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Methamphetamine use and cognitive function: A systematic review of neuroimaging research

Sabrini Sabrini[a], Grace Y. Wang[b], Joanne C. Lin[a], Ian J.K.[c], Louise E. Curley[a,*]

[a] School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
[b] Department of Psychology, Faculty of Health and Environmental Sciences, Auckland University of Technology, North Campus, 90 Akoranga Drive, Northcote, Auckland 0627, New Zealand
[c] School of Psychology, Faculty of Science, The University of Auckland, Science Centre, 23 Symonds Street, Auckland 1010, New Zealand

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ABSTRACT

Background: Long-term use of MA has been associated with cognitive dysfunction in several domains. Neuroimaging studies have also reported structural, metabolic, and functional changes in MA users. However, no systematic review has been conducted on those studies in MA users that combined neuroimaging and cognitive tasks.

Methods: This article systematically reviews correlation between brain imaging measures and cognitive performance in subjects with current and previous history of MA use. Findings are categorized based on cognitive domain.

Results: MA users performed more poorly than controls in all cognitive domains (psychomotor, working memory, attention, cognitive control, and decision- making) and a positive correlation has been repeatedly observed between performance and brain measures (regional volume/density, blood flow, glucose metabolism, FA value, NAA level, and activation) in MA users. Performance in cognitive control was consistently reported to show relationship with brain measures in the PFC and ACC, while decision- making consistently showed correlation with brain measures in the PFC, ACC, and striatum.

Conclusions: There is solid evidence for brain- behavior relationship in cognitive functioning in MA users, particularly in cognitive control and decision-making. More research with correlation analysis between brain-behavior and MA use parameters is strongly encouraged.

1. Introduction

Amphetamines, a group of stimulants that includes amphetamine and methamphetamine (MA), are the second most abused worldwide after cannabis (United Nations Office on Drugs and Crime, 2017a). Global prevalence for amphetamines in 2015 was estimated to be 0.8%. In some parts of the world, the numbers are higher; prevalence in North America was 2.0% and in Oceania was 1.9%. The global market for amphetamines was dominated by MA, which accounted for 72% of the global seizures of amphetamines (United Nations Office on Drugs and Crime, 2017b).

Chronic MA abuse has been associated with an impaired cognitive function in several domains: attention, memory, and executive function (Kalechstein et al., 2003; Rendell et al., 2009; Simon et al., 2000). However, as the studies in MA individuals were cross-sectional, it is not possible to conclude that the cognitive deficits were MA-related. Animal studies have provided some evidence for the cognitive decline as the result of repeated MA administration; memory deficits have been observed in rodents (Kamei et al., 2006; Mizoguchi et al., 2011; Nagai et al., 2007; Noda et al., 2010) and impaired inhibitory control has been observed in monkeys (Groman et al., 2012). Study in twins also reported that amphetamine users had poorer performance on attention and psychomotor functions than their non-using twins (Toomey et al., 2003). Interestingly, one study has reported that, despite the higher rates of impairment in the MA group relative to controls in learning, psychomotor, and attention domains, impaired and normal MA subjects were comparable in all MA use parameters, such as age of first use, years of use, amount of use, and length of abstinence, suggesting the potential contribution of other factors, e.g., genetics (Cherner et al., 2010; Dean et al., 2013). Taken together, these findings support the notion that MA abuse causes cognitive decline, at least in some individuals (Dean et al., 2013).

* Corresponding author at: School of Pharmacy, The University of Auckland, Private Bag 92019, Auckland 1142 New Zealand.
E-mail addresses: snol421@aucklanduni.ac.nz (S. Sabrini), grace.wang@aut.ac.nz (G.Y. Wang), joanne.lin@auckland.ac.nz (J.C. Lin), i.kirk@auckland.ac.nz (J.K. Ian), l.curley@auckland.ac.nz (L.E. Curley).

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Neuroimaging techniques have been used to study brain structure, metabolism, and function in MA users. Some regions have been reported to show significant differences between MA and control groups: cortical gray matter (GM), such as the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC); subcortical GM, such as the striatum; and the frontal white matter (WM). In early studies using Positron Emission Tomography (PET), lower dopamine transporters (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001c) and dopamine receptor availability (Lee et al., 2009; Volkow et al., 2001a), as well as lower serotonin transporter density (Sekine et al., 2006) have been observed in the striatal region in groups of MA subjects. Studies using Magnetic Resonance Imaging (MRI) have reported larger striatal volume (Jernigan et al., 2005) and smaller cortical volume in MA groups (Morales et al., 2012; Nakama et al., 2011). Meanwhile, studies using Magnetic Resonance Spectroscopy (MRS) in MA individuals have observed lower *N*-acetylaspartate (NAA) level, a proposed marker for neuronal integrity (Moffett et al., 2007; Sullivan et al., 2001), in the frontal WM and the ACC (Ernst et al., 2000; Nordahl et al., 2002; Sailasuta et al., 2010). Diffusion Tensor Imaging (DTI) studies have reported lower restricted diffusion or fractional anisotropy (FA) in frontal WM of MA groups (Alicata et al., 2009; Tobias et al., 2010). Lower restricted diffusion or higher apparent diffusion may indicate impaired WM integrity. Lastly, studies using Functional Magnetic Resonance Imaging (fMRI) have reported lower activation in the PFC and the ACC in groups of MA users during attention (Nestor et al., 2011) and decision-making tasks (Paulus et al., 2003; Stewart et al., 2014). Attenuated activation may reflect reduced resources to process information and may result in performance deficits.

Several articles have reviewed brain alterations and cognitive function in MA users. Salo and Fassbender (2012) reviewed neuroimaging studies (PET, MRI, MRS, DTI, and fMRI) conducted in long-term MA users and discussed relevant cognitive findings from MA and control groups. Another review by Jan et al. (2012a) focused on structural and functional imaging studies (PET, MRI, and fMRI) in MA abusers and the effect of abstinence on the brain measures. Hart et al. (2012) reviewed the findings from studies that assessed acute and long-term effects of MA use on cognitive functions and discussed relevant neuroimaging data (PET, MRI, DTI, and fMRI). While these reviews discussed neuroimaging and/or cognitive findings from MA subjects and controls, currently no review has been published on the relationship between cognitive function and brain measures in MA subjects. This review aims to fill the gap and systematically clarify the link between cognitive performance and brain measures, such as regional volume, glucose metabolism, NAA levels, FA values, and activation, in individuals with a history of MA or amphetamine abuse. In this review, we identify relevant studies using different imaging modalities such as PET, MRI, DTI, MRS, and fMRI. We believe that investigating the brain-behavior correlation will assist in understanding the neural mechanisms underlying cognitive impairment in MA individuals, providing data were available from different stages of MA abuse (e.g., recreational use, dependent use, early abstinence, and protracted abstinence). In addition, understanding the relationship between brain measures and cognitive function in MA users may help in identifying potential targets for MA abuse prevention and treatment. As the affected regions in drug addiction overlap with the regions involved in cognitive function, such as memory, cognitive control, and decision-making (Koob and Volkow, 2016; Schoenbaum et al., 2006), targeting these neurobiological circuits may help preventing transition from occasional to compulsive drug use, and may have clinical implications for preventing relapse (Hester et al., 2010; Suckling and Nestor, 2017; Verdejo-García et al., 2006).

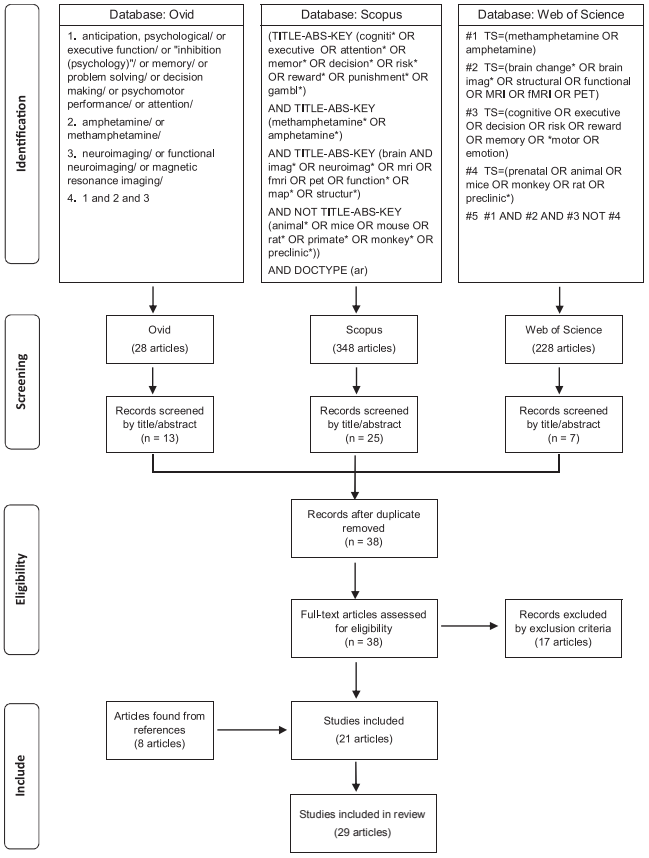

Fig. 1. Screening Flow Diagram.
Note:
TITLE-ABS-KEY = Title, Abstract, Keywords
TS = Topic
ar = article

2. Material and methods

2.1. Data source

Relevant articles were collected from three databases: Ovid, Scopus, and Web of Science between 1980 and January 2017. The search strategy was designed to retrieve as many studies as possible that were conducted using neuroimaging techniques and evaluated cognitive function in participants who were users or past users of MA. The search was performed using three groups of keywords: (1) terms related to cognitive function; (2) methamphetamine or amphetamine; and (3) terms related to neuroimaging (Fig. 1). Search strategies were defined specifically for each database; some terms were truncated, and some were found using subject headings. Terms in each group of keywords were combined with "OR", and the search was run by combining the three groups at once with "AND". The articles found from each database were screened by abstract and/or title. The results were combined and duplicates were removed. Full-text articles were then assessed for eligibility based on inclusion criteria.

2.2. Inclusion/Exclusion criteria

Studies were considered for potential inclusion if they met all the following criteria: (1) were original research; (2) were published in English; (3) studied MA or amphetamine effects on the human brain; (4) used a neuroimaging technique that could be applied globally to examine brain structure, function, or metabolism, along with a task to assess cognitive function; (5) MA or amphetamine was the primary drug of abuse; and (6) reported correlation analyses between cognitive

performance and brain imaging. Studies were excluded if they met any of the following criteria: (1) were reviews or case studies; (2) exposure to MA or amphetamine was prenatal; (3) MA or amphetamine use was comorbid with other diseases or neurological disorders (e.g., HIV, psychosis); (4) the task used did not have an objective measure for cognitive deficit (e.g., prediction task); and (5) correlations with task-specified cognitive performance were not clearly presented (e.g., scores from Stroop task and Wisconsin card sorting task are averaged for executive function).

2.3. Data extraction and analysis

One researcher (SS) extracted the characteristics from the identified studies using an extraction table. The researcher discussed any discrepancies with another researcher (LC) when necessary. Key categories were then identified based on cognitive functions, and data were presented in tables according to those categories.

