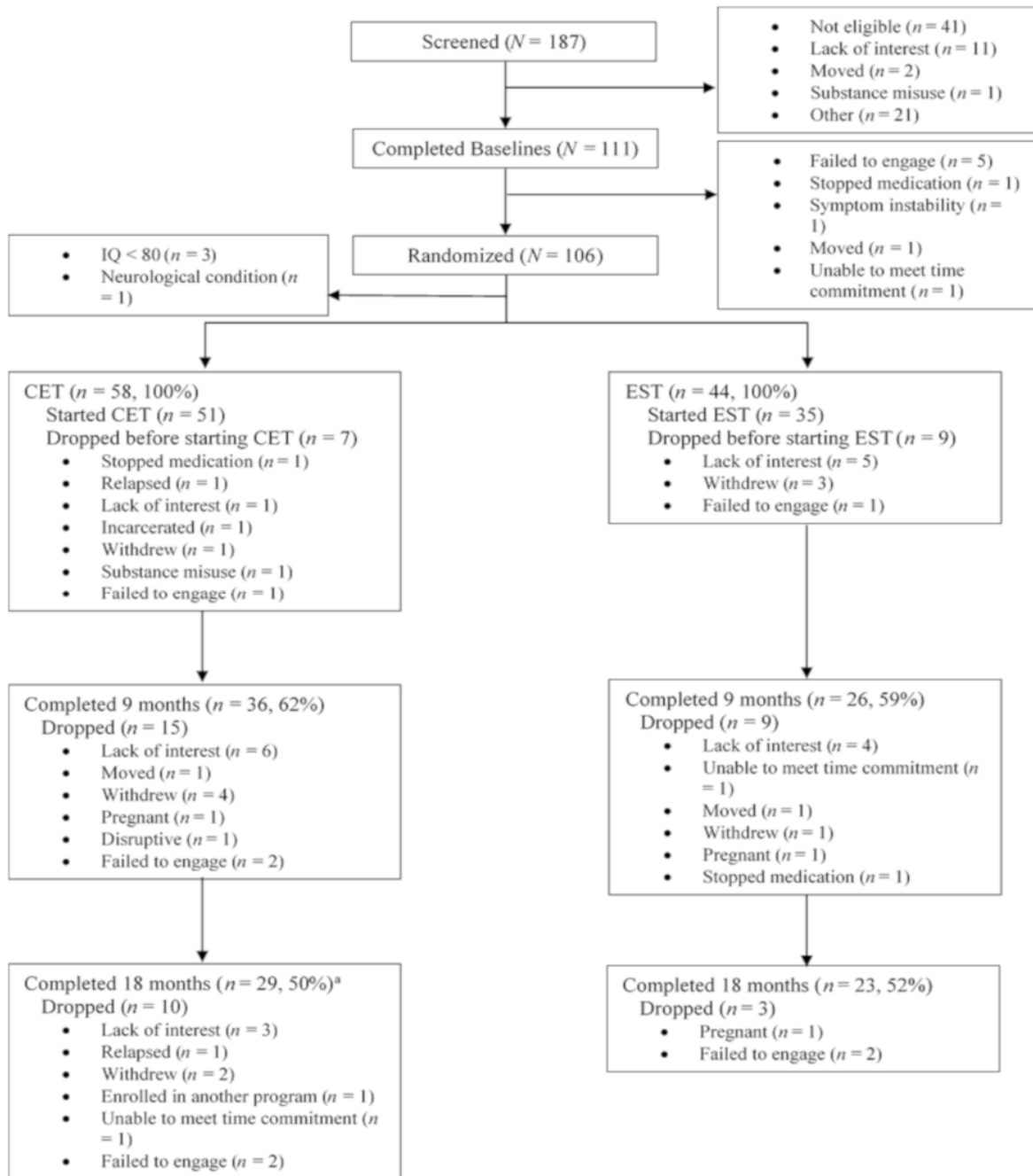


Confirmatory Efficacy of Cognitive Enhancement Therapy for Early Schizophrenia: Results from a Multi-Site Randomized Trial  
**ONLINE SUPPLEMENT**

CONSORT Diagram of Participant Flow Throughout a Multi-Site Trial of Cognitive Enhancement Therapy (CET) Versus Enriched Supportive Therapy (EST) for Early Course Schizophrenia (*Note.* <sup>a</sup>Three subjects who dropped prior to 18-months returned to complete 18-month assessments. These subjects are included in the intent-to-treat sample, but not included in the treatment completer sensitivity analyses.)



