were feasible for multiple sessions with patients. We piloted Cogpack on 6 additional patients who received training twice a week for four weeks. Each one-hour session consisted of different 3-7 exercises targeting higher-order cognitive functions. All patients successfully completed the 8 sessions, except for one patient who was hospitalized after completing 2 sessions. Based on this information, we consider the Cogpack exercises to be feasible for repeated and regular administrations.

To assess the magnitude of improvement in performance over the duration of the 8 training sessions, 3 of the exercises were administered with the same parameters 3 times (in sessions 1, 4, and 8).
These exercises included:

1) "Eyewitness", an attention and memory task that involves recalling short street scenes with random combinations of image, text, sound, and movement elements;
2) "Connect", a cognitive flexibility/ executive functioning task that involves connecting dots while switching between numbers and letters;
3) "Confusion", a problem-solving task that requires search strategies and involves reproducing a diagram using different keys without knowing what each key does.

Figure 4: Cogpack Pilot Results
Mean z-scores for 5 patients for 3 tests that were repeated (sessions 1, 4 & 8)

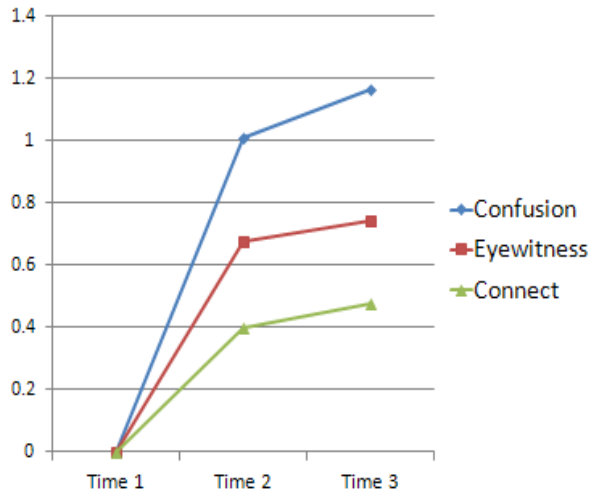

Figure 4 illustrates the mean performance of the 5 patients who completed these same 3 exercises in 3 separate sessions. Raw scores were converted into z-scores and averaged across subjects for each time point. The z-scores were rectified so that higher is always better. As seen in the figure, patients did show improvement across time; there was a medium to large effect-size improvement from Time 1 to Time 2 across all exercises with a slight improvement from Time 2 to Time 3 (see the Power Considerations section as well).

Research Design and Methods

Subject recruitment will be coordinated through Dr. Green's ongoing studies. The availability of recruitment infrastructure, trained clinical interviewers, and cognitive remediation software will greatly facilitate the launch and conduct of the project. All subjects interested in the study will be prescreened for general inclusion and exclusion criteria by the recruiter using HIPAA compliant procedures. During the first visit (approximately 2 hours), participants will be consented and receive standardized clinical interviews to ensure diagnosis and eligibility. Participants will also receive symptom ratings of general psychiatric and negative symptoms, as well as mood symptoms. Subjects who fit selection criteria for the study will be scheduled for another visit, within 1 week of their first visit. During the second visit, (approximately 3.5 hours), subjects will be administered a comprehensive battery of cognitive, electrophysiological, and functional capacity/community functioning measures. Subjects will then be randomly assigned to one of the two cognitive remediation treatments (BFP and Cogpack) or to the control treatment (see randomization and treatment procedure below). Subjects will participate in 3 treatment sessions a week (1 hour each) for 12 weeks. After 18 treatment sessions, subjects will come back for a midpoint assessment visit (1.5 hours) in which they will be administered the electrophysiological measures again and two brief questionnaires. Upon completion of treatment, subjects will be scheduled for a post-treatment visit within 2 weeks of the last treatment session. This visit will last approximately 3.5 hours and will include the same clinical, cognitive, electrophysiological, and functional capacity/community functioning assessments that were administered prior to treatment. A urine toxicology screen will be conducted as part of each assessment visit. In the rare instance when a subject tests positive on the urine toxicology screen, he/she will be rescheduled to come back on a different day to complete the assessments. Overall, the study will consist of 4 visits (11 hours total) and 36 treatment sessions (36 hours total). Subjects will be compensated $15/hour for the interview and testing sessions (first 2 visits, mid- and post-training visits) and $10/hour for the treatment sessions, a rate deemed acceptable by our IRB. Funding is requested for four years of data collection (see Table 1). The IRB application will be prepared prior to the grant being funded.

