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Resubmission 1: Mini review prepared for Neuroscience and Biobehavioral Reviews

Chronic methamphetamine self-administration disrupts cortical control of cognition

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Highlights

- Human methamphetamine abusers exhibit cognitive deficits to varying degrees
- Extended meth access in rats impairs attentional processing and recognition memory
- These deficits result from cortical alterations following extended meth access
- Other cognitive dimensions and related structures are largely unexplored
- Medication restoring these deficits may help to maintain abstinence in meth addicts

Abstract

Methamphetamine (meth) is one of the most abused substances worldwide. Chronic use has been associated with repeated relapse episodes that may be exacerbated by cognitive impairments during drug abstinence. Growing evidence demonstrates that meth compromises prefrontal cortex activity, resulting in persisting attentional and memory impairments. After summarizing recent studies of meth-induced cognitive dysfunction using a translationally relevant model of self-administered meth, this review emphasizes the cortical brain changes contributing to cognitive dysregulation during abstinence. Finally, we propose the use of cognitive enhancers during abstinence that may promote a drug-free state by reversing cortical dysfunction linked with prolonged meth abuse.

Keywords: Addiction, methamphetamine, cognitive deficits, prefrontal, perirhinal, glutamate, attention, object recognition.

1. *Background*

Methamphetamine addiction, as any addiction with other abused substances, is a chronic relapsing disorder meriting the need for effective treatment strategies. The development of such strategies relies on concerted efforts by researchers to integrate findings from basic animal scientists and human clinical scientists with those of practitioners conducting clinical trials. Despite gains in our knowledge of meth, the effects of repeated meth abuse, and the severity of this problem, no treatments to date have proven to be consistently effective for alleviating the symptoms of meth addiction, particularly in regards to cognitive deficits and drug-seeking [1, 2]. These seemingly intractable problems can dramatically reduce quality of life for addicts and contribute to sustained drug taking and relapse.

Executive function includes the domains of decision-making, attentional control, and working memory. The most pronounced and lasting deficits experienced by psychostimulant addicts occur in executive function, as well as in episodic memory and information processing [3]. These cognitive domains require intact cortical function and meth addicts often show impairments of working memory and memory recall [4], psychomotor function [5], response inhibition [6, 7], strategy shifting tasks [8], and risky decision-making [9]. These deficits likely contribute, at least in part, to continued drug taking and poor unhealthy decision-making underlying addiction.

Although there are multiple reports suggesting that abused drugs impact these cognitive domains, the relationship between impaired executive function, addiction, and relapse is not well understood. Several reviews of the human literature have already been written summarizing the effects of meth on human cognitive dysfunction and the clinical

relevance of these deficits [3, 10, 11]. In general, the majority of data indicates that chronic meth causes cognitive decline in some people, particularly during early-to-middle adulthood [11]. Importantly, the high incidence of cognitive dysfunction that occurs in chronic pathological meth addiction is distinct from acute or low dose effects of meth [12]. Under these low dose conditions, meth may act to enhance cognition, even after repeated use. Indeed, meth has a long history of being prescribed as a pharmacological therapy for attentional disorders [13]. Here we review the existing literature demonstrating the existence of cortically mediated cognitive dysfunction following chronic exposure to self-administered meth with a focus on animal models.

2. Models of meth administration used to study cognitive dysfunction.

Although there is a presumed relationship between drug-seeking, cognitive deficits, and neural dysfunction, it is difficult to establish whether these deficits are caused by meth or a cognitive predisposition, since human subjects undergo evaluation well after they have become addicted. A major strength of preclinical research is the ability to study these relationships in a controlled manner using translationally relevant animal models.

Experimenter-administered meth, consisting primarily of sensitization or a repeated single day treatment regimen, has typically been used to assess meth induced neurotoxic consequences (e.g., loss of dopamine transporters, glial fibrillary acidic protein, tyrosine hydroxylase). Thorough reviews of meth-induced neurotoxicity have recently been provided [13, 14]. While useful, these models do not use contingent drug delivery and so cannot account for motivational and cognitive facets of drug use, which

constitute core features of meth addiction. Additionally, overt markers of striatal toxicity do not always occur with adverse cognitive consequences (discussed further in section 5, 15]. As such, drug self-administration (SA) procedures allow rats to regulate drug intake by eliciting a behavioral output such as a lever press or nose poke into a hole. This benefit increases face and construct validity of the self-administration model relative to systemic drug administration. Additionally, the predictive validity of self-administration models of psychostimulant abuse liability is robust [16, 17]. Finally, self-administration has greater translational relevance due to the flexibility of self-administration to develop protocols assessing various dimensions of the addiction spectrum [18].

As an exemplar, increasing the amount of time drug is available during daily sessions further extends the translational impact. Standard session lengths during acquisition are typically conducted in the 1-2 hour range [i.e., short access to the drug (ShA)] resulting in a stabilization of daily drug intake. In contrast, rats given 6 or more hours of daily drug SA [i.e., long access to the drug, (LgA)] display an escalation of drug intake over time reminiscent of human compulsive drug taking, thereby inducing a long-lasting increase in set point for the drug in LgA as compared to ShA rats [19-21]. Moreover, recent evidence indicates that LgA meth rats exhibit enhanced drug seeking and cognitive impairments relative to control rats or ShA. These impairments observed in LgA rats include attentional and impulsivity deficits [22], higher vulnerability to relapse and deficits in episodic memory [23], and persistent alterations of monoamine systems in prefrontal and striatal brain areas [24], which constitute several potent examples related to the construct validity of this model. These findings suggest that increasing drug access provides a clinically relevant paradigm that can assess drug taking

during acquisition as well as motivational and cognitive processes when the drug has been discontinued. The next sections will therefore focus on studies that identify deficits during periods of withdrawal or abstinence (i.e., when the drug has been discontinued) from chronic meth SA.

