TRI-CITY MENTAL HEALTH SERVICES
MHSA Innovations Planning
Summary of Key Research Findings: Cognitive Enhancement Therapy
November, 2011

I. Purpose for this Summary of Key Research Findings

This summary is intended to foster shared understanding about key research findings for Cognitive Enhancement Therapy (CET), an evidence-based practice, being explored by the CET workgroup as part of the delegates' planning process for the Innovations Component of MHSA. This literature review relied on easily accessible data sources such as Google to identify key footnoted sources. Electronic databases used for more rigorous literature searches such as PsycINFO, MEDLINE, or PSYNDEX were not needed for this purpose.

II. Summary of Studies Focused on CET

1. Hogarty G, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, Kechavan M, Cooley S, DiBarry AL, Garrett A, Parepally H, Zoretich R. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. *Archives General Psychiatry*, v 61, Sep 2004, pp. 866-876. www.archgenpsychiatry.com
   a. Background:
      i. The University of Pittsburgh Institutional Review Board assessed the study annually
      ii. The National Institute of Mental Health (NIMH) sponsored the clinical trials - MH-30750
      iii. The Archives of General Psychiatry, sponsored by the American Medical Association, publishes original, peer reviewed articles. This journal has the highest impact factor in psychiatry in 2009. (Journal Citations Report and Journals Performance Indicators)
   b. Type of study:
      i. 2-year, randomized controlled trial with neuropsychological and behavioral assessments completed at baseline and at 12 and 24 months
   c. Study's objective:
      i. To determine the differential effects of CET on cognition and behavior compared with state-of-the-art enriched supportive therapy (EST). According to NIMH's clinical trial descriptor, "EST is the commonly recommended treatment for control and experimental subjects in psychosocial trials." http://clinicaltrials.gov/ct2/show/NCT00167362
   d. Participants:
      i. 121 symptomatically stable, non-substance-abusing but cognitively disabled and chronically ill patients with schizophrenia or schizoaffective disorder
         a) 59% males/41% female, 37.3 average age (standard deviation 8.9: 18 - 60 yrs), 89% White/11% African American, length of illness 15.7 years (9.3 standard deviations), time since last worked 4 years (25% not worked in 10 years), 25% completed high school or less, 44% attempted college, 31% completed college
         b) All participants were fluent in English, treated w/FDA approved antipsychotic medication, free of serious alcohol or drug abuse in the preceding 6 months, with an IQ of 80 or greater
   e. Results:
      i. By 2 years, effect sizes for CET exceeded 1 standard deviation for all composites (neurocognition, processing speed, cognitive style, social cognition, social adjustments) except symptoms. The clinical stability of participants at baseline and the efficacy of Personal Therapy in symptom management that participants had been in treatment with prior to the study were identified as possible dynamics influencing the lack of change in Symptoms.
      ii. In terms of "real-world" outcomes: relapse was not a hypothesized outcome because most participants were many years past their last psychotic episode. This study did not provide job finding, training, or placement; only referrals of interested participants to the local Office of Vocational Rehabilitation. Nonetheless, greater number of CET participants

(26%) than EST participants (8%) found volunteer positions at 24 months. Many participants were older and desired improved quality of life more than a job or return to school. In addition, work disincentives of disability programs and a difficult labor market also influenced the participants' decisions. In addition, Major Role Performance for CET participants (60%) vs EST participants (42%) equaled or exceeded the participants' best premorbid or previous functioning at 24 months.

