

Methamphetamine Abuse and Impairment of Social Functioning: A Review of the Underlying Neurophysiological Causes and Behavioral Implications

Bruce D. Homer, Todd M. Solomon, Robert W. Moeller, Amy Mascia, Lauren DeRaleau, and Perry N. Halkitis
New York University

The highly addictive drug methamphetamine has been associated with impairments in social cognitions as evidenced by changes in users' behaviors. Physiological changes in brain structure and functioning, particularly in the frontal lobe, have also been identified. The authors propose a biopsychosocial approach to understanding the effects of methamphetamine addiction by relating the physiological effects of the drug to the behaviors and social cognitions of its users, through the application of the theory of mind paradigm. Although onset of methamphetamine use has been linked to the desire for socialization, chronic use has been associated with an increase in depression, aggressiveness, and social isolation, behaviors that also implicate involvement of the frontal lobe. The reviewed literature provides strong circumstantial evidence that social-cognitive functioning is significantly impacted by methamphetamine use and that the social isolation, depression, and aggressiveness associated with chronic use is due to more than just the social withdrawal associated with addiction. Treatment considerations for methamphetamine must therefore consider the role of social cognition, and pharmacological responses must address the documented impact of the drug on frontal lobe functioning.

Keywords: methamphetamine, addiction, social cognition, brain function, theory of mind

Methamphetamine (MA) is a highly addictive stimulant that has significant effects on the CNS. In recent years, there has been a marked increase in the use and abuse of MA. The 2003 MA/amphetamine treatment admission rate in the United States was 56 admissions per 100,000 population (ages 12 or older), an increase of over 400% from the 1993 rate of 13 admissions per 100,000 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2006). Both human and animal studies have found a number of negative consequences to be associated with MA abuse, including neurological damage and altered cognitive and behavioral functioning.

The current article reviews both the short- and long-term physiological and psychological effects of MA abuse, with a particular emphasis on the neurophysiological damage caused by MA. Based on these data, it is argued that abuse of MA causes neurological damage of the specific brain regions associated with social cognition, leading to impairments in social-cognitive functioning, which in turn contributes to a number of the observed behavioral changes associated with chronic abuse of MA. The article concludes with

suggestions for future research and speculations on how social-cognitive deficits may affect the treatment and rehabilitation of MA abusers.

Physiological Effects of MA

MA is a cationic lipophilic molecule that has dramatic effects on both the sympathetic nervous system and central nervous system (CNS; Davidson, Gow, Lee, & Ellinwood, 2001). MA is more potent than its parent compound amphetamine because its lipophilic nature allows greater penetration of the CNS (Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Similar to amphetamine, MA stimulates the release of newly synthesized catecholamines in the CNS and partially blocks the presynaptic reuptake of these neurotransmitters (Cho & Melega, 2002). Animal studies have shown that amphetamines, including MA, target the dopamine transporter, which regulates dopaminergic transmission by facilitating dopamine reuptake (Davidson et al., 2001). Amphetamines have been shown to inhibit the reuptake of dopamine by reversing the direction of the dopamine transporter, leading to an increased dopamine release (Giros, Jaber, Jones, Wightman, & Caron, 1996).

Immediately after ingestion of MA, users experience a number of highly desirable sensations, including a sense of euphoria caused by an elevated level of dopamine. Other desirable sensations associated with MA include increased productivity, heightened attentiveness and curiosity, hypersexuality, decreased anxiety, and increased energy (Cretzmeyer, Sarrazin, Huber, Block, & Hall, 2003; Meredith et al., 2005). The euphoric feelings vary in intensity and duration, depending on mode of administration, with smoking or intravenous injecting leading to intense, but brief, euphoria and with oral ingestion or snorting leading to a slightly less intense, but more long-lasting, "high." (National Institute on

Bruce D. Homer, Department of Applied Psychology, New York University; Todd M. Solomon, Center for Health, Identity, Behavior & Prevention Studies (CHIBPS) and School of Medicine, New York University; Robert W. Moeller and Perry N. Halkitis, CHIBPS and Department of Applied Psychology, New York University; Amy Mascia and Lauren DeRaleau, CHIBPS, New York University.

Bruce D. Homer is now at the PhD Program in Educational Psychology, The Graduate Center, City University of New York (CUNY).