3. Attention, inhibitory control, and cognitive flexibility

The ability to adapt behavior according to current environmental or situational demands requires cognitive control by attending to task relevant information over extended periods of time, regardless of attentional interference [25]. These dimensions are particularly relevant to dissociate recreational from compulsive drug intake in addiction. For instance, deficits in response inhibition could account for the inability of a subject to resist the urge of drug taking when being in the presence of drug-associated cues, while deficits in strategy-shifting task could explain the difficulties of an addict in selecting alternatives to drug taking from a non-pathological behavioral repertoire. Based on the accumulation of 20 years of research, separate dimensions of impulsivity and attention shifting have been shown to be mediated by different cortical subregions [26, 27], which are disrupted by meth exposure.

3.1 Attentional set-shifting task.

In humans, the Wisconsin Card Sorting Task can identify specific deficits in attention and cognitive flexibility that correspond to prefrontal cortex function. This task assesses the adaptability to rule shift between a previously learned strategy and a new one, and is modelled in rodents by the Attentional Set-Shifting Task (ASST). In the most

well characterized protocol [28-32], rats are trained to dig in bowls for a food reward and then to discriminate between a baited and non-baited bowl based on a variety of dimensions (e.g., odor, digging media, and bowl texture). It must be noted that instead of not baiting the other bowl, crushed reinforcers are sometimes used as an alternative in order to avoid olfactory bias that would guide the rats to the only reinforced location [33]. Over the course of a single session, rats are presented with a series of discrimination phases that assess various components of learning (Figure 1), with advancement through the phases occurring after subjects reach the predetermined criteria. During the compound discrimination (CD), only one stimulus dimension reliably predicts food reward, while the other dimension is considered irrelevant. As illustrated in Figure 1, if a particular odor constantly predicts reward location (represented in blue color), it would be paired with different irrelevant digging media or bowl textures (represented by different shapes). Rats then undergo a reversal phase, in which the stimulus previously associated with the reward now predicts the absence of a reward, without changes in the relevant or irrelevant dimension. Then, intra- and extradimensional (ID and ED) shifts and reversals occur successively, assessing the adaptability of rats in novel learning paradigms. The ID shift requires the animal to learn a new discrimination between two novel stimuli of the same relevant dimension used for the CD phase (Figure 1, new odors represented with green and yellow colors); whereas, the ED introduces a novel discrimination between two stimuli among a dimension that was previously irrelevant (Figure 1, relevant digging media/bowl texture represented with the diamond shape), while the previously relevant dimension (i.e., odor) now becomes irrelevant. Correctly adjusting a learning strategy to perform an ED shift requires additional components

beyond just working memory and procedural learning. Specifically, the rats must attend to the fact that previous strategies no longer apply and must implement an alternative behavioral strategy, thus avoiding unsuccessful "perseverative" responding.

[Insert Figure 1 here]

Consistently, performance in this task relies on intact prefrontal cortex function in humans and animals. Lesions of the dorsolateral prefrontal cortex (primates) or medial prefrontal cortex (rodents) produce deficits shifting from one stimulus dimension to another (i.e., extra-dimensional shift), while similar damage to the orbital frontal cortex impairs reversal learning [28-31, 34]. Recently, using an automated variant of the task, data has shown that dorsal striatal neurons are involved in encoding rule representations during ASST [35]. Given the substantial amount of PFC efferents to dorsal striatal areas [36], together with the role of the dorsal striatum in encoding stimulus-response relations [37, 38], frontostriatal connectivity plays a key role in regulating set-shifting performance. Further indication that prefrontal dopamine levels constitute a key regulator of set-shifting performance comes from studies showing that infusions of a dopamine D₁ [39] or D₂ receptor antagonist [40] into the prelimbic cortex impaired ED set-shifting performance consisting of shifts from a response-based to a visual-based strategy.

3.2 *Five-Choice Serial Reaction Time Task.*

The 5-CSRTT is an automated operant procedure for measuring sustained visual attention and impulsivity in rats (see [41, 42] for review and detailed methodology). Briefly, to perform this task, a rat is placed in an apparatus with five holes equipped with photobeams to record head entries open for exploration. A stimulus light above each

hole signals the hole that a rat is supposed to explore. Upon a correct head entry, a sucrose pellet is delivered, and collection of the reward in the food magazine initiates the next trial. After several phases of training, attentional demand is progressively enhanced by decreasing the duration of the visual stimulus indicating the relevant hole. As shown in Figure 2, several types of responses are recorded in the test phase, namely incorrect, omission, premature, or perseverative responses. Correct responses are defined as a nose entry into the hole below visual stimulus, and lead to a reward delivery. Incorrect responses are defined as nose entries into a hole without the visual stimulus. An accuracy ratio of responding is calculated between correct and incorrect responses, reflecting the attentional performance of rats. Omissions are a lack of a response per trial. Premature responses, the main indicator of impulsive behavior in this task, occur when a rat makes a nose entry during the inter-trial interval, (i.e. before the light stimulus predicting reward delivery appears). These responses are evident with a constant inter-trial interval, and increasing this interval (usually from 5 to 7 seconds) enhances the propensity of premature responding. Perseverative responses are recorded when rats persist in responding into a hole after making a correct response, which is considered as a form of compulsive behavior.