f. Limitations of study:
   i. As is the case with most behavioral findings, assessments reflect "unblinded" clinicians. More research is needed to evaluate the success of blinding psychosocial treatments.
   ii. Clear reservations exist for using neuropsychological tests to assess longitudinal outcome measures - a condition for which these tests were not designed.
g. Recommendations:
   i. Study researchers do not recommend deconstructing the software exercises and group components. A study of the similarly organized Ben Yishay program shows the whole was clearly superior to the component parts. (Rattok J, Ben-Yishay Y, Lakin P, Piasetsky E, Ross B, Silver S, Vakil E, Zide E, Diller L, Outcome of differential mixes in a multidimensional neuropsychological rehabilitation program. *Neuropsychology*. 1991; 6:395-415.
   ii. CET results can not be generalized to all patients with schizophrenia.
      a) Behavioral, compensatory approaches might be preferable for the most severely impaired or intellectually compromised subpopulations of patients. (van der Gaag M, Kern RS, van den Bosch RJ, Liberman RP. A controlled trial of cognitive remediation in schizophrenia. *Schizophr Bull.* 2002; 28: 167-176.
      b) Cognitive behavior therapy, personal therapy, skills training, and family psychoeducation may be more appropriate for those in the subacute, stabilization phase. (Hogarty GE. *Personal Therapy for Schizophrenia and Related Disorders: A Guide to Individualized Treatment.* New York, NY: Guilford Press; 2002.

2. Hogarty G, Greenwald D, Eack. Durability and mechanism of effects of cognitive enhancement therapy. *Psychiatric Services*, v 57, 12, Dec 2006, pp. 1751-1757. www.psychiatryonline.org
   a. Background:
      i. The University of Pittsburgh Institutional Review Board assessed the study annually
      ii. The National Institute of Mental Health (NIMH) sponsored the clinical trials - MH-30750
      iii. Psychiatric Services is a journal of the American Psychiatric Association.
   b. Objective:
      i. To determine whether previously reported effects of CET were maintained one year after treatment.
   c. Participants:
      i. 106 of 121 participants who completed the 2004 clinical trials underwent behavioral and neuropsychological assessments one year later.
   d. Results:
      i. Except for neurocognition composite index, the four remaining composite measures that demonstrated a significant CET effect at two years (processing speed, social cognition, cognitive style, social adjustment) continued to be significant at 36 months. As was true at one and two years, no differential treatment effect on the symptom composite was evident at three years.
      ii. Given that improvement in processing speed was a strong partial mediator of both social cognition and social adjustment, the study proposes that early improvement in processing speed might be the condition upon which greater-than-expected treatment improvement in these areas depend
      iii. In terms of other "real-world" effects, the between-group difference in engagement in a social, recreational, or therapeutic group activity during year 3 was significant.
         a) 18 CET participants (30%) vs. 4 EST participants (9%) engaged in these activities.

a) 24 CET participants (40%) vs. 7 EST participants (16%) engaged in some type of vocational rehabilitation. No significant difference was found in the proportion of participants who had paid employment but 16 CET participants (27%) while 2 EST participants (4%) performed in a volunteer role during year 3.
b) Among participants who had been ill for less than 15 years, CET had a greater effect than EST on ability to shop for basic necessities and a marginally greater effect with regard to household cleaning.
c) Among participants who were less psychotic at baseline, those who received CET were better at managing finances than those who received EST.

b. Limitations:
   i. CET was developed for clinically stable but functionally disabled patients in the postacute, recovery phase of illness. Among these patients, neuropsychological and behavioral changes appear to follow a longitudinal course that is largely independent of symptom improvement. The same might not be true for acutely symptomatic patients who receive cognitive training.

