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Mediated and Moderated Effects of Neurocognitive Impairment on Outcomes of Treatment for Substance Dependence and Major Depression

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Abstract

Objective—Neurocognitive impairment has not consistently predicted substance use treatment outcomes but has been linked to proximal mediators of outcome. These indirect effects have not been examined in adults with substance dependence and co-occurring psychiatric disorders. We examined mediators and moderators of the effects of neurocognitive impairment on substance use among adults in treatment for alcohol or drug dependence and major depression (MDD).

Method—Participants were veterans (N = 197, mean age = 49.3 years, 90% male, 75% Caucasian) in a trial of two group interventions for alcohol/drug dependence and MDD. Measures examined here included intake neurocognitive assessments and percent days drinking (PDD), percent days using drugs (PDDRG), self-efficacy, 12-step affiliation, and depressive symptoms measured every 3 months from intake to the 18-month follow-up.

Results—Greater intake neurocognitive impairment predicted lower self-efficacy, lower 12-step affiliation, and greater depression severity, and these time-varying variables mediated the effects of impairment on future PDD and PDDRG. The prospective effects of 12-step affiliation on future PDD were greater for those with greater neurocognitive impairment. Impairment also interacted with depression to moderate the effects of 12-step affiliation and self-efficacy on PDD. Adults with greater impairment and currently severe depression had the strongest associations between 12-step affiliation/self-efficacy and future drinking.

Conclusions—Greater neurocognitive impairment may lead to poorer outcomes from group therapy for alcohol/drug dependence and MDD due to compromised change in therapeutic processes. Distal factors such as neurocognitive impairment can interact with dynamic risk factors to modulate the association between therapeutic processes and future drinking outcomes.

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Keywords

Neurocognition; mediators; moderators; substance use; depression

Introduction

Many individuals with alcohol or drug dependence (AODD) have deficits in neurocognitive abilities such as executive functioning and problem solving (Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Tucker et al., 2004), verbal or non-verbal memory (Dawson & Grant, 2000; Lamers, Bechara, Rizzo, & Ramaekers, 2006), cognitive efficiency (Nixon, Paul, & Phillips, 1998), and attention (Solowij et al., 2002), whether these deficits are due to the neurotoxic effects of substance use, preexisting characteristics, or a combination of both (Adams et al., 1993; Braun & Richer, 1993). Neurocognitive deficits are especially common in clinical settings, with prevalence up to 80% (Meek, Clark, & Solana, 1989; O'Malley, Adamse, Heaton, & Gawin, 1992). Although modest recovery in neurocognition is possible, improvement is often not clinically significant (Bates, Voelbel, Buckman, Labouvie, & Barry, 2005) and deficits often remain even after periods of extended abstinence (Parsons, 1998). Given the persistence of neurocognitive impairment and its prevalence in clinical settings, understanding its impact on AODD treatment is critical for optimizing long-term outcomes in this population.

The negative impact of neurocognitive deficits in substance users may be compounded by other psychiatric disorders, which are also common in AODD treatment settings (Chi, Satre, & Weisner, 2006; Lynskey, 1998). Major depressive disorder (MDD) is the most prevalent co-occurring Axis I disorder, and those with co-occurring MDD typically have poorer outcomes from AODD treatment (Gamble et al., 2010; Glasner-Edwards et al., 2009). Independently, MDD is associated with deficits in similar neurocognitive domains as substance use, including working memory, attention, verbal memory, and processing speed (Elgamal, Denburg, Marriott, & MacQueen, 2010; Landro, Stiles, & Sletvold, 2001). As in other co-occurring conditions (Levy, Monzani, Stephansky, & Weiss, 2008), the joint effects of AODD and MDD on cognition may be worse than in either disorder alone, suggesting the potential for a significant and negative impact on the outcome of psychotherapy.

Psychotherapy for AODD often involves learning and retaining new information, inhibiting impulsive responses, engaging in future-oriented behavior, and planning coping strategies. Neurocognitive impairment could be expected to interfere with internalizing and engaging in these skills, leading to poorer outcomes. Although some studies support these negative prognostic effects (Aharonovich, Brooks, Nunes, & Hasin, 2008; Aharonovich, Nunes, & Hasin, 2003), results have not been consistent, with many studies finding no direct relationship between neurocognition and AODD treatment outcomes (Aharonovich et al., 2006; Teichner, Horner, Roitzsch, Herron, & Thevos, 2002; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). However, studies utilizing "threshold" indices of severe neurocognitive impairment suggest that more indirect associations of impairment with proximal therapeutic factors are implicated in complex, behavioral therapeutic processes (Bates, Bowden, & Barry, 2002). In separate studies greater impairment was correlated

negatively with self-efficacy (Morgenstern & Bates, 1999) and lower self-efficacy mediated the effects of impairment on drinking (Bates, Pawlak, Tonigan, & Buckman, 2006). Neurocognitive impairment has also moderated the effects of proximal factors, with more impaired participants having weaker effects of AA and self-efficacy on drinking (Bates et al., 2006) but stronger effects of social support (Buckman, Bates, & Cisler, 2007; Buckman, Bates, & Morgenstern, 2008). Each of these studies provided preliminary evidence that severe impairment can impact AODD treatment via mediated and moderated pathways, but none focused on individuals with AODD and co-occurring disorders.