[Insert Figure 2 here]

The 5-CSRTT requires corticostriatal functional integrity, as well as cortically projecting dopamine, norepinephrine, acetylcholine, and serotonin brain neurotransmitter systems [26, 42, 43]. Interestingly, distinct cortical areas mediate the specific type of response errors. Accuracy involves the anterior cingulate and prelimbic cortices [44]. More specifically, attentional selectivity encompasses the pregenual region of the anterior

cingulate while impulsive premature responses depend upon the post-genual anterior cingulate and the infralimbic cortex [44-46]. Further, compulsive-like responding as assessed by perseverative errors involves the prelimbic and orbital frontal cortex [45, 46]. Taken together, these studies show specificity to a certain degree with some overlap of cortical areas that account for response errors in the 5-CSRTT. The striatum has also been identified as the main subcortical area underlying performance in the 5-CSRTT, primarily through its connection with the frontal cortex [47]. Lesions of the medial and lateral striatum produce global deficits in every parameter of the 5-CSRTT, with even an inability of lateral striatum-lesioned animals to perform this task [48]. This section reviewed the importance of corticostriatal circuitry in regards to 5-CSRTT. Additionally this circuitry underlies reward-guided decision-making [49]; therefore, this circuitry is also a critical component in the transition from recreational to compulsive drug use [16, 27]. A discussion of chronic meth's impact on this task is described in section 3.3.2.

3.3 Chronic meth SA disrupts cortical control of attention and cognitive flexibility

3.3.1. Attentional set-shifting task

Chronic meth addicts exhibit deficits in attentional set shifting akin to patients with prefrontal damage or disorders associated with frontal cortical pathology, and these impairments correspond with alterations of prefrontal white and grey matter [50, 51]. In rats, LgA meth caused selective impairments in the ED, but not in the ID shift, that also corresponded with deficits found following excitotoxic lesions to the mPFC [32]. This meth-induced impairment indicates that LgA meth rats were less efficient in executing a new behavioral strategy. Further, this specific finding suggests that LgA meth does not

cause global deficits in ASST, but suggests selectivity within a specific domain within the task. Similar results have been reported after a chronic five-week amphetamine treatment that induced drug sensitization, though amphetamine further induced some reversal deficits [52, 53]. In contrast, a single day high dose meth treatment (4 x 2 mg/kg meth) produced reversal deficits during the reversal component of both ID and ED shifts, while attentional set-shifting before reversal remained intact [54]. As such, discrepancies exist in the degree to which meth disrupts set-shifting and the cortical structures involved.

Clearly, methodological difference regarding meth administration could account for the discrepancies regarding set-shifting deficits. The absence of ED shift deficits after the single-day injection protocol might be linked with an absence of prefrontal alterations, though not assessed in that particular study. Indeed, alterations of medial prefrontal cortex functioning have been linked with LgA meth-induced deficits in ED attentional set-shifting [32]. Therefore, a single-day meth injection regimen might not be enough to induce neuronal alterations in this particular prefrontal region. In parallel, reversal deficits with binge regimen might indicate a specific regulation of the orbitofrontal cortex, a key region involved in behavioral flexibility and reversal learning [55, 56]. Such discrepancies merit future studies on the relationship between the degree of meth exposure, attentional flexibility and its neurobiological underpinnings, especially regarding the contribution of the prefrontal and orbitofrontal cortex.

3.3.2. Five-choice serial reaction time task

Meth, and several related compounds (amphetamine, methylenedioxy-methamphetamine (MDMA), or methylphenidate) impact responding on the 5-CSRTT in

multiple ways. An acute meth injection enhanced attention on a two lever version of the CSRTT as indexed by reduced choice reaction time and increased general responding [57]. Similar improvements of attentional performance have been observed after acute non-contingent injections of d-amphetamine or methylphenidate [58-60]. In contrast, an escalating dose of amphetamine (3 injections per week for 5 weeks at 1-5 mg/kg per week) reduced accuracy and increased omissions when rats were tested during withdrawal on the 5-CSRTT [61]. MDMA self-administration also impaired accuracy and increased omissions when rats performed the 5-CSRTT the day after the last self-administration session, though these effects diminished after the first week of abstinence [62]. Most relevant to this discussion are the studies by Dalley *et al*, [22, 63], which used extended daily access SA procedures followed by assessment of attention and impulsivity with the 5-CSRTT. In a first set of experiments, rats were given repeated cycles of amphetamine SA (5 x 5 days, 8 hrs) and tested on the 5-CSRTT for nine consecutive days between self-administration cycles. Impairments were found mostly on the attentional component, illustrated by decreased speed and accuracy of responding as well as an increase in omissions, while other parameters were not affected [63]. These impairments typically recovered 4-5 days after withdrawal with no evidence of lasting impairments. Nevertheless, this recovery of function is quite fragile, because subsequent amphetamine challenges with 0.2-1.6 mg/kg (ip) revealed deficits in rats with previous self-administration experience. Specifically, amphetamine experienced animals had increased omissions, slower response times, and decreased impulsivity at the higher end of the dose range.