2. Eack S, Greenwald D, Hogarty S, Cooley S, DiBarry AL, Montrose D, Keshavan, M. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatric Services*, v 60, 11, Nov 2009, pp. 1468-1476. www.psychiatryonline.org
   a. Background:
      i. The University of Pittsburgh Institutional Review Board assessed the study annually
      ii. The National Institute of Mental Health (NIMH) sponsored the clinical trials - MH-60902, MH-79537
      iii. Psychiatric Services is a journal of the American Psychiatric Association
   b. Type of study:
      i. Random assignment to CET or enriched supportive therapy (EST), an illness management intervention utilizing psychoeducational and applied coping strategies, and treated for 2 years. Multivariate composite indexes of cognitive, social adjustment, and symptom domains derived from assessment batteries administered annually by computer-based tests and raters not blind to treatment assignment.
   c. Objective:
      i. To examine the two-year effects of an integrated neurocognitive and social-cognitive rehabilitation program, CET, on cognitive and functional outcomes in early-course schizophrenia
   d. Participants:
      i. 58 early-course outpatients with schizophrenia or schizoaffective disorder
         a) Most participants had been ill for fewer than 5 years, with an average duration of 3.19 years (+ or - 2.24 years), illness had been stabilized on antipsychotic medication, first psychotic symptoms (including duration of untreated illness) within the past 8 years, not been abusing substances for at least 2 months before study enrollment, showed significant social and cognitive disability, IQ greater than or equal to 80
         b) Average age 25.92 (+ or - 6.31 years), 40 males (60%), 40 Caucasians (69%), 11 African Americans (19%), 6 Asians (10%), 1 other ethnicity, college education (67%), most were not employed at baseline (74%)
   e. Results:
      i. After two years of treatment, highly significant and large differential effects were observed favoring CET on the composite indexes of cognitive style, social cognition, social adjustment, and symptomatology. CET participants also showed significant and medium-size improvement on the neurocognitive composite by the second year of treatment.
      ii. Significant effects of CET were observed with regard to vocational and social functioning, global adjustment, activities of daily living, and instrumental task performance

a) 54% of CET participants were actively engaged in paid, competitive employment at the end of 2 years of treatment, compared with recipients of EST (18%)
b) Significant effects of CET were observed on multiple measures of negative symptoms, as well as on measures of anxiety and depression

iii. Largest cognitive effects observed through CET were in social cognition, a domain that has been linked to functional outcome and remained largely unresponsive to pharmacological treatment.

iv. Participants did not show significant improvement in processing speed - in contrast to the 2004 study with long-term patients. The pretreatment mean processing speed of individuals receiving CET in this study was comparable with that of patients with chronic illness after 2 years of CET treatment. Study researchers point to the possibility of a ceiling effect for speed of processing. That processing speed and other aspects of attention are less impaired among patients with early-course schizophrenic illness is not unexpected and this research suggests that more complex social-cognitive processes may be the most critical targets for early intervention programs.

f. Limitations:

i. The participants were mostly male and Caucasian - reducing the ability for the results to be generalized to more diverse samples.

ii. Treatment groups were not matched for the number of hours of clinician contact; therefore, results could reflect the nonspecific effects of increased clinician contact on outcome.

iii. Clinicians making the assessments were not blind to the treatments to which patients were assigned.

iv. The research had a somewhat modest sample size - N=58. This study is, however, the largest and longest early-course study of cognitive rehabilitation to date. A priori power analysis based on previous studies guided the researchers toward a sample size that was sufficient to reliably detect the medium to large CET effects observed in this study.

3. Eack S, Greenwald D, Hogarty S, Keshavan M. One-year durability of the effects of cognitive enhancement therapy on functional outcome in early schizophrenia. *Schizophrenia Research*, 120, 2010, pp. 210-216. www.elsevier.com

a. Background:

i. The National Institute of Mental Health (NIMH) sponsored the clinical trials - MH-60902, MH-79537

ii. Schizophrenic Research is the official journal of the Schizophrenia International Research Society

b. Objective:

i. To conduct a one-year follow-up study of functional outcome in early course schizophrenia patients treated with either CET or an Enriched Supportive Therapy control to examine the degree to which the previously reported significant effects of CET on functional outcome in this sample were maintained post treatment.

iii. Participants:

a. 42 (72%) of the original 58 early-course outpatients from study #3 were available for follow-up at one-year post-treatment.

iv. Results:

a. Findings indicated that the benefits of CET on broad functional outcomes (e.g. social functioning, major role adjustment, competitive employment) were maintained in the year following treatment completion, particularly among those demonstrating earlier neurocognitive improvement.

