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Pupillometer-based Neurofeedback Cognitive Training to Improve Processing Speed and Social Functioning in Individuals at Clinical High Risk for Psychosis

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Abstract

Objective—Among individuals at clinical high risk (CHR) for psychosis, processing speed (PS) has been related to social and role functioning regardless of conversion to schizophrenia. This information processing dysfunction is a gateway to broader behavioral deficits such as difficulty executing social behaviors. We examined the feasibility of improving information processing relevant to social situations in CHR, including its sustainability at 2-month follow-up, and its association with concurrent social function.

Methods—This was a double-blind RCT in which 62 CHR participants were randomized to Processing Speed Training (PST) or an active control matched for training format and the same dose and duration of treatment. PST is a tablet-based program that uses pupillometry-based neurofeedback to continually adjust training parameters for an optimal neurocognitive load and to

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improve visual scanning efficiency by inhibiting selection of non-essential targets and discriminating figure-ground details.

Results—The PST group showed faster motoric and non-motoric PS at post training and 2-month follow-up. At 2 month follow-up, the PST group reported better overall social adjustment. Changes in PS from baseline to 2 months were correlated with overall social adjustment and social avoidance in the entire sample.

Conclusions and Implications for Practice—This is the first study to test focal neurofeedback-based cognitive training for PS deficits in the putatively prodromal phase of schizophrenia to address associated social morbidity. Targeting PS appears to be a promising pathway to decreasing co-morbidity and mitigating a risk factor for psychosis.

Efforts in the last two decades to remedy cognitive deficits associated with psychosis have focused mainly on adults with established psychotic illness (Bell & Choi, 2008; Bowie, McGurk, Mausbach, Patterson, & Harvey, 2014; Kurtz, 2015; Twamley, Vella, Burton, Heaton, & Jeste, 2012; Wykes, Huddy, Cellard, McGurk, & Czobor, 2014), although more recent studies have also explored the efficacy of cognitive remediation for individuals in early course psychosis (Eack et al., 2009), adolescents with early onset psychosis (Wykes et al., 2007), and young adults experiencing their first psychotic episode (Nuechterlein et al., 2014). The premise behind targeting cognitive deficits early is that doing so may attenuate the functional decline following the initial psychotic break (McGorry, Killackey & Yung, 2007). More recently, researchers have begun to investigate whether these impairments predate the onset of psychosis (Kelleher et al., 2013), and whether they possess any predictive value in determining who transitions to full blown psychosis with the corresponding additional decline in psychosocial functioning (Lin et al., 2013).

Teenagers and young adults at Clinical High Risk (CHR) for psychosis have been found to demonstrate processing speed (PS) impairments that are evident as early as adolescence (Hawkins et al., 2008; Niendam et al., 2003) and emerge prior to the onset of psychotic symptoms (Eastvold, Heaton, & Cadenhead, 2007; Yung et al., 2007). While PS is no doubt an important cognitive domain regardless of the stage of psychosis, it seems to be of particular relevance at this prodromal stage as it may represent a specific risk marker for the social decline observed in this younger population (Carrión et al., 2011; Lencz et al., 2006). Several longitudinal studies in CHR have shown that impairments in PS as measured by the Wechsler Digit Symbol-Coding test differentiate participants with good and poor social outcomes in the ensuing months to years (Carrión et al., 2011; Niendam et al., 2003). Studies from the NIMH-funded North American Prodrome Longitudinal Study (NAPLS) consortium show that individuals at CHR who have better processing speed have a significantly lower likelihood of poor social functioning (Carrión et al., 2011). In one study, Carrion et al. (2013) followed 101 individuals at CHR for an average of 3 years. At the end of this period, he found that impaired social function and reduced PS at baseline predicted poor social function. Importantly, poor functional outcomes were not entirely dependent on the development of psychosis, as 40–45% of individuals who did not convert also exhibited reduced PS and poor social function years down the line.

The importance of understanding the mechanisms of and hence targeting the slowed PS that characterizes psychosis and its risk states is multifold. First, cognitive dysfunction is a hallmark of psychotic disorders that accounts for most of the functional morbidity, much more so than overt psychotic symptoms, many of which are amenable to pharmaceutical treatment (McGurk et al., 2015). Second, cognitive deficits characterize nearly all individuals at CHR, accounting for much of their functional impairment (Brewer et al., 2006; Cornblatt et al., 2015; Seidman et al., 2010). And third, while 20 to 25% of individuals identified as clinical high risk actually develop psychosis within one to two years (Fusar-Poli et al., 2012), the individuals who do not convert still exhibit marked social and functional impairments, which may be more closely related to cognitive deficits than to any attenuated psychotic symptoms present in CHR (Addington et al., 2011; Carrión et al., 2013). Hence, successfully remediating cognitive deficits in at-risk teens and young adults may not only influence eventual progression to psychosis, but also address current profound social morbidity and later functional outcome (Hooker et al., 2014; Niendam et al., 2007).

