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Cognitive deficits in individuals with methamphetamine use disorder: A meta-analysis

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HIGHLIGHTS

- Our meta-analysis reveals that methamphetamine use disorder is associated with moderate impairment in 7 cognitive domains.
- Deficits in impulsivity/reward processing and social cognition were more prominent.
- By comparison, visuo-spatial abilities were relatively spared.

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ABSTRACT

Background: Methamphetamine has long been considered as a neurotoxic substance causing cognitive deficits. Recently, however, the magnitude and the clinical significance of the cognitive effects associated with methamphetamine use disorder (MUD) have been debated. To help clarify this controversy, we performed a meta-analysis of the cognitive deficits associated with MUD.
Methods: A literature search yielded 44 studies that assessed cognitive dysfunction in 1592 subjects with MUD and 1820 healthy controls. Effect size estimates were calculated using the *Comprehensive Meta-Analysis*, for the following 12 cognitive domains: attention, executive functions, impulsivity/reward processing, social cognition, speed of processing, verbal fluency/language, verbal learning and memory, visual learning and memory, visuo-spatial abilities and working memory.
Results: Findings revealed moderate impairment across most cognitive domains, including attention, executive functions, language/verbal fluency, verbal learning and memory, visual memory and working memory. Deficits in impulsivity/reward processing and social cognition were more prominent, whereas visual learning and visuo-spatial abilities were relatively spared cognitive domains. A publication bias was observed.
Discussion: These results show that MUD is associated with broad cognitive deficits that are in the same range as those associated with alcohol and cocaine use disorder, as recently shown by way of meta-analysis. The prominent effects of MUD on social cognition and impulsivity/reward processing are based on a small number of studies, and as such, these results will need to be replicated. The functional consequences (social and occupational) of the cognitive deficits of methamphetamine will also need to be determined.

1. Introduction

Methamphetamine is the second most used illicit drug worldwide, after cannabis (Degenhardt & Hall, 2012). Although the methamphetamine epidemic feared a decade ago appears to have abated, 1.2 million people in the US and 17.2 million people around the globe, reported using methamphetamines in the past year (Degenhardt et al., 2010). Methamphetamine use disorder (i.e. chronic use; MUD) has been associated with multiple physical health problems, such as cardiovascular diseases and dental diseases (Barr et al., 2006), as well as mental health problems, namely psychosis and depression (Lecomte et al., 2013; Lecomte et al., 2013). Until recently, there has been a consensus

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in the literature suggesting that methamphetamine is a highly addictive neurotoxic drug which impacts the brain and creates cognitive deficits (Panenka et al., 2013; Scott et al., 2007). A critical review contested this view and has stirred a debate on the topic (Hart, Marvin, Silver, & Smith, 2012). Before addressing in more details this debate and presenting the current meta-analytical study on the topic, it is of importance to first describe the relevance of studying cognition in methamphetamine use disorder.

1.1. Relevance of cognition in methamphetamine studies

Cognition is the term used to describe various intellectual abilities, such as memory, attention, speed of processing, and executive functions (i.e. the ability to juggle with ideas, to reflect before acting, to tackle new challenges, to resist impulsions and to stay focused). It is also used under the appellation 'social cognition' to describe the abilities needed to socially interact, and includes social perception (recognizing facial emotions and social rules), theory of mind (recognizing mental states in others), and attribution style (not over-blaming self or others) (Pinkham et al., 2013). Cognitive abilities are essential for functioning in society – severe deficits in attention, memory, executive functions or in social cognition can lead to difficulties in performing activities in daily living, in social isolation and in unemployment (Dean, Groman, Morales, & London, 2013). Should individuals with MUD present with cognitive deficits, cognitive remediation training as well as treatment adaptations could be considered to maximize treatment gains (Vocci, 2008).

Methamphetamine affects the monoamine neurotransmitter systems of the brain, thus explaining the feelings of cognitive alertness and increased energy. In fact, increased cognitive abilities, particularly in terms of attention (vigilance) is one of the reasons why people use methamphetamines (Nordahl, Salo, & Leamon, 2003). Most illicit drugs have been reported as resulting in some cognitive deficits (Vik, Cellucci, Jarchow, & Hedt, 2004). The interest in cognitive deficits in MUD stems from the idea that the drug is neurotoxic and its prolonged and abusive use would therefore result in lasting brain damage, which would translate in sustained cognitive deficits.