Randomization and Treatment Procedure

To optimize power for the primary comparison between the active treatments, we will use a 2:2:1 asymmetrical randomization procedure resulting in a total of 48 subjects in the BFP group, 48 in the Cogpack group, and 24 in the control group. Subjects will be given sequential identification numbers and randomly assigned in blocks of 5 or 10 to maintain balance throughout the study. A random mixture of block lengths will be used to help ensure the integrity of the process and the preservation of the blind. The MIRECC Data Core will create an online randomization system for the project, which will be accessible only to the study coordinator who will perform the assignments. Randomization will be programmed in ASP (Active Server Pages).

Table 1: Enrollment for Each Year

	Year 1	Year 2	Year 3	Year 4
Interviews, BFP, Pre- and Post-Treatment Assessments	12	12	12	12
Interviews, Cogpack, Pre- and Post-Treatment Assessments	12	12	12	12
Interviews, Computer Games, Pre- and Post-Treatment Assessments	6	6	6	6

Patients will be scheduled for training during specific 60-min blocks of time (between 10:00 AM and 2:00 PM) every Monday, Wednesday, and Friday. Treatment will be administered individually in a designated room. However, up to 6 patients may be sharing the treatment room at a time. Each patient will work through different exercises (depending on their assigned treatment condition) on a personal computer station. Patients will be told that they are going to receive training exercises that might or might not improve their cognitive functions. The testers will be blind to the patient's treatment group membership. A staff person will be present in the treatment room and will be aware of the type of training that each patient is receiving, but this person will not administer any outcome measures. They will install the appropriate computer session for each patient and give individualized instruction in the use of the equipment and training program. To ensure maximum compliance, the trainer will provide encouragement, observe patients' behavior throughout the session, and monitor data storage after each session.

Recruitment will be ongoing and we expect to enroll 30 subjects/year. Based on dropout rates in our previous training intervention studies, we project 20% attrition, which will leave us with an estimate of 96 completers: 38 getting BFP training, 38 getting Cogpack training, and 19 getting the control intervention. We will make every effort to hold patients in the study protocol while emphasizing that their participation is strictly voluntary and that they can withdraw at any time. To minimize attrition, we will inform subjects that they will be in the study up to 17 weeks and ensure that they will not be leaving town or relocating during the study period. We will contact those who opt to discontinue treatment to request that they participate in a final outcome assessment. Details of the plan for handling missing data and minimizing potential threats to randomization caused by differential dropout rates are further described in the data analysis section.

Subjects

120 patients with schizophrenia and schizoaffective disorder will be included in the study. Our sample will consist of Veterans and non-Veterans who will be recruited from VA outpatient treatment clinics and board-and-care residences in the community through staff presentations and referral. All recruiting efforts will be coordinated through Dr. Green's laboratory. Approximately 8-10 patients with a schizophrenia/ schizoaffective diagnosis are admitted to VA clinics each week. The laboratory has had a successful history of meeting recruitment goals outlined in funded VA and NIMH projects. We will select clinically stable outpatients between the ages of 25 and 65 years old. Patients will be considered clinically stable if they had no medication changes in the past six weeks, no psychiatric hospitalization in the past three months, and no changes in housing in the past two months. Exclusion criteria will include having an estimated premorbid IQ below 70 based on reading ability, not meeting full criteria for schizophrenia or schizoaffective disorder, having an identifiable neurological disorder, seizures, or history of serious head injury, meeting criteria for substance dependence in the past 6 months or abuse in the past month, or being insufficiently fluent in English as determined by the participant's ability to understand the consent form. Most of the patients will be chronic and medicated, though we will not select patients based on chronicity. Duration of illness and medication information will be obtained through self-report and examination of medical records. All psychoactive medications and their dosages will be carefully recorded. Antipsychotic medication dosages will be

converted to chlorpromazine (CPZ) equivalent units [44, 45]. Specific selection criteria as well as projected demographic distribution are listed in the Human Subjects section.