*Description of Study Measures*

Measure	Description	Total or Subscales Scores Used in Composite
<b>Cognition Composite (<math>\alpha = .75</math>)</b>		
MATRICES Consensus Cognitive Battery (MCCB) (1, 2)	Standardized, reliable, and validated tool designed as an outcome measure for cognitive enhancing clinical trials in schizophrenia (1). 60 minute testing duration covering the cognitive domains most impaired by the condition of schizophrenia (subscales). A complete list of the cognitive measures included in the MCCB can be found at <a href="http://www.matricsinc.org/mccbtestlist/">http://www.matricsinc.org/mccbtestlist/</a> .	Processing speed, attention vigilance, working memory, verbal learning, visual learning, problem solving, and social cognition
<b>Social Adjustment Composite (<math>\alpha = .81</math>)</b>		
Major Role Adjustment Inventory (3)	32-item, structured interview-based scale assessing functional performance in the areas of employment, social functioning, role functioning, and overall community functioning. Has been a standard and reliable measure in all previous CET trials in schizophrenia.	Employment, relationships outside the home, relationships inside the home, major role adjustment, and overall functioning
Social Adjustment Scale-II (4)	45-item, structured interview-based assessment of functional performance in the general areas of work functioning, functioning in the household, external family relationships, social leisure, and personal well-being. Used in previous CET trial due to good reliability.	Work affinity, interpersonal anguish, primary relations, social leisure, self-care, and role functioning
Global Assessment of Functioning (GAF) (5)	Measure of global functioning in the week prior to evaluation that yields a single summary score. The GAF is a commonly used and psychometrically sound measure (6).	Summary score
Strauss-Carpenter Outcome Scale (SCOS) (7)	A short (4-item), interview-based assessment of four distinct outcome domains: (1) 'Duration of non-hospitalization or psychiatric disorder', (2) 'Social contacts', (3) 'Usefully employed', and (4) 'Absence of symptoms'. Only items (2) and (3) were used for the purposes of the social adjustment composite. SCOS is a reliable and commonly used measure of outcome in the schizophrenia (7).	Social contacts and usefully employed
<b>Symptom Composite (<math>\alpha = .86</math>)</b>		
Brief Psychiatric Rating Scale (BPRS) (8)	24-item interview-based measure of general psychiatric symptomatology (e.g., anxiety, tension, grandiosity, depressive mood, blunted affect, bizarre behavior) in the last week. The BPRS is a commonly used measure and has	Anxiety-depression, withdrawal-retardation, thought disorder, and hostility

	been a standard and reliable measure in all previous CET trials in schizophrenia.	
Raskin Depression Scale (9)	3-item scale assessing severity of depression based on verbal report, observed behavior, and report of secondary symptoms of depression (e.g., lack of appetite). Yields a total score. Has been a standard and reliable measure in all previous CET trials in schizophrenia.	Total score
Covi Anxiety Scale (10)	3-item scale assessing severity of anxiety based on verbal report, observed behavior, and report of somatic complaints (e.g., heart pounding or racing). Yields a total score.	Total score
Wing Negative Symptoms Scale (11)	6-item scale of severity of negative symptoms, including flat affect, poverty of speech, slowness of movement, underactivity, social withdrawal, and amotivation. Yields a total score. Has been a standard and reliable measure in all previous CET trials in schizophrenia.	Total Score
Scale for the Assessment of Negative Symptoms (12)	25-item, commonly used interview- and observational-based assessment of severity of negative symptoms. Items are categorized into subscales of affective flattening, alogia, avolition-apathy, role function, asociality anhedonia, and attention. The role function and attention subscales were not used. Both global ratings and average subscales scores are generated, for which only the average subscale scores were used in the symptom composite.	Affective flattening, alogia, avolition-apathy, and asociality anhedonia
Scale for the Assessment of Positive Symptoms (13)	34-item interview- and observational-based assessment of severity of positive symptoms in the last week. Items are categorized into subscales of hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Both global ratings and average subscales scores are generated, for which only the average subscale scores were used in the symptom composite.	Hallucinations, delusions, bizarre behavior, and thought disorder
Montgomery-Asberg Depression Rating Scale (MADRS) (14)	10-item interview- and observational-based assessment of severity of depressive symptoms (e.g., apparent sadness, inner tension, reduced appetite, concentration difficulties, suicidal thoughts). Yields a total score. MADRS is a reliable measure of depression symptomatology and is sensitive to change overtime (14).	Total Score
<b>Additional Social Cognition Measures</b>		
Mayer-Salovey-Caruso	141-item standardized computer-administered and performance-based assessment of emotion processing and management that yields 4 subscales scores. The MSCEIT has good reliability and validity (2, 16).	Perceiving, facilitating, understanding, and managing emotions

