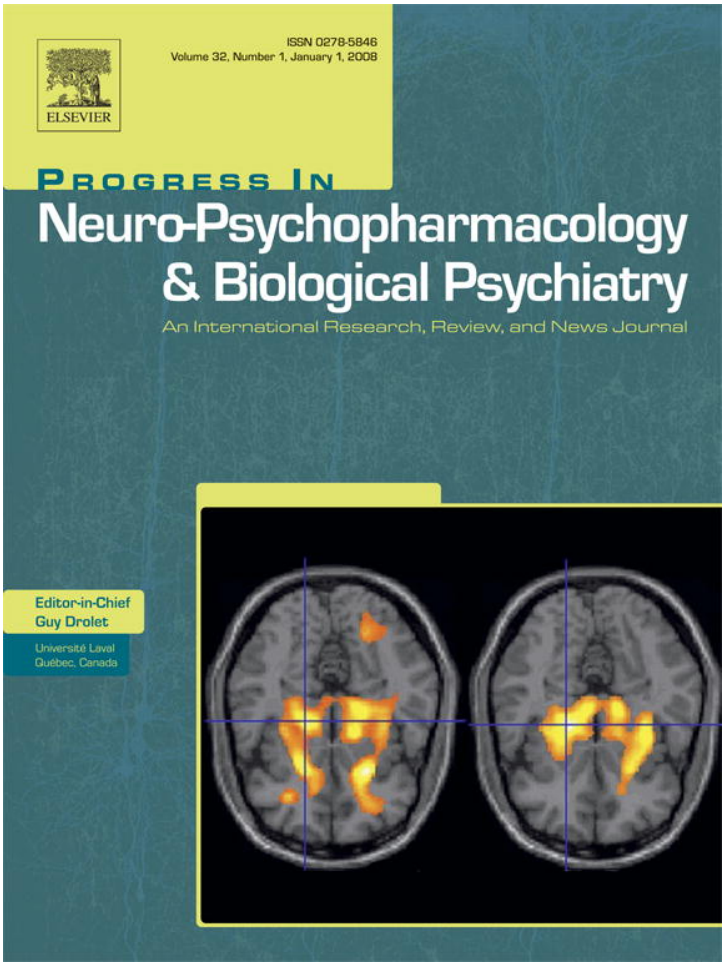

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Findings of preserved implicit attention in methamphetamine dependent subjects

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Abstract

Long-term methamphetamine (MA) abuse is associated with a wide range of deficits on explicit tasks of selective attention. Less is known however about the effects of MA abuse on implicit measures of attention. Accordingly, we used a computerized spatial priming task to assess implicit attentional processes in 54 MA dependent subjects (mean age = 37.04 ± 8.9 years) and 32 healthy controls without history of any form of substance abuse (mean age = 33.63 ± 7.05 years). The MA dependent subjects had been drug-abstinent a minimum of 3 weeks with a mean duration of MA use of 13.27 ± 7.75 years. The MA dependent subjects did not differ significantly from controls on either inhibitory priming [$p = .37$] or facilitory priming) [$p = .69$]. This result comports with our earlier findings of intact object-based priming in MA dependent individuals and suggests that intact priming effects extend across spatial domains. Further, this pattern of sparing suggests that cortical brain systems typically supporting implicit attentional functioning are relatively intact in long-term MA dependent individuals whereas brain systems supporting explicit attentional processes are affected.

Keywords: Cognition; Methamphetamine; Priming; Selective attention; Stimulant abuse; Substance abuse