How might PS impairments impact social functioning? PS impairments are a hallmark of schizophrenia, and have long been shown to be associated with poor functional outcomes (Dickinson, Ramsey, & Gold, 2007; Wykes et al., 1999). As speeded tasks become more difficult, individuals with schizophrenia exhibit slower processing speed relative to healthy controls; at the same time, individuals with schizophrenia show greater activation on the same task in the brain region responsible for processing speed--the prefrontal cortex (PFC) (Callicott et al., 2003; Kurtz, Ragland, Moberg, & Gur, 2004). This greater activation is an indication that people with schizophrenia seem to allocate more neural resources than healthy controls when a speeded task becomes difficult, leading to an overextension of available cognitive resources for a single task (Manoach, 2003; Rypma et al., 2006). When a single task requires such an exorbitant amount of cognitive resources, there is a bottleneck in the timely processing of other simultaneous tasks, which then degrades the ability to handle more than one cognitive chore at a time (Nuechterlein, Dawson, & Green, 1994). One obvious cost is that working memory becomes significantly compromised (De Herdt et al., 2013). Research suggests that strengthening more direct connections between task-critical brain regions may correspond to *decreases* in prefrontal cortex task-related neural activity, or less drain on neural resources when performing a speeded task, in turn leading to greater working memory capacity (Manoach, 2003; Piskulic, Barbato, Liu, & Addington, 2015; Wykes et al., 1999).

In terms of functioning, this information processing dysfunction is a gateway to broader behavioral deficits such as difficulty executing social behaviors (Dickinson, Bellack, & Gold, 2007; Sánchez et al., 2009). When processing speed is degraded, the brain must adjust to simultaneous social cues by exerting maximum effort to detect only some cues in the environment, all the while missing out on other cues to understand the content and context of a social exchange (Ojeda et al., 2012). This gives the impression that the person is a “step behind” in a social situation, as slower encoding and retrieval of relevant information during social interactions may make it difficult to track or follow the ebb and flow of conversations. Indeed, it has been suggested that social skill deficits so common in this population are often characterized by impairment in one specific skill component, meshing, or the ability to appropriately take turns in a conversation without either cutting the other person off or

taking too long to respond (Mueser, Bellack, Douglas & Morrison, 1991). Difficulties in social interactions can lead individuals to avoid social situations altogether and feel undue stress when encountering people, which can then reinforce the cycle of avoidance and social isolation. Taken together, this suggests that PS may be a pertinent mechanism to target for improving social functioning in individuals at CHR (Kelleher et al., 2013).

Given the presence of PS impairments in individuals at CHR and the relationship to functional outcome, it has been suggested that providing cognitive remediation prior to the first psychotic episode during a putative prodromal stage may have some value in reducing the risk of psychosis onset (Fisher, Hardy, Schlosser, & Vinogradov, 2013; Kline, Schiffman, Choi, Laitner, & Rogove, 2014). There are only a few published studies of CR in psychosis risk states, most of which are very small pilot trials that simultaneously target a broad range of cognitive domains. In a recently published pilot study of cognitive training in individuals at CHR, Hooker et al. (2014) confirmed the presence of significant PS impairments in individuals at CHR (relative to healthy controls), and also reported that broad-based training using online programs such as PositScience and Lumosity led to significant improvements on a processing speed index. While great caution must be used in interpreting results of uncontrolled studies, these results do suggest that PS may be malleable in CHR. In the only randomized controlled trial of CR in this population to date, Piskulic et al. (2015) randomized 32 individuals at CHR to either the online BrainFitness auditory cognitive training or to an active control condition consisting of commercially available computer games. While there was a notable trend for within-group improvement in PS and a significant improvement in social functioning in the BrainFitness group, the study was deemed underpowered due to an unexpectedly high attrition rate, with 28% of participants randomized to the BrainFitness group discontinuing from the intervention. In reflecting on the feasibility of cognitive training in CHR, the authors noted that many individuals who dropped out did so because they lost interest in the training program, which highlights the need for novel training programs that will be highly engaging for individuals at CHR.