In addition to therapeutic process variables, neurocognitive impairment may impact treatment for AODD and co-occurring MDD via indirect associations with proximal risk factors. Substance use is frequently precipitated by increased negative affect (Witkiewitz & Villarroel, 2009), especially for those with co-occurring MDD (Tomlinson, Tate, Anderson, McCarthy, & Brown, 2006). Worse fluid reasoning ability has predicted less improvement in depressive symptoms during CBT for depressed, hazardous drinkers (Hunt, Baker, Michie, & Kavanagh, 2009); similar effects could arise for those with AODD and MDD. Moderating effects of neurocognition on depressive symptoms are also plausible, as other neurobehavioral constructs such as impulsivity (King, Karyadi, Luk, & Patock-Peckham, 2011) and distress tolerance (Buckner, Keough, & Schmidt, 2007) have moderated relations between depressive symptoms and substance use. Lower cognitive ability has also predicted lower acquisition of coping skills for high-risk situations (Kiluk, Nich, & Carroll, 2011), suggesting that among those with AODD and MDD, greater impairment could amplify the risk for substance use in the context of high-risk a cue, such as increased depressive symptoms.

In prior research with the current sample of veterans diagnosed with AODD and independent MDD, Integrated Cognitive-Behavioral Therapy (ICBT) was compared to Twelve-Step Facilitation (TSF) on alcohol and drug use outcomes. Both groups had similar reductions in substance use during treatment, with less increase in substance use during follow-up for ICBT (Lydecker et al., 2010). During treatment greater 12-step affiliation and self-efficacy predicted less substance use (Glasner-Edwards et al., 2007), as did lower depressive symptoms (Worley, Tate, & Brown, 2012). Studies utilizing parallel-process latent growth curve models found longitudinal, correlated change between 12-step affiliation and drinking during follow-up (Worley, Tate, McQuaid, Granholm, & Brown, 2013) and between depression symptom severity and substance use during treatment and follow-up (Worley, Trim, et al., 2012). Contrary to hypotheses, those with poorer neurocognitive functioning had worse substance use outcomes in Twelve-Step Facilitation than in Cognitive-Behavioral Therapy (Granholm et al., 2011). Relations between neurocognitive impairment and proximal treatment mechanisms or risk factors have not been examined in this sample, or other samples characterized by co-occurring disorders.

The goal of this study was to explore the indirect impact of neurocognitive impairment on substance use outcomes in adults receiving treatment for co-occurring AODD and MDD. These aims are informed by recent models suggesting that substance use is a complex interplay of distal risk, proximal risks, intrapersonal processes, and contextual factors (Witkiewitz & Marlatt, 2004), and that investigations of treatment processes should examine

inter-relationships between these factors (Wirtz, 2007). We hypothesized that the effects of neurocognitive impairment on drinking and drug use during treatment and follow-up would be mediated by lower self-efficacy, lower 12-step affiliation and greater depressive symptoms. We also tested whether severity of neurocognitive impairment moderated the effects of self-efficacy, 12-step affiliation, and greater depressive symptoms on future drinking and drug use. Given that relations between therapeutic proximal factors and drinking outcomes have been weaker for impaired participants in some previous studies of AODD treatment (Bates et al., 2006; Morgenstern & Bates, 1999) but stronger in others (Buckman et al., 2007; Buckman et al., 2008), we expected these relations could be either stronger or weaker for impaired participants in this sample. A secondary aim was to examine higher-order interactions between time-varying therapeutic process variables and depressive symptom severity, given that prior research has not focused on adults with co-occurring MDD or considered the potential moderating impact of psychiatric symptoms. This aim was examined by testing three-way interactions between neurocognitive impairment, therapeutic process variables (self-efficacy, 12-step affiliation) and depression symptom severity.

Method

Participants

This study involved secondary analysis of veterans ($N = 197$) who participated in a controlled trial of outpatient group psychotherapy for co-occurring substance dependence and MDD (Lydecker et al., 2010) excluding nine study participants who did not complete intake neurocognitive testing. Inclusion criteria included a diagnosis of lifetime dependence on alcohol (91%), cannabis (29%), or stimulants (53%) with any use in the past 90 days, and DSM-IV diagnosis of MDD, with at least one depressive episode occurring independently of substance use. Participants were excluded if they were using opiates intravenously, had bipolar or other psychotic disorder, lived excessively far (> 50 miles) from the facility, or had severe memory impairments prohibiting accurate recall. The current sample averaged 49.3 years of age ($SD = 7.87$) and was mostly (90%) male and Caucasian (75%). At intake few participants were working (17.9%) or married (12%). In the three months preceding the study 85% of the sample had used alcohol, with an average of 15.07 ($SD = 13.56$) drinks per drinking day, 47% had used drugs, and 39% had used both alcohol and drugs. The average intake Hamilton Depression score was 28.35 ($SD = 10.65$), indicative of severe depressive symptoms.

