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Elevated intraindividual variability in methamphetamine dependence is associated with poorer everyday functioning

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Abstract

Methamphetamine (MA) dependence is associated with executive dysfunction, but no studies have evaluated MA-related elevations in neurocognitive intraindividual variability (IIV), an expression of cognitive dyscontrol linked to poor daily functioning in populations with frontal systems injury. We examined IIV during a vigilance task in a well-characterized sample of 35 MA-dependent (MA+) and 55 non-MA using comparison participants (MA−) as part of a larger neuropsychological battery that included self-report and performance-based measures of everyday functioning. A mixed model ANOVA was conducted while controlling for covariates, including factors that differed between the groups (e.g., education) and those with conceptual relevance to IIV: mean reaction time, global cognitive performance, and HIV-infection (which was comparable across groups; $p = .32$). This analysis revealed significantly elevated IIV among MA+ relative to MA− individuals that was comparable in magnitude across all trial blocks of the vigilance task. Within the MA group, elevated IIV was associated with executive dysfunction, psychomotor slowing, and recency of MA use, as well as poorer automobile driving simulator performance, worse laboratory-based functional skills, and more cognitive complaints. MA-users are vulnerable to IIV elevation, likely due to cognitive dyscontrol, which may increase their risk of real-world problems.

Keywords

Substance dependence; within-person variability; cognitive control; activities of daily living; neuropsychological assessment

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1. INTRODUCTION

Chronic use of methamphetamine (MA) can substantially disrupt an individual's biopsychosocial functioning at multiple levels, ranging from alterations in central nervous system (CNS) structure to declines in cognitive performance and even failures in real-world activities. In the CNS, MA induces neurotoxicity that preferentially impacts the structure, function, and metabolism of the prefronto-striato-thalamocortical loops (Panenka et al., in press). Likely as a combination of premorbid vulnerabilities and downstream effects, MA-dependent individuals are more likely to be neurocognitively impaired than non-MA users (Rippeth et al., 2004), particularly in domains subserved by frontal systems, including executive functions, the strategic aspects of memory, information processing speed, and attention (Scott et al., 2007). Importantly, among those with MA-dependence, deficient executive abilities appear to increase risk of poor everyday functioning status (Weber et al., 2012), including mismanagement of daily tasks, unemployment, and unsafe driving (Scott et al., 2007).

One aspect of neuropsychological functioning that has received very little study in MA users is intrainvidual variability in cognitive performance, or IIV. In contrast to the standard method for summarizing performance whereby measures of central tendency (such as mean performance) are emphasized, measures of IIV describe within-person fluctuations in an individual's cognitive performance across time. Under its broad definition, IIV can be measured in a number of ways, but many studies operationalize it as fluctuations in reaction time (RT), which is summarized as standard deviation of RT across trials, usually in the context of a sustained attention task. Although neurologically healthy individuals do show some degree of normal IIV (Schretlen et al., 2003), elevated levels of IIV are strongly associated with frontal systems dysfunction (see McDonald, Li, & Backman, 2009, for a review). Accordingly, IIV is purported to be an expression of cognitive dyscontrol (West et al., 2002), or a behavioral manifestation of a breakdown in top-down processes that regulate and allocate cognitive resources (e.g., attention) across trials of a task. IIV may appear in the early stages of CNS dysregulation due to insult, thus having the potential to identify those at risk for worse clinical outcomes in the future (MacDonald et al., 2009).

MA users can evidence a moderate deficit in sustained attention (Scott et al., 2007), which may be characterized by inconsistent performance across time. Specifically, one study reported elevated variability in response RT and a higher rate of omission errors over the course of a sustained attention task in a sample of mixed stimulant users (i.e., cocaine and/or MA) who were infected with HIV (HIV+; Levine et al., 2006). Interestingly, these findings were observed in the context of normal mean hit RT speed and signal detection (i.e., ability to discriminate between targets and non-targets), suggesting that the instability in response RT over time among the stimulant group was not simply due to overall poor performance. In fact, the typical effects of psychostimulants on task performance can include a decrease in response time, resulting in "better" performance as measured by RT speed, especially with more recent use (Toomey et al., 2003). Therefore the shift in perspective from mean level of performance to IIV could be particularly useful in characterizing the negative effect of MA use on sustained attention among MA users. Nevertheless, no study to date has conducted a targeted examination of the effect of MA on RT IIV.

From a clinical perspective, elevations in IIV may confer increased risk of difficulties with real world activities among MA users. Elevated IIV, as defined by RT variability, has been observed and linked to poor cognitive prognosis (i.e., decline and/or incipient cognitive disorder diagnosis) in several populations such as ADHD (e.g., Tamm et al., 2012), HIV (Ettenhofer et al., 2010), aging (e.g., Beilak et al., 2010; Hultsch et al., 2002), Parkinson's disease (Burton et al., 2006; de Frias et al., 2012), and traumatic brain injury (Burton et al., 2002). Notably, IIV may also identify those at risk difficulty with performing important everyday functions that require regulation of behavior over time. One striking example with considerable consequences is driving, which is a complex activity that draws heavily on stability, consistency, and vigilance for success. Recent evidence has shown that aging drivers perform poorly in a driving simulator across speed and traffic volume settings, characterized by greater variability in driving outcomes (i.e., maintaining proper headway and lane position; Bunce et al., 2012). Reaction time speed has long been associated with driving performance in numerous populations (e.g., aging; Anstey et al., 2005), and it is likely that RT variability, or IIV, would also relate to poor driving performance. Unsafe driving and an elevated rate of traffic violation and accidents have been observed among MA users (e.g., Logan, 1996), which may be due to the interference of high RT IIV on driving ability.