Given the putative role of PS in successful real-time social interactions and long-term social functioning outcomes, we sought to develop and evaluate the impact of PS-specific training on social functioning in individuals at CHR. We developed “refined behavioral tasks” that experimentally isolate, control and/or exaggerate processing speed subprocesses in order to target processing speed deficits to address social morbidity in teens and young adults at CHR and improve functional outcome. We specifically designed the training to promote sustained engagement in the exercises by enhancing standard behaviorally-based task progression with neurofeedback about cognitive load. The questions we asked were: (a) Is it possible to enhance PS in individuals at CHR using targeted processing speed training that incorporates neurofeedback? (b) Given the relationship between PS and social functioning in CHR, would improving PS lead to improvements in social functioning?

Methods

Participants

Sixty-two CHR individuals, ages 16 to 24, were recruited from the Child and Adolescents Early Psychosis Program at The Institute of Living at Hartford Hospital (n=18) and the

Center of Prevention and Evaluation (COPE)(n=44), a prodromal clinical research program at the New York State Psychiatric Institute at Columbia University Medical Center. Sixty-two participants were consented and completed baseline testing, 58 participants completed the intervention and end of treatment (2-month) post assessment, and 56 participants completed the 2-month post treatment follow-up.

The CHR designation was made on the basis of the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 2003), which was administered by trained raters with doctoral degrees. Participants fulfilled criteria for at least 1 of 3 prodromal categories: 1) Attenuated Positive Symptoms syndrome; 2) Brief Intermittent Psychotic syndrome and/or 3). Genetic Risk and Deterioration. Attenuated Positive Symptom Syndrome (APS) is characterized by subthreshold psychosis that has begun or worsened within the past year, which cannot be accounted for by another Axis I disorder, and occurs in the absence of any prior threshold psychotic symptoms. Subthreshold symptoms include compelling unusual thought content with insight maintained (attenuated delusions), perceptual disturbances (attenuated hallucinations), and conceptual disorganization consistent with subtle thought disorder. Brief Intermittent Psychotic Symptom syndrome (BIPS) comprises threshold psychotic symptoms occurring approximately once per month, whereas Genetic Risk and Deterioration (GRD) is comprised of a significant drop in function in the context of having a first-degree relative with psychosis or concurrent schizotypal symptoms. Nearly all participants fulfilled criteria for the prodromal category of attenuated positive symptoms syndrome, with a quarter additionally meeting criteria for the prodromal syndrome of genetic risk and recent deterioration. By contrast, brief intermittent psychosis syndrome was rare.

Inclusion criteria were: (a) fulfilled criteria for a prodromal syndrome using the SIPS/SOPS, (b) English-speaking, (c) age range 16–30 (this range comprises the main period of risk for psychosis), (d), processing speed at least 0.5 SD below the norm, as indexed by baseline performance on WAIS-III Digit Symbol Coding of 8 or below.

Exclusion criteria were: (a) prior diagnosis of an Axis I psychotic disorder, (b) major medical or neurological disorder, (c) WAIS IQ < 70, (d) attenuated positive symptoms occuring solely in the context of substance use or withdrawal, (e) risk for suicide or violence not commensurate with outpatient treatment, and (f) substance abuse diagnosis within past 3 months.

Participants at both sites were not routinely prescribed antipsychotics, and the treatment algorithm was: (a) initiation of (typically weekly) psychotherapy (individual or group); (b) targeted pharmacological treatment for anxiety and depression; (c) use of antipsychotics only if attenuated psychotic symptoms occur in the context of dangerousness (suicide or violence) or significant disability. The most commonly prescribed medications were antidepressants, typically SSRI’s, consistent with other CHR cohorts as depressive and anxiety symptoms are common. Participants continued with their regular treatment while participating in the study.

For participants under 18, written informed consent was obtained from a parent and assent obtained from the adolescent. For participants 18 and older, written consent was obtained from the participants. The data set used for this ongoing study was collected from April 2012 to August 2015, and the studies approved by local institutional review boards.

Procedures

This was a double-blind randomized clinical trial where participants were randomized 1:1 to 1) Processing Speed Training (PST), or 2) Active Control Group (ACG). The active control group was matched for the same dose and duration of treatment (exposure to computers and clinician contact). During each treatment session, participants worked in groups of 2 or 3 on tablets for approximately 30 hours over the course of 2 months, or about 3.5–4.0 hours per week, usually done over the course of 2 days when participants at both sites would be at the hospital for their regimen of treatments. If the participant was just beginning a set of exercises close to the 30 hour mark, the person was allowed to go over 30 hours in order to finish the set.

Assessments of cognition, symptoms, and function were administered at baseline, immediately post-treatment (2 months) and at 2-month follow-up (4 months after baseline). All assessments were conducted by a graduate-level research assistant blind to randomization status, while the intervention was conducted by a different graduate-level research assistant. The participants and research assistant conducting assessments completed a best guess rating form at 2 month follow-up to assess adequacy of the blind (adequate blind defined as rate of correct guessing <50%). As explained below, the format and structure of the PST were tailored into tablet-style games similar to the active control exercises.