Emotional Intelligence Test (MSCEIT) (15)		
Penn Emotion Recognition Test-40 (17)	Measures the ability to accurately identify different emotions (i.e., happy, sad, anger, and fear) in 40 colored images of human faces with a computer-administered, performance-based, and forced-choice format. Generates a total score of correctly identified emotions.	Total score
The Awareness of Social Inference Test (TASIT) (18)	Used the Social Inference-Enriched Test of the TASIT, which is a performance-based assessment that includes 16 short video vignettes (15 to 60 seconds) of social exchanges between actors. After watching a vignette, participants are asked four questions regarding their perceptions of lies or sarcasm in the social exchange. A total score is generated of correct responses.	Total score
Hinting Task (19)	Requires theory of mind to infer the genuine intentions of a character's indirect speech to a second character across 10 short stories read by the test administrator. Created as a performance-based measure of theory of mind ability in people with schizophrenia (19). A total score of correct responses is yielded reflecting a participant's ability to correctly perceive the hint of the character's true intention.	Total score

*Note.* CET = Cognitive Enhancement Therapy

*Effects of CET and EST on Individual Cognition, Social Adjustment and Symptom Measures (N = 102)*

Measure	CET (n = 58)			EST (n = 44)			18-Month Effect Size		
	Baseline <i>M (SE)<sup>a</sup></i>	Month 9 <i>M (SE)<sup>a</sup></i>	Month 18 <i>M (SE)<sup>a</sup></i>	Baseline <i>M (SE)<sup>a</sup></i>	Month 9 <i>M (SE)<sup>a</sup></i>	Month 18 <i>M (SE)<sup>a</sup></i>	<i>d<sup>CET</sup></i>	<i>d<sup>EST</sup></i>	<i>d</i>
<b>MCCB<sup>b</sup></b>									
Processing Speed	36.35 (1.51)	41.60 (1.66)	43.16 (1.88)	40.78 (1.72)	41.53 (1.94)	46.07 (2.15)	.60	.46	.14
Attention/Vigilance	37.74 (1.56)	43.26 (1.55)	42.28 (1.65)	39.81 (1.77)	37.15 (1.81)	38.96 (1.88)	.39	-.07	.46
Working Memory	42.45 (1.32)	43.79 (1.48)	46.26 (1.60)	43.42 (1.50)	42.19 (1.73)	44.01 (1.82)	.38	.06	.32
Verbal Learning	40.70 (1.22)	38.09 (1.47)	38.76 (1.73)	43.67 (1.38)	40.29 (1.73)	42.81 (1.97)	-.21	-.09	-.12
Visual Learning	40.12 (1.47)	43.84 (1.67)	42.53 (1.83)	41.55 (1.67)	44.03 (1.96)	42.77 (2.08)	.22	.11	.11
