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Structural, functional, and neurochemical neuroimaging of methamphetamine-associated psychosis: A systematic review

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ABSTRACT

Methamphetamine is a highly addictive psychostimulant. A subset of methamphetamine users develops methamphetamine-associated psychosis (MAP), which causes poorer prognoses and cognitive function than those with no psychosis (MNP). Comprehensive and integrative summaries of studies utilizing various neuroimaging modalities (structural, functional, and neurochemical) are limited. We conducted a systematic review of literature regarding clinical neuroimaging research published between January 1988 and July 2018 using the PubMed, Web of Science, Scopus, and ScienceDirect databases. Studies comparing the neuroimaging of patients with MAP with healthy controls or patients with MNP or schizophrenia were included to understand the distinct profiles associated with MAP. A total of six structural, three functional, and three neurochemical studies were reviewed. A general trend was identified that showed MAP-related brain alterations were mainly in the frontal lobe (especially the orbitofrontal cortex), striatum, and limbic systems (amygdala and hippocampus). Furthermore, some clinical manifestations, such as the severity of psychotic symptoms and cognitive performance, were correlated with neuroimaging abnormalities. In summary, distinct structural, functional, and neurochemical changes, especially in the frontostriatal circuit and network dynamic systems, play critical roles in the pathophysiology of MAP. Future studies using longitudinal study designs and including individuals with MNP and schizophrenia as controls are warranted.

1. Introduction

Amphetamine and its N-methylated derivative methamphetamine are psychostimulants that share a resemblance in chemical structures and pharmacokinetic properties (Melega et al., 1995). However, with an N-methyl group that decreases the polarity of the compound, methamphetamine has longer lasting and more potent effects and is associated with higher rates of abuse compared to amphetamine (Goodwin et al., 2009; Volkow Nora, 2006). Methamphetamine abuse has been escalating worldwide, causing harms to individuals and societies (Darke et al., 2008; Goodwin et al., 2009; Huang et al., 2016; Marshall andWerb, 2010; Melega et al., 1995; Nicosia et al., 2009; Volkow Nora, 2006). Almost one-third of methamphetamine users develop psychotic symptoms, including persecutory delusions, paranoid ideations, and auditory and visual hallucinations (McKetin et al., 2006). Methamphetamine-associated psychosis (MAP) has been associated with poor prognoses resulting from several adverse consequences, which include a high likelihood of comorbidity with psychiatric disorders, such as affective disorders and obsessive–compulsive disorder (Chen et al., 2003; Eslami-Shahrbabaki et al., 2015). Patients with MAP also have increased risks of suicide and violence (Glasner-Edwards et al., 2008; McKetin et al., 2014), lower daily functional ability, and worse cognitive function when compared with those using methamphetamines but with no psychosis (MNP) or those with alcohol dependence (Henry et al., 2010; Lin et al., 2010). The prevalence of psychotic symptoms resulting from methamphetamine use ranges from 10% to 60% (Hsieh et al., 2014), suggesting that there might be unique neurobiological dysregulations in individuals suffering from MAP. However, the characteristics of neurobiological alterations in MAP are not entirely clear in the existing literature.

It has been long recognized that MAP symptoms are similar to those of schizophrenia. Such similarity makes it difficult for clinicians to

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distinguish these two disease entities, particularly because of the similar positive symptom manifestations and neurocognitive functioning (Glasner-Edwards andMooney, 2014; Hsieh et al., 2014). Such similarities indicate a possible overlap in the pathophysiology of MAP and schizophrenia (Hsieh et al., 2014; Medhus et al., 2013; Srisurapanont et al., 2011). Previous animal studies have demonstrated that MAP could be used as a pharmacological model of schizophrenia . Despite abundant clinical and preclinical evidence supporting the link between MAP and schizophrenia, the similarities and differences in the neurobiologic manifestations of these two disorders have not been confirmed.