3. Results

Twenty-nine studies met the inclusion criteria: 28 studies of MA users and 1 study of polydrug users (Koester et al., 2013). Two studies were performed in active-users (Jan et al., 2012b; Kim et al., 2016), while the rest were carried out with abstinent subjects (n = 27). The neuroimaging techniques used in these studies were PET (n = 6), MRI (n = 6), perfusion MRI (n = 1), DTI (n = 3), MRS (n = 3), and fMRI (n = 10). The included studies were assessed and grouped by cognitive domain: psychomotor function (n = 3); working memory (n = 4); attention (n = 9); cognitive flexibility (n = 5); inhibitory control (n = 2); cognitive impulsivity (n = 4); and risky decision-making (n = 4).

3.1. Demographic characteristics

Demographic characteristics of the participants are presented in Table 1. All studies recruited non-users as comparison subjects, except for one study that did not have a control group (Gowin et al., 2014a). Most studies recruited males and females, and two studies recruited only male subjects (I. S. Kim et al., 2009a, b). The average age of participants in most studies was within the range of 30–39 years (n = 26). MA/amphetamine subjects had fewer years of education than controls, although not always significant. One-fourth of the studies (n = 7) did not report education level. Only half of the studies (n = 15) reported handedness, of which two excluded left-handedness (Berman et al., 2008; I. S. Kim et al., 2009a). The percentage of smokers was higher in MA/amphetamine groups than in control groups, except for one study, which recruited smokers for controls (Monterosso et al., 2007). Half of the studies (n = 13) did not report cigarette smoking. The majority of the studies were conducted in Caucasian countries (n = 22) and the rest were conducted in Asian countries.

3.2. Psychomotor function

Three studies identified in this review (2 PET and 1 MRI) assessed psychomotor function in abstinent MA subjects (Table 2). The psychomotor tasks used were the grooved pegboard task and the timed gait test (Table 9).

The MA group was not significantly different from the control group in psychomotor task performance (Chang et al., 2005). However, performance in MA subjects was positively correlated with regional volume and metabolism. Volkow et al. (2001b) reported a correlation between performance on the grooved pegboard task and glucose metabolism in the parietal cortex (higher in the MA group than in controls). In the following study by Wang et al. (2004), a positive correlation was observed between change in performance on the timed gait test and metabolic change in the thalamus after protracted abstinence (11–17 months). In an MRI study, Chang et al. (2005) also observed a correlation between performance on the non-dominant grooved pegboard task and the volumes of putamen and globus pallidus (larger in the MA group than in controls).

3.3. Working memory

Four studies (1 perfusion MRI, 1 PET, and 2 MRI) assessed working memory in abstinent MA users (Table 3). The memory tasks used were the one-back cued response task, the sequential number tasks (one-back task, two-back task, and one-increment task), the one card learning task, the Rey auditory verbal learning task (RAVLT), the repeated memory test, the international shopping list task, and task performance, failed to observe any correlation be task (Table 9).

MA subjects performed significantly more poorly than controls on the memory tasks (Chang et al., 2002). A positive correlation was observed between performance and brain measures (regional blood flow, metabolism, and volume), except in one study (Du et al., 2015). Chang et al. (2002) observed a correlation between performance on the one-back cued response task and regional cerebral blood flow (rCBF) in the right lateral parietal cortex (lower in the MA group than in controls). Wang et al. (2004) reported a correlation between performance on the RAVLT (delayed recall) and increased metabolism in the thalamus after protracted abstinence (≥ 9 months). Thompson et al. (2004) also observed a correlation between performance on the repeated memory test (word-recall) and hippocampal volume (smaller in the MA group than in controls).

3.4. Attention

Nine studies (3 PET, 3 MRS, 1 DTI, and 2 fMRI) assessed attention in MA individuals (Table 4). The attention tasks used were the symbol digit modalities task, the auditory continuous performance task (CPT), and the Stroop task (Table 9). One study was carried out with active adolescent MA users (Kim et al., 2016), while the rest were conducted in abstinent adults. Three pairs of studies had overlapping subjects: studies by Berman et al. (2008) and London et al. (2005); studies by Salo et al. (2011) and Salo et al. (2007); and studies by Salo et al. (2009b) and Salo et al. (2013).

MA groups showed poorer performance than control groups on the CPT and Stroop tasks (Kim et al., 2016; London et al., 2005; Salo et al., 2013, 2009a, 2009b, 2007), and the performance was positively associated with regional metabolism, volume, NAA level, and FA value. In one PET study, a correlation was observed between performance on the symbol digit modalities task and increased thalamic metabolism after protracted abstinence (Wang et al., 2004). In another PET study, a correlation was observed between performance on the CPT and glucose metabolism in the ACC (lower in the MA group than in controls), left insula, and left hippocampus (London et al., 2005). Three MRS studies observed a correlation between performance in the Stroop task and NAA level in the ACC (lower in the MA group than in controls) (Kim et al., 2016; Salo et al., 2011, 2007). And one study using DTI observed a correlation between Stroop performance and FA value in the genu of the corpus callosum (CC) (Salo et al., 2009a).

Two studies have reported a negative association between performance and regional metabolism or activation. Berman et al. (2008) observed a correlation between change in performance on the CPT and increased parietal metabolism after four weeks of prolonged abstinence, which was due to a decline in performance after retest. Meanwhile, Salo et al. (2013) reported a correlation between Stroop performance on conflict – conflict sequence (relative to non-conflict – conflict sequence) and PFC activation in the MA group; whereas a trend for positive correlation was observed in controls. It was observed that, while controls showed improvement in reaction time (RT) on conflict trials when preceded by conflict trials and increased PFC activation, MA subjects showed no advantage and reduced PFC activation.

Table 1
Subjects Demographic Characteristics.

Study Included	Sample Size (M/F)	Age (year)	Education (year)	Handedness (right-handed)	Cigarette Smokers	Major Ethnicity
Volkow et al. 2001	MA: 6/9 HC: 15/6	MA: 32 ± 7 HC: 31 ± 8	NA	NA	NA	NA (country: USA)
Chang et al. 2002	MA: 10/10 HC: 10/10	MA: 32.5 ± 1.4 HC: 35.0 ± 1.7	MA: 12.4 ± 1.5 HC: 13.2 ± 2.8	NA	NA	NA (country: USA)
Thompson et al. 2004	MA: 15/7 HC: 10/11	MA: 35.3 ± 1.7 HC: 31.9 ± 1.5	MA: 12.8 ± 0.4 HC: 15.2 ± 0.5	MA: 77.3% HC: 76.2%	MA: 68.2% HC: 9.5%	Caucasian Non-Hispanic MA: 59.1% HC: 66.7%
Wang et al. 2004	MA: 4/9 HC: 4/7	MA: 29 ± 3 (n = 5), 36 ± 3 (n = 8) HC: 31 ± 7	NA	NA	NA	NA (country: USA)
Chang et al. 2005	MA: 24/26 HC: 24/26	MA: 32.1 ± 7.1 HC: 31.7 ± 7.4	MA: 12.5 ± 1.4 (n = 44) HC: 14.3 ± 1.1 (n = 28)	NA	NA	NA (country: USA)
Kim et al. 2005	MA: 28/7 HC: 15/6	MA: 35.5 ± 6.4 HC: 33.2 ± 6.4	MA: 10.0 ± 2.1 HC: 15.3 ± 1.4	MA: 82.9% HC: 85.7%	MA: 60.0% HC: 28.6%	NA (country: South Korea)
London et al. 2005	MA: 11/17 HC: 10/16	MA: 34.7 ± 1.9 HC: 33.3 ± 2.0	MA: 12.8 ± 0.5 HC: 14.6 ± 0.5	MA: 82.4% HC: 75.0%	MA: 82.4% HC: 0%	Caucasian Non-Hispanic MA: 52.9% HC: 68.8%
Kim et al. 2006	MA: 27/2 HC: 15/5	MA: 36.5 ± 5.5 HC: 33.2 ± 6.5	MA: 10.7 ± 1.6 HC: 15.1 ± 1.7	MA: 89.7% HC: 85.0%	MA: 75.9% HC: 35.0%	NA (country: South Korea)
Chung et al. 2007	MA: 23/9 HC: 20/10	MA: 36.0 ± 6.7 (M), 29.0 ± 7.2 (F) HC: 33.3 ± 6.6 (M), 28.7 ± 6.0 (F)	NA	MA: 95.7% (M), 77.8% (F) HC: 90.0% (M), 90.0% (F)	MA: 78.3% (M), 77.8% (F) HC: 45.0% (M), 30.0% (F)	NA (country: South Korea)
Monterosso et al. 2007	MA: 8/4 HC: 12/5	MA: 33.8 ± 8.1 HC: 29.7 ± 7.2	NA	NA	MA: 75.0% HC: 94.1%	Caucasian Non-Hispanic MA: 66.7% HC: 50.0%
Salo et al. 2007	MA: 13/23 HC: 8/8	MA: 36.9 ± 1.6 HC: 32.2 ± 1.8	MA: 13.2 ± 0.2 HC: 14.4 ± 0.4	MA: 91.7% HC: 81.3%	MA: 83.3% HC: 32.0%	Caucasian Non-Hispanic MA: 80.6% HC: 50.0%
Berman et al. 2008	MA: 8/1 HC: 6/1	MA: 32.9 ± 7.2 HC: 33.1 ± 7.2	MA: 13.2 ± 2.1 HC: 15.0 ± 2.1	100%	MA: 88.9% HC: 0%	Caucasian Non-Hispanic MA: 44.4% HC: 71.4%
Hoffman et al. 2008	MA: 13/6 HC: 12/5	MA: 34.8 ± 10.0 HC: 36.7 ± 9.9	NA	MA: 89% HC: 88%	MA: 75% HC: 25%	Caucasian MA: 85% HC: 100%
Leland et al. 2008	MA: 17/2 HC: 16/3	MA: 40.4 ± 9.9 HC: 40.3 ± 8.1	MA: 13.4 ± 1.2 HC: 14.0 ± 1.6	MA: 89% HC: 89%	NA	Caucasian MA: 63% HC: 53%
Y.T. Kim et al. 2009	MA: 24/0 HC: 21/0	MA: 37.7 ± 5.5 HC: 39.1 ± 3.3	MA: 10.5 ± 2.2 HC: 12.4 ± 2.2	MA: 95.8% HC: 90.5%	NA	NA (country: South Korea)
I.S. Kim et al. 2009	MA: 11/0 HC: 13/0	MA: 34.4 ± 2.9 HC: 35.5 ± 2.1	NA	100%	NA	NA (country: South Korea)
Salo et al. 2009a	MA: 13/24 HC: 9/8	MA: 36.3 ± 8.7 HC: 32.2 ± 7.5	MA: 13.2 ± 1.4 HC: 14.5 ± 1.7	MA: 92% HC: 76%	MA: 81% HC: 24%	Caucasian Non-Hispanic MA: 81% HC: 47%
Salo et al. 2009b	MA: 5/7 HC: 8/8	MA: 35.7 ± 7.7 HC: 30.2 ± 8.9	MA: 12.3 ± 1.4 HC: 15.0 ± 1.2	NA	NA	NA (country: USA)
Schwartz et al. 2010	MA: 31/30 HC: 22/22	MA: 33.4 ± 8.4 HC: 34.1 ± 10.7	MA: 11.6 ± 0.7 HC: 15.7 ± 2.5	NA	MA: 88.5% HC: 38.6%	NA (country: USA)
Salo et al. 2011	MA: 14/37 HC: 13/9	MA: 38.2 ± 8.2 HC: 39.5 ± 10.3	MA: 12.9 ± 1.5 HC: 14.3 ± 2.2	MA: 90.2% HC: 95.5%	MA: 76.5% HC: 36.4%	NA (country: USA)
Jan et al. 2012	MA: 12/5 HC: 13/7	MA: 35.1 ± 6.6 HC: 30.9 ± 8.2	NA	NA	MA: 82.4% HC: 0%	NA (country: New Zealand)
Koester et al. 2013	AMP: 22/11 HC: 9/6	AMP: 25.6 ± 6.0 (n = 15), 22.9 ± 4.1 (n = 18) HC: 26.5 ± 4.2	AMP: 14.5 ± 2.0 (n = 15), 15.1 ± 2.5 (n = 18) HC: 17.5 ± 2.8	NA	NA	NA (country: Germany)
Salo et al. 2013	MA: 15/15 HC: 17/13	MA: 35.5 ± 7.9 HC: 29.0 ± 7.7	MA: 12.5 ± 1.6 HC: 15.2 ± 1.3	NA	NA	NA (country: USA)
Gowin et al. 2014b	MA: 53/15 HC: 26/14	MA: 38.2 ± 10.5 HC: 35.6 ± 11.5	MA: 13.0 ± 1.6 HC: 14.9 ± 1.7	NA	NA	Caucasian Non-Hispanic MA: 60.3% HC: 60.0%