1. Introduction

Long-term methamphetamine (MA) abuse is associated with impaired performance on a number of explicit cognitive tasks (Simon et al., 2000; Salo et al., 2002; Simon et al., 2002a; Kalechstein et al., 2003; Lawton-Craddock et al., 2003; Toomey et al., 2003; Salo et al., 2005). Explicit tasks require the subject to consciously carry out a specific operation or computation as a measure of cognitive performance (Tulving and Schacter, 1990; Schacter, 1998; Schacter and Buckner, 1998a). Explicit measures might include memory tasks in which a subject is to remember a list of words for subsequent recall or a visual search paradigm which requires the subject to actively search for a target amidst a set of distracting objects in an array. The majority of cognitive studies conducted in MA using individuals have employed explicit measures of cognition. Using a battery of explicit measures, Volkow et al. (Volkow et al., 2001c) tested a group of MA dependent subjects and found that these subjects exhibited performance deficits in both verbal memory and motor function. In one study of MA dependent subjects tested in early stages of drug abstinence, Kalechstein et al., reported deficits on a range of explicit tasks including those that measured attention/psychomotor speed, verbal learning and memory (Kalechstein et al., 2003). In another study of actively using MA users, deficits were reported on explicit measures of abstract reasoning, task shifting strategies, memory recall, and tests that required manipulation of information (Simon et al., 2002b). Deficits in the suppression of conflicting information have also been

Abbreviations: AD, Alzhemier's Disease; ANOVA, analysis of variance; AR, attend-repetition; IR, ignore repetition; MA, methamphetamine; ms, milliseconds; NART, National Adult Reading Test; NEU, neutral; HD, Huntington's Disease; RTs, reaction times; SCID, Structured Clinical Interview; RSI, response stimulus interval.

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observed across a number of explicit tasks in stimulant users and MA dependent individuals (Salo et al., 2002; Kalechstein et al., 2003; Toomey et al., 2003; Salo et al., 2005; Salo et al., 2007). Although some studies of stimulant users have reported intact performance on a subset of explicit measures (Toomey et al., 2003), the majority of studies in MA dependent subjects have reported deficits on explicit measures of attention and memory (Nordahl et al., 2003).

In contrast to explicit measures of cognitive function, implicit tasks measure the influence of past experiences on current performance even when the subject is unaware of the relationship (Squire et al., 1985; Schacter, 1987; Tulving and Schacter, 1990; Schacter, 1998). Implicit measures can generate what are known as "priming effects". Priming can be defined as a change of behavior based on previous exposure to a stimuli or event, such as a reduction in response time or an increased accuracy rate. Priming effects can be facilitory or inhibitory based on the sequence of events (Neill, 1977; Lowe, 1979). Processing previously selected objects or spatial locations can facilitate subsequent target identification or localization (i.e. positive priming). Conversely, requiring a subject to select a target which has previously appeared as a distractor can result in slowed response times or increased errors. Such deleterious effects have been termed "negative priming costs" (Tipper, 1985; Tipper and Cranston, 1985; Fox, 1995).

Priming is multi-dimensional with some forms of priming based on physical characteristics (spatial and object-based), others based on procedural learning and some priming effects based on higher level associations that are formed during processing, such as semantic relations (Graf et al., 1985; Heindel et al., 1989; Tulving and Schacter, 1990; Tulving, 1992; Schacter, 1998). Preserved priming has been reported in densely amnesic patients (Warrington and Weiskrantz, 1968, 1974; Shimamura, 1986; Shimamura et al., 1987), Huntington's Disease (HD) patients (Heindel et al., 1989) and Alzhemier's Disease (AD) patients (Keane et al., 1991). Interesting dissociations have been reported in priming studies with some patients (i.e. HD patients) exhibiting intact lexical priming but impaired procedural priming (Heindel et al., 1989). In contrast, AD patients, have demonstrated disrupted lexical but preserved priming in both perceptual and procedural domains (Heindel et al., 1989; Keane et al., 1991). Such dissociations support the claim that priming is multi-dimensional, and suggest that different forms of priming may be supported by distributed cortical mechanisms (i.e. sub-cortical and cortical).

1.1. Study rationale

Given our previous findings of intact object-based priming (Salo et al., 2002), as well as reports of intact object priming in cocaine dependent subjects (Jasiukaitis and Fein, 1999) and chronic alcoholics (Zhang et al., 1997), it was of interest to test a group of MA dependent individuals on a spatial priming task. As the majority of studies on domain specific processing have employed explicit performance tasks, it was of interest to see if implicit priming effects were similar across object and spatial domains (Salo and Robertson, 2003). If, however, priming effects are mediated by a general mechanism, then preserved implicit processing of spatial information (i.e. normal spatial priming) should appear across all subjects (MA dependent and controls). Based on the reports of intact object-based priming in stimulant abusing subjects (Jasiukaitis and Fein, 1999; Salo et al., 2002), we predicted that the MA dependent subjects in the current study would also display intact spatial priming.

