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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 include: 1) considerable and broad cognitive impairments at baseline testing in the ASD adults enrolled in this trial (n = 40), and 2) initial evidence of the effectiveness of CET in ameliorating deficits and enhancing adaptive function. Despite normal or higher levels of intelligence, this sample was performing at the 32th percentile on overall neurocognitive function with at least one domain score below the 1% in most individuals, indicating a clear need for cognitive rehabilitation. Preliminary analyses of treatment effects suggest a significant advantage of CET for improving social cognition (d = .63), neurocognition (d = .66), and major role function (d = .76) compared to the EST control condition. In addition, analyses of changes in brain function have indicated significant increases in brain activity supporting theory of mind and emotion regulation abilities in participants treated with CET compared EST. These findings suggest both the need and potential for CET to be a significant treatment advance for verbal adults with autism. Importantly, improvements were found in daily life function and in brain circuitry supporting core abilities.

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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, 2013), 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 1 year 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) which was 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. 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 on a limited budget.

2.2. Task Progress and Accomplishments

This project was awarded and began on September 30, 2011. We have completed 24.0 months of the project and have made substantial progress toward accomplishing our aims. Most notably, we have randomized 40 adults with ASD assigned to either CET (n = 22) or EST (n = 18), finished pre-treatment data collection with all 40 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 on schedule in the conduct of this clinical trial.

There have been no substantive modifications to the specific aims of this project during this year. However, we proposed an addition to Specific Aim #2 in our previous report. Given the faster than expected rate of participant enrollment which has allowed quick completion of recruitment, we will 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, and approval from DoD to expand the scope of this project, 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
Task 3 - Install subject tracking system (mos 1-3). Appropriate use of funds that are directly budgeted for this project.

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. Recent results from studies using this task in schizophrenia have shown hypofunction in orbitofrontal and anterior cingulate cortical regions, as well as connectivity between fronto-temporal regions when engaging in perspective-taking during the task (Eack et al., in press).

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 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 is 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 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 increases 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 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, we have conserved DoD funds in this project year in order to maintain this subject recruitment and diagnosis infrastructure into Year 03.

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 actively treating CET and EST cases, as well as receiving supervision by Drs. Eack, Greenwald, and Mrs. Hogarty in the implementation of these interventions.

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 37 additional participants that accumulated on the waiting list during the time the study was under consideration for funding and since the project has begun. Of these individuals 35
Given the faster than expected rate of recruitment, we have been extraordinarily high at 92.5%. That the majority of attrition has occurred prior to beginning the interventions, treatment retention to date has been high, and while this is a long-term controlled trial, attrition has been low at 15%. To date, 6 individuals have been lost to attrition: 1 individual withdrew from CET at 9 months due to residential instability, 1 withdrew from CET at 9 months due to transportation issues, 1 withdrew from CET prior to 9 months due to increased employment, and 1 withdrew from EST at study baseline due to lack of interest in the program. In addition, 2 early participants were withdrawn and allowed to switch treatment conditions prior to initiating treatment, because 1 CET participant had interest only in EST, and 1 EST participant had interest primarily in CET. These individuals were retained as "filler" participants in compassionate care in their desired condition, primarily to facilitate the formation of the first CET group.

Task 14 - Treatment Phase, participants treated with CET or EST (mos 6-42). All 40 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 have completed all 45 social-cognitive group sessions, all of the neurocognitive training, and have completed 18-month (treatment completion) assessments. The first cohort of EST participants (n = 6) have also completed individual stress management training and psychoeducation about ASD and have completed their 18-month (treatment completion) assessments during the same time frame. The second cohort of CET (n = 8) participants have been receiving their treatment condition for 16-18 months and have completed the social-cognitive group curriculum. The second cohort of EST (n = 6) participants are currently in the late stages of psychoeducation and learning how to manage their condition, and have also been treated for 16 to 18 months. These two cohorts will are expected to complete 18-month (treatment completion) assessments by November, 2013.