With the advancements in data acquisition and analytical methods, the information obtained from neuroimaging has greatly improved. These noninvasive techniques can detect structural, functional, and neurochemical brain alterations, which enable comprehensive assessments and investigations into psychiatric disorders, such as MAP (Dager et al., 2008; Lee et al., 2013; Nader et al., 2008; Nortje et al., 2013), ultimately optimizing MAP therapeutic strategies and reducing the risks of unfavorable outcomes. Studies increasingly apply neuroimaging methods to examine MAP; however, no comprehensive summaries of these results have been generated. More focused and concise studies could be designed and conducted if the available findings were thoroughly summarized. Therefore, we systematically reviewed the results of currently available studies that have compared the neuroimaging of patients with MAP with healthy controls or patients with MNP or schizophrenia to understand the differences of profiles associated with MAP. Studies using various modalities, including structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET), were considered.

2. Methods

2.1. Literature search and eligibility criteria

PRISMA 2009 checklist for systematic review was utilized in this study (Moher et al., 2009). The literature search for MAP neuroimaging studies used the string “(methamphetamine AND psychosis) AND (gray matter OR morphometry OR voxel-based morphometry (VBM) OR volume OR white matter OR DTI OR magnetic resonance spectroscopy OR MRS OR functional MRI OR resting state)”. The final search of PubMed, Web of Science, Scopus, and ScienceDirect databases was conducted on July 25, 2018. Studies published between 1988 and 2018 were included. Studies were excluded if they were not published in English, were review articles or poster abstracts, used nonhuman subjects, or largely overlapped cohorts with similar methods. In addition, those that did not provided a clear specification of psychosis related to methamphetamine use were also excluded.

2.2. Study selection and data extraction

Duplicate articles were automatically detected and removed using Endnote. CC and FCH screened titles, abstracts, and full texts according to the eligibility criteria. A flow chart of article selection is illustrated in Fig. 1. The following information was extracted from each study: name of first author, publication date, participant number in each group, data acquisition and analysis parameters, magnetic field strength, and main findings.

3. Results

3.1. Study identification

The study identification process of our analysis is demonstrated in Fig. 1. Eleven studies, including six structural, three functional, and three neurochemical studies from 155 potentially relevant articles were included in the systematic review (Aoki et al., 2013; Breen et al., 2017; Fassbender et al., 2015; Hsieh et al., 2014; Ipser et al., 2018; Orikabe et al., 2011; Sekine et al., 2002, 2001; Uhlmann et al., 2016a, 2016b; Zhang et al., 2018). All of the investigations were case-control observational studies (level of evidence – 3b, according to the Oxford Centre for Evidence-based Medicine). Owing to the nature of the neuroimaging studies included in our report, selection and publication bias could not be tested by the commonly-used funnel plot.

3.2. Structural MRI studies

3.2.1. Gray matter structural MRI

It has been shown that there are alterations of gray matter in psychosis among the patients with schizophrenia (Deng et al., 2009). As for the psychosis related with methamphetamine, four studies (Table 1) investigated gray matter alterations in MAP (Aoki et al., 2013; Orikabe et al., 2011; Uhlmann et al., 2016a; Zhang et al., 2018). Three studies suggested that gray matter volume decreased in the frontal or temporal cortices, and one study demonstrated that gray matter volume increased in multiple frontal regions in individuals with MAP. Compared with healthy controls, individuals with MAP exhibited lower volume of the anterior prefrontal/frontopolar (Aoki et al., 2013),inferior frontal, and superior temporal cortices (Uhlmann et al., 2016a); amygdala; and hippocampus (Orikabe et al., 2011), which are the regions related to emotional regulation and impulsivity (Chamberlain et al., 2008; Gopal et al., 2013; Kim et al., 2011; Kim and Lee, 2011). Uhlmann et al. demonstrated negative correlations between the cortical thickness of the inferior frontal cortex, orbital frontal cortex, and inferior temporal gyrus and the Emotion Reactivity Scale and “difficulties in emotion regulation” and “impulse control” subscale scores in patients with MAP (Uhlmann et al., 2016a). Such findings suggest that patients with greater decreases in inferior frontal cortical volumes have higher emotional reactivity and more dysregulated impulsivity. While most studies showed decreased gray matter in different regions in MAP, one study found higher gray matter volume of the anterior cingulate cortex and medial superior frontal cortex in MAP patients (Zhang et al., 2018). A direct comparison of results across studies that enrolled participants with different clinical and demographic characteristics, including sex and age ratios, could be difficult. A previous study showed that age and sex might affect the neuronal abnormalities of methamphetamine users (Cloak et al., 2011). Whether these factors could confound gray matter alterations in individuals with MAP remains unknown. In summary, decreases of gray matter were found in multiple brain regions, including frontal cortex and temporal cortex, in MAP patients. Such alterations in gray matter might be associated with certain characteristics of MAP such as high emotional reactivity and dysregulated impulsivity.