Correspondence concerning this article should be addressed to Bruce D. Homer, PhD Program in Educational Psychology, The Graduate Center, CUNY, 365 5th Avenue, New York, NY 10016. E-mail: Bhomer@gc.cuny.edu

Drug Abuse [NIDA], 2002; SAMHSA, 2004). The excessive stimulation of the sympathetic nervous system also leads to a number of undesirable physiological effects, including tachycardia, hypertension, papillary dilation, diaphoresis, tachypnea, peripheral hyperthermia, and hyperpyrexia (Meredith et al., 2005). Repeated use of MA results in a depletion of catecholamines and has been shown to produce withdrawal symptoms marked by psychiatric complaints (Meredith et al., 2005). Withdrawal from MA, also known as “crashing,” can produce a constellation of symptoms including anhedonia, irritability, fatigue, depressed mood, impaired social functioning, aggression, and an intense craving for the drug (Cantwell & McBride, 1998; Meredith et al., 2005; Newton, Kalechstein, Duran, Vansluis, & Ling, 2004).

A number of psychological and behavioral consequences have been identified as being related to chronic MA use, including euphoric disinhibition, impaired judgment, grandiosity, and psychomotor agitation (Batki & Harris, 2004; Meredith et al., 2005; Richards et al., 1999). Data from neuroimaging studies, neuropsychological testing, and psychiatric evaluation indicate that heavy use of MA contributes to a variety of psychiatric pathologies, including psychosis (Batki & Harris, 2004), mood disturbance (London et al., 2004), suicidal ideations (Zweben et al., 2004), anxiety (Zweben et al., 2004), hostility (Zweben et al., 2004), psychomotor dysfunction (Caligiuri & Buitenhuis, 2005), deficits in cognitive skills (Gonzalez et al., 2004), and, in extreme cases, paranoia, hallucinations, and delusion (Logan, 2002). There is compelling evidence that the negative consequences of MA abuse are due, at least in part, to damage to the brain caused by the neurotoxicity of MA.

Neurotoxicity of MA

Evidence for the neurotoxicity of MA comes from studies with a variety of mammalian species, including rodents and higher primates. MA has been found to have neurotoxic effects on both the dopaminergic and serotonergic transmitter systems, which can lead to the irreversible loss of nerve terminals or neuron cell bodies (Cho & Melega, 2002). Research on human MA abuse suggests a typical abuse pattern of repeated dosing between 1 and 6 times a day, which results in consumption of 0.5–1.0 grams during a 24 hour binge (Simon et al., 2002). Non-human primates treated with an equivalent dosing regimen of MA have significantly reduced dopamine axonal markers, significantly reduced serotonin axonal markers, and decreased striatal dopamine transporter density as measured by positron emission topography (PET) imaging (Villemagne et al., 1998). There is evidence from PET studies of damage to dopamine nerve terminals or cell bodies in chronic abusers of MA, even after a prolonged period of abstinence (McCann et al., 1998). Although the degeneration of dopamine nerve terminals and cell bodies associated with MA abuse may recover in younger populations (Wilson et al., 1996), the evidence of medium- to long-term neurotoxic effects of MA is quite conclusive.

Damage to the serotonin and dopamine systems caused by MA abuse can have a number of effects. Serotonin plays an important role in a wide range of physiological systems (e.g., cardiovascular regulation, respiration, thermoregulation), as well as a number of behavioral functions, including circadian rhythm entrainment, sleep/wake cycle, appetite, aggression, sexual behavior, sensorimotor reactivity, pain sensitivity, and learning (Meredith et al.,

2005). In the brain, dopamine plays a crucial role in a number of functions, including control of movement, regulation of emotional responses, and regulation of the reward system. Dopamine also plays an important role in the cardiovascular system, hormonal system, and CNS. Abuse of MA can cause disturbances in any of these systems, which can affect behavior (Cho & Melega, 2002).

In addition to disturbance to the dopaminergic and serotonergic transmitter systems, MA abuse also appears to cause localized damage to the brain, thereby causing deficits in specific cognitive functions. For example, in a proton MRS study, Ernst, Chang, Leonido-Yee, and Speck (2000) found that MA users had significantly elevated levels of glial repair cells—a neurocellular index of damage to the grey and white matter—in the basal ganglia and the right frontal white matter, suggesting structural damage to the frontostriatal areas. In an fMRI study, Paulus et al. (2002) examined neuronal activation in abstinent MA-dependent individuals during decision making. They found that, compared with age and education matched control participants, MA-dependent individuals had less prefrontal cortex activation during decision making. These and similar findings (e.g., Chang, Ernst, Speck, & Grob, 2005; Chang et al., 2002; Fishbein et al., 2005) indicate that MA use can lead to impaired brain functioning in ways that have significant ramifications for certain cognitive abilities.

