Cover Page: Visual Remediation in Schizophrenia

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B. Significance

There is a large body of research indicating that schizophrenia is characterized by visual perceptual deficits, with some impairments predating psychosis onset[33-35]. Indeed, visual distortions and anomalies, which are found in ~2/3 of individuals with schizophrenia[36-38], are among the strongest predictors of conversion to schizophrenia-spectrum disorders among high-risk youth[34;35;39]. It has been shown that in many cases, the impairments on visual processing tasks observed in schizophrenia are not manifestations of a generalized deficit, and are independent of medication effects[10;40-42]. Importantly, visual impairments in schizophrenia are significantly related to poorer performance on tasks of visual-related cognitive functions (e.g., visual working memory[13;29;43-45]), impaired social cognitive function[4;14;27;46-55], and worse community functioning[1;14;47]. Despite this growing literature regarding the significance of visual processing impairments in schizophrenia, there are no accepted visual remediation strategies for schizophrenia, and indeed, this issue has received almost no attention in the literature. Therefore, the goal of the proposed project is to identify a treatment that **fills the unmet therapeutic need** of alleviating visual perceptual difficulties and related cognitive and behavioral impairments in the disorder. We propose to assess the effects of two complementary forms of visual remediation. One targets the mechanism of *gain control*, and the other targets the mechanism of *integration*. We are using established tests of contrast sensitivity (CS) to operationalize gain control, and established tests of perceptual organization (PO) to operationalize integration. Gain control and integration were identified by the NIMH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative as the two core impairments responsible for altered visual processing in schizophrenia[26]. CS and PO have been extensively studied in schizophrenia, their neural mechanisms are relatively well-understood (as described later in this section), and their impairments predict higher-level dysfunction. For example, impaired CS has been demonstrated in psychophysical, electrophysiological, and brain imaging studies[1;27-31], and is associated with failures in the later process of PO [Section D.1 Preliminary Data], as well as with poorer facial affect recognition[27], reading[13;43], cognition [[29] and Section D.1], and community functioning[1] in schizophrenia. PO impairments in schizophrenia have been observed in over 50 laboratory studies[reviewed in 7;8;10], including psychophysical[10], ERP[7;56] and fMRI investigations[7;57;58]. These visual integration difficulties have also been reported in the clinical literature, an example of which is: "I have to put things together in my head. If I look at my watch I see the watch, the watchstrap, face, hands, and so on, then I have to put them together to get it into one piece"[59 (p 229)]. As with CS, PO deficits are associated with decrements in higher-level function: They are related to impairments in constructing visual representations such as faces from degraded stimuli[4;46], forming visual memory representations[44;45], and facial emotion decoding[54]. PO impairments are also related to poorer functional outcomes[60;61]. In addition, abnormal visual PO negatively predicted discharge to the community from a long-term inpatient psychiatric rehabilitation program better than neuropsychological measures of reaction time, attention, memory, and executive functioning, over a 3-year period[62]. Thus, impairments in both CS and PO have predicted poorer functioning. Consistent with this, structural equation modeling (SEM) studies indicate a single pathway from visual dysfunction to functional outcome, with mediating variables that include social cognition[14;47;63]. The finding of a single pathway supports a cascade model in which degraded visual representations contribute to difficulties in higher-level processing[14;64], and "helps to provide a rationale for early perceptual and cognitive interventions, such as plasticity-based training"[65;15 (p1223)].

Further motivation for a systematic attempt at visual remediation comes from a growing number of studies demonstrating that plasticity-based visual perceptual learning can occur in both healthy controls and individuals with schizophrenia[20-24,25]. We recently published a series of case studies demonstrating improvements in CS in schizophrenia using the CS training program proposed for the current project ([66], and see section D.1). Moreover, previous studies of visual interventions with non-psychiatric samples, including the CS intervention proposed here, have demonstrated treatment-related gains that generalized beyond the trained visual function, including improved reading skills in controls[21] and people with dyslexia[67-69], and improved batting averages in college baseball players[70], suggesting that improvements in low-level visual processes such as CS can lead to gains in real-world functioning. Regarding PO, we previously published a review on improvements in PO in schizophrenia after repeated task performance (typically over several days), based largely on a number of our earlier contour integration studies[25]. Several studies from other labs have also shown positive effects of perceptual learning-based training programs on visual function in schizophrenia. As noted, however, these investigations used small samples, lacked a control group, used training paradigms with a limited number of sessions, and/or focused on only a single visual task[17-19]. Finally, a body of work evaluating the effects of a cognitive training program that emphasizes auditory sensory processing has demonstrated significant treatment-related improvements in higher-level auditory and verbal functions in

schizophrenia, such as verbal working memory and verbal learning[65;71;72;73], suggesting that *training low-level processes can contribute to improving higher-order cognitive functions dependent on that sensory modality*. In short, enough evidence exists to suggest that remediation of visual function is possible, and that it could lead to gains in higher functions that rely on vision. However, despite this promise, and despite visual remediation being a well-developed field in its own right[74;75], **what is not known is whether, in a well-controlled study with a sufficient sample size and duration of treatment: a) visual processing can be significantly improved in schizophrenia; and b) improvements in visual processing will lead to improvements in higher-order cognition, social cognition, and functional capacity**. Therefore, we propose to examine these important questions. We will do so by studying the effects of interventions that have either demonstrated positive effects on visual processing in multiple studies in non-psychiatric populations, or that are based on laboratory measures on which individuals with schizophrenia have demonstrated impairments, *but also perceptual learning-based improvements*, in multiple prior studies[1-5;7;10;25;67-70;76]. Based on: a) data showing strong evidence for visual impairments in schizophrenia that are thought to reflect core components of the disorder; b) relationships between these impairments and cognition, social cognition, functioning, illness course, and treatment outcome in cross-sectional, SEM, and longitudinal studies; and c) knowledge that visual processing can be improved in psychiatrically-healthy subjects and (based on preliminary data) in people with schizophrenia[66], *this intervention, if effective, has the potential to significantly reduce the burden of serious mental illness by improving perceptual and cognitive functioning in schizophrenia.*

As noted, the first level of remediation that we will evaluate targets gain control, in the form of CS. To remediate CS impairments in schizophrenia, we will use the ULTIMEYES (UE) computerized intervention, which targets CS across a wide range of spatial frequencies. **UE is ready for early-phase testing** in participants with schizophrenia, as it has been successfully developed as a computer application by Dr. Aaron Seitz (a co-investigator on this grant proposal)[21;70;76].