Interventions

Processing speed training (PST)—PST is a program developed by JC and initially piloted in healthy controls and individuals with schizophrenia as a method to improve visual-motor and processing abilities (Choi, Corcoran, Dixon, Fiszdon, & Javitt, 2014). PST entails massed drill and practice on tasks intended to exercise relatively isolated speeded response skills with the aim of strengthening or resuscitating neuroanatomical connections linked to processing speed. While compensatory strategies to ‘work around’ cognitive deficits are often used in individuals with chronic psychosis (Twamley et al., 2012; Velligan et al., 2015), the restorative approach chosen here is more relevant to any cognitive training program for CHR. Restorative models are based on theories and principles of neural plasticity, with the aim of strengthening or resuscitating neuroanatomical connections linked to core neuropsychological abilities. Since the purpose of cognitive training for individuals at CHR is preemptive—to recover and preserve the essential neurocognitive skills the individual will need to be socially active and capable rather than circumvent the impaired deficits—the restoration of once compromised neural processes is the more appropriate approach (Hooker et al., 2014).

The training is delivered on Android-based tablets and consists of a situated regimen of drill and practice tasks centered on pupillometric cognitive load, working memory theory, and

motivational psychology. It is the first cognitive training program to include pupillometric neurofeedback techniques to adjust training parameters in real-time.

Pupillometric feedback: Pupil dilation is a barometer of sympathetic nervous system load, and dilation increases with sympathetic activity (Granholm & Steinhauer, 2004). Pupil dilation reveals underlying neurophysiologic engagement and serves as a precursor to disengagement on a behavioral task (Granholm, Verney, Perivoliotis, & Miura, 2007). Thus, we can determine a "sweet spot" for difficulty, in terms of whether a training task is not stimulating enough (pupils constricted), ideally stimulating, or if there is too much information and the task has become frustrating (pupils dilated). Pupillometry allowed us to optimize the training exercises by providing immediate biofeedback to the training software that then automatically adjusted training task parameters and levels for a personalized and efficient training program.

Pupillometry can provide a broad indication of how much a person is actively involved in the exercise at that very moment, even before performance is registered as a correct or incorrect response. This is important for several reasons. If using only performance feedback and the person is making numerous errors, the training may run the risk of the person disengaging from the exercises. Obtaining feedback prior to the person making a performance response allows the program to immediately and continually titrate the difficulty level so incorrect responses are minimized. While we do not use the term "errorless learning," the use of neurofeedback fits the theory of how errorless learning techniques can be applied to enhance self-efficacy for challenging tasks (Kern, Liberman, Kopelowicz, Mintz, & Green, 2014). Furthermore, pupillometry takes adaptation a step further—a person can do well on a task (and advance to the next difficulty level) without exerting much effort, but the person can also do well on a task (and advance) while exerting maximum effort, with any further increases in difficulty not resulting in performance increases and only causing significant strain on cognitive resources. In this way, pupillometry may provide an index of when saturation has reached a maximum point and further task increases should be at least temporarily halted, versus just looking at correct or incorrect responses, which would suggest that task difficulty should continue to be increased, even in cases when doing so may lead to cognitive overload.

At the beginning of each training session, participants were fitted with head-mounted Applied Science Lab 6000 series H6 pupillometers, and performed a brief working memory calibration task to determine each person's optimal task difficulty-based pupil dilation, which then allowed us to determine whether during the remainder of the training session, cognitive load was too high (pupil dilation above optimal level) or too low (pupil restriction below optimal level). Optimal pupil dilation was calibrated at each session because average pupil size and dilation may vary day-to-day depending on a host of factors outside experimental controls (e.g. consumption and quantity of caffeinated beverages before the test session, general variations in sympathetic arousal due to medications, etc). Participants were administered the working memory task at a range of difficulty levels, and Applied Science Laboratory EYENAL software calculated optimal pupil dilation based on highest detection accuracy. As an example, a person may have his or her highest detection accuracy with task difficulty set at a certain level and a corresponding pupil diameter of 3.90mm, with

an increase in task difficulty prompting dilation to 4.05mm and a drastic drop in detection accuracy. Conversely, decrease in task difficulty may lead to constriction of pupil size to 3.80mm and a corresponding decrease in task accuracy, as the task has now become too easy and the individual is bored and no longer paying full attention. In such a case, the person's optimal pupil dilation for the remainder of the session would be set at dilation associated with highest detection accuracy, 3.90 mm, and deviation from that dilation level would be used to continually and immediately titrate task difficulty throughout the session. Adjustments in task difficulty based on optimal pupil size during training could occur anywhere from 29 to 188 times, depending on how the participant responded to gradual increases in difficulty. For example, as the exercise became more difficult, if the participant's pupil size (cognitive load) did not change, no adjustments were made, and task difficulty slowly increased. At the point pupil size began increasing though, task difficulty would be immediately reduced until optimal pupil dilation was again achieved. Similarly, should pupil size decrease below optimal level at any point during the training, task difficulty would immediately be increased until pupil size returned to its optimal diameter.

