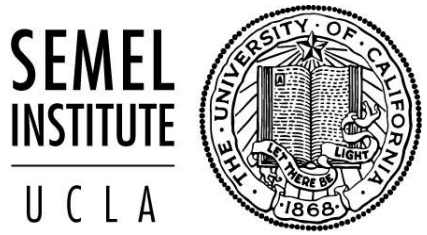

Testimony and Statement for the Record of

Edythe D. London, Ph.D.
Thomas and Katherine Pike Professor of Addiction Studies
Director of the Laboratory of Molecular Neuroimaging

David Geffen School of Medicine, UCLA

Hearing: "Methamphetamine Addiction: Using Science to Explore Solutions"

Before the

Subcommittee on Research and Technology,
Committee on Science, Space, and Technology
House of Representatives

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2321 Rayburn House Office Building
Washington, D.C.

Chairman Bucshon, Ranking Member Lipinski and Members of the Subcommittee, thank you for the opportunity to testify today concerning the use of science to address the problem of methamphetamine addiction in the United States. My name is Edythe London, and I am Director of the Laboratory of Molecular Neuroimaging of the David Geffen School of Medicine at the University of California at Los Angeles (UCLA).

Our program of research at UCLA began in 1999 with the generous support from the Office of National Drug Control Policy (ONDCP) and was one of the first major research efforts in the nation to address the growing problem of methamphetamine addiction. Here I would like to note at the outset that the strong support from the Congress to the National Institutes of Health and its research recipients over the past two decades have enabled both basic research as well as the development of new medications and treatment modalities. This critical area continues to be important, affects many lives in our nation, and needs your continued support.

Why is methamphetamine such a critical problem? Unlike other drugs of abuse, methamphetamine is relatively easy to manufacture; the street cost to the use is low compared to other drugs; and it produces a "high" that is long-lasting. At the same time there are very significant mental and physical effects from its use, and in far too many cases, it is a cause of early death.

1. Methamphetamine Abuse and the Scope of the Problem in the U.S.

Methamphetamine use disorders (classified as methamphetamine abuse and dependence in DSM-V) are major public health problems [1-3], with >14.3 million adults estimated to be using amphetamine-type stimulants for non-medical purposes worldwide. Among illicit substances, amphetamines are second only to marijuana in prevalence of use, exceeding heroin and cocaine combined [4]. In the United States, admissions to publicly funded drug treatment programs for amphetamine-related problems peaked at 8.1% in 2005 and increased from 3.7% to 5.7% between 2000 and 2010 [3]. The cost of MA abuse in the US in 2005 was estimated at $23.4 billion [5], and was associated with crime, premature mortality, lost productivity, and medical conditions, such as infectious disease and cardiovascular insults [6-8].

The illegal use of methamphetamine in our country is not as widespread as it was in the early to mid-2000s [9], now reduced to 50% of the levels of 2006; however, the problem is still severe in the communities where there still are established cores of users and supply connections set up with the Mexican cartels. In California, for example, admissions to treatment for methamphetamine use disorders in 2009 and 2010 exceeded admission rates for all other substances, including alcohol [10, 11].

2. How is Methamphetamine Different from Other Stimulants?

Among stimulants, methamphetamine is unique in its pharmacokinetic and pharmaco-dynamic properties, which render it more effective as a stimulant, more addictive, and more toxic. Methamphetamine is structurally very similar to amphetamine and related agents, such as MDMA (3,4-methylenedioxy-*N*-methylamphetamine), which is widely known as "ecstasy", and

designer drugs, such as cathinone derivatives (including "bath salts"). The amphetamines, including methamphetamine, are similar to cocaine in causing an increase of dopamine and other neurotransmitter levels in the synapse, augmenting their actions. Along with cocaine, the amphetamines have similar stimulant and euphorigenic properties. The amphetamines, however, have long durations of action (half-life of 9-12 hours for methamphetamine) [12] and, therefore, longer stimulant effects than cocaine, which has a half-life of 1 hour and behavioral effects that last up to an hour, depending on the dose and route of administration [13]. Methamphetamine also is well absorbed following administration by various routes, including inhalation; and it is highly lipophilic, entering the brain faster than other stimulants (including amphetamine), and is more stable to enzymatic degradation in the brain [14]. Finally, methamphetamine is more potent than other stimulants [15], leading to much higher concentrations of synaptic dopamine than cocaine, producing toxic effects on nerve terminals. These pharmacokinetic considerations, along with the lower cost as compared with cocaine, likely contribute to a more chronic and continuous use pattern of methamphetamine as compared with cocaine, which is used more in binges. They also may contribute to differences in addiction potential, with only 16-20% of cocaine abusers progressing from regular use to dependence [16, 17]. A corresponding figure for methamphetamine is not available.