To assess target engagement for CS, we will use two complementary paradigms, one psychophysical and the other electrophysiological, both of which were recommended by the CNTRICS initiative to assess the construct of gain control in vision[77;78]. Psychophysical CS assesses the lowest level of contrast needed to detect stimuli presented at different spatial frequencies (SFs) (i.e., fine to broad lines corresponding to high to low SF, respectively). Studies of psychophysical CS show that people with schizophrenia need greater contrast (i.e., show lower CS) than controls to detect contrast across the ronange of SFs, although deficits in processing *low* SF (LSF) stimuli have been more pronounced in most studies of schizophrenia[1;27;29;79]. In addition, deficits in LSF processing are related to object recognition[79] as well as to face and facial emotion processing deficits in schizophrenia[4;46;48-52;55]. Therefore, we focus primarily on CS for LSF stimuli. Because features within LSF stimuli are relatively large, there is less of an effect of acuity on those responses as opposed to fine-grained HSF stimuli that rely heavily on acuity. This helps to address the potential confound of impaired acuity in people with schizophrenia on task performance[80]. However, supporting the hypothesis that acuity was not driving past CS results are findings that the relationships between impaired CS and poorer facial emotion recognition, reading, visual learning, and PO in people with schizophrenia ([13;27;29;81] and Preliminary Data) are strongest for LSF stimuli[13;27;29;81]. Electrophysiological CS involves recording the steady-state visual evoked potential (ssVEP) in response to stimuli varying in contrast[1;77;78;82;83]. The ssVEP measure provides rapid, objective assessment of visual cortical responses to a range of contrast levels *without requiring behavioral responses from participants*. Studies of ssVEP in schizophrenia consistently show impairments, and these are most pronounced at low contrast levels[1;27;84;85]. Weaker ssVEP responses to contrast changes in schizophrenia are significantly correlated with behaviorally-assessed CS[1], facial emotion recognition[27], Global Assessment of Functioning (GAF) scores, and Problem Solving Factor scores on the Independent Living Scale[1].

The neural mechanisms involved in CS are relatively well understood. As noted above, CS has been viewed as a form of gain control[77;86]. Gain control involves both amplification and suppression of signals to keep neural activity at or near optimal levels; this homeostatic function thereby serves to reduce the risk of sensory deprivation-induced hallucinations with insufficient cortical activation[87], and stimulus overload with excess activation[26;86;88]. Weaker signals, such as those involving low contrast and/or LSFs are amplified, and stronger signals are attenuated, with the full contrast-response function therefore following a classic sigmoidal curve. At the neural level, both amplification and attenuation are thought to arise from divisive normalization[89-91], in which target signal strength is modulated as a function of total activation in the cortical region[1;27;82-84;92]. Evidence that observer CS in a psychophysical task corresponds with level of neural activation, and that it is modulated by gain control, comes from several sources. One is that, using single-unit microelectrode recording in cat V1, the inverse U-shaped psychophysical CS function (CSF) was highly correlated with the neuronal

CSF[93]. Another is that the fMRI BOLD response in V1 in humans covaries with contrast enhancement[94] and SF[95], with the relationship being especially tightly coupled for LSF stimuli[96]. In short, gain control keeps responses within an adaptively limited signaling range, and both of the CS assessment formats we propose to use generate data that can be interpreted clearly within cognitive neuroscience models of gain control in schizophrenia and healthy populations.

The second level of remediation in the R61 targets integration, in the form of PO. We are focusing specifically on the visual PO function of contour integration. We have developed a program for contour integration training (CIT), via modification of a contour integration task developed for use in schizophrenia by Dr. Silverstein and colleagues, and used previously in multiple behavioral, ERP, and fMRI studies[8;53;56-58;80]. Our hypothesis regarding the ability of CIT to drive gains in PO is based on prior demonstrations of perceptual learning in controls and participants with schizophrenia (albeit at a slower rate in the latter group) with similar versions of this task[8;25;60]. For example, healthy controls showed improved detection of a collinear path over 12 days of training[97], improved performance on a closed contour integration task across test sessions that spanned 2 consecutive days[98], and gains in identifying interpolated shapes over 4 days[99]. In addition, in monkeys, behavioral performance and V1 activity increased consistently over 10 days of contour integration training[100]. People with schizophrenia showed improved contour integration performance following 2-4 days of exposure to the task in the study cited above in which controls reached asymptotic performance after 2 days[60], and improved pattern recognition across a single session of training involving 600 trials[45;62]. In addition, there are numerous studies that provide validity, reliability, and short-term perceptual learning data for the contour integration paradigm[8;25;100]. A further advantage of this task is that the neural mechanisms underlying performance have been demonstrated in monkeys and healthy humans[101-105], and neural correlates of impairment (e.g., in V2, V3, V4, LOC, and frontal-parietal regions) have been identified in participants with schizophrenia[57;58]. Therefore, demonstration of improved performance after remediation would lead naturally to EEG and fMRI studies of training-related activation changes in specific regions of interest and brain networks.

To assess target engagement for the PO intervention (CIT), we will use two tasks. The first is the original contour integration test recommended by the CNTRICS initiative for use in treatment studies of schizophrenia[8], namely the Jittered Orientation Visual Integration (JOVI) task[8;25;58]. The JOVI involves identifying the direction of an egg-shaped contour made up of individual Gabor elements with gaps between them so that the participant has to perceptually integrate the Gabors to perceive the egg (see Fig. 3). The task has been optimized for use in clinical trials[8;58] (see D.6.b). Although there are differences between the PO training task (CIT) and the JOVI in terms of the specific stimuli (i.e., circular vs. oval shapes, respectively) and response requirements (identifying the location of the target circle vs. indicating whether the centrally-presented egg-shaped contour is pointing left or right), which should preclude confounds based on low-level perceptual learning (e.g., learning that is specific to one area of visual space, or to a single shape), *we will also include a second outcome measure, one that does not share method variance with the training task*. The second PO task uses the Ebbinghaus illusion, in which a center circle appears smaller if it is surrounded by (i.e., grouped with) larger circles and appears larger if it is surrounded by smaller circles (see Fig. 5). The task requires subjects to choose which display (on the left or right of the screen) contains the array with the larger central circle. By manipulating the difference between the actual sizes of the central circles, and whether the size of the surrounding circles causes the inner target circle to appear smaller or larger than its actual size, a psychophysically precise measure of illusion strength is obtained. Dr. Silverstein has used this task extensively[106-109], and one of its appealing aspects is that, due to their reduced grouping of the central target and the surrounding circles, people with schizophrenia perform more accurately (in all studies cited above) than controls on trials in which surrounding context is normally misleading (e.g., when the larger of the two inner circles is made to appear smaller by surrounding it with large circles). Evidence that both the JOVI and Ebbinghaus tasks involve PO comes from a significant *inverse* correlation between scores such that a lower score on the JOVI is associated with *higher* scores in the *misleading* condition on the Ebbinghaus task[107].

As with CS, the neural mechanisms of PO, and of contour integration in particular, are relatively well understood. One involves long-range horizontal connections between orientation-tuned spatial frequency detectors in V1 (especially important for integrating closely spaced elements)[97]. A second involves reentrant feedback from V4 and higher visual areas to V1 and V2 (most important for grouping more distantly spaced elements)[110-113] to amplify processing of elements belonging to a single contour, surface, or shape. Importantly, contour integration cannot be implemented purely by local spatial frequency detectors, or by orientation-tuned neurons with large receptive fields[111;114]; rather, integration of activity across sets of neurons is required. Single-cell studies in V1 suggest excitatory (facilitating) effects when contour elements are collinear, but not orthogonal, with a central target[115;116]. fMRI data in humans and monkeys[101;102;105;117] indicate that V1, V2, V3,

V4, and the LOC are more activated when processing Gabor-defined contours, in contrast to randomly-oriented Gabors. In addition, activation of the prefrontal cortex and posterior parietal lobe are associated with successful contour integration, presumably as a source of feedback to occipital regions. However, it has been shown that impaired contour integration in schizophrenia is not due to inattention or random responding during task performance[58;80]. Both lateral excitation and top-down feedback, as implemented in contour integration, and in PO in general, are thought to involve synchronization of beta- and gamma-band oscillatory activity between neurons signaling contour elements (which are typically collinear or co-circular), and also between these temporary networks and top-down attention signals[10;118-120]. Relatedly, impaired PO in schizophrenia is associated with reduced synchrony within these bands[119;121]. This impairment is thought to reflect both NMDA receptor hypofunction and reduced GABAergic signaling[reviewed in 86;122;123].

