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## **► To cite this version:**

Mayuri Shukla, Bruno Vincent. Methamphetamine abuse disturbs the dopaminergic system to impair hippocampal-based learning and memory: An overview of animal and human investigations. *Neuroscience and Biobehavioral Reviews*, 2021, 131, pp.541-559. <10.1016/j.neubiorev.2021.09.016>. <hal-03853069>

**HAL Id: hal-03853069**

**<https://hal.science/hal-03853069v1>**

Submitted on 16 Oct 2023

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# **Methamphetamine abuse disturbs the dopaminergic system to impair hippocampal-based learning and memory: An overview of animal and human investigations**

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**Keywords:** Methamphetamine, dopamine, hippocampus, learning, memory, cognitive dysfunctions

## **Abstract**

Diverse intellectual functions including memory are some important aspects of cognition. Dopamine is a neurotransmitter of the catecholamine family, which contributes to the experience of pleasure and/or emotional states but also plays crucial roles in learning and memory. Methamphetamine is an illegal drug, the abuse of which leads to long lasting pathological manifestations in the brain. Chronic methamphetamine-induced neurotoxicity results in an alteration of various parts of the memory systems by affecting learning processes, an effect attributed to the structural similarities of this drug with dopamine. An evolving field of research established how cognitive deficits in abusers arise and how they could possibly trigger neurodegenerative disorders. Thus, the drugs-induced tenacious neurophysiological changes of the dopamine system trigger cognitive deficits, thereby affirming the influence of this addictive drug on learning, memory and executive function in human abusers. Here we present an overview of the effects of methamphetamine abuse on cognitive functions, dopaminergic transmission and hippocampal integrity as they have been validated in animals and in humans during the past 20 years.

## Introduction

The growing increase in the prevalence of the misuse of amphetamine (amp), and more especially of its more potent derivative methamphetamine (meth), has raised these drugs as an international health hazard affecting millions of people worldwide ([United Nations, 2013](#)). The obvious interaction of these drugs with different brain regions has established cognition as a pivotal determinant in meth-induced neurodegenerative effects that are systematically evidenced in meth abusers ([Cadet et al., 2014](#); [Potvin et al. 2018](#); [Sabrini et al., 2019](#) for reviews) where the amount of meth consumption positively correlates with the extent of cognitive deficits ([Dean et al., 2013](#)).

Importantly, the perspicuous brain regions accountable for learning and memory that are targeted by drugs of abuse are not only limited to hippocampus, dorsal striatum, and amygdala but also include the medial prefrontal cortex and the nucleus accumbens ([Everitt and Robbins, 2005](#); [Hyman et al., 2006](#)). Indeed, structural and metabolic alterations in the basal ganglia, hippocampus, amygdala, thalamus and a range of cortical regions have been observed in both current and abstinent meth abusers ([Thompson et al., 2004](#); [Tanabe et al., 2009](#); [Orikabe et al., 2011](#)). Moreover, a decrease in grey matter in the cortical regions and some changes in the limbic region, particularly hippocampus, are responsible for meth-induced long-term cognitive dysfunctions ([Zhu et al., 2016](#)). In addition, that such drugs might affect neuronal plasticity underlying memory formation following associative learning becomes an appurtenant deliberation. As a matter of fact, meth use during pregnancy could disrupt the normal development of the frontal cortex ([Warton et al., 2018](#)) and affect the hippocampus ([Jalayeri-Darbandi et al., 2018](#)), this altogether resulting in significant cognitive disabilities.

Memory-related problems and executive dysfunctioning involving the frontostriatal and limbic circuits have been formally identified in meth abusers ([Scott et al., 2007](#)) with scores

obtained by control subjects being correlated to brain measures in the prefrontal cortex and the anterior cingulate cortex, while decision-making consistently showed correlation with brain measures in the prefrontal cortex, anterior cingulate cortex, and striatum ([Sabrini et al., 2019](#)).

Multitudinous investigations of meth intoxication in the brains of both humans and animals have revealed the damage of monoamine-containing nerve terminals where alteration in cognitive functioning has been observed. From neuropsychological studies of chronic meth addicts, the deficits in attention, working memory and decision-making have been meticulously detected ([Gonzalez et al., 2004](#); [Simon et al., 2002](#)) and are due to the neurotoxic and neuroadaptive changes imposed by the drug that directly impact the memory systems and lead to cognitive impairments ([Volkow et al., 2002](#); [Kalivas and Volkow, 2005](#)). More generally, drugs of abuse enhance the competitive interactions between the memory systems and modulate their functions ([White, 1996](#); [White and McDonald, 2002](#); [Robbins et al., 2008](#)), a phenomenon supported by the averment that the cognitive memory system (hippocampus) ([Lisman et al., 2017](#)) and the stimulus-dependent memory system (dorsolateral striatum), although being anatomically distinct, mediate the processing of various means of learning and memory ([Packard et al., 2013](#)).

To return more specifically to the case of meth and the dopaminergic system, meth-induced dopaminergic degeneration and memory deficits have been substantially explored in rodent models ([Leeboonngam et al., 2018](#); [Zhou et al., 2019](#)), in young adult rhesus macaques in which meth affects neuroplasticity in the hippocampus and influence functional properties of hippocampal neurons ([Dutta et al., 2018](#)) as well as in humans. Therefore, the incentive to the present systematic review was on the one hand to make an updated assessment of how meth modulates dopaminergic connections in the brain by affecting the

cognitive system and on the other hand to highlight the important contributions made on humans and animals that document meth-induced alterations in cognitive parameters.

### ***The dopaminergic pathways and their associated cognitive epitomes***

The physiological significance of the dopaminergic neurons in the brain is the synthesis and release of the neurotransmitter DA. Apart from many critical functions, the dopaminergic pathways are involved in climactic executive functions and learning. Thus, the mesolimbic pathway is associated with the transmission of DA from the ventral tegmental area (VTA) to the ventral striatum, which comprises of both nucleus accumbens and olfactory tubercle and sustains the aversion- and reward-related cognition. In addition, the mesocortical pathway supports executive functions including some basic cognitive processes such as working memory and transmits DA from the VTA to the prefrontal cortex. Yet, another decisive circuit is the nigrostriatal pathway, which operates the transmission of DA from the substantia nigra pars compacta to the caudate nucleus and putamen, thereby confederating the reward-related cognition and associative learning ([Adinoff, 2004](#); [Juárez Olguín et al., 2016](#)) ([Figure 1](#)).

That DA is involved in the modulation of integrated memory and learning systems in the cortical regions of the brain is a well-acquainted fact and has been comprehensively manifested in studies in humans, primates as well as rodents ([Puig et al., 2014](#)). As a consequence, there is a well-established association between alteration of the dopaminergic system and the development of neurodegenerative disorders as shown by the fact that both preclinical and clinical evidence support the involvement of DA-dependent regulation of cognition in the prefrontal cortex of Parkinson's disease patients ([Kulisevsky, 2000](#)), while dopaminergic neuron loss has been associated with memory dysfunction in a transgenic mouse model of Alzheimer's disease ([Nobili et al., 2017](#)). DA, in the prefrontal cortex, plays

a pivotal role in working memory (Roffman et al., 2016) and, considering the association of hippocampus with working memory (Leszczynski, 2011), it could be surmised how meth-induced dopaminergic alterations might modulate the working memory circuitry.

### ***Elemental mechanism of action of meth on dopamine transmission***

Meth competes with DA for dopamine transporter (DAT) and enters DA terminals via its binding to DAT at the plasma membrane or through passive diffusion. Meth-induced impairment in DAT activity occurs via direct inhibition or by reverting its direction, which ultimately leads to the abnormal accumulation of free DA. Furthermore, meth disrupts the proton gradient of vesicle monoamine transporter 2 (VMAT2) and enters the synaptic vesicles to cause excessive DA release (Figure 2). Additionally, meth binds to monoamine oxidase (MAO) and blocks the degradation of DA resulting in an increased availability of free DA (Figure 2). Such abnormally high free DA tend to auto-oxidize to form toxic quinones, consequently leading to an excessive production of hydrogen peroxides and superoxide radicals, ultimately accounting for the generation of oxidative stress. This disruption in the homeostasis of redox reactions further accelerates the production of reactive oxygen species (ROS), thus causing mitochondrial and endoplasmic reticulum dysfunctions. Finally, as the interaction of DA with its receptors leads to the activation of many transcription factors, it could be speculated that meth could trigger some alterations of various transcriptional decisive signaling pathways associated with DA (Limanaqi et al., 2018 for review).