3.2.2. White matter structural MRI

White matter microstructural alterations have been demonstrated in multiple neuropsychiatric disorders (Assaf and Pasternak, 2008). Through DTI, the integrity of white matter can be evaluated by fractional anisotropy (FA) and mean diffusivity (MD), which are indicators of white matter integrity (Basser andPierpaoli, 2011).

We found four studies that compared white matter characteristics (Table 2), either by volume or integrity, between participants with MAP and healthy controls (Aoki et al., 2013; Breen et al., 2017; Orikabe et al., 2011; Uhlmann et al., 2016b). Two studies investigating the same cohorts but using different analytical methods discovered that individuals with MAP have not only lower total white matter volumes but also lower focal orbitofrontal white matter volumes (Aoki et al., 2013; Orikabe et al., 2011). DTI studies regarding MAP have consistently shown widespread microstructural abnormalities and extensive loss of white matter integrity, including elevated MD and decreased FA in extensive white matter regions (Breen et al., 2017; Uhlmann et al., 2016b). Moreover, significant positive correlations between MD levels and negative psychotic symptoms were observed in widespread regions (Uhlmann et al., 2016b). In addition, MD of the right corona radiata is

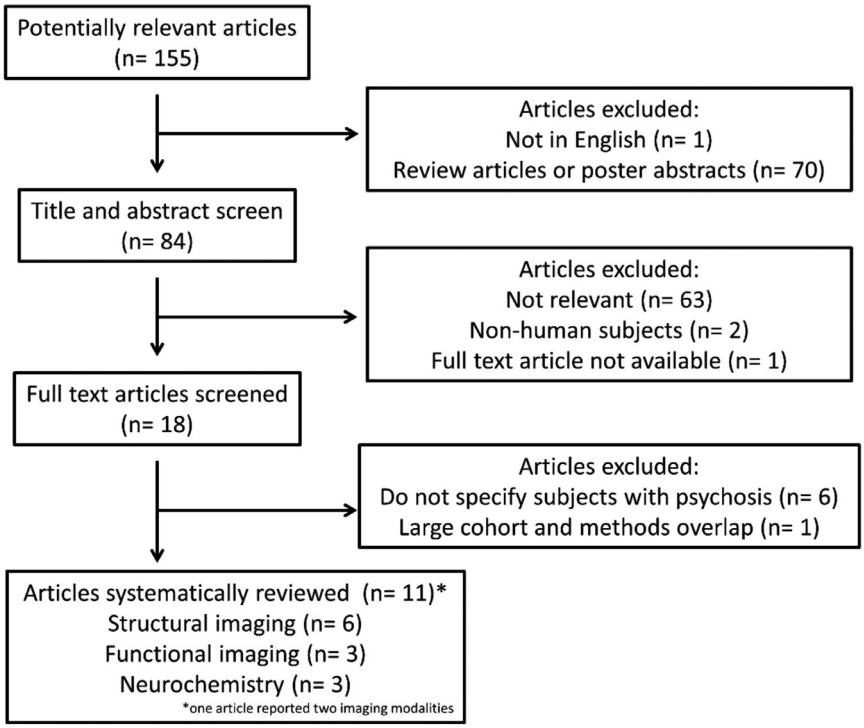

Fig. 1. Flow chart of study selection.

positively associated with two subscale scores of impulsivity (Uhlmann et al., 2016b). In short, not only the volume but also the integrity of white matter was altered in MAP, and the impaired white matter integrity was correlated with negative psychotic symptoms and impulsivity.

3.3. fMRI studies

Regional cerebral blood flow increases during neuronal activation and serves as a functional measurement of the brain (Lewin, 2003). Currently, task and resting-state fMRIs are the two most frequently used paradigms. In resting-state fMRI (rs-fMRI) studies, the synchronized activation of spatially disparate areas, namely, resting-state networks, such as the default mode network (DMN) and central executive network (CEN), can be evaluated (Beckmann et al., 2005; Menon, 2011). In addition, regional homogeneity (ReHo) can be calculated as an indicator of local brain synchronization .