Clear and refutable hypotheses of the R61 are: H1a) UE or UE&CIT will lead to significantly greater gains in CS than will ACCT and/or H1b) CIT or UE&CIT will produce significantly greater improvements in PO compared to ACCT. The **Go Signal** for continuing to the R33 will be a differential improvement, **with an effect size of at least d=0.4,** favoring UE or UE&CIT compared to ACCT on the psychophysical and/or electrophysiological CS task, *and/or* CIT or UE&CIT compared to ACCT on the JOVI and/or Ebbinghaus task. If a "go" signal is obtained, results of the R61 will be used to identify the most effective and efficient treatment (UE, CIT, or UE&CIT), and duration/dose, for use in the R33.

Clear and refutable hypotheses of the R33 are: H1) The optimal treatment identified in the R61 (e.g., UE&CIT) will be more effective than the control treatment (ACCT) in improving CS or PO in a new and larger sample; and H2) Improvements in target function will be related to changes on visual cognitive (i.e., visual learning and memory, reading), social cognitive (i.e., facial emotion recognition) and functional capacity measures. If the hypotheses in the R33 are confirmed, the results will inform the design of a later RCT to assess the efficacy of a visual remediation treatment for schizophrenia on a wider range of outcome variables. Instructions for the R33 state that it "should not be powered as strong tests of clinical efficacy but rather should test the link between… target engagement and functional outcome." Therefore, while we expect the correlations for R33 Aim 2 to be statistically significant, we do not hypothesize what the effect sizes will be. However, we would power a subsequent study based on the observed effect sizes in the R33.

This project will advance knowledge of intervention and disease mechanisms, whether the trial results are positive or negative. In the R61, we will learn whether targeting either or both levels of visual function improves the perceptual targets. The assessment of whether changes in the visual targets drive changes in other functions in the R33 will provide information about disease mechanisms by clarifying the links between visual perception and cognitive and social cognitive function. *We also wish to note that although there are multiple ways that a 'go' signal in the R61 can be achieved, each of these possibilities would represent a novel finding in its own right and motivate further studies of visual remediation in schizophrenia. More importantly, however, the R33 will serve, in part, as a replication and extension study of the R61: Observing that the optimal R61 intervention is effective in a second study, with a new and larger patient sample, and a similar degree of target engagement, would provide confidence that any R61 findings are not spurious.*

At a more basic level, as noted above, we are studying the effects of targeting basic forms of gain control and integrative processes on higher-level perceptual and cognitive processes. We are including two intervention components (UE and CIT) in order to explicitly target both CS and PO because there is evidence that both aspects of visual function are impaired in schizophrenia AND that impairments in both are related to poorer functioning in multiple domains. Because this is the first controlled study of perceptual remediation of these functions in schizophrenia, we wish to remain agnostic regarding whether the combined treatment (UE&CIT) will be more effective than either UE or CIT alone, although we anticipate that the combination may have additive or synergistic effects on one or both levels of vision. By assessing improvements related to the single treatment (UE or CIT) AND to the combined intervention at each level of vision, we will be able – at the end of the project – to provide a strong initial statement regarding the important question of differential and combined intervention effects. Future clinical trials will determine whether there are subgroups of individuals with schizophrenia (e.g., those who are more impaired on CS or PO at baseline) who are especially likely to benefit from these interventions. This is not a specific aim for this initial clinical trial because even people without visual impairment can improve their visual functioning[21;70;76]; however, our data will allow us to assess the degree to which improvement is a function of baseline CS and PO.

C. Innovation

This proposal is innovative in several respects. First, while there is a burgeoning literature on cognitive remediation in schizophrenia [(e.g., 65;124-126)], most of this work targets higher cognitive processes such as executive functioning and working memory, and assumes that perception is intact. As a result, despite the

large body of evidence showing impaired visual perceptual function in schizophrenia, the effects of visual training modules alone are virtually unstudied in this disorder. While CS and PO have been shown to be plastic in terms of performance improvement with repetition in prior laboratory studies, including in people with schizophrenia[21;23;25;70;76], the effects of systematic visual training of these processes for longer than a few days have not yet been studied in this population in a controlled study. Second, unlike many cognitive remediation interventions that use games with unclear 'doses' for specific functions, we are targeting two well-understood perceptual processes with interventions that clearly target these processes[26;77;78]. Third, UE has been shown to improve CS in non-psychiatric samples, but has never been used in a controlled study of schizophrenia. Fourth, many current perceptual learning approaches emphasize single processing mechanisms and produce results that are specific to the trained stimulus features[100;127], which has limited generalizability. The UE program addresses these issues by combining multiple perceptual learning approaches (e.g., engagement of attention, reinforcement) - each of which has been shown in past studies to contribute to increasing the speed, magnitude, and generalizability of improved CS - into an integrated perceptual learning application. UE has been shown to improve not only CS but also functioning in real-world activities[21;70;76] (see Section D.1). Fifth, the PO training program we developed (CIT) is innovative (we were able to identify only one published paper on improving PO in any population[128], and this was over 30 years old). Our proposed intervention is based on knowledge gained from our 30 years of studies in controls and patients about what factors contribute to PO, and how performance can change over time. Despite extensive evidence for PO impairment in schizophrenia[7], little is known about the maximum extent to which it can be improved, the amount of training needed to obtain gains, the durability of gains, and their functional significance. Sixth, the additive and/or interactive effects of multiple forms of visual remediation have never been investigated. This would be the first examination of whether targeting both CS and PO is more effective than targeting either single process alone. The construct of gain control (operationalized here in the form of CS) and the construct of integration (operationalized as PO) were identified by the NIMH-sponsored CNTRICS initiative, and the RDoC cognitive domain, as high-priority cognitive neuroscience constructs relevant to schizophrenia and its treatment[26]. This study targets both levels. Seventh, we will examine training effects on higher-level processes with a focus on comparing effects on visual vs. non-visual cognition, which has not yet been done in a controlled study.

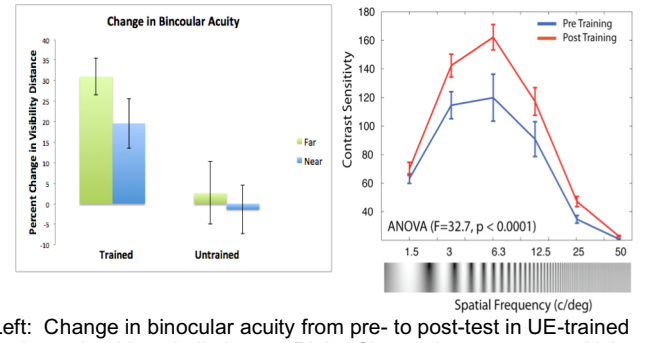
D. Approach

D.1 Preliminary Data

UE pilot study: Pilot data from patients with schizophrenia at the Nathan Kline Institute (NKI) and Rutgers show good retention with 6 of 7 patients (86%) completing at least 30 sessions. This is similar to previous single-site cognitive remediation studies[65;124] and to an average retention rate of 87% in a meta-analysis of 40 cognitive remediation studies in schizophrenia[129]. This also matches the 93% retention rate of UE studies in healthy young adults carried out by Dr. Seitz (co-investigator and developer of UE). Preliminary data show UE is well tolerated, and even enjoyed, as described in our recent publication[66]. Across participants, CS improved 32%, with an increase in the peak contrast spatial frequency of 1 cycle/degree (pre-training peak spatial frequency of 3.14 ± 0.24 vs. post-training of 4.15 ± 0.70, p=.14, d=0.96). Additionally, patients improved on contour integration (p=.11, d=0.85). With such a small sample (N=6), our results were not statistically significant. However, the magnitude of CS improvement is similar to that from published studies of UE.