Training task parameters: Adjusting training task parameters is grounded in working memory system theories developed by the late Edward E. Smith (Smith & Jonides, 1999; Smith & Grossman, 2008), who studied how healthy individuals make speeded responses when comparing stimuli, which is an essential underpinning aspect of most processing speed tasks. Aspects of training that were parametrically adjusted at each difficulty level were the speed needed to respond to comparing stimuli, visual/auditory degradation of the target stimuli, the degree of distractors on the screen, and graduated figure-ground discrimination.

Intrinsic motivation for learning: The training tasks incorporate enjoyable, game-like fantasy contexts with personalized features and choices from a menu of activities. These fantasy contexts (e.g. zombies, rock climbing) engage adolescents and young adults, and have been shown to instill intrinsic motivation for cognitive training in both non-psychiatric samples and in patients with schizophrenia (Choi & Medalia, 2010). This personalized fantasy context, along with pupillometry, is paramount to reducing user burden and maximizing adherence to ensure an adequate dose of cognitive intervention while engaging natural neurobiological reward and motivational systems. Importantly, enhancing motivation for the cognitive tasks tends to increase the likelihood that patients will complete the tasks within a specified therapeutic time period rather than become disengaged and at risk of attrition and/or insufficient treatment intensity. This is especially relevant to developing treatments in CHR since experiences of external reward and reinforcement seem to become diminished as psychosis progresses, resulting in an inability to represent and understand the inherent value of training tasks and the positive feedback provided to guide performance (Strauss, Waltz, & Gold, 2014). Therefore, it is pragmatic and empirically prudent to focus efforts on targeting and increasing the patient's innate enjoyment and the value they place on the training itself rather than relying on platforms of external reward. This also helped mask the training from the active control games and created better equipoise between research arms.

Active Control Group (ACG)—The ACG provided exposure to common tablet games in order to control for dose and duration of contact with tablets and research staff, and to gauge the impact on cognition and function of simple non-specific mental stimulation and interpersonal contact. Tablet games included commercially available arcade-style Android apps from Google Play that all required speed for players to achieve their objectives. The ACG had a similar group format, with rolling admissions, with facilitators available to assist participants in helping to load apps, explain how each game is played and/or provide instructions and answer questions as needed. To enhance blinding, participants in this group also wore the head-mounted pupillometer, though it was not turned on.

Instruments

Our assessments included measures that have previously been used in CHR research (Cressman et al., 2015). The primary outcome measure was processing speed as gauged by the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Symbol-Coding subtest (Wechsler, 1999). The Minnesota Clerical Test (MCT; Andrew, Paterson, & Longstaff, 1979) was also used to tap into processing speed and provide a secondary measure of clerical processing and accuracy without the reliance on motorical capacity needed for the Symbol-Coding subtest of the WAIS-III. These tertiary cognitive measures were included at baseline to gauge general attention and working memory capacity. Sustained attention/vigilance was measured using the Continuous Performance Test-Identical Pairs (CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988), while working memory was calculated from the WAIS-III Working Memory Index (WMI; Wechsler, 1999).

The primary social functioning measure was the Social Adjustment Scale-Self Report (SAS-SR), which is commonly used to document social adjustment in children, adolescents, and teenagers (Weissman & Bothwell, 1976). The Social Anxiety Scale for Adolescents (SAS-A) was used as a secondary measure of social function specific to the fear of negative evaluation by peers, social avoidance, and social response to new situations (La Greca & Stone, 1993). The SIPS/SOPS (Miller et al., 2003) were used to assess the severity of attenuated positive, negative, disorganized and general symptoms at baseline, while the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) was used to assess depression severity throughout the study.

Data analyses

We applied an intent-to-treat analysis to our study, and therefore included data from all 62 participants randomized to the PST or active control intervention. First, we confirmed that the distribution of all dependent measures conformed to assumptions underlying the use of parametric statistical procedures. To ensure that the two groups were similar in clinical characteristics and on baseline tests scores, scores were compared across the two conditions via paired t-tests. Paired t-tests were also used to compare the two conditions on treatment dosage (number of training hours) and treatment intensity (number of training hours per week). Attrition rate was also tabulated as the percentage of participants who completed the treatment phase, specifically the PST. We then computed chi-square to test if the best

guesses about study assignment by RAs and study participants (whether assignment was to experimental or active control) was significantly different than chance (50%).