Three fMRI studies related to MAP, one using task fMRI and two using rs-fMRIs, are shown (Table 3) (Fassbender et al., 2015; Ipser et al., 2018; Zhang et al., 2018). In the Stroop task, participants with MAP demonstrated higher intraindividual variability in reaction time compared with healthy controls, suggesting that MAP is associated with increased cognitive instability caused by more frequent lapses in attention, a phenomenon thought to be secondary to DMN intrusions and task-negative networks when performing a task (Fassbender et al., 2015; Liddle et al., 2011). Furthermore, variability and brain activity in the right prefrontal cortex has been observed in individuals with MAP. Ipser et al. found that negative correlations between the DMN and task-positive CEN were less common in patients with MAP compared with normal controls, and this was likely related to frontoparietal deficits (Ipser et al., 2018).

In an rs-fMRI study using ReHo and seed-based analysis, Zhang and colleagues found that individuals with MAP displayed elevated ReHo in the right hippocampus and left orbital inferior frontal gyrus (Zhang et al., 2018). Seed-based analysis in the same study further demonstrated that when using the right medial or superior frontal gyrus as the seed, functional connectivity between the seed and several regions, including the right frontal gyrus, left inferior frontal gyrus, and middle frontal gyrus, was increased. In summary, MAP has been characterized by diminished anticorrelation between the task-positive and task-negative networks as well as functional dysconnectivity in multiple frontal regions. These features might partly explain the increased cognitive instability in individuals with MAP.

3.4. Neurochemical studies

In vivo neurochemical measurements in the brain can be achieved through several methods, including PET and MRS (Hsieh et al., 2014; Sekine et al., 2002, 2001). In the only PET study of MAP (Table 4), individuals with methamphetamine dependence showed decreased dopamine transporter binding potential in the caudate, putamen, and prefrontal cortices . This study also demonstrated negative correlations between the caudate and putamen dopamine transporter binding potentials and both the total scores and positive symptoms assessed by Brief Psychiatric Rating Scale (BPRS) in methamphetamines users, suggesting that a greater reduction in dopamine transporter densities within the brain is associated with more severe psychiatric symptoms, including psychoses.

Two MRS studies examined the neurometabolites in several brain regions, including the basal ganglia and frontal lobe (Table 4) (Hsieh et al., 2014; Sekine et al., 2002). Sekine et al. found that creatine, which is an indicator of neuronal cellular energy status, was decreased in the bilateral basal ganglia of individuals with methamphetamine dependence (Sekine et al., 2002). Although this study did not distinguish participants with MAP from those without, it revealed a negative correlation between creatine in the basal ganglia and positive symptom subscale of BPRS. In addition, another study found N-acetylaspartate, an indicator of neuronal osmolarity and viability, to be decreased in the anterior cingulate cortex and dorsolateral prefrontal cortex of individuals with methamphetamine dependence (Hsieh et al., 2014). Furthermore, the negative correlations of N-acetylaspartate levels in the anterior cingulate cortex and both the age of initial methamphetamine use and duration of methamphetamine use were only apparent in those with MAP (Hsieh et al., 2014). Taken together, MAP might be

Table 1
Studies examining gray matter.

Author Year	N (HC/MNP/SZ/MAP)	Areas of interest	Analysis method	Tesla	Main findings
Orikabe et al. (2011)	20/0/0/20	Amygdala and hippocampus	ROI (manual tracing)	1.5	HC > MAP in amygdala, hippocampus and total grey matter volume.
Aoki et al. (2013)	20/0/0/20	Whole brain	VBM	1.5	HC > MAP in frontal and temporal cortex.
Uhlmann et al. (2016)	19/21/0/19*	Fronto-temporal brain and subcortical structures	Free Surfer	3	HC > MAP in frontal cortex and left hippocampus. MNP > MAP in frontal, orbitofrontal, temporal and insular cortex and hippocampus.
Zhang et al. (2018)	18/0/16/17	Whole brain	VBM	3	HC < MAP in anterior cingulate and frontal cortex. SZ < MAP in anterior cingulate and frontal cortex.

