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Patterns of Substance Use During Cognitive Enhancement Therapy: An 18-Month Randomized Feasibility Study

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Abstract

Objective—Substance use problems are common among people with schizophrenia, as are significant cognitive impairments. Because of potential shared neurobiological pathways, it is possible that cognitive remediation interventions may be associated with improvements in both substance use and cognition. This study examined the impact of cognitive remediation on alcohol and cannabis use, and the cognitive correlates of changes in substance use among outpatients with schizophrenia.

Methods—Individuals with schizophrenia who were receiving outpatient services at a psychiatric clinic and had moderate or higher addiction severity scores ($N = 31$) were randomized to 18 months of cognitive enhancement therapy ($n = 22$) or usual care ($n = 9$). Cognitive enhancement therapy is a cognitive remediation approach that integrates computer-based training in attention, memory, and problem-solving with a group-based social cognition curriculum. Usual care was provided to all participants and consisted of routine psychiatric care. Primary outcomes included days of alcohol and cannabis use, assessed with the Timeline Follow-Back method every six months and modeled using penalized quasi-likelihood growth curves.

Results—Participants were on average 38.23 ($SD = 13.44$) years of age, had been ill for 14.19 ($SD = 11.28$) years, were mostly male ($n = 22$, 71%), and about half were Caucasian ($n = 16$, 52%). Temporal patterns of substance use days were highly variable and followed non-linear trajectories. Intent-to-treat analyses indicated that, compared to patients only receiving usual care, those receiving cognitive enhancement therapy were significantly less likely to use alcohol ($OR = .22$, 95% CI [.05, .90], $p = .036$), but not cannabis ($OR = 1.89$, 95% CI [.02, 142.99], $p = .774$) over time, and they reduced their alcohol use at significantly accelerated rates ($OR = 1.02$, 95% CI [1.01, 1.03], $p = .003$). Changes in cognition were variably associated with substance use

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outcomes, although improvements in visual learning and reasoning and problem-solving were both consistently related to reduced alcohol and cannabis use.

Conclusions—Cognitive remediation may be effective for improving some substance use problems in schizophrenia. Visual learning and problem-solving deficits may be particularly important targets of such interventions, given their association with reduced alcohol and cannabis use. This study is registered at clinicaltrials.gov under #NCT01292577.

Keywords

cognitive remediation; schizophrenia; substance use disorder

Substance misuse is a common problem in people with schizophrenia, occurring in more than half of all individuals diagnosed (Volkow, 2009), and for which few targeted and effective treatments exist (Dixon et al., 2009; Drake, O'Neal, & Wallach, 2008). Schizophrenia is also characterized by significant impairments in social and non-social cognition (Heinrichs & Zakzanis, 1998; Savla, Vella, Armstrong, Penn, & Twamley, 2013), which begin early in the disorder and persist throughout its course (Braw et al., 2008; Green et al., 2012). While some research suggests that people with schizophrenia who misuse substances may be less affected by cognitive impairments (Yücel et al., 2012), large well-controlled studies have indicated that many patients with substance misuse experience ongoing impairments in attentional control, problem-solving, and social cognition that could contribute to substance abuse or dependence due to a lack of effective treatments for these cognitive problems (Bahorik, Newhill, & Eack, 2014; Wobrock et al., 2013). Data are emerging implicating shared neurobiological mechanisms producing cognitive impairment in both substance use disorders and schizophrenia (Green, Drake, Brunette, & Noordsy, 2007; Thoma & Daum, 2013; Volkow, 2009). For example, reduced lateral prefrontal cortical activity has been associated with working memory impairments in both schizophrenia (Perlstein, Carter, Noll, & Cohen, 2001) and substance use disorders (Schweinsburg et al., 2008). The advances in treating cognitive deficits in schizophrenia (McGurk, Twamley, Sitzler, McHugo, & Mueser, 2007) that may share a similar neural basis as those found in some substance use disorders has led to an increased interest in cognitive enhancing treatments for addiction (Bates, Buckman, & Nguyen, 2013; Sofuoglu, DeVito, Waters, & Carroll, 2013).

Cognitive remediation is a set of psychosocial approaches for the treatment of cognitive impairments in schizophrenia, which has been shown to be demonstrably effective for improving cognition in recent meta-analyses (McGurk, Twamley, Sitzler, McHugo, & Mueser, 2007; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Unfortunately, with few exceptions (e.g., McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007), people with comorbid substance use problems have been largely excluded from trials of cognitive remediation, bringing little evidence to bear on the potential benefits of these approaches to addiction problems in this population. Recently, we conducted an initial feasibility randomized trial of cognitive enhancement therapy (Hogarty & Greenwald, 2006) for outpatients with schizophrenia who were misusing alcohol and/or cannabis, and found significant and large improvements on neurocognition ($d = .93$), social cognition ($d = .62$), and functional outcome ($d = 1.15$) compared to usual care (Eack et al., 2015). We also

observed preliminary evidence that those receiving cognitive enhancement therapy may have been more likely to reduce the number of days they used alcohol than those receiving usual care.