To assess the direct impact of the interventions on processing speed and social functioning, we performed a repeated measures multivariate analysis of variance (RM-MANOVA), between conditions (PST vs. active control), with Coding subtest scaled score, MCT t-score, and raw scores on the SAS-SR and SAS-A as the dependent variables, and baseline, post, and 2-month follow-up as the three time points. As a post-hoc, we then performed an analysis of covariance (ANCOVA) using baseline scores as covariates, comparing the two groups at post and follow-up. This allowed for greater control for subtle but potentially influential baseline differences in performance that may not be detected in comparing seemingly similar baseline scores. Cohen's effect-sizes were computed for between-group effects when evident for each of the key outcome measures at each time point.

To examine the relationship between potential baseline to end of treatment changes in PS and co-occurring changes in social functioning, we computed and then correlated residualized change scores for our primary and secondary measures of PS (Coding, MCT), along with our measures of social functioning (SAS-SR, SAS-A). Residualized change scores take the baseline levels of a variable into account in order to provide a more sensitive measure of change, since the degree of change can be influenced by baseline level (Tucker et al., 1966).

Given that we tried to capitalize on the findings and conducted a RM-MANOVA and ANCOVA, and then performed two sets of correlations, we applied Bonferroni correction to adjust for multiple comparisons. All statistical tests were two-tailed and the overall alpha was set at .05. Alpha for the initial processing speed calculations were set at .04 while subsequent calculations for social function were set at a more conservative .01.

Results

No significant differences were evident between PST and ACG on demographic or clinical variables or any of the baseline measures (Table 1). There was no significant difference in the dosage of training between groups as participants in PST completed 30.32 (SD=0.92) hours versus 30.11 (SD=0.84) hours for ACG (t = 0.94, p=0.353). As expected, given the structured nature of the programs at both sites (participants were coming in for a regimen of treatments, usually 2 days per week), treatment intensity between groups was also not significantly different (PST, 3.37 hours per week, SD=1.03; ACG, 3.52 hours per week, SD=0.94; t=0.60, p=0.558). Of the 62 CHR participants who were consented and completed baseline testing, 58 completed the 2-month intervention (overall attrition 6%). In the PST arm itself, 30 individuals started the training and 27 completed it—an attrition rate of 10% for the training. Correct best guess for the assigned group by participants and post-assessment RA ratings was 52.7% (chi squared=1.15, p=0.28), thus not significantly different from the expected 50%, with the double blind remaining intact.

RM-MANOVA indicated a significant multivariate time by condition interaction (F[5, 51]=5.21, p=.037). There was a significant effect of time for both the Coding subtest, (F[5,

51]=6.02, p=.030), and the MCT (F[5, 51]=5.05, p=.042), with scores improving over time. For social functioning, the effect of time was not significant for overall social adjustment on the SAS-SR (F[5, 51]=1.05, p=.284) nor for any of the SAS-A subscales (F[5, 51]=1.11–2.03, p=.092–.171). There was a significant time by condition interaction for the Coding subtest (F[5, 51]=7.38, p=.012), MCT (F[5, 51]=6.90, p=.019), and overall social adjustment on the SAS-SR (F[5, 51]=4.87, p=.039).

Post-hoc ANCOVAs comparing processing speed in the two conditions at post training and 2-month follow-up (covarying for baseline), revealed a significant group difference on the Coding subtest both at post (F[3,55]=6.23, p=.039), as well as follow-up (F[5,51]=7.71, p=.019), with PST outperforming the active control. The same pattern emerged on the MCT, as the PST group performed much better at post (F[3,55]=4.22, p=.024) and follow-up (F[5,51]=4.03, p=.031) compared to active control. For social functioning, the PST had higher overall social adjustment at follow-up on the SAS-SR (F[5,51]=8.58, p=.009). There were medium to large between-group effect sizes noted on Coding, MCT, and the SAS-SR (Table 2).

When examining residualized changes scores from baseline to follow-up in the entire sample, significant correlations were noted between Coding and SAS-SR (r=0.25, p=.030) and Coding and SAS-A Avoidance/Distress for New Social Situations (r=0.23, p=.042). Hence, improvement on the Coding subtest was related to better overall social adjustment and less avoidance or feelings of distress for engaging in new social situations. There were no significant correlations between changes in MCT and measures of social functioning (p’s>.11).