Procedures

The procedures for this study were approved by the University of California, San Diego and Veteran's Affairs San Diego Healthcare System (VASDHS) Institutional Review Boards, have been described in detail previously (Brown et al., 2006; Lydecker et al., 2010) and are reviewed briefly here. Referrals from the VASDHS dual diagnosis clinic were reviewed for eligibility, and research staff conducted brief screenings before meeting to explain procedures and obtain informed consent. Veterans consented to sequential allocation to group psychotherapy, assessments every three months during 6 months of treatment and 12 months of follow-up, video recording of sessions, random toxicology screens, psychotropic medication consultation, and review of electronic medical records. After intake assessment

veterans were sequentially allocated to Twelve-Step Facilitation (TSF) or Integrated Cognitive-Behavioral Therapy (ICBT) on an alternating, two-week assignment schedule. Veterans agreed to receive no other formal treatment for AODD or MDD during study treatment; such services were allowed during follow-up.

Treatment group differences in outcomes and proximal variables were previously published (Brown et al., 2006; Lydecker et al., 2010); the interventions are described briefly here. The TSF in Project MATCH (Project Match Research Group, 1997) was modified to allow group delivery and targeting both drugs and alcohol, while ICBT was developed by integrating manuals for cognitive-behavioral relapse prevention (Kadden, 1995) and group cognitive-behavioral therapy for depression (Muñoz & Ying, 1993). In both treatments group sessions occurred twice/week for three months and weekly thereafter (Max = 36 sessions). Most of the sample (82%) progressed to the weekly phase of treatment, with 69% attending at least 75% of group therapy sessions. Therapists were trained via manual review, direct observation, and weekly supervision, and were rotated across conditions every 6–12 months. All participants scheduled pharmacotherapy appointments with VA physicians, and nearly all (99.4%) utilized medication management.

Measures

Measures utilized in this study include variables assessed at intake (Month 0) and at 3-month intervals until the one-year follow-up (Month 18). Rates of follow-up were generally high, decreasing gradually from Month 3 (99%) to Month 18 (75%). Summary statistics for each variable at each time point are provided in Table 1.

Frequency of drinking and drug use—Alcohol and drug use was assessed with the Timeline Follow-Back (TLFB; (Sobell & Sobell, 1992), a reliable and valid structured interview (Maisto, Sobell, & Sobell, 1982). At each assessment the TLFB was used to separately capture alcohol and drug use in the prior 90 days. Outcome variables from the TLFB were percent days drinking (PDD) and percent days using drugs (PDDRG), with all time points from Month 6 (end of treatment) to Month 18 (end of follow-up) included as the primary treatment outcomes.

Proximal variables—Self-efficacy, 12-step affiliation, and depressive symptoms (collectively referred to hereafter as “proximal variables”) were assessed at 3-month intervals during treatment and follow-up. Measures of these variables from all time points from Month 3 (mid-treatment) to Month 15 were utilized in our analyses.

Self-efficacy: Self-efficacy for maintaining abstinence was measured with the Drug-Taking Confidence Questionnaire (Sklar, Annis, & Turner, 1997), a 50-item self-report measure of one’s perceived confidence to resist the use of alcohol or drugs across a variety of high-risk situations. On each item respondents rate their perceived confidence on an ordinal scale (0 = 0%, 1 = 20%, 2 = 40%, 3 = 60%, 4 = 80%, 5 = 100%), and the average across all items was used as the self-efficacy score (Range = 0 – 5). Cronbach’s alpha for the scale was above 0.98 at all time points, with available data ranging from 70% to 78% at all follow-ups.

12-step affiliation: The Alcoholics Anonymous Affiliation Scale (Humphreys, Kaskutas, & Weisner, 1998) was used to measure 12-step affiliation in the past month. A single ordinal item captures the number of 12-step meetings attended (0 = 0, .25 = 1–10, .50 = 11–20, .75 = 21–30), while 12-step behaviors are measured with four binary items (e.g., have sponsor, read literature, did service, having a spiritual awakening). The 12-step affiliation score was the sum of the attendance item and the four 12-step behavior items (Range = 0–5). Cronbach's alpha for the scale ranged from 0.70 to 0.81 at each time point, with available data ranging from 71% to 78% at all follow-ups.

Depressive Symptoms: Severity of depressive symptoms in the past week was assessed with the Hamilton Depression Rating Scale, 23-item version (Hamilton, 1960), a structured clinical interview previously validated in samples with AODD dependence (Willenbring, 1986). The sum was used as the depressive symptom score. Across all follow-ups reliability of the HAMD ranged from .78 to .85, and available data ranged from 72% to 89%.