This research follows up on these promising results by conducting a secondary analysis of substance use trajectories from our previous clinical trial (Eack et al., 2015) using individual growth curve modeling of daily alcohol and cannabis use among the intent-to-treat sample of enrolled patients. Based on our preliminary results, we hypothesized that cognitive enhancement therapy would significantly reduce the likelihood of alcohol and cannabis use over the course of treatment compared to usual care. We hypothesized that patients receiving cognitive enhancement therapy would not only show greater reductions in use but also achieve those reductions at faster rates than those in usual care. Finally, we explored associations between cognitive improvement and substance use change to examine potential mechanisms of change in addictive behavior in this cognitive remediation trial.

Method

Procedures

This study was conducted between September, 2010 and May, 2014. Participants were recruited from Western Psychiatric Institute and Clinic, Pittsburgh, PA and nearby community clinics, and screened for eligibility by project clinicians and an expert diagnostician. Eligible participants were randomized to 18 months of cognitive enhancement therapy or usual care, and assessed every six months by blind interviewers and raters on substance use and cognitive assessments. Randomization was weighted toward a greater proportion of cognitive enhancement therapy assignments to facilitate social-cognitive group formation. Participants received payment for research assessments, and those assigned to cognitive enhancement therapy also received compensation to defray the costs of session attendance and to facilitate adherence to the treatment protocol. Of the 22 patients randomized to cognitive enhancement therapy, 10 completed the full 18-months of treatment (4 withdrew consent, 4 experienced significant symptom instability, 2 were later found to be ineligible, 1 failed to engage in treatment, and 1 was incarcerated); and of the 9 assigned to usual care, 8 completed the 18-month assessment protocol (1 withdrew consent); $\chi^2(1, N=31) = 3.33, p = .068$. A detailed description of participant flow throughout the study, including a discussion of attrition, has been provided elsewhere (Eack et al., 2015). All participants provided written informed consent prior to study participation, and the study was approved and reviewed annually by the University of Pittsburgh Institutional Review Board.

Participants

Participants included 31 outpatients with schizophrenia ($n = 17$) or schizoaffective disorder ($n = 14$) and substance misuse problems enrolled in an 18-month randomized feasibility trial of cognitive enhancement therapy ($n = 22$) or usual care ($n = 9$). A description of the trial methods and CONSORT diagram has been previously reported elsewhere (Eack et al., 2015) and this is a secondary analysis of substance use trajectories from the parent trial. Inclusion criteria consisted of (1) age 18-60 years, (2) diagnosis of schizophrenia or schizoaffective

disorder according to the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2002), (3) moderate or higher (≥ 4) addiction severity for cannabis or alcohol on the Addiction Severity Index (McLellan, Luborsky, Woody, O'Brien, 1980), (4) symptom stabilization (no significant exacerbations within the past month) on antipsychotic medications evaluated using the SCID and medical record review, (5) IQ ≥ 80, (6) fluency in English, and (7) significant cognitive and social disability on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). Exclusion criteria were used to reduce heterogeneity in this initial feasibility trial and consisted of (1) abuse or dependence on cocaine or opioids, (2) other persistent medical conditions producing significant cognitive impairment, (3) use of any substance abuse pharmacotherapies (e.g., naltrexone), and (4) persistent homicidality or suicidality as assessed by clinician judgment based on the SCID and medical record review.

Measures

Daily substance use was measured according to the Timeline Follow-Back method (Sobell & Sobell, 1992) using a 30-day window prior to treatment and every 6 months thereafter for the 18-month trial. The Timeline Follow-Back method has been widely used in the addiction literature for assessing patterns of alcohol and drug use, and makes use of a monthly calendar whereby participants are asked to recollect each day in the past 30 days and indicate whether they used a variety of substances, the amount of use, and the route of administration. Given the significant cognitive impairments in the sample being studied, a research assistant blind to treatment assignment facilitated the completion of all Timeline Follow-Back surveys using an interview-style approach to help patients adhere to the format, review their previous month of substance use, and answer any questions. The Timeline Follow-Back method has been shown to produce highly accurate estimates of substance use comparable to biological assays (Hjorthøj, Hjorthøj, & Nordentoft, 2012), and has shown adequate reliability and validity in patients with schizophrenia (Hjorthøj, Fohlmann, Larsen, Arendt, & Nordentoft, 2012). In addition, addiction severity was quantified using interviewer severity ratings (0 = least severe, 9 = most severe), for alcohol and drugs separately, based on the Addiction Severity Index (McLellan, Luborsky, Woody, O'Brien, 1980).