MA and Neurocognitive Impairments

Research with clinical populations has identified a number of characteristic neurocognitive impairments associated with MA abuse, with severity of symptoms linked to both dose and duration of use (Meredith et al., 2005). For example, compared with age matched control participants, MA abusers have severe grey matter deficits in the cingulate, limbic, and paralimbic cortices as well as significant shrinkage of hippocampal volume (8%) correlating with impaired verbal memory performance (Thompson et al., 2004). MA abusers also demonstrate deficits in tasks that involve perceptual speed and information manipulation (Simon et al., 2002). Much of the work on the neurocognitive deficits associated with MA, however, has focused on decision making (e.g., Fishbein et al., 2005; Paulus, Hozack, Frank, Brown, & Schuckit, 2003; Paulus, Tapert, & Schuckit, 2005; Semple, Zians, Grant, & Patterson, 2005). In making decisions, MA abusers will tend to choose an immediate reward at the expense of severe negative consequences in the future (Verdejo-Garcia, Perez-Garcia, & Bechara, 2006). Paulus et al. (2005) found that these decision-making deficits are predictive of subsequent relapse in recovering MA addicts. Imaging studies have indicated that the impaired decision making of MA users is associated with dysfunction in the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate, and parietal cortex (Paulus et al., 2003). Functional deficits have also been found in the anterior cingulum, which suggests that attention deficits may contribute to impaired decision making (Nordahl et al., 2002).

Given the scope of neurological damage associated with MA abuse, it seems likely that there are other neurocognitive deficits in addition to impaired decision making. Although, to date, no research has explicitly examined the affects of MA abuse on the neurocircuitry responsible for social-cognitive functioning, research with other populations has indicated that several of the brain regions affected by MA abuse are activated by tasks that

involve social cognition (Amodio & Frith, 2006; Frith & Frith, 2001). This suggests that MA abusers may also be suffering from brain-based impairments in their social-cognitive functioning.

MA and Social Cognition

Compared with those of other species, human social interactions are exceedingly complex. To navigate the complexities of these interactions requires representing and processing a wide array of information obtained from a variety of sources. We use the term *social cognition* (Fiske & Taylor, 1991) to refer to the broad set of processes involved in assessing social situations. Essential to understanding social situations is being able to quickly and accurately judge people's mental states, such as beliefs and desires. The ability to understand mental states in others as well as oneself has been called a *theory of mind* (ToM; Premack and Woodruff, 1978). ToM is first evident sometime around the age of 4 years, when children realize that people can have beliefs about the world that are false (Perner, Leekam, & Wimmer, 1987; Wimmer & Perner, 1983). The litmus test for possessing a ToM is being able to pass a false-belief task. In this task, participants are told a story in which a character has a false belief about the location of an object and must then predict the character's future action based on this false belief. In a classic version of the story, the character Maxi puts his chocolate into a cupboard and then leaves. While he is gone, Maxi's mother moves the chocolate from the cupboard to the refrigerator. Participants are then asked, "Where will Maxi look for his chocolate when he returns." Answers based on reality or participants' own beliefs will result in an incorrect answer of saying that Maxi will look in the refrigerator. To correctly predict that Maxi will look in the cupboard, participants must answer based on the understanding that Maxi's actions depend on his false belief about the location of the chocolate. Children under the age of 4 typically fail this task as do many individuals with autism.

Although false-belief understanding occurs sometime around the age of 4, ToM continues to develop and be refined throughout childhood (Sullivan, Zaitchik, & Tager-Flusberg, 1994) and even into late adulthood (Happé, Winner, & Brownell, 1998). For example, the understanding that preexisting biases or expectations influence people's interpretation of an ambiguous event does not develop until around age 6 (Pillow & Henrichon, 1996). A few factors have been identified as playing important roles for the development of ToM, including language ability (Astington & Jenkins, 1999; Hughes, 1998) and executive functions (Carlson, Moses, & Breton, 2002; Hughes, 1998). In adult populations, only executive functions have been found to relate significantly to ToM (Rowe, Bullock, Polkey, & Morris, 2001), with inhibition appearing to be of particular importance (Carlson et al., 2002).

Possessing a ToM enables representing and reasoning about mental states. It provides a conceptual framework for understanding social situations, in which people's behaviors are understood as being intentional and based on their desires and beliefs (Malle, 2005). The conceptual framework provided by ToM is essential for competent social functioning, and performance on ToM tasks is correlated with measures of social competence. For example, scores on advanced ToM tasks positively predict social competence in adolescents (Bosacki & Astington, 1999), and, conversely, deficits in ToM have been found to co-occur with problems in social functioning (Langdon, 2003).