### ***The dopaminergic regulation in the hippocampus - Implications of meth-induced dopamine-dependent modulation of learning and memory***

Hippocampus is an important part of the limbic system that regulates learning and memory and where memory is stored via synaptic changes. Dopaminergic signaling was found to play an important role in novelty-related modulation of hippocampal memory and previous studies have shown that hippocampal DA signaling is strongly involved in spatial learning (Kempadoo et al., 2016; Takeuchi et al., 2016). Although the actual source of dopaminergic innervation in the hippocampus is still a matter of debate, at least two possibilities have been discussed. On one side, the VTA has been established as an obvious source for DA supply to the hippocampus (Scatton et al., 1980; Gasbarri et al., 1994; Lisman and Grace, 2005) (Figure 1), while on the other hand, several findings have established noradrenergic neurons of the small brainstem nucleus locus coeruleus (LC) as an origin for the dopamine release to the dorsal hippocampus (Smith and Greene, 2012; Broussard et al., 2016; Kempadoo et al., 2016; Takeuchi et al., 2016) (Figure 1). While LC genuinely supports learning and memory processes (Bari et al., 2020), a close functional relationship has been established between meth, dopamine and noradrenaline (NE) (Ferrucci et al., 2013; Ferrucci et al., 2019), the latter being profusely provided by the LC to the brain. In this context, it has been evidenced in both mice and rats that genetic or pharmacological blockade of NE synthesis potentiates the meth-induced striatal dopamine depletion (Fornai et al., 1995; Fornai et al., 1998) as well as the meth-dependent neurochemical, behavioral and neurotoxic effects (Weinshenker et al., 2008), thereby suggesting that meth could impair hippocampal-based learning and memory functions via this circuitry.

Interestingly, the adult dorsal hippocampus is involved in the formation of context-specific memories associated with relapse to drug seeking (Fuchs et al., 2007; Wells et al., 2016), and the ventral hippocampus is important for reinstatement of drug-seeking behavior triggered by drug context, drug cues, or the drug itself (Rogers et al., 2007; Lasseter et al., 2010; Deschaux et al., 2014). These findings suggest that the neuroadaptive changes in the

dorsal and ventral hippocampus contribute to the craving state that drives reinstatement of drug seeking (Koob and Volkow, 2010) and there is evidence of a direct role of newly born immature neurons in the hippocampus in assisting maladaptive plasticity in the dentate gyrus to support meth context-driven drug-seeking behaviors in a pharmacogenetic rat model (Galinato et al., 2018).

The release of DA from the LC is considered to promote spatial learning and memory formation mediated by the dorsal hippocampus (Kempadoo et al., 2016), while VTA-derived DA seems to be involved in contextual fear conditioning that depends on the ventral hippocampus (de Souza Caetano et al., 2013). Hippocampus receives dopaminergic fiber projection from several sources in the brain and focusing on the distribution of DA-producing axon terminals and the resulting modes of action of DA release are necessary to understand the function of dopaminergic modulation. For example, neuromodulation can occur via direct actions of physically released DA from dopaminergic terminals onto postsynaptic structures that are located at soma, dendrites, and/or the axon of the target neurons. Alternatively, dopaminergic terminals might form contacts directly onto presynaptic terminals or postsynaptic structures of glutamatergic or GABAergic synapses (Edelmann et al., 2017). In addition, the volume transmission resulting from elevated ambient DA levels in the extracellular fluid that are generated by dissemination of released DA from axon terminals needs to be considered as a mode of dopaminergic action (Agnati et al., 1995; Borroto-Escuela et al., 2015).

In this context, it has to be reminded here that DA receptors are subdivided into D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors. While D1-like receptors (D1R) positively modulate adenylyl cyclase (AC) activity, thereby elevating intracellular cyclic adenosine monophosphate (cAMP) levels, D2-like receptors (D2R) induce a contrary effect by negatively regulating AC (Grilli et al., 1988; Beaulieu and Gainetdinov, 2011). In addition,

both D1R and D2R are involved in other signaling cascades not directly connected to cAMP that need to be considered in order to understand extensively dopaminergic effects in the hippocampus. For example, D2R, as G-protein-coupled receptors, trigger the inactivation of Akt1 via the stimulation of  $\beta$ -arrestin signaling (Beaulieu et al., 2011). Importantly, distinct patterns for D1R and D2R expression were described in both the dorsal and the ventral hippocampus. In the dorsal hippocampus, D1R are prominently expressed in granule cells of the dentate gyrus and less dense in the CA1 and CA3 area, whereas D2R are mainly found in hilar mossy cells (Wei et al., 2017). Moreover, a high density of D2R binding sites has been revealed in stratum lacunosum moleculare of the dorsal hippocampus, while D2R abundance seemed to be lower in the rest of hippocampus (Charuchinda et al., 1987). As far as the the ventral hippocampus is concerned, a high density of D1R and D2R was found in CA1 and in subicular areas (Puighermanal et al., 2017; Wei et al., 2017). Studies carried out in primates have also indicated that D5 receptors were detected in CA1 pyramidal cell somata with their apical dendrites located in stratum radiatum (Ciliax et al., 2000; Khan et al., 2000), whereas D1 receptor was predominantly expressed in dendritic spines of apical dendrites of pyramidal neurons and also in some types of interneurons (Yao et al., 2008). The distribution of subfamily members of D2R family remains to date very little known, although in rat hippocampus, the general presence of D3 and D4 receptors was verified by using pharmacological investigations (Sigala et al., 1997; Romo-Parra et al., 2005).

In the hippocampus, DA also functions as a modulator of hippocampal synaptic plasticity and its binding to DA receptors in the dorsal hippocampus is a major determinant of memory encoding (Rossato et al., 2009; McNamara et al., 2014; Broussard et al., 2016). In this context, some data have revealed that chronic meth treatment for two weeks decreases low molecular weight 75kDa DAT protein levels in the hippocampus of C57BL/6J adolescent male mice while synaptic plasticity in the CA1 region is impaired after meth abuse followed

by a 3-week abstinence period (North et al., 2013). Another study carried out in mice has indicated that repeated meth exposure induces memory deficits, possibly via the up regulation of hippocampal D2 receptors expression and the concomitant lessening of DAT protein levels, which affect downstream intracellular molecules and memory functions (Zhou et al., 2019). Indeed, it has been robustly established that D1 as well as D2 receptors are associated with meth-induced neurotoxicity as dopamine D1 or D2 receptors genetic inactivation could prevent the long-term effects of meth (Ares-Santos et al., 2013) while inactivation of D2 receptor prevents dopaminergic neuronal loss in the SNpc (Granado et al., 2011).

Another fact to carefully consider is that, in the hippocampus, the N-methyl-D-aspartate (NMDA) receptor is essential for encoding the associations between events or outcome and specific spatial locations within a cognitive map (Bannerman et al., 2014). In close connection with this point, it has been established that meth induces both a short-term increase and long-term decrease in spatial working memory by affecting DA and glutamate receptors in the hippocampus, which overall leads to poor memory performance (Braren et al., 2014). Chronic or high dose of meth led to learning and memory impairments (Meredith et al., 2005; Hart et al., 2012) and impaired spatial memory acquisition (Simoes et al., 2007). Collectively, one can safely say that due to its additional colossal affinity for hippocampus (Shukla and Vincent, 2020 for review) and its close structural similarity with DA, meth fulfils all the criteria required to considerably modulate the DA-mediated hippocampal memory circuitry.

### ***The effects of meth on cognition, the dopamine system and the hippocampus in animal models and in humans***

Meth abuse leads to reduced cognitive function across several domains. Both striatal and cortical/sub-cortical neurotoxicity are involved in meth-induced cognitive deficits. As such,

information processing, episodic memory, and executive functions like working memory decision-making and attentional control require imperforate cortical function (Bernheim et al., 2016). Moreover, the innervation of DA into the striatum and cortex is critical for working memory function and normal decision making at both cellular and behavioral levels (Hanganu et al., 2015).

Beyond the fact that animals exposed to meth have lower birth weights and an increased incidence of microgyria, they display significant deficits in different learning paradigms. The applicability and advantage of animal models has certainly proved useful in giving us a better understanding of the specific neuroanatomical, molecular and cellular alterations underlying the drug abuse in humans. Thus, the neurological consequences of meth exposure in prenatal, adolescent and especially adult mice and rats have been studied considerably. Table 1 illustrates the relevant animal studies carried out the past 20 years and describing how meth affects both cortical and striatal-mediated learning and memory performances.

Drugs like meth are known to modulate receptors, transporters, and other components of neurotransmission, many of which are expressed during prenatal stages of brain development, although their expression patterns and functions are sometimes quite different from their more typical roles later in life. Thus, the presence of these proteins in the developing brain underlies the well-documented impact of prenatal drug exposure on brain architecture, chemistry, and neurobehavioral function clinically.