To examine associations between substance use outcomes and cognitive improvement during this cognitive remediation trial, the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Green et al., 2004) was used to assess cognitive function prior to treatment and every 6 months for up to 18 months. The MATRICS battery was developed specifically for clinical trials of cognitive enhancing interventions in schizophrenia and collates field standard measures of processing speed, attention/vigilance, working memory, verbal learning, visual learning, problem-solving, and social cognition into a brief neuropsychological battery. The social cognition domain includes a single measure, the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Managing Emotions branch score (Mayer, Salovey, Caruso, & Sitarenios, 2003). The battery has a normative database upon which percentile scores are calculated, and has shown high levels of reliability and validity in patients with schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008).

Psychosocial Treatments

Cognitive Enhancement Therapy—Cognitive enhancement therapy is a comprehensive, developmental approach to the treatment of social and non-social cognitive impairments in schizophrenia, which has been previously described in detail elsewhere (Hogarty et al., 2004; Hogarty & Greenwald, 2006; Eack, 2012). During the 18-month course of cognitive enhancement therapy, 60 hours of computer-based training in attention, memory, and problem-solving are integrated with 45 structured social-cognitive groups that target the achievement of key adult social milestones (e.g., perspective-taking, social context appraisal, and emotion management). Neurocognitive training makes use of software developed by Ben-Yishay, Piasetsky, and Rattok (1985) and Bracy (1994), is strategic in nature, and takes place in pairs with a cognitive enhancement therapy therapist/coach to facilitate socialization, engagement, support, and strategic problem-solving. Social-cognitive groups are educational and experiential, and include in-group social-cognitive exercises, psychoeducational lectures, and homework assignments designed to facilitate the transfer of learning. For this trial of cognitive enhancement therapy for substance misuse and schizophrenia, additional psychoeducational content on substance use was developed for the social-cognitive groups, and a greater emphasis was placed on utilizing Personal Therapy (Hogarty, 2002) stress management principles and enhancing motivation for treatment in individual therapy appointments. Cognitive enhancement therapy was provided by master's and doctoral-level study therapists with extensive experience in the treatment of schizophrenia and background training in nursing, psychology, and social work.

Usual Care—Usual care was the contrasting treatment condition for this feasibility trial and consisted of traditional mental health and social services available to all participants, regardless of treatment assignment, including medication visits, individual supportive therapy, case management, vocational rehabilitation services, dual diagnosis treatments, and community-driven substance use treatments.

Data Analysis—Investigation of patterns of substance use trajectories for all participants randomized into the trial, regardless of attrition, was accomplished using individual growth curve modeling, a special form of mixed modeling that accounts for the dependent nature of multiple measurement occasions within individuals over time. A basic unconditional growth curve model in hierarchical format is presented in Eq. 1-4:

Level 1:

$$Y_{ti} = \beta_{0i} + \beta_{1i}(\text{Time})_{ti} + \beta_{2i}(\text{Time}^2)_{ti} + r_{ti} \quad (1)$$

Level 2:

$$\beta_{0i} = \gamma_{00} + \mu_{0i} \quad (2)$$

$$\beta_{1i} = \gamma_{10} + \mu_{1i} \quad (3)$$

$$\beta_{2i} = \gamma_{20} + \mu_{2i} \quad (4)$$

This growth curve models outcome Y at time point t for individual i as a function of the average linear (γ_{10}) and quadratic (γ_{20}) growth trajectories for the sample (fixed effects) plus individual variation (μ_{0i} - μ_{2i}) in these effects (random effects). Under this framework, individual linear time effects (β_{1i}) represent change over time, and quadratic effects (β_{2i}) represent acceleration in change over time. Time was coded continuously, 0-119 (30 days assessed $\times$ 4 time points), to represent the day of assessment for the Timeline Follow-Back, such that 0 represented the first day of substance use assessment in the trial at baseline and 119 represented the last day of substance use assessment in the trial at 18 months to facilitate the interpretation of the intercept as average initial status (γ_{00}) and individual variation (μ_{0i}) in outcome. Using this approach, individual growth curve trajectories were modeled for all participants, with missing data handled at the time of parameter estimation using the expectation-maximization approach (Dempster, Laird, & Rubin, 1977), and each trajectory was extracted to examine patterns of substance use among patients treated with cognitive enhancement therapy versus usual care. A total of 12 (56%) participants in cognitive enhancement therapy and 8 (89%) in usual care had Timeline Follow-Back data for at least one follow-up time point. Subsequently, conditional growth curve models were fit by expanding Eq. 2-4 to include treatment assignment as a predictor to directly assess the differential effects of cognitive enhancement therapy on linear and quadratic growth trajectories. Finally, these conditional models were further expanded by adding time-varying MATRICS domain scores to Eq. 1 to examine the association between cognitive change and outcome over time. In the context of growth models, time-varying covariates represent the longitudinal association between change in the covariate and change in the outcome (Singer & Willet, 2003). Given that substance use (binary coded) was the primary outcome of interest, generalized mixed effects models were used and parameters estimated with penalized quasi-likelihood estimation and a binomial distribution (Breslow & Clayton, 1993). All models accounted for individual variation in initial status, and because treatment groups were comparable, no additional covariates were included to conserve power.