(*continued on next page*)

Table 1 (*continued*)

Study Included	Sample Size (M/F)	Age (year)	Education (year)	Handedness (right-handed)	Cigarette Smokers	Major Ethnicity
Gowin et al. 2014a	Abstinent: 34/11 Relapsed: 14/4	Abstinent: 38.8 ± 11.1 Relapsed: 37.4 ± 9.2	Abstinent: 12.8 ± 1.7 Relapsed: 13.3 ± 1.5	NA	NA	Caucasian Non-Hispanic Abstinent: 53.3% Relapsed: 66.7%
Kohno et al. 2014	MA: 12/13 HC: 16/11	MA: 35.7 ± 1.6 HC: 33.9 ± 2.3	MA: 13.0 ± 0.4 HC: 13.6 ± 0.4	NA	MA: 80.0% HC: 59.3%	NA (country: USA)
Du et al. 2015	MA: 20/10 HC: 19/10	MA: 34.0 ± 4.9 (M), 30.3 ± 8.7 (F) HC: 33.4 ± 6.5 (M), 32.0 ± 8.2 (F)	MA: 9.5 ± 1.9 (M), 10.4 ± 2.2 (F) HC: 11.1 ± 2.4 (M), 13.0 ± 2.6 (F)	NA	NA	NA (country: China)
Kim et al. 2016	MA: 35/9 HC: 41/12	MA: 18.1 ± 1.3 HC: 17.9 ± 1.2	MA: 10.8 ± 1.7 HC: 11.4 ± 1.1	MA: 86.4% HC: 83.0%	MA: 77.3% HC: 18.9%	Asian 100%
Bischoff-Grethe et al. 2017	MA: 17/0 HC: 20/3	MA: 38.0 ± 8.7 HC: 38.0 ± 11.9	MA: 12.1 ± 2.0 HC: 14.4 ± 2.2	MA: 94% HC: 96%	MA: 43% HC: 14%	Caucasian Non-Hispanic MA: 59% HC: 70%

Abbreviations: AMP amphetamine group; F female; HC control group; M male; MA methamphetamine group; NA not available.

3.5. Cognitive flexibility

Five studies (2 PET, 1 MRI, and 2 DTI) assessed cognitive flexibility in abstinent MA subjects (Table 5) using the Wisconsin card sorting task (WCST) (Table 9). All of these studies were conducted in South Korea. Three studies had partially overlapping subjects (Chung et al., 2007; Kim et al., 2006, 2005).

Poorer performance was observed in the MA group relative to the control group in all five studies. In addition, a positive correlation was observed between WCST performance and brain measures, except in one study (Y. T. Kim et al., 2009b). In the three studies with overlapping subjects, performance was correlated with glucose metabolism and FA value in the right frontal WM (lower in the MA group than in controls) (Chung et al., 2007; Kim et al., 2005), as well as with GM density in the right PFC (lower in the MA group than in controls) (Kim et al., 2006). Y. T. Kim et al. (2009b) did not observe any correlation between performance and glucose metabolism in the left inferior frontal WM (lower in the MA group than in controls), while I.S. Kim et al., (2009a) observed a correlation between performance and FA value in the genu of the CC (lower in the MA group than in controls).

One study compared two groups of MA subjects in short-term (< 6 months) and protracted abstinence (≥ 6 months) (Kim et al., 2006). Subjects in short-term abstinence showed lower GM density in the PFC and had worse performance than those in protracted abstinence. However, when compared to controls, subjects in protracted abstinence still showed lower PFC density and performed more poorly.

3.6. Inhibitory control

Two studies (1 fMRI and 1 MRI) assessed inhibitory control in MA users (Table 6) using the Go/No-Go task (Table 9). One study was conducted in abstinent subjects (Leland et al., 2008) and the other study was conducted in active-users (Jan et al., 2012b).

Abstinent MA subjects made more errors on the task but performed comparably to controls on the trials preceded by cues (Leland et al., 2008). In addition, MA subjects activated the ventral ACC in response to the predictive cues and this activation was positively associated with performance. In another study, Jan et al. (2012b) also observed a positive correlation between performance and GM density in the right putamen (higher in the MA group than in controls).

Table 2
Study of Psychomotor Function in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Volkow et al. (2001a,2001b,2001c), USA	• MA dependent • n = 15 (f = 9) • age: 32 ± 7 • abstinence: 2 weeks-5 months (n = 12), 11-35 months (n = 3)	**PET** • parietal cortex, CMRglc: MA > control • thalamus, caudate, and putamen, CMRglc: MA < control	**Grooved Pegboard** • [performance in MA] x [CMRglc in parietal cortex]: positive correlation
Wang et al. (2004), USA	• MA dependent • tested short-term & protracted abstinence: n = 5 (f = 3), protracted only: n = 8 (f = 6) • age: 29 ± 3 (tested twice), 36 ± 3 (protracted only) • abstinence: 3 ± 1.6 months (short-term, n = 5), 14 ± 2 months (protracted, n = 5), 17 ± 10 months (protracted, n = 8)	**PET** • thalamus, CMRglc: short-term < protracted = control • striatum, CMRglc: short-term = protracted < control	**Timed Gait** • [change in performance after protracted abstinence] x [change in CMRglc in thalamus after protracted abstinence]: positive correlation
Chang et al. (2005), USA	• MA dependent • n = 50 (f = 26) • age: 32.1 ± 7.1 • abstinence: 4.0 ± 6.2 months (1 week-36 months)	**MRI** • globus pallidus and putamen, volume: MA > control • [volumes of globus pallidus and putamen] x [cumulative MA use]: negative correlation	**Grooved Pegboard** • performance: MA = control • [performance on non-dominant hand in MA] x [volumes of globus pallidus and putamen]: positive correlation

Abbreviations: CMRglc = cerebral metabolic rate of glucose consumption; f = female; MA = methamphetamine; MRI = Magnetic Resonance Imaging; n = number of subjects; PET = Positron Emission Tomography.

Table 3
Study of Memory in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Chang et al. (2002), USA	• MA dependent • n = 20 (f = 10) • age: 32.5 ± 1.4 • abstinence: 8.0 ± 2.2 (0.5-36) months	**pMRI** • left occipital and right posterior parietal lobe, rCBF: MA > control • bilateral putamen/insular cortex and right lateral parietal lobe, rCBF: MA < control • right occipital cortex, rCBF: female MA > female control, male MA < male control • [rCBF in any region] x [MA use]: no correlation	**One-Back Cued Response, n-Back, and One-Increment Tasks** • performance (one-back cued response, one-back, two-back, and one-increment tasks): MA < control • [performance on one-back cued response in MA] x [rCBF in right lateral parietal cortex]: positive correlation • [performance on any task] x [MA use]: no correlation
Wang et al. (2004), USA	• MA dependent • tested short-term & protracted abstinence: n = 5 (f = 3), protracted only: n = 8 (f = 6) • age: 29 ± 3 (tested twice), 36 ± 3 (protracted only) • abstinence: 3 ± 1.6 months (short-term, n = 5), 14 ± 2 months (protracted, n = 5), 17 ± 10 months (protracted, n = 8)	**PET** • thalamus, CMRglc: short-term < protracted = control • striatum, CMRglc: short-term = protracted < control	**Rey Auditory Verbal Learning Task** • [change in performance on delayed recall after protracted abstinence] x [change in CMRglc in thalamus after protracted abstinence]: positive correlation
Thompson et al. (2004), USA	• MA dependent • n = 22 (f = 7) • age: 35.3 ± 1.7 • abstinence: 6.6 ± 5.2 days	**MRI** • right cingulate gyrus, GMD: MA < control • hippocampus, volume: MA < control • WM near hippocampus: MA > control	**Repeated Memory Test** • [performance on word-recall in MA] x [hippocampal volume]: positive correlation
Du et al. (2015), China	• MA dependent • n = 30 (f = 10) • age: 34.0 ± 4.9 (m), 30.3 ± 8.7 (f) • abstinence: 6.4 ± 1.0 months (m), 3.8 ± 0.8 months (f)	**MRI** • right hippocampus, volume: female MA < female control (NS) • [hippocampal volume] x [MA use]: no correlation	**Two-Back, One Card Learning, International Shopping List, Continuous Paired Association Learning, and Groton Maze Learning** • [performance on any task in MA] x [hippocampal volume]: no correlation

Abbreviations: CMRglc = cerebral metabolic rate of glucose consumption; f = female; GMD = gray matter density; m = male; MA = methamphetamine; MRI = Magnetic Resonance Imaging; n = number of subjects; NS = not significant; PET = Positron Emission Tomography; pMRI = perfusion Magnetic Resonance Imaging; rCBF = regional cerebral blood flow; WM = white matter.

3.7. Cognitive impulsivity

Four studies (3 fMRI and 1 MRI) assessed impulsivity in abstinent MA individuals (Table 7). Three studies used the delay discounting task (DDT), and the other study used the Iowa gambling task (IGT) (Table 9).

MA groups discounted more heavily on the DDT (Hoffman et al., 2008; Monterosso et al., 2007; Schwartz et al., 2010) and had lower scores on the IGT relative to the control group (Bischoff-Grethe et al., 2017). A negative correlation was observed between impulsivity and regional activation or GM density. Monterosso et al. (2007) observed that delay discounting across subjects was associated with activation in the left PFC on the "hard choice > no choice" contrast (lower in the MA group than in controls). Schwartz et al. (2010) also observed a negative correlation between impulsivity and GM density in the left PFC (lower in the MA group than in controls).

