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TITLE: A Randomized Clinical Trial of Cognitive Enhancement Therapy for Adults with Autism Spectrum Disorders

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14. ABSTRACT
This project is focused on conducting the first randomized-controlled trial of Cognitive Enhancement Therapy (CET) in 54 verbal adults with autism spectrum disorders and assessing the efficacy of this approach in comparison to an active Enriched Supportive Therapy (EST) intervention. Major findings to date have demonstrated considerable and broad cognitive impairments in adults actively enrolled in the trial (n=24) as well as promising initial results on the effects of CET. Despite high levels of intelligence (average IQ = 112), this sample is performing at the 36th percentile on overall neurocognitive function, indicating a clear need for cognitive rehabilitation. Preliminary analyses of interim 9-month treatment effects among the initial cohort of participants (n=12) in this clinical trial has suggested a strong advantage of CET for improving social cognition (d>.77) and adaptive function (d>1.14), and a medium advantage of CET for improving processing speed (d>.40), compared to those receiving the EST control condition. These findings suggest both the need and potential for CET to result in a significant treatment advance for underserved adults with autism, and this project holds the potential to considerably improver the lives of the many individuals and families living with these conditions.

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1. INTRODUCTION

This project constitutes the first clinical trial of a novel cognitive rehabilitation program, Cognitive Enhancement Therapy (CET), previously shown to be effective in improving adaptive function and work skills in patients with schizophrenia (Hogarty et al., 2004; Eack et al., 2009; Eack, Hogarty, Greenwald, Hogarty, & Keshavan, 2011), in a group of adults with autism spectrum disorders (ASD). Currently, there are few interventions for adults with ASD (Fitzpatrick, Minshew, & Eack, in press), and none that are effective at remediating the broad range of information processing impairments characteristic of ASD. This project will randomize a total of 54 adults with ASD to CET (*n* = 27) or an Enriched Supportive Therapy (EST) control group (*n* = 27) and treat them for 18 months to examine the relative efficacy of CET compared to EST for remediating the core social and non-social information processing deficits that limit adaptive function and quality of life in adults with ASD. Specific aims of this project are to: (1) estimate the effects of CET and EST on cognition and behavior; (2) examine the durability of CET and EST effects on cognition and behavior after treatment completion; and (3) explore the effects of CET and EST on brain structure, function, and connectivity.

2. BODY

2.1. Overview of Study Infrastructure Development

This DoD-funded clinical trial is the first rigorous controlled study of CET and includes a comparison to an active EST intervention in adults with autism. The considerable progress that we have made already in this study is due to (1) the infrastructure support provided by the University of Pittsburgh Autism Center of Excellence (ACE) funded by the NICHD until 7/31/12; (2) the completed uncontrolled pilot trial of CET in 14 adults with ASD supported by the NIMH; and (3) early support provided by Autism Speaks to begin components of this trial while our application was being considered for funding by the DoD. **Table 1** outlines the progression of these infrastructure developments to demonstrate how they have led to the early success of this project.

Table 1. Infrastructure and Resources for Conducting a First Clinical Trial of CET in Adults with Autism

Activity/Grant	ACE	NIMH R21	Autism Speaks	NIMH R33	**DoD Trial**
Initial Funding Date	August, 2007	May, 2009	August, 2010	May, 2011	Sept., 2011
Infrastructure Setup					
Recruitment	X	-	-	-	-
Diagnostic	X	-	-	-	-
Clinical Trial	X	-	X	X	X
Cognitive Enhancement Therapy					
Uncontrolled Pilot Cohort (N = 14)	X	X	-	-	-
Trial Cohort #1 (N = 6)	X	-	X	-	-
Trial Cohort #2 (N = 6)	X	-	X	X	X
Remaining Cohorts (N = 15)	?	-	-	X	X
Enriched Supportive Therapy					
Trial Cohort #1 (N = 6)	X	-	X	-	-
Trial Cohort #2 (N = 6)	X	-	X	X	X
Remaining Cohorts (N = 15)	?	-	-	X	X

Initial recruitment, diagnostic, and clinical trial infrastructure development was completely supported by the ACE. In August, 2010 Autism Speaks awarded us with a small grant to begin the development of a randomized-controlled trial of CET in verbal adults with autism based on promising preliminary findings from our uncontrolled trial of 14 adults that was funded by the NIMH. This early support provided by Autism Speaks allowed us to spend the first 6 months of the project developing the clinical infrastructure needed to conduct a randomized trial, including hiring and training our first full-time therapist, although no support for neuroimaging was provided. Importantly, after finalizing the development of this infrastructure we were able to enroll and randomize our first 12 of the many participants that the ACE had placed on a waiting list for this trial, which enabled this DoD-funded project to meet and exceed its aggressive recruitment and randomization schedule.

Currently the DoD, Autism Speaks, the NIMH, and the ACE all provide needed resources for this first controlled trial of CET. DoD provides the foundation of support for all treatment, neuroimaging, assessment, and follow-up activities. Autism Speaks provided support for infrastructure development and early enrollment,

and continues to provide some support for treatment activities. NIMH adds neuroimaging time needed for structural, fMRI, and high-definition fiber tracking data collection, as well as research assistant and clinician support. Finally, the ACE provides the majority of support for participant recruitment and diagnosis. Given that the ACE has not been renewed by the NICHD, we have tried to conserve DoD funds to ensure this infrastructure for recruitment and diagnosis remains for Year 02, and anticipate needed additional funds to maintain these recruitment and diagnostic resources in subsequent years.

2.2. Task Progress and Accomplishments

This project was awarded and began on September 30, 2011. We have completed 12.0 months of the project and have made substantial progress toward accomplishing our aims. Most notably, we have randomized 24 adults with ASD assigned to either CET (*n* = 12) or EST (*n* = 12), finished pre-treatment data collection with all 24 randomized individuals, have begun treatment with these individuals, and are in the process of collecting post-treatment data on these participants to assess the efficacy of CET compared to EST in adults with autism. Given this progress, *we are ahead of schedule in the conduct of this clinical trial.*

There have been no substantive modifications to the specific aims of this project during this first year. However, we propose an addition to Specific Aim #2. Given the faster than expected rate of participant enrollment which has allowed quick completion of recruitment, we plan to conduct 1-year post-treatment durability assessments on participants instead of 6-month post-treatment assessments. This longer follow-up period will enhance the assessment of the long-term maintenance of treatment gains. In addition, due to support obtained for neuroimaging from the NIMH, we have been able to include a sample of healthy control individuals for the imaging component of this study. Many of the fMRI tasks employed in this research are novel. Including these healthy control individuals will give us a normative sample for defining typical brain activity on these tasks to which the imaging data from the ASD participants in this trial can be compared. These normative data are essential for understanding the treatment effects of CET and EST on neural circuitry.

Progress and specific accomplishments with regard to the Statement of Work originally outlined in our proposal is summarized below:

Task 1 - Secure final IRB approvals at University of Pittsburgh, Carnegie Mellon University, and USAMRMC (mos 1-6). Institutional review board approvals have been secured for this clinical trial at the University of Pittsburgh, Carnegie Mellon University, and the US Army Medical Research and Materiel Command. Ongoing revisions to the study protocol have been minimal, and our Continuing Renewal Report to these human subjects organizations has been submitted for review. Approval to renew the project for another year has already been received from the University of Pittsburgh and Carnegie Mellon University IRBs. These approvals have been forwarded to the US Army Medical Research and Materiel Command along with renewal materials for approval. Strict surveillance over confidential data and human subjects research regulations outlined by the federal government, Belmont Report, and the Department of Defense has been maintained through weekly meetings to ensure data confidentiality and integrity.

Task 2 - Establish university accounts, subcontracts, and consultant contracts (mos 1-3). All university accounts have been established, including accounts at Western Psychiatric Institute and Clinic and the School of Social Work at the University of Pittsburgh, as well as with the Scientific Imaging and Brain Research Center at Carnegie Mellon University. Transactions on these accounts are regularly reviewed by the PI to ensure appropriate use of funds that are directly budgeted for this project.

Task 3 - Install subject tracking system (mos 1-3). A system for tracking participant recruitment and flow throughout this trial has been installed in a centralized SQL database that includes information on the number of times the participant was contacted for study participation, eligibility status, any exclusion criteria met, dates of screening, informed consent, and start of treatment, post-treatment due dates, treatment end dates, and notes regarding contact with participants and their status in the study.

Task 4 - Install data management tables compatible with NDAR; install GUID and randomization program (mos 1-3). NDAR-compatible data tables have been installed so that the data from this study can be transferred to NDAR when appropriate. The GUID system of assigning unique subject identifiers (IDs) has been installed for anonymous subject and data tracking. Randomization tables have been generated for the study, and are maintained, kept confidential, and subjects are assigned by the independent data management team to avoid bias in subject randomization.

Task 5 - Establish CET For ASD Clinical Trial procedures book; establish schedule of QC procedures (mos 1-3). A study procedures book has been created with all assessment forms, order of administration, role of study staff, and quality assurance procedures.

Task 6 - Train project coordinator (mos 1-6). A study coordinator (Summer McKnight - Research

Specialist) for this project has been recruited, hired, and trained by the PIs and study staff. She has completed study protocol training by the PIs and is supervised weekly in the implementation and maintenance of these procedures. She has also received project coordinator training at Western Psychiatric Institute and Clinic and participant reimbursement training at the University of Pittsburgh Medical Center. The study coordinator has also been trained in the reliable collection of all neuropsychological and interview assessment data associated with this clinical trial by Drs. Minshew, Eack, and Greenwald and Mrs. Hogarty. Her training has been supplemented with specific neuropsychological training on the MATRICS Consensus Cognitive Battery at the Department of Psychology at Harvard University. She continues to be supervised in neuropsychological testing and clinical interviewing by Dr. Greenwald and Mrs. Hogarty.

Task 7 - Finalize fMRI tasks at CCBI Laboratory, Carnegie Mellon University (mos 1-6). All fMRI tasks have been created for the project in collaboration with Dr. Keller at the Center for Cognitive and Brain Imaging (CCBI) Laboratory, Carnegie Mellon University. This included the adaptation of Emotion Regulation, Perspective-Taking, and Inference Making tasks for this scanning facility, and the creation of a Processing Speed task to assess the effects of CET on neural functions associated with cognitive efficiency and speed of processing in ASD. All paradigms were programmed and refined to remove software bugs, and instruction scripts were created to ensure standardized delivery.

Task 8 - Pilot fMRI paradigms at SIBR, Carnegie Mellon University (mos 6-9). The four fMRI tasks developed and adapted for this project were piloted successfully using healthy volunteers at the Scientific Imaging and Brain Research Center (SIBR), Carnegie Mellon University. The perspective-taking fMRI task was adapted from a visual perspective-taking paradigm used in developmental psychology and previously pilot tested in patients with schizophrenia (Epley, Morewedge, & Keysar, 2004). Participants are asked to identify objects inside of a two-way grid array from the perspective of a virtual actor on the other side of the array. Purposely ambiguous trials are included that require the participant to shift from their perspective to that of the virtual actor in order to identify the correct item. This task has now been piloted and successfully implemented with adults with ASD with no major modifications.

The emotion regulation fMRI task used in this study makes use of a negative emotion induction paradigm in which participants play a computer game to earn a prize. The game has several blocks, the first consisting of easy trials where the participant wins points toward the prize, then difficult trials where the participant loses points toward the prize, and finally easy trials again when they ultimately win enough points to obtain the prize. This task allows for the induction of negative emotion and its regulation (during difficult trials) in a manner that evokes modulation of the emotion regulation neural circuitry of the brain, while at the same time still being an acceptable task for participants for individuals with ASD. This task was previously piloted with adults with ASD (Perlman & Pelphrey, 2010), and we adapted it to the hardware used at SIBR for this project.