The data from the NIDA-supported Infant Development, Environment, and Lifestyle (IDEAL) study has revealed that prenatal meth exposure not only leads to a reduced neonatal size but also significantly disrupts the normal development of the brain cortex circuitry. Identifying such problems at an early age is critical to prevent child's emotional, behavioral, and cognitive difficulties from accelerating and persisting at adulthood. Thus, a steady follow up is necessary in order to intervene as soon as possible and to better understanding the long-

term implications of such findings (Derauf et al., 2007; Derauf et al., 2012). Children exposed to meth during prenatal development clearly have attention, long-term spatial and verbal memory problems and altered visual motor integration, while neuroimaging studies have reported smaller striatum and hippocampus volumes (Chang et al., 2004; Chang et al., 2007). Meth usage during pregnancy causes increased cognitive problems in children as recorded at 7.5 years of age where prenatal meth exposure was 2.8 times more likely to have cognitive problem scores than children who were not exposed to the drug (Diaz et al., 2014). As a matter of fact, *in utero* meth exposure represents a major brake for fetal brain development (Li et al., 2021) as shown by the fact that it has strong effects on the neurotransmitters like dopamine, serotonin, glutamate and GABA at adulthood, even on limited exposure to this drug (Fujáková-Lipski et al., 2017). In addition, it triggers some changes in the mesolimbic dopaminergic system with more sensitivity to the administration of acute dose of meth at adulthood, thereby indicating that offspring exposed to meth *in utero* could be more sensitive to meth and potentially to other psychostimulants (Bubenikova-Valesova et al., 2009). These developmental and behavioral changes in animals having experienced *in utero* meth exposure provide insights into the mechanisms causing changes in affective, behavioral, and cognitive outcomes in exposed children (Ross et al., 2015). Despite the lack of data so far concerning alteration of components of the dopamine system in children having beforehand suffered prenatal meth exposure, several works carried out in rats have reported slight decreases of TH mRNA levels in dopaminergic neurons (Gomes-da-Silva et al., 2002), of DAT expression in the striatum (Sirova et al., 2016) and of D1R expression in the motor cortex and substantia nigra (Farar et al., 2018) as well as a moderate increase in D3R mRNA levels in the striatum (Zoubkova et al., 2019) of prenatally meth-exposed animals when compared to controls. The studies having evidenced some effects of

prenatal meth exposure on cognitive functions and on the integrity of brain structures in young humans are presented in [Table 2](#).

Meth abusers display smaller hippocampal volumes and enlargement of white matter in the temporal and occipital regions in close proximity to areas of reduced grey matter. This particular enlargement is observed as an after effect of post glial changes and disrupted myelination processes. Such significant reductions in grey matter are responsible for learning and memory impairments both in the hippocampus and parietal lobe, with social cognition impairments associated with the insular cortex and decreased activity in the ACC, ventro- and dorsolateral prefrontal cortices, thus exhibiting executive dysfunctions. Collectively, such cognitive deficits may vary pertaining to the cogent differences between the dependent and occasional meth users ([Guerin et al., 2019](#)). Although all types of memory were not yet assessed in meth abusers, explicit investigations indicating meth-induced alterations in brain structure and cognitive function in adolescent ([Table 3](#)) and adult humans ([Table 4](#)) are summarized.

Variations in DA levels induce cognitive changes in many neurological and psychiatric conditions where it influences the neurophysiological mechanisms of both cognitive control and performance monitoring ([Wilson et al., 2016](#)). Importantly, DA markers measure the severity of addiction and plays pivotal role in identifying individuals who might benefit from pro-cognitive treatments. In this context, the circulating levels of DA receptor mRNA have been measured as a biomarker for drug severity and dependence ([Ersche et al., 2011](#)). Pertaining to the effect of meth on DA markers, [Table 5](#) illustrates the changes observed in DA markers post meth administration in both animals and humans and [Table 6](#) lists the meth-induced effects on DA signaling components in mice and rat models.

Distinctly for hippocampus, DA when released into the dorsal hippocampus promotes spatial learning, attention, episodic memory formation and synaptic plasticity by binding to

D1/D5 receptors ([Kempadoo et al., 2016](#)). How meth affects the hippocampus both structurally and functionally has been discussed earlier in the text. Nevertheless, [Table 7](#) sums up some relevant investigations in both humans and animals evidencing how meth alters the various parameters of DA signaling and learning and memory dependent functions of the hippocampus.

## **Conclusion**

The interpretations evidenced by a consistent number of neuropathological and neuroimaging findings in humans have shown that meth undoubtedly leads to neurodegeneration in the brain of addicts, which manifests as an incessant decline in learning and memory. However, it has to be noted that these brain functions have sometimes been shown unaffected by the drug depending on the models used, the tests performed, the duration of abuse, the amounts of meth consumed, gender, age and duration of the abstinence period. In this context, although a substantial amount of data is further required to establish the precise networking of meth and the neurocognitive circuitry in the respective brain areas. Nonetheless and thus far, the investigations overall suggest that chronic and high doses of meth can efficaciously and resentfully modulate the cognitive abilities in both humans and animals. Importantly, understanding the integrity of the dopaminergic associations in the hippocampus may further give useful insights in understanding how such deficits in cognitive functions arise post meth exposure, thereby predisposing the brain to accelerated ageing and brain disorders like AD ([Shukla and Vincent, 2020](#)), PD ([Lappin et al., 2018](#)) and schizophrenia ([Guerin et al., 2019](#)). However, further human investigations with diverse dosage paradigm and improvements in animal research models are required to maximize our understanding of the neurobiological aspects and the potential therapeutic perspectives.

## Acknowledgments and disclosures

We wish to apologize for not having cited all the studies related to the field due to space limitation. This work was supported by Mahidol University to BV (NDFR 13/2564) and The Thailand Research Fund to BV (BRG6180002). Authors declare no conflict of interest.

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## Legends to figures

**Figure 1: The dopaminergic pathways, learning and memory.** The neurotransmitter DA is synthesized in the cell bodies of dopaminergic neurons that features a complex system including substantia nigra, the ventral tegmental area and the hypothalamus accounting for cognition, emotions, and psychomotor functions along with endocrine control. Dopaminergic pathways send projections to multiple brain areas where dopamine is stored and released. Regarding learning and memory, the mesocortical dopaminergic pathway is involved with executive functions and working memory, the mesolimbic pathway accounts for aversion and reward related cognition as well as episodic memory due to the projection of the VTA to the ventral hippocampus to control contextual fear conditioning, learning and long-term potentiation (LTP). Additionally, the dopaminergic projection from the Locus coeruleus to the dorsal hippocampus has been suggested to regulate spatial learning and memory formation. Finally, the nigrostriatal dopaminergic pathway regulates and modulates the associative learning processes in the brain.

**Figure 2: Dopaminergic synapse under physiological and meth-induced conditions.** (a) Dopamine (DA) is produced in a two-step mechanism where tyrosine is transformed into L-DOPA (L-dihydroxyphenylalanine) by tyrosine hydroxylase (TH), which is then converted to dopamine by DOPA decarboxylase (AADC) in the presynaptic terminal of dopaminergic neurons (1). Dopamine is then sequestered into the synaptic vesicles by VMAT2 (2) from where it is released in the synaptic cleft (3). After the binding of DA to its receptors located

at the postsynaptic membrane and the perpetuation of signaling transduction (4), it is recycled (via recapture by DAT) to the cytoplasm (5) where it can even reincorporate synaptic vesicles through VMAT2 (6) or be catabolized by enzymes such as MAO<sub>B</sub> and catechol-O-methyl transferase (COMT) (7). (b) Meth mostly acts on DA transmission by disrupting intravesicular proton gradient and dynamics, reducing the VMAT2 function and reversing transport of DA back to the cytoplasm. This severely impairs the reuptake of DA and lessens its concentration within synaptic vesicles. Meth also triggers a pronounced DA transporter (DAT) dysfunction at the presynaptic plasma membrane, thereby resulting in further higher cytosolic concentrations of DA in nerve terminals. Altogether, this leads to an excessive DA concentration in the synaptic cleft altering the basal homeostasis of transmission thus engendering long lasting neuro-adaptation to affect cognition. On the other hand, meth binds to monoamine oxidase (MAO) and blocks the degradation of DA, thereby resulting in an increased availability of free DA that causes damage to the dopaminergic system via the over activation of DA receptors that ultimately leads to the persistent loss of dopaminergic nerve terminals.

**Table 1**

Effect of methamphetamine on cortical and striatal-mediated learning- and memory-related performances in animal models (references are listed in chronological and alphabetical ascending order).

<b>Age at treatment</b>	<b>Age at test</b>	<b>Animal model</b>	<b>Dose</b>	<b>Effects observed</b>	<b>Reference</b>
Adulthood	Adulthood (+4d)	Male SD rats	3x10mg/kg at 2h intervals	↘ non spatial memory (NOR task)	<a href="#">Bisagno et al. (2002)</a>
Adulthood	Adulthood (+1 or 3w)	Male SD rats	4x4mg/kg at 2h intervals	↘ short- and long-term recognition memory (NOR task)	<a href="#">Schroder et al. (2003)</a>
11 to 20d	60 to 67d	SD rats	4x5mg/kg/d (mother)	↘ spatial learning (BM test)	<a href="#">Williams et al. (2003a)</a>
Adulthood	Adulthood (+1w)	Male SD rats	4x4mg/kg (NOR task)	↘ short-term recognition memory	<a href="#">Belcher et al. (2005)</a>
Adulthood	Adulthood (+3w)	Male SD rats	4x10mg/kg at 2h intervals	↘ sequential motor learning (RAM test)	<a href="#">Daberkow et al. (2005)</a>
Adulthood	Adulthood (+28d)	Male SD rats	4x5mg/kg at 2h intervals	↘ recognition memory (NOR task)	<a href="#">He et al. (2006)</a>
Adulthood	Adulthood (1w post treatment)	Male SD rats	4x1-4mg/kg (single day treatment)	↘ recognition memory (NOR task)	<a href="#">Belcher et al. (2008)</a>
Adulthood	Adulthood (+5d to 52d)	Male SD rats	4x10mg/kg at 2h intervals or 24x1.67mg/kg at 15m intervals	↘ recognition memory (NOR task) ↘ integration learning (CWM test)	<a href="#">Herring et al. (2008)</a>
Adulthood	Adulthood (+3 to 5d)	Male LE rats	4x2mg/kg at 2h intervals	↘ reversal learning (TBDR and ASS tasks)	<a href="#">Izquierdo et al. (2010)</a>
Adulthood (6w)	Adulthood (+15 to 19d)	Male ICR mice	1mg/kg for 7d	↘ recognition memory (NOR task)	<a href="#">Lu et al. (2010)</a>
11 to 20d	28 to 46d (adolescent)	C57BL/6 mice	5mg/kg/d (mother)	↘ recognition memory (NOR task)	<a href="#">Siegel et al. (2011)</a>
Adulthood (90d)	Adulthood (+16d)	Male Wistar Rats	4x5mg/kg/d at 2h intervals for 10d	↘ long-term recognition memory (NOR task)	<a href="#">Melo et al. (2012)</a>
Adulthood (6-10w)	Adulthood (+5d)	Male SW mice	4x20mg/kg at 2h intervals	↘ learning and memory (PA test)	<a href="#">Murnane et al. (2012)</a>
Adulthood	Adulthood (+22d)	Male Wistar rats	Self-administered 0.05mg/injection 6h/d for 22d	↘ spatial memory (Y-maze) ↘ working memory (T-maze)	<a href="#">Recinto et al. (2012)</a>
Adulthood (7w)	Adulthood (+42d)	Male C57BL/6 mice	30mg/kg/w for 2w + 5w abstinence	↘ reference and working memory (RAM test)	<a href="#">Braren et al. (2014)</a>
Adolescence (4w)	Adulthood 20w	Male SD rats	4 or 8mg/kg/d for 16w	↘ short-term recognition memory (NOR task) (not for 4mg/kg/d)	<a href="#">Thanos et al. (2017)</a>