Meanwhile, a positive correlation was also observed between impulsivity and brain measures. Hoffman et al. (2008) observed a correlation between delay discounting in MA subjects and differential activation in the PFC on the "hard task – control task" contrast (lower in the MA group than in controls). The MRI study by Schwartz et al. (2010) also reported a positive correlation between impulsivity and GM density in the putamen-ventral striatum. In another study, Bischoff-Grethe et al. (2017) found that, within the MA group, higher impulsivity (lower IGT score) was associated with activation in the ventral striatum (VS) in response to loss outcomes. In addition, MA subjects exhibited greater activation in the caudate on loss outcomes relative to gain outcomes, whereas controls did not show differential activation between the two outcomes.

3.8. Risky decision-making

Four studies in this review, all using fMRI, assessed risky decision-making in abstinent MA/amphetamine subjects (Table 8). The tasks used were the decision-making task (DMT), the balloon analog risk task (BART), and the risky gains task (RGT) (Table 9). One study was conducted in polydrug (amphetamine and ecstasy) users (Koester et al., 2013), and one study recruited only MA subjects (no controls) (Gowin et al., 2014a).

MA/amphetamine users made more risky decisions (Gowin et al., 2014b; Koester et al., 2013) and earned less money than controls (Kohno et al., 2014). In two studies, Gowin et al., (2014a, 2014b) reported a negative correlation between the frequency of risky decisions in MA subjects and activation in the rostral ACC and anterior insula. The other two studies did not observe any correlation between behavioral performance and regional activation in MA/amphetamine users (Koester et al., 2013; Kohno et al., 2014). However, both studies observed lower activation in the lateral PFC associated with high gain risky decisions in the MA/amphetamine group relative to the control group. In addition, higher activation in the VS was observed in MA group as a function of risk-taking, relative to controls (Kohno et al., 2014).

One study compared the behavior and regional activation between MA subjects who maintained abstinence and those who relapsed in the following year (Gowin et al., 2014a). No behavioral difference was observed between groups, but relapsed subjects showed less or no activation in the anterior insula on the "risky decisions > safe decisions" contrast, relative to non-relapsed subjects. In addition, there was a negative correlation between differential activation in the right insula and probability of relapse.

Table 4
Study of Attention in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Wang et al. (2004), USA	• MA dependent • tested short-term & protracted: n = 5 (f = 3), protracted only: n = 8 (f = 6) • age: 29 ± 3 (tested twice), 36 ± 3 (protracted only) • abstinence: 3 ± 1.6 months (short-term, n = 5), 14 ± 2 months (protracted, n = 5), 17 ± 10 months (protracted, n = 8)	**PET** • thalamus, CMRglc: short-term < protracted = control • striatum, CMRglc: short-term = protracted < control	**Symbol Digit Modalities** • [change in performance after protracted abstinence] x [change in CMRglc in thalamus after protracted abstinence]: positive correlation
London et al. (2005), USA	• MA dependent • n = 17 (f = 6) • age: 34.7 ± 1.9 • abstinence: 4-7 days	**PET** • right PCC, CMRglc: MA > control • left ACC, CMRglc: MA < control	**Auditory CPT** • performance: MA < control • [performance] x [CMRglc in ACC]: positive correlation in MA; negative correlation in control • [performance] x [CMRglc in left insula]: positive correlation in MA; no correlation in control • [performance] x [CMRglc in left hippocampus]: positive correlation
Salo et al. (2007), USA	• MA dependent • n = 36 (f = 23) • age: 36.9 ± 1.6 • abstinence: 19.9 ± 5.4 months	**MRS** • ACC, Cho/NAA: MA > control • ACC, NAA/Cr: MA < control	**Stroop Task** • performance: MA < control • [performance in MA] x [NAA/Cr level in ACC]: positive correlation
Berman et al. (2008), USA	• MA dependent • n = 9 (f = 1) • age: 32.9 ± 7.2 • abstinence: 5-9 days, with additional 4 weeks	**PET** • parietal cortex, CMRglc: retest > first test (MA group)	**Auditory CPT** • performance (MA): retest < first test (NS) • performance (control): retest > first test (NS) • [change in performance in MA] x [change in CMRglc in parietal cortex]: negative correlation
Salo et al. (2009a), USA	• MA dependent • n = 37 (f = 24) • age: 36.3 ± 8.7 • abstinence: 21.0 ± 31.9 months (3 weeks-10 years)	**DTI** • genu of CC, FA: MA < control (NS) • CC, ADC: MA = control	**Stroop Task** • performance: MA < control • [performance in MA] x [FA value in genu of CC]: positive correlation
Salo et al. (2009b), USA	• MA dependent • n = 12 (f = 7) • age: 35.7 ± 7.7 • abstinence: 4.1 ± 2.8 (2-12) months	**fMRI** • right MFG, activation: MA < control [conflict – conflict vs non-conflict – conflict)	**Stroop Task** • performance (MA): conflict – conflict < non-conflict – conflict • performance (control): conflict – conflict > non-conflict – conflict • [performance between trials in MA] x [PFC activation]: no correlation
Salo et al. (2011), USA	• MA dependent • n = 51 (f = 37) • age: 38.2 ± 8.2 • abstinence: 25.1 ± 31.0 months	**MRS** • ACC, NAA/Cr: MA < control • ACC, Cho/NAA: MA = control	**Spatial Stroop Task** • performance: MA = control • [performance in MA] x [NAA/Cr level in ACC]: positive correlation
Salo et al. (2013), USA	• MA dependent • n = 30 (f = 15) • age: 35.5 ± 7.9 • abstinence: 13.7 ± 15.4 (2-60) months	**fMRI** • PFC, activation: MA < control [conflict – conflict vs non-conflict – conflict)	**Stroop Task** • performance (MA): conflict – conflict < non-conflict – conflict • performance (control): conflict – conflict > non-conflict – conflict • [performance between trials in MA] x [PFC activation]: negative correlation
Kim et al. (2016), South Korea	• MA dependent (active users, adolescent) • n = 44 (f = 9) • age: 18.1 ± 1.3	**MRS** • ACC, NAA: MA < control • ACC, Cr and Cho: MA = control • ACC, Cr: early onset MA subjects (< 15 years old) < late onset MA subjects (≥ 15 years old) • [NAA level in ACC] x [age of first MA use]: positive correlation • [NAA level in ACC] x [cumulative MA use]: no correlation	**Stroop Task** • performance: MA < control (NS) • [performance in MA] x [NAA level in ACC]: positive correlation • [performance in MA] x [cumulative MA use]: no correlation

Abbreviations: ACC = anterior cingulate cortex; ADC = apparent diffusion coefficient; CC = corpus callosum; Cho = choline; CMRglc = cerebral metabolic rate of glucose consumption; CPT = continuous performance task; Cr = creatine; DTI = Diffusion Tensor Imaging; f = female; FA = fractional anisotropy; fMRI = functional Magnetic Resonance Imaging; MA = methamphetamine; MFG = middle frontal gyrus; MRI = Magnetic Resonance Imaging; MRS = Magnetic Resonance Spectroscopy; n = number of subjects; NAA = *N*-acetylaspartate; NS = not significant; PCC = posterior cingulate cortex; PET = Positron Emission Tomography; PFC = prefrontal cortex; RT = reaction time.

4. Discussion

The main finding of this review is that there is a strong indication of the relationship between brain imaging measures and cognitive performance in MA users. In all cognitive domains, MA subjects showed poorer performance than controls. Qualitative comparisons across different imaging modalities showed that in the majority of cases, poorer performance was associated with deficits in the brain measures, such as lower metabolism, GM density, FA, NAA, and activation. In this discussion, deficits in cognitive control and neural correlates of impulsivity have been identified as the core issues. In addition, the disparities of findings and limitations of the review will be discussed.

Table 5
Study of Cognitive Flexibility in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Kim et al. (2005), South Korea	• MA dependent (route: IV) • n = 35 (f = 7) • age: 35.5 ± 6.4 • abstinence: 19.1 ± 27.2 months (at least 4 weeks)	**PET** • right superior frontal WM, CMRglc: MA < control • right superior frontal WM, CMRglc: female MA = female control	**Wisconsin Card Sorting Task** • performance: male MA < male control • performance: female MA = female control • [performance in MA] x [CMRglc in right frontal WM]: positive correlation
Kim et al. (2006), South Korea	• MA dependent (route: IV) • protracted: n = 18 (f = 2), short-term: n = 11 (m) • age: 36.5 ± 5.5 • abstinence: 30.6 ± 39.2 months (protracted), 2.6 ± 1.6 months (short-term)	**MRI** • right MFG, GMD: short abstinence < protracted abstinence < control)	**Wisconsin Card Sorting Task** • performance: control > protracted abstinence > short abstinence • [performance in MA] x [GMD in right MFG]: positive correlation
Chung et al. (2007), South Korea	• MA dependent (route: IV) • n = 32 (f = 9) • age: 36.0 ± 6.7 (m), 29.0 ± 7.2 (f) • abstinence: 24.3 ± 37.5 months (m), 43.1 ± 65.9 months (f)	**DTI** • frontal WM, FA: MA < control • frontal WM, FA: female MA = female control	**Wisconsin Card Sorting Task** • performance: male MA < male control • performance: female MA = female control • [performance in MA] x [FA value in right frontal WM]: positive correlation
Y.T. Kim et al. (2009b), South Korea	• MA dependent • n = 24 (m) • age: 37.7 ± 5.5 • abstinence: 20.5 ± 8.3 days (at least 1 week)	**PET** • left inferior frontal WM, CMRglc: MA < control • [CMRglc in inferior frontal WM] x [cumulative MA use]: negative correlation	**Wisconsin Card Sorting Task** • performance: MA < control • [performance in MA] x [CMRglc in left inferior frontal WM]: no correlation
I.S. Kim et al. (2009a), South Korea	• MA dependent (route: IV) • n = 11 (m) • age: 34.4 ± 2.9 • abstinence: 18 ± 7 days	**DTI** • genu of CC, FA: MA < control	**Wisconsin Card Sorting Task** • performance: MA < control • [performance in MA] x [FA value in genu of CC]: positive correlation

Abbreviations: CC = corpus callosum; CMRglc = cerebral metabolic rate of glucose consumption; DTI = Diffusion Tensor Imaging; f = female; FA = fractional anisotropy; GMD = gray matter density; IV = intravenous; m = male; MA = methamphetamine; MFG = middle frontal gyrus; MRI = Magnetic Resonance Imaging; n = number of subjects; PET = Positron Emission Tomography; WM = white matter.

4.1. Cognitive control deficits in MA dependence

Cognitive control or executive function is the ability to pursue goal-directed behavior (Cohen, 2017). Cognitive control in this review has been studied using the auditory CPT, Stroop task, WCST, and Go/No-Go tasks. The ACC has been most consistently observed to show group difference on these tasks. Lower metabolism (London et al., 2005) and NAA levels (Kim et al., 2016; Salo et al., 2011, 2007) in the ACC have been associated with poorer performance on the auditory CPT and the Stroop task, while ACC activation has been associated with better performance in the Go/No-Go task (Leland et al., 2008). Meanwhile, studies using the WCST have reported prefrontal deficits (lower glucose metabolism, GM density, and FA) in MA subjects, and these deficits were associated with poorer performance on the task (Chung et al., 2007; Kim et al., 2006, 2005).