The inference making fMRI task used in this study has been previously employed by Dr. Marcel Just in studies of ASD (Mason, Williams, Kana, Minshew, & Just, 2008) and included in this trial based on his recommendation that it provides a strong test of neural systems supporting theory of mind ability. The task requires participants to read paragraphs of different social scenarios that involve making inferences about the people depicted in the scenarios; adults with ASD have previously shown hypoactivation in the temporo-parietal-junction theory of mind (**ToM**) network when completing this task, providing support for this circuitry as the neural basis of the ToM aspect of the social deficit in autism. While the stimuli for the task were already developed, the task needed to be programmed in a standardized stimulus presentation software suite, which was carried out by our team.

Finally, the processing speed task was newly created for this project to capture the neural basis for the strong effects of CET on processing speed observed in our pilot ASD data, as well as on speed of processing in CET trials of patients with schizophrenia. This processing speed task was designed to replicate those activities used during neurocognitive training in CET and consists of visual reaction time tasks in which participants must respond to a visual (center light) cue as quickly as possible with the press of a button. The fMRI task involves a mixed blocked/event-related design in which participants will perform separate blocks involving performance of the task at variable or fixed interstimulus intervals that employ either simple or choice reaction time tasks. This task needed to be completely programmed and piloted by our group, and was fully tested in healthy volunteers prior to beginning this project.

Task 9 - Revise study brochure and advertisements (mos 1-6). New study brochures and advertisements were created specifically for this trial that outlined the procedures involved, the content of both of the interventions, expected time commitments for each treatment, supports provided by the study, and funding by the Department of Defense. In addition to these brochures for families and clinicians, a social

stories electronic slide show was created specifically for individuals with ASD. Individuals affected by ASD rely more heavily on visual information processing; the ability to meet the study staff and know the exact procedures involved in the study through this visual display greatly increase their comfort with the program. Families and individuals with ASD have noted repeatedly the helpfulness of this approach, which has served well as a recruitment and enrollment tool.

Task 10 - Faculty/staff recruitment activities (mos 1-24). The PIs and study staff have worked diligently to engage in recruitment activities throughout Pittsburgh and surrounding areas. This has included giving presentations on autism at local universities, clinical centers providing services, support groups, and other organizations that serve adults with ASD and their families. The longstanding connection of Dr. Minshew and the University of Pittsburgh Autism Center of Excellence to the community has strongly facilitated the ability of the program to reach out to this community and engage them in the importance of participating in this research for advancing the treatment of adults with autism. The ACE recruiter continues to maintain these connections with considerable regularity in presentations and visits. *While the recent loss of NIH support for the University of Pittsburgh ACE has jeopardized support for recruitment efforts and the recruiter and diagnosis positions that were provided by the ACE core, NIH carry-over funds have been used for this year to ensure that necessary recruitment activities remain in place. In addition, because of funds provided by Autism Speaks, we have been able to aggressively conserve DoD Year 01 funds (~35%) in order to maintain this subject recruitment and diagnosis infrastructure into Year 02. It will be essential to obtain additional support in subsequent years to maintain the core infrastructure required to successfully recruit, screen, and test subjects for this trial.*

Task 11 - Train new CET therapist (mos 1-6). A new therapist, Shannon A. Sloan, M.Ed., has been hired to expand the number of participants we can simultaneously treat in this trial to ensure we meet study milestones on time. She has experience in the treatment of individuals with ASD, as well as individual and group therapy modalities. She has read literature on autism and schizophrenia, as well as CET and EST interventions. Ms. Sloan is currently shadowing active clinicians in CET and EST, as well as receiving supervision by Drs. Eack, Greenwald, and Mrs. Hogarty in the implementation of these interventions. It is anticipated that her training will continue for an additional 1 month before she is assigned cases in this trial.

Task 12 - Begin baseline testing and diagnosis of participants on waiting list (*N* = 31) (mos 6-9). Diagnostic testing of all study volunteers who met preliminary eligibility requirements has been completed. This included ADOS and ADI-R testing of all of the 31 participants on the study waiting list at the time this proposal was submitted, as well as 21 additional participants that accumulated on the waiting list during the time the study was under consideration for funding. Of these individuals 28 (54%) met criteria for autism and 17 (33%) met criteria for autism spectrum disorder on the ADOS; 7 (13%) did not meet criteria for either autism or autism spectrum disorder. A total of 40 individuals received an ADI-R assessment; individuals not receiving this assessment either presented with no available family (e.g., both primary caregivers were deceased) or did not have a family member or close relative/friend willing to complete the assessment. Of the 40 individuals assessed with the ADI-R, 38 (95%) met criteria for autism and 2 (5%) were below the threshold for full autism criteria. All diagnostic assessments were conducted at no cost to the study by ACE staff, reviewed by a trained psychologist, and diagnostic decisions were made based on all available evidence in consensus conferences with the study team. *Given the recent loss of NIH support for the ACE, additional resources from the DoD will be needed in later years to maintain this diagnostic infrastructure for the study.*

Task 13 - Begin screening and diagnostic assessment of volunteers (*N* = 31) on CET wait list (mos 6-9). All 31 of the individuals who were on the study waiting list at the time of our application have been screened for eligibility and study enrollment. In addition, 102 subsequent referrals have also been screened to date. Bridge funding from Autism Speaks allowed us to begin screening this large number of potential participants while our application was under consideration for funding by the DoD. A total of 24 individuals meeting all eligibility criteria have been randomized to CET (*n* = 12) or EST (*n* = 12). An additional 28 individuals are pending enrollment once these first two study cohorts near completion and the clinical team can enroll more concurrent participants. The remaining 81 individuals were excluded primarily due to a lack of interest in participating in a research treatment trial (40%), IQ < 80 (12%), failing to meet research criteria for ASD (11%), travel distance from the study (11%), substance use (5%), or marked speech pathology (5%). It is our experience that when participants come to our program and are excluded for a lack of interest, it is the family members who are often most interested in their participation, but the participants themselves are not ready to consider enrolling in a randomized treatment trial.

Task 14 - Treatment Phase, participants treated with CET or EST (mos 6-42). All 24 individuals randomized to CET or EST have begun their study treatment condition with considerable success. CET participants have begun receiving individual therapy, computer-based neurocognitive training, and group-

based training in social cognition. The first cohort of CET (*n* = 6) participants has completed all 45 social-cognitive group sessions and the majority of the neurocognitive training, and will be completing 18-month (treatment completion) assessments between September and November, 2012. The first cohort of EST participants (n = 6) have also completed individual emotion management training and psychoeducation about ASD and will be completing their 18-month (treatment completion) assessments during the same time frame. The second cohort of CET (*n* = 6) participants have been receiving their treatment condition for 4 to 6 months, are participating in individual therapy and computer-based neurocognitive training in attention. The social-cognitive group therapy component of CET will begin in November, 2012 for these individuals. The second cohort of EST (*n* = 6) participants are currently in the early stages of psychoeducation and learning how to manage their condition, and have also been treated for 4 to 6 months. These two cohorts will begin completing 9-month (mid-treatment) assessments in January, 2013.

Treatment satisfaction has been high, and while this is a long-term controlled trial, attrition has been low at 15%. To date, 4 individuals have been lost to attrition: 1 individual withdrew from CET at 9 months due to residential instability, 1 withdrew from EST at study baseline due to lack of interest in the program, 1 withdrew from CET at study baseline due to interest only in EST, and 1 withdrew from EST at baseline due to interest only in CET. Given that the majority of attrition has occurred prior to beginning the interventions, treatment retention to date has been extraordinarily high at 95%. The two individuals who refused their assigned treatment condition were retained as "filler" participants in compassionate care in their desired condition, primarily to facilitate the formation of the first CET group.

Task 15 - Follow-up testing (mos 12-48). Due to the bridge funding provided by Autism Speaks, we were able to begin this controlled trial earlier than anticipated and have completed 9-month (mid-treatment) testing with the first cohort of participants (*N* = 12). The first series of 18-month (treatment completion) assessments has begun (1 person has completed his 18-month assessment) and will be completed by November, 2012. After completing CET or EST, participants will also be followed-up for 1-year post-treatment to assess treatment durability; these assessments will begin in the fall of 2013 and proceed throughout the remainder of the study.

Task 16 - Volunteer Closeout and Final Feedback (mos 36-48). To be completed.

Task 17 - Preliminary and final data analyses of baseline data (mos 12-24). Pretreatment data among the 24 individuals randomized to this trial have been completed and preliminarily analyzed. This consisted of comprehensive data collection on numerous measures of autism, cognition, and functional ability. Perhaps most striking is the clear support these data provide for the need for an effective cognitive rehabilitation program for verbal adults with ASD by highlighting the broad impairments in cognition such individuals experience. As shown in **Table 2**, *overall* neurocognitive functioning for the sample was at the 36th percentile based on 50% normative performance. Although performance varied, significant impairments (at times as low as < 1%) were observed in all individuals across cognitive domains. Such findings indicate large impairments across multiple cognitive domains in this sample despite above-average IQ, which clearly supports the need for a comprehensive cognitive rehabilitation approach. A paper outlining these findings is currently under review at the *Journal of Autism and Developmental Disorders* (see Appendix). No significant differences emerged between CET and EST participants in demographic or pre-treatment cognitive characteristics.

Table 2. Pre-Treatment Characteristics of Adults with ASD Randomized to an 18-Month Trial of CET or EST (*N* = 24).

	CET		EST	
Variable	*M* / *N*	*SD* / %	*M* / *N*	*SD* / %
Demographics				
Age	25.08	7.51	23.83	4.20
% Male	10	83%	12	100%
% College Educated	6	50%	10	83%
Full Scale IQ	111.25	16.86	112.00	14.40
Neurocognition Composite[a]	36.12	32.47	36.56	29.37
Processing Speed	47.38	38.32	38.95	35.27
Vigilance	43.07	29.10	46.23	37.66
Working Memory	32.98	18.93	36.98	34.92
Verbal Learning	36.21	28.82	53.27	28.20
Visual Learning	36.28	33.36	39.56	29.78
Reasoning	59.38	33.93	37.64	21.99
Social Cognition	35.44	27.75	43.11	29.59

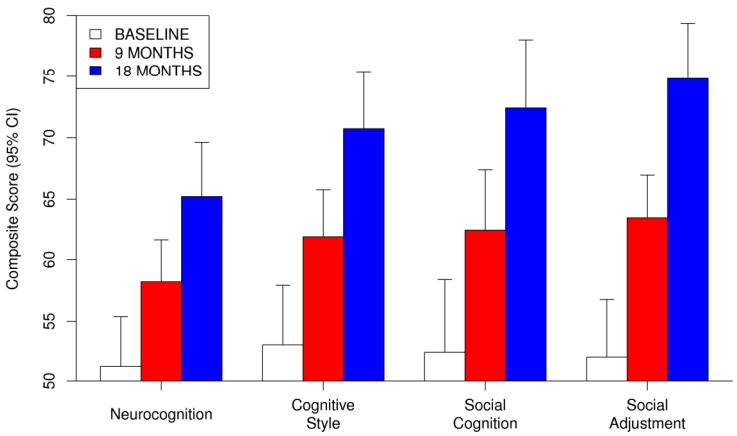
[a]Composites are given in percentile scores

Pre-treatment MRI data have also been collected with processing speed, perspective-taking, theory of mind, and emotion regulation fMRI measures on 11 of the 12 participants randomized since DoD support for this project began (1 participant did not complete pre-treatment MRI assessments due to claustrophobia that was not apparent when conducting a mock scanning session; attempts to collect subsequent interim neuroimaging data will be made to facilitate treatment analyses). Of the 24 individuals randomized, 12 were recruited and randomized before this project began with initial funding from Autism Speaks, which did not support MRI data collection. While these individuals did not receive baseline MRI scans, treatment completion

MRI data will continue to be collected on them, which will be compared with a healthy control sample to facilitate post-treatment analyses of CET effects on neural function and connectivity.