In regards to meth, an even more pronounced attentional deficit exists based on 5-CSRTT performance. Dalley *et al* [22] directly compared MDMA, d-amphetamine, and meth. Rats were initially trained on the attentional task before self-administration training with amphetamine, meth, or MDMA for 3 weeks (8 hrs daily). During withdrawal from meth, attention was impaired as evidenced by decreased accuracy, together with increased omission response latencies, while impulsive premature responding was transiently increased [22]. Although amphetamine and MDMA also resulted in impairments, deficits by these drugs were only apparent for a few days, consistent with other findings [62].

Altogether, it appears that dose, contingency and length of drug administration constitute critical factors to understand discrepancies in meth-induced effects on attentional performance, in both ASST and 5-CSRTT. Further studies are needed to elucidate the specific impairments of meth compared to other amphetamine-like drugs, as well as the structures involved. Indeed, while most studies investigating the effects of drugs of abuse on the 5-CSRTT have focused on impulsivity and inhibitory control (see [47] for a review), less interest has been accorded to attentional deficits induced by drugs of abuse in this task. Prefrontal corticostriatal connections and dopaminergic regulation, largely implicated in impulsivity, are also involved in attentional performance in the 5-CSRTT, as reviewed by Robbins [42]. In addition to dopamine, dysregulation of other neurotransmitter systems following meth may also contribute to performance on the task. Meth alters serotonin levels [64, 65] and most studies agree that the serotonergic system mediates impulsivity rather than the attentional aspect of the 5-CSRTT [66-71] (but see [72, 73]). In contrast, acetylcholine and norepinephrine levels are changed during

the 5-CSRTT [74], and both locus coeruleus [75] and basal forebrain nuclei [76] have been shown to constitute critical brain components driving attention in the 5-CSRTT. The impact of meth self-administration on these systems and brain areas are not completely known, but it is clear that meth impinges on cholinergic [77, 78] and noradrenergic [79, 80] structures, so these systems might further underlie meth-induced attentional deficits. It would be therefore interesting to test the role of these structures and their cortical outputs after acute or prolonged meth administration.

4. Recognition Memory

In humans, episodic memory is a form of declarative memory that implies the use of previously acquired autobiographic information for conscious recall [81]. Meth impacts this particular type of memory [3], and this impairment has been proposed to contribute to relapse in meth addicts [82]. For example, addicts that had just relapsed for meth had higher deficits in episodic memory than abstinent meth addicts, and also when compared to individuals who persisted in meth use during the course of the study. Since the possible mechanisms establishing the link between episodic memory deficits and relapse are not yet understood, rodent models constitute a useful tool to investigate to what extent meth impairs episodic memory, and the possible link between these impairments and features of addiction. Although tests of declarative memory are not possible with rodents in the same manner as humans, several rodent models have been proposed to mirror components of episodic memory, including object recognition tasks.

[Insert Figure 3 here]

4.1 *Object Recognition Memory*

Object recognition tasks can be used to evaluate different aspects of working and/or episodic memory depending on the specifics of the task. These tasks are based on the natural tendency of a rat to spend more time interacting with novel stimuli compared to familiar ones and have the advantages of being one-trial memory tests that do not involve learning a rule or changes in motivational state [83]. The most widely studied protocols are illustrated in Figure 3. Typically, these tasks are conducted in three parts: First, rats are generally acclimated to the testing apparatus before the familiarization phase, since environmental exposure before sampling objects can directly impact the interaction with objects [84]. Then rats go through familiarization with objects (sampling phase) and test for recognition memory.

In the novel object recognition task, during the sampling phase, rats are placed into the environment with two identical objects and are allowed to interact with both objects. Rats are then returned to the home cage for a predetermined retention interval. After this time, testing occurs in which rats are placed back into the apparatus with an object from the sampling phase and a novel object. Memory for the sample object is inferred by the amount of time rats spend with the novel object. Other variants of recognition memory protocols assess object location, object-in-place, or temporal order memory (See Figure 3). During object location testing, both objects remain the same between sampling and testing phase, but the location of one of these objects is changed prior to the test. Regarding object-in-place, four distinct objects are presented during the sampling phase; during the test phase, position of two objects is switched, while the two other ones remain

in the same place. Memory in these variants is inferred by the amount of time rats explore the object that have changed location or place during the test phase. In the temporal version, a pair of objects is presented during the first sampling phase, followed by a second sampling phase of a different pair of objects. After the retention interval, rats are tested simultaneously with one object from each sampling phase. Here, although none of the objects are completely unfamiliar, memory is assessed through the exploration time of the object presented during the first sampling phase (the oldest one) compared to the object that has been explored more recently.

Recognition memory relies on functional connectivity between the PFC, perirhinal cortex (PRH) and hippocampus, a neurocircuit identified through anatomical tracing studies (for an in depth review see [85]). The PRH cortex has a reciprocal connection to the PFC [86, 87] and projects to the hippocampus, relaying information reciprocally via the entorhinal cortex [88, 89]. Further, there are anatomical connections between the PFC and the hippocampus [90, 91]. The subiculum and CA1 region of the hippocampus are the major output structures projecting to the prefrontal cortex [90, 92]. This connection is not reciprocal in the rat [93, 94], but instead the medial PFC indirectly projects back to the hippocampus via the entorhinal cortex [95].