Problem-Solving	41.81 (1.41)	42.12 (1.63)	45.08 (1.87)	43.59 (1.60)	44.01 (1.91)	47.63 (2.14)	.31	.38	-.07
Social Cognition	44.18 (1.78)	48.76 (2.13)	49.79 (2.61)	45.78 (2.00)	45.77 (2.50)	44.43 (2.99)	.42	-.10	.52
<b>Social Adjustment</b>									
MRAI: Employment	-.17 (.14)	.08 (.15)	.27 (.20)	.21 (.15)	.42 (.18)	.51 (.23)	.45	.31	.14
SAS-II: Work Affinity	.07 (.18)	.31 (.17)	.58 (.19)	-.06 (.18)	.10 (.17)	.23 (.19)	.60	.34	.26
MRAI: Relationships Outside the Home	.06 (.12)	.03 (.15)	.05 (.20)	-.04 (.14)	.30 (.18)	.20 (.22)	-.01	.26	-.27
SAS-II: Interpersonal Anguish	.18 (.13)	.29 (.13)	.28 (.15)	-.20 (.14)	.22 (.15)	.05 (.16)	.11	.27	-.16
SAS-II: Primary Relations	.08 (.14)	.26 (.14)	.24 (.15)	-.10 (.17)	.01 (.17)	-.07 (.18)	.16	.03	.13
SAS-II: Social Leisure	.02 (.13)	-.07 (.16)	.02 (.19)	-.01 (.15)	.11 (.19)	-.10 (.20)	-.01	-.11	.10
MRAI: Major Role Adjustment	-.16 (.13)	.83 (.19)	1.25 (.26)	.21 (.15)	.66 (.23)	.76 (.28)	1.41	.55	.86
MRAI: Overall Functioning	.00 (.14)	.36 (.19)	.76 (.26)	-.02 (.15)	.45 (.23)	.35 (.29)	.74	.36	.38
GAF	.06 (.12)	.44 (.15)	.66 (.22)	-.03 (.14)	.67 (.17)	.64 (.24)	.67	.74	-.07
SAS-II: Self-Care	-.16 (.13)	.08 (.15)	.13 (.18)	.22 (.14)	.13 (.18)	.09 (.19)	.31	-.14	.45
MRAI: Relationships Inside the Home	.03 (.14)	.24 (.15)	.34 (.16)	-.05 (.16)	.06 (.19)	-.06 (.20)	.32	-.00	.32
SAS-II: Role Functioning	-.10 (.13)	.18 (.17)	.35 (.20)	.14 (.15)	.63 (.19)	.40 (.22)	.45	.26	.19
SCOS: Social Contacts	-.12 (.13)	-.22 (.16)	-.00 (.21)	.19 (.14)	.06 (.19)	-.35 (.23)	.13	-.57	.70
SCOS: Usefully Employed	-.10 (.13)	.21 (.16)	.21 (.22)	.13 (.15)	1.02 (.19)	.72 (.24)	.31	.59	-.28
<b>Symptoms</b>									
BPRS: Anxiety-Depression	.13 (.12)	.38 (.13)	.42 (.14)	-.13 (.14)	.07 (.16)	.37 (.15)	.31	.54	-.23
Raskin Depression	.09 (.11)	.14 (.13)	.39 (.15)	-.05 (.13)	.07 (.16)	.25 (.16)	.35	.35	.00
Covi Anxiety	.17 (.12)	.20 (.14)	.36 (.16)	-.18 (.14)	.06 (.16)	.20 (.17)	.21	.41	-.20
BPRS: Withdrawal-Retardation	-.11 (.13)	.04 (.14)	.09 (.19)	.13 (.15)	.02 (.17)	-.02 (.21)	.20	-.15	.35
Wing Negative Symptom	-.09 (.14)	.30 (.16)	.36 (.23)	.14 (.15)	.24 (.19)	.20 (.26)	.44	.06	.38
BPRS: Thought Disorder	-.08 (.13)	.08 (.15)	-.01 (.19)	.10 (.15)	.39 (.17)	.22 (.21)	.06	.12	-.06
BPRS: Hostility	-.04 (.14)	.31 (.14)	.40 (.17)	.06 (.16)	.08 (.17)	.18 (.18)	.43	.11	.32