Task 18 - Preliminary and final data analyses of 9 mos post-treatment data (mos 18-36). Since beginning this project we have also completed the 18-month uncontrolled pilot study of CET in 14 adults with ASD that was supported by the NIMH. These data have now been fully cleaned and a manuscript outlining the preliminary effects of CET has been submitted to the *Journal of Autism and Developmental Disorders* (see Appendix). **Figure 1** presents the findings of that study which constitute the first documentation of the effects of CET on broad domains of cognition and behavior in adults with autism. Highly significant (all $p <$ .001) and large (d = 1.40 to 2.29) levels of improvement were observed across composite domains of neurocognition, cognitive style, social cognition, and social adjustment. Neurocognitive improvement was particularly large in the domain of processing speed, which was also the greatest area of non-social cognitive impairment in the sample prior to treatment. In addition, all clinician-rated aspects of dysfunctional cognitive style showed significant levels of improvement. Social cognition was also significantly improved across both clinician-rated and performance-based measures, particularly with regard to emotion understanding and management. Importantly, these social-cognitive gains generalized to broader improvements in adaptive function and social adjustment, as large and highly significant levels of improvement were observed in vocational effectiveness, interpersonal effectiveness, and participants' ability to adjust to their condition, as measured by the Cognitive Styles and Social Cognition Eligibility Interview. These findings, while suggestive of the benefits of CET, have many limitations that this DoD-sponsored clinical trial was designed to address. In particular, the absence of an active control group raises limitations regarding testing-effects and treatment specificity, and assessments were taken by raters not blind to treatment assignment, which could particularly affect clinician ratings of social adjustment.

Figure 1. Uncontrolled Pilot Effects of Cognitive Enhancement Therapy in Adults with Autism (N = 14).

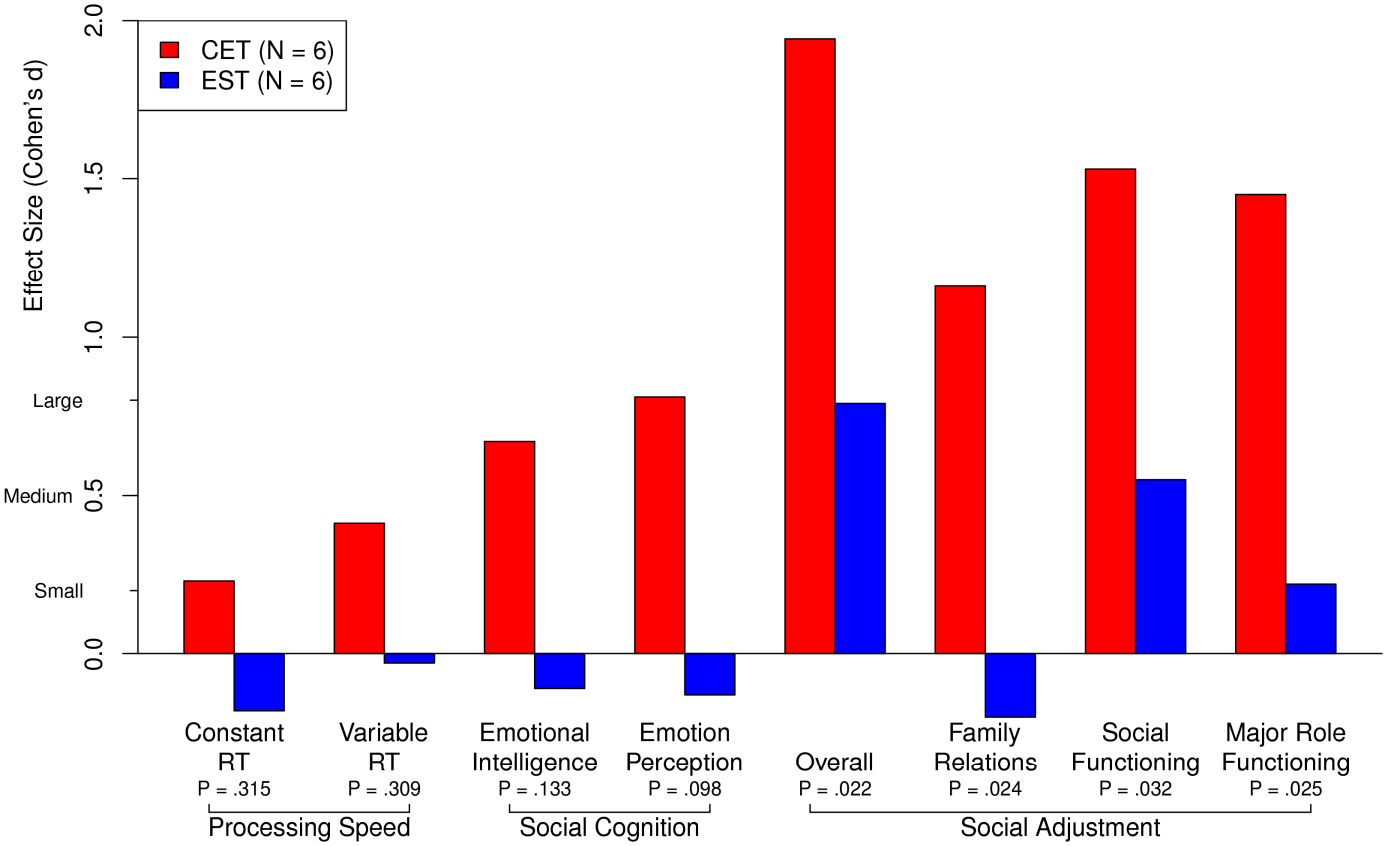


While we are in the early phases of our controlled trial sponsored by the DoD, results from interim 9-month assessments of treatment efficacy are demonstrating promise. **Figure 2** presents 9-month interim treatment findings from select cognitive and behavioral domains in the first cohort of 12 participants treated with either CET or EST. While significance tests are premature at this stage, one-tailed tests of statistical significance are provided as instructed.

As can be seen in these preliminary findings, CET is demonstrating medium-level improvements in the neurocognitive domain of processing speed compared to those treated with EST; this is particularly promising given that our pilot data demonstrated that processing speed was the largest neurocognitive domain improved by CET. In addition, large improvements are present in critical social-cognitive domains favoring CET, particularly emotional intelligence and emotion perception, both of which are approaching statistical significance even at this early phase of the study. Finally and perhaps most promising are the functional gains that are being observed by blind raters in various domains of social adjustment. As can be seen in **Figure 2**, overall social adjustment has improved at a strikingly larger magnitude in participants treated with CET (d = 1.94) compared to those treated with EST (d = .79), which is already statistically significant in this small sample. Key contributors to this improvement in adaptive function appear to be improved family relations, social functioning, and major role functioning among participants receiving CET. While these findings suggest that CET is having a key advantage over EST in multiple cognitive domains and in terms of adaptive function, results should be interpreted cautiously as they represent interim treatment results and these individuals have not yet completed the entire course of CET. In addition, it is important to note that as expected, EST participants are also demonstrating medium-to-large levels of improvement in social adjustment, indicating that this intervention is also helping participants. Further, other measures (e.g., the MATRICS) have not yet demonstrated differential change at this point in the treatment, and the possibility that these findings are due to chance cannot be ruled out at this time. It is hypothesized that as the study sample increases and more

individuals complete 18 months of treatment, clearer effects favoring CET on cognition and adaptive function will be observed.

Figure 2. Interim (9-month) Effects of Cognitive Enhancement Therapy Versus Enriched Supportive Therapy on Cognitive and Functional Domains



Task 19 - Preliminary and final data analyses of outcome data at 18 mos (mos 24-48+). To be completed.

Task 20 - Preliminary and final data analyses of outcome data 6mos post treatment (durability) (mos 36-48+). To be completed.

Task 21 - Analyses of fMRI data at baseline (mos 6-24). Baseline fMRI data has been transferred to our image processing servers and pre-processing of these data have begun. Structural MRI images have been manually inspected for data quality, and rescanning of participants (n = 1) with significant variations in data quality have been conducted. We have also begun preprocessing of fMRI data and inspected it for time course outliers. During the next year of this award, we anticipate finalizing baseline data preprocessing in all patients, collecting cross-sectional MRI data in healthy controls, and completing analyses of differences between ASD patients and controls in brain function and connectivity during the 4 fMRI tasks employed in this study. We also plan to examine the association between brain activity, connectivity, and cognitive/behavioral outcome measures. Manuscripts on these findings will be prepared for publication by the end of Year 02.

Task 22 - Analyses of fMRI data at 18 mos (mos 25-48). To be completed.

Task 23 - Prepare final report of results for funder (mos 42-48). To be completed.

Task 24 - Prepare newsletter of results for all participants (mos 12, 24, 36, 48). This task will be completed once the first cohort of participants have completed their 18-month assessments (end of treatment), and these data are analyzed. Interim treatment data will not be reported in a newsletter to participants.

Task 25 - Prepare report for distribution by Autism Speaks (mos 12, 24, 36, 48). A recruitment report has been prepared and delivered to Autism Speaks. A report on study progress and treatment effects will be prepared as more participants complete the active treatment phase of the study.

Task 26 - Prepare large scale study for NIH multi-site RO1 guided by results of above study with new hypotheses guiding new advances in treatment. To be completed.

Task 27 - Dissemination of findings to lay and scientific audiences throughout the third and fourth years as evidence for each cohort is completed. To be completed.