Neurocognitive Impairment—Our “threshold” index of neurocognitive impairment was modeled after previous studies examining similar indirect effects in AODD treatment samples (Bates et al., 2006; Morgenstern & Bates, 1999). At intake participants completed eight neurocognitive tests with known sensitivity to common deficits in chronic, heavy substance users (Knight & Longmore, 1994; Weinstein & Shaffer, 1993). Neurocognitive tests and scores included the Wechsler Adult Intelligence Scale III (WAIS-III) Digit Symbol and Block Design subtests (Wechsler, 1997), Halstead-Reitan Trail Making A and B tests time to completion (Heaton, Grant, & Matthews, 1991), Golden Stroop Color and Word test color-word interference score (Golden, 1978), Wisconsin Card Sorting Test perseveration errors (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), California Verbal Learning Test II (CVLT-II) long delay recall (Delis, Kaplan, Kramer, & Ober, 2000), and Rey-Osterrieth Complex Figure test 30-minute delay (Rey, 1941). This general battery was selected to assess a broad array of domains including executive functioning, processing speed, and both verbal and non-verbal memory. For each test the raw score was converted to a *T*-score according to normative data adjusted for age and race (and education when available). Each test score was coded as “impaired” if falling at least 1.5 standard deviations below the adjusted mean, and the continuous neurocognitive impairment score was the total number of tests on which performance was impaired (Range = 0–8).

Covariates—Several variables were included as static covariates of PDD and PDDRG. Demographic covariates included age, gender, ethnicity (white vs. nonwhite), employment status (working vs. non-working), and years of education. Other covariates included treatment group (TSF vs. ICBT), baseline PDD/PDDRG, therapy attendance (number of group sessions attended), and post-traumatic stress disorder (PTSD), as 40% of the sample had co-occurring PTSD. Treatment compliance and comorbid anxiety have previously been associated with neurocognitive performance; we included therapy attendance and PTSD to control for these potentially confounding effects.

Statistical Analysis

Analyses were structured to address two overarching research questions: (1) whether effects of neurocognitive impairment on substance use were mediated by self-efficacy, 12-step affiliation, or depressive symptoms, and (2) whether impairment moderated the effects of these proximal variables on substance use. Hierarchical linear models (HLMs) are ideally suited for examining these questions in longitudinal data. By allowing random effects (e.g., intercepts and slopes) multiple time points nested within individuals can be included in a single analysis, with both time-invariant and time-varying predictors. All available data were included via maximum likelihood estimation, a preferred method for handling missing data when assumed missing-at-random (Schafer & Graham, 2002). We found no significant differences on study variables between participants with complete data vs. those with any missing data, supporting this assumption. Except for group and time, all predictor variables were grand-mean centered prior to analyses. Although outcome variables (e.g., PDD, PDDRG) were not normally distributed, visual inspection of all models revealed no violations of HLM assumptions (Raudenbush & Bryk, 2002). All analyses were performed in Stata 10.1 (StataCorp, 2007). For primary results we reported effect size measures according to recent guidelines in multilevel modeling (Peugh, 2010), including pseudo- R^2 for global effect size, and proportion reduction in variance (PRV) for local effect size.

Preliminary models examined static predictors of PDD and PDDRG to identify statistically significant covariates, including the static covariates listed above, time (linear and quadratic), and the treatment group by time interaction. To examine the effects of neurocognitive impairment on substance use and proximal variables, separate HLMs examined impairment as a person-level (i.e., static) predictor of PDD, PDDRG, self-efficacy, 12-step affiliation, and depression, controlling for effects of time, group, and the group by time interaction. The effects of each proximal variable on PDD/PDDRG were examined in separate HLMs by including each variable as a time-varying predictor. Proximal variables were lagged, such that self-efficacy, 12-step affiliation, and depression predicted future (i.e., 3 months later) PDD/PDDRG. Consistent with modern mediation methods (MacKinnon, 2008), we estimated the mediated effect and statistical significance using the products-of-coefficients with asymmetric 95% confidence limits (MacKinnon, Fritz, Williams, & Lockwood, 2007). This method has more accurate Type I error rates and greater power to detect mediated effects than alternate approaches (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002), and is appropriate for the analysis of nested data structures (Krull & MacKinnon, 2001). We reported effect sizes of mediated effects with the proportion of direct effect mediated (MacKinnon, 2008).

In a second series of models we tested whether neurocognitive impairment moderated the effects of proximal variables on future PDD/PDDRG. First, a main effects model was estimated that included covariates, impairment score, and all proximal variables as predictors of PDD/PDDRG. To test moderation of proximal variable effects by neurocognitive impairment, cross-level interactions were created, with all predictor variables grand-mean centered to reduce multicollinearity, (Kreft, Deleeuw, & Aiken, 1995), and a separate HLM examined each interaction term separately. We then created three-way interaction terms between neurocognitive impairment, therapeutic process variables (12-step

affiliation, self-efficacy) and depression, and tested these three-way interactions with all lower-order main effects and interactions in HLM, to test whether the strength and direction of impairment's moderating effects depended on current severity of depression.

Results

Prevalence of Neurocognitive Impairment

The mean neurocognitive impairment score was 1.05 ($SD = 1.15$), indicating that the average participant in our sample was impaired in at least one neurocognitive domain. Less than half of the sample (37.06%) had no impairments, 36.55 % were impaired on one measure, 16.75% on two, and the remaining 9.63% were impaired on three or more neurocognitive measures. The percentage of the sample impaired on each individual measure ranged from 7.14% on WAIS-III block design to 22.84% on CVLT-II long delay free recall (see Figure 1).