Treatment satisfaction has been high, and while this is a long-term controlled trial, attrition has been low at 15%. To date, 6 individuals have been lost to attrition: 1 individual withdrew from CET at 9 months due to residential instability, 1 withdrew from CET at 9 months due to transportation issues, 1 withdrew from CET prior to 9 months due to increased employment, and 1 withdrew from EST at study baseline due to lack of interest in the program. In addition, 2 early participants were withdrawn and allowed to switch treatment conditions prior to initiating treatment, because 1 CET participant had interest only in EST, and 1 EST participant had interest primarily in CET. These individuals were retained as "filler" participants in compassionate care in their desired condition, primarily to facilitate the formation of the first CET group.

Given the majority of attrition has occurred prior to beginning the interventions, treatment retention to date has been extraordinarily high at 92.5%.

Task 15 - Follow-up testing (mos 12-48). Given the faster than expected rate of recruitment, we have been able to begin treatment with participants quickly and have been completing 9-month (mid-treatment) and 18-month (post-treatment) assessments with them as they progress through CET and EST. To date, 24 9-month assessments (14 in CET; 11 in EST) and 17 18-month assessments (7 in CET; 10 in EST) have been completed. These have included comprehensive batteries of neurocognition, social cognition, and adaptive function, as well as fMRI and structural neuroimaging assessments. For individuals who complete CET or EST, they will also be followed-up for 1-year post-treatment to assess treatment durability, which have already begun. To date, 2 participants have reached and completed their 30-month (1-year post-treatment) assessments (1 in CET; 1 in EST).
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 40 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. No significant differences have emerged between CET and EST participants in most demographic or pre-treatment cognitive characteristics, although slightly more EST participants have completed some college education than CET participants ($p = .033$). 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 1, overall neurocognitive functioning for the sample was at the 32th 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. Given the often overlooked cognitive deficits verbal adults with ASD experience, we have published a paper outlining these findings (Eack et al., 2013). In addition, we have demonstrated that the level of cognitive impairment experienced by this and the combined pilot sample of adults with ASD we have studied at baseline is highly deficient compared to healthy volunteers and is in fact, comparable to patients with schizophrenia across both social and non-social cognitive domains (see Figure 1; Eack et al., in press). Taken together these findings increasingly indicate that verbal adults with ASD experience significant impairments in neurocognition and social cognition that are likely to be responsive to CET.


Task 19 - Preliminary and final data analyses of outcome data at 18 mos (mos 24-48+). We have now published the preliminary pilot study of CET in 14 verbal adults with ASD and shown considerable levels of improvement in cognition and adaptive function (Eack et al., in press). While we are in the middle phases of our controlled trial sponsored by the DoD, results from interim 9 and 18-month assessments of treatment efficacy are demonstrating promise. Figure 2 presents interim treatment findings on composite indices of neurocognitive and social-cognitive function using field standard measures administered by raters blind to treatment assignment. The neurocognitive composite consisted of the MATRICS Consensus Cognitive Battery, as well as Trails B and the Wisconsin Card Sorting Test to provide additional measures of cognitive flexibility. The social-cognitive composite consisted of the Mayer-Salovey-Caruso Emotional Intelligence Test, and the Penn Emotion Recognition Test, both performance-based measures of social cognition that have been well-validated in previous psychiatric research. Composites were scaled with a mean (SD) of 50 (10) at baseline, with higher scores reflecting better performance. Analyses include all 26 participants who have reached their 9- or 18-month time point (14 in CET; 12 in EST), as well as those who have withdrawn early.