3. KEY RESEARCH ACCOMPLISHMENTS

- Identification of core deficits in elementary cognitive abilities in verbal adults with autism, despite intact levels of intelligence
- Adaptation of two promising intervention approaches (CET and EST) to adults with ASD
- Ahead of schedule recruitment and randomization of 24 adults with ASD to this clinical trial
- Promising interim analyses demonstrating medium-to-large levels of improvement in social adjustment among *both* CET and EST treated participants
- Promising interim analyses demonstrating differential advantages of CET *over* EST on cognition and adjustment
- Development of a comprehensive neuroimaging protocol to identify neural mechanisms of effects

4. REPORTABLE OUTCOMES

- Manuscripts, abstracts, presentations:
  1. Eack, S. M., Greenwald, D. P., Hogarty, S. S., Bahorik, A. L., , Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J. (under review). Cognitive Enhancement Therapy for adults with autism spectrum disorder: Results of an 18-month feasibility study.
  2. Eack, S. M., Bahorik, A. L., Hogarty, S. S., Greenwald, D. P., Litschge, M. Y., Mazefsky, C. A., & Minshew, N. J. (under review). Is cognitive rehabilitation needed in verbal adults with autism? Insights from initial enrollment in a trial of Cognitive Enhancement Therapy.
  3. Eack, S. M. (in press). Cognitive Enhancement Therapy. In F. R. Volkmar (Ed.), Encyclopedia of Autism Spectrum Disorders. New York: Springer.
  4. Fitzpatrick, L. B., Minshew, N. J., & Eack, S. M. (in press). A systematic review of psychosocial interventions for adults with autism spectrum disorders. Journal of Autism and Developmental Disorders.
  5. Mazefsky, C.A., Oswald, D.P., Day, T., Eack, S., Minshew, N.J., & Lainhart, J. (in press). ASD, a comorbid psychiatric disorder, or both? Psychiatric diagnoses in high-functioning adolescents with ASD. Journal of Clinical Child and Adolescent Psychology.
- Licenses applied for and/or issued: None
- Degrees obtained that are supported by this award: None
- Development of cell lines, tissue or serum repositories: None
- Infomatics such as databases and animal models, etc:
  1. NDAR-compatible database
  2. Subject tracking database
- Funding applied for based on work supported by this award: None
- Employment or research opportunities applied for and/or received based on experience/training supported by this award:
  1. K23 MH-95783, Eack (PI), Social-Cognitive Rehabilitation and Brain Function in Early Schizophrenia, NIH/NIMH (Awarded)
  2. R01 MH-92440, Keshavan & Eack (PIs), Brain Imaging, Cognitive Enhancement and Early Schizophrenia, NIH/NIMH (Awarded)

5. CONCLUSION

This research is dedicated to the conduct of the first randomized-controlled trial of a comprehensive cognitive rehabilitation intervention in verbal adults with ASD. Cognitive rehabilitation has been shown to be effective in many other neurological conditions, and Cognitive Enhancement Therapy (CET) in particular has demonstrated considerable success in patients with schizophrenia who share similar social-cognitive and neurocognitive impairments. Findings to date indicate that (1) the population of verbal adults with ASD is in great need of cognitive rehabilitation, exhibiting medium to large deficits in a variety of cognitive domains; (2) CET can be feasibly implemented with adults with ASD with minimal attrition and high degrees of satisfaction; and (3) CET offers a potentially highly significant advantage over routine supportive therapies in its ability to improve cognitive and functional outcomes in this population.

So What? The need for interventions to treat the core cognitive problems present in adults with ASD is great. The potential, especially for high functioning adults with ASD, to have productive and satisfying lives exists but will not be achieved without more effective interventions. CET is a cognitive rehabilitation intervention that aims to address the cognitive impairments that markedly limit adaptive behavior, work capacity, and independent functioning in adults with ASD. The intervention is provided over a long-term, 18-month period, which is necessary to address the entrenched behavior patterns that many adults with ASD experience. This project is significant in that it is, for the first time, systematically testing the efficacy of a comprehensive cognitive rehabilitation approach in ASD in contrast to an Enriched Supportive Therapy (EST). Current findings suggest the benefits of both CET and EST to adults with ASD pointing to novel avenues for effective intervention on core deficits in this population. While a considerable advantage of CET over EST is being demonstrated on numerous domains, non-trivial levels of improvement in adjustment and adaptive function are also being observed in those treated with EST. Ultimately it is expected that this investigation will result in significant treatment advances for this highly underserved group of individuals.

6. REFERENCES

1. Eack, S. M., Greenwald, D. P., Hogarty, S. S., Cooley, S. J., DiBarry, A. L., Montrose, D. M., & Keshavan, M. S: Cognitive Enhancement Therapy for early-course schizophrenia: Effects of a two-year randomized controlled trial. Psychiatric Services 60:1468-1476, 2009
2. Eack, S. M., Hogarty, G. E., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S: Effects of Cognitive Enhancement Therapy on employment outcomes in early schizophrenia: Results from a two-year randomized trial. Research on Social Work Practice 21:32-42, 2011
3. Epley, N., Morewedge, C. K., & Keysar, B: Perspective taking in children and adults: Equivalent egocentrism but differential correction. Journal of Experimental Social Psychology 40:760-768, 2004
4. Fitzpatrick, L. B., Minshew, N. J., & Eack, S. M: A systematic review of psychosocial interventions for adults with autism spectrum disorders. Journal of Autism and Developmental Disorders. :-, in press
5. Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Keshavan, M., Cooley, S., DiBarry, A. L., Garrett, A., Parepally, H., & Zoretich, R: Cognitive enhancement therapy for schizophrenia. Effects of a 2-year randomized trial on cognition and behavior. Archives of General Psychiatry 61:866-876, 2004
6. Mason, R. A., Williams, D. L., Kana, R. K., Minshew, N., & Just, M. A: Theory of Mind disruption and recruitment of the right hemisphere during narrative comprehension in autism. Neuropsychologia 46:269-280, 2008
7. Perlman, S. B., & Pelphrey, K. A: Developing connections for affective regulation: Age-related changes in emotional brain connectivity. Journal of Experimental Child Psychology 108:607-620, 2010

7. APPENDICIES

Running Head: COGNITIVE REHABILITATION CHARACTERISTICS IN HFA

Is Cognitive Rehabilitation Needed in Verbal Adults with Autism?

Insights From Initial Enrollment in a Trial of Cognitive Enhancement Therapy

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Running Head: COGNITIVE REHABILITATION CHARACTERISTICS IN ADULT HFA

Is Cognitive Rehabilitation Needed in Verbal Adults with Autism?

Insights From Initial Enrollment in a Trial of Cognitive Enhancement Therapy

Abstract

Cognitive rehabilitation is an emerging set of potentially effective interventions for the treatment of autism spectrum disorder, yet the applicability of these approaches for "high functioning" adults who have normative levels of intelligence remains unexplored. This study examined the initial cognitive performance characteristics of 40 verbal adults with autism enrolled in a pilot trial of Cognitive Enhancement Therapy to investigate the need for cognitive rehabilitation in this population. Results revealed marked and broad deficits across neurocognitive and social-cognitive domains, despite above-average IQ. Areas of greatest impairment included processing speed, cognitive flexibility, and emotion perception and management. These findings indicate the need for comprehensive interventions designed to enhance cognition among verbal adults with autism who have intact intellectual functioning.

Autism spectrum disorder (ASD) is a family of persistent neurodevelopmental conditions that emerge early and continue to present many challenges to affected individuals in adulthood (Kanner, 1971). Despite growing recognition of the continued need for treatment and other supports in adults with ASD, intervention research has been largely focused on early childhood (Kasari & Lawton, 2010). Remarkably few empirically supported treatments are available for verbal adults with these conditions who do not have a comorbid intellectual disability. Longitudinal studies of "high functioning" individuals with autism have shown consistent and persistent disability across educational, social, and vocational domains, despite supposedly intact verbal and intellectual abilities (Howlin, 2000), indicating a significant need for effective treatments for these functional disabilities.

As the neurobiological basis of autism is becoming increasingly clear (Abrahams & Geschwind, 2008; Minshew & Williams, 2007), attention has been focused on remediating the core brain deficits that underlie social and non-social cognitive dysfunction in ASD. Impairments in information processing are considerable in these conditions and place significant limitations on adaptive function. A group of treatment approaches known as cognitive rehabilitation have emerged in other disorders that may be potentially effective non-pharmacologic interventions for core information processing deficits in adults with ASD. Although cognitive rehabilitation approaches vary widely in their scope and targets, most use progressive computer-based exercises that are designed to enhance specific domains of cognitive function (e.g., attention, memory). For the past several decades, cognitive rehabilitation has been used with considerable success in a wide variety of brain disorders, such as traumatic brain injury (Ben-Yishay, Piasetsky, & Rattok, 1985), stroke (Cicerone et al., 2005), Alzheimer's disease (Sitzer, Twamley, & Jeste, 2006), and schizophrenia (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011).

One particularly promising cognitive rehabilitation intervention for verbal adults with ASD is Cognitive Enhancement Therapy (CET; Hogarty & Greenwald, 2006), which was originally developed for individuals with schizophrenia (Hogarty et al., 2004; Eack et al., 2010). CET is a developmental approach designed to remediate social and non-social cognitive deficits through the integration of computer-based neurocognitive training with a group-based social-cognitive curriculum focused on the achievement of key adult social-cognitive milestones (e.g., perspective-taking, social context appraisal). CET may be uniquely relevant for individuals with ASD, in that it is the only cognitive rehabilitation intervention that takes a comprehensive approach to integrating social-cognitive and neurocognitive rehabilitation into a single treatment to address the broad array of social and non-social information processing deficits experienced by this population.

Targeting broad brain-based cognitive deficits using cognitive rehabilitation in verbal adults with ASD is novel and promising. However, many verbal adults with ASD present with average or even above-average intellectual functioning, which has led some to raise important questions regarding the need for cognitive rehabilitation, particularly neurocognitive training, in this population. This investigation presents the baseline cognitive characterization of verbal adults with ASD enrolled in an initial trial of CET. While this trial is ongoing and treatment data will be forthcoming, the enrollment characteristics of this study afforded the unique opportunity to examine the degree to which adults with high functioning ASD have specific cognitive impairments that could indicate a need for cognitive rehabilitation. It was hypothesized that despite average or above-average intelligence scores, verbal individuals with ASD would demonstrate broad and pervasive deficits in social and non-social cognition that would indicate the need for a comprehensive cognitive rehabilitation approach to address these functionally disabling impairments.

Method

Participants

Participants consisted of 40 verbal adults with ASD recruited for a pilot trial of Cognitive Enhancement Therapy (Hogarty & Greenwald, 2006). Eligibility criteria for the study included a diagnosis of autism or ASD using the Autism Diagnostic Observation Schedule (Lord et al., 2000), age 16 to 45, IQ $\geq$ 80 assessed by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), ability to speak and read English, the presence of significant social and cognitive disability based on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004), and the absence of significant substance use problems within the past 3 months. The Cognitive Styles and Social Cognition Eligibility Interview is a structured interview developed specifically for trials of CET (Hogarty et al., 2004), which is designed to elicit information from participants on the degree to which they experience social and cognitive disability that could represent meaningful targets for treatment. Of the over 100 participants screened, none were excluded because they failed to demonstrate significant cognitive and social disability during this interview. Participants were excluded primarily due to lack of willingness to enroll in a experimental treatment trial (39%), IQ < 80 (13%), and the absence of a research diagnosis of ASD (12%). Sample characteristics are presented in Table 1. Participants were young, most were male, and the sample was predominantly Caucasian. Over half of the participants met ADOS criteria for autism, with the remaining meeting criteria for ASD. While most participants had attended some college, less than half were employed and only 6 (15%) were living independent of family.

Measures

A comprehensive battery of neuropsychological tests and performance-based assessments of social cognition was used to characterize the degree of cognitive disability experienced by

verbal adults with ASD. Neurocognitive assessments included the NIMH-recommended MATRICS Consensus Cognitive Battery, which was designed to provide a broad assessment of cognitive function for use in clinical trials of cognitive enhancement interventions in patients with schizophrenia (Green et al., 2004). This battery consists of a package of standardized neuropsychological tests for assessing processing speed, attention, verbal and non-verbal working memory, verbal learning, visual learning, problem-solving, and social cognition. The MATRICS battery was originally developed for patients with schizophrenia, and while the cognitive domains it covers are highly relevant to ASD, its assessment of cognitive flexibility and social cognition is minimal. As such, the Wisconsin Card Sorting Test was also utilized to assess cognitive flexibility (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and social-cognitive assessments were greatly expanded.