Preliminary Covariate Models

Static covariates of PDD/PDDRG included demographics, baseline PDD/PDDRG, treatment group, group therapy attendance, PTSD, time, time-squared, and group $\times$ time. For PDD age ($b = 0.39, p < 0.01$), years of education ($b = -1.09, p < 0.05$), baseline PDD ($b = 0.19, p < 0.001$), therapy attendance ($b = -0.77, p < 0.001$), group ($b = -5.97, p < 0.05$) and the group $\times$ time interaction ($b = 0.57, p < 0.05$) were significant covariates. For PDDRG only therapy attendance ($b = -0.24, p < 0.01$) and baseline PDDRG ($b = 0.16, p < 0.001$) were significant covariates. All subsequent models of PDD/PDDRG controlled for these effects.

Effects of Neurocognitive Impairment on Outcomes and Proximal Variables

We then tested the effects of intake neurocognitive impairment on post-intake substance use outcomes and proximal variables. These analyses separately examined whether the predictor (impairment) was significantly related to the outcome (PDD/PDDRG) and the mediating variables (self-efficacy, 12-step affiliation, and depression). Neurocognitive impairment did not predict PDD ($b = 0.76, SE = 0.91, p = 0.41$), or PDDRG ($b = -0.57, SE = 0.57, p = 0.32$) directly, but as hypothesized greater impairment did significantly predict lower self-efficacy ($b = -0.15, SE = 0.05, p < 0.01, \text{pseudo-}R^2 = .08, \text{PRV} = .02$), lower 12-step affiliation ($b = -0.17, SE = 0.08, p < 0.05, \text{pseudo-}R^2 = .06, \text{PRV} = .03$), and HAMD ($b = 1.93, SE = 0.54, p < 0.001, \text{pseudo-}R^2 = .11, \text{PRV} = .07$). Thus, while participants with greater impairment, on average, did not drink or use drugs more frequently, they did have significantly lower self-efficacy, lower 12-step affiliation, and greater depressive symptoms at post-intake follow-ups.

With support established for relations between impairment and the mediators, the next step examined whether these mediators predicted future drinking and drug use. Each proximal variable was tested separately as a lagged, time-varying predictor of PDD and PDDRG, controlling for covariates and neurocognitive impairment. Greater self efficacy ($b = -2.22, SE = 0.55, p < 0.001, \text{pseudo-}R^2 = .15, \text{PRV} = .14$), greater 12-step affiliation ($b = -1.86, SE = 0.43, p < 0.001, R^2 = .15, \text{PRV} = .20$), and lower HAMD ($b = 0.15, SE = 0.05, p < 0.01, \text{pseudo-}R^2 = .13, \text{PRV} = .13$) significantly predicted lower future PDD. Greater self-efficacy

($b = -1.04$, $SE = 0.41$, $p < 0.05$, pseudo- $R^2 = .05$, PRV = .18), greater 12-step affiliation ($b = -0.86$, $SE = 0.31$, $p < 0.01$, pseudo- $R^2 = .05$, PRV = .17), and lower HAMD ($b = 0.10$, $SE = 0.04$, $p < 0.05$, pseudo- $R^2 = .04$, PRV = .13) significantly predicted lower future PDDRG. These results indicated that individuals with greater self-efficacy, greater 12-step affiliation, and lower depressive symptoms had lower future drinking and drug use frequency.

Statistical Mediation Tests

With these results providing presumptive support for mediation, we obtained estimates of the mediated effect and joint standard error for a formal statistical test of mediation (MacKinnon, 2008). Results from HLMs were used to estimate each mediated effect and associated asymmetric 95% confidence interval. For PDD the effects of neurocognitive impairment were significantly mediated by self-efficacy ($b = 0.33$, 95% CI [0.10, 0.64], $p < 0.05$, proportion of direct effect (PDE) = 43%), 12-step affiliation ($b = 0.32$, 95% CI [0.02, 0.69], $p < 0.05$, PDE = 42%) and HAMD ($b = 0.29$, 95% CI [0.08, 0.58], $p < 0.05$, PDE = 38%). The effects of neurocognitive impairment on PDDRG were also significantly mediated by self efficacy, ($b = 0.28$, 95% CI [0.08, 0.53], $p < 0.05$, PDE = 49%), 12-step affiliation ($b = 0.15$, 95% CI [0.005, 0.35], $p < 0.05$, PDE = 26%), and HAMD ($b = 0.19$, 95% CI [0.03, 0.41], $p < 0.05$, PDE = 33%). These tests confirmed that greater intake neurocognitive impairment predicted greater post-intake PDD and PDDRG indirectly via these proximal variables.

Neurocognitive Impairment as a Moderator of Proximal Variable Effects

To determine whether the severity of baseline neurocognitive impairment moderated relations between time-varying, lagged proximal variables and future substance use, we tested cross-level interactions between neurocognitive impairment and proximal variables, controlling for covariates, impairment, and all proximal variable main effects on PDD and PDDRG. A separate HLM tested each interaction term separately. Results for PDD indicated that neurocognitive impairment did not moderate the effects of self-efficacy ($b = -0.13$, $SE = 0.47$, $p = 0.78$) or HAMD ($b = -0.05$, $SE = 0.05$, $p = 0.22$). However the interaction between 12-step affiliation and neurocognitive impairment was statistically significant ($b = -1.04$, $SE = 0.41$, $p < 0.05$, pseudo- $R^2 = .20$, PRV = .008). The association between greater 12-step affiliation and lower future PDD was relatively stronger for those with greater impairment (see Figure 2). For descriptive and graphical purposes we refer to impairment scores as “no” (impairment score = 0), “low” (1), “moderate” (2), or “severe” (2). When 12-step affiliation was low (score = 0), those with “moderate/severe” impairment had nearly twice the estimated PDD ($M = 24\%$) of those with “no/low” impairment ($M = 13\%$), whereas when 12-step affiliation was high (score = 5) estimated PDD was similar regardless of neurocognitive impairment severity.