(Table 1 continued)

Adulthood (8w)	Adulthood (+32 to 49d)	Male C57BL/6 mice	5.23mg/kg/d for 28d + 5d abstinence	<ul style="list-style-type: none"> <li>↘ working memory (RAM test)</li> <li>↘ spatial learning/cognitive flexibility (RAM test)</li> </ul>	<a href="#">Avila et al. (2018)</a>
Entire gestation	60 to 69d	C57BL/6 mice	4mg/kg every other day (mother) (+meth escalating doses before pregnancy from PD33 to PD60)	<ul style="list-style-type: none"> <li>↘ short-term recognition memory (NOR task)</li> </ul>	<a href="#">Dong et al. (2018)</a>
Adulthood	Adulthood (+15 to 76d)	Male SD rats	40mg/kg	<ul style="list-style-type: none"> <li>↘ integration learning (CWM test)</li> <li>↘ learning strategy (SWM test)</li> </ul>	<a href="#">Gutierrez et al. (2018)</a>
Adulthood (60-70d)	Adulthood (+15 to 76d)	Male SD rats	40mg/kg	<ul style="list-style-type: none"> <li>↘ integration learning (CWM test)</li> <li>↘ learning strategy (SWM test)</li> </ul>	<a href="#">Gutierrez et al. (2019)</a>
6 to 15d	30d to 75d	Male SD rats	4x10mg/kg at 2h intervals for 10d	<ul style="list-style-type: none"> <li>↘ integration learning (CWM test)</li> </ul>	<a href="#">Jablonski et al. (2019)</a>
Adulthood	Adulthood (+3d)	Male C57BL/6 mice	2mg/kg/d for 3d	<ul style="list-style-type: none"> <li>↘ recognition memory (NOR task)</li> <li>↘ short-term spatial memory (Y-maze)</li> </ul>	<a href="#">Zhao et al. (2019)</a>
Adulthood	Adulthood (+7d)	Male C57BL/6 mice	10mg/kg/d for 7d	<ul style="list-style-type: none"> <li>↘ recognition memory (NOR task)</li> </ul>	<a href="#">Zhou et al. (2019)</a>
Adulthood (16w)	Adulthood (+5-7d)	Male SD rats	2mg/kg/d for 3d + 5mg/kg/d for 4d	<ul style="list-style-type: none"> <li>↘ working memory (Y-maze)</li> <li>↘ long-term memory (PA test)</li> </ul>	<a href="#">Golsorkhdan et al. (2020)</a>
Adulthood (7-8w)	Adulthood (+21d)	Male ICR mice	1mg/kg/d for 7d	<ul style="list-style-type: none"> <li>↘ novel object recognition (NOR task)</li> </ul>	<a href="#">Lwin et al. (2021)</a>
Adulthood (6-8w)	Adulthood (+12d)	Male KM mice	1mg/kg every other day for 7d	<ul style="list-style-type: none"> <li>↘ reward-related learning and memory (CPP test)</li> </ul>	<a href="#">Wang et al. (2021)</a>

Abbreviations: ASS, attentional set shift; BM, Barnes maze; CPP, conditional place preference; CWM, Cincinnati water maze; d, day; h, hours; ICR, Institute for Cancer Research; kg, kilogram; KM, Kun-Ming; m, minute; LE, Long-Evans; mg, milligram; NOR, novel object recognition; PA, passive avoidance; PD, post-natal day; RAM, radial-arm maze; SD, Sprague-Dawley; SW, Swiss Webster; SWM, star water maze; TBDRL, touchscreen-based discrimination-reversal learning; w, week.

Grey highlights shows negative results under particular conditions.

**Table 2**

Effect of methamphetamine prenatal exposure (maternal self-report) on learning- and memory-related brain structure and functions in young humans (references are listed in chronological and alphabetical ascending order)

<b>Age</b>	<b>Mother's abuse</b>	<b>Cohorts</b>	<b>Effects observed</b>	<b>Reference</b>
3 to 16y	Methamphetamine  10 + 9 CT	13 + 15 CT	<ul style="list-style-type: none"> <li>↘ putamen, globus pallidus &amp; hippocampus size</li> <li>↘ visual motor integration</li> <li>↘ attention</li> <li>↘ verbal memory</li> <li>↘ long-term spatial memory</li> </ul>	<a href="#">Chang et al. (2004)</a>
3 to 4y	Methamphetamine	49 + 49 CT	<ul style="list-style-type: none"> <li>↘ visual motor integration</li> </ul>	<a href="#">Chang et al. (2009)</a>
3 to 4y	Methamphetamine	29 + 37 CT	Alterations in white matter maturation	<a href="#">Cloak et al. (2009)</a>
7 to 15y	Methamphetamine + alcohol	12 + 20 CT	<ul style="list-style-type: none"> <li>↘ verbal memory</li> </ul>	<a href="#">Lu et al. (2009)</a>
5 to 15y	Methamphetamine + alcohol	18 + 27 CT	<ul style="list-style-type: none"> <li>↘ striatal and thalamus volume</li> <li>↗ limbic structures volume</li> <li>↗ cognitive deficits (FSIQ score)</li> </ul>	<a href="#">Sowell et al. (2010)</a>
7 to 9y	Methamphetamine + polysubstance	31 + 35 CT	<ul style="list-style-type: none"> <li>↘ executive functions (behavior regulation and metacognition)</li> <li>↘ spatial performance</li> </ul>	<a href="#">Piper et al. (2011)</a>
1 to 3y	Methamphetamine	204 + 208 CT	<ul style="list-style-type: none"> <li>↘ fine motor performance (at 1y but not 3y)</li> <li>No effect on cognition</li> </ul>	<a href="#">Smith et al. (2011)</a>
5.5y	Methamphetamine + caregiver psychological distress + child maltreatment	137 + 130 CT	<ul style="list-style-type: none"> <li>↘ inhibitory control</li> </ul>	<a href="#">Derauf et al. (2012)</a>
7.5y	Methamphetamine	151 + 147 CT	<ul style="list-style-type: none"> <li>↗ cognitive problems (CPRS-R:SF test)</li> </ul>	<a href="#">Diaz et al. (2014)</a>
6 to 7y	Methamphetamine	17 + 15 CT	<ul style="list-style-type: none"> <li>↘ executive function</li> <li>Disruption of white matter integrity</li> </ul>	<a href="#">Roos et al. (2015)</a>
Birth to 7.5y	Methamphetamine	204 + 208 CT	<ul style="list-style-type: none"> <li>↘ inhibitory control</li> </ul>	<a href="#">Smith et al. (2015)</a>
6 to 7y	Methamphetamine	23 + 22 CT	<ul style="list-style-type: none"> <li>↘ IQ</li> <li>↘ learning and memory</li> <li>↘ confrontation naming</li> <li>↘ visual-motor integration</li> </ul>	<a href="#">Kwiatkowski et al. (2018)</a>

Abbreviations: CPRS-R:SF, Conner's Parent Rating Scale-Revised:Short Form; CT, controls; d, day; FSIQ, full-scale intelligent quotient; IQ, Intelligence Quotient; y, year.