Social cognition was assessed using the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer, Salovey, Caruso, & Sitarenios, 2003). The measure is computerized and performance-based, in that it requires participants to solve emotional problems, rather than relying on self-report about emotional understanding and capacity. A series of 141 items across 8 distinct tasks assess emotion perception, facilitation, understanding, and management. Answers are scored based on consensus norms, and domain scores are scaled with a mean (*SD*) of 100 (15) based on a large normative sample. Previous research has documented the reliability and validity of the MSCEIT in healthy (Mayer, Salovey, Caruso, & Sitarenios, 2003) and psychiatric samples (Eack et al., 2010a). All components of the MSCEIT were utilized in this research, with the exception of the emotion perception branch. Facial emotion perception was more comprehensively assessed using the Penn Emotion Recognition Test-40 (Kohler et al., 2003), which asks participants to choose the appropriate emotional label associated with 40 emotional (happy, sad, angry, and fearful) and non-emotional (neutral) facial stimuli. Previous

research has established the reliability and validity of this measure, as well as the neural pathways involved in its completion in non-ASD samples (Carter et al., 2009).

Procedures

Participants were recruited for a study of CET from local organizations, support groups, and research registries. Individuals were enrolled who met study criteria and were willing to commit to two 1.5-hour treatment sessions per week for 18 months. Upon recruitment, participants were assessed for ASD using the Autism Diagnostic Observation Schedule by trained reliable interviewers. All diagnostic interviews were videotaped, reviewed, and verified by a doctoral-level study clinician, and IQ eligibility assessments were conducted by trained research associates. Eligibility interviews to establish the degree of social and cognitive disability were completed by master's- and doctoral-level clinicians, and finalized based upon consensus meetings using all available interview and screening data. After determining eligibility, participants were assessed using the aforementioned measures of neurocognition and social cognition by a trained neuropsychological tester who was supervised by a licensed clinical psychologist. This study was approved and reviewed annually by the University of Pittsburgh Institutional Review Board, and all individuals provided written informed consent prior to participation.

Results

Clinical and cognitive characteristics of ASD participants are presented in Table 1. Full scale IQ scores were within or above normative ranges (range = 80 to 157) for the sample. Despite above average intelligence scores, performance on tests of neurocognition and social cognition were substantially impaired. Overall neurocognitive performance was below the 35th percentile, and ranged from a low of 0% to a high of 81.60%. Nearly half (45%) of the sample performed below the 25th percentile for neurocognitive functioning, with the most marked

impairments observed in speed of processing, working memory, and visual learning. All but four participants demonstrated moderate (≥ .50 *SD*) or greater deficits in at least one neurocognitive domain on the MATRICS battery, and most (75%) displayed impairments in multiple domains. With regard to social cognition, participants also displayed substantial impairments in overall emotional intelligence, particularly emotion understanding and management. In addition, significant impairments in facial emotion perception were observed.

The functional consequences of this vast array of cognitive impairment were clear, as all individuals demonstrated at least moderate vocational impairment based on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004) that was completed during eligibility screening. Evidence also suggested that poorer neurocognition was significantly associated with the severity of ASD symptomatology regarding reciprocal social interaction (r_s = -.40, p = .010) and stereotypic behavior and restricted interests (r_s = -.33, p = .039), as well as greater social-cognitive impairment as assessed using the MSCEIT (r_s = .50, p = .001). Taken together, these findings indicate significant cognitive disability among verbal adults with ASD.

Discussion

The development of effective interventions designed to address core cognitive deficits in adults with ASD is an area of great need. Neurocognitive and social-cognitive impairments have a significant impact on social, vocational, and academic functioning and quality of life. Cognitive rehabilitation interventions, and CET in particular, offer significant promise for remediating the broad social and non-social cognitive impairments associated with ASD. However, questions have been raised regarding their applicability to high functioning verbal adults, especially those with normal IQ scores. This study sought to examine the nature and degree of cognitive deficits experienced by high functioning adults with autism, in an effort to elucidate the relevance of applying cognitive rehabilitative interventions to this population. The

initial cognitive characterization of a sample of 40 verbal adults enrolled in a pilot trial of CET revealed that despite above-average intellectual functioning, marked cognitive impairments were observed across every domain, with considerable heterogeneity in performance. All but four participants demonstrated at least medium-sized impairments in neurocognition, with most exhibiting impairments in multiple domains. Social-cognitive deficits were equally prominent, and related to degree of non-social cognitive impairment. These deficits were often not appreciated as issues by treating clinicians who had previously seen participants.

While this study is limited by a modest sample size consisting primarily of males, these findings have important implications for the treatment needs of verbal adults with ASD. The results suggest the presence of cognitive disability that could be easily overlooked when using standardized intelligence testing. The absence of a general intellectual disability and the presence of developed formal speech did not spare such individuals from significant cognitive and functional impairment, and the significant degree of cognitive impairment in the sample indicates the need for targeted intervention approaches designed to address these deficits in social and non-social cognition. CET was originally designed to address similar cognitive deficits in patients with schizophrenia through the integration of computer-based neurocognitive training in attention, memory, and problem-solving with a structured small-group social-cognitive treatment curriculum (Hogarty & Greenwald, 2006). The treatment has demonstrated considerable success in remediating social and non-social cognitive impairments, as well as adaptive function (Hogarty et al., 2004; Eack et al., 2010). The results of an adaptation and application of this comprehensive cognitive rehabilitation approach in verbal adults with ASD is eagerly anticipated and expected to demonstrate the feasibility of targeting cognitive impairments in this population using cognitive rehabilitation.

Acknowledgments

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References

Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: on the threshold of a new neurobiology. *Nature Reviews Genetics, 9*(5), 341-355.

Ben-Yishay, Y., Piasetsky, E. B., & Rattok, J. (1985). A systematic method for ameliorating disorders in basic attention. In M. J. Meir, A. L. Benton, & L. Diller (Eds.), *Neuropsychological rehabilitation,* pp. 165-181. New York: Guilford Press.

Carter, C. S., Barch, D. M., Gur, R., Gur, R., Pinkham, A., & Ochsner, K. (2009). CNTRICS Final Task Selection: Social Cognitive and Affective Neuroscience--Based Measures. *Schizophrenia Bulletin, 35*(1), 153-162.

Cicerone, K. D., Dahlberg, C., Malec, J. F., Langenbahn, D. M., Felicetti, T., Kneipp, S., Ellmo, W., Kalmar, K., Giacino, J. T., Harley, J. P., et al. (2005). Evidence-Based Cognitive Rehabilitation: Updated Review of the Literature From 1998 Through 2002. *Archives of Physical Medicine and Rehabilitation, 86*(8), 1681-1692.

Eack, S. M., Greeno, C. G., Pogue-Geile, M. F., Newhill, C. E., Hogarty, G. E., & Keshavan, M. S. (2010). Assessing social-cognitive deficits in schizophrenia with the Mayer-Salovey-Caruso Emotional Intelligence Test. *Schizophrenia Bulletin, 36*(2), 370-380.

Eack, S. M., Hogarty, G. E., Cho, R. Y., Prasad, K. M. R., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2010). Neuroprotective effects of Cognitive Enhancement Therapy against gray matter loss in early schizophrenia: Results from a two-year randomized controlled trial. *Archives of General Psychiatry, 67*(7), 674-682.

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S. et al. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. *Biological*

Psychiatry, *56*(5), 301-307.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual: Revised and Expanded*. Odessa, FL: Psychological Assessment Resources Inc.

Hogarty, G. E., & Greenwald, D. P. (2006). *Cognitive Enhancement Therapy: The Training Manual*. University of Pittsburgh Medical Center: Authors. Available through www.CognitiveEnhancementTherapy.com.

Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Keshavan, M., Cooley, S., DiBarry, A. L., Garrett, A., Parepally, H., & Zoretich, R. (2004). Cognitive enhancement therapy for schizophrenia. Effects of a 2-year randomized trial on cognition and behavior. *Archives of General Psychiatry*, *61*(9), 866-876.

Howlin, P. (2000). Outcome in adult life for more able individuals with autism or Asperger syndrome. *Autism*, *4*(1), 63-83.

Kanner, L. (1971). Follow-up study of eleven autistic children originally reported in 1943. *Journal of Autism and Developmental Disorders*, *1*(2), 119-145.

Kasari, C., & Lawton, K. (2010). New directions in behavioral treatment of autism spectrum disorders. *Current Opinion in Neurology*, *23*(2), 137-143.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., Gur, R. E., & Gur, R. C. (2003). Facial Emotion Recognition in Schizophrenia: Intensity Effects and Error Pattern. *American Journal of Psychiatry*, *160*(), 1768-1774.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., Pickles, A., & Rutter, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. *Journal of Autism and Developmental Disorders*, *30*(3), 205-223.

Mayer, J. D., Salovey, P., Caruso, D. R., & Sitarenios, G. (2003). Measuring emotional intelligence with the MSCEIT V2.0. *Emotion, 3*(1), 97-105.

Minshew, N. J., & Williams, D. L. (2007). The new neurobiology of autism. *Archives of Neurology, 64*(7), 945-950.

Sitzer, D. I., Twamley, E. W., & Jeste, D. V. (2006). Cognitive training in Alzheimer's disease: a meta-analysis of the literature. *Acta Psychiatrica Scandinavica, 114*(2), 75-90.

Wechsler, D. (1999). *Manual for the Wechsler Abbreviated Intelligence Scale*. San Antonio, T: The Psychological Corporation.

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry, 168*(5), 472-485.

Table 1

Demographic, Cognitive, and Clinical Characteristics of Verbal Adults with Autism Spectrum Disorders.

			Range		Normative Difference
	M / *N*	*SD* / %	Low	High	*d*[a]
Demographic					
Age	25.20	5.82	16.00	44.00	-
Male	36	90%	-	-	-
White	34	85%	-	-	-
Attended Some College	28	70%	-	-	-
Employed	16	40%	-	-	-
Clinical					
Diagnosis					
Autism	23	57%	-	-	-
Autism Spectrum	17	42%	-	-	-
IQ	113.22	15.47	80.00	157.00	.87
Verbal IQ	112.88	13.39	82.00	138.00	.91
Performance IQ	108.65	14.61	76.00	137.00	.58
Cognitive					
Neurocognition (percentile)					
Overall Composite	34.79	26.76	.00	81.60	-.60
Processing Speed	38.58	31.89	.00	97.10	-.46
Vigilance	46.79	31.24	.30	95.60	-.16
Working Memory	38.02	31.08	.00	99.90	-.37
Verbal Learning	46.76	29.71	1.10	94.50	-.12
Visual Learning	37.57	28.23	1.10	90.30	-.45
Problem Solving	45.71	30.71	1.40	93.30	-.16
Cognitive Flexibility					
WCST - Perseverative Errors	14.90	9.49	4.00	41.00	-.54
WCST - Non-Perseverative Errors	14.50	9.67	2.00	37.00	-.46
Social Cognition					
Emotional Intelligence[b]	93.44	19.06	9.55	116.57	-.38
Emotion Facilitation	94.12	20.65	1.46	124.28	-.33
Emotion Understanding	92.60	16.33	24.04	117.96	-.47
Emotion Management	89.78	12.73	41.55	110.14	-.73
Facial Emotion Perception[c]	30.82	4.19	19.00	37.00	-.75
Vocational Impairment[d]	3.90	.67	3.00	5.00	-

Note. ADOS = Autism Diagnostic Observation Schedule, WCST = Wisconsin Card Sorting Test

[a]Effect sizes are based upon comparisons with normative test values

[b]Scores are standardized with a mean (*SD*) of 100 (15)

[c]Emotion perception accuracy scores range from 0 to 40

[d]Impairment was rated on a 5-point scale (1 = rare, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) using the Cognitive Styles and Social Cognition Eligibility Interview

Running Head: CET FOR ADULTS WITH ASD

Cognitive Enhancement Therapy for Adults with Autism Spectrum Disorder: Results of an 18-Month Feasibility Study

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Running Head: CET FOR ADULTS WITH ASD

Cognitive Enhancement Therapy for Adults with Autism Spectrum Disorder: Results of an 18-Month Feasibility Study

Abstract

Adults with autism experience significant impairments in social and non-social information processing for which few treatments have been developed. This study conducted an 18-month uncontrolled trial of Cognitive Enhancement Therapy (CET), a comprehensive cognitive rehabilitation intervention, in 14 verbal adults with autism spectrum disorder to investigate its feasibility, acceptability, and initial efficacy in treating these impairments. Results indicated that CET was satisfying to participants, with high treatment attendance and retention. Effects on cognition and behavior were also large (range of $d = 1.40$ to 2.29) and highly significant (all $p < .001$). These findings suggest that CET is a feasible, acceptable, and potentially effective approach to the remediation of social and non-social cognitive impairments in verbal adults with autism.