SANS: Affective Flattening	-.12 (.13)	.05 (.15)	.07 (.18)	.12 (.14)	.17 (.17)	.08 (.20)	.20	-.04	.24
SANS: Alogia	-.10 (.13)	.12 (.13)	.26 (.15)	.12 (.15)	.10 (.15)	.07 (.16)	.37	-.05	.42
SANS: Avolition-Apathy	-.11 (.12)	.29 (.16)	.19 (.22)	.19 (.14)	.38 (.19)	.45 (.25)	.33	.29	.04
SANS: Asociality	.06 (.13)	.06 (.15)	.35 (.18)	-.07 (.15)	.47 (.18)	.16 (.20)	.29	.22	.07
SAPS: Hallucinations	-.06 (.13)	.18 (.12)	.16 (.13)	.07 (.15)	.25 (.14)	.14 (.14)	.22	.07	.15
SAPS: Delusions	.02 (.13)	.17 (.13)	.18 (.15)	-.03 (.15)	.36 (.15)	.25 (.16)	.17	.29	-.12
SAPS: Bizzare Behavior	.05 (.13)	.28 (.15)	.31 (.17)	-.03 (.15)	-.08 (.18)	-.04 (.18)	.26	-.01	.27
SAPS: Thought Disorder	-.09 (.13)	.24 (.15)	.05 (.17)	.10 (.15)	.16 (.18)	.18 (.18)	.14	.08	.06
MADRS Depression	.16 (.11)	.28 (.12)	.45 (.14)	-.15 (.13)	.22 (.15)	.30 (.16)	.34	.53	-.19