Table 1
Demographic and use characteristics of 54 MA abusers and 32 control subjects

	Methamphetamine abusers ($n=54$)	Control subjects ($n=32$)
Demographic variables		
Age, years, mean (SEM)	37.04 (1.2)	33.63 (1.25)
Females	34	12
Subject's education, years, mean (SEM)	12.67 (.24)[a]	14.84 (.44)
Parental education, years, mean (SEM)	13.69 (.43) a	15.00 (.51)
NART	106.42 (.79)	114.0 (1.35)
Right-handed	49	29
Clinical variables		
Methamphetamine use		
Duration, years, mean (SEM)	13.29 (1.05)	
Months Abstinent, mean (SEM)	22.65 (4.42)	
Age of first use, years, mean (SEM)	19.08 (.93)	
Tobacco smokers	42	9

[a] Significantly different from control group.

2. Methods

2.1. Participants

The MA group comprised 34 females and 20 males recruited from residential and outpatient substance abuse treatment centers all of whom met DSM-IV criteria for MA dependence determined from the Structured Clinical Interview (SCID) (First et al., 1995).[1] On average the group was 37.04±8.8 years old, had 12.67± 1.8 years of education, and an estimated premorbid intelligent quotient of 106.4±5.75 derived from the National Adult Reading Test (NART) (Nelson, 1982). All subjects reported normal color vision and normal or corrected to normal visual acuity. Exclusionary criteria were: 1) history of significant head trauma or neurological injury; 2) co-existing non-substance related Axis I disorder; 3) non-nicotine/caffeine substance dependence other than MA within the past year (except nicotine); and 4) self-reported history of a seropositive test for HIV.[2]

The control group comprised 12 females and 20 males who were recruited through advertisements and flyers in the surrounding community. The control subjects were also screened with the SCID. The mean age of the controls was 33.63± 7.05 years. Exclusionary criteria were the following: 1) history of significant head trauma or neurological injury; 2) presence of an Axis I disorder; and 3) history of drug dependence. The groups did not differ significantly in age [F (1, 84)=3.43; $p>.05$) but differed in years of education [F (1, 84)=3.72; $p<.05$]. Group differences in years of parental level of education approached

[1] Random drug screens were administered at the referring treatment centers.
[2] Formal HIV testing was available on a subset, but not all of the subjects.

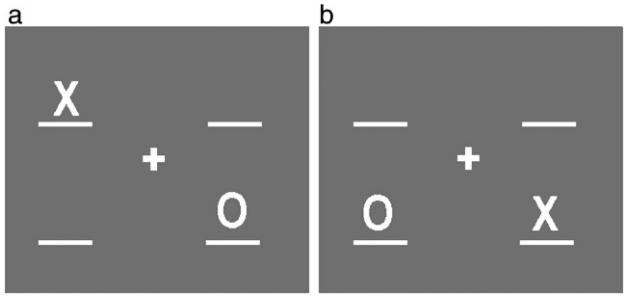

Fig. 1. Ignored repetition (IR) sequences were those trial pairs in which the target location on trial *n* (1b) was the same as the distractor location (i.e. the location of the "O") on trial n–1 (1a).

significance [F (1, 84)=3.73; p=.06] (Table 1). All subjects signed informed consent approved by the University of California, Davis Institutional Review Board and were paid a modest stipend for their participation in the study.

2.2. Apparatus

Stimuli were presented on a 14 inch VGA color monitor. Stimuli presentation and data collection were controlled by an IBM compatible computer. Manual responses were recorded through the keyboard.

2.3. Stimuli

Four locations were marked by white lines presented near the center of the computer monitor. The 4 locations were presented in 2 rows. The target was an 'X' and the distracter was an 'O'. The targets distended approximately 1 vertical degree and were presented in white against a dark background. The stimuli were presented above the white lines. See Figs. 1 and 2.