Keywords: Cognitive Enhancement Therapy, cognitive rehabilitation, cognitive remediation, psychosocial treatment, cognitive therapy, adult treatment

Autism spectrum disorder (ASD) is characterized by significant impairments in social interaction, verbal and non-verbal communication deficits, and restricted and repetitive interests and behaviors. Underlying these broad behavioral impairments are core neurobiologically-based deficits in social and non-social information processing (Minshew & Williams, 2007), which result in significant functional disability throughout the lifespan (Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002; Howlin, Goode, Hutton, & Rutter, 2004) at great cost to society (Ganz, 2007). While advances in early detection and intervention approaches attempting to limit the impact of ASD on individuals and their families have been achieved (e.g., Dawson et al., 2010), surprisingly few efforts have been dedicated to advancing the treatment of adults with ASD (Fitzpatrick, Minshew, & Eack, in press). The majority of intervention efforts have focused on children, yet most individuals encounter significant challenges in adulthood due ASD, which result in unemployment and underemployment, poor academic performance, limited social functioning, and a poor quality of life (Howlin, Goode, Hutton, & Rutter, 2004). Growing evidence indicates that the deficits in social and non-social cognition that adults with ASD experience significantly contribute to poor adaptive function in these domains (Berger, Aerts, van Spaendonck, Cools, & Teunisse, 2003; García-Villamisar, Rojahn, Zaja, & Jodra, 2010). Unfortunately, comprehensive approaches designed to address core neurocognitive and social-cognitive impairments in adults with autism have yet to be developed.

Cognitive rehabilitation represents a potentially effective approach to the remediation of information processing impairments in ASD, and has demonstrated considerable efficacy in other populations (e.g., Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Such approaches employ computer-based and/or group-based exercises designed to improve diverse areas of social and non-social cognitive function through repetitive practice and strategic training (Eack, in press). Cognitive Enhancement Therapy (CET; Hogarty & Greenwald, 2006) is an 18-month

integrated, developmental approach to the treatment of impairments in social and non-social cognition through the use of computer-based training exercises in attention, memory, and problem-solving and a small, group-based curriculum designed to facilitate the development of adult social-cognitive milestones. This treatment represents one of the most promising cognitive rehabilitation interventions for verbal adults with ASD due to its developmental approach, comprehensive treatment of deficits in both neurocognition and social cognition, and its targeting of critical domains of impairment in autism.

CET was originally developed for individuals with schizophrenia and trials of the approach with this population have demonstrated large effects on social and non-social cognition (Hogarty et al., 2004; Eack et al., 2009), which have been durable (Hogarty, Greenwald, & Eack, 2006; Eack, Greenwald, Hogarty, & Keshavan, 2010) and generalized to meaningful improvements in key domains of functioning (e.g., Eack, Hogarty, Greenwald, Hogarty, & Keshavan, 2011). The benefits of CET in adults with schizophrenia suggested the possibility that this approach might prove to be feasible and effective for the treatment of similar deficits in verbal adults with autism. Although there are considerable differences between schizophrenia and ASD, remarkable similarities do exist, particularly with regard to impairments in social cognition (Couture et al., 2010). In addition, striking overlap has been observed in the pathophysiology of these disorders (Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2007; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). The core treatment targets of CET (i.e., perspective-taking, social context appraisal, and speed of processing) are also central to the challenges experienced by adults with ASD. Finally, recent evidence of the neuroprotective effects of CET on social and cognitive neural networks has suggested that the approach might affect a shared neurobiologic pathway in both disorders in service of social-cognitive enhancement (Eack et al., 2010b).

To examine the feasibility, acceptability, and potential efficacy of CET in adults with ASD, two initial cohorts of verbal adults with these conditions were recruited to participate in an uncontrolled, 18-month trial of CET adapted for ASD. Primary outcomes included treatment adherence and satisfaction, and secondary outcomes included cognition and social adjustment. We hypothesized that CET could be feasibly applied to verbal adults with ASD once appropriate adaptations were made, and that the intervention would be well-tolerated and acceptable to individuals with these conditions. In addition, we hypothesized that the application of CET to adults with ASD in this feasibility study would provide preliminary evidence of benefits to cognition and adaptive behavior in this population.

Method

Participants

Participants included 14 verbal adults enrolled in a feasibility study of CET for ASD. Individuals were included if they met expert clinical opinion and research criteria for ASD using the Autism Diagnostic Observation Schedule (Lord et al., 2000), criteria for autism on the Autism Diagnostic Interview-R (Lord, Rutter, & Couteur, 1994), were age 18-45, had an IQ $\geq$ 80 as assessed by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), had not abused substances in 3 months prior to enrollment, did not exhibit behavioral problems that would negatively impact other participants in the program, and demonstrated cognitive and social disability on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). This semi-structured interview has been validated in previous studies of CET for patients with schizophrenia, and is used to provide a clinical assessment of cognitive dysfunction and social impairment indicative of the need for treatment.

Enrolled participants were mostly young, with an average age of 25.29 (*SD* = 5.72) years, predominantly male (*n* = 12), and all Caucasian. Over half (*n* = 8) of the participants met criteria

for autism, with the remaining meeting criteria for ASD. Although the majority (n = 12) of individuals had attended some college and the average full scale IQ for the sample was above average (M = 117.70, SD = 16.77, range = 92 to 157), only half (n = 7) of the participants were employed, and all participants, except for one, were living with their family. Of those individuals employed, all were in jobs below levels commensurate with their education and intellectual level.

Measures

Treatment acceptability and adherence.

Measures of treatment acceptability and adherence represented the primary outcome measures for this initial feasibility study of CET in verbal adults with ASD. Treatment acceptability and satisfaction was measured using the Client Satisfaction Questionnaire-8 (CSQ-8; Larsen, Attkisson, Hargreaves, & Nguyen, 1979) with wording adapted for CET. This measure consists of 8 items rated between 1 ("quite dissatisfied") and 4 ("very satisfied") to assess self-reported satisfaction with treatment programs. The CSQ-8 has been widely studied as a reliable and valid measure of treatment acceptability (Larsen, Attkisson, Hargreaves, & Nguyen, 1979), and was completed during the first quarter of treatment and at the end of treatment by research staff independent of the treating clinicians providing CET. Treatment adherence was assessed throughout the course of the study by the treating clinician using attendance logs for neurocognitive training and social-cognitive group session appointments.

Cognitive and behavioral outcomes.

An abbreviated battery of measures of cognition and behavior were included in this research to provide an initial assessment of the efficacy of CET adapted for adults with ASD. Neurocognition was assessed using the NIMH MATRICS Consensus Cognitive Battery (Green et al., 2004), which is a battery of standardized neuropsychological tests originally compiled to

assess the efficacy of cognitive enhancing medication in patients with schizophrenia. This battery assesses neurocognitive dysfunction in a variety of domains relevant to the treatment of ASD, including processing speed, attention/vigilance, verbal and non-verbal working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition. Since the MATRICS battery does not include an assessment of cognitive flexibility, which is a critical domain of impairment in ASD, the battery was expanded to include the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Multiple additional measures of social cognition, which is minimally assessed in the MATRICS battery, included the full Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer, Salovey, Caruso, & Sitarenios, 2003), the Penn Emotion Recognition Test-40 (Kohler et al., 2003), and the Social Cognition Profile (Hogarty et al., 2004). The MSCEIT is a 141-item performance-based measure of emotional intelligence that has been validated for assessing the domains of emotion perception, facilitation, understanding, and management (Mayer, Salovey, Caruso, & Sitarenios, 2003). The Penn Emotion Recognition Test is a 40-item test of facial emotion recognition, which has been shown to assess brain functions supporting emotion perception (Gur et al., 2002a). The Social Cognition Profile is a 50-item clinician-rated measure of social-cognitive behaviors used in previous studies of CET (Hogarty et al., 2004; Eack et al., 2009), which assesses the domains of tolerant (e.g., accepting, cooperative, flexible), perceptive (e.g., foresightful, gistful, sensitive to others' feelings), supportive (e.g., empathic, reciprocal, friendly), and self-confident (e.g., comfortable, assertive, involved) behaviors indicative of adequate social cognition.

Finally, dysfunctional cognitive style and social adjustment were repeatedly assessed using the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004), which is a semi-structured interview designed, in part, to elicit responses and behaviors from participants about cognitive and functional challenges in their lives that reflect the core cognitive

profiles or "styles" that become key treatment targets in CET. Items are rated based on behavioral adjectives from the interview on a 1 ("rare") to 5 ("very severe") scale and provide a dimensional assessment of impoverished (e.g., reduced affect, lack of motivation, difficulty planning), disorganized (e.g., difficulty maintaining attention/staying on task, ineffective inhibition, chaotic/imprecise planning), and inflexible (e.g., obsessive/repetitive thinking, fixed cognitive schema, preoccupation with details) cognitive functioning. Separate interview items covering vocational ineffectiveness, interpersonal ineffectiveness, and adjustment to disability provided a basic assessment of social adjustment and adaptive function.

Cognitive Enhancement Therapy

Cognitive Enhancement Therapy (CET) is a comprehensive, developmental approach to the treatment of social and non-social cognitive impairments that was originally developed for patients with schizophrenia (Hogarty et al., 2004). Over the course of 18 months, CET integrates 60 hours of computer-based neurocognitive training in attention, memory, and problem-solving with a structured 45-session social-cognitive group curriculum designed to facilitate the achievement of adult social-cognitive milestones, particularly perspective-taking and social context appraisal. Neurocognitive training is strategic in nature, and is designed to help individuals improve core deficits in basic information processing that contribute to poor social cognition and social adjustment. A CET coach pairs and guides two individuals to participate in computer-based cognitive exercises for 1 hour each week to develop and practice strategies for improving cognition, including increasing processing speed, appropriately orienting attention, developing a schematization or categorizing capacity, increasing cognitive flexibility, managing frustration, becoming more strategic and foresightful in planning, and increasing their ability to engage in conversations and give support to each other. After several months of neurocognitive training in attention, 6 to 8 participants (3 to 4 pairs) come together to form a social-cognitive

group. Through the use of *in vivo* cognitive exercises and psychoeducation, the weekly 1.5 hour social-cognitive group sessions provide rich secondary socialization experiences that target a broad, theoretically-driven array of social-cognitive abilities ranging from abstracting the "gist" from spontaneous, unrehearsed social interactions to understanding the perspectives of others, accurately appraising novel social contexts, and managing emotions. Generalization of these abilities to everyday life is a key emphasis of the CET group and is supported through homework assignments, individually-tailored recovery/treatment plans, and generalization exercises designed to consolidate learning. Neurocognitive training proceeds concurrently with the social-cognitive groups throughout the remaining course of treatment. The practice principles and methods of the treatment originally developed for patients with schizophrenia are described in detail in the CET manual (Hogarty & Greenwald, 2006).