Methamphetamine users stay under the influence for longer stretches of days and weeks, with extensive sleep deprivation, possibly contributing to the greater incidence of associated psychosis than with cocaine, along with poor health maintenance and hence more medical consequences (e.g., cardiovascular, neurological) than with cocaine. One notable problem involves dental problems, referred to as "meth mouth", due to diminished saliva production and other putative mechanisms; this problem is most commonly seen in intravenous users of the drug [18]. Other problems are the potential for prolonged psychosis [19, 20] and high rates of suicide attempts [21].

Finally, methamphetamine is used heavily in the community of men who have sex with men worldwide, and its use is connected to risky sexual behavior among these individuals more than cocaine abuse. Methamphetamine use is highly associated with HIV infection in gay men [22], and is the only drug whose use has shown significant correlation with the incidence of HIV infection among gay and bisexual men who are methamphetamine users [23]. No other drug has shown consistent and significant correlations with HIV transmission. Moreover, metabolic abnormalities in the brain due to HIV and chronic methamphetamine use are additive [24].

3. How have Basic Science Studies Advanced Knowledge about Addiction to Methamphetamine?

Building on a large body of preclinical research, controlled laboratory studies of human volunteers have provided critical insights into the factors that influence methamphetamine use, and the maladaptive consequences of chronic exposure. Noninvasive brain imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), have proven to be particularly valuable for this purpose, clarifying the effects of methamphetamine use on brain chemistry, structure, and function. In related studies, neuroimaging procedures have assisted in the elucidation of the neural mechanisms underlying key behavioral abnormalities thought to promote compulsive drug use and predict poor treatment response. A

synthesis of the findings indicate that chronic use of methamphetamine is associated with deficits in the cerebral cortex and striatum, which accompany and appear to contribute to cognitive deficits, including impaired inhibitory control [25 review].

Molecular Neuroimaging. Human molecular neuroimaging studies suggest that, in addition to effects on other neurotransmitter systems [e.g., 26-28, 29 review], chronic methamphetamine use causes a down-regulation of dopamine neurotransmission in the striatum, which can disrupt cognitive processes in ways that may undermine the user's ability to remain abstinent. Dopamine signaling in the brain is critically involved in reward processing and motivation [30 review], and is linked to activity in the prefrontal cortex, with bi-directional influences guiding reward-related behavior and decision-making [31]. Dopamine signaling in the brain is influenced by the integrity of receptors for the neurotransmitter (D_1 and D_2 subtypes), by activity-dependent release of the transmitter from the neuronal terminals into to the synapse, by its reuptake to the presynaptic terminal, and by metabolic enzymes.

These studies have revealed that chronic methamphetamine abuse is associated with deficits in several markers of dopamine signaling in the striatum, including dopamine D_2-type receptor availability [32-35], dopamine transporter availability [36-40], and activity of the presynaptic dopaminergic terminal, indexed by dopamine release [34]. These deficits may contribute to a "Reward Deficiency Syndrome", characterized by anhedonia and a dysfunctional "impulsive-addictive-compulsive" trajectory of behaviors, in which one rewarding substance or activity is substituted for another. During early abstinence, methamphetamine addicts exhibit unusually high caloric intake, presumably reflecting the substitution of food for methamphetamine, and caloric intake is negatively correlated with striatal D_2-type dopamine receptor availability [35]. Moreover, low striatal D_2-type receptor availability has been linked with greater self-reported impulsivity in abstinent methamphetamine users [33], and along with reduced striatal dopamine release, with greater likelihood of relapse during treatment [34]. Although there is evidence for recovery of the dopamine transporter protracted abstinence [39], this is not true for D_2-type dopamine receptors. A direct relationship between the recovery of dopamine transporters and duration of abstinence from methamphetamine [37] suggests that reductions in the striatal dopamine transporter associated with methamphetamine dependence may reflect short-term, drug-induced neuroadaptations.