Clinical Evaluation

All patients will receive a diagnostic interview with the Structured Clinical Interview for DSM-IV (SCID-I; [46]) as part of their participation in Dr. Green's lab. The SCID-I will be conducted by interviewers trained to reliability through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC) based on established procedures [47]. Psychiatric symptoms will be evaluated using the expanded 24-item UCLA version of the Brief Psychiatric Rating Scale (BPRS; [48]) and negative symptoms will be assessed with the Scale for the Assessment of Negative Symptoms (SANS; [49]). The Hamilton Depression Rating Scale (Ham-D; [50]) and the Young Mania Rating Scale (YMRS; [51]) will also be administered to assess depression and mania, respectively, in schizoaffective patients. All symptom rating scales will be administered by the PI pre- and post-treatment.

Electrophysiological Recording Procedures

EEG Recording

All EEG recording and processing will be conducted using existing equipment in Dr. Green's lab at the VA. EEG recordings will be acquired with a 64-channel BioSemi ActiveTwo amplifier (Biosemi B. V., Amsterdam, Netherlands). Data will be sampled at 1024 Hz with filter settings of 0 to 100 Hz. Electrode caps using an array of 64 active electrodes will be attached in accordance with the international 10-10 scheme. To monitor blinks and eye movements, four additional electrodes will be placed above and below the left eye (to measure vertical electrooculogram; EOG) and at the outer canthi of both eyes (to measure horizontal EOG). Biosemi utilizes active electrodes that are measured with respect to a common mode sense electrode during data collection, forming a monopolar channel. An additional electrode will be placed at the nose tip and all EEG data will be re-referenced offline to this electrode.

Visual Long-Term Potentiation (LTP) paradigm

The paradigm will involve assessment of visual evoked potentials (VEPs) before and after exposure to tetanizing visual high frequency stimulation (HFS). While maintaining focus on a central fixation cross, subjects will view visual stimuli presented centrally against a white background on a computer monitor located 57 cm in front of them. Each 2-minute VEP assessment block will consist of a pseudorandom oddball sequence of 90% standard (circle) and 10% target (square) stimuli (duration 33 msec) presented at ~.83 Hz (1216 msec mean SOA, range 1075-1340 msec). Subjects will be asked to respond to the target square with a right-handed button press. VEP assessment blocks will be administered 4 minutes (baseline-1) and 2 minutes (baseline-2) before HFS and 2 minutes (post-1), 4 minutes (post-2), and 20 minutes (post-3) after HFS. The 2-minute HFS block designed to induce potentiation will consist of repeated presentation of the standard circle at ~8.87 Hz (113 msec mean SOA, range 99-116 msec), a rapid flicker rate below the perceptual fusion threshold. Subjects will be administered the auditory MMN paradigm (described below) in the interval between the post-2 and post-3 VEP blocks.

Mismatch Negativity (MMN) Paradigm

A passive auditory oddball paradigm will be used to assess basic auditory processing. Subjects will be presented with standard and duration-deviant tones binaurally using foam ear inserts (1 kHz 85 dB sound pressure level, with 10 ms rise/fall) with a fixed stimulus onset asynchrony of 500 ms, using E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA). Standard (90% probability; 50 ms duration) and deviant (10% probability; 100 ms duration) tones will be presented in a fixed, pseudorandom order (with the restriction that at least 4 standard tones are presented between deviant tones). Two-thousand total trials will be administered. During the 25-minute EEG recording,

subjects will be instructed to watch a silent movie to divert attention from the stimuli. The EEG session (including electrode placement and recording) will last approximately 45 minutes.