Separate analyses of drug use found that impairment did not moderate the effects of self-efficacy ($b = 0.48$, $SE = 0.35$, $p = 0.17$) 12-step affiliation ($b = -0.16$, $SE = 0.27$, $p = 0.55$), or HAMD ($b = -0.13$, $SE = 0.07$, $p < 0.065$) on future PDDRG, suggesting that impairment did not moderate the effects of these proximal variables on drug use outcomes.

Three-way interactions of neurocognitive impairment and therapeutic process variables

These analyses were conducted to determine whether the strength and/or direction of the moderating effects of impairment on therapeutic process variables depended on current depression symptom severity. For PDD the three-way interaction between impairment, 12-step affiliation, and HAMD was statistically significant ($b = -1.04$, $SE = 0.41$, $p < 0.05$, pseudo- $R^2 = .21$, $PRV = .007$). As displayed in Figure 3, for participants with “no/low” impairment and “moderate” impairment, the association between 12-step affiliation and future PDD did not depend on current HAMD. However, for those with “severe” impairment, the effect of 12-step affiliation on future PDD depended on depressive symptoms, such that the association was strongest when depressive symptoms were most severe. A similar pattern was observed for self-efficacy, which also had a statistically significant three-way interaction with impairment and HAMD, ($b = -0.08$, $SE = 0.4$, $p < 0.05$, pseudo- $R^2 = .21$, $PRV = .004$). For those with no/low or moderate impairment, the relationship between self-efficacy and future PDD was negative and did not depend on current depression (see Figure 4). However, for those with severe impairment, the association between self-efficacy and future PDD depended on current depression severity, with strongest effects for those with currently severe depression. Overall, these results indicate that the effects of both 12-step affiliation and self-efficacy on future drinking were greatest for those with “severe” neurocognitive impairments when they were severely depressed, whereas current depression severity did not moderate these proximal variables effects for less impaired participants. For PDDRG, neither of these three-way interactions were statistically significant, suggesting that they were limited to alcohol use in the current sample.

Discussion

In a sample of adult veterans receiving treatment for co-occurring AODD and MDD, we found that more severe baseline neurocognitive impairment predicted poorer alcohol and drug use outcomes via lower self-efficacy, lower 12-step affiliation, and greater depressive symptoms. Furthermore, we found that greater intake neurocognitive impairment amplified the associations between greater 12-step affiliation and lower future drinking. Furthermore, we this interaction was further moderated by current depression severity, such that 12-step affiliation was more strongly related to future drinking when those with severe neurocognitive impairment were severely depressed. A similar pattern was observed for self-efficacy, such that on average, greater self-efficacy predicted lower future drinking, but this association was especially strong for severely impaired participants when they had severe depressive symptoms. These findings illustrate complex relations between neurocognitive impairment and time-varying protective and risk factors that may influence substance use outcomes for individuals receiving treatment for AODD and co-occurring psychiatric disorders.

We found that lower self-efficacy mediated the effects of neurocognitive impairment on future drinking and drug use. Prior studies of adults in treatment for AODD had similar results, with greater impairment related to lower self-efficacy (Bates et al., 2006; Morgenstern & Bates, 1999). Our study extends these findings to those with co-occurring

MDD. Self-efficacy, typically defined as the confidence to abstain from substance use in high-risk situations, consistently predicts substance use treatment outcomes, but factors leading to individual differences in self-efficacy are poorly understood (Kadden & Litt, 2011). Although therapy attendance was not impacted by neurocognitive impairment in this study, impaired clients may have experienced less perceived benefit from group therapy sessions, leading to reduced confidence they could resist urges to use alcohol or drugs in risky situations. Poorer cognitive ability has also predicted poorer quality of coping response following computerized CBT for AODD, suggesting that impairment may interfere with skill acquisition (Kiluk et al., 2011). Future studies should explore if difficulty acquiring coping skills or engaging in other aspects of group treatment explain lower self-efficacy for adults with severe impairment, and whether modifications to standard interventions are indicated.

Individuals with greater neurocognitive impairment also had lower levels of 12-step affiliation. In a prior study of this sample, those with poorer neurocognition were expected to fare worse in ICBT, due to its theoretically greater cognitive demands; however, these participants actually had better long-term substance use outcomes in ICBT than in TSF (Granholm et al., 2011). The current study provided some insight into these findings by demonstrating that participants with greater impairment engaged less fully in the prescribed behavioral mechanisms of TSF. Interestingly, a previous study of the Project MATCH sample found the reverse pattern, with greater impairment predicting greater AA affiliation (Bates et al., 2006). All of our participants were diagnosed with independent, co-occurring MDD, and most had severe depressive symptoms when entering treatment. These discrepant findings suggest that greater neurocognitive impairment does not limit 12-step engagement in all circumstances, but is more likely to impede 12-step affiliation in the context of a co-occurring psychiatric disorder.