2.4. Procedure

Each of 4 keys (C, D, M, and K) was assigned as a response key on the computer keyboard. The keys were marked with color tags so as to make the response key mapping clear. The subjects were told to press the key that matched the location of the 'X' as quickly as possible, without making too many errors. Subjects used the index and middle fingers of each hand to make responses on the keyboard. Subjects were given 30 practice trials. Following the practice trials, the main experiment was administered. A fixed response stimulus interval (RSI) of 2000 ms was employed. The experiment contained 5 blocks of 70 trials each for a total of 350 trials. The experiment took approximately 20 min to administer.

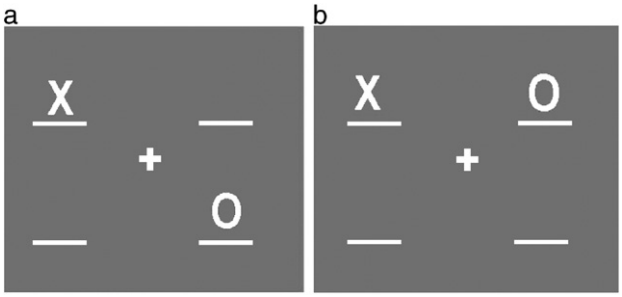

Fig. 2. Attended repetition (AR) sequences were those trial pairs in which the target location on trial *n* (2b) was the same as the target location on trial $n-1$ (2a).

Table 2
Median reaction times for priming conditions across groups in milliseconds± standard deviations

	Neutral (NEU)	Attend repetition (AR)	Ignore repetition (IR)	% Errors
Controls				
	490.09 (106.65)	460.63 (97.30)	513.30 (107.37)	.04 (.04)
Negative priming	23 ms (15.48)			
Positive priming	29 ms (21.12)			
MA abusers				
	535.87 (98.13)	502.74 (82.54)	563.53 (103.49)	.04 (.02)
Negative priming	28 ms (17.89)			
Positive priming	33 ms (34.39)			

2.5. Data analysis

Median reaction times (RTs) recorded in ms for correct responses for every condition were computed for each subject. Medians were used instead of means to reduce the influence of outlier responses, which can exaggerate group differences, especially in clinical studies (Ratcliff, 1993).[3] Analysis of variance procedures (ANOVA) for repeated measures were used to analyze the data in a 2×3 mixed ANOVA with group as a between subjects factor (patients vs controls) and priming (attend-repetition=AR; ignore repetition=IR; neutral=NEU) as within subjects variables. NEU sequences were those trial pairs in which the target location (i.e. the location of the "X" stimulus) on trial *n* was unrelated to the distractor location (i.e. the location of the "O" stimulus) on trial $n-1$. IR sequences were those trial pairs in which the target location (i.e. the location of the "X" stimulus) on trial *n* was the same as the distractor location (i.e. the location of the "O" stimulus) on trial $n-1$. AR sequences were those trial pairs in which the target location on trial $n-1$ was the same as the target location on trial *n* (i.e. target repetition). Using the same method employed by Tipper (1985), priming effects were calculated across pairs of trials by measuring the median RT on the second trial in a pair (trial n) as a function of its relationship to the preceding trial in the pair (trial $n-1$). Thus, negative priming effects were calculated by subtracting the median RT on trial *n* of NEU sequences from the median RT on trial *n* of IR sequences. Positive priming effects were calculated by subtracting the median RT on trial *n* of AR sequences from the median RT on trial *n* of NEU sequences. Planned comparisons of negative

[3] Group analyses using means also failed to reach significance in both priming conditions.

priming and positive priming effects were performed across all subjects. Incorrect responses were not included within the analysis of variance for RT but additional analyses examined the effect of error responses on priming effects.

