Psychiatry Research: Neuroimaging 211 (2013) 234–238

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Behavioral regulation in methamphetamine abusers: An fMRI study

Ruth Salo [a,b,*], Catherine Fassbender [a,b], Michael H. Buonocore [b,c], Stefan Ursu [a,b]

[a] Deparment of Psychiatry and Behavioral Sciences, University of California, Davis, CA, USA
[b] Imaging Research Center, University of California, Davis, CA, USA
[c] Department of Radiology, University of California, Davis, CA, USA

ARTICLE INFO

Article history:
Received 11 August 2012
Received in revised form
16 October 2012
Accepted 18 October 2012

Keywords:
Methamphetamine
Prefrontal
Cognitive control
Functional magnetic resonance imaging (fMRI)
Imaging

ABSTRACT

The goal of this study was to extend our previous findings of abnormal prefrontal function in methamphetamine (MA) abusers and controls and to link the imaging data to behavioral, demographic and drug use variables. We used a fast event-related functional magnetic resonance imaging (fMRI) design to examine trial-to-trial reaction time (RT) adjustments in 30 MA abusers and 30 controls. A variant of the Stroop task was employed to measure influence of response conflict on RT, including the level of trial-to-trial RT adjustments seen after conflict trials. Compared to control subjects, MA abusers exhibited reduced RT adjustments and reduced activation in the prefrontal cortex (PFC) after conflict trials. RT adjustment correlated negatively with PFC brain activity in the MA group, while a trend for a positive correlation was observed in controls. No correlations were observed between task performance or brain activity and age, education or drug use variables. These data support our previous findings that the ability to adapt a behavioral response based on prior experience is compromised in MA abusers. Interestingly, these impairments do not appear to be linked to drug use patterns or to educational levels.

1. Introduction

Worldwide use of methamphetamine (MA) is now estimated to be at 51 million users (Degenhardt et al., 2008; Roehr, 2005; United Nations, 2008, 2009), with global abuse of amphetamine/methamphetamine now surpassing that of cocaine and opiates combined (United Nations, 2009). Approximately 5% of the adult population in the United States has used MA on at least one occasion and Emergency Department admissions related to MA use have doubled during the period of 1994 to 2002 (SAMSHA, 2004). Numerous imaging studies suggest that fronto-cingulate regions of the brain are affected by MA abuse (Ernst et al., 2000; London et al., 2004; Nordahl et al., 2005; Salo et al., 2007; Volkow et al., 2001). Consistent with abnormalities in brain structure and function, cognitive impairments have also been observed in MA abusers on tasks that require the suppression of task irrelevant information (Monterosso et al., 2005; Salo et al., 2007), decision-making (Kalechstein et al., 2003; Paulus et al., 2003), working memory (McKetin and Mattick, 1998) and cognitive control (Nestor et al., 2011; Salo et al., 2009a). Neurobiological models of addiction propose that ventral brain regions (i.e., orbital frontal cortex and nucleus accumbens) contribute to the impulse to seek drugs, whereas the recruitment of fronto-cingulate regions may be critical to control those prepotent impulses (i.e., cognitive control) (Jentsch and Taylor, 1999). In the context of addiction, cognitive control can be interpreted as the inhibition of a prepotent response (e.g., habitual drug use) in order to carry out behaviors associated with long-term rewards and positive outcomes (e.g., abstaining from drug use).

1.1. Study rationale

The goal of the current study was to replicate and extend our preliminary findings that examined cortical mechanisms of cognitive control in a small group of MA abusers (Salo et al., 2009b). In the current study we increased our sample significantly in order to examine correlations between brain activity and behavior. In order to examine the neural substrates of cognitive control relevant to addiction, we conducted a fast event-related functional magnetic resonance imaging (fMRI) study in which we examined trial-to-trial reaction time (RT) adjustments using a variant of the single-trial Stroop task in 30 chronic MA abusers and 30 controls. This version of the Stroop task (Kerns et al., 2004) creates conditions in which performance (RT and accuracy) reflects the ability to recognize and resolve conflict at the time of response selection (i.e., within a trial), as well as the ability to flexibly adapt behavior, such as using

* Corresponding author at: University of California, Department of Psychiatry and Behavioral Sciences, UC Davis Imaging Research Center, 4701 X St., Sacramento, CA 95817, USA. Tel.: +1 916 734 7909; fax: +1 916 734 8750.
E-mail address: resalo@ucdavis.edu (R. Salo).

0925-4927/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pscychresns.2012.10.003

exposure to conflict situations to change subsequent behavior (i.e., trial-to-trial adjustments after conflict trials). Many lines of research have shown that the information-processing system can adjust its strategy on a trial-to-trial basis and that the utilization of such a plan of action may be coupled with the subjective view that a particular strategy will produce a positive outcome (Gratton et al., 1992). Given that one of the hallmark behaviors associated with addiction is the failure to choose adaptive strategies to achieve future positive outcomes, this paradigm is well suited to examine the role of cognitive control in MA dependence. We hypothesized that in this increased sample of MA abusers we would observe correlations between abnormal patterns of trial-to-trial RT adjustments (i.e., conflict adaptation) and reduced PFC activity. Given the recent claim that many cognitive studies in MA abuse are confounded by group differences in age and education, we also wanted to test these relationships directly.

2. Materials and methods

2.1. Subjects

Two groups were studied: 30 MA-abusing subjects and 30 age-matched non-substance-abusing control subjects. Data from 12 MA subjects and 16 controls were reported in our previous preliminary findings (Salo et al., 2009b). The MA abusers met DSM-IV criteria for lifetime MA dependence determined from the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992) but had been abstinent for a minimum of 3 weeks. See Table 1 for demographic and drug use characteristics.