Lesion and inactivation studies confirm that these brain areas are uniquely involved in recognition memory depending on specific task parameters. Lesions to the PRH cortex impair object recognition memory [96-99], object-in-place recognition memory, and temporal order recognition memory [100, 101], while object location memory is largely unaffected [101, 102]. In contrast, PFC lesions have no effect on object recognition memory [101-104], but do impair temporal order and object-in-place recognition memory

[101]. Hippocampal lesions impair object location, object-in-place, and temporal order memory, but not novel object recognition [105]. In summary, the PRH cortex is crucial for judgment of a prior occurrence or object, but when the task involves multiple items and/or contextual associations, recognition depends on interactions between the PRH, PFC, and hippocampus.

4.2 Chronic meth SA disrupts cortical control of recognition memory

Meth impairs object recognition under several different drug administration procedures. For example, an experimenter-administered binge regimen (4 injections of 4 mg/kg at 2 hr intervals) of meth severely impaired long and short-term recognition memory in rats after 1 or 3 weeks of withdrawal [106]. Additionally, rats sensitized to meth (3 mg/kg on alternating days for a total of 10 injections) had impaired object recognition memory one week later. The deficit was not complete, as both meth-sensitized rats and control subjects had significantly more interaction with the novel object; however, control subjects interacted with the novel object significantly more than meth-treated rats.

Our laboratory has found that LgA meth SA impaired novel object recognition [23]. In the first demonstration, a non-traditional object recognition was used to assess multiple components of recognition memory. In that task, rats were familiarized to 5 objects to incorporate both a test of object-in-place and a subsequent introduction of a novel object in a final test session. Tests were conducted both pre- and post-meth self-administration. Spatial reconfiguration remained unaffected; however, novel object interaction decreased depending on cumulative daily meth exposure (1, 2, or 6-hr/day), with 6-hr/day subjects

showing significant deficits relative to saline controls. This study was the first to demonstrate that a translationally relevant meth SA procedure impaired object recognition memory. In subsequent studies, we have consistently found that LgA meth SA impairs short and long-term recognition memory in a traditional two-item novel object recognition task in both males and females [107, 108], as well as in an object-in-place memory [15, 109]. Given the extensive schedule of drug self-administration in LgA rats, it is possible that LgA meth rats have elevated anxiety during withdrawal that could interfere with expression of object memory [110, 111]. Enthusiasm for an anxiety account is, however, dampened because in our studies, LgA meth rats have not differed from control rats on thigmotaxis or motor activity when introduced to the novel environment (unpublished data from our lab), nor do they differ in object exploration during sampling phase [107, 108, 109, 118].

We suggest that the PFC and PRH might be particularly vulnerable to damage by LgA meth SA. Chronic meth dysregulates serotonin, cannabinoids, and glutamate in the PRH. Among these changes are reduced levels of CB₁ receptors [112] and reduced monoamine transporters [15, 113] in the PRH. Noteworthy, meth-induced reduction of monoamine transporters in this region has been correlated with object recognition deficits [114]. Regarding glutamate receptors, LgA meth decreased expression of mGluR5 and GluN2b in a crude membrane fraction of the PRH cortex after 2 weeks of abstinence [107, 118]. These receptors are important in recognition memory, as blockade of both mGluR5 and GluN2b containing NMDA receptors before sampling objects impairs memory after a 24-hour interval [115, 116]. Interestingly, interactions between mGluR5 and GluN2b form a unique type of long-term depression in the PRH [117]. Moreover,

LgA meth SA disrupts this PRH long-term depression, which can be restored by PRH micro-infusion of D-cycloserine [118]. Thus, targeting meth-induced alterations of PRH glutamatergic receptors and the related neurophysiology may be a promising approach to treat working memory deficits following meth abuse.

In the PFC, chronic meth SA decreased gliogenesis, altered neuronal firing states, and reduced glutamate homeostasis [32, 119, 120]. Similar reductions in glutamate homeostasis in the nucleus accumbens have been reported after cocaine self-administration, and are attributed in part to a reduction in the cysteine-glutamate exchanger [121, 122]. This reduction could result in decreased basal extra synaptic glutamate levels, and subsequent reduced glutamatergic tone on presynaptic mGluR2/3 receptors [123]. A similar mechanism may occur in the PFC of meth SA rats, since mGluR2/3 receptors show downregulation following 14 days of abstinence [124]. mGluR2/3 receptors are one of the most abundant presynaptic glutamate receptors found on corticostriatal glutamatergic terminals [125], and their activation inhibits drug seeking [126, 127]. Conversely, a decrease in the function of this autoreceptor may contribute to increased striatal glutamate release and an enhancement of drug seeking [128, 129]. Further, prefrontal glutamatergic dysregulation may impact recognition memory given that PRH-PFC-hippocampal communications are necessary for some types of recognition memory [101]. Thus, the combined vulnerability of the PFC and PRH to repeated meth exposure could be considered as a prominent target to investigate cognitive deficits during abstinence and the propensity towards relapse.