UE findings in non-psychiatric samples: In previous research on UE conducted by Dr. Seitz, CS improved in healthy normal-sighted individuals after ~30 sessions of training[76], with effect sizes ranging from d=1.6 for LSF to 0.63 for HSF stimuli. In another study, college baseball players displayed significant improvements in CS (Fig. 1) and batting average[70] after UE training, with effect sizes ranging from d=0.34 to 0.59 (with the lowest effect size for CS to HSF stimuli). Additionally, university students demonstrated improved reading ability after UE training. Specifically, reading acuity improved an average of 13% (d=0.38), moving from a pre-training mean logMAR acuity of -0.06 to a post training value of -0.11, (SD=0.02). Reading speed improved 13% (d=0.57), moving from a pre-training mean value of 240.0 words/minute to a post-training value of 270.6 words/minute (SD=8.28)[21]. In addition, older adults with presbyopia displayed improved CS after undergoing UE training[21]. It is important to note that in the studies of UE in which

Figure 1



Left: Change in binocular acuity from pre- to post-test in UE-trained and untrained baseball players; Right: Change in contrast sensitivity from pre- to post training (higher scores represent better performance).

CS was assessed[21;70;76], CS improved significantly, as seen in a shift upward across spatial frequencies (see Fig. 1). Effect sizes were relatively large in the trained group in these studies and the average d for LSFs, which is the target for this proposal, ranged from 0.45 to 1.0 across studies. Based on these data and our pilot data in patients described above, we expect UE to lead to significant gains in CS in schizophrenia.

Preliminary and related data that motivate the targeting of CS: In an ongoing study in Dr. Silverstein's lab (N=17 thus far), we have found that lower peak CS is related to poorer contour integration (r=.69, p<.01). In a recently completed study in Dr. Butler's lab (N=32), we found that lower CS at 1 cycle/degree is related to poorer performance on the WAIS PO Index (r=.41, p=.02) and the MATRICS visual learning domain (r=.46, p=.006) in people with schizophrenia. In addition, a cluster analysis showed that people with schizophrenia who were more impaired on CS were also more impaired on speed of processing, PO, visual learning, and emotion recognition (p=0.02 to <0.001), but not on verbal working memory, verbal learning, or symptoms ($p \geq$ 0.05), suggesting that our visual targets are not manifestations of a generalized deficit[130]. These data fit current models in which CS occurs very early during visual processing, whereas PO is an integrative process that occurs later and involves binding of feature representations (whose quality is determined in part by CS). In addition to effects of low CS on PO, studies have shown that participants with schizophrenia who have impaired CS have greater reading deficits[13;43], and poorer facial emotion detection[27]. Further, in pilot work using structural equation modeling (SEM), we have found relationships between abnormal VEPs and impaired visual learning and PO that were significantly mediated by CS[131]. In short, there is reason to expect that improving both CS and PO will lead to higher-level changes in perception and cognition.

D.2 Inclusion/Exclusion Criteria for R61 and R33

Inclusion: 1) SCID-5 diagnosis of schizophrenia; 2) 18-60 years old; 3) speaks English; 4) able to complete the MATRICS Consensus Cognitive Battery (MCCB) at the baseline assessment (for R33); 5) a raw score of 37 or greater on the Wide Range Achievement Test, Reading subtest (WRAT-3), to establish a minimum reading level (6th grade) and to estimate premorbid IQ; and 6) clinically stable as indicated by no antipsychotic medication changes in the last month or if on depot, no change in the past 2 months. **Exclusion**: 1) history of intellectual disability, or developmental or neurological disorder; 2) history of brain trauma associated with loss of consciousness for > 10 minutes or behavioral sequelae; 3) alcohol or substance use disorder within the last 6 months; and 4) history of eye disease (e.g., glaucoma, retinopathy). Effects of tobacco use and medication dose equivalents[132], including an index of anticholinergic load[133], will be explored in data analyses.

D.3 R61 Phase

Aims: (i) To evaluate the effects of UE and CIT on the CS and PO targets, respectively; (ii) to determine if the criterion for continuing to the R33 phase is met; and (iii) if the criterion is met, to determine the most effective intervention condition and optimal duration of treatment, to inform the R33 study design.

Study design: 80 subjects will be enrolled in this study: 20 per arm. 40 will be recruited at each site (Rutgers and NKI). The intervention will continue for 40 sessions, with targets assessed before training, after every 10 sessions, and at 6 months post-training for a total of 6 visual assessments. With 3 sessions per week, the intervention will take between 13-14 weeks. Each site will enroll ~ 2 participants/month, beginning after the first half of Y1, which is similar to what Keefe et al.[72] estimated as a "reasonable rate of recruitment for a large-scale efficacy trial" of cognitive remediation. Because, at the 6-month follow-up, nearly all patients are expected to still be in the partial hospital program, or an outpatient program (at Rutgers), or on inpatient units at the Rockland Psychiatric Center (RPC) or NKI, we expect attrition to be minimal. However, several methods, including monthly phone calls (see Recruitment and Study Timeline), will be used to maximize retention. For the R61 and R33, training sessions will be run in small groups by front-line staff who have already received training in these interventions, or whom we will train, with no more than a 3:1 participant:staff ratio.

Randomization: Subjects will be randomly assigned, within site, to one of the 4 conditions (UE&ACCT, CIT&ACCT, UE&CIT and ACCT&ACCT) in a ratio of 1:1:1:1. The treatment assignment will be made after a subject has met all entry criteria and completed baseline testing, to avoid bias.

Milestones (Go/No-Go Criterion): We will proceed to the R33 phase if: 1) the UE-related effect size (i.e., the effect size of the difference between the UE&ACCT (or UE&CIT) and ACCT&ACCT groups in the degree of change in CS) is greater than or equal to Cohen's d=0.4 for **either** the psychophysical **or** ssVEP CS task; and/or 2) the CIT-related effect size (i.e., the effect size of the difference between CIT&ACCT (or UE&CIT) and ACCT&ACCT groups in the change on **either** of the PO tasks) is greater than or equal to d=0.4. Pre-post change scores for CS and PO target assessments will be calculated for each individual and used to determine effect sizes between groups. We will not control for baseline values consistent with recommendations to use "straight" change scores when examining cognitive change across two time points[134-140].

