

## Neuroimaging Findings in Methamphetamine Abusers

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### Abstract

Methamphetamine (MA) is a drug which has got a considerable prevalence of abuse in the world. Therefore, it is of great importance to understand the deficits and problems that it makes in brain, structurally and functionally, in order to increase knowledge of people about it and help finding better ways of treatments. Neuroimaging techniques as the most powerful tools to study the brain functions and structures, in the recent decades have been used to find out the brain deficits caused by the MA abuse. Here we would have a short review on the neuroimaging findings in MA abusers and the children with prenatally exposure to MA, with the focus on electroencephalography (EEG), magnetic resonance imaging (MRI) and functional MRI studies.

**Keywords:** Methamphetamine; Magnetic resonance imaging; Electroencephalography

### Introduction

Methamphetamines are increasingly popular drugs of abuse in many countries, such as Australia, China, Taiwan, Iran and USA, causing dramatic individual, social and economic problems [1-4]. Methamphetamine (MA) abusers exhibit deficits behaviourally, from anxiety and impulsivity to perceptual disturbances and hallucinations, neurochemically, mainly in dopaminergic and serotonergic systems, and cardiovascularly [1,5-8]. Here we would have a brief review of the effects of MA abuse on central nervous system based on neuroimaging findings. The review consists of the findings of high temporal

resolution techniques such as electroencephalography (EEG), suitable to find changes in temporal dynamics of cortical activities, and high spatial resolution techniques such as structural and functional magnetic resonance imaging (MRI and fMRI, respectively), suitable for detecting and allocating deficient cortical and subcortical regions.

### EEG

EEG has helped researchers to discover abnormalities of cortical dynamics in many brain disorders. There are several studies using linear and nonlinear analyses, synchronization algorithms, graph-based algorithms, etc. have reported changes in different aspects of the cortical dynamics and cortical connectivity in MA abusers. Table 1 briefly shows the details of the EEG studies reviewed in this article.

Reference	Number of subjects (Number of males)	Age (year) mean (Std)	Abuse Duration (year)	Abstinence Duration (day)	Task	Finding
	MA/C	MA/C	Mean (Std)	Mean (Std)		
Newton et al. [9]	11/11 (8/8)	32.7 (7.5)/ 36.5 (7.3)	11.0 (3.5)	4 (0)	no task	increased delta and theta power
Newton et al. [10]	9/10 (7/8)	Age (year) mean (Std)	At least 0.5 (no more info.)	4 (0)	working memory and reaction time tasks (N-back, computerized reaction time battery, and etc.)	increased theta power correlated with accuracy in working memory performance and reaction time
Yun et al. [11]	48/20 all males	37.0 (5.8) / 34.5 (7.7)	11.8 (6.5)	30.5 (27.2)	no task	decreased cortical complexity
Ahadlou et al. [12]	36/36 all males	31.7 (8.8)/ 32.7 (6.8)	6.42 (3.13)	Range 7 to 21 days (no more info.)	no task	disrupted functional connectivity of

							brain network in gamma band
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**Table 1:** Information about the subjects, the performing tasks (if there is any), and the main findings of the EEG studies, MA: MA Abusers; C: Control; STD: Standard Deviation.

Newton et al. comparing resting-state EEGs of 11 MA abusers (abstinent for 4 days) and 11 healthy subjects reported an increased EEG power at slow frequency bands (delta and theta) in the MA abusers [9]. Later, in another small sample-size study, Newton et al. reported a correlation between EEG power at beta frequency band and episodic memory performance in the MA abusers [10]. Using approximate entropy (AE) analysis of EEGs, Yun et al. quantified the degree of cortical complexity in former MA dependent adult males (abstinent for more than 6 days) and reported decreased cortical complexity, compared to the healthy adult males [11]. The decreased cortical complexity may indicate a general reduction of cortical interactions and functional connectivity. Ahmadlou et al. using functional connectivity and graph theoretical analysis of resting-state EEGs, showed that topology of the functional brain connectivity is disrupted in male MA abusers (abstinent for more than 7 days) in gamma band, which makes the brain network inefficient in the range of gamma frequency band (30-60 Hz) [12].