Both the PFC and ACC are engaged in cognitive control and have been proposed to be connected through dopamine projections that run from the ACC to the PFC (Botvinick et al., 2001; MacDonald et al., 2000). The ACC detects the occurrence of conflict, while the PFC is responsible for maintaining goal-directed behavior (Botvinick et al., 2001). PFC activation in the absence of ACC activation has been observed in the tasks that require maintenance and manipulation of information in working memory (MacDonald et al., 2000), e.g., the WCST. On the other hand, the ACC has been found more active than the PFC in the tasks that require divided attention (MacDonald et al., 2000), such as the Stroop task and the Go/No-Go task. In a more difficult task, however, it becomes impossible to dissociate the roles of the PFC and ACC as there is a demand for more resources to process the information.

4.2. The neural correlates of impulsivity in MA subjects

Despite using different tasks, studies of decision-making in this review have consistently provided evidence for impulsive behavior in MA subjects. Studies using the DDT and the IGT have reported higher rates of delay discounting in MA groups (a higher tendency to choose a smaller-immediate reward over a larger-delayed reward) relative to controls (Bischoff-Grethe et al., 2017; Hoffman et al., 2008; Monterosso et al., 2007; Schwartz et al., 2010). Delay discounting has been associated with lower activation (Monterosso et al., 2007) in the PFC, but higher activation in the striatum (Bischoff-Grethe et al., 2017). The MA group exhibited similar PFC activation during “hard” and “easy” trials

Table 6
Study of Inhibitory Control in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Leland et al., (2008), USA	• MA dependent • n = 19 (f = 2) • age: 40.4 ± 9.9 • abstinence: 33.9 ± 5.9 (25-50) days	**fMRI** • ventral ACC, activation: MA > control (predictive cue vs no cue)	**Go/No-Go Task** • performance (MA): cue > no cue • performance (control): cue = no cue • [performance in MA] x [activation in ventral ACC]: positive correlation
Jan et al. (2012a, 2012b), New Zealand	• MA dependent (active users) • n = 17 (f = 5) • age: 35.1 ± 6.6	**MRI** • right putamen, GMD: MA > control • [volume of putamen] x [MA use]: no correlation	**Go/No-Go Task** • [performance in MA] x [volume of right putamen]: positive correlation

Abbreviations: ACC = anterior cingulate cortex; f = female; fMRI = functional Magnetic Resonance Imaging; GMD = gray matter density; MA = methamphetamine; MRI = Magnetic Resonance Imaging; n = number of subjects.

Table 7
Study of Cognitive Impulsivity in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Monterosso et al. (2007), USA	• MA dependent • n = 12 (f = 4) • age: 33.8 ± 8.1 • abstinence: 5-7 days	**fMRI** • left dlPFC, activation: MA < control (hard choice vs easy choice)	**Delay Discounting Task** • delay discounting: MA > control • [delay discounting] x [activation in left vlPFC on hard choice]: negative correlation
Hoffman et al. (2008), USA	• MA dependent • n = 19 (f = 6) • age: 34.8 ± 10.0 • abstinence: 48 ± 17 days (at least 2 weeks and not more than 8 weeks)	**fMRI** • ACC and SFG, activation: MA < control (hard task vs control task)	**Delay Discounting Task** • delay discounting: MA > control • [delay discounting] x [activation in SFG, PPC, and amygdala on hard task]: positive correlation
Schwartz et al., (2010), USA	• MA dependent • n = 61 (f = 30) • age: 33.4 ± 8.4 • abstinence: 63.7 ± 32.7 days (at least 2 weeks and not more than 160 days)	**MRI** • bilateral insula and left MFG, GMD: MA < control • [GMD in amygdala] x [abstinence]: positive correlation • [GMD in right MFG] x [abstinence]: negative correlation	**Delay Discounting Task** • delay discounting: MA > control • [delay discounting] x [GMD in PCC and putamen-VS]: positive correlation • [delay discounting] x [GMD in left SFG]: negative correlation
Bischoff-Grethe et al., 2017, USA	• MA dependent (route: smoking) • n = 18 (m) • age: 38.0 ± 8.7 • abstinence: 173 ± 160 (9-539) days	**fMRI** • VS and posterior caudate, activation: MA < control (loss anticipation) • caudate, activation: MA > control (loss outcome vs gain outcome)	**Iowa Gambling Task** • performance: MA < control • [performance in MA] x [activation in VS on loss outcome]: negative correlation

Abbreviations: ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; f = female; fMRI = functional Magnetic Resonance Imaging; GMD = gray matter density; m = male; MA = methamphetamine; MFG = middle frontal gyrus; MRI = Magnetic Resonance Imaging; n = number of subjects; PCC = posterior cingulate cortex; PPC = posterior parietal cortex; SFG = superior frontal gyrus; vlPFC = ventrolateral prefrontal cortex; VS = ventral striatum.

Table 8
Study of Risky Decision-Making in MA Users.

Author, Year, Country	MA Subjects	Neuroimaging Technique and Findings	Task and Findings
Koester et al. (2013), Germany	• amphetamine & MDMA users • low exposure: n = 18 (f = 6), experienced: n = 15 (f = 5) • age: 22.9 ± 4.1 (low exposure), 25.6 ± 6.0 (experienced) • abstinence: 380.5 ± 804.0 days (low exposure), 22.6 ± 28.1 days (experienced)	**fMRI** • lateral frontal cortex, activation: experienced < low exposure = control (high reward) • right parietal lobe, activation: experienced = low exposure > control (high chance)	**Decision-Making Task** • risky decision: experienced = low exposure > control • money earned: experienced = low exposure = control • [performance] x [activation] x [drug use]: no correlation
Kohno et al., (2014), USA	• MA dependent • n = 25 (f = 13) • age: 35.7 ± 1.6 • abstinence: 4-7 days (n = 11) and 5.8 ± 1.8 days (n = 14)	**fMRI** • VS, activation: MA > control (by risky decision) • right dlPFC, activation: MA < control (by risky decision)	**Balloon Analogue Risk Task** • money earned: MA < control • [money earned] x [activation-by-risky-decision in anterior insula and right caudate]: negative correlation in control, no correlation in MA
Gowin et al., (2014b), USA	• MA dependent • n = 68 (f = 15) • age: 38.2 ± 10.5 • abstinence: 34.0 ± 3.4 (15-207) days	**fMRI** • left posterior insula, activation: MA > control • rostral ACC, activation: MA < control • right mid-insula, activation: MA > control (risky decision vs safe decision) • left dorsal ACC, activation: MA < control (safe decision vs risky decision) • [activation in mid-insula] x [years of MA use]: positive correlation • [activation in right rostral ACC] x [cumulative MA use]: positive correlation	**Risky Gains Task** • risky decision (post-loss): MA > control • [frequency of risky decision in MA] x [activation in right mid-insula]: positive correlation • [frequency of risky-decision in MA] x [activation in right rostral ACC]: negative correlation
Gowin et al. (2014a), USA	• MA dependent • abstinent: n = 45 (f = 11), relapsed: n = 18 (f = 4) • age: 38.8 ± 11.1 (abstinent), 37.4 ± 9.2 (relapsed) • abstinence: 34.0 ± 3.4 (15-207) days	**fMRI** • anterior insula, activation: relapsed < abstinent (risky decision vs safe decision) • [activation in right insula on risky decision] x [relapse probability]: negative correlation	**Risky Gains Task** • risky decision: relapsed = abstinent • [frequency of risky decision] x [activation in anterior insula]: negative correlation

Abbreviations: ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; f = female; fMRI = functional Magnetic Resonance Imaging; MA = methamphetamine; MDMA = 3,4-methylenedioxymethamphetamine (ecstasy); n = number of subjects; VS = ventral striatum.

(Monterosso et al., 2007), and during "hard" and "control" tasks (Hoffman et al., 2008), suggesting an inefficiency in cortical processing that may contribute to delay discounting. In addition, MA subjects showed a lower striatal response on loss anticipation, but higher on loss outcome, suggesting an impaired ability to evaluate future risks and benefits (Bischoff-Grethe et al., 2017).

Meanwhile, studies using tasks to assess risky decision-making (DMT and BART) have also suggested higher impulsivity in the MA group. When choosing experimental gamble, experienced users exhibited lower PFC activation when the reward was high but higher parietal activation when the probability was high, suggesting that they were more attracted by the availability of reward rather than the

Table 9
Tasks Performed.

Task	Description	Cognitive Domain
Grooved Pegboard	Subjects are asked to insert pegs in small holes angled in different directions. Performance is measured by RT.	Psychomotor
Timed Gait	Subjects are asked to walk in a straight line for a defined distance. Performance is measured by RT.	Psychomotor
One-Back Cued Response Task	Subject are asked to respond whenever 'X' follows 'A'. Performance is measured by RT and accuracy.	Working Memory
One-Back Task	Subject are asked to respond when two targets in sequence are identical. Performance is measured by RT and accuracy.	Working Memory
Two Back Task	Subject are asked to respond when the current target is the same as the target that appeared two back in the sequence. Performance is measured by RT and accuracy.	Working Memory
One-Increment Task	Subject are asked to respond when two numbers are in ascending sequence. Performance is measured by RT and accuracy.	Working Memory
One Card Learning	A card is presented face up in the center of the screen. Subjects must decide whether they have seen the card before. Performance is measured by accuracy.	Working Memory
Rey Auditory Verbal Learning Task (RAVLT)	Subjects are required to learn and recall lists of unrelated words immediately, after a time delay, and after a distractor. Performance is measured by accuracy.	Working Memory
Repeated Memory Test	The task presents words and drawings for 1 second each. Subjects are asked to perform unrelated tasks to distract them, and then they will be tested for recall and recognition. Performance is measured by accuracy.	Working Memory
International Shopping List	Subjects are asked to read a shopping list and to remember as many items as they can. Performance is measured by accuracy.	Working Memory
Continuous Paired Association Learning	A picture is presented in the centre of the screen surrounded by several pictures, one of them matches the picture in the centre. Next, all the surrounding pictures are covered, showing only the central picture. Subjects must tap on the location where the picture previously appeared. Performance is measured by accuracy.	Working Memory
Groton Maze Learning	A 10 × 10 grid of tiles is presented on the screen. A 28-step pathway is hidden among these tiles. A blue tile indicates the start and a tile with red circles indicates the finish. Subjects must move one step at a time from the start toward the end by touching a tile next to their current location. A green checkmark appears if the correct move is made, and a red cross is revealed if the move is incorrect. Once completed, they are returned to the start location to repeat the test and must try to remember the pathway they have just completed. Performance is measured by accuracy.	Working Memory
Symbol Digit Modalities	Subjects are asked to identify the number associated with each one of the symbols arranged randomly in a row. Performance is measured by accuracy.	Attention
Auditory Continuous Performance Task (CPT)	The task presents tones every 2 seconds, and subjects are required to respond to the target tones (high pitch) that are presented within a sequence of distracting tones (lower pitch). Performance is measured by RT and accuracy	Attention
Stroop Task (Word)	In each trial, task displays a word (name of a colour), tinted with the colour of the word itself (congruent/non-conflict), or with a different colour (incongruent/conflict). The conflict occurs when the colour does not match the word; naming a colour takes longer than reading a word. Performance is measured by the Stroop effect (RT from incongruent trials – RT from congruent trials) or the Stroop interference (RT from incongruent trials – RT from neutral trials). The higher the Stroop effect or the Stroop interference, the poorer the performance is.	Attention
Spatial Stroop Task	In each trial, task displays a word (UP or DOWN), located at the top or bottom of the screen. The conflict occurs when the word does not match the position (i.e., UP located at the bottom of the screen). Performance measures are identical to the word Stroop task.	Attention
Wisconsin Card Sorting Task (WCST)	The task requires subjects to sort the cards based on colour or shape or number. Subjects are not informed on how to sort the card, but they will get feedback whether it is right or wrong. The rule keeps changing after *n* number of trials. Performance is measured by accuracy.	Cognitive Flexibility
Go/No-Go Task	Subjects are instructed to press the button ('go') when they see some stimuli, and not to press ('no go') when they see a different stimulus. Performance is measured by RT and accuracy.	Inhibitory Control
Iowa Gambling Task (IGT)	Subjects are presented with four decks of cards. Unbeknown to subjects, two decks are the "good" decks, associated with small rewards and low penalties (overall net gain); whereas the other two decks are the "bad" decks, associated with large rewards and high penalties (overall net loss). Performance is measured by net score (number of "good" cards – number of "bad" cards).	Decision-Making (Impulsivity)
Delay Discounting Task (DDT)	In each trial, subjects are given two choices of hypothetical rewards. One offers a smaller reward in a short delay, and the other one offers a larger reward with a longer delay. Performance is measured from *k* value, where a higher value is associated with a higher impulsivity.	Decision-Making (Impulsivity)
Decision-Making Task (DMT)	Subjects are presented with two choices of gamble depicted in histogram, showing the probability ratio of winning ¢X0 or losing ¢Y0 amount of money. One histogram is the control gamble, offering a small amount of money (¢10) with equal chances (50:50) of winning and losing. The other histogram is the experimental gamble, offering a higher amount of money (¢20 or ¢80) with low chance (25:75) or high chance (75:25) of winning. Performance is measured by frequency of experimental gamble and money earned.	Decision-Making (Risk-Taking)
Balloon Analogue Risk Task (BART)	Subjects are given two choices: to pump the balloon or to cash out. With each pump, subject may gain more money ($0.25), or may also gain nothing if the balloon explodes. Performance is measured by number of pumps and money earned.	Decision-Making (Risk-Taking)
Risky Gains Task (RGT)	In each trial, the points are presented in an ascending order (20 – 40 – 80). The task consists of +20, +40, and +80 unpunished trials, and -40 and -80 punished trials, presented in randomized order. Subjects may either respond to take the points on display, or wait for the higher points to appear with the risk of losing more points. For example, on -80 punished trial, subjects can earn the points if they respond to 40, but once 80 is on display, they will lose 80 points. Performance is measured by frequency of risk-taking.	Decision-Making (Risk-Taking)