Results

Participant Characteristics

Enrolled participants were on average 38.23 ($SD = 13.44$) years of age and had been ill for 14.19 ($SD = 11.28$) years. Of those participants, 71% ($n = 22$) were male, 52% ($n = 16$) were Caucasian, 68% ($n = 21$) had attended some college prior to enrollment and 19% ($n = 6$) were employed at enrollment. The majority ($n = 29$, 94%) of participants had a comorbid SCID substance abuse or dependence diagnosis at baseline, the most common being cannabis ($n = 23$, 74%) and alcohol dependence ($n = 17$, 55%). Average Addiction Severity Index scores for alcohol and cannabis were 4.06 ($SD = 2.42$) and 4.52 ($SD = 2.17$), respectively. No significant differences emerged between treatment groups on demographic, clinical, substance use, or medication variables prior to initiating psychosocial treatment.

Substance Use Trajectories in Cognitive Enhancement Therapy Versus Usual Care

We began our examination of alcohol and cannabis use trajectories among patients with schizophrenia and substance misuse randomized to cognitive enhancement therapy or usual care by first investigating individual growth curves for participants treated in each of these conditions. As can be seen in Figure 1, trajectories of alcohol and cannabis use were highly variable and demonstrated considerable non-linearity, as is expected among individuals recovering from addiction problems (Prochaska & DiClemente, 1983). Visually, there appeared to be a greater proportion of patients treated with cognitive enhancement therapy who reduced their likelihood of using alcohol, and variable and no clear effect on cannabis use. When fitting intent-to-treat conditional mixed-models to these growth curves to explicitly examine differential trajectories between those treated with cognitive enhancement therapy or usual care, results indicated that patients receiving cognitive enhancement therapy were significantly less likely to use alcohol over the course of the study (see Table 1). Investigation of effects on quadratic growth (acceleration) patterns indicated that patients receiving cognitive enhancement therapy also displayed significantly faster reductions in alcohol use likelihood compared to those in usual care. Not only did patients treated with cognitive enhancement therapy reduce their use but those reductions tended to happen to a greater extent (linear effect) and more rapidly (quadratic effect) than individuals receiving usual care. No significant linear or quadratic differential treatment effects were observed for cannabis use, indicating that the efficacy of cognitive enhancement therapy on substance use was limited to alcohol in this sample.

Associations Between Cognitive Improvement and Substance Use Outcomes

Having found that cognitive remediation was associated with some reductions in participants' alcohol use, we proceeded to examine the correlation between improved cognition and substance use outcomes with a series of conditional growth curve models. As shown in Table 2, increased speed of processing was associated with a reduced likelihood of using alcohol, but not cannabis. Improvements in visual learning and problem-solving composites were significantly and consistently associated with a reduced likelihood of using alcohol and cannabis. The relationship between visual learning improvements and cannabis use was particularly pronounced, as a 10-point increase in MATRICS visual learning percentile scores was associated with a 75% reduction in probability of using alcohol within the past 30 days. Unexpectedly, improved verbal learning scores were associated with greater likelihood of using alcohol and cannabis, and improved social cognition (MSCEIT Managing Emotion) scores were associated with a slight ($OR = 1.14$), but significant increase in likelihood of using alcohol (see Table 2). Visual inspection of data points and model diagnostics did not indicate significant outliers driving this effect, but highlighted the variable nature of the relationship between these cognitive domain scores and substance use. Attention and working memory improvements were not associated with either alcohol or cannabis use. Taken together, these findings suggest that cognitive remediation may support improvement in some aspects of addictive behavior change among patients with schizophrenia, and that changes in cognition are variably associated with patterns of use, with improved visual learning and problem-solving skills being most consistently related to reduced substance use.