**Additional Social Cognition Measures**

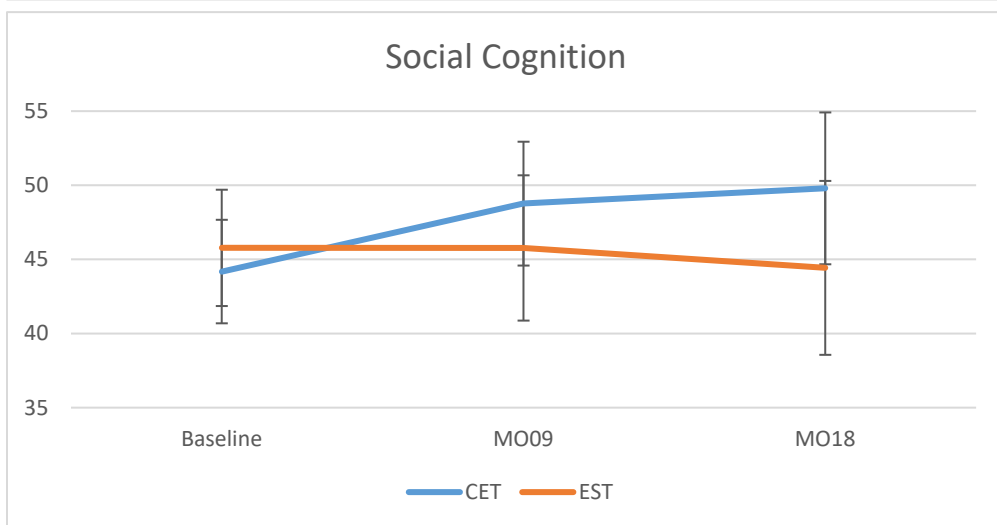
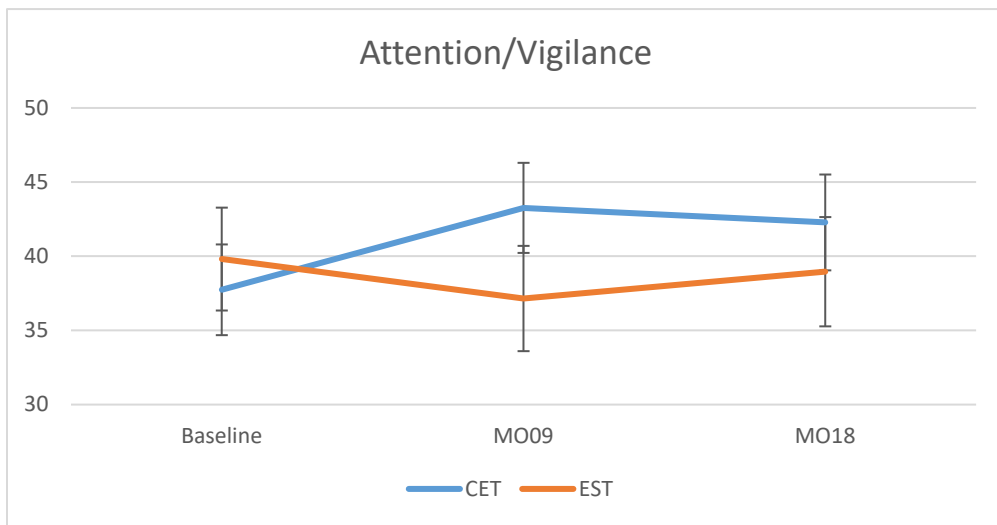
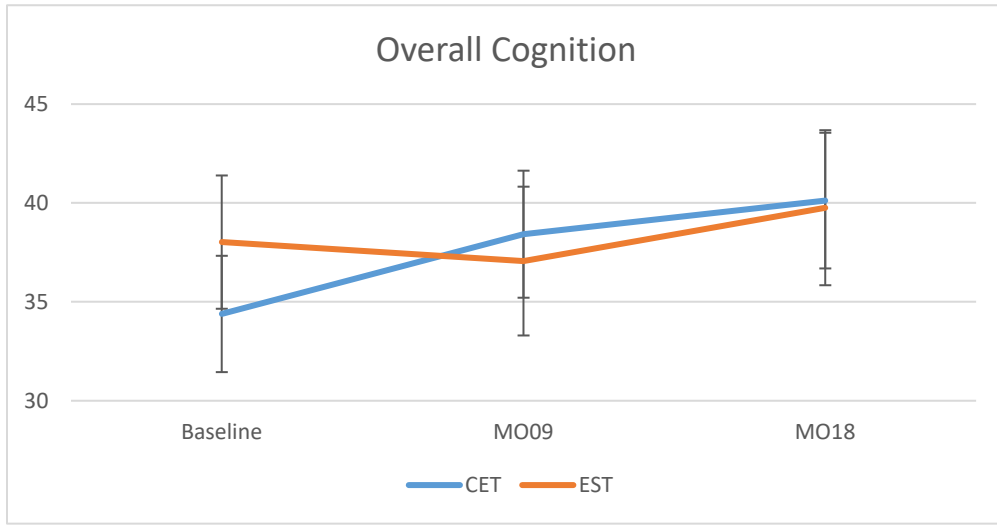
MSCEIT: Perceiving Emotions	-.04 (.13)	.13 (.13)	.23 (.16)	.04 (.15)	.19 (.15)	-.03 (.18)	.27	-.07	.34
MSCEIT: Facilitating Emotions	.00 (.13)	.17 (.15)	.40 (.15)	-.06 (.15)	.13 (.17)	-.08 (.17)	.40	-.02	.42
MSCEIT: Understanding Emotion	-.02 (.13)	.20 (.16)	.14 (.17)	.01 (.15)	-.18 (.18)	.04 (.19)	.16	.03	.13
MSCEIT: Managing Emotions	-.03 (.13)	.31 (.15)	.36 (.16)	.03 (.15)	.11 (.17)	.07 (.18)	.39	.04	.35
Penn: Emotion Recognition	.02 (.13)	.02 (.16)	-.03 (.18)	-.02 (.16)	-.06 (.19)	.26 (.20)	-.05	.28	-.33
TASIT: Social Inference	-.11 (.14)	.34 (.15)	.36 (.16)	.15 (.16)	.32 (.17)	.43 (.18)	.46	.27	.19
Hinting Task: Theory of Mind	-.17 (.13)	-.10 (.17)	-.25 (.20)	.23 (.15)	-.43 (.20)	-.25 (.23)	-.08	-.47	.39