Abbreviations: RT = reaction time.

magnitude of reward (Koester et al., 2013). Similarly, another study observed a decreased sensitivity (change in activity as a function of risk-taking) of the dorsolateral PFC and increased sensitivity of VS in MA group (Kohno et al., 2014). MA subjects also took fewer risks and earned less money than controls. The authors argued that the activation of dorsolateral PFC was responsible for the selection of large, long-term reward despite incurring small immediate losses, while the activation of VS led to the selection of short-term reward, hence resulting in the lower risk-taking observed in MA subjects.

Dopamine has long been thought to play a significant role in impulsivity. It has been proposed that reward-directed behavior is regulated by the balance between cortical and striatal dopamine levels, as

PFC dopamine promotes cognitive stability, while striatal dopamine promotes cognitive flexibility (Cools, 2008). Increasing dopamine level in the PFC has been reported to reduce impulsivity in healthy subjects performing the DDT (Kayser et al., 2012). On the contrary, greater striatal dopamine transporter availability was associated with higher impulsivity in healthy individuals (Costa et al., 2013). In addition, impulsivity in MA-dependent subjects seems to be mediated by dopamine D2 receptors (autoreceptors), which regulate the release and uptake of dopamine (Ford, 2014; Kohno et al., 2016). Lower dopamine D2 receptor availability in the striatum has been observed in MA users and has been associated with higher impulsivity (Kohno et al., 2016; Lee et al., 2009; Volkow et al., 2001a).

4.3. Disparities and absence of findings

Five studies in this review reported no correlation between brain measures and behavioral performance. The absence of a brain-behavior correlation may simply mean there is no correlation between the region of interest and the behavior studied. One study failed to find a correlation between number of errors on the WCST and glucose metabolism in the left frontal WM (the region of significant group difference) (Y. T. Kim et al., 2009b), while it has been reported to be associated with the right frontal WM (Kim et al., 2005). Another possible reason is the small sample size. Salo et al., (2009b) failed to observe a significant correlation between RT on the Stroop task and PFC activation. However, with a larger sample size (including subjects from the previous study), a negative correlation was observed in the subsequent study (Salo et al., 2013). Poor task design can also contribute to the lack of correlation. Koester et al. (2013), who also did not find a correlation between neuronal activation and behavioral performance in their study, argued that "*the paradigm at hand was potentially not specific enough in a way that the gap between risky choices and safe choices was too big*". Appropriate identification of an objective behavioral measure is also critical. For example, money earned and regional activation may not reflect a brain-behavior relationship (Kohno et al., 2014). Lastly, segmentation techniques may also play a significant role. Using an automatic extraction method, one study failed to observe a correlation between hippocampal volume and memory performance (Du et al., 2015). However, an early study using a manual tracing technique has observed a group difference in hippocampal volume as well as a positive correlation with performance on memory task (Thompson et al., 2004).

In most studies, a positive association was observed between task performance and brain measure. However, four studies have reported the opposite, where increased metabolism and activation were associated with poorer performance. One study observed a negative correlation between change in glucose metabolism and change in performance after retest (one week versus four weeks later) (Berman et al., 2008). The correlation emerged from a decline in performance, accompanied by increased metabolism in the parietal cortex, which may be attributed to reactive gliosis that occurred after the first week of abstinence. One study observed a negative correlation between RT adjustment between trials on the Stroop task and PFC activation in MA group, with a trend for positive correlation in control group (Salo et al., 2013). The authors suggested that, while control subjects activated the PFC in response to RT adjustments, MA subjects failed to activate the PFC in order to sustain adaptive trial-to-trial RT adjustments. The other two studies reported regional activation associated with poorer performance on impulsivity task (higher impulsivity) (Bischoff-Grethe et al., 2017; Hoffman et al., 2008). The latter cases are commonly observed in functional imaging, where one task can activate several regions (task-positive network) and deactivate other regions (task-negative network) (Cabeza and Nyberg, 2000; Fox et al., 2005).

Lastly, not all studies observed differences between MA and control groups in both brain measure and behavioral performance. Comparable performance between groups has been observed with significant group differences in brain measures. On one hand, normal performance in MA group may be a result of compensatory responses of the brain (striatal enlargement) to maintain function (Chang et al., 2005; Jan et al., 2012b). On the other hand, the task may be too easy (spatial Stroop task) (Salo et al., 2011) or lack the sensitivity to detect a behavioral difference between two similar groups (relapsed versus non-relapsed subjects) (Gowin et al., 2014a). Interestingly, one study has reported a group difference in performance but not in the brain measure (Salo et al., 2009a). In this case, it appears that the region of interest (CC) might not best represent the cognitive function measured by the task (Stroop task).

4.4. Limitations of the review

The current article summarized brain-behavior correlations from different imaging modalities which measured different properties. This review was not designed to directly compare the regions of interest between studies, and hence readers are advised to treat the imaging results as relevant data rather than the main findings.

Second, the effect of comorbid cigarette smoking, which is highly prevalent in MA subjects, cannot be ruled out as a potential confounder. Nicotine withdrawal during scanning may lead to confounding results, and to avoid this, some studies allowed subjects to smoke on the day of scanning (Hoffman et al., 2008; Kim et al., 2005; London et al., 2005). Chronic cigarette smoking may also partially contribute to GM deficits observed in the PFC, ACC, and caudate (Brody et al., 2004; Fritz et al., 2014; Morales et al., 2012). To account for this, some studies used smoking status as a covariate, while others did post-hoc analysis on smoker versus non-smoker MA subjects. However, half of the studies did not report smoking status, and none of the studies provided the duration of abstinence from nicotine.

Third, multiple studies with overlapping samples may lead to potential bias. Findings across studies may seem consistent when, in fact, were attributed to the same subjects, only scanned for different measures. For example, the right frontal WM was found to correlate positively with WCST performance in two studies with partially overlapping subjects, one using DTI and the other one using MRI (Chung et al., 2007; Kim et al., 2005). Multiple studies from the same authors may also be subject to bias, as they often focused on specific regions of interest based on findings from their previous studies.

Finally, despite our objective to review brain-behavior relationship in individuals with MA use history, we did not take into consideration the correlation with MA use parameters, e.g., cumulative dose, years of use, length of abstinence, etc. In fact, only three studies actually observed significant correlations between brain measures and MA use, as well as between brain measure and performance (Chang et al., 2005; Gowin et al., 2014b; Schwartz et al., 2010). Two-thirds of the studies did not report regression analyses between MA use parameters and brain measures or performance. And several studies, despite reporting significant correlations between brain measures and task performance, failed to observe any correlation between brain measure and MA use parameters (Chang et al., 2002; Jan et al., 2012b; Kim et al., 2016). Therefore, caution is advised when interpreting the findings in this review as MA-related.

5. Conclusions

Recent studies have provided some evidence for altered cognitive function in MA users in several domains, notably in cognitive control and decision-making. Consistent correlations have also been observed between performance on these functions and brain measures in some regions, particularly in the ACC, PFC, and striatum. Future research that investigates the relationship between the brain-behavior data and MA use parameters is essential to identify regions that are more vulnerable to the neurotoxic effects of MA and, at the same time, rule out the findings unrelated to MA use, and is, therefore, strongly encouraged.

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Contributors

SS: Performed the systematic search, article retrieval, screening and analysis of the review. Also, was the lead author to write the manuscript. Approved the final version of the manuscript.

GYW: Was involved in drafting the objectives of the review, analysis, interpretation of results and writing of the manuscript. Approved the final version of the manuscript.

JCL: Was involved in the analysis, interpretation of results and writing of the manuscript. Approved the final version of the manuscript.

IK: Was involved in the conception of the review, the interpretation of results and writing of the manuscript. Approved the final version of the manuscript.

LEC: Was involved in the conception of the review, assisted with the article screening and analysis and interpretation of results. Was also involved in the writing of the manuscript and approved the final version.

Conflict of interest

No conflict declared

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References

Alicata, D., Chang, L., Cloak, C., Abe, K., Ernst, T., 2009. Higher diffusion in striatum and lower fractional anisotropy in white matter of methamphetamine users. Psychiatry Res. 174, 1–8. https://doi.org/10.1016/j.pscychresns.2009.03.011.

Berman, S.M., Voytek, B., Mandelkern, M.A., Hassid, B.D., Isaacson, A., Monterosso, J., Miotto, K., Ling, W., London, E.D., 2008. Changes in cerebral glucose metabolism during early abstinence from chronic methamphetamine abuse. Mol. Psychiatry 13, 897–908. https://doi.org/10.1038/sj.mp.4002107.