3. Results

3.1. Reaction time analyses

Analyses revealed a main effect of group [F (1, 84)=4.53; $p<.05$] such that the MA dependent subjects displayed increased RTs compared to control subjects when analyses were collapsed across trial conditions [F (1, 84)=4.53; $p=.034$]. There was also a main effect of priming [F (2, 168)=176.975; $p<.0001$] such that reaction times to IR sequences were slower (539 ms) than to either NEU sequences (513 ms) or AR sequences (482 ms). (see Table 2). This pattern did not differ significantly between groups with both the MA dependent subjects and controls displaying similar priming effects in both negative [$p=.37$] and positive priming [$p=.69$] sequences. A calculation of the effect size of the group difference in priming measures revealed a small effect size r of .102 (Cohen's $d=.204860$) for negative priming and a small effect size r of .046 for positive priming (Cohen's $d=.0931$). No other main effects or interactions reached statistical significance.

3.2. Error analyses

Error analyses revealed that error rates did not differ between the MA dependent group and the controls (F (1, 84)=.146; $p=.70$). A calculation of the effect size of the group difference in error rates revealed a small effect size r of .032 (Cohen's $d=.065198$). Planned comparisons also revealed that both groups had similar error rates in all 3 priming conditions (see Table 2). There was no evidence of a speed-accuracy trade-off as RT was uncorrelated with error rate in either group MA dependent subjects (1, 52); $r=.003$, $p=.98$; Controls (1, 30) $r=.118$, $p=.52$). The error rates did not correlate with any clinical variable (years use, months MA abstinent, first age of MA use) or with any or demographic variable (age, education, NART score).

3.3. Correlations with cognitive measures and usage patterns

Increased years of MA use was correlated with slower RTs [$r=.26$; $p=.05$]. Neither length of drug abstinence nor age of first MA use correlated with RT. Negative and positive priming effects failed to correlate with clinical variables (years use, months MA abstinent, first age of MA use) or with demographic variables (age, education, NART score).

4. Discussion

The MA dependent subjects tested in the current study did not differ significantly from controls on either inhibitory (i.e. negative priming) or facilitory spatial priming effects (i.e. positive priming). This result is consistent with our earlier findings of intact object-based Stroop priming in MA dependence and suggests that intact priming effects extend across object and spatial domains in long-term MA users who are currently drug abstinent. The findings from the current study are also consistent with other priming studies that have been conducted in chronic alcoholics (Zhang et al., 1997), subjects with a history of cocaine abuse (Jasiukaitis and Fein, 1999) and subjects with acute exposure to alcohol (Ray and Bates, 2006). In contrast to preserved priming effects, performance deficits on explicit tasks have been widely reported in substance abusing populations (Nixon et al., 1996; McKetin and Mattick, 1997; Ornstein et al., 2000; Simon et al., 2000; Volkow et al., 2001c; Simon et al., 2002a; Kalechstein et al., 2003; Lawton-Craddock et al., 2003; Paulus et al., 2003; Hyman, 2005; Monterosso et al., 2005; Paulus et al., 2005; Salo et al., 2005; Monterosso et al., 2006; Salo et al., 2007). This pattern of sparing suggests that cortical brain systems supporting implicit attentional functioning may be relatively intact in long-term MA dependent individuals whereas brain systems supporting explicit processes, may be more affected (Ernst et al., 2000; Volkow et al., 2001b; Volkow et al., 2001a; Volkow et al., 2001c; London et al., 2005; Monterosso et al., 2006; Salo et al., 2007).

Imaging studies have identified multiple neural regions in mediating performance on implicit memory tasks. These brain areas include occipital–temporal regions (Squire et al., 1992; Buckner et al., 1995), inferior frontal regions (Berns et al., 1997; Wagner et al., 2000; Cardillo et al., 2004; Lustig and Buckner, 2004; Wright et al., 2006) as well as the fusiform gyrus (Vuilleumier et al., 2002; Vuilleumier et al., 2005). Some studies (Hester et al., 2005; Lau and Passingham, 2007; O'Connell et al., 2007), but not all (Dehaene et al., 2003) have suggested that the anterior cingulate cortex also participates in implicit processing. See also van Veen and Carter and Mayr for reviews (van Veen and Carter, 2002; Mayr, 2004).