In addition to daily functioning difficulties, elevated IIV among MA users may be associated with behaviors involved in the addiction cycle itself. That is, an individual with elevated IIV might also evidence greater problematic drug use behaviors than someone with better consistency in RT responding. Given that the mechanism purportedly underlying elevated expression of IIV is cognitive dyscontrol, in the same way that MA-users poorly regulate speed of responding on a sustained attention task they may also have difficulty controlling various aspects of drug use relating to initiating drug use, density and duration of use, and maintaining abstinence from drug use. That is, control of drug behavior likely requires consistent focus and effort toward that goal, particularly when immersed in an environment full of drug-related cues and opportunities, and inconsistency in effort and focus could lead to greater frequency or quantity of use, and could result in greater propensity for relapse. Moreover, in much the same way that more recent use of stimulants results in increased speed of RT responding (Toomey et al., 2003), greater RT IIV may also be observed in the context of more recent use.

Based on the evidence above the present study aimed to take a hypothesis-driven approach to examining the profile of IIV in MA users. To demonstrate the hypothesized MA-related IIV elevation, the performance of a group of MA-dependent individuals was investigated relative to a non-MA using comparison group in controlled analyses. A proportion of the sample was HIV+ (proportions within the two study groups were comparable), and therefore HIV status was included in the evaluation of this hypothesis, which allows for generalizability to prior work and to the larger population of MA users given the comorbidity of HIV and MA use. Within the MA-dependent group, the cognitive correlates of IIV were examined, and it was hypothesized that IIV would be significantly associated with a domain summary score measuring executive functions given that poor cognitive control purportedly underlies elevated IIV expression. MA use parameters were also explored as correlates of IIV in the MA-dependent group. Additionally, IIV was expected to

be a unique predictor of everyday functioning outcomes in the MA-using group as defined by self-report (i.e., daily functioning problems and cognitive complaints) and laboratory (i.e., tests of functional capacity, including instrumental activities of daily living and driving) measures.

2. METHOD

2.1 Participants

Participants for the present study were community-dwelling individuals recruited via advertisements and targeted outreach from the San Diego area (including outpatients recruited from substance use clinics) into the larger, ongoing Translational Methamphetamine Research Center (TMARC) study, which broadly investigates the independent and combined CNS effects of MA and HIV infection. TMARC was approved by the UCSD human research protections program, and all participants provided written, informed consent. The present study sample represents a subset of the TMARC sample comprising 35 MA-dependent participants (MA+) and 55 comparison participants who had never met criteria for MA dependence (MA−). Only male participants were included in the study because very few female participants were available in the larger MA+ TMARC sample, limiting the ability to account for potential influence of gender in the subset. All MA-dependent participants met criteria for MA dependence within the past 18 months as determined by the Composite International Diagnostic Interview (CIDI v. 2.1; World Health Organization, 1998), and their lifetime MA use history was fully characterized using a timeline follow-back interview, which yielded the variables shown in Table 1. Exclusion criteria for both groups included histories of severe psychiatric (e.g., schizophrenia) or neurologic illness (e.g., seizure disorders), or a verbal IQ estimate <80 based on the Reading subtest of the Wide Range Achievement Test – 4th edition (WRAT-IV; Wilkinson & Robertson, 2006). Participants were also excluded for hepatitis C infection, histories of alcohol dependence within the past year, other drug dependence within the past 5 years, and drug abuse within the past year, or lifetime history of Attention-Deficit/Hyperactivity Disorder. Exceptions to these exclusion criteria included a history of alcohol abuse or marijuana abuse/dependence given their high comorbidity rate in MA-dependence. Although there was not a required minimum number of days of abstinence from alcohol or substances use prior to testing, participants were not assessed if their Breathalyzer or urine toxicology screenings were positive on the day of testing. This necessitated approximately 72 hours since MA last use in the MA group, and the duration of abstinence from other substances varied based on their respective rates of metabolism. HIV serostatus was determined by enzyme-linked immunosorbent assays and confirmed by a Western Blot test.

Sample characteristics are displayed in Table 1. To minimize the likelihood that demographic, psychiatric, medical (i.e., HIV), and substance use factors commonly comorbid with MA use would confound our findings, the MA− comparison group was recruited to have similar levels of exposure to these factors. As such, the groups were comparable with the exception of significantly fewer years of education, greater current depressive symptoms (i.e., Beck Depression Inventory-II; Beck et al., 1996), and higher rates of “Other Substance Use Disorder” diagnoses (i.e., remote abuse or dependence for

alcohol, cocaine or opioids) in the MA+ group relative to the MA− group. Of note, the groups were comparable with regard to the proportion of individuals with HIV infection, and when the subsets of individuals with HIV were compared across MA status, their HIV disease characteristics were comparable as well (*p*s > .05, as shown in Table 1).

2.2 Procedures

All participants completed a comprehensive battery of neuropsychological tests assessing seven cognitive domains (see Table 1). Demographically-adjusted normative standards correcting for age, education, gender, and ethnicity were applied to raw scores, and the resulting T-scores were transformed into weighted deficit scores that emphasize greater degrees of impairment (range = 0-5, with higher numbers indicating higher impairment according to the following convention: ≥ 40T = 0; 39T - 35T = 1; 34T - 30T = 2; 29T - 25T = 3; 24T - 20T = 4; and ≤ 19T = 5; a cutpoint of 0.5 determined impairment). Deficit scores were averaged within domains and across the battery to yield Domain Deficit Scores (DDS) and a Global Deficit Score (GDS), respectively, according to a standardized approach (Carey et al., 2004).