**Table 3**

Effect of methamphetamine abuse in adolescent humans on learning- and memory-related brain structure and functions (references are listed in chronological ascending order)

<b>Mode of abuse (means)</b>	<b>Cohorts</b>	<b>Effects observed</b>	<b>Reference</b>
Age: 18.4y (CT: 17.7y) Duration: 29.6m Dose: 0.8g/d Abstinence: 226d	54 (20 men) + 74 CT (37 men)	↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">King et al. (2010)</a>
Age: 18y (CT: 18y) Duration: 25m Dose: 118.6g/lifetime Abstinence: none	51 (40 men) + 60 CT (48 men)	↘ thickness of grey matter in orbitofrontal cortex, precuneus and inferior parietal cortex (worse than in adults) ↘ white matter integrity in PFC-striatum tract, OFC-NA tract and corpus callosum (FA) (worse than in adults) ↘ executive function (WCS, TM-B and SCW tests) (worse than in adults) ↘ working memory (DS and SS tasks) ↘ memory performance (ROCF and CVL tests) ↘ learning performance (CVL test)	<a href="#">Lyo et al. (2015)</a>
Age: 18.1y (CT: 17.9y) Duration: 25.5m Dose: 125.2g/lifetime Abstinence: none	44 (35 men) + 53 CT (41 men)	↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">Kim et al. (2018)</a>

Abbreviations: CT, controls; CVL, California verbal learning; d, day; DS, Digit symbol; FA, fractional anisotropy; g, gram; m, month; OFC-NA, orbitofrontal cortex-nucleus accumbens; PFC, prefrontal cortex; ROCF, Rey-Osterrieth complex figure; SCW, Stroop color word; SS, spatial span; TM, Trail making; WCS, Wisconsin card sorting; y, year. Grey highlights shows comparison between adolescents and adults (from the same study).

**Table 4**

Effect of methamphetamine abuse in adult humans on learning- and memory-related brain structure and functions (references are listed in chronological and alphabetical ascending order)

<b>Mode of abuse (means)</b>	<b>Cohorts</b>	<b>Effects observed</b>	<b>Reference</b>
Age: 32y (CT: 31y) Duration: 11.25y Dose: 720mg/d Abstinence: none	65 (36 men) + 65 CT (26 men)	<ul style="list-style-type: none"> <li>↘ memory recall</li> <li>↘ ability to manipulate information (DS and TM-B test)</li> <li>↘ ability to ignore irrelevant information (SCW test)</li> </ul>	<a href="#">Simon et al. (2000)</a>
Age: 32.5y (CT: 32.6y) Duration: >2y Dose: >2g/w Abstinence: 8m	20 (10 men) + 20 (10 men)	<ul style="list-style-type: none"> <li>↘ working memory (CalCAP test)</li> </ul>	<a href="#">Chang et al. (2002)</a>
Age: 31.7y (CT: 35.7y) Duration: 17.25y Dose: NI Abstinence: 3m	8 (8 men) + 12 CT (12 men)	<ul style="list-style-type: none"> <li>↘ cognitive inhibition (focus/attention) (SCW test)</li> </ul>	<a href="#">Salo et al. (2002)</a>
Age: 32y (CT: 30y) Duration: NI Dose: NI Abstinence: none	40 (20 men) + 40 CT (12 men)	<ul style="list-style-type: none"> <li>↘ cognitive inhibition (focus/attention) (SCW test)</li> <li>↘ executive function (WCS test)</li> <li>↘ memory (WR test)</li> </ul>	<a href="#">Simon et al. (2002)</a>
Age: 35.4y (CT: 32.7y) Duration: NI Dose: 2.1g/w Abstinence: 9.5d	27 (19 men) + 18 CT (15 men)	<ul style="list-style-type: none"> <li>↘ verbal learning (RAVLT, DR and WMS-III LM tests)</li> <li>↘ attention/psychomotor speed (SDM test)</li> <li>↘ cognitive inhibition (focus/attention) (SCW test)</li> </ul>	<a href="#">Kalechstein et al. (2003)</a>
Age: 41.4y (CT:38.7y) Duration: 16.8y Dose: NI Abstinence: 25d	14 (14 men) + 14 CT (10 men)	<ul style="list-style-type: none"> <li>Impaired decision making</li> <li>↘ task-related activation of orbitofrontal, dorsolateral prefrontal, anterior cingulate and parietal cortices (fMRI)</li> </ul>	<a href="#">Paulus et al. (2003)</a>
Age: 39.4y (CT: 34.6y) Duration: NI Dose: NI Abstinence: NI	26 (14 men) + 41 CT (20 men)	<ul style="list-style-type: none"> <li>↘ memory performance (SMTR)</li> <li>↘ learning performance (SM and FM tests)</li> </ul>	<a href="#">Gonzalez et al. (2004)</a>
Age: 37.7y (CT: 34.4y) Duration: 12.1y Dose: NI Abstinence: 4.5m	47 (35 men) + 60 CT (30 men)	<ul style="list-style-type: none"> <li>↘ working memory (PASA and WAIS-III LNS tests)</li> <li>↘ memory performance (BVM-DR and HVL-DR tests)</li> </ul>	<a href="#">Rippeth et al. (2004)</a>
Age: 35.3y (CT: 31.9y) Duration: 10.5y Dose: 3.44g/w Abstinence: none	22 (15 men) + 21 CT (10m/11f)	<ul style="list-style-type: none"> <li>↘ grey matter in cingulate, limbic and paralimbic cortices</li> <li>↘ hippocampal volume</li> <li>↗ overall white matter density</li> <li>↘ memory performance (RM test)</li> </ul>	<a href="#">Thompson et al. (2004)</a>
Age: 27.5y (overall) Duration: 7.7y Dose: 4.8g/w Abstinence: none	11 (7 men) + 43 CT (19m/23f)	<ul style="list-style-type: none"> <li>↘ cognitive inhibition (focus/attention) (Stop-Signal task)</li> </ul>	<a href="#">Monterosso et al. (2005)</a>

(Table 4 continued)

Age: NA (CT: NA) Duration: NA Dose: NA Abstinence: 9.2m	87 (60 men) + 71 CT (42 men)	↘ verbal memory (HVL test)	<a href="#">Woods et al. (2005)</a>
Age: 37.9y (CT: 35.2y) Duration: 2.55y Dose: 1.39g/d Abstinence: 13w	41 (31 men) + 41 CT (30 men)	↘ memory (RAVL and BSR tests) ↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">Hoffman et al. (2006)</a>
Age: 32y (CT: 31y) Duration: 10.3y Dose: 1.39g/d Abstinence: 1y	16 (11 men) + 18 CT (12 men)	↘ explicit (verbal) memory (CVL test)	<a href="#">Johanson et al. (2006)</a>
Age: 36.5y (CT: 33.2y) Duration: 5.35y Dose: 0.62g/d Abstinence: 20m	29 (27 men) + 20 CT (15 men) (MR scan)	↘ cognitive inhibition (focus/attention) (WCS test) ↘ grey matter in the right middle frontal cortex	<a href="#">Kim et al. (2006)</a>
Age: 35.4y (CT: 31.1y) Duration: 16.7y Dose: NI Abstinence: 29.9d	16 (12 men) + 19 CT (12 men)	↘ working memory (DNM to sample task)	<a href="#">Gonzalez et al. (2007)</a>
Age: 40.6y (CT: 40y) Duration: 12.84y Dose: NI Abstinence: 1.79y	19 (19 men) + 18 CT (18 men)	↘ visual memory (IVR and DVR tests)	<a href="#">Moon et al. (2007)</a>
Age: 36.9y (CT: 32.1y) Duration: 12.4y Dose: NI Abstinence: >3w	36 (13 men) + 16 CT (8 men)	↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">Salo et al. (2007)</a>
Age: 27.8y (CT: 29.7y) Duration: 5.1y Dose: NI Abstinence: 19d	16 (11 men) + 14 CT (11 men)	↘ memory performance (CVL test) ↘ perceptual speed (TM-A test) ↘ verbal short-term memory (WMS-III LM test)	<a href="#">Boileau et al. (2008)</a>
Age: 33.4y (CT: 34.8y) Duration: 8.44y Dose: 0.91g/d Abstinence: >2w	22 (12 men) + 17 CT (13 men)	↘ verbal learning and memory (WMS-III LM test) ↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">McCann et al. (2008)</a>
Age: 27.5y (CT: 28.2y) Duration: 3.9y Dose: 3.6g/w Abstinence: 5.9m	20 (12 men) + 20 CT (12 men)	↘ retrospective memory/verbal learning (RAVL test)	<a href="#">Henry et al. (2009)</a>
Age: 27.5y (CT: 28.2y) Duration: 3.85y Dose: 3.6g/w Abstinence: 5.9m	20 (12 men) + 20 CT (12 men)	↘ prospective memory (VW board game) ↘ retrospective memory/verbal learning (RAVL test)	<a href="#">Rendell et al. (2009)</a>

(Table 4 continued)