If implicit processes are spared in stimulant dependence how might these current findings inform us about substance abuse and drug-seeking behaviors? Although, we acknowledge that letter-displays are not equivalent to the complex nature of environmental events that substance abusers encounter in their everyday lives, the use of targeted tasks of cognition allows one to dissociate the component processes of attention. (Posner, 1980, 1986). As addiction may represent abnormal stimulation of some normal processes coupled with pathological functioning of others, the dissociation of component processes of attention is essential to identify which processes are intact vs those which are dysfunctional. One possibility suggested by this study is that intact implicit processes in stimulant abusers may facilitate or enable the ability of subtle drug-related or subliminal environmental cues to induce craving and/or relapse in the addicted individual (Berke and Eichenbaum, 2001; Hyman, 2005). Recent animal studies have shown that stimulation of brain structures associated with memory and associative learning have a more powerful effect of reinstating drug-seeking behavior than exposure to the drug itself (Berke and Eichenbaum, 2001; Vorel et al., 2001). The neural substrates that support implicit processing may play a fundamental role in conveying basic perceptual information to other brain regions that are involved in the emotional processing

of drug cues (e.g. nucleus accumbens) (Kuehn, 2006; Muller et al., 2007). Although, the addicted individual may attempt to consciously refrain from drug-seeking behavior, environmental cues, such as visiting previously locations of drug use or encountering a former drug dealer on the street, may trigger unconscious memories that impact resultant drug craving and subsequently contribute to relapse. If the basic perceptual building blocks of implicit memories were not intact in the addicted individual, one might question if these unconscious memories would have the same ability to impact drug-seeking behavior.

4.1. Limitations

As with any study that fails to find group differences, it is reasonable to question if there were any factors that might have limited the ability to detect meaningful disparities in performance. One possible limitation might be group size, although the size of the 2 groups in the current study (MA dependent subjects = 54; Controls = 32) should have been adequate to detect differences in performance. Another limitation that must always be considered is the possibility of a ceiling effect. In other words, was the spatial priming task employed in the current study too easy to detect performance deficits in a clinical population? That possibility cannot be ruled out in the current study, but one factor that argues against a ceiling effect is the fact that the MA dependent subjects were significantly slower than the controls and both groups exhibited significant priming effects. Although generalized slowing could be associated with long-term MA abuse, it is not a pattern that we have observed consistently across cognitive studies from our laboratory that have employed explicit tasks in MA dependent subjects (Salo et al., 2005; Salo et al., 2007).[4] If priming effects are mediated by automatic processes then it is reasonable to hypothesize that task difficulty would have less of an effect on implicit tasks compared to explicit measures that tap into more controlled cognitive processes. Another limitation of the current study was that formal HIV testing was only available on a subset of the subjects. Thus assessment of HIV status was reliant on self-report status alone on some of the MA dependent subjects.

4.2. Summary

Given the importance of associated memories in addiction, the finding that implicit processes are intact in long-term MA dependent subjects, as well as the findings of intact priming effects reported in previous studies (Jasiukaitis and Fein, 1999; Salo et al., 2002; Ray and Bates, 2006) suggest that systems supporting implicit or unconscious memories of basic visual perceptual information may be intact in persons who abuse substances. Although a large number of addiction studies have examined how structures within the memory circuit of the brain (i.e. amygdala and hippocampal formation) might contribute to the reinstatement of drug use and relapse in the addicted individual (Berke and Eichenbaum, 2001; Black et al., 2004; Bowyer and Ali, 2006), few studies have systematically examined implicit cognitive processing of basic visual information as a contributing factor. As multiple regions and networks have been identified in mediating implicit processes, (Berns et al., 1997; Schacter and Buckner, 1998b; Wagner et al., 2000; Cardillo et al., 2004; Lustig and Buckner, 2004; Wright et al., 2006; Klein et al., 2007; Lau and Passingham, 2007; Schacter et al., 2007) studies that provide increased knowledge about the basic cognitive mechanisms underlying behaviors that promote and sustain substance use will constitute an important contribution to the neuroscience of drug addiction. The recent surge of MA worldwide, as well as preliminary reports of subsequent effects on behavior and cognition, add to the urgency of understanding how MA use affects neural function and cognition (Gibson et al., 2002; Cretzmeyer et al., 2003; Nordahl et al., 2003).

[4] Slowed RT was observed in a small ($n = 8$) group of MA abusers (Salo et al., 2002).

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