Discussion

This study examined patterns of alcohol and cannabis use among outpatients treated in a first randomized-controlled trial of cognitive enhancement therapy for substance misuse problems in schizophrenia. As expected, daily patterns of substance use were non-linear and highly variable across participants, highlighting the challenges in adequately powering clinical trials of cognitive remediation in this population. Patients treated with cognitive enhancement therapy demonstrated significantly greater and faster reductions in alcohol, but not cannabis use compared those treated with usual care. Cognitive improvements in processing speed, visual learning, and problem-solving were all related to reduced likelihood of alcohol and/or cannabis use over the course of the 18-month trial. When combined with previously reported evidence on the large benefits of cognitive enhancement therapy to cognition and functional outcome in this sample (Eack et al., 2015), these preliminary findings suggest that cognitive remediation may be beneficial for supporting some aspects of addictive behavior change in schizophrenia and point to the specific cognitive domains of processing speed, visual learning, and problem-solving as relevant therapeutic targets for patients misusing substances.

There is a growing and significant body of evidence now supporting the efficacy of psychosocial treatments for substance use problems in schizophrenia and severe mental illness (Dixon et al., 2009). Bellack, Bennett, Gearon, Brown, and Yang (2006) used a novel behavioral treatment including social skills training and contingency supports, and found significant increases in clean urine screens and prolonged abstinence compared to supportive therapy. Barrowclough and colleagues (2010) integrated cognitive behavior therapy and motivational interviewing and found no significant benefits with regard to substance use frequency, although individuals treated with the integrated approach did display reductions in the amount of substances used. Reviews of this literature indicate considerable heterogeneity in efficacy and outcome (Drake, O'Neal, & Wallach, 2008), and the treatment of cognitive impairments using cognitive remediation interventions, such as cognitive enhancement therapy, may provide additional benefits to addictive behavior change in this population.

This study provides the first evidence suggesting that cognitive enhancement therapy may be effective at reducing alcohol use problems in patients with schizophrenia and substance misuse. Results suggest that treating cognitive impairments using cognitive remediation is a promising approach for helping to address the substance use issues in this underserved population. These improvements in substance use problems may, in turn, provide broader long-term therapeutic benefits to functioning, symptomatology, and quality of life. The results of the current study also suggest that improved cognition is variably related to reductions in substance use. Further studies are warranted to replicate, clarify, and extend these findings.

The implications of this research need to be understood in the context of several limitations. First, the sample of 31 participants was small and likely precluded the detection of smaller effects on the extremely variable cannabis use outcome. Power analyses based on sample variability estimates indicate that a minimum 128 of participants would be required to detect

medium-sized differences given this level of variation (Raudenbush & Xiao-Feng, 2001), clearly indicating a need for large-scale randomized trials to definitively test the effects of cognitive remediation in this population.

Second, attrition in this study was large, similar to other long-term trials of psychosocial interventions in addiction (Dutra et al., 2008). Most attrition in the study occurred early (first 6 months) and was due primarily to symptom exacerbation or medication non-adherence, highlighting the well-documented stability challenges in this population (Drake, Osher, & Wallach, 1989). Providing stabilization and engagement interventions before and during cognitive remediation may be particularly important for patients with schizophrenia.

Third, this initial feasibility study only made use of a usual care comparison, and the non-specific effects of cognitive enhancement therapy (e.g., provision of a skilled empathic therapist, psychoeducation on schizophrenia) and compensation for treatment attendance may have contributed to its observed benefits on substance use outcomes. The exclusive use of retrospective accounts of substance use patterns is a limitation, and future studies should incorporate biological and collateral assays. Further, associations between cognitive and substance use change were correlational in nature, and while we hypothesize that cognitive gains contributed to improved substance use outcomes, it is possible that the significant reductions in alcohol use observed in cognitive enhancement therapy also contributed to cognitive improvement.

Finally, analyses of associations between changes in cognitive functioning and substance use were exploratory, and the finding that improvements in social cognition were associated with greater alcohol use was unexpected. These analyses made use of MATRICS domain scores, which are limited to a single measure of social cognition (MSCEIT Managing Emotions). There may be reciprocal effects between emotion regulation and alcohol use, such that greater alcohol use may have also led to an increased need to manage one's emotions, perhaps due to exacerbated symptomatology. Future studies will need to more comprehensively examine the social-cognitive correlates of substance misuse in schizophrenia.