The most well-documented example of deficits in ToM relating to impaired social functioning comes from research on autism. Baron-Cohen, Leslie, and Frith (1985) were the first to demonstrate that individuals with autism fail tests for understanding beliefs and other mental states, such as the false-belief task. Even if individuals with autism are able to pass a simple false-belief task, they often fail more advanced tasks such as the Faux Pas Recognition Task (Baron-Cohen, O'Riordan, Jones, Stone, & Plaisted, 1999). This task assesses the ability to understand a *faux pas*, which is an awkward social situation that occurs when someone says something that they should not have said without realizing that they should not have said it. Understanding a faux pas requires a person to represent the mental states of both the speaker and hearer of the faux pas, as it requires an understanding that the speaker does not realize they should not have said something and that the person on the receiving end of the faux pas will feel hurt or insulted.

Numerous studies have found that individuals with autism have difficulty in making mental-state-based explanations of behavior, establishing ToM deficit as one of the core cognitive impairments associated with autism (Baron-Cohen, 1995). Furthermore, several studies have found that, in individuals with autism, deficits in ToM are associated with impaired frontal lobe functioning (e.g., Happé, 1994; Hughes, Soares-Boucaud, Hochmann, & Frith, 1997; Ozonoff & McEvoy, 1994). These studies and research with other populations have begun to identify the neurophysiological underpinnings of ToM and social cognition.

Neurophysiological Correlates of ToM

Broadly speaking, research on the neurophysiological correlates of ToM has implicated the frontal lobes. Evidence supporting frontal lobe involvement has come from a number of sources, including studies of individuals diagnosed with an autistic spectrum disorder, neuropsychological lesion studies with adult brain injured patients, and functional neuroimaging studies with normal adults (e.g., Baron-Cohen et al., 1994; Fletcher et al., 1995; Goel, Grafman, Sadato, & Hallett, 1995; Stone, 1998). For example, data from PET studies have indicated a relationship between the frontal lobes and deficits associated with the ToM. For example, Happé et al. (1996) found structural and metabolic abnormalities in the brains of individuals diagnosed with Asperger's syndrome (a variant of autism). In their PET study, Happé et al. (1996) found abnormal metabolic activity in a highly specific brain region adjacent to the left medial prefrontal cortex, a region that has previously been found to show increased activation during ToM tasks (Fletcher et al., 1995). In a recent review, Sabbagh (2004) concluded that deficits in the orbitofrontal and medial temporal circuits may be at the root of abnormal social-cognitive functioning associated with autism.

Neuroimaging studies in normally functioning adults have also implicated regions of the frontal lobes as playing a vital role in social cognition. Baron-Cohen et al. (1994) found that the right frontal cortex was activated when participants were asked to distinguish different actions of "mind." Fletcher et al. (1995) found that the left medial prefrontal cortex was activated when participants performed ToM tasks, a finding that has since been replicated (Gallagher et al., 2000). In addition to activation of the left medial prefrontal cortex, Gallagher et al. (2000) also found sec-

ondary activation in the temporal parietal regions of the brain during ToM tasks. Finally, Frith and Frith (2003) in their review of ToM-related neuroimaging studies identified three regions that show selective activation during tasks that involve reasoning about mental states: the medial prefrontal cortex, the temporal poles, and the posterior superior temporal sulcus. The authors suggest that the medial prefrontal cortex region is of particular importance for distinguishing mental state representations from physical state representations.

The literature cited above and related studies have clearly established the importance of the frontal lobes for ToM; however, data specifying the lateralization of brain region for ToM have been inconclusive. Much of this work has been with individuals who have experienced some form of brain injury. Overall, studies have found that injury to either the left or right frontal lobe is detrimental to ToM performance. Winner, Brownell, Happé, Blum, and Pincus (1998), for example, found that individuals with acquired right frontal brain damage had difficulty with ToM-like tests. Sabbagh and Taylor (2000) found that evoked potential activation in participants performing the false-belief test was strongest in the left frontal region. Stuss, Gallup, and Alexander (2001) and Rowe et al. (2001) found that lesions in either the left or right frontal lobe lead to ToM impairment. Similarly, Homer, Ramsay, and McFadden (2001) found that injury to either the left or right frontal lobe during childhood resulted in impaired ToM and predicted maladaptive social functioning.

In summary, there is clear evidence that the frontal lobes, particularly the prefrontal cortex, play a vital role in ToM. Impaired functioning in this brain region can affect ToM, thereby impairing social-cognitive functioning. In the case of autism, impairments to frontal lobe functioning are most likely due to genetic factors leading to abnormal brain development, which means that a proper ToM may never develop. In the case of individuals who have suffered strokes or brain injury, trauma to the brain leads to impaired functioning. This means that these individuals who were once functioning normally have an impaired ToM and altered social-cognitive functioning. We are proposing that abuse of MA may have a similar effect.