### Table 1. Pre-Treatment Characteristics of Adults with ASD Randomized to an 18-Month Trial of CET or EST ($N = 40$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CET</th>
<th>SD / %</th>
<th>EST</th>
<th>SD / %</th>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>22.95</td>
<td>6.35</td>
<td>23.00</td>
<td>4.19</td>
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<tr>
<td>% Male</td>
<td>18</td>
<td>82%</td>
<td>17</td>
<td>94%</td>
</tr>
<tr>
<td>% College Educated</td>
<td>11</td>
<td>55%</td>
<td>16</td>
<td>89%</td>
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<tr>
<td>Full Scale IQ</td>
<td>109.73</td>
<td>15.10</td>
<td>109.56</td>
<td>16.13</td>
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<tr>
<td>Neurocognition Composite</td>
<td>27.94</td>
<td>26.91</td>
<td>36.28</td>
<td>32.46</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>41.75</td>
<td>34.04</td>
<td>49.07</td>
<td>34.82</td>
</tr>
<tr>
<td>Vigilance</td>
<td>34.45</td>
<td>28.92</td>
<td>41.77</td>
<td>36.87</td>
</tr>
<tr>
<td>Working Memory</td>
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<td>23.77</td>
<td>34.24</td>
<td>34.34</td>
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<tr>
<td>Verbal Learning</td>
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<tr>
<td>Visual Learning</td>
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<td>30.69</td>
<td>38.12</td>
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<td>Reasoning</td>
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<tr>
<td>Social Cognition</td>
<td>30.13</td>
<td>24.29</td>
<td>34.25</td>
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</tbody>
</table>

$^a$Composites are given in percentile scores

![Figure 1](image_url)
Results show medium-to-large levels of improvement in neurocognitive ($d = .66$) and social-cognitive ($d = .63$) function favoring CET at treatment completion compared to EST (see Figure 2). Mid-treatment effects at 9-months were showing trend-level improvement in social cognition, although as expected, by the time participants were exposed to the full course of CET significant gains in both social cognition and neurocognition were observed. The greatest domains of neurocognitive improvement in CET were cognitive flexibility ($d = .79$) and visual learning ($d = .68$). The greatest domains of social-cognitive improvement were the use of emotions to facilitate thinking ($d = .64$) and facial emotion perception ($d = .61$). It should be noted that despite the preliminary nature of these analyses and the use of a small sample size, CET effects on composite indexes neurocognitive and social-cognitive function are already reaching conventional two-tailed significance thresholds at treatment completion, which is highly encouraging. Taken together, these findings suggest that this novel cognitive rehabilitation intervention is having an impact on core cognitive deficits in ASD. Significant improvements, particularly in anxiety ($p = .025$) and depression ($p = .008$), are also being observed in EST, which is focusing on the stress-related aspects of ASD. Consequently, it is expected that this trial will not only produce evidence supporting cognitive rehabilitation in adult ASD, but also the novel individual-based approach to stress regulation and illness management that is provided in EST.

**Figure 2.** Effects of Cognitive Enhancement Therapy Versus Enriched Supportive Therapy on Composite Indexes of Neurocognition and Social Cognition at Baseline, 9 Months of Treatment and 18 Months of Treatment.

*Note. Composite indexes are scaled with a mean (SD) of 50 (10) at baseline, with higher scores reflecting better performance.*

With regard to the translation of these effects to domains of adaptive function, clinical interview data from blind raters and family/collateral reports are in the process of being cleaned for participants with post-treatment data. Preliminary analyses of data on major role functioning (performance and independence in...
major life activities, such as school, work, and independent living) indicate that both individuals in CET ($d = 1.73$) and EST ($d = .97$) are demonstrating large improvements in role functioning, with CET showing a statistically significant advantage over EST by treatment completion ($p = .038$). In other functional domains, such as participation in social leisure activities, CET participants demonstrated a more rapid improvement than EST participants at 9-months ($p = .039$), but large and equivalent levels of improvement in CET ($d = 1.39$) and EST ($d = 1.43$) were observed by treatment completion that were not significantly different ($p = .927$). Although these findings must be interpreted with caution until functional outcome data are cleaned and finalized, such results suggest that as hypothesized, the gains in cognitive function that are resulting from CET are producing meaningful and considerable improvements in adaptive function in this sample of verbal adults with ASD. It should be noted that EST, which focuses on stress and illness management, is also demonstrating efficacy for improving some domains of functional outcome in this population.

**Task 20** - Preliminary and final data analyses of outcome data 1-year post treatment (durability) (mos 36-48+). To be completed.