b. Functional improvement was observed in both CET and EST. Improvements in EST likely reflect the benefits of psychoeducation and relapse prevention strategies, including stress reduction techniques, based on the effective Personal Therapy.

c. Patients treated with CET continued to demonstrate significant improvements in social adjustment compared to EST.
d. Previously noted differential benefits of CET on competitive employment at the end of treatment were not maintained at one-year post-treatment - not due to loss of employment among CET participants (48%) but rather improved post-treatment improvement of EST participants. The continued improvement of EST participants is likely reflective of lasting benefits of stress regulation on functioning.
e. The strongest effects from CET accrued only after 2 years of treatment.

4. Eack S, Keshavan M. Foresight in schizophrenia: a potentially unique and relevant factor to functional disability. *Psychiatric Services*, 59, Mar 2008, pp. 256-260. www.psychiatryonline.org
   a. Background:
      i. The National Institute of Mental Health (NIMH) sponsored the clinical trials - MH-60902, MH-79537
      ii. Psychiatric Services is a journal of the American Psychiatric Association.
   b. Objective:
      i. This research reports on the results of an opportunistic, exploratory longitudinal study of foresight among persons in the early course of schizophrenia and its unique predictive utility in regard to functional outcome. Foresight is the ability to think of long-term consequences of one's behavior and apply this information to guide present and future actions. Data were used from an on-going clinical trial of cognitive enhancement therapy (see study #3).
   c. Design and Methods:
      i. One factor that has been largely overlooked in schizophrenia research on functional disability is the ability to think of the long-term consequences of one's behavior and use this information to guide present and future actions.
   d. Participants:
      i. 58 early-course outpatients who participated in study #3
   e. Results:
      i. Persons with schizophrenia were impaired on global measures of foresightfulness and that foresight was significantly predictive of future functional outcome, above and beyond the effects of psychopathology and neurocognitive ability.
   f. Limitations:
      i. As an exploratory study, this study highlighted many future areas of further study: development and psychometric evaluation of expanded measures of foresightfulness, development of performance-based measures, comparison with an age-matched group of participants without schizophrenia, and larger sample size.

5. Eack S, Hogarty G, Cho R, Prasad KMR, Greenwald D, Hogarty S, Keshavan M. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia. *Archive General Psychiatry*, v 67, 7, July 2010, pp. 674-682. www.archgenpsychiatry.com
   a. Background:
      i. The University of Pittsburgh Institutional Review Board assessed the study annually
      ii. The National Institute of Mental Health (NIMH) sponsored the clinical trials - MH-60902, MH-79537
      iii. The Archives of General Psychiatry, sponsored by the American Medical Association, publishes original, peer reviewed articles. This journal has the highest impact factor in the field of psychiatry. (Journal Citations Report and Journals Performance Indicators)
   b. Type of study:
      i. 2-year randomized clinical trials comparing CET to enriched supportive therapy, including annual structural magnetic resonance imaging and cognitive assessments.

c. Objective:
   i. To examine differential changes in brain morphology in early course schizophrenia during cognitive rehabilitation vs supportive therapy. No study prior to this research examined the long-term neurobiologic effects of cognitive rehabilitation in schizophrenia.
d. Participants:
   i. 53 participants who previously participated in study #3
e. Results:
   i. Results support the study's hypothesis that cognitive rehabilitation provides a neuroprotective effect against gray matter loss in key regions of the brain implicated in social and non-social cognitive impairment in schizophrenia.
   ii. The differential effects of CET on gray matter change were significantly related to improved cognitive outcome, with patients who experienced less gray matter decline and greater gray matter increases also demonstrating significantly greater cognitive improvements over the 2 years of study.
   iii. The neurobiologic changes were found to be significant mediators of CET effects on cognition.
   iv. These findings persisted after adjusting for a variety of potential demographic, illness, and medication confounders and suggest that CET can have direct benefits to the brains of patients with schizophrenia.
f. Limitations:
   i. Functional neuroimaging data are needed to better understand the effects of CET on brain function.
   ii. CET effects on brain regions commonly implicated in neurocognitive dysfunction in schizophrenia were quite modest. While this study provides important information on the potential neuroanatomical effects of cognitive rehabilitation in early schizophrenia, future studies are clearly needed to continue to characterize the effects of CET on a variety of neurobiologic parameters.
   iii. Associations between gray matter and cognitive change were exploratory and not corrected for multiple inference testing, as a result, these findings need to be interpreted with caution until confirmatory replications are available.
   iv. This study is also limited by the absence of an appropriately matched group of healthy individuals
   v. Although replication and further neurobiologic characterization is needed, these findings support the potential for cognitive rehabilitative approaches to positively affect the brain in schizophrenia.