Age: 36.1y (CT: 33.9y) Duration: 13.4y Dose: NI Abstinence: 2.6m	38 (19 men) + 33 CT (22 men)	↘ cognitive inhibition (focus/attention) (SCW test) (not observed when abstinence >1y)	<a href="#">Salo et al. (2009a)</a>
Age: 35.7y (CT: 30.2y) Duration: 13.9y Dose: NI Abstinence: 4.1m	12 (5 men) + 16 CT (8 men)	↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">Salo et al. (2009b)</a>
Age: 30.7y (CT: 28.9y) Duration: 7.8y Dose: NI Abstinence: >15d	38 (13 men) + 36 CT (19 men)	↘ working memory (TTT test) ↘ cognitive flexibility (Switch task)	<a href="#">van der Plas et al. (2009)</a>
Age: 36.3y (CT: 35.1y) Duration: 12y Dose: 87.4mg/d Abstinence: 129d	54 (40 men) + 46 CT (23 men)	↘ learning performance (BVM and HVL tests) ↘ memory performance (HVL-DR test and SMTR)	<a href="#">Cherner et al. (2010)</a>
Age: 38.5y (CT: 35.4y) Duration: 7.6y Dose: 0.77g/d Abstinence: none	58 (53 men) + 38 CT (31 men)	↘ speed of information processing ↘ learning ability (HVL and BVM tests) ↘ executive function (HC, WCS, TM-B and SCW tests)	<a href="#">Iudicello et al. (2010)</a>
Age: 33.9y (CT: 33.3y) Duration: 7.6y Dose: 4.7g/w Abstinence: 6.5d	27 (17 men) + 28 CT (14 men)	↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">Simon et al. (2010)</a>
Age: 35.9y (CT: 31.1y) Duration: 10.1y Dose: 2.6g/w Abstinence: none	24 (12 men) + 17 CT (8 men)	↘ cognitive inhibition (focus/attention) (SCW test)	<a href="#">Dean et al. (2011)</a>
Age: 36y (CT: 33.7y) Duration: 10.3y Dose: 3.1g/w Abstinence: 11.5d	16 (10 men) + 19 CT (9 men)	↘ learning performance (RL task)	<a href="#">Ghahremani et al. (2011)</a>
Age: 41.6y (CT: 40.6y) Duration: 4.6y Dose: 0.63g/d Abstinence: 3m	39 (36 men) + 26 CT (11 men)	↘ prospective memory (MIS test)	<a href="#">Iudicello et al. (2011)</a>
Age: 40.2y (CT: 38.9y) Duration: 13.93y Dose: 311mg/d Abstinence: 19.46d	28 (28 men) + 27 CT (27 men)	↘ cognitive flexibility (WCS test)	<a href="#">Kim et al. (2011)</a>
Age: 33.5y (CT: 36.4y) Duration: 8.3y Dose: 8.4g/w Abstinence: 5.5d	10 (5 men) + 18 CT (11 men)	↘ cognitive inhibition (focus/attention) (SCW test) prefrontal hypoactivation during tasks (fMRI)	<a href="#">Nestor et al. (2011)</a>

(Table 4 continued)

Age: 36.2y (CT: 33.8y) Duration: 14.2y Dose: NI Abstinence: 2.7m	41 (19 men) + 38 CT (21 men)	↘ cognitive inhibition (focus/attention) (SCW test) (not observed when abstinence >1y)	<a href="#">Salo et al. (2011)</a>
Age: 37.3y (CT: 37.6y) Duration: 10.8y Dose: 0.73g/d Abstinence: 91d	114 (80 men) + 110 CT (70 men)	↘ visual memory (BVM test)	<a href="#">Morgan et al. (2012)</a>
Age: 35.5y (CT: 29y) Duration: 14y Dose: 1.3g/d Abstinence: >3w	30 (15 men) + 30 CT (17 men)	↘ cognitive inhibition (focus/attention) (Stroop task)	<a href="#">Salo et al. (2013)</a>
Age: 41.5y (CT: 41.5y) Duration: 6.9y Dose: 378.6g/lifetime Abstinence: none	54 (44 men) + 60 CT (48 men)	↘ thickness of grey matter in temporolimbic cortex ↘ white matter integrity in prefrontolimbic tracts (FA) ↘ executive function (WCS, TM-B and SCW tests) ↘ working memory (DS and SS tasks) ↘ memory performance (ROCF and CVL tests) ↘ learning performance (CVL test)	<a href="#">Lyo et al. (2015)</a>
Age: 31.5y (CT: 46y) Duration: NI Dose: NI Abstinence: none	194 (160 men) + 378 CT (149 men)	↘ immediate and delayed memory	<a href="#">Su et al. (2015)</a>
Age: 33.9y (CT: 30.5y) Duration: 4.14y Dose: NI Abstinence: 44.85d	54 (40 men) + 58 CT (37 men)	↘ verbal learning and memory (ISL task) ↘ working memory (TB task) ↘ learning ability (GML task) ↘ visual special working memory (GML task)	<a href="#">Zhong et al. (2016)</a>
Age: 29.9y (CT: NI) Duration: 8.3y Dose: 0.7-1.38g/d Abstinence: 9.9m	13 (8 men) + 32 CT (NI)	↘ cognitive inhibition (focus/attention) (SCW test) (not observed when abstinence >2y)	<a href="#">Stock et al. (2019)</a>
Age: 30-34y (CT: NI) Duration: 5.5-6.1y Dose: 0.7-1.38g/d Abstinence: 3.4-4.1y	42 (32 men) + 31 CT (20 men)	↘ learning ability (GML task) ↘ working memory (CPAL task)	<a href="#">Chen et al. (2020)</a>
Age: 18-45y (CT: NI) Duration: NI Dose: NI Abstinence: <3m	106 (106 men) + 76 CT (76 men)	↘ immediate memory (SM task) ↘ delayed memory (SMTR, FMTR)	<a href="#">Zhao et al. (2020)</a>

Abbreviations: BSR, Babcock story recall; BVM, brief visuospatial memory; CalCAP, California computerized assessment package; CT, controls; CPAL, continuous paired association learning; CVL, California verbal learning; d, day; DNMT, delayed non-match; DR, delayed recall; DS, Digit symbol; DVR, delayed visual recall; FA, fractional anisotropy; FM, figure memory; fMRI, functional magnetic resonance imaging; FMTR, figure memory test retention; g, gram; GML, Groton maze learning; HC, Halstead category; HVL, Hopkins verbal learning; ISL, international shopping list; IVR, immediate visual recall; m, month; mg, milligram; MIS, memory for intentions screening; NI, not indicated; PASA, paced auditory serial addition; RAVL, Rey auditory verbal learning; RL, reversal learning; ROCF, Rey-Osterrieth complex figure; RM, repeated memory; SCW, Stroop color word; SDM, symbol digit modalities; SM, story

memory; SMTR, story memory test retention; SS, spatial span; TB, two back; TM, Trail making; TTT, tic tac toe; VW, virtual week; w, week; WAIS-III LNS, Wechsler adult intelligence scale-III letter-number sequencing; WCS, Wisconsin card sorting; WMS-III LM, Wechsler memory scale-III logical memory; WR, word recall; y, year.  
Grey highlights shows additional data observed for longer abstinence.

**Table 5**

Effect of methamphetamine on dopamine markers (references are listed in chronological and alphabetical ascending order)

Age at treatment	Age at test	Model	Dose	Effects observed	Reference
Adulthood	29-35y	Humans	>0.25g/d 4d/w for >2y	↘ DAT binding in caudate and putamen (not for long-term abstinence)	Volkow et al. (2001a)
Adulthood	31-32y	Humans	1.6g/d for 11y	↘ DAT binding in caudate and putamen	Volkow et al. (2001b)
Adulthood	Adulthood (+4d)	Male SD rats	3x10mg/kg at 2h intervals	↘ DA in the striatum	Bisagno et al. (2002)
Adulthood	Adulthood (+3w)	Male SD rats	4x4mg/kg at 2h intervals	↘ DAT binding in striatum	Schroder et al. (2003)
11 to 20d	60 to 67d	SD rats	4x5mg/kg/d (mother)	↘ striatal monoamine levels	Williams et al. (2003a)
Adulthood	Adulthood (+8d)	Male SD rats	4x4mg/kg	↘ DAT binding in vCPu	Belcher et al. (2005)
Adulthood	Adulthood (+9w)	Male SD rats	4x10mg/kg at 2h intervals	↘ DA in medial and lateral striatum	Daberkow et al. (2005)
Adulthood	Adulthood (+31d)	Male SD rats	4x5mg/kg at 2h intervals	↘ TH immunostaining in CPu	He et al. (2006)
Adulthood (9w)	Adulthood (+3d)	Male SW mice	3x5mg/kg	↘ TH-positive neurons in striatum	Achat-Mendes et al. (2007)
Adulthood	Adulthood (+1w)	Male SD rats	4x1-4mg/kg (single day treatment)	↘ binding to monoamine transporters in striatum	Belcher et al. (2008)
Adulthood	Adulthood (+72h)	Male SD rats	4x10mg/kg at 2h intervals or 24x1.67mg/kg at 15min intervals	↘ DA in neostriatum	Herring et al. (2008)
Adulthood (8-9w)	Adulthood (+2w)	Male C57BL/6J mice	3x10mg/kg	↘ DA in PC, striatum and NAc ↘ DAT protein levels in striatum	Ke et al. (2008)
Adulthood	33-34y	Humans	0.91g/d for 8.44y	↘ DAT binding in putamen and caudate nucleus	McCann et al. (2008)
Adulthood	Adulthood (+1w)	Male LE rats	4x2mg/kg at 2h intervals	↘ DAT binding in dorsal and ventral CPu	Izquierdo et al. (2010)
Adulthood (6w)	Adulthood (+20d)	Male ICR mice	1mg/kg for 7d	↘ DA in PC	Lu et al. (2010)
Adulthood (5-9y)	Adulthood (+2 to 6m)	Male <i>sabaeus</i> monkeys	Escalating doses (0.1mg/kg/d to 4mg/kg/d) for 31d and VMes	↘ D2R availability in CN and putamen ↘ DAT availability in CN, putamen, VS	Groman et al. (2012)
Adulthood (90d)	Adulthood (+18d)	Male Wistar	4x5mg/kg/d at 2h intervals	↘ DA levels in striatum	Melo et al. (2012)

rats for 10d

(Table 5 continued)