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REFERENCES

- Bahorik AL, Newhill CE, Eack SM. Neurocognitive functioning of individuals with schizophrenia using and not using drugs. *Schizophrenia Bulletin*. 2014; 40(4):856–867.10.1093/schbul/sbt099 [PubMed: 23884348]
- Barrowclough C, Haddock G, Wykes T, Beardmore R, Conrod P, Craig T, Tarrier N. Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: Randomised controlled trial. *BMJ*. 2010; 341:c6325.10.1136/bmj.c6325 [PubMed: 21106618]

- Bates ME, Buckman JF, Nguyen TT. A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. *Neuropsychology Review*. 2013; 23(1):27–47.10.1007/s11065-013-9228-3 [PubMed: 23412885]
- Bellack AS, Bennett ME, Gearon JS, Brown CH, Yang Y. A randomized clinical trial of a new behavioral treatment for drug abuse in people with severe and persistent mental illness. *Archives of General Psychiatry*. 2006; 63(4):426–432.10.1001/archpsyc.63.4.426 [PubMed: 16585472]
- Ben-Yishay, Y.; Piasetsky, EB.; Rattok, J. A systematic method for ameliorating disorders in basic attention. In: Meir, MJ.; Benton, AL.; Diller, L., editors. *Neuropsychological rehabilitation*. Guilford Press; New York: 1985. p. 165-181.
- Bracy, OL. PSSCogRehab [computer software]. Psychological Software Services Inc; Indianapolis, IN: 1994.
- Braw Y, Bloch Y, Mendelovich S, Ratzoni G, Gal G, Harari H, Levkovitz Y. Cognition in young schizophrenia outpatients: comparison of first-episode with multiepisodic patients. *Schizophrenia Bulletin*. 2008; 34(3):544–554.10.1093/schbul/sbm115 [PubMed: 17984299]
- Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. *Journal of the American Statistical Association*. 1993; 88(421):9–25.10.1111/j.1467-9469.2008.00621.x
- Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data using the EM algorithm. *Journal of the Royal Statistical Society. Series B (Methodological)*. 1977; 39(1):1–38.10.1016/j.fss.2011.05.022
- Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, Kreyenbuhl J. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophrenia Bulletin*. 2009; 36(1):48–70.10.3410/f.13847960.15286060 [PubMed: 19955389]
- Drake RE, O'Neal EL, Wallach MA. A systematic review of psychosocial research on psychosocial interventions for people with co-occurring severe mental and substance use disorders. *Journal of Substance Abuse Treatment*. 2008; 34(1):123–138.10.1016/j.jsat.2007.01.011 [PubMed: 17574803]
- Drake RE, Osher FC, Wallach MA. Alcohol use and abuse in schizophrenia: A prospective community study. *Journal of Nervous and Mental Disease*. 1989; 177(7):408–414.10.1097/00005053-198907000-00004 [PubMed: 2746194]
- Dutra L, Stathopoulou G, Basden S, Leyro T, Powers M, Otto M. A meta-analytic review of psychosocial interventions for substance use disorders. *American Journal of Psychiatry*. 2008; 165(2):179–187.10.1176/appi.ajp.2007.06111851 [PubMed: 18198270]
- Eack SM. Cognitive remediation: A new generation of psychosocial interventions for people with schizophrenia. *Social Work*. 2012; 57(3):235–246.10.1093/sw/sws008 [PubMed: 23252315]
- Eack SM, Hogarty SS, Greenwald DP, Litschge MY, McKnight SAF, Bangalore SS, Cornelius JR. Cognitive Enhancement Therapy in substance misusing schizophrenia: Results of an 18-month feasibility trial. *Schizophrenia Research*. 2015; 161(2-3):478–483.10.1016/j.schres.2014.11.017 [PubMed: 25510926]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. *Structured Clinical Interview For DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. Biometrics Research, New York State Psychiatric Institute; New York: 2002.
- Green AI, Drake RE, Brunette MF, Noordsy DL. Schizophrenia and co-occurring substance use disorder. *American Journal of Psychiatry*. 2007; 164(3):402–408.10.1093/schbul/sbl020 [PubMed: 17329463]
- Green MF, Bearden CE, Cannon TD, Fiske AP, Helleman GS, Horan WP, Nuechterlein KH. Social cognition in schizophrenia, Part 1: Performance across phase of illness. *Schizophrenia Bulletin*. 2012; 38(4):854–864.10.3410/f.9900956.10612054 [PubMed: 21345917]
- Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Keefe RS. Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICES conference to select cognitive domains and test criteria. *Biological Psychiatry*. 2004; 56(5):301–307.10.1016/j.biopsych.2004.06.023 [PubMed: 15336511]
- Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*. 1998; 12(3):426–445.10.1037/0894-4105.12.3.426 [PubMed: 9673998]