HC healthy control, *MNP* methamphetamine without psychosis, *SZ* schizophrenia, *MAP* methamphetamine-associated psychosis, *ROI* region of interest, *VBM* voxel-based morphometry,
* median abstinence = 50 days

Table 2
Studies examining white matter.

Author Year	N (HC/MNP/MAP)	Areas of interest	Analysis method	Tesla	Main findings
Orikabe et al. (2011)	20/0/20	Whole brain	VBM	1.5	HC > MAP in total white matter volume.
Aoki et al. (2013)	20/0/20	Whole brain	VBM	1.5	HC > MAP in orbitofrontal white matter volume.
Uhlmann et al. (2016)	40/39/30	Whole brain	TBSS	3	HC/MNP < MAP in MD in widespread white matter regions. HC > MAP in FA in 10 regions including cingulum and corpus callosum.
Breen et al. (2017)	16/14/12	Whole brain	TBSS	3	HC/MNP < MAP in MD in widespread white matter regions. Serum protein A1AT shows positive associations with the RD of multiple regions in HC but not in MAP.

HC healthy control, *MNP* methamphetamine without psychosis, *MAP* methamphetamine-associated psychosis, *VBM* voxel-based morphometry, *TBSS* tract-based spatial statistics, *MD* mean diffusivity, *FA* fractional anisotropy, *RD* radial diffusivity, *median abstinence = 41 days

Table 3
Functional imaging studies.

Author Year	N (HC/MNP/SZ/MAP)	Condition	Analysis method	Tesla	Main findings
Fassbender et al. (2015)	27/11/0/19*	Stroop task	Blocks and ROI	3	HC = MNP < MAP in intraindividual variability. Diminished conflict-related activity in left BA 10 region in MAP.
Ipser et al. (2018)	26/27/0/19**	Resting state	ICA	3	HC > MAP in the anticorrelation between CEN and DMN. Increased functional connectivity between CEN and left precuneus in MAP.
Zhang et al. (2018)	18/0/16/17	Resting state	Seed	3	Right hippocampus and left orb-IFG ReHo HC > MAP. Negative correlation between PANSS positive subscale and left orb-IFG in MAP.

HC healthy control, *MNP* methamphetamine without psychosis, *SZ* schizophrenia, *MAP* methamphetamine-associated psychosis, *ROI* region of interest, *BA* Broca's area, *ICA* independent component analysis, *CEN* central executive network, *DMN* default mode network, *orb-IFG* orbital inferior frontal gyrus, *ReHo* regional homogeneity, *PANSS* positive and negative syndrome scale,

* mean abstinence = 13.7 months, mean use duration = 14 years,

** mean abstinence = 58.57 days, mean use duration 5.16 years

Table 4
Neurochemical studies.

Author Year	N (HC/MNP/MD/MAP)	Method of measurement	Sequence and Tesla of MRS	Areas of interest	Main findings
Sekine et al. (2001)	9/0/11*/0	PET		Basal ganglia and prefrontal cortex	HC > MD in dopamine transporter binding potential in caudate putamen nucleus accumbens and prefrontal cortex. Negative correlations between total BPRS/positive subscale and dopamine transporter binding potential in caudate putamen nucleus accumbens in MD.
Sekine et al. (2002)	11/0/13**/0	MRS	PRESS, 1.5	Basal ganglia	HC > MD in creatine in bilateral basal ganglia. Negative correlation between creatine in basal ganglia and BPRS positive subscale.
Howells et al. (2014)	19/16/0/10***	MRS	PRESS, 3	ACC, DLPFC and frontal white matter	HC > NAA in NAA in right ACC and right DLPFC. Positive correlation between right ACC NAA and age of initial MA use.

HC healthy control, *MNP* methamphetamine without psychosis, *MD* methamphetamine dependence, *MAP* methamphetamine-associated psychosis, *MRS* magnetic resonance spectroscopy, *PET* positron emission tomography, *BPRS* brief psychiatric rating scale, *PRESS* point resolved spectroscopy, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *NAA* N-acetylaspartate,

* mean abstinence = 5.6 months, mean use duration = 4.8 years,

** mean abstinence = 1.5 years, mean use duration = 3.2 years,

*** mean abstinence = 60 days, mean use duration = 7.1 years,

associated with reduction of dopamine transporter density and alterations in neurometabolites, such as creatine and N-acetylaspartate, in basal ganglia and prefrontal cortex.