EEG Processing

Data processing will be performed offline using BrainVision Analyzer 2 software (Brain Products, Gilching, Germany). Based on visual inspection, bad electrodes will be removed from the recording and a spherical spline interpolation will be used to recreate the electrode [52]. Data will be high-pass filtered at 1 Hz to remove slow drifts. Eye movement artifacts will be removed from the data using a regression-based algorithm [53]. Continuous data will then be divided into epochs relative to stimulus onset (-100 to 500 ms) and baseline corrected to the average of the prestimulus interval (-100 ms to 0). Only electrodes at frontocentral sites that are representative of neural activity generated by the MMN paradigm based on our previous studies (AF3, AF4, AF7, AF8, AFz, Cz, F1, F2, F3, F4, F5, F6, F7, F8, FC1, FC2, FC3, FC4, FC5, FC6, FCz, Fp1, Fp2, Fpz, Fz) will be examined. Following eyeblink correction, epochs that contain activity exceeding ± 75 μV at these electrode sites will be automatically rejected. Only data from subjects who have at least 100 acceptable deviant trials (out of 200) will be included in the analyses. MMN waveforms will be generated by subtracting ERP waveforms in response to standard tones from the ERPs generated in response to the deviant tones. The resultant MMN subtraction waveforms will then be low-pass filtered at 20 Hz (zerophase shift, 24 dB/octave rolloff) to remove any residual high-frequency artifact. MMN amplitude will be measured as the mean activity (expressed in μV) in the 135-205 ms latency range. This time window was chosen based on prior studies in schizophrenia [25]. Butterfly plots and 2-dimensional scalp topography of grand average MMN responses will be inspected to ensure that each subject is showing the expected pattern of activity (i.e., negativity at frontocentral regions and polarity inversion at the mastoids). Furthermore, only MMN responses that are at least 2 times the amplitude of any activity present in the 100 ms before stimulus onset will be considered valid [26]. The MMN amplitude at Fz will serve as the primary EEG outcome measure.

Behavioral Assessments

Neurocognition

To assess neurocognitive functioning, the MATRICS Consensus Cognitive Battery (MCCB; [54]) will be administered. The tests in the MCCB were selected from over 90 nominated tests and represent 7 separable cognitive domains [55, 56]. The MCCB takes approximately 60 minutes to administer and provides normed scores, including a summary score and cognitive domain scores. The MCCB includes one social cognition domain (the Managing Emotions component of the MSCEIT) which will not be included in the summary score but rather incorporated into a social cognitive composite score (see below). The remaining 6 domain t-scores from the MCCB will be averaged to create a composite score representing basic cognition as has been done previously [43]. Table 2 shows the tests that comprise the battery and the 6 cognitive domains they represent. The MCCB composite score will serve as the primary cognitive outcome measure. The individual MCCB domain scores will be used in secondary analyses to determine whether an overall effect is driven by any particular aspect of neurocognition.

Table 2: MCCB Cognitive Domains and Tests

Domain Assessed	Measure
Speed of Processing	Trail Making Test (TMT): Part A Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding Category Fluency: Animal Naming
Verbal Memory	Hopkins Verbal Learning Test–Revised (HVLT-R)
Visual Memory	Brief Visuospatial Memory Test–Revised (BVMT-R)

Working Memory	Wechsler Memory Scale–Third Edition (WMS-III): Spatial Span Letter–Number Span (LNS)
Attention / Vigilance	Continuous Performance Test–Identical Pairs (CPT-IP)
Reasoning and Problem Solving	Neuropsychological Assessment Battery (NAB): Mazes

Social Cognition

To assess emotional processing, the Managing Emotions component of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; [57]) will be administered. Managing Emotions has 2 subscales that examine the regulation of emotions in oneself and in one's relationships with others. These subscales include vignettes of various situations, along with ways to cope with the emotions depicted in these vignettes. Subjects are required to indicate the effectiveness of each solution, ranging from 1 (very ineffective) to 5 (very effective). It takes about 15 min to complete this measure.

In addition to this high-level social cognitive test, a low-level social cognitive test, the Affective Prosody Task (APT; [58]), will be used to measure auditory emotion recognition. Stimuli consist of audio recordings of semantically neutral sentences spoken with different voice tones. The sentences are either statements or questions and conveyed in 6 emotions (fear, anger, happiness, sadness, disgust, or neutral). After each stimulus, a list of the 6 possible choices is presented on the computer screen and the participant selects one emotion. It takes about 15 min to complete this task.

A social cognitive composite score will be created by standardizing (z-scoring) then summing the total scores from the MSCEIT Managing Emotions subtest and the APT. The social cognitive composite score will be included in exploratory analyses.

Functional Capacity and Community Functioning

To assess functional capacity, the UCSD Performance-based Skills Assessment (UPSA; [59]) will be administered. The UPSA assesses five skill areas that are considered essential to functioning in the community: General Organization; Finance; Social/Communications; Transportation; and Household Chores. The UPSA involves role-play tasks with props that are administered in the laboratory as simulations of events that the person may encounter in the community. These tasks are similar in complexity to situations that a community-dwelling person with chronic mental illness is likely to encounter. Inter-rater reliability of ratings are excellent (intraclass correlation coefficient = .91, $p<.001$). The UPSA takes 25 minutes to administer and yields a total score and domain scores. The UPSA total score will serve as the primary functional outcome measure.