2.2.1. Sustained Attention/Vigilance—Participants were administered the Conners' Continuous Performance Test, Second Edition (CPT-II; Conners, 2000), which is a commonly used sustained attention task that produces IIV indices as part of its scoring program. As such, it has characterized expression of IIV and the relationship of IIV to clinical outcomes in other populations (e.g., ADHD, Tamm et al., 2012; HIV, Ettenhofer et al., 2010). The CPT-II is a 14-minute computerized test in which participants are instructed to quickly press the space bar whenever any letter except "X" appears on the screen, and to inhibit responding when presented with the letter "X." Stimuli were presented for 250 ms per trial, with varying inter-stimulus intervals (ISIs; either 1, 2, or 4 s). Six trial blocks were further divided into three 20-trial sub-blocks, for which the ISI was 1, 2, or 4 s. The CPT-II program has a standard scoring procedure that yields raw score variables as well as *T*-scores adjusting for age and gender (Conners, 2000). Notably, indices of IIV are included as part of the standard score report yielded by the CPT-II. For this study, T-scores were used in analyses unless otherwise noted, with lower scores representing better performance. The current study extracted the following variables from the CPT-II for descriptive and analytic purposes (see Table 1): (1) *Hit RT* (i.e., mean RT latency); (2) *Hit SE per block* (i.e., standard error of *Hit RT* within a block; raw scores in milliseconds were transformed into population-based z-scores referencing MA− group; see Figure 1); (3) *Hit SE Variability* (i.e., standard deviation of Hit SE across trial sub-blocks); (4) *Hit SE Block Change* (i.e., overall slope of change in Hit SE across blocks; higher values indicate increased variability as test progresses); (5) *Omission errors* (i.e., false-negative); (6) *Commission errors* (i.e., false-positive); (7) *d'* (i.e., signal detection). For the purposes of the present study, within-block IIV is represented as *Hit SE per block* and overall task IIV is *Hit SE Variability*.

2.2.2. Performance-based Measure of Everyday Functioning—Participants completed the UCSD Performance-based Skills Assessment (UPSA; Patterson et al, 2001). The UPSA evaluates ability to perform everyday tasks necessary for independent functioning in the community across five subscales: Household Skills, Communication,

Finances, Medication Management, Transportation, and Comprehension/Social Planning. Subscale scores summed to create a Total score (range 0 – 100) in which higher scores reflect better performance.

Participants also completed a challenge drive in a driving simulator (Systems Technology, Inc.; Hawthorne, CA). The simulator included a steering wheel, accelerator and brake pedals, and auditory feedback. The simulator task has a 10-minute time limit to complete a route (countdown timer provided) in order to receive a $15 reward, and participants must also successfully avoid penalties that reduce the amount of that reward, including crashes (e.g., pedestrians, slow-moving vehicles; $1.00 penalty), speeding (i.e., $0.50 penalty), and running traffic signals i.e., $0.50 penalty). Total Crashes and Tickets (TCT) provides an unweighted sum of these two types of challenge failures.

2.2.3. Self-report Measures of Everyday Functioning—A modified version of the Lawton and Brody (1969) Activities of Daily Living (ADL) scale was used. A summary of "current" self-ratings for performance of instrumental activities of daily living (IADL; i.e., grocery shopping, housekeeping, finance management, transportation, shopping, medication management) was derived, with higher scores denoting greater difficulty with functioning (range 0–3 per item, 0–18 total). This modified measure was chosen over a traditional index of decline from "best" level of functioning given that MA-dependent individuals may not have previously achieved a higher better level of functioning.

The Patient's Assessment of Own Functioning Inventory (PAOFI; Chelune et al., 1986) is a 41-item questionnaire in which participants rate cognitive complaints in their daily lives using 6-point Likert-type responses, with higher scores indicating greater daily cognitive difficulty. The PAOFI reflects the frequency that participants experience difficulties with work and recreation, memory, language and communication, sensory-perceptual skills, and higher-level cognitive and intellectual functions.

3. RESULTS

3.1. MA-associated IIV Elevation

3.1.1. Analytic Approach—To examine the effect of MA on IIV as measured by the CPT-II, a mixed-model ANOVA was conducted with MA group as the between-subjects factor and Hit SE per Trial Block (1-6) as the within-subjects factor. Two types of covariates were included to establish the unique contribution of IIV. Several factors were included to account for factors on which the groups differed, including years of education, BDI-II Total Score, and Other LT SUD (see Table 1). In addition, and theory-driven factors that were likely to be associated with IIV were also included as covariates, including CPT Hit Reaction Time T-score to account for the relationship between reaction time speed and variability; GDS, which addresses the possible relationship between global impairment and CPT performance; and HIV status, given that prior evidence has revealed elevated IIV among individuals living with HIV (Ettenhofer et al., 2010), including stimulant users (Levine et al., 2006).

3.1.2. Findings—A significant main effect of group (MA+ vs MA−) was revealed [F(1, 83)=0.08, *p*=.03] but no main effect of trial block and no MA × trial block interaction (ps>. 1) were observed. Figure 1 shows z-score transformed mean Hit SE scores by block presented for each group. Regarding the covariates, CPT Hit Reaction Time T-score and GDS were significantly associated with IIV across trial blocks (*p*s < .001) but all other covariates were non-significant (*p*s > .05). Given the relevance of HIV to IIV in prior literature (e.g., Ettenhofer et al., 2010), this model was also run with an interaction term for MA group by HIV status, which was not significant (*p* = .55).