3.5. Comparison of MAP with MNP or schizophrenia

In addition to healthy controls, several studies compared MAP with MNP or schizophrenia. Six studies directly compared MAP with MNP (Breen et al., 2017; Fassbender et al., 2015; Hsieh et al., 2014; Ipser et al., 2018; Uhlmann et al., 2016a, 2016b). Studies focused on structural imaging demonstrated that MAP was associated with decreased volumes of the orbitofrontal cortex, inferior frontal gyrus, inferior temporal gyrus, fusiform gyrus, and hippocampus (Uhlmann et al., 2016a). Uhlmann et al. demonstrated negative correlations between cortical thickness and the Emotion Reactivity Scale and difficulties in emotion regulation and impulse control subscale scores in patients with MAP, suggesting that thinner cortices are associated with dysregulated emotions and increased impulsivity, which could be specific to patients that experience psychotic symptoms (Uhlmann et al., 2016a). However, no significant white matter differences were observed between patients with MNP and those with MAP (Uhlmann et al., 2016b). In a functional study, individuals with MAP displayed higher intraindividual reaction time variability during the Stroop task compared with individuals with MNP (Fassbender et al., 2015). Regarding functional connectivity, one study using network–network connectivity analyses found that individuals with MAP had decreased functional connectivity between subnetworks in the DMN compared with individuals with MNP (Ipser et al., 2018). Conversely, network–voxel analyses revealed increased functional connectivity between the CEN and multiple regions in the frontopolar cortex (Ipser et al., 2018). Finally, the MRS study demonstrated that the brain regions with low N-acetylaspartate levels in the MAP group were similar to those in the MNP group whereas the decreased choline metabolite, an indicator of brain lipid metabolism and membrane function (Rae, 2014), found in the MNP group was not noted in the MAP group (Hsieh et al., 2014). Collectively, these observations indicated the gray matter, functional connectivity and neurometabolites associated MAP might be dissimilar to MNP.

Regarding the comparison between schizophrenia and MAP, only one study directly examined the differences of brain imaging both structurally and functionally (Zhang et al., 2018). This study found higher gray matter densities in several regions in the MAP group, including the bilateral anterior cingulate cortex, bilateral medial superior frontal gyrus, and left operculum inferior frontal gyrus. Interestingly, these regions also had increased gray matter densities when compared with healthy controls, which indicated that these alterations might be unique to individuals with MAP. Similar findings were also seen in the left orbital inferior frontal gyrus, with the MAP group showing higher ReHo than both the schizophrenia and control groups. In contrast, a gradient in the ReHo of the left medial superior frontal gyrus was detected, with healthy controls showing the highest levels, followed by the MAP group, which had higher ReHo levels than the schizophrenia group. In seed-based functional connectivity studies, several regions exhibited differences in the schizophrenia group compared with the control group, while these regions were comparable to those in the MAP group. These alterations included hyperconnectivity between the right hippocampus and left insula and hypoconnectivity between the right and left medial superior frontal gyri in patients with schizophrenia. In summary, the existing evidence suggests that MAP is distinct from schizophrenia in neuroimaging both structurally and functionally.

4. Discussion

Although the available data are currently insufficient to perform quantitative assessments, structural and functional alterations in the brains of MAP individuals are found mainly in the frontal lobes (especially the orbitofrontal cortex) and striatum and limbic systems (amygdala and hippocampus).

The orbitofrontal cortex is part of the prefrontal cortex and plays a crucial role in impulsivity (Zeeb et al., 2010). In some psychiatric disorders with psychotic symptoms, patients have significantly higher impulsivity than healthy controls, and such impulsivity is negatively correlated with orbitofrontal cortical volume (Nanda et al., 2016). Greater orbitofrontal cortex gray matter loss is also related to a higher probability that individuals will develop psychoses, suggesting these brain changes likely play a role in the psychopathology of psychosis (Cannon et al., 2015). A study that focused on MAP demonstrated that the hemodynamic response of the prefrontal region, which includes the orbitofrontal cortex, during the Stroop task was reduced and negatively correlated with impulsivity (Yamamuro et al., 2016). One study indicated that patients with MAP who are high in impulsivity are the most hostile (Lapworth et al., 2009); therefore, further investigations examining interactions among impulsivity, psychotic symptoms, and decreased orbitofrontal gray and white matter (Aoki et al., 2013; Uhlmann et al., 2016a) are warranted to provide insight for the treatment and management of MAP.