5. Chronic meth SA neurotoxicity in subcortical areas

The cognitive impairments reviewed above focused on cortical dysfunction. However, extended meth access could also affect subcortical areas to induce cognitive sequelae. Standard markers of neurotoxicity after meth include marked reduction of dopamine and serotonin levels, reduction in striatal monoamine transporters, and gliosis. As reviewed by Krasnova and colleagues, repeated meth injections result in consistent signs of neurotoxicity in subcortical regions [14]. In particular, “binge” meth regimens have profound effects on dopaminergic striatal neuron integrity, including marked reduction of striatal dopamine transporters and monoamine levels [15, 54, 130-133]. However, some discrepant findings have emerged regarding LgA meth on subcortical toxicity. After LgA meth exposure, some studies report reduced dopamine transporters (DAT) levels in the striatum following protracted abstinence (between 7 and 30 days) [24, 134, 135], while other studies report no changes in neurotoxic markers in this region [15, 136]. Interestingly, increased DAT levels were reported after a short abstinence period (3 days) [137], suggesting dynamic regulation of striatal dopaminergic processing during withdrawal. Regarding signs of gliosis, increased levels of glial fibrillary acidic protein (GFAP) are thought to indicate neurotoxicity by reflecting the accumulation of glial filaments in response to neuronal injury [138]. Most studies report no change in striatal GFAP after LgA meth SA [15, 24, 135]. Although one group reports increased GFAP levels in the striatum [134], it should be noted that this study used a particularly extended LgA meth SA protocol (15h/day, compared to 6-8 hours in other studies). Interestingly, progressively increasing doses of meth protect against further meth-induced neurotoxicity, a phenomenon known as meth-preconditioning [139, 140]. This effect may account for discrepancies in subcortical neurotoxicity found after “binge” regimens of

meth but not after SA protocols during which meth intake might be progressively developed.

Several lines of evidence report striatal-dependent impairments after a systemic neurotoxic meth regimen (7.5 to 10 mg/kg, 4 injections separated by 2h each), including shifts from action-outcome to stimulus-response strategies [133] or sequential motor learning in a radial maze [132]. Reduced striatal DAT levels are also found with lower meth doses (4 x 2 mg/kg) along with impairments in reversal learning [54]. Since these deficits have been attributed to the neurotoxic effect of meth, it remains to be determined whether similar cognitive alteration could be found following meth SA protocols, in which neurotoxicity might not occur.

LgA meth SA also interferes with hippocampal neurogenesis in the dentate gyrus [141, 142], which seems restricted to dorsal areas of the hippocampus [143]. However, to date, only one study has investigated the behavioral consequences of meth-induced reduction of hippocampal neurogenesis by comparing ShA and LgA meth rats [144]. In this study, rats were assessed for spatial and working memory using a Y-maze and T-maze, respectively, following ShA or LgA meth SA. These rats were further injected with BrdU, a substance used to label neuronal progenitors in the hippocampus, after the last SA session and were killed either 2 hours or 28 days after the injection. Both spatial and working memory was impaired in LgA, but not ShA rats, and these deficits were negatively correlated with 2-hour labelling of neuronal progenitors. Additionally, this study reported higher meth-primed reinstatement in LgA rats, associated with increased Fos expression in the dentate gyrus, which could suggest a direct implication of the hippocampus in addiction-like behaviors. Given the emerging implication of

hippocampal neurogenesis in psychostimulant addiction [145], further investigations of LgA meth-induced alterations in the hippocampus are merited.

[Insert Figure 4 here]

6. Medications that reduce cognitive deficits without abuse potential

Some cognitive and neuronal deficits induced by meth appear to recover with time [6, 146]. However, in the interim, cognitive dysfunction may distract users from treatment compliance as addicts often report continued use of meth to “make them feel normal” [147]. Unfortunately, other cognitive impairments seem to persist even after protracted period of abstinence. Besides displaying even more cognitive impairments than opiate abusers, meth addicts did not differ from 1-year abstinent meth users on cognitive tasks assessing visual memory and executive function [148]. Moreover, a longitudinal study of meth users seeking outpatient treatment reported that both abstinent meth users (6 months) or those that have recently relapsed were even more impaired on memory tests than continuous meth users [82].

Meth users are a heterogeneous population meriting individualized treatment strategies [149]. Several reviews have detailed the cognitive deficits observed in meth addicts [3, 150] and other stimulant abusers [151, 152]. A general consensus is that prefrontal mediated cognitive deficits interfere with treatment programs aimed at increasing abstinence duration, and measures directed at normalizing these deficits should therefore be implemented in treatment programs [153, 154]. In regards to cognitive deficits, cognitive-behavioral therapies designed to improve attention, memory, problem solving, and spatial skills have had some success in both inpatient and outpatient

settings [151]. However, development of pharmacotherapies aimed specifically at improving cognitive deficits during abstinence from meth is currently in the nascent stages.

To date, there are no medications that have been approved for psychostimulant abuse, let alone pharmacotherapies that target specific aspects of relapse such as the attenuation of drug reward or cognitive impairments [155]. Many drugs have been suggested and reviewed for the treatment of meth addiction [156-158], but most of the suggested compounds have only been assessed off-label. For example, bupropion blocks dopamine, serotonin, and norepinephrine reuptake, and is approved for smoking cessation, attention deficit hyperactivity disorder, and depression. In regards to meth, bupropion increased days of abstinence in mild to moderate users [159], and decreased meth intake in rodents [160]. Mirtazapine, another antidepressant acting on norepinephrine and serotonin systems [161], has shown some potential in clinical trials [162]. A recent review promoted cholinergic and noradrenergic-based pharmacotherapies, due to the cognitive enhancing properties of many of these compounds [152, 153, 163]. Cholinesterase inhibitors are generally well tolerated [163] and attenuated some of meth's subjective effects [164, 165], but have not been studied systematically in abstinent meth users. Norepinephrine reuptake inhibitors such as atomoxetine enhance synaptic norepinephrine and dopamine levels in the PFC [165]. To date, this drug has not been tested in clinical trials of psychostimulant abusers [153]. However, although the use of atomoxetine in stimulant-dependent patients does not pose any untoward health risks, the usefulness of this treatment on meth's subjective effects or abstinence promotion have been called into question [166].