Adulthood (6-10w)	Adulthood (+6d)	Male SW mice	4x20mg/kg at 2h intervals	↘ DA in anterior and posterior striatum	<a href="#">Murnane et al. (2012)</a>
Adulthood	Adulthood (+3 to 7w)	Male SD rats	4x10mg/kg at 2h intervals	↘ DA in striatum (+3w) ↘ DAT binding in DM and DL striatum (+7w)	<a href="#">Pastuzyn et al. (2012)</a>
Adulthood	Adulthood (+7d)	Male SD rats	4x7.5mg/kg at 2h intervals	↘ DAT activity in striatum ↘ DA in striatum	<a href="#">Baladi et al. (2014)</a>
Adulthood (7w)	Adulthood (+51d)	Male C57BL/6 mice	30mg/kg/w for 2w + 5w abstinence	↗ TH levels in striatum ↗ DAT levels in striatum	<a href="#">Braren et al. (2014)</a>
Adulthood	Adulthood (+2w)	Male SD rats	4x10mg/kg at 2h interval (single day treatment)	↘ DA in neostriatum and NAc	<a href="#">Gutierrez et al. (2017)</a>
11 to 15d 11 to 20d	15 or 20d	Male SD rats	4x5-7.5mg/kg/d for 5 or 10d	↘ DA in neostriatum	<a href="#">Jablonsky et al. (2017)</a>
Adolescence (4w)	Adulthood 20w	Male SD rats	4 or 8mg/kg/d for 16w	↘ DAT levels in DL, DM, VL and VM striatum and NAc ↘ D1R levels in DL, DM, VL and VM striatum, NAc and OT ↘ D2R levels in DL, DM and VL striatum (not for 4mg/kg/d) ↘ D2R binding availability in striatum (not for 4mg/kg/d)	<a href="#">Thanos et al. (2017)</a>
Adulthood	Adulthood (+76d)	Male SD rats	40mg/kg	↘ DA in neostriatum and NAc	<a href="#">Gutierrez et al. (2018)</a>
Adulthood (60-70d)	Adulthood (+2w-+76d)	Male SD rats	40mg/kg	↘ DA in neostriatum and NAc	<a href="#">Gutierrez et al. (2019)</a>

Abbreviations: CN, caudate nucleus; CPu, caudate putamen; d, day; DA, dopamine; DAT, dopamine transporter; DL, dorsolateral; DM, dorsomedial; DR, dopamine receptor; g, gram; h, hours; ICR, Institute for Cancer Research; kg, kilogram; LE, Long-Evans; m, month; mg, milligram; NAc, nucleus accumbens; OT, olfactory tubercle; PC, prefrontal cortex; SD, Sprague-Dawley; SW, Swiss Webster; TH, tyrosine hydroxylase; vCPu, ventral caudate putamen; VL, ventrolateral; VM, ventromedial; VMes, ventral mesencephalon; VS, ventral striatum; w, week; y, year.

Grey highlights shows data discrepancies between conditions.

**Table 6**

Specific involvement of dopamine signaling components in methamphetamine-induced effects (references are listed in chronological and alphabetical ascending order)

Age at treatment	Age at test	Model	Dose	Effects observed	Reference
Adulthood	Adulthood (+7d)	Male SD rats	4x7.5mg/kg at 2h intervals	D3R antagonist (PG01037) alleviates meth-induced $\searrow$ in DAT activity in striatum by $\searrow$ meth-induced hyperthermia (no effect on DA levels)	Baladi et al. (2014)
Adulthood (60-70d)	Adulthood (+2w to 76d)	Male SD rats	40mg/kg	D1R (SCH23390) and D2R (sulpiride) antagonists alleviates meth-induced $\searrow$ in striatal DA D1R and D2R antagonists alleviates meth-induced deficits in integration learning (CWM test), learning strategy (SWM test) and spatial learning and memory (MWM test)	Gutierrez et al. (2019)
6 to 15d	30d to 75d	Male SD rats	4x10mg/kg at 2h intervals for 10d	D1R antagonist (SCH23390) alleviates meth-induced deficits in integration learning (CWM test) (no effect on meth-induced deficits in spatial learning and memory (MWM test))	Jablonski et al. (2019)
Adulthood (8-12w)	Adulthood (+7d)	C57BL/6 mice	2mg/kg/d for 5d	Conditional D1R (but not D2R) knockout in NAc aggravates meth-induced impairment in spatial learning and memory (MWM test)	Tu et al. (2019)
Adulthood	Adulthood (+7d)	Male C57BL/6 mice	10mg/kg/d for 7d	D1R agonist/D2R antagonist (L-stepholidine) Protects against meth-induced deficits in recognition memory (NOR task)	Zhou et al. (2019)

Abbreviations: CWM, Cincinnati water maze; d, day; DA, dopamine; DAT, dopamine transporter; DR, dopamine receptor; h, hours; kg, kilogram; mg, milligram; meth, methamphetamine; MWM, Morris water maze; NAc, nucleus accumbens; NOR, novel object recognition; SD, Sprague-Dawley; SWM, star water maze; w, week.

Grey highlights shows negative results under the same experimental conditions.

**Table 7**

Effects of methamphetamine on the structure, dopamine markers and learning- and memory-dependent functions of the hippocampus (references are listed in chronological and alphabetical ascending order)

Age at treatment	Age at test	Model	Dose	Effects observed	Reference
11 to 20d	50 to 56d	SD rats	4x10mg/kg/d 2x20mg/kg/d (mother)	↘ spatial learning and memory (MWM test)	Vorhees et al. (2000)
11 to 15d 16 to 20d	50d	SD rats	4x10mg/kg/d (mother)	↘ spatial learning and memory (MWM test) (only at 11 to 15d treatment)	Williams et al. (2003b)
11 to 20d	50 to 145d	SD rats	4x5-15mg/kg/d (mother)	↘ memory-based spatial learning (MWM test)	Williams et al. (2003c)
Entire gestation	70 to 90d	Male Wistar rats	5mg/kg/d (mother)	↘ performance in place navigation (MWM test, stable platform position)	Slamberova et al. (2005)
Adulthood (90d)	Adulthood (+18d)	Male Wistar rats	4x5mg/kg/d at 2h intervals for 10d	↘ DA levels in HPC	Melo et al. (2012)
Adulthood	Adulthood (+22d)	Male Wistar rats	Self-administered 0.05mg/injection 6h/d for 22d	↘ NPG proliferation in SGZ and DG	Recinto et al. (2012)
Adolescence (4-5w)	Adulthood (63-70d)	Male C57BL/6 mice	24mg/kg/d for 14d + 21d abstinence	↘ synaptic plasticity (LTP in the CA1 region of HPC) (14d + 21d abstinence) ↘ TH protein levels in HPC (14d) ↘ low MW 75kDa DAT protein levels in HPC (14d)	North et al. (2013)
Adulthood (7w)	Adulthood (+51d)	Male C57BL/6 mice	30mg/kg/w for 2w + 5w abstinence	↗ DAT levels in HPC ↘ D1R levels in HPC	Braren et al. (2014)
Adulthood (26y)	Adulthood (32y)	Humans	0.66g/occasion for 6.16y + 5.52m abstinence	↘ of HPC volume in females (not in males)	Du et al. (2015)
Adulthood	Adulthood (2w post treatment)	Male SD rats	4x10mg/kg at 2h intervals (single day treatment)	↘ spatial learning and memory (MWM test)	Gutierrez et al. (2017)
Adulthood (8w)	Adulthood (+38d)	Male C57BL/6 mice	5.23mg/kg/d for 28d + 5d abstinence	↘ cytosolic TH levels in HPC ↘ synaptic DAT levels in HPC ↗ synaptic D1R levels in HPC	Avila et al. (2018)
Entire gestation	60 to 69d	C57BL/6 mice	4mg/kg every other day (mother) (+meth escalating doses before pregnancy from PD33 to PD60)	↘ long-term spatial memory retention (MWM test) (not in females)	Dong et al. (2018)

Table 7 (continued)