MA and Social Interactions

The neurological damage caused by MA is known to affect frontal lobe functioning that, we suggest, can result in impairments in ToM. As reviewed above, MA abuse has been shown to cause damage to the frontal lobes, including regions of the prefrontal cortex. Impairments of certain cognitive functions in MA abusers have been associated with damage to these regions of the brain. This suggests that MA abuse can lead to impaired social-cognitive functioning as a result of damage to the frontal lobes. Although no study has explicitly examined the link between the neurological damage caused by MA abuse and impairments in social cognition, there is evidence from many studies indicating that MA abuse can lead to impairments in social functioning.

Evidence for the effects of MA on social functioning comes from studies that have noted changes in social behavior associated with chronic MA exposure (e.g., Clemens et al., 2004; Semple et al., 2005). Furthermore, many of the behavioral changes associated with MA abuse, such as depression and aggression, are linked to impaired social functioning. One of the paradoxes associated with

MA use and abuse is that MA is widely used as a means of increasing the desire and ability to have social interactions. Decreased social or sexual inhibitions, increased energy, and the desire to lengthen social interactions or to socialize with others using the drug as a means of achieving a similar mental state are behaviors that have all been associated with MA use (Halkitis, Parsons, & Wilton, 2003; Halkitis, Shrem, & Martin, 2005; Kurtz, 2005; Semple, Patterson, & Grant, 2004). MA use and abuse has also been highly correlated with social venues such as bars, clubs, and sex and circuit parties (Halkitis et al., 2003, 2005; Semple et al., 2004). Other studies have indicated that negative side effects, such as paranoia, depression, and increased aggressiveness (Gorman, Nelson, Applegate, & Scrol, 2004), as well as the need to hide increased usage, eventually lead to social isolation for users (Gorman et al., 2004; Kurtz, 2005). Thus, despite the original intention to use MA to facilitate and enhance social interactions, MA abuse often erodes social connection.

Altered social functioning has also been found in animals exposed to MA. A number of studies have found that rats injected with MA make significantly less body contact with other rats compared with that of control rats (Clemens et al., 2004; Syme & Syme, 1974). Similarly, Schiörring (1977) found that both acute and chronic MA exposure lead to extreme social withdrawal in monkeys. More recently, Clemens et al. (2004) found that even several weeks after being injected with a dose of MA, rats were significantly less social than rats that had not been exposed to MA. Because animals are free of the social stigma of addiction, but still become socially withdrawn, it is most likely that desire to hide excessive MA usage is not the only factor in the eventual self-isolation of some MA users. Instead, these findings suggest that changes in social behavior (e.g., social withdrawal, aggression, depression) associated with chronic MA abuse have a physiological basis and may, in part, be explained by impairments in social-cognitive functioning.

If social-cognitive deficits do develop as a result of MA abuse, then there should be additional psychological and behavioral consequences of impaired social-cognitive functioning. The research reviewed above indicates that MA use can cause physiological changes that results in altered social behavior and possible social isolation. Research on the consequences of impaired social cognition indicates two primary psychological consequences of having impairments in social-cognitive functioning: depression and increased aggression. In the sections below, each of these symptoms is described in detail and the underlying causes are discussed, with attention being given to the possible role that impaired social cognitions may play.

MA and Depression

By far the most common psychiatric symptom associated with chronic MA use is depression. In a study with one of the largest samples of MA users ($N = 1,016$), Zweben et al. (2004) examined co-occurring psychiatric symptoms and found particularly high scores on depression scales for MA users. Specifically, 68% of the women and 50% of the men reported feeling depressed at some point in their lives, and 28% of the women and 13% of the men reported at least one suicide attempt. Frequency of use and injection were both associated with higher reported BDI scores and

users who injected also reported more suicide attempts and suicidal thoughts.

The relationship between depression and MA use appears to be bidirectional. A number of studies have found that depression is a risk factor for subsequent abuse of drugs, including MA. For example, Grant (1995) found that lifetime risk of amphetamine abuse or dependence was 6.19 times more likely for individuals with major depression than among those without major depression. The risk decreased to 4.04 times for amphetamine abuse only and increased to 8.89 times for dependence (Grant, 1995). Similarly, in a study of young club-drug users, Clatts, Goldsamt, and Yi (2005) found high rates of prior suicide attempts (34%) and clinically significant depressive symptoms in over half (58%) of all users.