Another drug, modafinil, shows clear and growing promise as a pharmacotherapy for meth addiction [167, 168]. Despite sharing a similar mechanism with amphetamine via inhibition of dopamine reuptake through its transporter [169], the effects of modafinil are more complex, involving a global regulation of all the main neurotransmitter systems in the brain [170], and may further have some antioxidative and neuroprotective effects [171]. The clinical data shows modafinil to be safe for use in meth addicts [167, 172] and suggests some efficacy for treating meth addiction. Selective populations show more promising results including subjects with access to counseling [168], baseline high-frequency meth use, and low cognitive behavioral therapy attendance [173]. Consistently, modafinil alleviates working memory deficits in meth users demonstrating relatively poor baseline performance [174].

In rodents, acute modafinil decreased responding on a drug-associated lever following reinstatement conditions induced by either context, conditioned cue and meth prime, without reinstating meth seeking when tested alone [175, 176], suggesting little or no abuse liability. Modafinil also restored memory function during abstinence from LgA meth SA, by reversing meth-induced deficits in an object-in-place task that requires intact function between the PFC and PRH [109]. Modafinil may therefore rectify impaired prefrontal cortical ability to integrate object and location information in meth-experienced rats. As such, modafinil is one of the first cognitive enhancing drugs to alleviate both cognitive impairments and relapse in animal models [109, 175, 176]. Further, based on data using a cocaine SA model, this combined effect may be due to the ability of modafinil to increase extracellular glutamate during abstinence and interactions with mGluR2/3 receptors [177].

Glutamate has been well implicated in relapse to multiple types of addictive drugs [178, 179], with the most extensive evidence having been found in regards to cocaine addiction. Cocaine withdrawal causes reductions in basal extracellular glutamate concentrations [122]. Additionally, the glutamate/cystine antiporter, which regulates basal glutamate levels, shows downregulation during withdrawal [180, 181]. *N*-acetylcysteine (NAC) is a cystine prodrug that restores basal glutamate levels, blocks cocaine-primed reinstatement of drug seeking, and attenuates increased glutamate levels during reinstatement by reversing glutamate dysregulation due to cocaine self-administration in rats [123, 128, 180]. This drug further has antioxidant properties that have been shown to prevent neurotoxicity and improves memory performance in rodents [182, 183]. Although not tested within a meth SA procedure, NAC protects against experimenter-delivered methamphetamine-induced toxicity in primates and rodents [184, 185]. In humans, NAC reduces cocaine desire [186], and a reduction of oxidative stress in human brain endothelial cells following NAC treatment confirms preclinical evidence on possible neuroprotective effects [187]. Therefore, one could propose that protection from meth-induced neurotoxicity could help alleviate its cognitive sequelae, and possibly maintain abstinence. However, NAC was administered in these studies before meth injections, an approach not relevant to the human drug-taking situation whereby treatment occurs after years of repeated meth intoxication. Until now, the treatment efficacy of NAC has been mixed regardless of drug class [188]. For example NAC treatment combined with naltrexone had no effect on meth abusers [189], but a recent study by Mousavi and colleagues (2015) found that NAC reduced craving for meth [190]. Within that study, meth addicts benefited from a weekly cognitive and psychological

approach according to the Matrix model [191], thus highlighting the importance of combining different therapeutic approaches to achieve potent results in the treatment of addictive disorders.

7. Concluding remarks

The studies reviewed here highlight some of the key cognitive domains as a result of extended access to methamphetamine self-administration. The impairments in attentional processing (5-choice serial reaction time task), cognitive set-shifting, and object recognition memory pinpoint a particular vulnerability in cortical areas to meth-induced dysregulation (Figure 4). The use of contingent models of meth self-administration show that long access, but not short access to meth, is more likely to produce such deficits. Extended access to meth self-administration may therefore represent a good framework to further evaluate drug-induced cortical dysfunction and cognitive impairments in the context of drug addiction. It is also likely that subcortical areas are involved in many of these cognitive tasks, notably through cortical-subcortical connections. Subcortical structural integrity and function may also be affected by extended meth self-administration, although only one study has so far investigated the role of subcortical alterations in drug-induced cognitive dysfunction [144]. Future studies should therefore address how key structures such as the dorsal and ventral striatum are affected by extended access to self-administered meth. Although both contingent and non-contingent meth administration could sometimes result in similar cognitive consequences (e.g., object recognition), some distinct neurochemical alterations between these two models suggest that striatal neurotoxicity may not be sufficient to explain meth-induced cognitive

deficits. Noteworthy, the schedule and duration of meth SA may drive specific neurochemical alterations and related cognitive impairments that deserve future investigations.

While this review focused on the consequences of extended meth use in preclinical models, individual predispositions before the onset of drug use also represent a critical factor in the etiology of drug addiction. For instance, several endophenotypes have been proposed to explain interindividual variability to drug addiction [192-194]. On the other hand, these pre-existing individual specificities may also account for the beneficial effects on cognition provided by some psychostimulants. For instance, amphetamine-like substances such as methylphenidate produce opposite brain activation pattern between ADHD and healthy children [195], and the effectiveness of this treatment has further been corroborated with striatal DAT bioavailability [196, 197]. Similarly in rats, methylphenidate increased impulsivity in rats characterized as low-impulsive in the 5-CSRTT, but decreased impulsivity of pre-established high-impulsive rats [198]. To our knowledge, no study has yet investigated how attentional performance or recognition memory could constitute predisposing factors for drug abuse. Nonetheless, it would be important to assess to what extent drug-induced cortical alterations occur in relation with specific traits present before the onset of drug abuse.