Several adaptations to CET were made to ensure the applicability of the treatment to the unique needs of adults with ASD. The largest adaptations occurred with regard to the early components of the social-cognitive group curriculum, which originally focused on psychoeducation about schizophrenia. Such content was removed and replaced with the latest knowledge and understanding of ASD and its impact upon cognition, information processing, social cognition, sensory perception, and emotion management. In addition, some of the computer exercises in the neurocognitive training produced sounds that were uncomfortable to some participants, and these exercises were altered to mute such sounds. Coaches also had to alter their approach in working with participants with ASD, who unlike individuals with schizophrenia, often do not ask for help and commonly needed greater clinical outreach and engagement. A more guided, repetitive, and elaborated approach was also employed in the training of some advanced abilities (e.g., providing support, perspective-taking) in the social-cognitive groups, as the impairments in social cognition experienced by individuals with ASD

who have not had normal early periods of social development were at times considerably greater than those observed in schizophrenia. Furthermore, the length of CET treatment was reduced from 2 years to 18 months because of the lack of need for psychiatric stabilization among adults with ASD. Overall, however, we found the need for adaptations to be surprisingly minimal compared to initial expectations, as the majority of the content in CET was perceived as highly applicable by both ASD participants and clinicians. These adaptations are being collated in a supplement to the existing CET treatment manual.

Procedures

Participants were recruited from support groups, community colleges and universities, previous research studies, specialty clinics, and local advocacy groups for an 18-month study of CET for verbal adults with ASD. Upon recruitment, participants were assessed for diagnostic and IQ eligibility by trained research staff experienced with autism and supervised by a study psychologist. A member of the clinical team then conducted a videotaped interview of the participant using the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). Final eligibility determinations were made in consensus meetings based on review of all available diagnostic, testing, and interview data. Eligible participants were then assigned to 18 months of active treatment with CET, and administered cognitive and behavioral outcome measures prior to initiating treatment and every 9 months thereafter. Cognitive assessments were administered by master's-level neuropsychological testers supervised by a study psychologist, and clinical and behavioral assessments were completed by the treating CET clinician. CET was provided by master's and doctoral-level clinicians who were experts in its use in schizophrenia and had been trained in the treatment of ASD. This research was conducted between August, 2009 and December, 2011, and was reviewed and approved annually by the University of Pittsburgh Institutional Review Board. All participants provided written, informed consent prior

to participation.

Results

Treatment Acceptability and Adherence

The primary goal of this study was to assess the feasibility of recruiting an initial sample of adults with ASD and treating them with CET. The community response to recruitment and intake was largely positive. Within a 6-month period, 25 individuals were referred for potential participation in the study, 14 of whom met full study inclusion criteria. Among those who were not enrolled, the majority failed to meet inclusion criteria with 2 individuals not meeting research diagnostic criteria for ASD, 2 demonstrating an IQ < 80, 1 experiencing active substance use problems, and 1 demonstrating behavioral problems that were contraindicated to group participation. In addition, 4 individuals were not interested in participating in an experimental treatment study despite their parents contacting the study to express interest, and 1 individual was interested but could not feasibly participate due to distance from the program.

Of the 14 individuals who enrolled in the study, 11 (79%) completed the entire 18 months of treatment. One participant withdrew at 9 months due to increased hours of employment; 1 was administratively terminated at 9 months due to personality disorder instability; and 1 completed the entire 18 months of the study, but could not attend the social-cognitive groups due to persistent family and transportation problems, and thus was not considered to have completed treatment. Treatment adherence was high across both neurocognitive training (89%) and social-cognitive group (85%) sessions, with an 87% average overall attendance rate at treatment sessions. In addition, treatment satisfaction among all participants (treatment completion ratings for completing participants and interim ratings for partial completers) was also high with average CSQ-8 total and overall satisfaction scores for the program of 3.27 (*SD* = .46) and 3.57 (*SD* = .51) out of 4.00, respectively. These ratings indicate that individuals were "mostly satisfied" to

"very satisfied" with CET.

Effects on Cognition and Behavior

Although the emphasis of this study was to assess the feasibility of adapting and applying CET to verbal adults with ASD, preliminary cognitive and behavioral outcome data were examined to provide an initial assessment of treatment efficacy. Efficacy analyses made use of intent-to-treat linear mixed-effects models that included all 14 individuals who received any exposure to CET, and allowed unequal variances across study timepoints to account for heteroscedasticity (Raudenbush & Bryk, 2002). Unsuccessful attempts were made to collect reliable 18-month data on the two individuals who either withdrew early or were administratively terminated at 9 months. Missing data were therefore handled using the expectation-maximization approach to facilitate intent-to-treat analyses (Dempster, Laird, & Rubin, 1977).

As can be seen in Figure 1, highly significant (all $p < .001$) and large ($d = 1.40$ to 2.29) levels of improvement were observed across composite domains of neurocognition, cognitive style, social cognition, and social adjustment. Neurocognitive improvement was particularly large in the domain of processing speed, which was also the greatest area of non-social cognitive impairment in the sample prior to treatment, and significant levels of improvement were observed in all neurocognitive domains, with the exception of attention/vigilance (see Table 1). In addition, all clinician-rated aspects of dysfunctional cognitive style showed significant levels of improvement.

Social cognition was also significantly improved across both clinician-rated and performance-based measures, particularly with regard to emotion understanding and management. A trend-level ($p = .055$) effect was observed for improvements in emotion perception, which was primarily due to an improvement in accuracy in the perception of sad

faces, $t(25) = 2.43$, $p = .023$, $d = .61$. Importantly, these social-cognitive gains generalized to broader improvements in adaptive function and social adjustment, as large and highly significant levels of improvement were observed in vocational effectiveness, interpersonal effectiveness, and participants' ability to adjust to their condition, as measured by the Cognitive Styles and Social Cognition Eligibility Interview. Taken together, such findings suggest that CET is a feasible, acceptable, and potentially effective approach to the treatment of cognitive impairments in adults with ASD.

Discussion

Adults with ASD experience significant impairments in social and non-social cognition that place profound limitations on their ability to function adaptively. Treatment development efforts for autism have focused primarily on childhood (Kasari & Lawton, 2010), and interventions designed to address the vast array of core neurocognitive and social-cognitive deficits that limit functional outcome in adults with these conditions have yet to be developed. This is the first study to examine the feasibility and applicability of CET, a comprehensive cognitive rehabilitation intervention, in adults with ASD. Results revealed that CET was well tolerated by participants, who were not compensated for attending treatment. Rates of neurocognitive and social-cognitive training session attendance were consistently high, and 79% of the sample was retained for the entire 18-month course of treatment. In addition, when asked about their experience in the program by an independent rater, participants reported high degrees of satisfaction with CET. The results of efficacy analyses were also positive, with large and highly significant levels of improvement observed across all cognitive and behavioral domains assessed. These findings provide the first evidence of the feasibility, acceptability, and initial efficacy of long-term cognitive rehabilitation with CET for verbal adults with ASD.

The results of this feasibility study have several important potential implications for the

treatment of verbal adults with autism. Despite having above-average intelligence scores and being labeled as "high-functioning," it was clear that this sample experienced substantial disability that would warrant the need for cognitive rehabilitation; all participants met study criteria for significant social and cognitive disability. Half of this working-age sample of participants were not employed, those who were employed held jobs well below their academic qualifications, and the majority of the sample was dependent upon their families. The high levels of satisfaction and treatment attendance observed in this study are indicative not only of the feasibility of CET for this population, but also confirm that verbal adults with ASD are interested in continuing to receive treatment in adulthood and are willing to devote a substantial amount of time to participating in interventions that they find beneficial. This further underscores the general need for effective treatments and supports for verbal adults with ASD. Findings regarding treatment efficacy have implications for the plasticity of the adult autism brain. Given that many of these cognitive impairments have been present since early childhood, the large levels of improvement in cognition observed in this preliminary study suggest that there remains a window of opportunity to capitalize on neuroplasticity and positively affect cognition in these conditions well into adulthood. Neuroimaging studies are currently in progress to characterize the neuroplastic effects of CET in autism, and identify the neural mechanisms underlying these improvements.

Despite the implications of this research for understanding and advancing the treatment of adults with ASD, these findings need to be interpreted in the context of a number of limitations. This study was characterized by a modest sample size, which was appropriate for a first feasibility study, but also limits inferences regarding the generalizability of these results. The repeated use of cognitive tests could have also introduced testing effects that resulted in some gains in cognition, although the magnitude of cognitive improvements observed in this

study are unlikely to be fully accounted for by assessments repeated on a 9-month basis. In addition, some behavioral assessments were completed by study clinicians involved in the treatment of participants, although large and significant levels of improvement were also observed on more objective performance-based measures of social and non-social cognition. Finally, the absence of a treatment control condition limits inferences regarding the specificity of the effects of CET compared to usual care or other active treatment approaches. A randomized-controlled trial of CET compared to an appropriately-matched active treatment control is in progress, and further conclusions regarding the efficacy of CET in verbal adults with ASD will be reserved until the completion of this trial.

In summary, this research provides the first evidence of the feasibility of CET, a comprehensive neurocognitive and social-cognitive remediation approach, in verbal adults with ASD. Such cognitive rehabilitation interventions have been available and highly successful to individuals with other neurological disorders, and although these results are limited by a modest sample size and the absence of a treatment control condition, findings suggest that CET is an acceptable and satisfying treatment for verbal individuals with ASD that may have substantial benefits for cognitive and functional outcomes in this population.

References

Berger, H. J. C., Aerts, F. H. T. M., van Spaendonck, K. P. M., Cools, A. R., & Teunisse, J. P. (2003). Central Coherence and Cognitive Shifting in Relation to Social Improvement in High-Functioning Young Adults with Autism. *Journal of Clinical and Experimental Neuropsychology, 25*(4), 502-511.

Couture, S. M., Penn, D. L., Losh, M., Adolphs, R., Hurley, R., & Piven, J. (2010). Comparison of social cognitive functioning in schizophrenia and high functioning autism: more convergence than divergence. *Psychological Medicine*, *40*(4), 569-579.

Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., Donaldson, A., & Varley, J. (2010). Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*, *125*(1), e17.

Dempster, A. P., Laird, N. M., & Rubin, D. B. (1977). Maximum likelihood from incomplete data using the EM algorithm. *Journal of the Royal Statistical Society. Series B (Methodological)*, *39*(1), 1-38.

Eack, S. M. (in press). Cognitive remediation: A new generation of psychosocial interventions for people with schizophrenia. *Social Work.*

Eack, S. M., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2010). One-year durability of the effects of Cognitive Enhancement Therapy on functional outcome in early schizophrenia. *Schizophrenia Research*, *120*(1), 210-216.

Eack, S. M., Greenwald, D. P., Hogarty, S. S., Cooley, S. J., DiBarry, A. L., Montrose, D. M., & Keshavan, M. S. (2009). Cognitive Enhancement Therapy for early-course schizophrenia: Effects of a two-year randomized controlled trial. *Psychiatric Services*, *60*(11), 1468-1476.

Eack, S. M., Hogarty, G. E., Cho, R. Y., Prasad, K. M. R., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2010). Neuroprotective effects of Cognitive Enhancement Therapy against gray matter loss in early schizophrenia: Results from a two-year randomized controlled trial. *Archives of General Psychiatry, 67*(7), 674-682.