Rationale for our effect size choice: The effect size criterion we have chosen for the R61 "go" signal (d=0.4)

is similar to that observed in many studies of cognitive remediation, and of other treatments for this population, such as skills training and family psycho-education[124;126;141;142]. However, less is known about effect sizes of perceptual remediation, and most of the evidence on this in schizophrenia comes from studies of auditory remediation using the Posit Science auditory training module[65;71;72], which includes training on both low-level auditory targets and higher-level auditory-verbal cognition (e.g., verbal working memory and learning)[71;143]. Results from one study indicated an improvement in the target of auditory-processing speed[71] that was of large effect (d=0.875). The authors also observed a medium-large effect on global cognition (d=0.73). Results from other studies of this auditory training module in schizophrenia have indicated large treatment effects (d=0.86) for both verbal learning and global cognition, and a medium effect (d=~0.65) on the auditory target of P50 gating[65;143]. While these effect sizes are larger than our chosen criterion (d=.4), it is also important to note that some studies of Posit Science modules have not demonstrated significant improvement on non-trained tasks[72;144]. Moreover, across studies, the largest effects have tended to come from studies where daily training (5 days a week) was used, and subjects were paid for completing training sessions, and these are two conditions that can rarely be met in real world psychiatric clinics. These considerations have informed our choice of the 'go signal' criterion (i.e., d=.4), because there are as of yet very few published studies of visual remediation in schizophrenia. One small (N=9) uncontrolled study of visual backward masking training found an effect size of d=.43 for improvement in the MATRICS domain of Visual Learning[19]. Within our group, Dr. Silverstein observed an improvement in contour integration performance among participants with schizophrenia after 4 consecutive days of practice on a contour integration task (phi=0.63, which corresponds to a large effect)[60]. Even larger effect sizes were seen for changes in CS (d=0.96), and PO (d=0.85) in our small pilot sample of patients with schizophrenia (Section D1), but given the small sample size and lack of a control group in that study it can be assumed that the real effect size is lower. Thus, findings from these initial evaluations of visual remediation support our use of d=0.4 as a conservative level of change on the outcome measures and as a "go" signal for target engagement. However, we acknowledge that it is not yet clear from the literature how an effect of this size relates to meaningful improvements in visual and higher-order cognitive processing, and/or functional capacity. *The proposed R33 will allow us to address this question in a preliminary manner.* If results from this trial are positive, we will seek funding for a larger trial to evaluate the impact of this treatment on functional outcomes, and to identify mediators/moderators of treatment response.

If the Go criterion is met for any of the treatment conditions, we will perform a thorough investigation of the effects of UE, CIT, and UE&CIT on the CS and PO target scores to determine which remediation strategy to use for the R33. Analyses will also include (i) assessment of the trajectory of performance on the target measures over the course of treatment; (ii) determinations of whether the improvements plateau prior to the 40th session or whether they continue throughout the training period; and (iii) evaluations of whether any combined effects of UE and CIT are additive or multiplicative. These goals will be accomplished by first graphically examining the trajectories of target change to assess whether they are linear, monotonic non-linear, quadratic, or any other shape. After that, appropriate models for longitudinal data analysis will be applied to estimate improvement rate and time to asymptote. We will account for CPZ-equivalent dose of antipsychotic medications in all models, using CPZ dose as a time-varying covariate if necessary, and will also account for type of antipsychotic medication and anticholinergic load. Those models will also be used to examine whether baseline characteristics moderate the effect of UE and/or CIT on the targets. These analyses will allow us to ascertain: 1) whether UE alone, by targeting CS function, has a cascading effect on PO; 2) whether CIT improves CS while targeting PO function; and 3) whether UE&CIT has a stronger effect than either intervention alone for any outcome. Based on these results, the optimal intervention will be determined based on it having a significantly larger effect size for at least one target. If all 3 treatment conditions are effective to an equivalent degree, the criterion will be reaching asymptotic level of improvement earliest.

Sample size determination:

The sample size of the R61 study (n=20/group) was selected to ensure that when the true size of the effect of UE or UE&CIT on the CS target, or CIT or UE&CIT on the PO target, is d=0.4, the 95% confidence interval (CI) for the effect size does not contain zero. Given data on the CS measure over time in the UE pilot study described earlier, a 95% confidence interval for an effect size of magnitude 0.4 is between .02 and .91. Since the observed effect size in that pilot data was actually much larger, 0.96, we are confident that we will be adequately powered to detect a meaningful effect. Since patients also improved on a measure of contour integration (d=0.85) in the pilot study, even though training was focused only on CS (our low-level visual target), setting the effect size at d=0.4 for both CS and PO seems reasonable. Note that although contour integration improved without PO training in the pilot study, this was unlikely due to practice effects on the test alone since two prior large studies did not find practice effects on the JOVI, in either healthy controls or

patients, over two or three repeated presentations separated by days or weeks[145;146], and a third study found improvements only with daily exposure to two versions of the task, and this did not occur for the schizophrenia group until the third day[25;60]. Subjects who do not complete all 40 sessions of training will be invited to complete a "post-treatment" assessment after their last session; for non-completers who decline to participate in a post-treatment evaluation, the last post-baseline assessment will be used, unless the participant dropped out before the 10th session (the time of 1st post-baseline assessment), in which case his/her data will be not be used in the analyses. In such cases, we will recruit additional participants to reach the target sample size. We expect minimal dropout since most participants will be long-stay inpatients or partial hospital patients who are present on a nearly daily basis. For any dropout that does occur, we expect rates to be uniform across conditions, given that we have designed all conditions, including the active control, to be similarly engaging. Sufficient patients are available at both sites to recruit new subjects to replace any who discontinue.

D.4 R33 Phase

Aims: (i) To replicate and extend R61 results supporting initial visual target engagement using the optimal R61 treatment, in a new and larger sample; and (ii) to determine if visual target engagement is associated with improvements in specific cognitive *(i.e., visual working memory, visual learning and memory, reading)* and social cognitive *(i.e., facial emotion recognition)* outcomes, as well as with changes in functional capacity.

Study design: The R33 will be a two parallel-arm RCT comparing the optimal R61 treatment to the control (ACCT) treatment. 100 subjects will be enrolled over 3 years, 50 from NKI and 50 from Rutgers. Visual and clinical outcome assessments will be conducted at baseline, and at intervals determined based on R61 results, including a 6-month follow-up (with attrition considerations and procedures identical to the R61 (see D.3).

Randomization: Subjects will be randomly assigned, within site, to the optimal or control treatment in a ratio of 1:1. Treatment assignment for eligible subjects will occur after completion of baseline testing, to avoid bias.

Assessments: Visual Targets and Cognitive, Social Cognitive, and Functional Capacity. No matter which intervention is used for the R33, visual tests will include both tests of CS, and both tests of PO used in the R61. See below (section D.6.c) for descriptions of the cognitive, social cognitive, and functional capacity measures.