Although meth abuse in humans has been correlated with cognitive decline, it has been questioned to what extent these cognitive deficits might fall outside the range of significant clinical impairment [10]. Another recent review highlighted the importance of inter-individual variability in meth users undergoing psychological assessment, suggesting that cognitive deficits should be highly attributable to meth abuse in

vulnerable individuals [11]. This heterogeneity emphasizes an emerging area of research to focus on inter-individual variability of meth-induced deficits. Ultimately, newer studies focused on the ability of meth to disrupt the entire circuits involved in attention, impulsivity, and memory will help inform clinical researchers aimed at using cognitive enhancers as treatments for relapse.

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Figure 1. Attentional set-shifting task protocol. Each bowl is characterized by a specific digging medium (shape) and a specific odor (shape's color). Rats undergo several phases in sequential order (here noted from 1 to 6), progressing from one phase to another after reaching predetermined criteria. The different phases are the compound discrimination (CD, top panel), the intradimensional shift (ID, mid panel), the extradimensional shift (ED, low panel), and each of these phases are followed by reversal testing (right side of panels). In this example, CD consists of associating reward location with a particular odor, regardless of digging medium; the ID consists of associating reward location with another odor, still regardless of the digging medium; and the ED consists of associating reward location with a specific digging medium, regardless of the odors presented. In every choice, only one bowl is baited (left of dotted line), and pairs of stimuli among each bowl are pseudo randomly assigned. Adapted from [28].

Figure 2. Five-choice serial reaction time task. In a classical protocol, rats initiate a trial by poking their nose into the food magazine, which triggers the illumination of a cue light located in one of the 5 holes. A nose poke into the previously illuminated hole results in reward delivery, while nose entries into non-illuminated holes or no response are punished by a timeout period. Impulsive behaviors are determined by the number of nose pokes occurring before presentation of the cue light and are termed premature responses. Attentional performance is determined by the accuracy of responding before the end of the response delay, inferred by the ratio of correct over incorrect responses.

Figure 3. Object recognition memory protocols. After habituation to the arena, animals explore the objects during an initial sampling phase. After a retention delay, memory is inferred by the amount of time spent interacting with a novel object (first panel), an object in a new location (second panel), or pair of objects that place has been switched (third panel), compared to the unchanged objects. During temporal order recognition (fourth panel), two sampling phases with distinct pairs of objects are followed by a recognition test with both objects. For this latter protocol, memory is inferred by the exploration time of the oldest object. Adapted from [199].

Figure 4. Summary of cognitive deficits after extended meth self-administration.

Among the few studies investigating cognitive alterations induced by LgA meth SA, some vulnerable structures have been reported (bold arrows), while other related structures have not been fully explored (dotted arrows). The lower level depicts neurophysiological alterations that have been corroborated with LgA meth-induced cognitive impairments, in the PFC [32, 124], striatum [15, 24, 124], hippocampus [142-144] and perirhinal cortex [107, 109, 118]. 5-CSRTT: five-choice serial reaction time task; ASST: Attention set-shifting task; PFC: prefrontal cortex; Str: striatum; Hipp: hippocampus; PRH: perirhinal cortex; DAT: dopamine active transporter; LTD: long term depression.

Figure 1

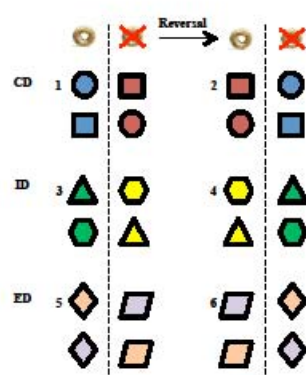


Figure 2

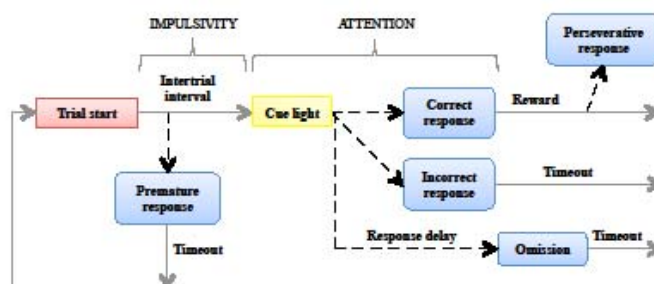


Figure 3

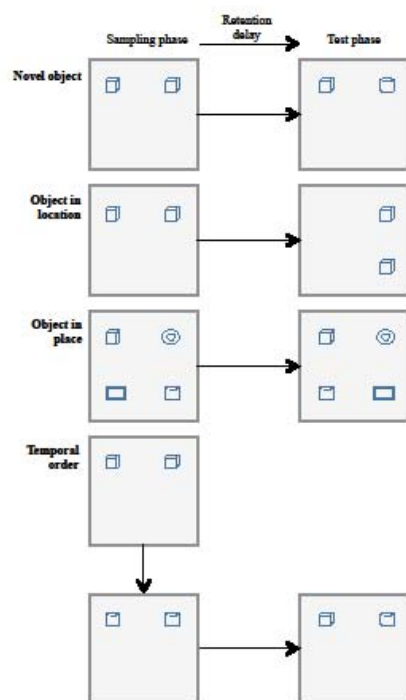


Figure 4