Other studies have found that MA abuse is a risk factor for subsequent depression. Semple et al. (2005) found that 40% of their sample of MA users met criteria for moderate to severe depression and that greater intensity of use was associated with higher levels of depressive symptoms, even controlling for demographic characteristics, stigma, and social and health problems. They also found that perceived stigma had a significant positive direct effect on depressive symptoms, whereas social and health problems did not. Multivariate analyses indicated that MA use uniquely accounted for 11% of the explained variance in depressive symptoms. In a retrospective study, Kalechstein et al. (2000) found that in the 12 months prior to assessment, MA-dependent individuals were more likely to report depressive symptoms and suicidal ideation than were non-dependent individuals, even after controlling for demographic profile and dependence on other substances. They also found that MA-dependent participants were more likely to report a need for psychiatric assistance.

A number of factors seem to contribute to the development of depression in MA abusers. Altered brain metabolism appears to be one important factor. For example, London et al. (2004) found that, compared with non-users, abusers of MA had higher self-ratings of depression and showed lower regional glucose metabolism in the anterior cingulate and insula and higher glucose metabolism in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum. Depressive symptoms in MA abusers were found to correlate significantly with glucose metabolism in the perigenual anterior cingulate gyrus and amygdala, both of which are part of the limbic system. The researchers also found that in MA abusers self-reports of depressive symptoms co-varied positively with relative glucose metabolism in limbic regions (e.g., perigenual anterior cingulate gyrus and amygdala), and ratings of state and trait anxiety co-varied negatively with relative activity in the anterior cingulate cortex and left insula. London et al. concluded that MA abusers have abnormalities in brain regions that can result in mood disorders, including depression and anxiety. They suggest that the resulting affective deficits may have implications for addiction recovery during MA abusers' initial periods of abstinence.

In addition to altered affect regulation, the social isolation associated with chronic MA abuse is also likely to play a causal role in the development or the heightening of depression. Lack of social connection is a well-established risk factor for depression (e.g., Costello, 1982; George, Blazer, Hughes, & Fowler, 1989), and impairments in social cognition may be partially to blame for the social isolation associated with depression. A number of studies have found a link between impairments in social cognition and

depression (e.g., Inoue, Tonooka, Yamada, & Kanba, 2004; McClure et al., 2005). For example, Kerr, Dunbar, and Bental (2003) found that patients with bipolar depression demonstrated impairments in ToM performance. Similarly, Lee, Harkness, Sabbagh, and Jacobson (2005) found that women diagnosed with clinical depression had significant impairments in their ability to identify mental states compared with that of control participants. The authors suggest that these impairments in social cognition contribute to depression by causing a breakdown in depressed individuals' everyday social interactions. These and related findings suggest that impairment in social cognition makes an important contribution to the depression that is associated with MA abuse.

MA and Aggression

Substance abuse in general has been linked to violence and aggression, and this link is particularly strong for abuse of amphetamine and MA (Boles & Miotto, 2003). Studies of amphetamine and MA users have indicated elevated levels of violent behaviors as well as problems controlling aggression and aggressive outbursts (Hall, Hando, Darke, & Ross, 1996; Vincent, Schoonbridge, Ask, Allsop, & Ali, 1998; Wright & Klee, 2001). For example, Makusa, Nakamura, Yamada, Inoue, and Nakazawa (1990) found that MA-dependent individuals were significantly more impulsive and less able to inhibit aggression than were control participants and had significantly more verbal and physical aggression than did alcohol dependents. Similarly, Brecht, O'Brien, von Mayrhauser, and Anglin (2004) found that violent behaviors were reported by 57% of MA users, and Zweben et al. (2004) found that 43% of MA users reported having problems controlling their angry or violent behavior. These problems exist even for MA abusers who are not abusing any other substances, indicating that MA abuse alone can contribute to increases in violent behavior (Sekine et al., 2006).

Evidence also suggests that the aggression and violence associated with MA abuse is somewhat context dependent. In a study that analyzed life histories of MA users, Sommers and Baskin (2006) found that 26.8% had committed violence while under the influence of MA. More than half of the reported violent events occurred in domestic relationships, and more than two-thirds of incidents occurred in private homes. MA-related violence, therefore, seems more likely to occur in private, domestic settings rather than the public, street settings associated with other drugs. Sommers and Baskin (2006) supported this claim with their finding that although the use of alcohol and MA were both significantly correlated with reported partner violence in college students, only alcohol use correlated with assault. These data again suggest that MA is more likely to increase the risk of private, domestic violence rather than violence or aggression committed in public.