**Task 21** - Analyses of fMRI data at baseline (mos 6-24). Pre-treatment MRI data have been collected with processing speed, perspective-taking, theory of mind, and emotion regulation fMRI measures on participants randomized since DoD support for this project began. Of the 40 individuals randomized, 12 were recruited and randomized before this project began with initial funding from Autism Speaks, which did not

*Figure 3. Functional Brain Activity Differences Between Adults with Autism Spectrum Disorder ($N = 27$) and Healthy Volunteers ($N = 19$).*
support MRI data collection. While these 12 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. Of the remaining individuals, 27 have completed their baseline MRI, and 1 could not complete the MRI due to claustrophobia that was not apparent at screening in a mock scanner. In addition, 19 healthy volunteers have completed identical scanning procedures. Results of comparisons between adults with ASD and healthy volunteers at baseline have helped provide standardization estimates for healthy brain function and regions of interest for areas that are most likely to be affected by CET.

As can be seen in Figure 3, expected regions of interest in social-cognitive brain networks are showing consistent abnormalities in the sample of adults with ASD compared to healthy controls across the 4 tasks. For the theory of mind task, ASD participants are demonstrating hyperactivity in the medial prefrontal cortex during mentalizing conditions compared to controls, potentially signifying greater difficulty in recruiting this circuitry during theory of mind (Figure 3a). Similar prefrontal hyperactivity was found in the left dorsolateral prefrontal cortex during for the perspective-taking task, where those with autism demonstrated significantly greater activation in this region during perspective-taking than controls (Figure 3b). Such findings could suggest the reliance on more executive and problem-solving networks rather than social-cognitive networks for understanding the perspective of others. For the processing speed task, individuals with ASD are demonstrating reduced insular activity, particularly in the left insula during increased processing load, which has been associated with selective attention and arousal (Figure 3c). For the emotion regulation task, participants with ASD are showing significantly reduced activity in the right dorsolateral prefrontal cortex during the frustration components of this task compared to controls, indicating difficulty in using prefrontal networks to regulate emotion during cognitive processing (Figure 3d). All of these findings not only provide loci for subsequent treatment effect analyses, but also elucidate social-cognitive brain dysfunction that may be indicative of the pathophysiology of ASD and will be the focus of subsequent published reports.

Task 22 - Analyses of fMRI data at 18 mos (mos 25-48). Preliminary post-treatment (9- or 18-month, depending on length of enrollment) analyses of all fMRI tasks have been completed in 15 participants (8 in CET; 7 in EST). As can be seen in Figure 4a, those treated with CET are demonstrating significant differential increases in brain activity in the bilateral amygdala during our emotion regulation task, suggesting an increase in emotion regulation circuitry function during the course of CET compared to those treated with EST (all uncorrected p < .002). Figure 4b presents treatment x time interactions favoring CET improvement over EST during our theory of mind task, where participants treated with CET are showing a large and robust increase in the left temporo-parietal junction (uncorrected p = .001), which is a key region in the theory of mind network. Interestingly, the medial prefrontal hyperactivity that was observed compared to controls at baseline is also somewhat increased in the CET group post-treatment, which is perhaps now more coordinated with temporal regions to improve theory of mind abilities. This finding will be followed-up with functional connectivity analyses in future reports. Figure 4c presents areas of differential decrease in activation during our perspective-taking task. Prominent increases in BOLD-signal activity were not observed in CET compared to EST during this task. However, a broad bilateral decrease in insular cortex and superior temporal gyrus activity was found in CET compared to EST participants (all uncorrected p < .001). Reduction in insular cortex activity likely reflects a disengagement of self-appraisal (first-person perspective) functions with the onset of third-person perspective-taking. The superior temporal gyrus has been repeatedly implicated in theory of mind and the down-regulation of this region in CET participants may indicate a greater efficiency of processing the perspectives of others or could reflect a compensatory reliance on other brain regions to complete the task. These questions will be more thoroughly investigated as the sample size grows to allow for connectivity and brain-behavior analyses. Finally, Figure 4d presents data on treatment x time interactions for our processing speed task, in which CET participants are demonstrating a smaller, but significant (uncorrected p < .001) increase in medial prefrontal activity around the anterior cingulate cortex during greater processing speed load compared to EST. This might suggest an important increase in executive and attentional control functions during the task that is improving speed of processing in CET participants. Correlations with cognitive and behavioral data will be forthcoming and are expected to connect these changes in brain function to improved social and non-social cognitive processes. While preliminary, these findings support the feasibility of elucidating and characterizing the neural mechanisms of response to cognitive rehabilitation in adults with ASD, and indicate the potential of neuroplasticity well into adulthood in these disorders.
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). The first cohort of participants in the study has now completed 18-month assessments and we are preparing a newsletter of these findings to distribute to participants and their family members.
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 preliminary report on study progress and treatment effects has also been prepared as more participants are completing 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.
Task 28 - Recruitment of healthy volunteers (N = 40) (mos 12-36). We have created a sub-study brochure and advertisements for healthy volunteers, received IRB approval for these materials, and with the support of the ACE, contacted healthy volunteers in our previous studies as well as wider research registries.
and the community. This has given us access to a large pool of potentially eligible healthy volunteers from which to draw our sample.