2.2. Procedure

A single-trial Stroop task was administered during the scanning session that employed both incongruent (conflict) and congruent (non-conflict) trials (see Supplemental material for detailed task description). Behavioral analyses contrasted the groups on RT Stroop conflict effect (conflict minus non-conflict), mean error rates and the level of trial-to-trial adjustments seen after conflict trials. Analysis of variance procedures (ANOVA) for repeated measures were used to analyze the data in a 2×2 mixed ANOVA with group as a between-subjects factor (patients vs. controls) and word type (incongruent vs. congruent) as within-subjects variables. Incorrect responses were not included within the analysis of variance for RT. Analyses were carried out to examine trial-to-trial adjustments to conflict-conflict (iI) compared to non-conflict-conflict (cI) sequences. Accuracy data were analyzed using the same design.

Table 1
Demographic and clinical characteristics of 30 methamphetamine (MA) abusers and 30 control subjects.

	Methamphetamine abusers ($n=30$)	Control subjects ($n=30$)
Demographic variables		
Age, *y*, mean (S.D.)	35.5 (7.9)[a]	29.0 (7.7)
Range	21 –48 years	20– 48 years
Females	15	13
Subject's education, y, mean (SEM)	12.5 (1.6)[a]	15.2 (1.3)
Parental education, y, mean (SEM)	13.2 (2.3)	14.3 (2.5)
NART	108.2 (5.0)[a]	111.6 (4.7)
Clinical variables		
Methamphetamine use		–
Duration, *y*, mean (S.D.)	14.0 (6.4)	–
Range	4– 28 years	
Months abstinent, mean (S.D.)	13.7 (15.4)	–
Range	2– 60 months	
Age of 1st MA use, *y*, mean (S.D.)	17.7 (4.4)	–
Mean daily MA dosage (grams)	1.3 (0.85)	–
History of cannabis abuse	24	–
Age of 1st cannabis use. *y*, mean	15.0 (3.8)	

[a] Significantly different from control group.

2.2.1. Imaging

Functional MRI data were collected on a 3T Siemens Trio Total imaging matrix (Tim) MRI System (Erlangen, Germany: see Supplemental material for scanning parameters and image preprocessing details). Analyses were performed using a general linear model (GLM) as implemented in SPM5. In a first-level analysis, individual subject GLMs were fitted to each subject's functional data. The statistical models included regressors coding for 7 covariates (cC, iC, iI, cI, errors, post-errors and non-responses). Parameter estimates obtained from this first level analysis were used to compute maps of the contrasts of interest for effects of conflict and trial-to-trial effects (I–C for RT conflict, and iI–cI for trial-to-trial RT adjustments). Maps of the contrasts of interest for effects of error conflict were also computed. Hypotheses put forth within this proposal regarding activity in specific regions of interest (ROIs) including anterior cingulate cortex (ACC) and prefrontal cortex (PFC) were tested in a second level random-effects analysis of these contrast maps. The volume of search was restricted to areas for which we had specific hypotheses by using an explicit mask of lateral and medial prefrontal cortical areas. The mask used was the same as employed in our 2009 study and was built using the AAL atlas in the SPM5 toolbox (see Supplemental material for details). Clusters of active voxels reported were corrected for multiple comparisons at a set level of $p<0.05$ (Friston et al., 1996).

3. Results

3.1. Behavioral data

3.1.1. Reaction time analyses

Analyses revealed main effects of Stroop word type [$F(1,58)=157.49$, $p<0.0001$] and trial-to-trial adjustments [$F(1,58)=14.58$, $p<0.0001$]. Planned analyses also revealed that the trial-to-trial adjustment RT effect (cI–iI) differed significantly between the MA abusers and controls [$F(1,58)=4.37$; $p<0.05$]. While the controls showed an RT advantage (26-ms benefit) to conflict trials that were preceded by conflict trials (iI), the MA abusers showed no advantage and were actually slower (4-ms cost). These group differences in Stroop performance endured with age, education, NART scores as covariates. Correlational analyses revealed no relationship between education levels and trial-to-trial adjustments in the MA abusers ($r=.11$; $p=0.57$) or the controls ($r=.15$; $p=0.44$). No correlations were observed between measures of age and premorbid IQ (i.e., NART scores) and trial-to-trial adjustments in either group. Similar to our previously published findings, no group differences were observed on within-trial Stroop conflict effects ($F<1$) (Table 2).

3.1.2. Error analyses

Analyses revealed a main effect of word type [$F(1,58)=36.13$, $p=0.0001$] with both groups making significantly more errors in the incongruent condition (6%) than in the congruent condition (3%). There were no group differences in incongruent [$F(1,58)=2.28$; $p=0.13$] or congruent errors [$F(1,58)=1.5$; $p=0.22$]. There was no evidence of a speed-accuracy trade-off for both groups (MA abusers; $r=0.293$; $p=0.10$, controls: $r=0.096$; $p=0.61$].

3.2. Imaging results

We first examined whether activity within the ACC and PFC was associated with within-trial conflict monitoring (I–C) and trial-to-trial adjustments (iI–cI). Using ANOVA procedures with subject as a random variable, significant activation to conflict contrasts (I–C) was observed in the ACC in both groups with no differences observed between groups. In contrast, when we examined the pattern of activation for the trial-to-trial RT adjustments, we found that controls exhibited increased PFC activity on iI sequences compared to the cI sequences. In contrast