Data analysis: An intention to treat approach to data analysis will be used in this clinical trial. For all analyses, statistical significance will be defined as $p < 0.05$, unless specified otherwise. Bonferroni corrections will be applied to multiple testing, as appropriate. H1: The optimal R61 treatment will be more effective than the control treatment (ACCT) in improving CS and/or PO test scores (to be determined based on the R61 outcome). This will be tested using a linear mixed effects model in which the values of the target(s) at each time point are modeled as a function of treatment group (experimental, control), time, time x group, and potential moderators and mediators (e.g., age). We will use Akaike's Information Criterion (AIC) as the deciding metric to determine the optimal model to account for within-subject correlations between repeated measures (e.g., autoregressive of order 1, AR(1), which assumes stronger within-person correlation for measurements closer in time, or other structures). If the time x group interaction is significant, we will use model-based estimation procedures to estimate the magnitude of the effect. We will also explore differential effects of the treatment on CS vs. PO. H2: Improvements in visual processing, as observed in CS and/or PO (based on R61 results), will be related to changes on specific cognitive *(i.e., visual working memory, visual learning and memory, reading),* social cognitive *(i.e., emotion recognition)*, and functional capacity measures. We will assess correlations between visual target scores and cognition, social cognition, and functional capacity, and also evaluate whether changes in the target(s) either mediate or moderate treatment effects on these outcomes. An approach and computational tool described by Hayes[147] will be used to model any mediation and /or moderation effects, including indirect effects in models that involve mediation.

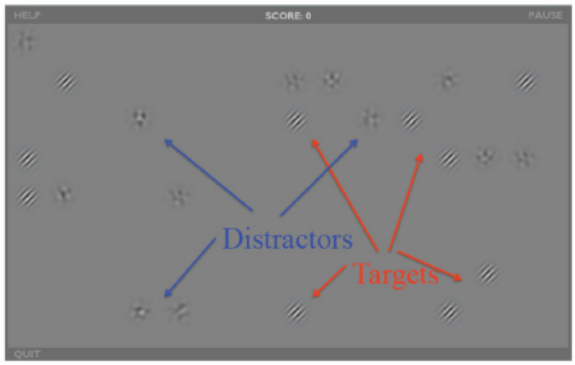
Sample size determination: The sample size for the RCT in the R33 phase was selected to ensure sufficient power to detect medium effects of the experimental intervention on the target(s). For Aim 1 of the R33, 50 subjects per condition allows 80% power for a 2-tailed test with α=0.05 to detect d=0.57. For Aim 2, with n=50 in the active perceptual training group, correlations of at least r=0.38 between changes in performance on target measures (CS and/or PO) and changes in cognitive, social cognitive, and functional capacity can be detected with 80% power using a 2-tailed test with α=0.05. Also, for Aim 2, n=50 (i.e., active perceptual intervention only) allows for detecting a correlation of r=0.43 when making a strict Bonferroni adjustment for 3 outcomes (2-tailed α=0.017), and r=0.51 when correcting for 15 outcomes (2-tailed α=0.003). In accordance with instructions that the R33 "should not be powered as a strong test of clinical efficacy…", our focus on effect size is exploratory and not confirmatory. We will use our observed effect sizes to power a later RCT.

D.5 Interventions

ULTIMEYES (UE) Training: The UE training procedure was developed by Dr. Seitz and colleagues at UCR[70;76]. The program uses video game-based custom software, and the training stimuli consist of Gabor

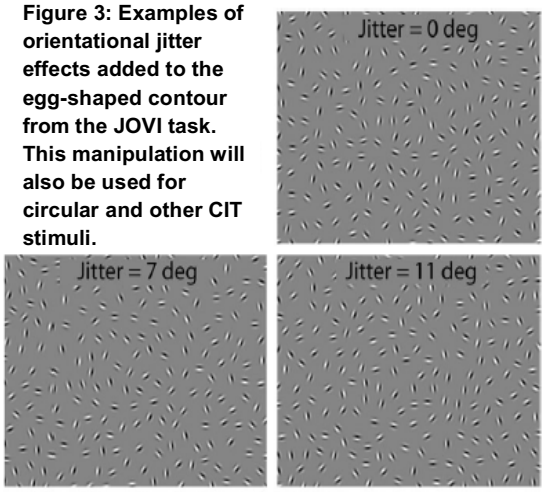
patches (game "targets") at 6 SFs (1, 2, 4, 8, 16 and 32 cycles/degree), and 8 orientations (22.5°- 337.5°). We describe this program as a "video-game" because numerous elements were introduced to its design with the goal of promoting task engagement and user enjoyment. For instance, points are given each time a target is selected (and taken away when distractors are selected), and levels increase in difficulty throughout training. At the beginning of each session a calibration is run to determine the initial contrast values for each SF to be displayed during the training exercises. Each session consists of 8-12 training exercises that last approximately 2 minutes each for a total of ~25 min. The participant's task is to click on all the Gabor targets as quickly as possible. The first few exercises consist of only targets, but distractors are added as the training progresses (Fig. 2). Throughout training, distractors become more similar to the targets (starting off as blobs, then oriented patterns, then noise patches of the same SF as the targets). Targets that are not selected in time start flickering at a 20-Hz frequency, to attract attention[148]. At higher levels, targets and distractors appear and disappear when not selected quickly enough. Many parameters are adjusted based on ongoing participant performance, including contrast (using a 3/1 staircase for each SF), number of stimuli per trial, and presentation rate (determined by tracking average response times on prior trials for each SF).

Figure 2: UE targets and distractors



Contour Integration Training (CIT): The CIT program was developed by co-investigator Dr. Seitz and is based largely on two contour integration tasks we developed and have used in multiple studies of visual PO in schizophrenia [8;80]. There are two PO exercises used for this program, which are presented in alternating blocks of individual trials. Target stimuli in both exercises consist of contours that are formed by fragmented paths of individual Gabor elements, which are embedded within an array of noise Gabors. For one of the exercises, the participant's task is to detect and click on the circular contour formed by a set of target Gabors. Difficulty level is manipulated by varying the degree of orientational jitter of the Gabors making up the target contour (see Fig. 3), which is done within block, and by varying the number of elements that make up the circle, which is done between blocks. The degree of jitter is determined adaptively using a '3 up, 1 down' staircase at steps of 1 degree; jitter values and element density were chosen based on data from multiple previous studies with patients and controls[8;25;58;149]. For the other exercise, orientational and positional jitter of contour elements are systematically added to increase task difficulty over time. In addition, several basic discriminations will be included to promote generalization, including those involving shapes (e.g., circles vs. ellipses) and numbers (e.g., '2' vs. '5'). For both exercises, the arrays of Gabor elements have a peak SF of 4 cycles/degree (to eliminate potential effects related to impairments in processing LSFs) and a Gaussian envelope SD of 7.3 arcmin. Like UE, CIT is presented as a game: Participants are provided with feedback about their response accuracy, points are given for each correct response, and positive feedback is provided when participants progress to the next difficulty level. This program also uses a staircase procedure to automatically adjust the current difficulty level based on recent performance so that it becomes more challenging as performance improves; this feature is designed to drive performance gains, and to continuously challenge participants while ensuring continued success. Each session consists of 8-12 training exercises that last approximately 2 minutes, for a total of ~25 min.

Figure 3: Examples of orientational jitter effects added to the egg-shaped contour from the JOVI task. This manipulation will also be used for circular and other CIT stimuli.



Active Computer-Based Control Treatment (ACCT): Our control condition is a cognitively challenging remediation program that does not specifically target perception. MyBrainSolutions (MBS; Brain Resource, Inc.) is a suite of online games and exercises targeting the domains of: 1) cognition (attention and memory); 2) emotion regulation (using imagery, and breathing rate–based biofeedback); and 3) goal setting and attainment (using individualized goals, reminders, feedback, and problem solving suggestions). It has been used extensively in workplace settings and via the internet to promote wellness and employee productivity[150;151]. Dr. Silverstein has previously used MBS clinically for cognitive remediation of patients with psychosis since 2010.