3.1.3. Post-hoc Analyses—Given the lack of trial block main effect or interaction with MA group, follow-up analyses were conducted with Hit SE Variability T-score, which is a standard CPT-II summary score representing IIV across the trial blocks. Two sets of post-hoc analyses were conducted to enhance interpretability of the main effect of MA group on IIV reported above.

To provide an interpretive anchor for the degree of IIV observed in the MA+ and MA− groups, 1-sample chi-square tests were conducted within each group to compare proportions of individuals with elevated IIV, as defined by greater than 60 relative to the expected normative proportion (i.e., 15.9%). In the MA+ group, the proportion of individuals with clinically elevated IIV was significantly greater than the normative proportion (x^2 = 5.1, *p* = .02), whereas there was no difference between the proportion of individuals with elevated IIV in the MA− comparison and the normative proportion (x^2 = 1.2, *p* = .28).

Using the summary IIV variable (Hit SE Variability T-scores), we also demonstrated that there were no univariate effects between four groups defined by HIV and MA status (ps > . 10), which is consistent with the non-significant MA by HIV interaction term reported above.

3.2. IIV as a Predictor of Real World Outcomes

3.2.1. Analytic Approach to Performance-Based Outcomes—Two multivariable regressions evaluated Hit SE Variability as a predictor of performance-based everyday functioning in the MA+ group. Hit RT was included as a covariate in the models to control for the influence of average response speed on these outcomes. Recency of MA use was selected as another covariate based on its association with both IIV, (i.e., correlation between MA use recency and Hit SE Variability; *rho* = −0.37, *p* = .03), and to account for its potential relationship to everyday functioning capacity. No other candidate covariate, including HIV status, BDI-II score, or GDS, was significantly related to the primary independent variable (Hit SE Variability) or to the functional capacity outcomes (*p*s > .05).

3.2.2. Findings in Performance-Based Outcomes—Hit SE Variability was the only significant predictor of each criterion (all other *p*s > .05): **UPSA** (*Model*: Adjusted R^2= 0.19, *F*= 3.41, *p*= .03; *Hit SE Variability*: *B* = −0.58, *p* = .005), **Driving TCT** (*Model*: Adjusted R^2 = 0.4, *F* = 7.78, *p* =. 001; *Hit SE Variability*: *B* = 0.72, *p* < .0001).

3.2.3. Analytic Approach to Self-Reported Outcomes—Two multivariable regression analyses evaluated Hit SE Variability as a predictor of self-reported daily

functioning difficulties. The models were similar to those described above, with the exception that recency of MA use was replaced with level of depression symptoms (BDI-II Total score) given the strong association between current depression and complaints, as well as the limited number of predictors that could be included due to the small sample size.

3.2.4. Findings in Self-Reported Outcomes—IIV was a significant predictor of cognitive difficulties in daily life, as measured by the **PAOFI** (*Model*: Adjusted R^2= 0.23, F = 4.1, p = .02; *Hit SE Variability*: B = 0.56, p = .002). However, it was not a significant predictor of **IADL severity** (*Model*: Adjusted R^2 = 0.01, F = 1.11, p = .36; *Hit SE Variability*: B = 0.29, p = .12).

3.2.5. Parallel Analyses in MA− Comparison Participants—A similar set of four regression models was run in the MA− comparison group. The overall model was not significant for Driving TCT (*Model*: Adjusted R^2 = −0.02, F = 0.68, p = .57), but was significant for UPSA Total Score (*Model*: Adjusted R^2 = 0.49, F = 13.1, p < .0001; *Hit SE Variability*: B = −0.28, p = .03). For the models in which self-report measures were the criterion variables, BDI-II Total Score replaced HIV status as a covariate (as was done in the MA+ group). The model predicting IADL complaints was not significant overall (*Model*: Adjusted R^2 = 0.07, F = 2.41, p = .08), and although the model predicting PAOFI was significant (*Model*: Adjusted R^2 = 0.24, F = 6.70, p = .0007), the only significant predictor was BDI-II Total Score (p < .0001).

3.3. Cognitive Mechanisms of Elevated IIV

Within the MA+ group, Hit SE Variability was significantly correlated with the Executive Function Domain Deficit Score (*rho*=0.34, *p*=.04) and Speed of Information Processing Domain Deficit Score (*rho*=0.35, *p*=.04), but not with the other domains (*p*s>.05). In the MA− comparison group, none of the domain deficit scores was significantly correlated with Hit SE Variability (*p*s > .05).

3.4. MA Use Parameters as Correlates of Elevated IIV

We examined the MA use parameters shown in Table 1 as correlates of IIV. As reported above, more recent MA use was significantly associated with higher IIV, but none of the other MA use parameters was significantly correlated with IIV (ps > .10). In contrast to the IIV finding, none of the cognitive domain deficit scores was significantly correlated with duration of MA abstinence (*p*s > .10).