- Hjorthøj CR, Fohlmann A, Larsen AM, Arendt M, Nordentoft M. Correlations and agreement between delta-9-tetrahydrocannabinol (THC) in blood plasma and timeline follow-back (TLFB)-assisted self-reported use of cannabis of patients with cannabis use disorder and psychotic illness attending the CapOpus randomized clinical trial. *Addiction*. 2012; 107(6):1123–1131.10.1111/j.1360-0443.2011.03757.x [PubMed: 22151583]
- Hjorthøj CR, Hjorthøj AR, Nordentoft M. Validity of timeline follow-back for self-reported use of cannabis and other illicit substances—systematic review and meta-analysis. *Addictive behaviors*. 2012; 37(3):225–233.10.1016/j.addbeh.2011.11.025 [PubMed: 22143002]
- Hogarty, GE. *Personal Therapy for schizophrenia and related disorders: A guide to individualized treatment*. Guilford; New York: 2002.
- Hogarty, GE.; Greenwald, DP. *Cognitive Enhancement Therapy: The Training Manual*. University of Pittsburgh Medical Center: Authors; 2006. Available through www.CognitiveEnhancementTherapy.com
- Hogarty GE, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, Zoretich R. Cognitive enhancement therapy for schizophrenia. Effects of a 2-year randomized trial on cognition and behavior. *Archives of General Psychiatry*. 2004; 61(9):866–876.10.1001/archpsyc.61.9.866 [PubMed: 15351765]
- Kern RS, Nuechterlein KH, Green MF, Baade LE, Fenton WS, Gold JM, Marder SR. The MATRICS Consensus Cognitive Battery, Part 2: Co-norming and standardization. *American Journal of Psychiatry*. 2008; 165(2):214–220.10.1176/appi.ajp.2007.07010043 [PubMed: 18172018]
- Mayer JD, Salovey P, Caruso DR, Sitarenios G. Measuring emotional intelligence with the MSCEIT V2.0. *Emotion*. 2003; 3(1):97–105.10.1037/1528-3542.3.1.97 [PubMed: 12899321]
- McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A. Cognitive training for supported employment: 2-3 year outcomes of a randomized controlled trial. *American Journal of Psychiatry*. 2007; 164(3):437–441.10.1176/appi.ajp.164.3.437 [PubMed: 17329468]
- McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A Meta-Analysis of Cognitive Remediation in Schizophrenia. *American Journal of Psychiatry*. 2007; 164(12):1791–1802.10.3410/f.9528958.12046055 [PubMed: 18056233]
- McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients: The Addiction Severity Index. *Journal of Nervous and Mental Disease*. 1980; 168(1):26–33.10.1097/00005053-198001000-00006 [PubMed: 7351540]
- Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Marder SR. The MATRICS Consensus Cognitive Battery, Part 1: Test Selection, Reliability, and Validity. *American Journal of Psychiatry*. 2008; 165(2):203–213.10.1176/appi.ajp.2007.07010042 [PubMed: 18172019]
- Perlstein WM, Carter CS, Noll DC, Cohen JD. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *American Journal of Psychiatry*. 2001; 158(7):1105–1113.10.1176/appi.ajp.158.7.1105 [PubMed: 11431233]
- Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *Journal of Consulting and Clinical Psychology*. 1983; 51(3):390–395.10.1037//0022-006x.51.3.390 [PubMed: 6863699]
- Raudenbush SW, Xiao-Feng L. Effects of study duration, frequency of observation, and sample size on power in studies of group differences in polynomial change. *Psychological Methods*. 2001; 6(4):387–401.10.1037/1082-989x.6.4.387 [PubMed: 11778679]
- Savla GN, Vella L, Armstrong CC, Penn DL, Twamley EW. Deficits in domains of social cognition in schizophrenia: A meta-analysis of the empirical evidence. *Schizophrenia Bulletin*. 2013; 39(5):979–992.10.1093/schbul/sbs080 [PubMed: 22949733]
- Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF. Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Research: Neuroimaging*. 2008; 163(1):40–51.10.1016/j.pscychresns.2007.04.018 [PubMed: 18356027]
- Singer, JD.; Willet, JB. *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford University Press; New York: 2003.
- Sobell, LC.; Sobell, MB. Timeline follow-back. In: Litten, RZ.; Allen, J., editors. *Measuring alcohol consumption: Psychosocial and biological methods*. Humana Press; Totowa, NJ: 1992. p. 41-72.