1.2. Current debate concerning cognitive deficits in methamphetamine use disorder

The last meta-analysis focusing on cognitive deficits linked to MUD was that of Scott et al., 2007, which included 18 studies for a total of 951 participants, including 487 participants with MA abuse/dependence and 464 normal controls. A total of nine cognitive domains were found to be impaired: simple reaction time, attention/working memory, executive functions, learning, memory, motor skills, language, speed of information processing, and visuoconstruction. The results supported that chronic methamphetamine use was associated with cognitive deficits (medium effect size) for most domains but they were more important for episodic memory, executive functions, information processing speed, and psychomotor functions. In addition, no social cognitive domains were assessed as well as impulse- and reward-related cognitive processes (e.g. response inhibition and emotional decision-making).

Since, Hart et al. (2012) have argued that these results might be biased by poorly matched normal controls, cross-sectional designs, that only a few cognitive deficits have been documented and these could be considered within the normal range when compared with normative data. In response, Payer, Dean, and Boileau (2012) wrote a commentary agreeing with the need for better matched normal controls in studies and for a better operationalized definition of clinical significance of deficits, but also pointed out that Hart et al.'s paper is not a systematic review of the literature and the authors chose to only present studies supporting their arguments. Dean et al. (2013) replied further by proposing to review six types of studies that would allow to conclude if MUD causes cognitive deficits. As such, they reviewed: animal studies; cross-sectional human studies; twin studies; studies of changes in cognition during abstinence from methamphetamine; studies of changes in brain structure and function with abstinence from methamphetamine; and studies linking the severity of methamphetamine abuse to the degree of cognitive deficits observed. Four out of the six types of studies supported the link between methamphetamine consumption and cognitive deficits. In contrast, the relationship regarding the severity of the abuse was not supported whereas the improvements in cognition during abstinence demonstrated mixed results (Dean et al., 2013). Furthermore, the review's results presented some limitations including a small number of studies for specific categories of studies (ex. only one twin study reported) and a methodology poorly described as it was not clear if the review was systematic or not. Since this study was not a meta-analysis, the effect size estimates were not presented and no studies pertaining to social cognition were included.

Given the importance of cognition for daily functioning, as well as the current debate concerning the validity of the conclusions suggesting that methamphetamine is neurotoxic and causes cognitive deficits, a new and updated meta-analysis looking into cognition as well as social cognition in MUD is warranted.

2. Methods

2.1. Literature search and study selection

An exhaustive search of Pubmed, PsycInfo, Google Scholar, Embase and Scopus was performed using the following key words: "methamphetamine" and "cognit*" or "problem solving" or executive functions" or "memory" or "attention" or "cognitive training". Publications were also identified by cross-referencing of studies included in the meta-analysis, and of the previous meta-analysis from Scott et al. (2007). A consensus was reached between the authors (SP, SG & TL) on which studies to include and which to exclude from the analysis, based on the following criteria. Studies were included if they met the following criteria: (i) studies had involved individuals with a MUD; (ii) had involved a control group of healthy volunteers; (iii) had measured cognitive performance with validated neuropsychological tests; (iv) had been published before May 1st 2017. Studies that reported neuropsychological task performance while subjects were being scanned (electro-encephalography or magnetic resonance imaging) were excluded, as these settings are not optimal for measuring cognitive performance.

2.2. Cognitive domains

The neuropsychological tests measured within each of these studies were grouped according to 12 cognitive domains: attention, problem solving/executive functions, reward- or impulse-related functions, social cognition, speed of processing, verbal fluency/language, verbal learning, verbal memory, visual learning, visual memory, visuo-spatial abilities and working memory. To determine which neuropsychological tests and their sub-scores would be assigned to which cognitive domain, the authors based their final decisions on test classification according to Lezak, Howieson, Bigler, and Tranel (2012), and other meta-analytic studies on psychoactive substance dependence and cognition (Potvin, Joyal, Pelletier, & Stip, 2008; Potvin, Stavro, Rizkallah, & Pelletier, 2014; Stavro, Pelletier, & Potvin, 2013). Examples of neuropsychological tests included in each domain are as follows: *attention* [Continuous Performance Test-omission errors]; *executive functions* [Wisconsin Card Sorting Test, Stroop (interference)]; *reward- or impulse-related functions* [Stop-Signal task, Go/NoGo task, Delay discounting task, Iowa Gambling Task]; *speed of processing* [WAIS-Digit Symbol, Trail Making Test A and B (TMT-A, TMT-B), Stroop reaction time, Grooved Pegboard]; *verbal fluency/language* [FAS verbal fluency, Shipley-Hartford Vocabulary]; *verbal learning* [California Verbal Learning Test (CVLT) trials, Rey Auditory Verbal Learning Test (RAVLT) trials]; *verbal memory* [CVLT-delayed recall, RAVLT-delayed recall]; *visual learning* [CANTAB Paired