To follow-up on the significant negative correlation between the number of days since last MA use and expression of IIV, recency of MA use was binned according to the following convention: within 30 days (≤ 30 days, n = 10), greater than 30 days but less than or equal to 6 months (> 1 month / ≤ 6 months, n = 16), or greater than six months ago (≥ 6 months, n = 9). Duration of MA abstinence ranged from 3 days to 18 months, with a median of 61 days (IQR = 21, 243). A oneway ANOVA revealed a significant omnibus difference in IIV between these three groups [F(2, 32) = 4.81, p = .01]. As displayed in Figure 2, periods of MA abstinence were grouped into bins that were informed by substance dependence disorder remission specifiers as defined by the Diagnostic and Statistical Manual of Mental

Disorders, Fourth Edition (DSM-IV, 2000), including cutpoints at ≤ 30 days (which reflects the period of time that must elapse between the end of dependence symptoms and the beginning of the remission phase) and ≥ 6 months (which was chosen instead of the 12 month mark suggested by the DSM-IV because too few participants in the present sample have greater than one year of MA abstinence). Tukey's HSD group comparisons confirmed that the level of IIV observed among individuals who had used MA within 30 days was elevated relative to the groups with longer durations of abstinence (> 1 month / ≤ 6 months, $p = .05$, Hedges $g = 0.80$; ≤ 6 months, $p = .017$ Hedges $g = 1.19$), which did not differ from each other ($p = .69$; Hedges $g = 0.28$).

4. DISCUSSION

Findings from the present study revealed an effect of MA dependence on expression of IIV. Specifically, MA-dependent individuals were more inconsistent in speed of responding (i.e., RT) over the course of a sustained attention task relative to non-MA users. In terms of the relative degrees of IIV elevation observed in the groups, the proportion of MA+ individuals with clinically elevated levels of IIV was significantly higher than would be expected in the general population (based on normative proportions), whereas this elevation was not observed in the MA− comparison group. Notably, this effect was independent of potential confounding factors, and the results were not better explained by overall slowed speed of responding or impaired signal detection in the MA+ group. Interestingly, greater expression of IIV was associated with more recent MA use, as well as cognitive correlates including executive dysfunction and slowed speed of information processing. Emphasizing the real-world relevance of this finding, MA-associated IIV elevations significantly predicted a variety of everyday functioning outcomes. These findings further characterize the neurocognitive profile of MA dependence by elucidating a novel cognitive feature of chronic MA users, and this study further validates IIV as an important clinical index in populations with frontal systems dysfunction, such as MA-dependence.

Regarding the pattern of IIV observed in the present study, our findings indicate that in addition to the greater IIV shown by MA users relative to non-MA users was observed throughout the entire duration of the sustained attention task. These findings contrast slightly with those of Levine and colleagues (2006), whose study of HIV+ mixed stimulant users on the same sustained attention task indicated that the slope of IIV increased over the course of the task (i.e., Hit SE Block Change), indicating that participants' variability in response speed was highest toward the end of the task. Considered together, these findings support the hypothesis that MA users demonstrated elevated IIV, and the subtle discordance in the patterns observed may reflect differences in the samples, including the focus on MA exclusively in the present study, and the fact that only a proportion of our sample was HIV+ (compared to all participants in the prior study). The present study did test for a moderating effect of HIV on the relationship between MA status and IIV expression, but found no evidence of such a relationship in our data. Explicit examination of a main effect of HIV status was not explored (i.e., HIV status was considered a covariate in subsequent analyses) because a separate set of regression analyses correcting for statistical (e.g., group differences on demographic, psychiatric characteristics) and theoretical factors relevant to HIV infection would need to be run, which is beyond the scope of the present study. Moreover, the HIV

sub-sample in the present study was relatively young and demonstrated a low rate of neurocognitive impairment, which indicates that it is not an adequately representative sample to support an exploration of the effect of HIV on IIV, especially given that a recent study demonstrated synergistic effects of HIV and age (Morgan et al., 2011). Given prior evidence for additivity of HIV and MA on cognitive and everyday functioning difficulties (Blackstone et al., 2013; Rippeth et al., 2004), future studies may prospectively examine this question in greater depth.

Notably, the inverse correlation between recency of MA use and IIV is consistent with previously observed recovery of overall cognitive function with abstinence from MA (Iudicello et al., 2010). In the present study, only IIV was significantly related to recency of MA use, whereas none of the cognitive domain deficits scores nor the global deficit score showed this association. Considered against the findings of the earlier study by Iudicello and colleagues (2010), which employed a longitudinal study design to carefully examine the effects of MA abstinence on cognition, our more gross correlational finding with regard to IIV along could suggest that IIV may be particularly sensitive to the timing of MA use. This interpretation is supported by the fact the pattern of MA abstinence effects on cognitive control, which purportedly underlies IIV expression, appears to be similar to those reported for IIV in the present study (i.e., poorest performance among those with recent MA use compared to comparable performance between non-drug using controls and those with a year or greater of MA abstinence; Salo et al., 2009), whereas prior evidence examining episodic memory among those with various patterns of MA use may be more complex (i.e., MA-abstinent groups performed better than MA-relapsers, but worse than those with continuous use; Salo et al., 2004). Regarding the quantification of the abstinence pattern, the most pronounced effects of MA on IIV were observed among those who had last used MA within 30 days, which is consistent with DSM-IV guidelines for applying remission specifiers for substance dependence disorders that require a one-month buffer in which no dependence criteria are met before the modifier can be assigned. This finding also supports the notion that elevated IIV might influence drug use behaviors. Although inferential, it is possible that the association between higher IIV and shorter duration of abstinence may suggest that people who have difficulty consistently sustaining attention are more prone to use MA and/or relapse. This association also may suggest that the MA-related impact on IIV, and perhaps its downstream effects on daily functioning described below, can be prevented and/or reversed, which emphasizes the importance of treatment for MA use disorders.