The orbitofrontal cortex is functionally connected with the striatum, which is also a part of the reward network (comprising the ventromedial prefrontal cortex, orbitofrontal cortex, striatum, amygdala, insula, and substantia nigra) (Beck et al., 2010; Kahnt et al., 2012). In addition to those of the orbitofrontal cortex, alterations of many parts of this network, including putamen, caudate nucleus, amygdala, and insula have been associated with MAP. The striatum, which is composed of the nucleus accumbens, olfactory tubercle, putamen, and caudate nucleus, is rich in dopaminergic neurons and linked to the neurobiological mechanisms of psychotic disorders (Weinstein et al., 2017). In schizophrenia, dopamine synthesis and storage of is elevated, but the availability of the dopamine transporter remains unchanged (Weinstein et al., 2017). The only dopamine-related PET study concerning MAP showed that, by contrast, the availability of the striatal dopamine transporter, which is negatively correlated with the presence of psychotic symptoms, is decreased (Sekine et al., 2001). These inconsistent findings might suggest that a pathophysiologic difference in dysregulation of the dopaminergic system exists between schizophrenia and MAP (Zhang et al., 2018).

In addition to the prefrontal cortex, the striatum has bidirectional interactions with the hippocampus and amygdala (Pennartz et al., 2011; Roy et al., 2009). Aberrant hippocampal glutamatergic–striatal dopaminergic interactions were demonstrated in individuals at ultra-high risk of psychosis (Stone et al., 2010). Furthermore, a study found that the volumes of both the hippocampus and amygdala decrease with the progression of psychosis (Ebdrup et al., 2011). In individuals with MAP, the hippocampal volume is lower compared with not only healthy controls but also individuals with MNP (Orikabe et al., 2011; Uhlmann et al., 2016a). To better understand the role of the hippocampus in MAP, further functional and neurochemical studies are needed.

As for the amygdala, structural studies have shown simultaneous decreases in the amygdala and hippocampus in both MAP and schizophrenia groups (Orikabe et al., 2011; Watson et al., 2012). Functionally, the amygdala is responsible for processing threat-related and other types of stimuli, such as novel, ambiguous, and extremely positive signals (Cunningham and Brosch, 2012). When the brain perceives cognitively challenging stimuli, the activity of the DMN decreases, whereas that of the CEN increases (Menon, 2011), with a negative correlation believed to be regulated by the salience network (Goulden et al., 2014). The amygdala and insula, both of which are smaller in MAP compared with MNP, are part of the salience network and responsible for the switching between the DMN and CEN and facilitating attentional processing in response to stimuli (Menon and Uddin, 2010). Consistent with the observations of structural changes, individuals with MAP also display increased reaction time variability, an indicator of attention disruption during the Stroop task (Fassbender et al., 2015). These findings support the idea that MAP is