To assess community functioning, the Role Functioning Scale (RFS; [60]) will be administered. The RFS assesses patients' current level of functioning in four areas: independent living skills, social (both family and non-family) functioning, and work functioning. The subscale ratings range from 1 (severely impaired) to 7 (maximal functioning) and include anchor points that detail both the quantity and quality of functioning. The RFS will be administered as part of an approximately 30-minute interview and rated by one of several trained interviewers in our lab. The RFS yields a total score and domain scores.

Although we are evaluating whether our relatively brief clinical trial affects proximal constructs such as cognition and functional capacity, we are unlikely to see significant changes in real-world functioning after only 3 months of cognitive training. Nonetheless, we will include the RFS total score in exploratory analyses, and these results might provide a basis for future work.

Half-way through the training, subjects will be administered two questionnaires, the Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR) and Theories of Intelligence Scale (TIS). The IMI-SR is a task-specific measure of intrinsic motivation. It consists of 21 items rated on a 7-point Likert scale with responses ranging from “not at all true” to “very true”. It is designed to assess

patients' subjective experience of an activity in an experimental setting (i.e., cognitive training). The instrument has 3 subscales: 1) perceived interest and enjoyment due to task, 2) perceived value and usefulness of the task, and 3) perceived autonomy to perform the task. The TIS assesses subjects' beliefs about the nature of intelligence (as an unchangeable, fixed entity or as a malleable quality that can be developed). It consists of 8 items: 4 entity theory statements (e.g., "You have a certain amount of intelligence, and you really can't do much to change it") and 4 incremental theory statements (e.g., "You can always substantially change how intelligent you are").

Cognitive Training Interventions

Specific Perceptual Training: Brain Fitness Program, Posit Science, San Francisco, California www.positscience.com

This computerized cognitive intervention is designed to improve the speed and accuracy of auditory information processing through increasingly more difficult stimulus recognition, discrimination, sequencing, and memory tasks under conditions of close attentional control, high reward, and novelty [61]. BFP consists of 6 exercises (Table 3). Stimuli across the exercises are chosen such that they span the acoustic and organizational structure of speech, from very simple acoustic stimuli and tasks (e.g., time order judgments of rapidly successive frequency-modulated sweeps) to complex manipulations of continuous speech (e.g., narrative memory). The exercises adaptively progress based on the subject's individual performance during a training session and become more challenging as the subject's abilities improve. Participants will work with 4 of the 6 exercises (for 15 min per exercise) in each session. Duration of training is 1 hour per day, 3 days per week, for 12 weeks, for a total of 36 hours.

Table 3: Brain Fitness Program Exercises

Exercise Name	Description
High or Low?	Reconstruct the identity (upward or downward) and sequence of frequency-modulated sweeps. The task progresses by changing the duration and interstimulus interval between the sweeps
Tell Us Apart	Identify a synthetically generated syllable (e.g.,_ba_) from a confusable pair (e.g.,_ba_vs._da_). The task progresses by changing the duration and intensity of the sweep component of the initial consonant.
Match It!	Match short spoken confusable consonant–vowel–consonant words (e.g., bad, dad) from a spatial grid. The task progresses by changing the number of potential matches and processing the spoken speech to stretch and emphasize rapid transitions.
Sound Replay	Reconstruct a sequence of short spoken words (identical to the third exercise stimuli). The task progresses by changing the number of words in the sequence and the level of speech processing.
Listen and Do	Reconstruct a spoken series of instructions by using the computer mouse to click and drag icons on the computer screen. The task progresses by changing the number and complexity of the instructions and the level of speech processing.
Story Teller	Answer questions regarding short narratives. The task progresses by changing the length of the narratives and the level of speech processing.

BFP has a strong theoretical rationale based on systems neuroscience principles. The goal of this neuroplasticity-based training program is to harness the brain's inherent plasticity through implicit

learning mechanisms. This training approach relies on the premise that the effects of implicit learning and repetitive practice are intact in schizophrenia despite the fact that explicit learning/memory and the motivation/reward systems are impaired [62]. The training employs intensive, repetitive, adaptive practice of well-defined skills to maximize enduring plastic changes in the brain. To drive learning and preserve reward schedules [63], the difficulty level for each subject is adjusted to maintain an approximately 85% correct rate and each correct trial is rewarded immediately with points and animations.