D.6 Assessments

Standardized protocols including written instructions and scripts will be used at both sites for each test. VEPs will be obtained using an EvokeDx device with the active electrode over the occipital lobe (Oz). EvokeDx has FDA 510(k) clearance for assessment of visual neural function. It generates the stimuli, records and analyzes the electrophysiological signals, and stores the data. Psychophysical CS will also be performed using the EvokeDx, which utilizes an organic LED display that enables accurate linearization of the voltage-to-luminance relationship through customized gamma correction so that precise specification of contrast can be achieved. These features, in addition to the carefully calibrated amplifiers contained in the system, afford high reliability/reproducibility of stimulus presentation and VEPs collected with multiple EvokeDx devices, which is critical when testing at multiple sites. The same stimulus parameters and testing conditions will be used at the Rutgers and NKI sites, and automated luminance calibration will be performed monthly at each site using the photometric device provided with the EvokeDx by Konan medical. Amplifier settings will be as follows: gain=20K, bandpass filter=0.5–100 Hz. It should also be noted that an earlier version of the system now provided by Konan equipment for assessing CS was successfully used in a prior multi-site trial[152]. The JOVI has also been successfully used in prior multi-site studies[8;58]. For all luminance and contrast calibrations of monitors used for PO assessments, and for UE and CIT training, a photometer will be used initially and annually, and Spyder 3 Elite software will be used weekly, with gamma set to 1.0 (i.e., linearized).

D.6.a Diagnostic and Clinical Assessments for R61 and R33

Diagnosis: The Structured Clinical Interview for DSM-5 (SCID-5)[153] and all available clinical information will be used to assign a consensus diagnosis.

Verbal IQ estimate: WRAT-III, reading subtest. The recognition and pronunciation of printed words is particularly resistant to the effects of deterioration associated with brain disease and is considered to be an estimate of premorbid IQ[154].

Symptoms: The Positive and Negative Syndrome Scale (PANSS) assesses the presence and severity of symptoms commonly found in schizophrenia; it is a semi-structured interview. There are a total of 30 items[155].

Suicidal Ideation and Behavior: The Columbia-Suicide Severity Rating Scale (C-SSRS)[156]. This will allow the investigators to determine if participants have suicidal ideation or behavior. This will be used at baseline and at the end of the intervention. Crisis service staff will be contacted at once if suicidal ideation or behavior is found.

Reliability assessment: For all clinical and cognitive assessment measures, research assistants from both sites will be trained by Dr. Judy Thompson at the beginning of the study, and through annual booster sessions. Training will follow our typical protocol and involve didactic training, group viewing and discussion of training videos for the interview measures and all individual items, and individual rating of additional videos until reliability criteria are achieved. These are: 1) for PANSS - intraclass correlations (ICC) of 0.80 or higher between each rater and our existing gold standard, and an overall group ICC of 0.80; and 2) for SCID and C-SSRS, kappas of 0.80 or higher between each rater and our gold standard and between each rater pair. Trainees will also observe more senior interviewers administering these clinical measures (for other ongoing studies), and then be observed administering these measures by Dr. Thompson or Dr. Nolan before they conduct assessments for this study on their own, to ensure appropriate skill level in working with patients.

Other: Smoking: Recent and typical tobacco use, and tobacco use disorder will be assessed with a smoking history and the Fagerström Test for Nicotine Dependence[157].

D.6.b Visual Targets

Contrast Sensitivity: CS functions will be obtained by presenting 5 horizontal sine-wave gratings at the following SFs: 0.5, 1, 4, 7, and 21 cycles per degree. Spatial frequency is the number of pairs or cycles of light and dark bars in 1 degree of visual angle, expressed as cycles/degree, with fewer pairs corresponding to lower SF. Each grating will be presented for 32 milliseconds. An up-and-down transformed response method will be used to obtain contrast thresholds with a criterion of 70.7% correct responses for each SF. The mean of 10 reversals will be used to obtain thresholds. Presentation of the different SF gratings will be interleaved in a random order. A spatial 2-alternative forced-choice procedure will be used. Gratings will be presented on either the right or left side of the screen, and the participant's task is to determine on which side the gratings appeared. Results will be plotted as CS (which is the reciprocal of threshold) vs. SF. Increased CS indicates better performance. Participants will be tested binocularly after being light-adapted to the background luminance of the display for 15 minutes. Test re-test reliability of this measure in a group of 15 controls and 31 patients (tested at the Butler lab at NKI) was an ICC of .76 at 0.5 cpd and .67 and 1 cpd. The test-retest reliability is weaker at the peak SF of 4 cpd (.25) and improves with higher SFs (ICC=.69 for 7 cpd and .57 for 21 cpd). The target variable is the average CS for the two LSFs (0.5 cpd and 1 cpd). We expect to see more of an effect of the remediation on LSF, but we will also assess CS at the other SFs, and specifically compare LSF

results to results at 7 cpd, which also has high reliability, to determine if effects are LSF-specific.

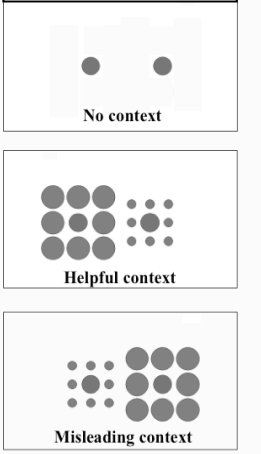
VEP Contrast Responses: This VEP technique was developed by Dr. Vance Zemon and colleagues[83] and has been used in studies of schizophrenia [1;27;28], autism[82], and glaucoma detection[152]. The response measures are quickly and easily obtained, requiring no behavioral response from the participant. Parameters to be used have been optimized in our studies of schizophrenia[1;84]. Steady-state VEPs are elicited to checkerboard patterns that are luminance-modulated sinusoidally (~12 Hz) with contrast increases in 7 discrete octave steps. Each step is ~1.6 sec in duration to yield an entire contrast-response function in less than 10 seconds (Fig. 4). The initial step has 0% depth of modulation (DOM) and this is followed by steps of 1, 2, 4, 8, 16, and 32% DOM. The set of steps is presented 10 times. In the contrast response function, as the DOM rises, the signal-to-noise ratio (SNR) increases from below a value of 1 to a value greater than 1. To obtain the contrast at which SNR=1 (i.e., the contrast threshold), linear interpolation will be done for the first two consecutive contrasts (DOMs) at which SNR is less than one and then greater than one [158]. Test-retest reliability of low-contrast VEP responses in schizophrenia (N=32) is good (ICC=0.70; Butler lab, unpublished data). In addition, the 95% confidence regions for the 10 runs per person show good reliability within an individual[83]. Dr. Butler has observed a within-subjects correlation of r=.41, (p<0.001; N=74) between indices from these VEP and psychophysical CS assessments.