Bischoff-Grethe, A., Connolly, C.G., Jordan, S.J., Brown, G.G., Paulus, M.P., Tapert, S.F., Heaton, R.K., Woods, S.P., Grant, I., 2017. Altered reward expectancy in individuals with recent methamphetamine dependence. J. Psychopharmacol. (Oxford) 31, 17–30. https://doi.org/10.1177/0269881116668590.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychol. Rev. 108 (3), 624–652. https://doi.org/10.1037/0033-295X.108.3.624.

Brody, A.L., Mandelkern, M.A., Jarvik, M.E., Lee, G.S., Smith, E.C., Huang, J.C., Bota, R.G., Bartzokis, G., London, E.D., 2004. Differences between smokers and non-smokers in regional gray matter volumes and densities. Biol. Psychiatry 55, 77–84.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J. Cogn. Neurosci. 12, 1–47.

Chang, L., Cloak, C., Patterson, K., Grob, C., Miller, E.N., Ernst, T., 2005. Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. Biol. Psychiatry 57, 967–974. https://doi.org/10.1016/j.biopsych.2005.01.039.

Chang, L., Ernst, T., Speck, O., Patel, H., DeSilva, M., Leonido-Yee, M., Miller, E.N., 2002. Perfusion MRI and computerized cognitive test abnormalities in abstinent methamphetamine users. Psychiatry Res. 114, 65–79. https://doi.org/10.1016/S0925-4927(02)00004-5.

Cherner, M., Suarez, P., Casey, C., Deiss, R., Letendre, S., Marcotte, T., Vaida, F., Atkinson, J.H., Grant, I., Heaton, R.K., 2010. Methamphetamine use parameters do not predict neuropsychological impairment in currently abstinent dependent adults. Drug Alcohol Depend. 106, 154–163. https://doi.org/10.1016/j.drugalcdep.2009.08.010.

Chung, A., Lyoo, I.K., Kim, S.J., Hwang, J., Bae, S.C., Sung, Y.H., Sim, M.E., Song, I.C., Kim, J., Chang, K.H., Renshaw, P.F., 2007. Decreased frontal white-matter integrity in abstinent methamphetamine abusers. Int. J. Neuropsychopharmacol. 10, 765–775. https://doi.org/10.1017/S1461145706007395.

Cohen, J.D., 2017. The Basics of Cognitive Control: Core Constructs and Current Considerations. Wiley Handb. Cogn. Control, pp. 3–28.

Cools, R., 2008. Role of dopamine in the motivational and cognitive control of behavior. Neuroscientist 14, 381–395. https://doi.org/10.1177/1073858408317009.

Costa, A., la Fougère, C., Pogarell, O., Möller, H.J., Riedel, M., Ettinger, U., 2013. Impulsivity is related to striatal dopamine transporter availability in healthy males. Psychiatry Res. 211, 251–256. https://doi.org/10.1016/j.pscychresns.2012.07.011.

Dean, A.C., Groman, S.M., Morales, A.M., London, E.D., 2013. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology 38, 259–274. https://doi.org/10.1038/npp.2012.179.

Du, J., Quan, M., Zhuang, W., Zhong, N., Jiang, H., Kennedy, D.N., Harrington, A., Ziedonis, D., Fan, X., Zhao, M., 2015. Hippocampal volume reduction in female but not male recent abstinent methamphetamine users. Behav. Brain Res. 289, 78–83. https://doi.org/10.1016/j.bbr.2015.04.033.

Ernst, T., Chang, L., Leonido–Yee, M., Speck, O., 2000. Evidence for long-term neurotoxicity associated with methamphetamine abuse. Neurology 54, 1344 LP–1349.

Ford, C.P., 2014. The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. Neuroscience 282, 13–22. https://doi.org/10.1016/j.neuroscience.2014.01.025.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673 LP–9678.

Fritz, H.-C., Wittfeld, K., Schmidt, C.O., Domin, M., Grabe, H.J., Hegenscheid, K., Hosten, N., Lotze, M., 2014. Current smoking and reduced gray matter volume — a voxel-based morphometry study. Neuropsychopharmacology 39, 2594.

Gowin, J.L., Harlé, K.M., Stewart, J.L., Wittmann, M., Tapert, S.F., Paulus, M.P., 2014a. Attenuated insular processing during risk predicts relapse in early abstinent methamphetamine-dependent individuals. Neuropsychopharmacology 39, 1379–1387. https://doi.org/10.1038/npp.2013.333.

Gowin, J.L., Stewart, J.L., May, A.C., Ball, T.M., Wittmann, M., Tapert, S.F., Paulus, M.P., 2014b. Altered cingulate and insular cortex activation during risk-taking in methamphetamine dependence: losses lose impact. Addiction 109, 237–247. https://doi.org/10.1111/add.12354.

Groman, S.M., Lee, B., Seu, E., James, A.S., Feiler, K., Mandelkern, M.A., London, E.D., Jentsch, J.D., 2012. Dysregulation of D2-mediated dopamine transmission in monkeys after chronic escalating methamphetamine exposure. J. Neurosci. 32, 5843–5852. https://doi.org/10.1523/JNEUROSCI.0029-12.2012.

Hart, C.L., Marvin, C.B., Silver, R., Smith, E.E., 2012. Is cognitive functioning impaired in methamphetamine users? A critical review. Neuropsychopharmacology 37, 586–608. https://doi.org/10.1038/npp.2011.276.

Hester, R., Lubman, D.I., Yucel, M., 2010. The role of executive control in human drug addiction. Curr. Top. Behav. Neurosci. 3, 301–318. https://doi.org/10.1007/7854_2009_28.

Hoffman, W.F., Schwartz, D.L., Huckans, M.S., McFarland, B.H., Meiri, G., Stevens, A.A., Mitchell, S.H., 2008. Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. Psychopharmacology (Berl.) 201, 183–193. https://doi.org/10.1007/s00213-008-1261-1.

Jan, R.K., Kydd, R.R., Russell, B.R., 2012a. Functional and structural brain changes associated with methamphetamine abuse. Brain Sci. 2, 434–482. https://doi.org/10.3390/brainsci2040434.

Jan, R.K., Lin, J.C., Miles, S.W., Kydd, R.R., Russell, B.R., 2012b. Striatal volume increases in active methamphetamine-dependent individuals and correlation with cognitive performance. Brain Sci. 2, 553–572. https://doi.org/10.3390/brainsci2040553.

Jernigan, T.L., Gamst, A.C., Archibald, S.L., Fennema-Notestine, C., Mindt, M.R., Marcotte, T.L., Heaton, R.K., Ellis, R.J., Grant, I., 2005. Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am. J. Psychiatry 162, 1461–1472. https://doi.org/10.1176/appi.ajp.162.8.1461.

Kalechstein, A.D., Newton, T.F., Green, M., 2003. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. J. Neuropsychiatry Clin. Neurosci. 15, 215–220. https://doi.org/10.1176/jnp.15.2.215.

Kamei, H., Nagai, T., Nakano, H., Togan, Y., Takayanagi, M., Takahashi, K., Kobayashi, K., Yoshida, S., Maeda, K., Takuma, K., Nabeshima, T., Yamada, K., 2006. Repeated methamphetamine treatment impairs recognition memory through a failure of novelty-induced ERK1/2 activation in the prefrontal cortex of mice. Biol. Psychiatry 59, 75–84. https://doi.org/10.1016/j.biopsych.2005.06.006.

Kayser, A.S., Allen, D.C., Navarro-Cebrian, A., Mitchell, J.M., Fields, H.L., 2012. Dopamine, corticostriatal connectivity, and intertemporal choice. J. Neurosci. 32, 9402–9409. https://doi.org/10.1523/JNEUROSCI.1180-12.2012.

Kim, I.S., Kim, Y.T., Song, H.J., Lee, J.J., Kwon, D.H., Lee, H.J., Kim, M.N., Yoo, D.S., Chang, Y., 2009a. Reduced corpus callosum white matter microstructural integrity revealed by diffusion tensor eigenvalues in abstinent methamphetamine addicts. Neurotoxicology 30, 209–213. https://doi.org/10.1016/j.neuro.2008.12.002.

Kim, J.E., Kim, G.H., Hwang, J., Kim, J.Y., Renshaw, P.F., Yurgelun-Todd, D.A., Kim, B., Kang, I., Jeon, S., Ma, J., Lyoo, I.K., Yoon, S., 2016. Metabolic alterations in the anterior cingulate cortex and related cognitive deficits in late adolescent methamphetamine users. Addict. Biol. https://doi.org/10.1111/adb.12473.

Kim, S.J., Lyoo, I.K., Hwang, J., Chung, A., Hoon Sung, Y., Kim, J., Kwon, D.-H., Chang, K.H., Renshaw, P.F., 2006. Prefrontal grey-matter changes in short-term and long-term abstinent methamphetamine abusers. Int. J. Neuropsychopharmacol. 9, 221–228.

Kim, S.J., Lyoo, I.K., Hwang, J., Sung, Y.H., Lee, H.Y., Lee, D.S., Jeong, D.U., Renshaw, P.F., 2005. Frontal glucose hypometabolism in abstinent methamphetamine users. Neuropsychopharmacology 30, 1383–1391. https://doi.org/10.1038/sj.npp.1300699.

Kim, Y.T., Lee, S.W., Kwon, D.H., Seo, J.H., Ahn, B.C., Lee, J., 2009b. Dose-dependent frontal hypometabolism on FDG-PET in methamphetamine abusers. J. Psychiatr. Res. 43, 1166–1170. https://doi.org/10.1016/j.jpsychires.2009.03.011.

Koester, P., Volz, K.G., Tittgemeyer, M., Wagner, D., Becker, B., Gouzoulis-Mayfrank, E., Daumann, J., 2013. Decision-making in polydrug amphetamine-type stimulant users: an fMRI study. Neuropsychopharmacology 38, 1377–1386. https://doi.org/10.1038/npp.2013.43.

Kohno, M., Morales, A.M., Ghahremani, D.G., Hellemann, G., London, E.D., 2014. Risky

decision making, prefrontal cortex, and mesocorticolimbic functional connectivity in methamphetamine dependence. JAMA Psychiatry 71, 812–820. https://doi.org/10.1001/jamapsychiatry.2014.399.

Kohno, M., Okita, K., Morales, A.M., Robertson, C.L., Dean, A.C., Ghahremani, D.G., Sabb, F.W., Rawson, R.A., Mandelkern, M.A., Bilder, R.M., London, E.D., 2016. Midbrain functional connectivity and ventral striatal dopamine D2-type receptors: link to impulsivity in methamphetamine users. Mol. Psychiatry 21, 1554–1560. https://doi.org/10.1038/mp.2015.223.

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3, 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8.

Lee, B., London, E.D., Poldrack, R.A., Farahi, J., Nacca, A., Monterosso, J.R., Mumford, J.A., Bokarius, A.V., Dahlbom, M., Mukherjee, J., Bilder, R.M., Brody, A.L., Mandelkern, M.A., 2009. Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J. Neurosci. 29, 14734–14740. https://doi.org/10.1523/JNEUROSCI.3765-09.2009.