A large-scale RCT comparing BFP to a general cognitive stimulation program in healthy adults found greater improvements in auditory processing and better performance on untrained neurocognitive measures of attention and memory in the BFP group [64]. As mentioned above (Preliminary Studies), our laboratory has previously used Posit Science software with patients and found it to be very well tolerated.

Broad Cognitive Training: Cognitive Package (Cogpack; version 8.5, Marker Software, Ladenburg, Germany) www.cogpack.de
This computerized cognitive intervention is designed to provide training across a broad range of cognitive functions. Cogpack is well established in psychiatric hospitals and clinics in German-speaking countries [65] and has been translated into several languages, including English. Cogpack consists of domain-specific exercises, aimed at training specific cognitive areas (attention, working memory, verbal and visual memory, executive functioning, reasoning, language) and non-domain-specific exercises that require the use of several functions at a time. Although Cogpack includes low-level cognitive exercises (i.e., scanning, hand-eye coordination, and psychomotor speed), these exercises will not be included in this protocol to better separate bottom-up from top-down training interventions. Participants will complete a total of 48 exercises. All exercises are included within the first 9 sessions. Then, variants of the same exercises with different levels of difficulty are repeated over the remaining 27 sessions for further practice. In each session, the participant will work on a different subset of 4 to 6 exercises. Duration of training is 1 hour per day, 3 days per week, for 12 weeks, for a total of 36 hours.

Table 4: Cogpack Exercises

Domain Trained	**Examples of Exercises**
Attention	Sort out products on a conveyer belt, find the repeated character on a screen full of characters, press the bar when a number directly follows the previous one
Verbal and Visual Memory	Learn and memorize a list of words, remember addresses, images, labels, patterns, routes, details from lively scenes
Reasoning and Executive Functioning	Solve arithmetic problems and deductive comparisons, complete a block, continue a series, connect dots
Language	Use various clues to find words, answer questions about text-content, attribute quotations to authors or titles to poems, place syllables in order, solve anagrams
Knowledge and Everyday Skills	Demonstrate knowledge of facts, history, geography, country abbreviations, count bills, balance scale, use compass, estimate calories

Similar to the Brain Fitness Program, a motivational enhancement component is embedded in Cogpack to enhance intrinsic motivation and perceived competency, two client factors that influence responsiveness to treatment [66]. The exercises are designed to be enjoyable, reinforcing to

complete, and challenging, with difficulty gradually increasing over time. The level of difficulty is set based on the subject's performance during the course of the session. Moreover, the program provides regular individualized feedback on the subject's performance during the session and over the course of treatment.

Control Treatment: Commercial Computer Games (CCG).
This treatment condition is designed to control for the effects of computer exposure, contact with research personnel, time spent being cognitively active, and financial compensation for participation. A similar control condition of commercially available computer games has been used in previous cognitive remediation studies with schizophrenia [14]. This "placebo" condition also controls for the non-specific engagement of attentional systems through the reinforcement of graphics-based computer games and allows for responses to visual and motor stimuli and action events via computer-generated tasks. However, these games do not have the specific and systematic approach of highly focused, intensive, individualized neuroadaptive training of BFP, and they do not have the conceptual and higher-level training of Cogpack.

Participants in this condition will play highly enjoyable commercially available computer games for a total of 36 hours and will receive the same amount of contact with personnel and the same monetary and other reinforcements as participants in the experimental treatment groups. Subjects will participate in three 60-min sessions per week and will play 4 computer games, at 15 minutes per type of game, in each session. We will use 10 computerized games (e.g., visuospatial puzzle games, pinball-style games, target-aiming games). These games have been used by Dr. Vinogradov's group and selected according to the following criteria: 1) The game is subjectively challenging, reinforcing, and can hold subjects' interest and motivation for the required intervention period; 2) the game encourages the development of psychomotor skills (e.g. reaction time, hand-eye coordination); and 3) the game has no disturbing or highly emotional violent or sexual content as rated by the Entertainment Software Rating Board.