Figure 4: VEP Contrast stimuli examples

Jittered Orientation Visual Integration (JOVI) Task[8;57;58]: Stimuli consist of oval contours, made up of 18 Gabor elements separated by 1° of visual angle, that either point left or right (Fig. 3). The contours are embedded in 298 distractor Gabors. Difficulty is manipulated by increasing the degree of orientational jitter of the Gabors making up the contour. Jitter levels will be 7°, 9°, 11°, 13°, and 15°, as in recent studies. Trials will be blocked according to the amount of orientational jitter, with 12 trials per block. Blocks will be presented in increasing order of difficulty, with each block presented 4 times for a total of 240 trials (4 repetitions x 5 blocks x 12 trials). In addition, each block will contain 4 catch trials in which a contour with no orientational jitter is presented without background elements, or is presented with background elements but with a line drawn along the contour. These trials are included to identify subjects who respond randomly or who are not paying adequate attention to the task. As in past studies, only subjects who obtain 75% or higher accuracy on these trials will be included in data analyses. Each stimulus is shown for 2 seconds, followed by a 1 second inter-stimulus interval. The participant presses a right or left arrow key to indicate the direction of the contour. There will be practice trials prior to the task, using the format in past studies. This task was optimized for use with participants with schizophrenia in a previous 5-site study[8], which found good test-retest reliability[145]. The dependent variable is number correct, corrected for guessing (to equate with subjects who respond when unsure of the correct answer, who will be right 50% of the time).

Ebbinghaus Illusion Task[108;159-161]. On each experimental trial, subjects are shown two target circles—one on the left of the screen and one on the right, and their task is to indicate which is larger. On half the trials, these circles are presented by themselves (i.e., the no-context condition). On the other half, the targets are surrounded by larger or smaller circles that either *facilitate* perceiving the true size difference of the target circles (*helpful condition*: the larger inner circle is surrounded by smaller circles, making it appear larger than its actual size, and the smaller inner circle is surrounded by larger circles, making it appear smaller than its actual size, and these effects combine to amplify the real size difference between the target circles; see Fig. 5, where the target circle on the right is 2% larger in each of the 3 panels), or *hinder* perceiving the true size difference (*misleading condition*: the larger inner circle is surrounded by larger circles, making it appear smaller than its actual size, and the smaller inner circle is surrounded by smaller circles, making it appear larger than its actual size). Stimuli remain on the screen until the subject responds or for 2 seconds (whichever occurs first). If a response is not recorded within 2 seconds, the trial is recorded as a guess (0.5 correct). Trials are separated by 200 msec. The two target circles always differ in actual size and this size difference varies in magnitude across trials. The order of trial types is randomized for each subject, as is the side on which the larger inner circle appears on each trial. In total, the task contains 192 trials, and typically takes 7 minutes. The key metric from this task is the difference between the helpful and misleading conditions, controlling for no-context performance, or: [(Helpful – no context) – (misleading – no context)]. Reduced grouping is reflected in scores closer to 0.

Figure 5. Examples of the 3 Ebbinghaus task conditions.



Visual Acuity: While not a target for this study, acuity will be assessed to determine whether it moderates the effects of UE and/or CIT[4;162]. We will use ETDRS charts, which are the "gold standard" for acuity testing[163].

D.6.c Other Outcome Measures for R33

MATRICS Consensus Cognitive Battery (MCCB): The MCCB assesses multiple cognitive domains: Speed of Processing, Attention/Vigilance, Working Memory (visual and verbal), Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition[164;165]. The ICC for the MCCB composite score was 0.9 in the initial validation study and has been similarly high in multisite clinical trials[165-168]. Outcomes are T-scores for each of the domains and the composite score[164;165] (number of scores=8). In addition, exploratory analyses will assess whether treatment effects on **visual** working memory and **visual** learning are stronger than for non-visual memory and learning subtests.

Minnesota Low-Vision Reading Test (MNREAD): This test assesses reading speed ability. The charts contain 19 English sentences (60 characters each) with print sizes ranging from 1.3 to -0.5 logMAR at a distance of 16 inches (0.41 meters). Participants are instructed to read each sentence aloud as quickly and as accurately as possible. Outcomes are reading acuity, speed, and critical print size (number of scores=3). The MNREAD is resistant to practice effects and has strong test-retest reliability[169].

Penn Emotion Recognition Test (ER-40): This computerized task comprises 40 photographs of actors expressing one of 4 basic emotions (happiness, sadness, anger, fear) or a neutral expression[170]. The outcome variable is total percent correct (number of scores=1). The ER-40 has been used widely including in multi-site studies (e.g.,[171]). The ER-40 demonstrates sound convergent and discriminant validity and good test-retest reliability in participants with schizophrenia [ICC=.75[172]].

University of California, San Diego Performance Based Skills Assessment, 2nd Edition (UPSA-2): This is a performance-based measure of the extent to which participants are capable of performing specific living skills such as household chores, communication, finance, transportation, and planning recreational activities[173]. We will use the total score, which ranges from 0 to 100 (number of scores=1). Test-retest reliability is 0.63-0.80 over periods of up to 36 months[174]. UPSA scores significantly predict residential independence[175;176].

D.7 Clinical Research Data Management: The Innovative Clinical Research Solutions (ICRS) group at NKI will conduct data management and data quality assurance for this study. The ICRS has been providing data management support for research studies for over 35 years, including for numerous schizophrenia studies funded by the NIMH. ICRS will develop all study Case Report Forms to standardize data collection. A comprehensive web-based data acquisition and management system, Acquire, will be programmed to process, edit and store all study data in a centralized database. ICRS personnel will implement rigorous data editing/validation using the Acquire system to ensure the highest possible level of data accuracy. ICRS personnel will review and monitor the completeness and accuracy of study data throughout the study, and deliver locked data sets to Dr. Gara at the end of both the R61 and R33 phases.

D.8 Combined Expertise of the Research Team: Drs. Silverstein and Butler have over 30 and 20 years of experience, respectively, in vision research in schizophrenia, expertise and publications in general and social cognition, track records of recruitment and assessment of individuals with schizophrenia for NIMH grants, and a track record of working and publishing together. Their respective foci on CS (Butler) and PO (Silverstein) provides particular synergy for this project. In addition, Dr. Silverstein has delivered cognitive remediation interventions for schizophrenia patients since 1994. Dr. Seitz is an expert in perceptual learning and in development of scientifically principled brain games such as UE. Dr. Gara has over 30 years of experience in designing and analyzing data from longitudinal efficacy and multi-site data. Drs. Nolan and Thompson are experienced in clinical trial project management and in cognitive and clinical assessment of individuals with schizophrenia. Dr. Robinson directs the NKI ICRS group, with 35+ years of experience in data management.

D.9 Governance and Organizational Structure for Conducting Study within Specified Timelines: Drs. Silverstein and Butler will be PIs of the overall grant and will be responsible for its implementation, progress, data collection, supervision, coordination, and fiscal management. Drs. Silverstein, Butler, and Seitz will have primary responsibility for the guidance and fiscal management of relevant aspects of the study at their respective institutions. Dr. Silverstein will lead weekly calls with key personnel to ensure that all timeline goals are met. He will also lead weekly data management calls with ICRS personnel and all research assistants.

D.10 Feasibility of the Approach: All of the elements are in place to carry out recruitment, remediation, and data analysis in a timely manner. Rutgers and NKI have on-site clinics that will be used for recruitment and treatment of patients, as in many past studies. Both sites have personnel trained in use of all measures. The UE program is fully developed and tested, and the CIT training program is currently in use in an initial study at Rutgers. Target and clinical outcome measures already exist. The ICRS data management group is in place.