7. Eack S, Hogarty G, Greenwald D, Hogarty S, Keshavan M. Effects of cognitive enhancement therapy on employment outcomes in early Schizophrenia: results from a 2-year randomized trial. *Research on Social Work Practice, 21(1),* pp. 32-42.
   a. Background:
      i. The University of Pittsburgh Institutional Review Board reviewed and approved the study annually.
   b. Type of study
      i. 2-year randomized controlled trial comparing CET and EST with a variety of employment and cognitive measures prior to participation and every year following

c. Study's objective:
   i. To examine the effects of psychosocial cognitive rehabilitation on employment outcomes in a randomized controlled trial for individuals with early course schizophrenia
d. Participants:
   i. 58 symptomatically stable, non-substance abusing but cognitively disables and chronically ill schizophrenia and schizoaffective patients who had experienced the onset of first psychotic symptoms with the last 8 years: majority male, (n=40), 29.92 average age (SD= 6.31), majority male (n=40), Caucasion (n=40), length of illness average 3.19 (SD=2.24) years since first psychotic symptom, few employed at baseline (n=15), most had attended college (n=39)
e. Results:
   i. Examination of the 2 year results on CET employment outcomes compared to EST employment outcomes shows that a greater proportion of individuals receiving CET were competitively employed in paid jobs. Individuals receiving CET earned significantly more money per week and were more satisfied with their employment status. No significant difference emerged with regard to full-time employment, but CET participants were more likely to work on a part-time basis. Individuals receiving CET engaged in more skilled work, although the difference was only significant at a trend level (p=.110).
   ii. Together the findings suggest that not only did CET improve the likelihood that early course individuals with schizophrenia would engage in employment, but participation in CET also resulted in greater income and satisfaction with employment.

III. Summary of Other Reviews: Expert Panel Review of CET + Meta Analysis

1. Meeting Summary: role of cognitive enhancement therapy in public mental health systems, New York State Psychiatric Institute, New York, NY, June 5, 2008
   a. Source: http://www.nyebpcenter.org/LinkClick.aspx?fileticket=Rc1hjBZxDrk%3D&tabid=169
   b. Attendees:
      i. Expert advisors from New York Office of Mental Health (NYOMH), Yale University School of Medicine, University of Maryland School of Medicine, Dartmouth Medical School, Columbia University, University of Medicine & Dentistry of New Jersey, University of North Carolina at Chapel Hill, and JFK - Johnson Rehabilitation Institute
   c. Purpose
      i. To review the evidence on the practical impact of cognitive enhancement for persons with schizophrenia and the implications of this evidence for the investment of finite public mental health funds
      ii. With improvements in pharmacology and psychiatric rehabilitation, cognitive deficits remain a barrier to recovery for some consumers. Some MYOMH service providers and private not-for-profit agencies have started using various approaches to cognitive enhancement, and cognitive enhancement has been added to the personalized recovery oriented services license as an optional service.

iii. To date, providers typically have focused on computer-based technologies with a wraparound of appropriate individualized assessments. Informal feedback and observations from both providers and consumers suggest that these strategies are popular with consumers, can increase self-esteem among participants, and can help with functional outcomes when linked to a specific goal.