Conclusions

In this study, we found that neurofeedback-based PST improved PS and social functioning in a cohort of individuals at risk for psychosis. While both the PST and active control showed some immediate post-treatment improvements on motorical and non-motorical PS, these improvements were maintained for 2 months after the intervention ended only in the PST condition. While there were no group differences in social adjustment or social anxiety immediately post-training, individuals in the PST condition reported significantly higher overall social adjustment (SAS-SR) at two-month follow-up. Attrition in the PST condition was only 10% at end of the intervention, suggesting that we were able to maintain participants’ engagement in the training. Moreover, in the whole sample, improvement on the primary, motorically-based measure of processing speed (Coding subtest) was related to improvements in both overall social adjustment and social anxiety.

The nature of self-reporting social adjustment may have been a factor in the delay following the end of treatment and an effect in social function in the PST condition. As PS improved by the end of treatment, patients may have become more open to social encounters, which gradually led to more social interactions and a better feeling of social engagement and adjustment at 2-month follow-up. This robust relationship between PS and social adjustment was seen in the sample as a whole, as improvements in PS were associated with improvements in social functioning regardless of the condition.

As mentioned, attrition for PST was 10% compared to 28% in the only other randomized controlled trial of cognitive remediation in individuals at CHR (Piskulic et al., 2015), suggesting that the neurofeedback-based PS approach may be useful in maintaining adherence to cognitive remediation. Pupillometry may have some utility as a neurobiological gauge of task engagement with implications for reducing errors and negative experiences in cognitive remediation therapies. Pupillometry may provide a broad indication of how much a person is actively involved in the exercise at that very moment, even before performance is registered as a correct or incorrect response. This is important because if only performance feedback is used, poor performance may lead to lower-adjusted training levels that are too easy for the person and lead to disengagement from the exercises. Hence, pupillometry may provide the additional “fine tuning” of difficulty levels to maximally engage individuals undergoing cognitive training.

To the best of our knowledge, this is the first study to show that there is a way to engage this younger population in cognitive remediation and produce lasting PS improvements through focal, cognitive training that includes neurofeedback. Given the relationship between PS and social functioning and the risk for psychosis in individuals at CHR, improving PS may change the trajectory of functional decline in this population and possibly mitigate the risk for psychosis.

The current study has several limitations. First, our design was such that the active ingredient in the treatment could not be identified, nor the mechanisms by which it had its effect. Specifically, novel components of the intervention included both a specific targeted PS training as well as neurofeedback to titrate training task difficulty. An ideal study would have included another arm to test the PS training without pupillometry to determine whether it was the PS training itself, or the inclusion of pupillometry-based neurofeedback that resulted in enhanced outcomes. Without knowing to what extent the inclusion of pupillometry-based feedback contributed to the training’s efficacy, at this stage, we can only cautiously surmise that the neurofeedback-based PS training appears to improve PS and social function compared to active control. We also do not know the specificity of using PS targeted approach, and whether a top-down approach, such as training that focuses on overall executive ability rather than solely focusing on PS, could have been equally effective in improving PS along with social function.

Second, the use of pupillometry in cognitive training is experimental. While there are EEG-based neurofeedback attention training programs that have been tested in children and college students with ADHD (Arns et al., 2009), this manuscript reports the very first study to pilot pupillometry-based neurofeedback training in any population so we cannot compare our findings with other studies in order to try to draw firmer conclusions. The intended innovation reported here should be balanced with cautious interpretation of what pupillometry adds to training efficacy.

Third, our social assessments were comprised of self-report and questionnaires, although studies have shown that in individuals at CHR, these measures have neural correlates, specifically anhedonia and reduced metabolism in nodes of the reward network (Cressman et al., 2015). While participants were blind to group assignment, given which subjective report

was unlikely to be influenced by the perception of being in the treatment condition, there is disagreement as to whether self-report or performance-based or observational measures might be more appropriate for studying functional outcome in psychosis (Elliot & Fiszdon, 2014; Holshausen, Bowie, Mausbach, Patterson, & Harvey, 2014).

Finally, PS is more complex than the unitary construct suggested here. While we focused on cognitive load and its subcomponents of working memory systems and speeded response, Cella and Wykes (2013) found that age and symptom severity made a difference in how PS impacted behaviors in social situations in schizophrenia, while illness duration was related to processing information quickly and accurately. They recommended that distinguishing between how information is processed accurately and how social behavior is executed might hone our understanding of processing speed impairment in psychosis.