Participants with more severe neurocognitive impairment had greater depressive symptoms during treatment and follow-up, which in turn predicted greater future drinking and drug use. In studies of individuals without AODD, more severe depression has been linked to poorer neurocognitive functioning (McClintock, Husain, Greer, & Cullum, 2010). Our findings are similar to a prior study of depressed, hazardous drinkers, in which those with worse cognitive functioning had less improvement in depression during CBT (Hunt et al., 2009). Negative affect is a frequent precursor to relapse in adults with co-occurring MDD (Tomlinson et al., 2006) and is often tied to substance use over time for adults with co-occurring MDD (Worley, Trim, et al., 2012), and for those with AODD in general (Jaffe, Shoptaw, Stein, Reback, & Rotheram-Fuller, 2007; Witkiewitz & Villarroel, 2009), but this is the first known study to link neurocognitive impairment, depressive symptoms, and substance use via formal mediation analyses. On average, participants in this study improved in depression over time (Lydecker et al., 2010), but impaired individuals may have had greater difficulty with some elements of treatment (e.g., pharmacotherapy compliance, coping skills) that prevented improvement in depressive symptoms. Alternatively, individuals with greater neurocognitive impairment may have been more likely to present to treatment with greater psychosocial difficulties (e.g., unemployment, social isolation) and related negative cognitions or self-appraisals that contributed to persistent depressive symptoms.

Despite these mediated links between neurocognitive impairment and alcohol/drug use, in models examining direct effects of impairment there was no association with substance use outcomes. However, mediated effects can occur in the absence of direct associations, such as in the context of “suppressor” variables or unobserved moderator effects (MacKinnon, 2008). Despite their greater depression, lower self-efficacy, and lower 12-step affiliation, those with greater neurocognitive impairment may have benefited from unmeasured factors that mediated substance use in the opposite direction, such as greater motivation for abstinence. Greater severity of health problems has predicted lower odds of post-treatment relapse (Tate, McQuaid, & Brown, 2005). Participants with greater neurocognitive impairment may have been more motivated to abstain from substance use due to impairment or other health factors.

Clarity for the absence of a direction association between cognitive impairment and drinking was also provided by significant moderating effects. We found that the prospective association between greater 12-step affiliation and lower future drinking was strongest for those with more severe neurocognitive impairment. Although severely impaired participants had lower 12-step affiliation, they apparently derived relatively greater benefits from 12-step affiliation than non-impaired participants. Furthermore, this interaction depended on current severity of depression. The association between 12-step affiliation and future drinking for severely impaired participants was especially strong when depressive symptoms were severe; a similar pattern was observed for self-efficacy. In other words, engagement in 12-step practices and self-efficacy were most strongly tied to future drinking under the dual conditions of (a) severe neurocognitive impairment and (b) having currently severe depressive symptoms. Although some prior studies found reduced benefits of 12-step affiliation for impaired patients (Bates et al., 2006; Morgenstern & Bates, 1999), others found greater effects of social support for those with greater impairment (Buckman et al., 2007; Buckman et al., 2008). Our results suggest the influence of neurocognitive impairment on the link between therapeutic process variables and substance use treatment outcomes is complex, and may depend on other dynamic risk factors that change over time (e.g., depressive symptoms), and may moderate the risk linked to a distal factor such as severe neurocognitive impairment.

Limitations of this study include the consideration that findings may not be immediately generalizable to the broad population of individuals with AODD and co-occurring psychiatric disorders, as we only studied adults with AODD and MDD. Additionally, this sample was composed of veterans who were predominantly male and Caucasian. Clinical trials of treatments for AODD frequently suffer similar demographic limitations, and replication of these findings in a broader context is needed before making wider generalizations. Although we examined complex mediated and moderated pathways to substance use, there are relationships among the variables in this study that could merit further exploration but were outside the scope of this study, including the potential moderating effects of PTSD and/or demographic variables, such as age and years of education. The effects of mediating variables were examined in separate models due to sample size considerations, and more stringent “multiple mediator” models can be used to examine independent effects and discover the most integral mediators. Although the current study met some criteria for testing mechanisms of change (e.g., statistical mediation,

temporal precedence), meeting further criteria would be necessary before concluding these processes are true mechanisms of change (Nock, 2007). Because our index of neurocognitive impairment reflected deficits across a variety of domains, we did not examine whether specific deficits predicted proximal variables or substance use. We also could not differentiate underlying causal factors for neurocognitive impairment, such as whether chronic substance use or MDD related more strongly to the observed cognitive deficits. Future studies achieving these aims are needed to increase the specificity of clinical recommendations in response to particular neurocognitive deficits in adults with AODD and co-occurring disorders, such as MDD.