Data Management

Data management and statistical support will be provided by the VISN 22 MIRECC Data Core, directed by the co-investigator and statistical consultant, Dr. Sugar. The data core is made up of multiple senior consulting faculty from the UCLA Departments of Biostatistics and Psychiatry as well as full-time staff statisticians, database and applications programmers, data managers and web designers. Its personnel have extensive experience supporting studies ranging from small pilot projects to large multisite centers and have a long history of collaboration on schizophrenia studies at the VA with Drs. Jahchan, Green and their research team. For this project, the data core will develop a customized VA intranet-based data system, including the subject registry, data dictionary, randomization system, data entry forms, project management tools and the centralized database which can accommodate both manual entry and electronic upload and merging of data from other sources. In particular, EEG data will be collected and processed on a separate computer, and the primary amplitude measures will be extracted and uploaded into the primary database. The system will be housed on the data core's secure VA servers and will feature numerous security and quality assurance features including double entry to verify data correctness, automatic logic and range checking, and strict protocols for data confidentiality, transfer and back-up including anonymized ID coding to protect subject privacy. All files are encrypted and the systems and tools are protected by 128-bit SSL, the secure socket layer technology used for sensitive transactions on the web. The system will be accessible only via the VA intranet and will employ a hierarchical system of password protected logins, allowing differential access to project team members as appropriate to their roles. Data will be accessed only through the system, not transported, and analyses will be performed on de-identified and aggregated data in consultation with the MIRECC Data Core.

Statistics and Power Analysis

Statistical Plan

The experimental design for this study is a 3-group randomized clinical trial, with assessments at baseline and the 12-week treatment endpoint. The aims correspond to comparisons of the effects of two active treatments to each other and to a control condition on neurocognition, EEG, and functional capacity. For each of these domains, we specify a primary outcome measure. For neurocognition we will use a composite score created by averaging the t-scores for the 6 neurocognitive domains of the MCCB. The main EEG measure will consist of the MMN amplitude at electrode Fz. For functional capacity we will use the total score from the UPSA. If significant treatment effects are found on any of the primary outcomes, we will perform secondary analyses on the corresponding components or subscale scores to determine whether the results are driven by particular aspects of the main constructs. To further characterize the treatment response profiles, exploratory analyses will be performed to examine the effects of the interventions on composite scores of social cognition and community functioning. We are well aware of the risk of Type I error inherent in a study with a large battery of assessments and have protected against it by clearly specifying a limited a priori set of primary outcome measures and contrasts of interest and designating all others as exploratory. However, since this is a preliminary study, designed to obtain estimates of treatment effects and to identify optimal intervention components and measures for a future definitive efficacy study, it is equally important not to miss any potentially relevant outcomes. All results will therefore be reported using an uncorrected two-sided significance level of $\alpha=.05$.

Prior to performing the primary analyses, descriptive statistics and graphical summaries will be obtained for all outcomes to check for missing data, outliers and the need for transformations or non-parametric methods. To assess the success of randomization, ANOVAs and chi-square tests will be used to test for baseline group differences on the primary outcomes as well as on demographic (age, gender, parental/personal education) and clinical (medication, duration of illness, and symptom severity) characteristics. Measures that show significant differences will be included as covariates in subsequent analyses. Below we give a detailed description of the analytic plan by specific aim.

Analysis Plan By Specific Aim:

Specific Aim #1: To compare the treatment effects of bottom-up training (BFP) to top-down training (Cogpack) as well as to a control condition on neurocognition.

Specific Aim #2: To compare the treatment effects of bottom-up training (BFP) to top-down training (Cogpack) as well as to a control condition on EEG (MMN).

Specific Aim #3: To compare the treatment effects of bottom-up training (BFP) to top-down training (Cogpack) as well as to a control condition on functional capacity.

Exploratory Aims: 1) To compare the treatment effects of bottom-up training (BFP) to top-down training (Cogpack) as well as to a control condition on social cognition and community functioning and 2) to assess whether changes in MMN are associated with changes in cognition and functioning.