Eack, S. M., Hogarty, G. E., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2011). Effects of Cognitive Enhancement Therapy on employment outcomes in early schizophrenia: Results from a two-year randomized trial. *Research on Social Work Practice, 21*(3), 32-42.

Fitzpatrick, L. B., Minshew, N. J., & Eack, S. M. (in press). A systematic review of psychosocial interventions for adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders.*

Ganz, M. L. (2007). The Lifetime Distribution of the Incremental Societal Costs of Autism. *Archives of Pediatrics and Adolescent Medicine, 161*(4), 343-349.

García-Villamisar, D., Rojahn, J., Zaja, R. H., & Jodra, M. (2010). Facial emotion processing and social adaptation in adults with and without autism spectrum disorder. *Research in Autism Spectrum Disorders*, *4*(4), 755-762.

Gilotty, L., Kenworthy, L., Sirian, L., Black, D. O., & Wagner, A. E. (2002). Adaptive skills and executive function in autism spectrum disorders. *Child Neuropsychology*, *8*(4), 241-248.

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S. et al. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. *Biological Psychiatry*, *56*(5), 301-307.

Gur, R. C., Schroeder, L., Turner, T., McGrath, C., Chan, R. M., Turetsky, B. I., Alsop, D.,

Maldjian, J., & Gur, R. E. (2002). Brain Activation during Facial Emotion Processing. *Neuroimage*, *16*(3PA), 651-662.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual: Revised and Expanded*. Odessa, FL: Psychological Assessment Resources Inc.

Hogarty, G. E., & Greenwald, D. P. (2006). *Cognitive Enhancement Therapy: The Training Manual*. University of Pittsburgh Medical Center: Authors. Available through www.CognitiveEnhancementTherapy.com.

Hogarty, G. E., Flesher, S., Ulrich, R., Carter, M., Greenwald, D., Pogue-Geile, M., Keshavan, M., Cooley, S., DiBarry, A. L., Garrett, A., Parepally, H., & Zoretich, R. (2004). Cognitive enhancement therapy for schizophrenia. Effects of a 2-year randomized trial on cognition and behavior. *Archives of General Psychiatry*, *61*(9), 866-876.

Hogarty, G. E., Greenwald, D. P., & Eack, S. M. (2006). Durability and mechanism of effects of Cognitive Enhancement Therapy. *Psychiatric Services*, *57*(12), 1751-1757.

Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2004). Adult outcome for children with autism. *Journal of Child Psychology and Psychiatry*, *45*(2), 212-229.

Kasari, C., & Lawton, K. (2010). New directions in behavioral treatment of autism spectrum disorders. *Current Opinion in Neurology*, *23*(2), 137-143.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., Gur, R. E., & Gur, R. C. (2003). Facial Emotion Recognition in Schizophrenia: Intensity Effects and Error Pattern. *American Journal of Psychiatry*, *160*, 1768-1774.

Larsen, D. L., Attkisson, C. C., Hargreaves, W. A., & Nguyen, T. D. (1979). Assessment of client/patient satisfaction: development of a general scale. *Evaluation and Program Planning*, *2*(3), 197-207.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., Pickles, A., & Rutter, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. *Journal of Autism and Developmental Disorders*, *30*(3), 205-223.

Lord, C., Rutter, M., & Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659-685.

Mayer, J. D., Salovey, P., Caruso, D. R., & Sitarenios, G. (2003). Measuring emotional intelligence with the MSCEIT V2.0. *Emotion*, *3*(1), 97-105.

Minshew, N. J., & Williams, D. L. (2007). The new neurobiology of autism. *Archives of Neurology*, *64*(7), 945-950.

Pinkham, A. E., Hopfinger, J. B., Pelphrey, K. A., Piven, J., & Penn, D. L. (2007). Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophrenia Research*, *99*(1-3), 164-175.

Raudenbush, D. S. W., & Bryk, D. A. S. (2002). *Hierarchical Linear Models: Applications and data analysis methods*. Thousand Oaks, CA: Sage.

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., & Frangou, S. (2011). Autism spectrum disorders and schizophrenia: Meta-analysis of the neural correlates of social cognition. *PloS One*, *6*(10), e25322.

Wechsler, D. (1999). *Manual for the Wechsler Abbreviated Intelligence Scale*. San Antonio, T: The Psychological Corporation.

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American*

Journal of Psychiatry, *168*(5), 472-485.

Table 1

Univariate Effects of Cognitive Enhancement Therapy on Cognition and Behavior in Adults with Autism Spectrum Disorder (N = 14).

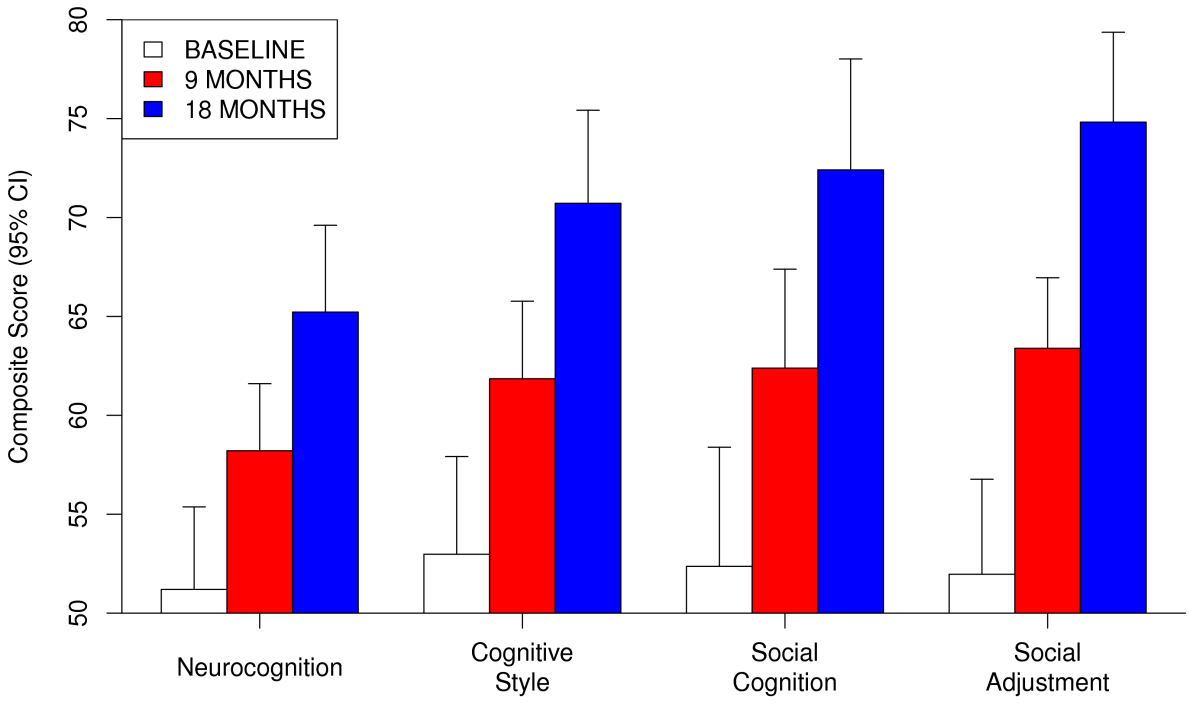
	Baseline		9 Months		18 Months		Analysis		
Variable	*M*	*SE*	*M*	*SE*	*M*	*SE*	*t*	*p*	*d*
Neurocognition[a]	51.20	2.13	58.21	1.73	65.22	2.24	5.23	.000	1.40
Processing speed[b]	38.69	8.26	57.33	6.96	75.98	8.30	4.16	.000	1.22
Attention/vigilance[b]	49.28	8.90	50.97	8.08	52.66	8.93	.45	.657	.12
Working memory[b]	55.59	8.32	71.66	6.84	87.72	7.57	3.96	.001	.81
Verbal learning[b]	53.20	8.10	60.12	7.55	67.03	8.23	2.24	.034	.43
Visual learning[b]	41.03	6.28	55.47	4.26	69.92	6.15	3.19	.004	1.13
Problem-solving[b]	45.82	8.93	56.85	8.18	67.88	7.99	5.00	.000	.63
Cognitive Flexibility									
WCST: Perseverative errors (log)	2.23	.16	1.78	.08	1.32	.19	-2.80	.010	-1.33
WCST: Non-perseverative errors (log)	2.10	.19	1.69	.10	1.27	.19	-2.54	.018	-.93
Cognitive Style[a]	52.98	2.52	61.85	2.00	70.72	2.40	6.15	.000	1.77
Impoverished style[c]	9.54	.44	8.34	.37	7.14	.42	-5.27	.000	-1.01
Disorganized style[c]	8.71	.57	7.68	.50	6.65	.55	-4.22	.000	-.95
Rigid style[c]	10.71	.52	9.49	.44	8.26	.46	-5.81	.000	-1.42
Total impairment, disability, and social handicap[d]	28.77	.99	25.32	.76	21.87	.94	-5.79	.000	-1.69
Highest cognitive style score[c]	11.59	.46	10.13	.40	8.67	.45	-6.28	.000	-1.70
Social Cognition[a]	52.37	3.07	62.39	2.55	72.41	2.86	6.60	.000	2.00
Social Cognition Profile[e]									
Tolerant factor	3.35	.11	3.73	.09	4.11	.10	8.02	.000	1.75
Supportive factor	2.45	.14	3.05	.13	3.65	.14	9.79	.000	2.39
Perceptive factor	2.58	.13	3.15	.08	3.72	.11	7.09	.000	2.04
Confident factor	2.62	.13	3.10	.09	3.58	.10	6.38	.000	1.36

MSCEIT									
Emotion facilitation (*z*)	.21	.28	.16	.23	.11	.23	-.44	.661	-.10
Emotion understanding (*z*)	-.11	.31	.26	.25	.63	.28	2.35	.027	.73
Emotion management (*z*)	-.02	.27	.30	.20	.61	.21	2.19	.038	.62
Penn Emotion Recognition Test-40[f]	30.80	1.09	31.32	1.08	31.85	1.12	2.01	.055	.24
Social Adjustment[a]	51.97	2.45	63.39	1.82	74.82	2.32	7.43	.000	2.29
Vocational ineffectiveness[g]	3.77	.16	3.24	.13	2.71	.17	-5.53	.000	-1.52
Interpersonal ineffectiveness[g]	4.03	.13	3.43	.12	2.82	.16	-7.48	.000	-2.54
Adjustment to disability[g]	3.12	.15	2.52	.09	1.92	.08	-7.22	.000	-1.82

Note. Means and standard errors are adjusted from linear mixed-effects intent-to-treat models.
[a]Composite score scaled with a mean (*SD*) of 50 (10), with higher scores indicating better cognitive and behavioral functioning
[b]Percentile score
[c]Scores range from 3 to 15, with higher scores indicating greater cognitive dysfunction
[d]Scores range from 9 to 45, with higher scores indicating greater impairment from cognitive dysfunction
[e]Scores range from 1 to 5, with higher scores indicating better social-cognitive functioning
[f]Scores range from 0 to 40, with higher scores indicating better social-cognitive functioning
[g]Scores range from 1 to 5, with higher scores indicating worse social adjustment
MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test, WCST = Wisconsin Card Sorting Test

Figure Caption

Figure 1. Effects of Cognitive Enhancement Therapy on Composite Indexes of Cognition and Behavior in Adults with Autism Spectrum Disorder (N = 14).


BASELINE
9 MONTHS
18 MONTHS
Composite Score (95% CI)
50
55
60
65
70
75
80
Neurocognition
Cognitive Style
Social Cognition
Social Adjustment