**MRI**

In the last two decades, structural brain abnormalities of MA abusers have been investigated with different volumetric and pattern analysis methods and the studies have shown correlation of some of

the structural deficits with the cognitive/behavioural deficits. Table 2 shows a summary of information about the subjects, the performing tasks (if there is any), and the main findings of the MRI studies.

Using MRI and surface-based computational image analyses, Thompson et al. found significant grey matter impairments in cingulate, limbic, and paralimbic cortices of MA abusers [13]. They also reported a significantly lower hippocampal volumes (compared to the control group) and significant white-matter hypertrophy. There was a significant correlation between hippocampal deficits and episodic memory performance (using a test of recall and recognition of pictures and words). Chang et al. reported enlarged striatum in recently abstinent methamphetamine abusers (abstinent for more than 7 days) and surprisingly the striatum size was correlated with their cognitive performance on verbal fluency and Grooved Pegboard (the reason is not clear yet) [14]. Kim et al., comparing short-term (with mean (Std) of 2.6 (1.6) months) and long-term (with mean (Std) of 30.6 (39.2) months) abstinent MA abusers and healthy subjects in a decision making task (Wisconsin card sorting task), showed that MA abusers have prefrontal grey matter deficit correlated with total errors in decision making, which may partially recover with long-term abstinence [14].

Reference	Number of subjects (Number males)	Age (year) mean (Std)	Abuse Duration (year) mean (Std)	Abstinence duration (month) mean (Std)	Task	Finding
	MA/C	MA/C				
Thompson et al. [13]	22/21 (15/10)	31.9 (1.7) / 35.3 (1.5)	26.1 (1.8)	No abstinence	Episodic memory task (recall and recognition of pictures and words)	Gray matter impairments in cingulate, limbic and paralimbic cortices; lower hippocampal volumes; white-matter hypertrophy; hippocampal deficits correlated with episodic memory performance
Chang et al. [14]	50/50	32.1 (7.4) / 31.7 (7.1)	9.2 (5.7)	4.0 (6.2)	Battery of neuropsychological tests designed to assess cognitive functions	Enlarged Striatum correlated with cognitive performance on verbal fluency and Grooved Pegboard
Kim et al. [15]	29/20 (27/15)	36.5 (6.5) / 33.2 (5.5)	5.3 (3.7)	20.0 (33.5)	Decision making task (Wisconsin card sorting)	Prefrontal grey matter deficit correlated with total errors in decision making

**Table 2:** Information about the subjects, the performing tasks (if there is any), and the main findings of the MRI studies, MA: MA Abusers; C: Control; Std: Standard Deviation.

The chronic abuse even can affect the brain and cognitive functions of the children prenatally exposed to MA for at least two thirds of pregnancy of their MA-dependent mothers. The prenatally MA-exposed children have deficits in visual motor integration, attention, verbal memory and long-term spatial memory. More surprisingly, compared to healthy children, they have smaller subcortical structures

(including putamen, globus pallidus, and hippocampus) which are correlated with their performance on sustained attention and delayed verbal memory [16].

## fMRI

Using the magnetic properties of deoxygenated and oxygenated blood, fMRI measures a blood-oxygen-level-dependent (BOLD) signal [17]. The high spatial resolution and the ability of showing brain activity from cortical and subcortical regions, makes fMRI as a powerful tool to study functional brain abnormalities, not only in resting state, but also during performing different tasks. Here we have a brief review of fMRI finding in functional abnormalities in MA abusers. Table 3 is shortly representing the information about the subject, tasks and findings.