*Note.* CET = Cognitive Enhancement Therapy; EST = Enriched Supportive Therapy; MCCB = MATRICS Consensus Cognitive Battery (1, 2); MRAI = Major Role Adjustment Inventory (3); SAS-II = Social Adjustment Scale-II (4); GAF = Global Assessment of Functioning (5); SCOS = Strauss-Carpenter Outcome Scale (7); BPRS = Brief Psychiatry Rating Scale (8); Raskin = Raskin Depression Scale (9); Covi = Covi Anxiety Scale (10); Wing = Wing Negative Symptoms Scale (11); SANS = Scale for the Assessment of Negative Symptoms (12); SAPS = Scale for the Assessment of Positive Symptoms (13); MADRS = Montgomery-Asberg Depression Rating Scale (14); MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test (15); Penn ER-40 = Penn Emotion Recognition Test-40 (17); TASIT = The Awareness of Social Inference Test (18), Hinting Task (19).

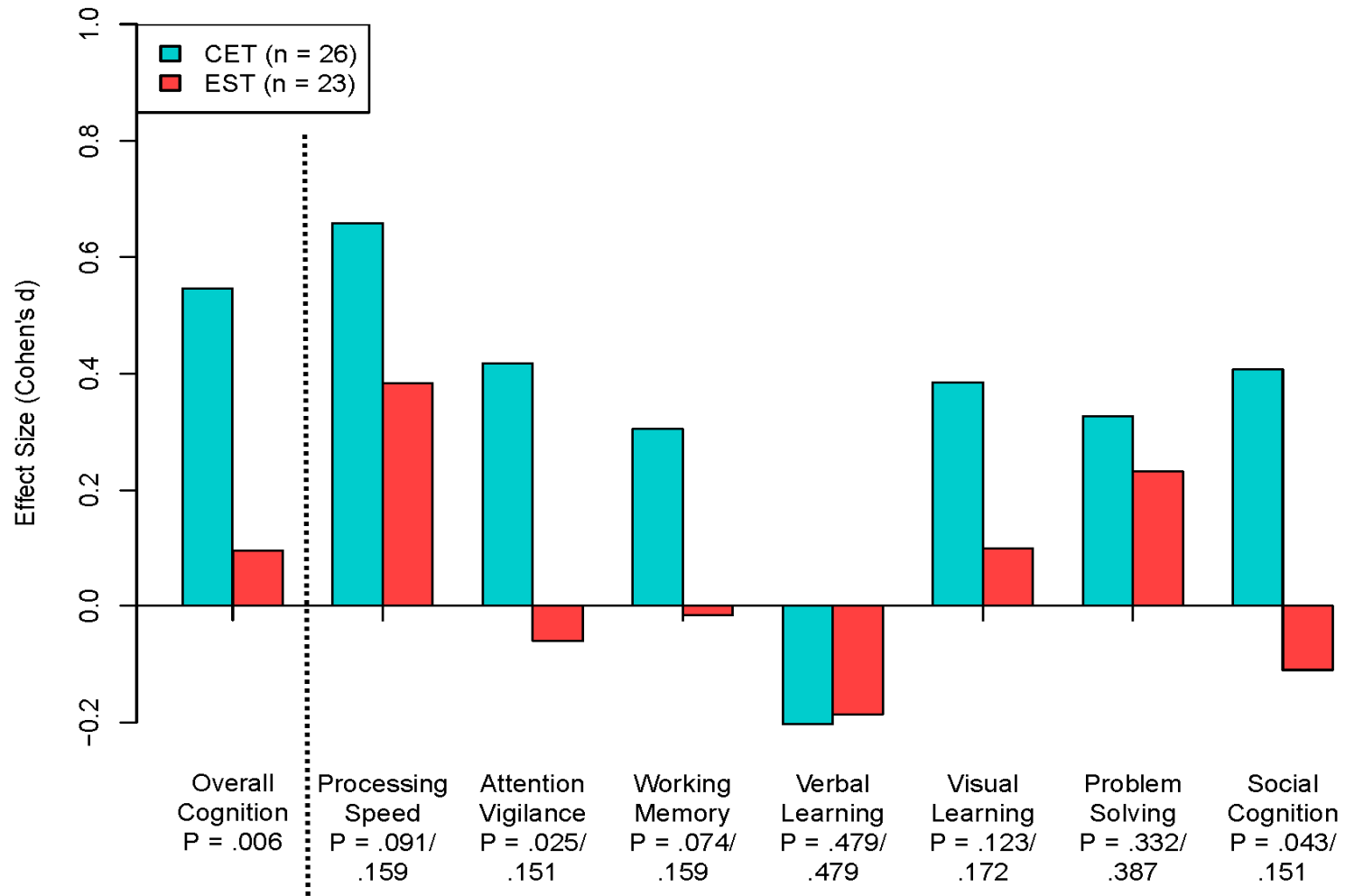
<sup>a</sup>Estimated marginal means.