- Sofuoglu M, DeVito EE, Waters AJ, Carroll KM. Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology*. 2013; 64:452–463.10.1016/j.neuropharm.2012.06.021 [PubMed: 22735770]
- Thoma P, Daum I. Comorbid substance use disorder in schizophrenia: A selective overview of neurobiological and cognitive underpinnings. *Psychiatry and Clinical Neurosciences*. 2013; 67(6): 367–383.10.1111/pcn.12072 [PubMed: 23890122]
- Volkow ND. Substance Use Disorders in Schizophrenia--Clinical Implications of Comorbidity. *Schizophrenia Bulletin*. 2009; 35(3):469–472.10.1093/schbul/sbp016 [PubMed: 19325163]
- Wobrock T, Falkai P, Schneider-Axmann T, Hasan A, Galderisi S, Davidson M, EUFEST study group. Comorbid substance abuse in first-episode schizophrenia: Effects on cognition and psychopathology in the EUFEST study. *Schizophrenia Research*. 2013; 147(1):132–139.10.1016/j.schres.2013.03.001 [PubMed: 23537477]
- Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *American Journal of Psychiatry*. 2011; 168(5):472–485.10.3410/f.9528958.12046055 [PubMed: 21406461]
- Yücel M, Bora E, Lubman DI, Solowij N, Brewer WJ, Cotton SM, Pantelis C. The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin*. 2012; 38(2):316–330.10.1093/schbul/sbq079 [PubMed: 20660494]

Figure 1.
Patterns of Substance Use During an 18-Month Trial of Cognitive Enhancement Therapy or Treatment as Usual for Substance Misusing Schizophrenia.

Table 1

Effects of Cognitive Enhancement Therapy Versus Treatment as Usual on Alcohol and Cannabis Use Trajectories in Substance Misusing Patients with Schizophrenia (N = 31).

Fixed Effect	<i>B</i>	<i>SE</i>	<i>OR^a</i> [95% CI]	<i>p</i>
Alcohol Use				
Initial status, β_{0i}				
<i>M</i> , γ_{00}	-4.12	.85	-	.000
CET, γ_{01}	1.66	.98	-	.100
Growth rate, β_{1i}				
<i>M</i> , γ_{10}	.04	.02	3.24 [.93,11.30]	.065
CET, γ_{11}	-.05	.02	.22 [.05,.90]	.036
Acceleration rate, β_{2i}				
<i>M</i> , γ_{20}	-.00	.00	.98 [.98,.99]	.001
CET, γ_{21}	.00	.00	1.02 [1.01,1.03]	.003
Cannabis Use				
Initial status, β_{0i}				
<i>M</i> , γ_{00}	-2.04	2.00	-	.308
CET, γ_{01}	-1.26	2.37	-	.600
Growth rate, β_{1i}				
<i>M</i> , γ_{10}	-.06	.06	.18 [.00,7.53]	.372
CET, γ_{11}	.02	.07	1.89 [.03,142.99]	.774
Acceleration rate, β_{2i}				
<i>M</i> , γ_{20}	.00	.00	1.02 [.97,1.06]	.475
CET, γ_{21}	-.00	.00	.98 [.93,1.04]	.543

Note. B = unstandardized regression coefficient; SE = standard error; OR = odds ratio; CI = confidence interval; M = mean; CET = cognitive enhancement therapy.

^aOver the past 30 days.

Table 2

Association Between Changes in MATRICS Cognitive Domain Scores and Substance Use Likelihood in Substance Misusing Patients with Schizophrenia (N = 31).

Cognition	Alcohol Use			Cannabis Use		
	<i>B</i>	<i>SE</i>	<i>OR^a</i> [95% CI]	<i>B</i>	<i>SE</i>	<i>OR^a</i> [95% CI]
Speed of Processing	-.01 *	.01	.87 [-.03,-.00]	-.01	.01	.93 [-.02,.00]
Attention/Vigilance	.00	.00	1.02 [-.01,.01]	.01	.01	1.07 [-.01,.02]
Working Memory	.00	.01	1.02 [-.01,.01]	.01	.01	1.13 [-.00,.03]
Verbal Learning	.02 **	.01	1.23 [.01,.03]	.05 **	.01	1.58 [.02,.07]
Visual Learning	-.01 *	.01	.88 [-.02,-.00]	-.14 **	.01	.25 [-.16,-.12]
Reasoning /Problem-Solving	-.01 *	.00	.90 [-.02,-.00]	-.01 *	.01	.87 [-.03,-.00]
Social Cognition	.01 **	.00	1.14 [.01,.02]	.00	.01	1.04 [-.01,.02]

Note. = change in; B = unstandardized regression coefficient; SE = standard error; OR = odds ratio.

^aOdds ratios are scaled to reflect a 10-point change on MATRICS percentile composites.

*
 $p < .05$,

**
 $p < .01$