Using fMRI during a double-choice decision making task, Paulus et al. showed that, compared to the control group, dorsolateral prefrontal cortex of MA abusers (abstinent for more than 6 days) are less activated and ventromedial cortex is not activated during the task [18]. The impaired activity of prefrontal cortex is consistent with later

studies during other cognitive tasks [19-21]. Salo et al. showed that a trial-to-trial reaction time adjustment in a single-trial Stroop task (which is reduced in MA abusers) has a negative correlation with prefrontal cortical activity in the MA abusers (abstinent for a minimum of 3 weeks) [19].

fMRI studies have also shown the deficient brain regions in emotional tasks and understanding others. Orbitofrontal cortex, temporal poles, and hippocampus in male MA abusers (mean period of abstinence was 20.5 days) are less activated during processing of empathy information compared to healthy males [22]. Later Kim et al. reported a decreased activation in the dorsolateral prefrontal cortex and insula, and an increased activation in the fusiform gyrus, hippocampus, parahippocampal gyrus and posterior cingulate cortex (compared to healthy subjects) during watching visual scenes depicting fear or threat [23].

References	Number of subjects (Number of males)	Age (year) mean (Std)	Abuse duration (year)	Abstinence duration (month)	Task	Finding
	MA/C	MA/C	Mean (Std)	Mean (Std)		
Paulus et al. [18]	10/10 all males	41.1 (2.4)/42.3 (1.9)	19.6 (6.9)	0.75 (0.12)	A two-choice prediction task	No activity of ventromedial cortex and lower activity of dorsolateral prefrontal cortex during decision making
Salo et al. [19]	12/16 (5/8)	35.7 (7.7)/30.2 (8.9)	13.9 (5.7)	4.1 (2.8)	Stroop task	Reduced activity of right prefrontal cortex correlated with trial-to-trial reaction time adjustments in Stroop task
Nestor et al. [20]	10/18 (5/11)	33.5 (9.3)/36.4 (10.4)	8.3 (3.7)	4 to 7 days (no more info)	Stroop task	Reduced activity of prefrontal cortex in Stroop task
Kim et al. [22]	19/19 all males	36.0 (range: 31-52)/37.0 (range: 33-42)	13.6 (7.3)	0.68 (0.28)	An empathy task	Lower activity of orbitofrontal cortex, temporal poles, and hippocampus during empathy processing
Kim et al. [23]	19/19 (11/12)	36.0 (5.4)/37.0 (3.0)	13.6 (7.3)	0.68 (0.28)	An emotion matching task	Decreased activity of dorsolateral prefrontal cortex and insula, and an increased activity of fusiform gyrus, hippocampus, parahippocampal gyrus and posterior cingulate cortex during watching

						visual scenes of fear or threat
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**Table 3:** Information about the subjects, the performing tasks (if there is any), and the main findings of the fMRI studies, MA: MA Abusers; C: Control; Std: Standard Deviation.

Unfortunately, prenatally MA-exposure would also cause brain deficits and cognitive impairments. Lu et al. found more diffuse activation in prenatally MA-exposure children during a verbal memory task (compared to the children exposed only to alcohol) [24]. fMRI can also be used to predict relapse. Interestingly, Clark et al., using functional patterns of brain at an early stage of abstinence predicted which patients later relapse and which ones remain abstinent. Using fMRI amplitude in right posterior cingulate and insular cortex, they reached accuracy around 80%.

### Conclusion

Neuroimaging techniques have a high potential to find brain deficits and correlations between the deficient brain regions and cognitive/behavioural performances in MA abusers. However most of the studies have been done on the abstinent MA abusers and more studies need to be done to exclude the effects of abstinence. And of course results of the neuroimaging studies with small sample-sizes should be proved with larger sample-sizes to be valid enough to be used clinically. The EEG studies are mostly on the short-term abstinent MA abusers and it's necessary to see whether the changes in the brain dynamics is still there after a long-term abstinence or not. Moreover, usually MA abusers are highly stressed are heavy smokers and have lower educational level. However, unfortunately there is not enough control to exclude these effects on the neuroimaging findings [12].

Taking advantages of the neuroimaging techniques, more studies should be done to find out the possibilities of predicting the treatment outcome and relapse of the abstinent MA abusers, which would be helpful in choosing the most effective therapeutic strategies for each patient. Another question which is yet difficult to answer by these studies is about the causality: to what extent and the brain abnormalities are caused by the toxic effects of drug exposure and to what extent they may have predated drug-taking and/or predisposed individuals for the development of drug dependence.

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