IIV (as measured by the Hit SE Variability summary score) was indeed a robust and unique predictor of everyday functioning among MA-dependent individuals. These findings are concordant with prior evidence showing an association between IIV and medication nonadherence among HIV+ stimulant users (Ettenhofer et al., 2010), and they extend that work by focusing on chronic MA users only with controlled analyses (i.e., inclusion of mean RT and MA use recency or depressive symptoms as covariates) across a broad range of daily functioning outcomes. Moreover, several of the outcomes in the present study evaluate functional capacity through laboratory assessment of complex daily life skills. Driving is a real-world activity that draws heavily on intact vigilance (e.g., Bunce et al., 2012), and IIV was a significant predictor of driving performance whereas average RT speed was not. This

suggests that among chronic MA users, who often show unsafe driving behaviors (e.g., Logan, 1996), it is elevated cognitive fluctuations that increase risk for driving problems, rather than overall slowed responses.

Interestingly, the use of performance-based laboratory outcomes in the present study appears to have revealed problems for which the individuals may not be fully aware and/or may still be able to compensate. That is, IIV was significantly associated with a performance-based evaluation of IADL (i.e., UPSA), but not with self-reported severity of IADL difficulties. Moreover, IIV was associated with cognitive complaints (i.e., PAOFI), which reflects problems with higher-level real world functions. The fact that problems due to IIV emerged under demanding test conditions and/or related to complex tasks but have not yet been elicited in IADL performance is consistent with the theory that IIV represents a relatively early marker of loss of neural and cognitive integrity (MacDonald et al., 2009). As such, the IIV signal for higher-level tasks may be a harbinger of later real-world IADL difficulties. Although not mutually exclusive from this interpretation, the restricted range of the IADL questionnaire may have contributed to the lack of an association with IIV.

The pattern of findings in the present study supports the purported cognitive dyscontrol mechanism of IIV (e.g., West et al., 2002) as being the factor underlying the expression of elevated IIV among chronic MA users. Specifically, in the MA+ group, as IIV increased there was a corresponding increase in the level executive dysfunction, which was largely characterized by measures of cognitive flexibility that were not exclusively based on speeded and/or RT responding (see Carey et al., 2004). Evidence of worse cognitive flexibility in those with higher IIV provides indirect support for the notion that poor regulation and allocation of cognitive resources in response to task demands may underlie the associated difficulties with real-world daily activities. Moreover, the profile of CPT-II variables observed in the present study (i.e., elevated and fluctuating IIV throughout a sustained attention task as indicated by Hit SE per trial and Hit SE Variability, respectively) is consistent with deficient cognitive control. Notably, Salo and colleagues (in press) demonstrated in another sample of MA users that an irregular, variable pattern of RT responses following conflict presentation (i.e., poor adjustment of RT response) among MA users, which is likely a representation of elevated IIV, was negatively correlated with PFC activity. In sum, these findings extend our understanding of the dysexecutive and strategic-deficit pattern of MA-dependence previously described (Scott et al., 2007). It should be noted that slowed information processing speed was also associated with greater IIV expression in the current study. This finding is interesting because mean level of hit RT on the CPT-II did not differ between the groups (hence our interpretation that the IIV signal is not solely due to slower performance in the MA+ group). Information processing speed is a fairly diffuse and sensitive measure, suggesting that it's association with IIV may be consistent with the theory that IIV is an early marker of nonspecific loss of cognitive integrity (MacDonald et al., 2009). It may be the case that both executive functions and speed of information processing are required to regulate performance on this speeded task, or these domains may contribute differentially at various points across the task.

The absence of consistent findings in the MA− comparison group is inconclusive. Although the clinical IIV elevation demonstrated in MA+ group but not the MA− group provided firm

supporting evidence regarding the effect of MA on IIV, it does not suggest that the psychiatric and disease factors present in the comparison group do not also have the potential to increase expression of IIV. On the contrary, problematic IIV elevations have indeed been reported previously in studies with the proper design for investigating the effect of those factors on IIV (e.g., Bunce et al., 2008; Ettenhofer et al., 2010). By its very nature, the MA− comparison sample is a mixed clinical and healthy group that provides a methodologically sound contrast to the MA+ group but could not serve as an accurate representation of the IIV signal associated with any of the individual factors present within that group. Similarly, the lack of an association between IIV and everyday functioning outcomes or clinical correlates cannot be meaningfully interpreted because the "noise" within this mixed group may have dampened a potential signal.

Limitations and Future Directions

Potential future directions for exploring these findings may address the limitations herein and expand the results. For example, a study with a larger sample size may reveal a trial block effect and/or a MA group by trial block interaction, allowing for direct exploration of the cognitive mechanisms underlying performances at various time blocks. Additionally, with a larger sample the analyses involving error types, which did not differ between the MA+ and MA− groups in the present study, might reveal a signal that could bolster evidence of MA-related IIV, consistent with findings of increasing omission errors over the course of an attentional vigilance task in mixed-stimulant users (e.g., Levine et al., 2006). Inclusion of a healthy comparison group was beyond the scope of the present study given that our aim was to investigate a MA-specific IIV signal in relation to real world functioning. Some level of IIV is considered "normal" even among healthy adults (Schretlen et al., 2003), and expression of IIV can be increased by many factors, including disease (e.g., HIV; Ettenhofer et al., 2010) and psychiatric factors (e.g., depression and anxiety; Bunce et al., 2008). Therefore, demonstration of MA-related IIV "elevation" in the present study was a relative determination that was established through comparison of the MA+ group to a non-MA using group that was similar on as many other factors as possible to isolate the effect of MA. However, the absence of a healthy comparison group did not allow us to fully anchor our findings with regard to a "normal" level of IIV expression and its relationship to our selected outcomes and correlates. Given that our IIV measure was a demographically-corrected T-score (Hit SE Variability) from the CPT-II, we approximated the comparison of our study groups to healthy adults through the use of expected normative proportions of clinically elevated IIV (i.e., 15.9%). However, future studies may wish to include a healthy comparison group in order to provide more direct evidence contrasting level of IIV and its relationships to outcomes of interest between healthy adults and clinical groups. It should also be noted that the index of IIV used in the present study was derived from a single attentional vigilance task that did not vary with regard to difficulty or cognitive load. Although this is a standard approach in the study of IIV, this lack of ecological validity may limit the degree to which the IIV signal measured in the present study represents how IIV is expressed in the real world. Nevertheless, this is likely a conservative bias because the IIV signal was shown to be statistically and clinically meaningful via the demonstrated relationship to performance-based measures of everyday activities. Future studies may seek to expand upon these findings by examining IIV with more sophisticated and complex RT