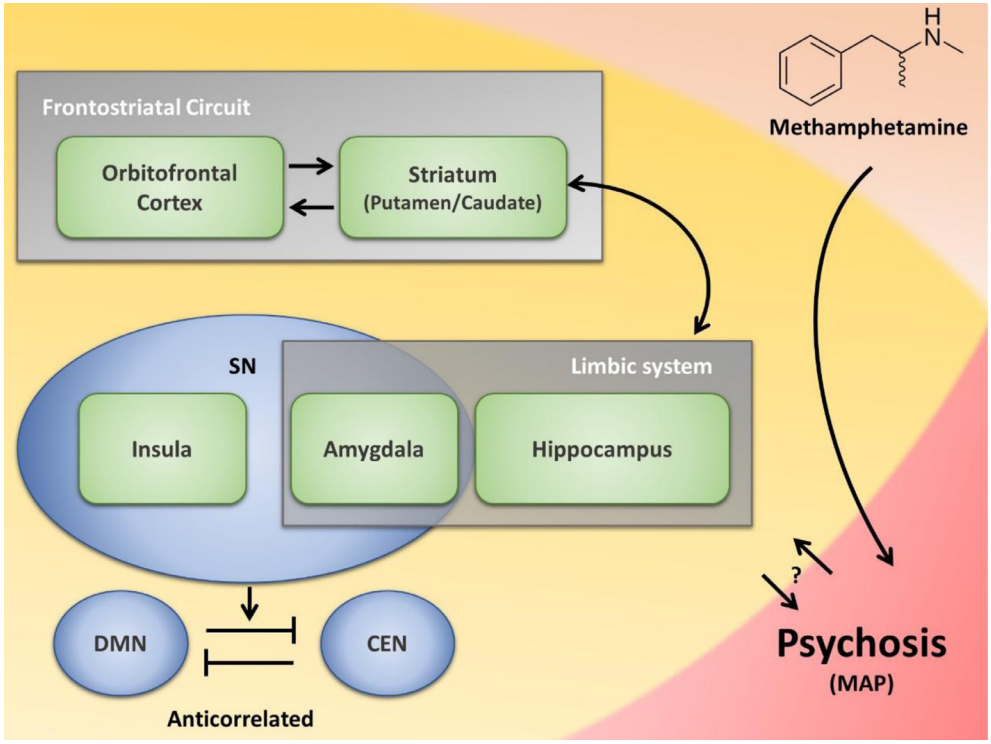

Fig. 2. Schematic highlighting key alterations found in methamphetamine-induced psychosis (MAP) neuroimaging studies. Multiple regions are affected in the images of brains with MAP, including the orbitofrontal cortex, striatum, amygdala, hippocampus, and insula. These regions are involved in functionally different networks such as the salience network, limbic system, and frontostriatal circuit. However, the detailed pathological relationships between such changes and MAP require further investigations. Abbreviations: SN, salience network; DMN, default mode network; CEN, central executive network; MAP, methamphetamine-associated psychosis.

associated with a decreased anticorrelation between the DMN and CEN compared to the control group (Ipser et al., 2018) and suggest pivotal roles of network–network dynamics in the neurobiological basis of MAP. This review identified several possible directions for the future MAP studies. First, MNP instead of healthy control groups should be used for comparison to elucidate the structural, functional, and neurochemical changes in brains specific to psychoses associated with methamphetamine use. Second, the only study thus far that compared MAP and schizophrenia has found no similarities in the affected areas of structural brain changes (Zhang et al., 2018). Furthermore, the areas (orbitofrontal cortex, striatum, and hippocampus) that have been associated with schizophrenia in some studies (Harrison, 2004; Kanahara et al., 2013; Simpson et al., 2010) seemed to overlap with the regions affected by MAP. Therefore, future studies should consider the potential confounders that influence the differentiation between MAP and schizophrenia (e.g. antipsychotic medications) or adopting research designs based on specific neurochemical characteristics (e.g. dopamine transporter reduction) to explore the underlying distinct mechanisms.

Another potential direction for future research is a multimodal approach that improves the understanding of the interactions between the structure, function, and neurochemistry of MAP. For example, studies using fMRI with MRS or PET could substantially increase the current knowledge regarding the association between functional connectivity and the glutamatergic and dopaminergic systems (Enzi et al., 2012; Simonyan et al., 2013). Finally, all studies in this review were cross-sectional studies, which do not allow for long-term monitoring of changes with disease progression or the effects of abstinence or medical treatment. In addition, the duration of methamphetamine use and abstinence varied across studies, from several months to over ten years (shown in Tables 1–4), and may have influenced the imaging results. Only one study so far has addressed the correlation between the duration of methamphetamine use and neuroimaging findings (n-acetyl-aspartate metabolite on MRS) (Hsieh et al., 2014). Longitudinal or prospective studies are needed to clarify the causality of associations specific to MAP and impact of abstinence or duration of methamphetamine use on MAP.

In summary, neuroimaging studies indicate that structural, functional, and neurochemical changes, especially in the frontostriatal circuit and network dynamic systems, play critical roles in the pathophysiology of MAP (Figure 2). However, additional studies are required to reach definitive conclusions. Future multimodal studies using prospective or longitudinal designs that include individuals with MNP and schizophrenia as controls could resolve unanswered questions.

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Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

CC and FCH conceived the study, analyzed the data, and drafted the paper. CWL commented on drafts and evaluated the intellectual content of the paper. MCH incorporated edits from coauthors, revised the final version, and was responsible for communication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.06.002.

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