iv. NYOMH is interested in learning which ingredients of cognitive enhancement are necessary for demonstrated improvements (e.g. computer-based technology, high quality assessment, other techniques).

d. What is currently known about enhancing functional outcomes - work, social relationships, and living independently

i. Meta-analysis of 26 randomized, controlled trials of cognitive enhancement in schizophrenia including 1,151 participants found that: (McGurk S, Twamley E, Sitzer D, McHugo G, Mueser K. A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry*, 164: 12, December 2007, pp. 1791 - 1802, www.ajp.psychiatry.org)

a) Cognitive enhancement was associated with significant improvements in cognitive performance (effect size = 0.41), psychosocial functioning (effect size = .36), and symptoms (effect size - 0.28)

b) The effects of cognitive enhancement on psychosocial functioning were significantly stronger in studies that provided adjunct psychiatric rehabilitation compared to those that provided cognitive enhancement alone

c) In five of six studies providing both psychiatric rehabilitation and cognitive enhancement, cognitive enhancement improved outcome beyond the effect of psychiatric rehabilitation alone

ii. No single cognitive enhancement program will work for everyone. A variety of different approaches demonstrated a positive impact on functional outcomes measured in a variety of ways.

e) Practitioners are cautioned to proceed carefully with this emerging promising area:

i. Avoid premature adoption before designing studies that parse out components to determine which aspects of cognitive enhancement are necessary and sufficient for improved outcomes. (Note recommendation from CET researchers to avoid deconstructing components for implementation - II.1.g.i on page 2)

ii. Develop a manual to standardize treatment and provide fidelity measurements

iii. Design studies that also track long-term recovery; don't get lost in short-term or intermediate goals

iv. Design scientifically fair studies (such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

f) Parallels to Traumatic Brain Injury

i. Cognitive enhancement is a system of therapeutic activities based on brain behavior relationships. Its goal is to achieve functional change by re-establishing learned patterns of behavior, establishing new patterns of cognitive activity, establishing external compensatory mechanisms, and enabling people to adapt to their cognitive disability to improve overall functioning.

ii. The relationship between cognitive functioning and global functioning is not evident in the literature, and strikingly little is known about who benefits from which interventions

g) Under what conditions can a cognitive-enhancement or remediation intervention be expected to have a significant impact on a person's everyday functioning?

i. When it is linked with an evidence-based practice where the functional goal is clear

ii. This intervention should possibly be reserved for individuals without grave intellectual disabilities; the literature on this topic only includes people with an IQ above 70.

h. How does impact vary by type of cognitive enhancement intervention and by type of collateral intervention (i.e. what else, if anything, must be present for cognitive enhancement to improve functional outcomes)?

    i. Cognitive enhancement is not something everyone receives and it cannot be limited to a single intervention; an expert is needed to match cognitive enhancement treatment to outcome

i. What are the simplest ways to determine whether these interventions are being implemented and sustained?
    i. Documentation of how cognitive enhancement fits into overall goals and how it interfaces with other treatments provided in centers
    ii. Documentation that cognitive enhancement strategy is individualized and linked to a clear functional goal
    iii. Need to develop manualized intervention with affordable staff training and fidelity measures
    iv. Develop statewide system of outcomes monitoring that can be summarized for providers with suggestions for improving fidelity. A shared decision-making tool can provide one source of data.

x. Implications for research data
    i. Provide more data on the incremental benefit of cognitive enhancement beyond an otherwise comprehensive package of care
    ii. Provide data delineating the necessary and sufficient principles of cognitive enhancement (e.g., Do you need this computer piece? What is the benefit of neuropsychological testing? and how they contribute to outcomes such as work and the ability to live independently. However, the number of participants required for such a study may make it unfeasible.
    iii. Examine variety of cognitive enhancement approaches
    iv. Include intervening variables - e.g. hope, self-efficacy, therapeutic alliance, that might mediate the effect of cognitive enhancement on outcomes