Task 29. Screen healthy volunteers for eligibility (mos 12-36). We have currently screened 29 healthy volunteers and matched them to the current sample of trial participants. Of these individuals screened, 19 have been enrolled and 17 have completed all aspects of their participation in the study.

Task 30. Collect cross-sectional neuroimaging data in healthy volunteers (mos 12-36). We have currently completed neuroimaging data collection on 19 age- and gender-matched healthy volunteers. These data are being preprocessed and analyzed to determine the number of additional healthy volunteers needed to standardize the fMRI tasks, which may be up to 40 healthy controls.

Task 31. Collect cross-sectional cognitive and clinical data in healthy volunteers (mos 12-36). We have currently completed cognitive and clinical data collection on 18 age- and gender-matched healthy volunteers.

3. KEY RESEARCH ACCOMPLISHMENTS

- Identification of core deficits in elementary cognitive abilities in verbal adults with autism, despite intact levels of intelligence
- Identification of cross-diagnostic similarities in cognitive deficits in ASD and schizophrenia, the disorder for which the efficacy of CET and EST were previously demonstrated and the disorder with which verbal adults with ASD are often misdiagnosed
- Adaptation of two promising intervention approaches (CET and EST) to adults with ASD
- On schedule recruitment and randomization of 40 adults with ASD to this controlled clinical trial
- Significant and medium-to-large differential levels of social and non-social cognitive improvement favoring participants treated with CET, but with significant improvements in EST as well
- Promising interim analyses demonstrating large levels of improvement in social adjustment among both CET and EST treated participants, with significant advantages in major role adjustment in CET compared to EST
- Identification of significant differential changes in underlying neural circuitry in CET compared to EST participants reflecting neuroplastic changes in social-cognitive brain networks modulated by cognitive rehabilitation

4. REPORTABLE OUTCOMES

- Manuscripts, abstracts, presentations:
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
Informatics 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. Because there was no community treatment as usual for verbal adults with ASD, we designed an enriched supportive treatment approach for this trial, which focused on understanding the disorder and managing stress and emotions. As a result, this study assesses the comparative efficacy of two new treatment approaches for verbal adults with ASD. Study 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 social and nonsocial cognitive domains; (2) CET and EST can be feasibly implemented with adults with ASD with minimal attrition and high degrees of satisfaction; (3) CET offers a potentially highly significant advantage over routine supportive therapies in its ability to improve cognitive and functional outcomes in this population; and (4) CET may achieve its benefits on social and non-social cognition through altering neural networks that underlie these abilities.

So What? The need for interventions to treat the core cognitive problems present in adults with ASD is great. Individuals with ASD live 60 years of their lives as adults and yet there are no existing evidence-based treatments. The potential, especially for high functioning adults with ASD, to have productive and satisfying lives certainly exists but will not be achieved without more effective interventions. CET is a cognitive rehabilitation intervention that aims to address the core 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 comparison to an Enriched Supportive Therapy (EST). Current findings suggest that there are 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