Adulthood	Adulthood (+15 to 76d)	Male SD rats	40mg/kg	↘ spatial learning and memory (MWM test)	<a href="#">Gutierrez et al. (2018)</a>
Adulthood (60-70d)	Adulthood (+15 to 76d)	Male SD rats	40mg/kg	↘ spatial learning and memory (MWM test)	<a href="#">Gutierrez et al. (2019)</a>
6 to 15d	30d to 75d	Male SD rats	4x10mg/kg at 2h intervals for 10d	↘ spatial learning and memory (MWM test)	<a href="#">Jablonski et al. (2019)</a>
Adulthood (8-12w)	Adulthood (+7d)	C57BL/6 mice	2mg/kg/d for 5d	↘ spatial learning and memory (MWM test)	<a href="#">Tu et al. (2019)</a>
Adulthood	Adulthood (+7d)	Male C57BL/6 mice	10mg/kg/d for 7d	↘ DAT protein levels in HPC ↗ D2R protein levels in HPC	<a href="#">Zhou et al. (2019)</a>
Adulthood (16w)	Adulthood (+8d)	Male SD rats	2mg/kg/d for 3d + 5mg/kg/d for 4d	↘ HPC volume	<a href="#">Golsorkhdan et al. (2020)</a>
Adulthood (7-8w)	Adulthood (+21d)	Male ICR mice	1mg/kg/d for 7d	↘ spatial learning and memory (MWM test)	<a href="#">Lwin et al. (2021)</a>
Adulthood (7-8w)	Adulthood (+21d)	Male ICR mice	1mg/kg/d for 7d	↘ spatial learning and memory (MWM test)	<a href="#">Veschsanit et al. (2021)</a>

Abbreviations: CA1, cornu Ammonis 1; d, day; DA, dopamine; DAT, dopamine transporter; DG, Dentate gyrus; DR, dopamine receptor; h, hours; HPC, hippocampus; ICR, Institute for Cancer Research; kg, kilogram; LTP, long-term potentiation; m, month; mg, milligram; MWM, Morris water maze; NPG, neural progenitor cells; PD, post-natal day; SD, Sprague-Dawley; SGZ, sub-granular zone; TH, tyrosine hydroxylase; w, week; y, year.

Grey highlights shows negative results under particular conditions.

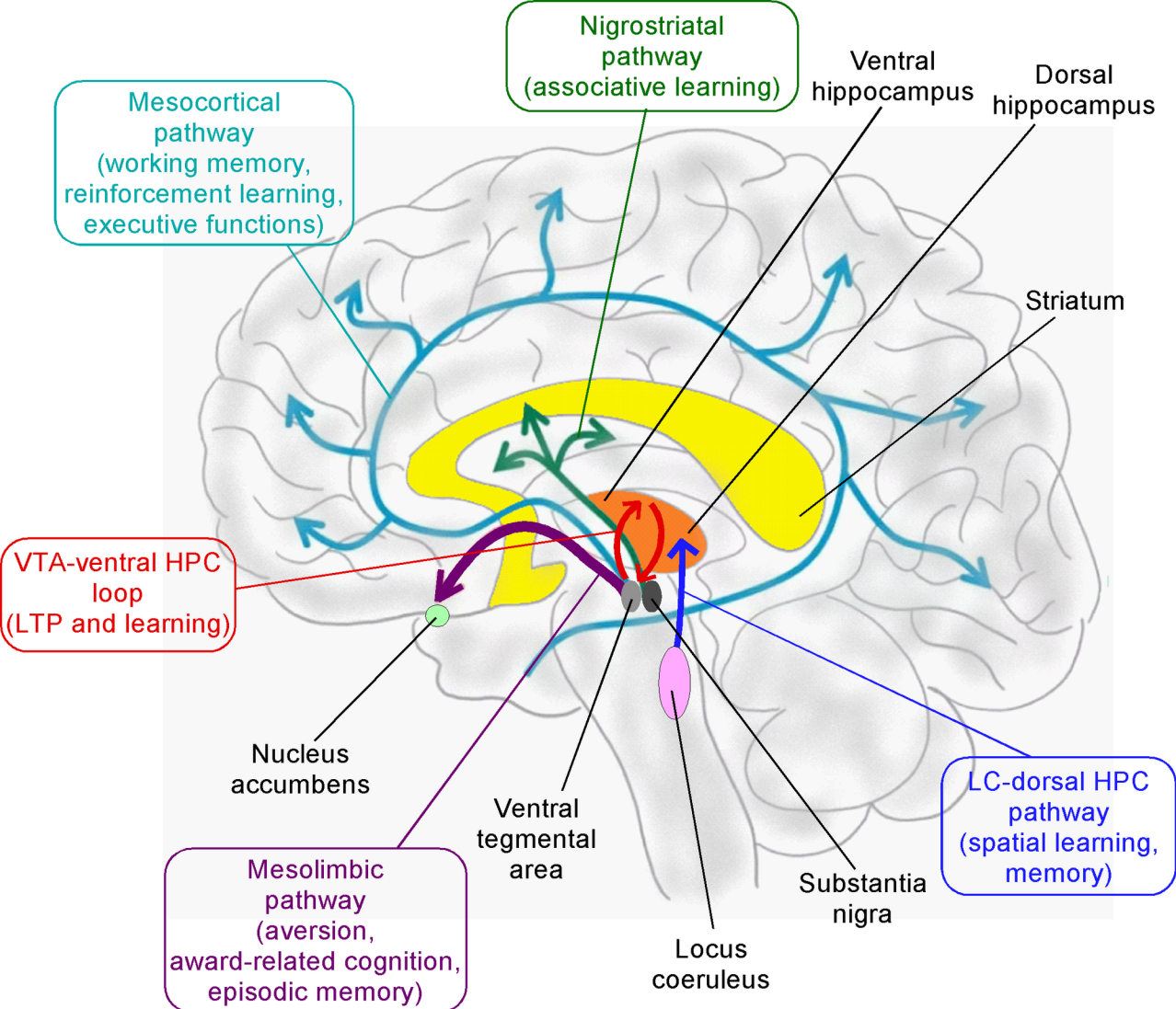


Figure 1

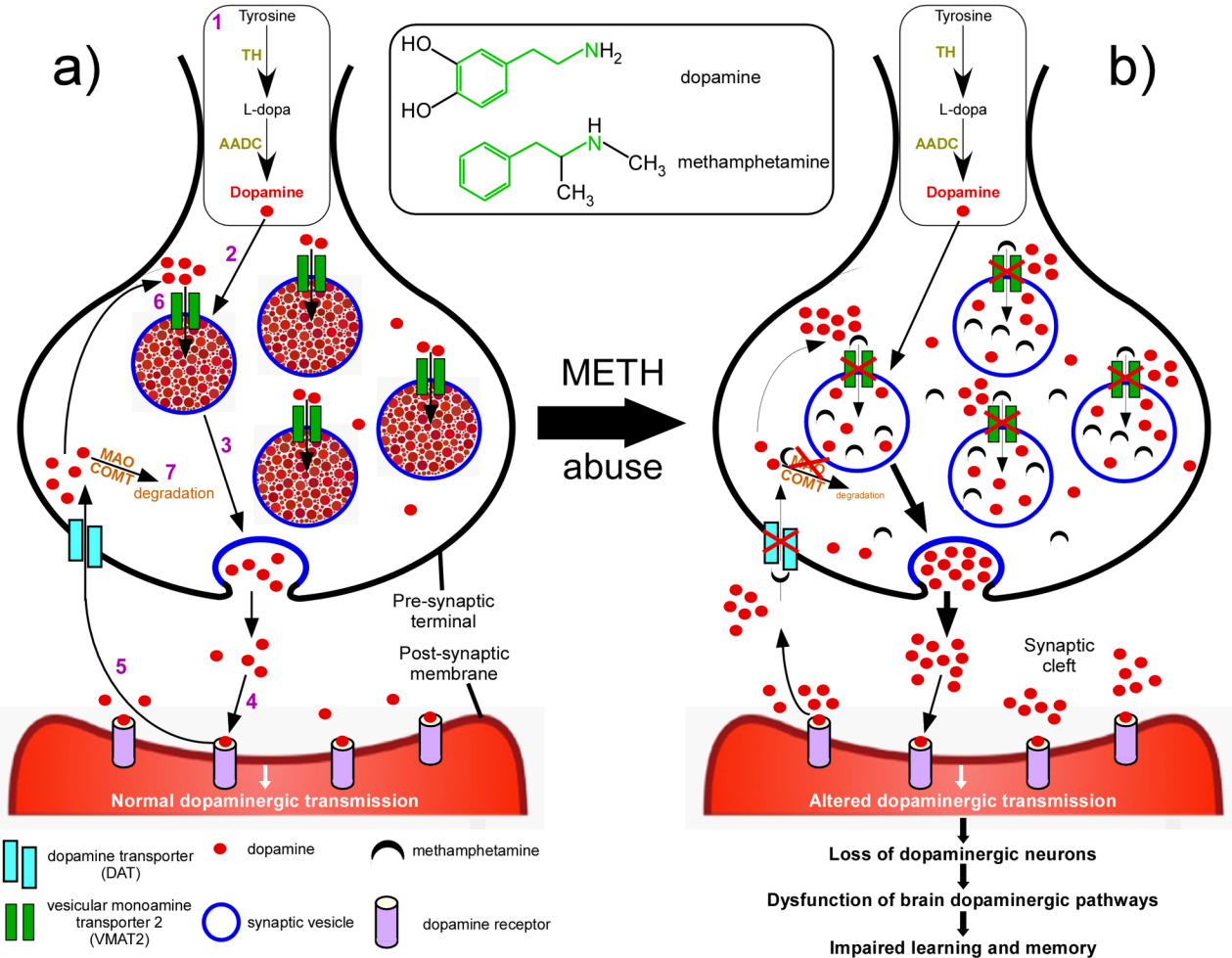


Figure 2