In the current manuscript, we present a randomized clinical trial focused on PS remediation in individuals at CHR, demonstrating that PS can be improved in a sustained fashion, and that these improvements are associated with improvements in social function. As both slowed PS and social impairment are known risk factors for psychosis onset in individuals at CHR, we are continuing to prospectively follow this treatment cohort to determine rates of conversion to psychosis in the treatment versus active control group, and also to compare this to general conversion rates in CHR individuals who did not participate in this study. We also continue to examine if and how social avoidance may play a prominent role in the genesis of negative symptoms, as negative symptoms are robustly related to poor social functioning in prodrome as well as chronic psychosis (Piskulic et al., 2012). In these analyses of prediction of conversion, we will also examine whether risk reduction is modified by variance in processing speed and function over time.

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Table 1

Baseline characteristics (N=62)

Baseline character	Processing Speed Training (n=30) Mean (SD)	Active Control (n=32) Mean (SD)	t-test or chi square	P value
Age	18.17 (3.81)	18.53 (3.72)	.37	.71
Gender (female)	48%	50%	.00	.99
Education (years)	15.29 (1.94)	15.81 (2.03)	1.02	.30
Ethnicity (%)				
Caucasian	54	48	.07	.80
Hispanic	30	39	.13	.72
African American	16	13	.01	.92
Premorbid IQ Estimate				
WRAT3 Reading (standard score)	108.01 (6.15)	107.43 (4.52)	.42	.67
WAIS-R Vocabulary (scaled score)	11.43 (2.05)	11.20 (1.73)	.47	.63
Antipsychotic use (%)	25%	24%	.02	.89
Antidepressant use (%)	36%	33%	.01	.93
Depression (BDI-II)	13.42 (5.22)	12.77 (4.98)	.50	.62
SIPS/SOPS positive symptoms	14.92 (3.80)	13.28 (4.32)	1.58	.12
SIPS/SOPS negative symptoms	12.48 (5.32)	11.97 (3.27)	.45	.65
Working Memory Index	92.89 (13.54)	91.23 (11.97)	.51	.61
Processing speed				
Digit Symbol Coding (Scaled Score)	7.23 (0.68)	7.31 (0.43)	.55	.58
Clerical test (T score)	34.15 (7.23)	35.27 (6.40)	.65	.52

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Table 2

Performance scores and effect sizes in processing speed, social functioning, and depression

	Processing Speed Training (n=30) Mean (SD)	Active Control (n=32) Mean (SD)	ANCOVA Significance (p-value)	Effect Size
Processing speed				
Primary				
Digit Symbol Coding (SS)				
Baseline	7.23 (0.68)	7.31 (0.43)	--	--
Post (2mo)	9.53 (0.84) *	8.84 (1.72)	.03	.50
Follow-up (4mo)	9.01 (1.47) *	7.32 (2.44)	.01	.84
Secondary				
Minnesota Clerical Test (T score)				
Baseline	34.15 (7.23)	35.27 (6.40)	--	--
Post (2mo)	47.27 (6.31) *	41.63 (8.74)	.02	.73
Follow-up (4mo)	44.94 (9.36) *	38.69 (8.89)	.03	.68
Social Functioning				
Primary				
Overall Social Maladjustment (SAS-SR)				
Baseline	2.31 (0.34)	2.43 (0.40)	--	--
Post (2mo)	2.14 (0.28)	2.27 (0.52)	.13	--
Follow-up (4mo)	1.93 (0.32) *	2.57 (0.81)	.01	1.04
Secondary				
Fear of Negative Evaluation (SAS-A)				
Baseline	19.03 (10.31)	17.64 (12.92)	--	--
Post (2mo)	18.72 (8.55)	17.37 (11.27)	.33	--
Follow-up (4mo)	19.43 (11.42)	18.78 (11.73)	.29	--
Avoidance/Distress New Situations (SAS-A)				
Baseline	15.37 (6.85)	16.83 (7.97)	--	--
Post (2mo)	13.76 (8.37)	14.52 (5.78)	.29	--
Follow-up (4mo)	12.18 (5.35)	15.73 (8.24)	.03	--
Social Avoidance & Distress (SAS-A)				

	Processing Speed Training (n=30) Mean (SD)	Active Control (n=32) Mean (SD)	ANCOVA Significance (p-value)	Effect Size
Baseline	9.11 (3.97)	8.86 (4.78)	--	--
Post (2mo)	8.86 (2.73)	7.22 (3.51)	.07	--
Follow-up (4mo)	8.87 (4.03)	8.41 (4.68)	.32	--
Depression (BDI-II)				
Baseline	13.42 (5.22)	12.77 (4.98)	--	--
Post (2mo)	14.28 (3.72)	13.75 (4.18)	.32	--
Follow-up (4mo)	14.93 (5.26)	13.94 (5.63)	.25	--

* ANCOVA post-hoc significant $p < .04$