The current study provides preliminary evidence that severe neurocognitive impairment adversely impacts alcohol drug use during and following group psychotherapy for co-occurring AODD and MDD, through the mediating variables of self-efficacy, 12-step affiliation, and depressive symptoms. Furthermore, we found evidence of interactions between neurocognitive impairment and dynamic proximal variables, such that 12-step affiliation had stronger effects on future drinking for adults with greater severity of neurocognitive impairment, especially when they were severely depressed. Self-efficacy was also linked more closely to future drinking for individuals with severe intake impairment and currently severe depression. These findings highlight the importance of considering interactions between distal factors, proximal risks, and proximal therapeutic factors in understanding the outcomes of psychological treatments for AODD and potentially other co-occurring conditions. Failing to consider relations between distal and more dynamic, proximal factors may have the unintended effect of clouding clinically-meaningful interactions that influence substance use during and following treatment.

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Figure 1.
Proportion of sample classified as “impaired” on each neurocognitive measure.

Figure 2.
Pre-treatment neurocognitive impairment moderates the relationship between time-varying 12-step affiliation and future drinking.

Figure 3. Three-way interaction between pre-treatment neurocognitive impairment, time-varying 12-step affiliation, and time-varying depression in the prediction of future drinking frequency.

Figure 4. Three-way interaction between pre-treatment neurocognitive impairment, time-varying self-efficacy, and time-varying depression in the prediction of future drinking frequency.

Table 1

Descriptive statistics of substance use outcomes and proximal variables for veterans with substance dependence and major depression (N = 197).

	Month						
	0	3	6	9	12	15	18
<i>n</i> (%)	197 (100)	196 (99)	188 (95)	178 (90)	173 (88)	163 (83)	147 (75)
PDD							
<i>M</i>	23.63	7.57	10.65	11.89	13.09	12.99	15.92
<i>SD</i>	23.63	16.71	22.08	22.69	24.11	25.79	29.73
PDDRG							
<i>M</i>	10.04	2.66	3.95	4.48	5.34	4.87	7.34
<i>SD</i>	19.56	10.36	12.17	14.65	15.66	14.28	18.92
Self-efficacy							
<i>M</i>	3.24	3.64	3.65	3.64	3.64	3.58	
<i>SD</i>	1.16	1.11	1.13	1.22	1.21	1.29	
12-step affiliation							
<i>M</i>	2.67	2.70	2.45	2.17	2.10	2.01	
<i>SD</i>	1.48	1.61	1.65	1.74	1.74	1.71	
HAMD							
<i>M</i>	28.35	24.94	22.02	22.03	21.51	22.61	
<i>SD</i>	10.65	12.50	12.69	13.71	12.19	12.74	

Note. PDD: percent days drinking; PDDRG: percent days using drugs; HAMD: Hamilton Depression Rating Scale. Month 18 proximal variables not included in analyses.

Table 2

Interactions between intake neurocognitive impairment, time-varying process variables (TVPVs), and time-varying depression on future percent days drinking (PDD).

	TVPV: 12-step affiliation		TVPV: Self-efficacy
	<i>b</i> (<i>SE</i>)	<i>b</i> (<i>SE</i>)	<i>b</i> (<i>SE</i>)
Month	0.17 (0.48)	0.19 (0.48)	0.07 (0.48)
Month ²	0.005 (0.02)	0.004 (0.02)	0.009 (0.02)
Group (TSF vs. ICBT)	− 3.58 (2.39)	− 3.95 (2.37)	− 3.69 (2.37)
Group × month	0.35 (0.25)	0.36 (0.25)	0.38 (0.25)
Group sessions	− 0.64 (0.12)***	− 0.63 (0.12)***	− 0.61 (0.12)***
Age	0.31 (0.13)*	0.31 (0.13)*	0.28 (0.13)*
Years of education	− 0.73 (0.44)	− 0.75 (0.44)	− 0.67 (0.44)
Baseline PDD	0.14 (0.04)***	0.13 (0.04)***	0.15 (0.04)***
HAMD ^a	0.08 (0.06)	0.07 (0.06)	0.08 (0.06)
12-step ^a	− 1.72 (0.45)***	− 1.60 (0.45)***	− 1.62 (0.45)***
Self-efficacy ^a	− 1.53 (0.57)**	− 1.55 (0.57)**	− 1.15 (0.59)*
Impairment (IMP)	0.73 (0.88)	0.49 (0.88)	0.02 (0.88)
IMP × TVPV ^a	− 1.02 (0.39)**	− 1.03 (0.39)**	− 0.17 (0.53)
IMP × HAMD ^a	—	− 0.03 (0.04)	− 0.06 (0.05)
HAMD × TVPV ^a	—	− 0.005 (0.03)	− 0.08 (0.04)*
IMP × HAMD ^a × TVPV ^a	—	− 0.07 (0.03)*	− 0.08 (0.04)*

Note. PDD: percent days drinking; PDDRG: percent days using drugs; TSF: Twelve-Step Facilitation; ICBT: Integrated Cognitive-Behavioral Therapy; HAMD: Hamilton Depression Rating Scale; TVPV: Time-varying process variable.

^aLagged values (i.e., prior wave) used as time-varying predictor

* $p < .05$

** $p < .01$

*** $p < .001$.