tasks that vary with regard to task demands (e.g., divided attention) to determine the association between these measures and everyday functioning. Of note, all of our participants were male, which limits the generalizability to female MA-users. Future studies should include female participants to investigate potential gender effects.

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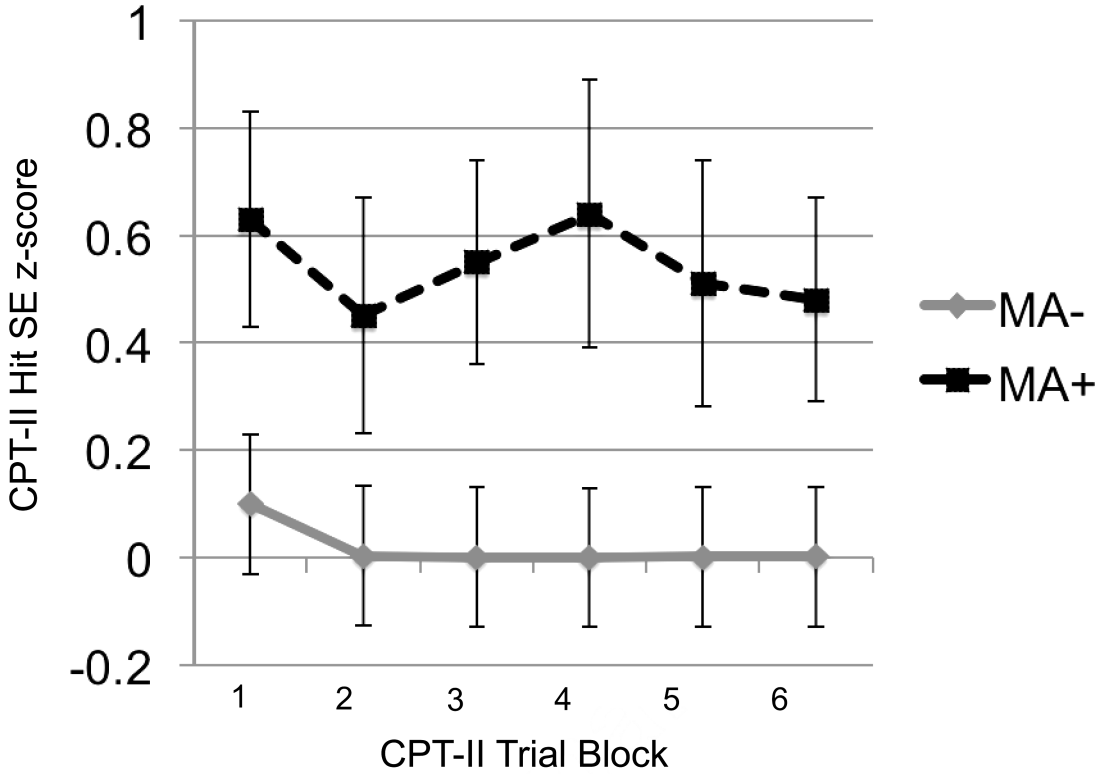