Primary Analyses: To make the most efficient use of our data, our primary analytical technique will be the general linear mixed model (GLMM). GLMMs account for correlations induced by repeated measures within subjects, allow for both fixed and time-varying covariates and automatically handle missing data, producing unbiased parameter estimates provided that observations are missing at random. This allows us to include all available data from all subjects in the analyses, regardless of the degree of study participation or treatment dosage received, consistent with the intent to treat framework. For each of our primary outcomes (MCCB neurocognitive composite for Aim1, MMN amplitude at Fz for Aim 2, UPSA total score for Aim 3), our core model will include group (BFP, Cogpack, control) as the between subject factor, time (baseline, end of treatment) as the within subject factor, and a group by time interaction. Our primary hypotheses correspond to the group by time interactions comparing the outcome trajectories for the two active treatments, which can be obtained as post-hoc contrasts. Such contrasts can also be used to compare each of the active

treatments to the control condition, to test for within group change and to examine the magnitudes of group differences at the end of treatment.

Exploratory Analyses: Significant results for the primary global measures will be followed by equivalent models for the component subdomain scores to identify the primary drivers of treatment effects. Parallel models will also be fit for the exploratory analyses of social cognition and community functioning measures. To examine the relationships between MMN and cognition and functioning, we will add this EEG index as a time-varying covariate to the primary GLMM models for the other outcome domains. Although we are underpowered for a full mediation analysis, this will also allow us to obtain a preliminary indication of whether treatment effects operate through their effect on electrophysiology. Given that age, duration of illness, symptom severity, medication (indexed by CPZ units) and dosage of treatment (number of sessions) may all impact treatment response, we will also add these measures and their interactions with treatment group and time to the primary models to (i) determine whether they explain additional variation in the outcomes and (ii) obtain preliminary information about potential treatment moderators.

Attrition and Missing Data: We plan an intent-to-treat approach, using all available data from all subjects, regardless of the degree of program participation. As noted above, our GLMM models automatically handle missing data, making the most efficient use possible of available measurements. However, with this study population there is likely to be moderate data loss (up to 20% due to attrition and EEG artifacts based on our prior experience) and we recognize the potential for bias due to differential dropout. The impact of attrition will be evaluated by comparing dropout rates in the treatment arms using chi-square tests, and by comparing baseline characteristics of dropouts with those who have outcome data. If there is evidence that attrition patterns might introduce bias into the analyses, we will perform supplementary analyses adding propensity-score adjustments to the primary models. In the propensity score framework, baseline characteristics are used to develop a predictive model for attrition (e.g., via logistic regression), and the probability of dropout is used either as a covariate or to weight the observations in the subsequent models. In essence, cases who are similar to dropouts are weighted more heavily to “make up” for others like them who dropped out. As noted above, we will also explore treatment dosage as a covariate in secondary models. Finally, scattered missing data on covariates will be handled using multiple imputation procedures.

Power Considerations

We plan to enroll 120 subjects (n=48 for each of the two treatment conditions and n=24 for the control group) to obtain a final sample of n=96 subjects with complete data after accounting for attrition and data loss. Power calculations are conservatively based on these numbers and assume a two-sided significance level of α=.05. We also assume a within-subject autocorrelation of r = .7, a value based on our experience with similar studies in the past. Our primary hypotheses all involve comparisons (parameterized as group by time interactions) among the 3 treatment groups. Our design provides over 80% power to detect overall effects as small as f=.13 which is sufficient to detect any pattern of changes in the three study arms for which the difference between the two most extreme groups is at least d=.6 at study endpoint. For the post-hoc comparison of primary interest, namely the group by time interaction examining the outcome trajectories for the two active treatment groups, this design provides sufficient power to detect an effect equivalent to a change from no difference at baseline to a difference of d=.5 at the post-treatment point. In addition, we note that we have over 80% power to detect within group changes from baseline to end of treatment of d = .35 in the active treatment groups and d = .5 in the control group, small to medium effects using the conventions of Cohen. For the exploratory analyses, the relationships will be assessed using the entire sample. This yields 80% power to detect a correlation of r = .28 between measures at any time point; power for the model with time-varying covariates will be higher due to the repeated measures.

In our pilot data, which examined performance on Cogpack training tasks in patients receiving two sessions per week over a 1 month period, we observed within group changes ranging from d = .5 (connect task) to d = 2.5 (confusion task). While these effect sizes cannot be used directly to compute power for our primary hypotheses (since they involve different measures and only a single group) they do show that patients can experience large cognitive changes over a much shorter period and with a lower intensity intervention than what is planned for this study. Since we are powered to detect small to medium effect-sizes magnitudes, we should be in a strong position even if effects are smaller on the global cognitive and functioning batteries.