Although the association between MA and violence is well supported, violence is not a certain outcome of even chronic use of MA. A number of factors have been found to influence the MA–violence link. Austin (2004) identified several factors as predictive of the age at which MA abusers first committed violence against another person. These included age at first MA use, current use, frequency of use in last month, and age at which person became a regular user. Hall et al. (1996) found that mode of MA use also made a difference, with users who injected being significantly more likely to exhibit violent behavior. Sommers and

Baskin (2006) found that the main predictors of MA-related violence were exposure to family deviance, such as arrests and child abuse, previous substance-related violence, age at first MA use, childhood fighting, and social functioning problems. Other studies have found a number of psychosocial factors, such as family violence, loose parental supervision, early exposure to violence, early exposure to substance abuse, and an individual history of aggressive behavior, are linked to subsequent MA-related violence (Cohen et al., 2003; Semple et al., 2005; Zweben et al., 2004), possibly via changes in early behavioral patterns (Boles & Miotto, 2003).

There is also evidence that altered brain function caused by MA abuse is related to increased aggression and violence. In a study on the neurophysiology of aggression, Amen, Stubblefield, Carmichael, and Thisted (1996) found that, compared with control participants, aggressive participants had decreased activity in the prefrontal cortex as well as increased activity in the medial frontal lobes and left basal ganglia and/or limbic system. Buffenstein, Heaster, and Ko (1999) found that MA abusers who experience psychotic symptoms after the onset of MA use have a pattern of altered brain function similar to the altered brain patterns associated with aggression in the Amen et al. (1996) study, with 76% of patients showing localized blood flow deficits in the frontal, parietal, and temporal lobes. The overlap between neural deficits seen in aggressive participants and MA abusers suggests a strong relation between the two.

One likely cause of increased aggression in MA abusers is a decrease in the ability to inhibit impulsive behavior. A strong association exists between impulsivity and aggression (e.g., Tremblay, Pihl, Vitaro, & Dobkin, 1994). In a sample of MA abusers who had been abstinent for an average of 19 months, Kim et al. (2005) found decreased cerebral metabolic rate of glucose (CM-Rglc) in frontal white matter that correlated with impairments in executive functioning as measured by the Wisconsin Card Sorting Test, including the inability to inhibit impulsive acts.

Impaired social cognition is another factor that is likely to play a role in the increase in aggression associated with MA abuse. Several studies have found deficits in social-cognitive functioning to be associated with aggression (e.g., Holmes-Lonergan, 2003; Johoda, Pert, & Trower, 2006; Weimer & Guajardo, 2005; Yiwen, Chongde, & Wenxin, 2004), and many chronic MA users report disorganized cognitions and distorted perception such as paranoia and psychotic episodes (Cretzmeyer et al., 2003). This means that deficits in social-cognitive functioning could result in harmless situations being misinterpreted as threatening by MA users, making it more likely that they would resort to violence or aggressive behavior.

In sum, research on the relation between MA abuse and aggression suggests a complex interaction. Although MA abuse is a risk factor for aggression and violence, not every abuser becomes violent. Sommers and Baskin (2006) suggest a path from youth aggression to adult violence, with various long-term factors leading to individual tendencies toward violence and additional short-term factors leading to variations in these tendencies. The link between impaired social cognition and aggression suggests that one of the ways in which MA is responsible for increased aggression and violence is by altering the way in which MA abusers are able to interpret social situations. For those individuals whose life

history puts them at higher risk, this frustration may be expressed by violent acts.

Discussion

Although no study to date has explicitly examined social-cognitive functioning in MA abusers, the research presented above provides strong circumstantial evidence that social-cognitive functioning may be significantly impacted by MA use. MA users report increased social isolation, which seems to be due to more than just the social withdrawal associated with addiction. Difficulties with social cognition also appear to make significant contributions to the depression that is associated with MA abuse. Finally, impaired social-cognitive functioning seems to be one of the factors involved in the tendency for the increased aggression and violence associated with MA use.

Research is needed to first establish that, as argued above, MA users do demonstrate deficits in social-cognitive functioning. Empirical data are needed to determine if MA use is associated with impaired performance on ToM tasks, particularly on the more advanced ToM tests such as the Eyes Task (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997), which requires participants to identify mental states based solely on viewing the eyes, and the Faux Pas Recognition Task (Baron-Cohen et al., 1999), which requires participants to reason about mental states embedded in a social context. If the hypothesized cognitive deficits are found, then structural and functional neuroimaging studies should be conducted to determine the specific brain regions that are involved. Social-cognitive deficits would also have implications for treatment.