Figure 1.
Elevated IIV (Hit SE) across trial blocks in MA+ relative to MA−

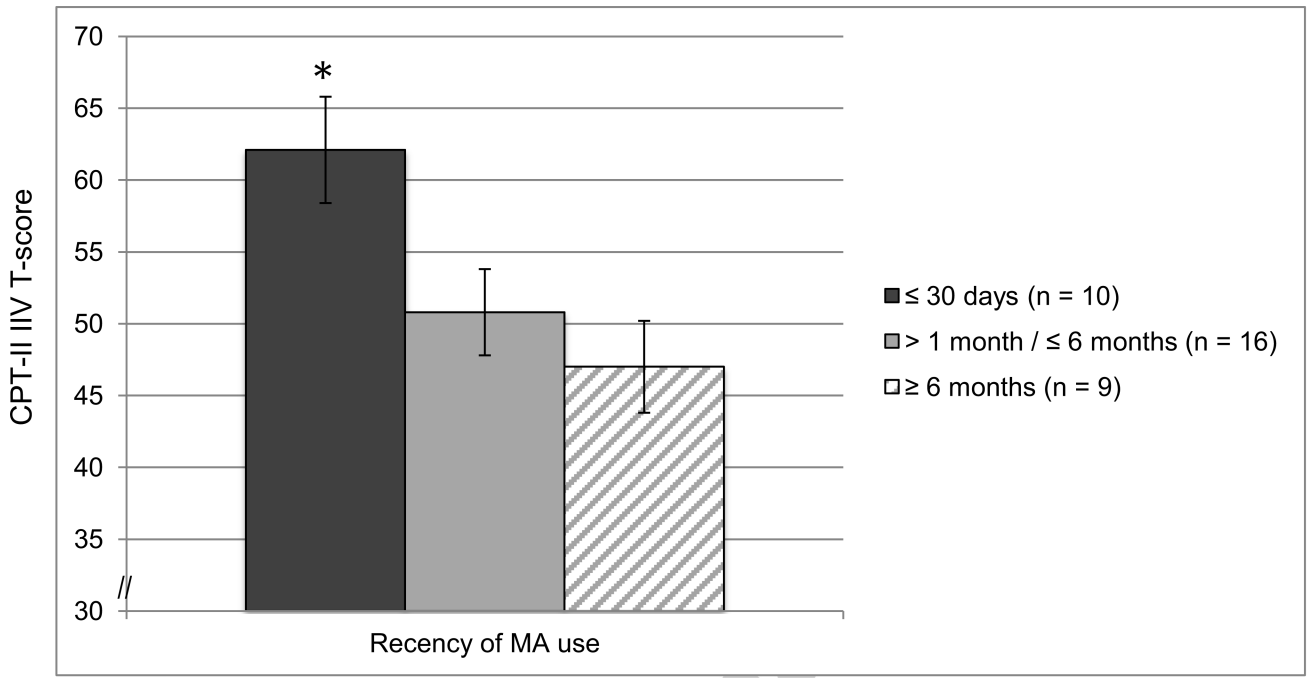

Figure 2.

IIV expression was higher among participants whose last use of MA was within the last 30 days relative to those with longer duration of abstinence

Table 1

Descriptive Characteristics of the Study Participants

Characteristics	MA− (n = 55)	MA+ (n = 35)	p
Demographics			
Age (years)	38.1 (11.8)	40.5 (8.9)	.35
Education (years)	14.0 (2.2)	12.9 (2.2)	.02
Ethnicity (% Caucasian)	56.4	65.7	.38
Estimated verbal IQ[a]	103.2 (11.7)	104.3 (11.5)	.44
Psychiatric			
Current Major Depressive Disorder (%)	14.6	37.1	.01
Lifetime Major Depressive Disorder (%)	32.7	45.7	.22
BDI-II Total[b]	7.1 (9.7)	14.4 (10.5)	.001
Substance Use			
Methamphetamine Use [c]			
Age at first use (years)	--	24 (18, 30)	--
Last use (days since)	--	61 (21, 243)	--
Cumulative duration of use (days)	--	1627 (432, 3341)	--
Cumulative quantity of use (grams)	--	845 (163, 1614)	--
Density of use (grams / days)	--	0.43 (0.25, 1.07)	--
Other Substance Use Disorders[d]	34.6%	68.6%	.002
HIV Disease			
Proportion with HIV infection	43.6%	54.3%	.32
Proportion with AIDS[e]	37.5%	52.6%	.37
HIV plasma viral load[e, f]	1.7 (1.6, 4.2)	1.6 (1.6, 3.7)	.32
Current CD4 count[e, f]	522 (332, 736)	544 (363, 613)	.85
Proportion on cART (%)[g]	60.9	73.7	.38
Cognitive			
Global Deficit Score[f]	.21 (.11, .42)	.26 (.11, .47)	.62
Proportion Impaired[h]:			
Attention/Working Memory	15.4%	21.9%	.48
Speed of Information Processing	12.8%	15.6%	.74
Learning	41.0%	46.9%	.62
Memory	23.1%	28.1%	.63
Executive Functions	20.5%	25.0%	.65
Verbal Fluency	23.1%	15.6%	.43
Motor	20.5%	28.1%	.45

Note.

[a] Based on the WRAT-4 Reading standard score;

[b] Beck Depression Inventory-II;

[c] Lifetime MA use characteristics

[d] Lifetime diagnosis of remote abuse (i.e., >1 year ago) or dependence (i.e., >5 years ago) for alcohol, cocaine, or opioids;

[e] Values reflect the HIV+ subgroup within the MA− and MA+ groups;

[f] Median (interquartile range);

[g] cART = Combined antiretroviral therapy;

[h] Impairment in each cognitive domain is defined by a cutpoint of 0.5

Table 2

Group differences by MA status on attentional vigilance and everyday functioning measures

Characteristics	MA− (n = 55)	MA+ (n = 35)	p
CPT-II T-scores			
Hit RT	48.5 (1.3)	51.9 (1.7)	.12
Hit SE Variability	48.1 (10.1)	53.0 (12.5)	.04
Hit SE Block Change	49.2 (6.5)	46.9 (12.3)	.26
d' (Detectability)	57.7 (11.8)	60.7 (13.6)	.26
Omission Errors	45.4 (42.1, 48.8)	45.4 (42.1, 55.4)	.47
Commission Errors	46.1 (42.7, 53.2)	47.4 (39.2, 53.5)	.37
Everyday Functioning			
Performance-Based			
UPSA Total	96.5 (1.8)	91.6 (2.0)	.08
Driving: Total Crashes & Tickets (TCT)[e]	3 (2, 6)	4 (3, 7)	.07
Self-Report			
PAOFI	2.8 (4.1)	5.9 (6.8)	.01
IADL Complaint Severity [range: 0-4][e]	0 (0, 0)	0 (0,1)	.02

Note. UPSA = UCSD Performance-Based Skills Assessment; PAOFI = Patient's Assessment of Own Functioning; IADL = Instrumental Activities of Daily Living