<sup>b</sup>all measure  $M(SE)$ s are displayed as  $z$ -scores, with the exception of the MCCB subscales presented as T-scores corrected for age and sex.

*Plots of MCCB Cognition Composite, Attention/Vigilance, and Social Cognition Change Trajectories in the Intent-to-Treat Sample*



Completer Analysis Within-Group 18-Month Effect Sizes for CET and EST on the MATRICS Consensus Cognitive Battery (Note. p-values are one-tailed, P = unadjusted/adjusted with false discovery rate)





*Comparison of Baseline Characteristics Between Treatment Completers and Non-Completers*

Variable	Completer ( <i>n</i> = 49)	Non-Completer ( <i>n</i> = 53)	<i>p</i> <sup>j</sup>
Age	26.36 (6.58)	23.28 (3.58)	.004
Sex (% male)	38 (78%)	38 (72%)	.650
Racial Minority (%)	21 (43%)	23 (43%)	1.00
Race			
African American	11 (22%)	13 (24%)	
White	28 (57%)	30 (57%)	
Hispanic	0 (0%)	1 (2%)	
Asian	4 (8%)	1 (2%)	
Hawaiian/Pacific Islander	1 (2%)	0 (0%)	
More than one race	2 (4%)	5 (9%)	
Other	3 (6%)	3 (6%)	
IQ <sup>a</sup>	110.43 (10.91)	105.43 (9.38)	.015
Education (% some college) <sup>b</sup>	37 (77%)	32 (70%)	.487
Employed (% employed) <sup>c</sup>	13 (27%)	18 (35%)	.398
Illness Length (years) <sup>d,e</sup>	4.32 (2.47)	3.09 (1.94)	.006
Schizophrenia Diagnosis (% with)	37 (76%)	45 (85%)	.319
Substance Use Disorder History (% with)	21 (43%)	29 (55%)	.243
Antipsychotic Dose (CPZ equivalent) <sup>f</sup>	520.65 (377.00)	345.68 (270.63)	.008
Antipsychotic Adherence (% adherent) <sup>c,g</sup>	39 (80%)	36 (69%)	.262
MCCB Overall Cognition Composite <sup>h</sup>	36.80 (12.52)	35.14 (10.81)	.476
Social Adjustment Composite <sup>i</sup>	48.53 (8.80)	51.42 (10.81)	.144
Symptom Composite	49.73 (9.18)	50.67 (11.11)	.641

*Note.* CPZ = Chlorpromazine, MCCB = Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery

<sup>a</sup>Measured with Wechsler Abbreviated Scale of Intelligence 2<sup>nd</sup> Edition (WASI-II)

<sup>b</sup>Based on a total sample of 94 with available data (CET: *n* = 55, EST: *n* = 39)

<sup>c</sup>Based on a total sample of 101 with available data (CET: *n* = 57, EST: *n* = 44)

<sup>d</sup>Based on a total sample of 101 with available data (CET: *n* = 58, EST: *n* = 43)

<sup>e</sup>Since the onset of psychotic symptoms

<sup>f</sup>Based on a total sample of 98 with available data (CET: *n* = 55, EST: *n* = 43)

<sup>g</sup>Estimated by clinical team

<sup>h</sup>Age- and sex-corrected T-score

<sup>i</sup>See “Measures” in the Methods section and supplementary table above for a description of the measures included in the social adjustment and symptoms composite indexes

<sup>j</sup>Results from independent samples t-tests or Fisher’s exact tests, two-tailed.

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