Treatment Considerations

The multiple effects of MA abuse clearly suggest that treatment models be holistic in their approach and consider the interplay between psychological, biological, and social factors. As of yet, studies from community-based, clinical, and research settings have not found any single treatment for MA addiction to be completely effective (Halkitis, in press). Furthermore, although certain medications show signs of reducing the "high" associated with MA and reducing cravings during withdrawal, pharmaceutical therapies remain relatively elusive (NIDA, 2002). Several treatment approaches have been tried with varying degrees of success, including cognitive behavioral therapy, motivational interviewing, and contingency management, 12-step/12-step facilitation, aversion therapy, and psychoeducational approaches (Halkitis, in press). In general, treatment models that are directed by social-cognitive theory and principles of cognitive behavioral therapy (CBT), such as the matrix model (Anglin & Rawson, 2000), appear to be the most effective in treating MA abuse (NIDA, 2002). Central to this theoretical approach is the attempt to increase knowledge, motivation, and behavioral skills in an attempt to reduce MA use and provide mechanisms that address the link between MA use and faulty decision making in social situations while under the influence. As Fisher and Fisher (1993) suggest, information alone is insufficient for behavior change; motivation and skills building must also be included. Thus, to accomplish this, a program based on CBT and informed by the principles of motivational interviewing (Miller & Rollnick, 1991) serves to both increase individuals'

motivations to reduce their MA use as well as to promote skills necessary to achieve behavioral change with regard to use and social malfunctioning. In the substance abuse treatment field, the integration of motivational interviewing and CBT has been viewed as an approach providing maximum flexibility to meet the needs of clients (Baer, Kivlahan, & Donovan, 1999). It has been further argued that relapse prevention (which is critical when addressing MA use) requires both support for pursuing change (motivational interviewing) and behavioral techniques to be successful (CBT). Such integrated interventions are effective in cognitive-behavioral outpatient counseling programs for substance abuse (Annis, Schober, & Kelly, 1996) and in relapse prevention programs for problem drinkers (Allsop, Saunders, Phillips, & Carr, 1997).

If, as we have argued, MA abuse results in impaired social functioning, then treatments must consider social interactions and social settings, including but not limited to sexual contexts and interactions that are associated with MA use. Moreover, the association of MA abuse with depression and aggression further implies that MA treatments must consider the psychological dynamics which act as precursors to abuse of the substance and which are exacerbated by use of the drug itself (Shrem & Halkitis, in press). In this view, "re-learning" social interactions and behaviors must be central to the treatment of MA abuse. At the same time, the effects of MA abuse on brain functioning, as indicated by reduced cellular activity in the frontal cortex, suggest that treatments must not neglect the biological elements of addiction.

Conclusions

The research reviewed above points to a fundamental problem for the social functioning of MA abusers as the drug itself may be causing damage to regions of the brain responsible for social cognition. Therefore, even users who eventually become abstinent from MA may face irreversible neurological deficits resulting in long-term difficulties with social cognition. The deficits in social-cognitive functioning may contribute to a number of related psychological and behavioral problems that are associated with MA use. The extent to which duration of use, amount used, and mode of administration may affect social-cognitive functioning or the extent to which such deficits can be overcome through various types of therapy remains to be seen. However, if MA use and abuse truly do produce permanent and neurophysiologic and social-cognitive deficits, this may change the way that both the medical and psychological communities view and treat the use of MA.

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Received January 16, 2007
 Revision received August 7, 2007
 Accepted October 12, 2007 ■

UNITED STATES POSTAL SERVICE Statement of Ownership, Management, and Circulation (All Periodicals Publications Except Requester Publications)

1. Publication Title: Psychological Bulletin
 2. Publication Number: 9 3 1 1 - 1 4 0
 3. Filing Date: October 2007
 4. Issue Frequency: Bimonthly
 5. Number of Issues Published Annually: 6
 6. Annual Subscription Price: Mbr \$93, Indiv \$198, Inst \$555
 7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®): 750 First Street, N.E., Washington, D.C. 20002-4242
 Contact Person: Barbara Spruill, Telephone (include area code): 202 336-5578
 8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer): 750 First Street, N.E., Washington, D.C. 20002-4242
 9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank):
 Publisher (Name and complete mailing address): American Psychological Association, 750 First Street, N.E., Washington, D.C. 20002-4242
 Editor (Name and complete mailing address): Harris Cooper, Duke University, Box 9073B, Durham, N.C. 27708-0739
 Managing Editor (Name and complete mailing address): Susan J.A. Harris, American Psychological Association, 750 First Street, N.E., Washington, D.C. 20002-4242
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13. Publication Title: Psychological Bulletin
 14. Issue Date for Circulation Data Below: September 2007

15. Extent and Nature of Circulation

	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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f. Total Distribution (Sum of 15c and 15e)	3204	3142
g. Copies not Distributed (See instructions to Publishers #4 (page #3))	195	108
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 If the publication is a general publication, publication of this statement is required. Will be printed in the JANUARY 2008 issue of this publication. Publication not required.
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