Leland, D.S., Arce, E., Miller, D.A., Paulus, M.P., 2008. Anterior cingulate cortex and benefit of predictive cueing on response inhibition in stimulant dependent individuals. Biol. Psychiatry 63, 184–190. https://doi.org/10.1016/j.biopsych.2007.04.031.

London, E.D., Berman, S.M., Voytek, B., Simon, S.L., Mandelkern, M.A., Monterosso, J., Thompson, P.M., Brody, A.L., Geaga, J.A., Hong, M.S., Hayashi, K.M., Rawson, R.A., Ling, W., 2005. Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. Biol. Psychiatry 58, 770–778. https://doi.org/10.1016/j.biopsych.2005.04.039.

MacDonald, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science (80-) 288, 1835–1838.

McCann, U.D., Wong, D.F., Yokoi, F., Villemagne, V., Dannals, R.F., Ricaurte, G.A., 1998. Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. J. Neurosci. 18, 8417–8422.

Mizoguchi, H., Ibi, D., Takase, F., Nagai, T., Kamei, H., Toth, E., Sato, J., Takuma, K., Yamada, K., 2011. Nicotine ameliorates impairment of working memory in methamphetamine-treated rats. Behav. Brain Res. 220, 159–163. https://doi.org/10.1016/j.bbr.2011.01.036.

Moffett, J.R., Ross, B., Arun, P., Madhavarao, C.N., Namboodiri, A.M.A., 2007. N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog. Neurobiol. 81, 89–131. https://doi.org/10.1016/j.pneurobio.2006.12.003.

Monterosso, J.R., Ainslle, G., Xu, J., Cordova, X., Domier, C.P., London, E.D., 2007. Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. Hum. Brain Mapp. 28, 383–393. https://doi.org/10.1002/hbm.20281.

Morales, A.M., Lee, B., Hellemann, G., O'Neill, J., London, E.D., 2012. Gray-matter volume in methamphetamine dependence: cigarette smoking and changes with abstinence from methamphetamine. Drug Alcohol Depend. 125, 230–238. https://doi.org/10.1016/j.drugalcdep.2012.02.017.

Nagai, T., Takuma, K., Dohniwa, M., Ibi, D., Mizoguchi, H., Kamei, H., Nabeshima, T., Yamada, K., 2007. Repeated methamphetamine treatment impairs spatial working memory in rats: reversal by clozapine but not haloperidol. Psychopharmacology (Berl.) 194, 21–32. https://doi.org/10.1007/s00213-007-0820-1.

Nakama, H., Chang, L., Fein, G., Shimotsu, R., Jiang, C.S., Ernst, T., 2011. Methamphetamine users show greater than normal age-related cortical gray matter loss. Addiction 106, 1474–1483. https://doi.org/10.1111/j.1360-0443.2011.03433.x.

Nestor, L.J., Ghahremani, D.G., Monterosso, J., London, E.D., 2011. Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. Psychiatry Res. 194, 287–295. https://doi.org/10.1016/j.pscychresns.2011.04.010.

Noda, Y., Mouri, A., Ando, Y., Waki, Y., Yamada, S.N., Yoshimi, A., Yamada, K., Ozaki, N., Wang, D., Nabeshima, T., 2010. Galantamine ameliorates the impairment of recognition memory in mice repeatedly treated with methamphetamine: involvement of allosteric potentiation of nicotinic acetylcholine receptors and dopaminergic-ERK1/2 systems. Int. J. Neuropsychopharmacol. 13, 1343–1354. https://doi.org/10.1017/S1461145710000222.

Nordahl, T.E., Salo, R., Possin, K., Gibson, D.R., Flynn, N., Leamon, M., Galloway, G.P., Pfefferbaum, A., Spielman, D.M., Adalsteinsson, E., Sullivan, E.V., 2002. Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine-dependent subjects: a preliminary proton MRS study. Psychiatry Res. 116, 43–52. https://doi.org/10.1016/S0925-4927(02)00088-4.

Paulus, M.P., Hozack, N., Frank, L., Brown, G.G., Schuckit, M.A., 2003. Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. Biol. Psychiatry 53, 65–74. https://doi.org/10.1016/S0006-3223(02)01442-7.

Rendell, P.G., Mazur, M., Henry, J.D., 2009. Prospective memory impairment in former users of methamphetamine. Psychopharmacology (Berl.) 203, 609–616. https://doi.org/10.1007/s00213-008-1408-0.

Sailasuta, N., Abulseoud, O., Hernandez, M., Haghani, P., Ross, B.D., 2010. Metabolic abnormalities in abstinent methamphetamine dependent subjects. Subst. Abus. Res. Treat. 4, 9–20.

Salo, R., Fassbender, C., 2012. In: Carter, C.S., Dalley, J.W. (Eds.), Structural, Functional and Spectroscopic MRI Studies of Methamphetamine Addiction BT - Brain Imaging in Behavioral Neuroscience. Springer, Berlin Heidelberg, Berlin, Heidelberg, pp. 321–364. https://doi.org/10.1007/7854_2011_172.

Salo, R., Fassbender, C., Buonocore, M.H., Ursu, S., 2013. Behavioral regulation in methamphetamine abusers: an fMRI study. Psychiatry Res. 211, 234–238. https://doi.org/10.1016/j.pscychresns.2012.10.003.

Salo, R., Nordahl, T.E., Buonocore, M.H., Natsuaki, Y., Waters, C., Moore, C.D., Galloway, G.P., Leamon, M.H., 2009a. Cognitive control and white matter callosal microstructure in methamphetamine-dependent subjects: a diffusion tensor imaging study. Biol. Psychiatry 65, 122–128. https://doi.org/10.1016/j.biopsych.2008.08.004.

Salo, R., Nordahl, T.E., Buonocore, M.H., Natsuaki, Y.T., Moore, C.D., Waters, C., Leamon, M.H., 2011. Spatial inhibition and the visual cortex: a magnetic resonance spectroscopy imaging study. Neuropsychologia 49, 830–838. https://doi.org/10.1016/j.neuropsychologia.2011.01.014.

Salo, R., Nordahl, T.E., Natsuaki, Y., Leamon, M.H., Galloway, G.P., Waters, C., Moore, C.D., Buonocore, M.H., 2007. Attentional control and brain metabolite levels in methamphetamine abusers. Biol. Psychiatry 61, 1272–1280. https://doi.org/10.1016/j.biopsych.2006.07.031.

Salo, R., Ursu, S., Buonocore, M.H., Leamon, M.H., Carter, C., 2009b. Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. Biol. Psychiatry 65, 706–709. https://doi.org/10.1016/j.biopsych.2008.11.026.

Schoenbaum, G., Roesch, M.R., Stalnaker, T.A., 2006. Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci. 29, 116–124. https://doi.org/10.1016/j.tins.2005.12.006.

Schwartz, D.L., Mitchell, A.D., Lahna, D.L., Luber, H.S., Huckans, M.S., Mitchell, S.H., Hoffman, W.F., 2010. Global and local morphometric differences in recently abstinent methamphetamine-dependent individuals. Neuroimage 50, 1392–1401. https://doi.org/10.1016/j.neuroimage.2010.01.056.

Sekine, Y., Iyo, M., Ouchi, Y., Matsunaga, T., Tsukada, H., Okada, H., Yoshikawa, E., Futatsubashi, M., Takei, N., Mori, N., 2001. Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. Am. J. Psychiatry 158, 1206–1214. https://doi.org/10.1176/appi.ajp.158.8.1206.

Sekine, Y., Ouchi, Y., Takei, N., et al., 2006. Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. Arch. Gen. Psychiatry 63, 90–100.

Simon, S.L., Domier, C., Carnell, J., Brethren, P., Rawson, R., Ling, W., Brethen, P., 2000. Cognitive impairment in methamphetamine. Am. J. Addict. 9, 222–231. https://doi.org/10.1080/10550490050148053.

Stewart, J.L., May, A.C., Poppa, T., Davenport, P.W., Tapert, S.F., Paulus, M.P., 2014. You are the danger: attenuated insula response in methamphetamine users during aversive interoceptive decision-making. Drug Alcohol Depend. 142, 110–119. https://doi.org/10.1016/j.drugalcdep.2014.06.003.

Suckling, J., Nestor, L.J., 2017. The neurobiology of addiction: the perspective from magnetic resonance imaging present and future. Addiction 112, 360–369. https://doi.org/10.1111/add.13474.

Sullivan, E.V., Adalsteinsson, E., Spielman, D.M., Hurd, R.E., Pfefferbaum, A., 2001. N-acetylaspartate–a marker of neuronal integrity. Ann. Neurol. 50, 823.

Thompson, P.M., Hayashi, K.M., Simon, S.L., Geaga, J.A., Hong, M.S., Sui, Y., Lee, J.Y., Toga, A.W., Ling, W., London, E.D., 2004. Structural abnormalities in the brains of human subjects who use methamphetamine. J. Neurosci. 24, 6028 LP–6036.

Tobias, M.C., O'Neill, J., Hudkins, M., Bartzokis, G., Dean, A.C., London, E.D., 2010. White-matter abnormalities in brain during early abstinence from methamphetamine abuse. Psychopharmacology (Berl.) 209, 13–24. https://doi.org/10.1007/s00213-009-1761-7.

Toomey, R., Lyons, M.J., Eisen, S., Xian, H., Chantarujikapong, S., Seidman, L.J., Faraone, S.V., Tsuang, M.T., 2003. A twin study of the neuropsychological consequence of stimulant abuse. Arch. Gen. Psychiatry 60, 303–310.

United Nations Office on Drugs and Crime, 2017a. World Drug Report 2017. Global Overview of Drug Demand and Supply: Latest Trends, Cross-cutting Issues. . https://www.unodc.org/wdr2017/field/Booklet_2_HEALTH.pdf.

United Nations Office on Drugs and Crime, 2017b. World Drug Report 2017. Market Analysis of Synthetic Drugs: Amphetamine-type Stimulants, New Psychoactive Substances. . https://www.unodc.org/wdr2017/field/Booklet_4_ATSNPS.pdf.

Verdejo-García, A., Pérez-García, M., Bechara, A., 2006. Emotion, decision-making and substance dependence: a somatic-marker model of addiction. Curr. Neuropharmacol. 4, 17–31.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C., Pappas, N., 2001a. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am. J. Psychiatry 158, 2015–2021. https://doi.org/10.1176/appi.ajp.158.12.2015.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Franceschi, D., Sedler, M.J., Gatley, S.J., Hitzemann, R., Ding, Y.S., Wong, C., Logan, J., 2001b. Higher cortical and lower subcortical metabolism in detoxified methamphetamine abusers. Am. J. Psychiatry 158, 383–389. https://doi.org/10.1176/appi.ajp.158.3.383.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Leonido-Yee, M., Franceschi, D., Sedler, M.J., Gatley, S.J., Hitzemann, R., Ding, Y.S., Logan, J., Wong, C., Miller, E.N., 2001c. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am. J. Psychiatry 158, 377–382. https://doi.org/10.1176/appi.ajp.158.3.377.

Wang, G.J., Volkow, N.D., Chang, L., Miller, E., Sedler, M., Hitzemann, R., Zhu, W., Logan, J., Ma, Y., Fowler, J.S., 2004. Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. Am. J. Psychiatry 161, 242–248. https://doi.org/10.1176/appi.ajp.161.2.242.