Studies of the vesicular monoamine transporter (VMAT2), which is present in all monoaminergic neurons, also have pointed to a transient neuroadaptation in response to methamphetamine exposure. Lower striatal VMAT2 was seen in postmortem brain tissue from former methamphetamine abusers [41], and PET studies of striatal VMAT2 in vivo showed lower levels in methamphetamine users even after 3 months of abstinence [40]. In another study, however, recently abstinent methamphetamine-dependent individuals had greater VMAT2 binding availability than controls [42], but increases relative to control subjects were seen only in those who had most recently used methamphetamine (<12 days) [42]. Collectively, these findings suggest that increased VMAT2 may be a transient response to drug exposure and the reduction in VMAT2 binding observed after longer abstinence may indicate lasting damage to neuronal terminals as a consequence of drug use.

With respect to D_2-type dopamine receptor deficits, methamphetamine abusers are not unique, as chronic users of cocaine [43], alcohol [44], opiates [45], or nicotine [46, 47] all

display below normal levels of striatal D_2-type receptor availability. This commonality across several addictive disorders raises questions regarding the extent to which low D2/D3 receptor availability predates drug abuse, or is an effect of chronic drug exposure. For ethical reasons, this question could be answered only by measuring D_2-type receptor availability before any drug use and performing a longitudinal study in which individuals naturalistically self-administer the drug, or by animal studies in which the agent is administered under controlled conditions. In this regard, Vervet monkeys exposed to a methamphetamine dosing regimen designed to mimic human consumption of the drug showed significant decreases in striatal D_2-type receptor availability after 2 weeks of methamphetamine exposure. These deficits persisted for at least 7 weeks following cessation of treatment [48], indicating deleterious effects that are long lasting. Taken together, these findings indicate that while D_2-type receptor deficiencies in methamphetamine users may, to some extent reflect a vulnerability to drug abuse, chronic methamphetamine abuse negatively impacts the dopamine system in the brain.

Other relevant data center on the D_3 receptor, a member of the D_2-type receptor family. The PET studies showing low striatal D_2-type receptor availability in methamphetamine users employed radiotracers that do not distinguish between D_2 and D_3 receptors (both in the D_2-type family). Development of a D_3-preferring radiotracer, [^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin [49], now allows assessment of D_3 receptors in the living human brain. D2 dopamine receptors are distributed uniformly throughout the striatum [50], but D3 receptors are localized primarily to the ventral striatum, which functions in reward processing and motivation [50, 51], making them of special interest with respect to addiction. A recent study has shown higher binding of the D_3-preferring tracer in D_3-rich regions of the brain in methamphetamine users than in healthy controls, with D_3 receptor binding in the midbrain (*substantia nigra*) related to self-reports of "drug wanting" [52]. Therefore, unlike the D_2 receptor, the D_3 receptor may be upregulated in those who use methamphetamine chronically.

In addition to the dopamine system, another subject of interest with respect to the effects of methamphetamine in the human brain is the serotonin system. For example, PET was used to show that compared with healthy controls, methamphetamine users had lower density of the serotonin transporter in the midbrain, thalamus, caudate, putamen, cerebral cortex, and cerebellum [28]. This reduction was inversely correlated with the duration of methamphetamine use; and the density in the orbitofrontal, temporal, and anterior cingulate areas was associated with aggression in the methamphetamine abusers.

Microglial cells are activated in associated with neurodegenerative processes, and there is evidence that reactive microgliosis accompanies methamphetamine toxicity in animals [53-55]. Using PET, and a radiotracer for activated microglia, [^{11}C](*R*)-(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isoquinoline carboxamide) ([^{11}C](*R*)-PK11195), an elevation in activated microglia was shown in methamphetamine users, suggesting that chronic self-administration of methamphetamine can cause reactive microgliosis in the human brain [56].

Functional Brain Imaging. Brain function can be evaluated using PET imaging and the radiotracer [^{18}F]fluorodeoxyglucose, which can provide maps of how fast glucose is utilized throughout the brain. PET studies of cerebral glucose metabolism in meth-amphetamine users, who had remained abstinent for periods varying from weeks to over 2 years, showed elevated

activity relative to control in cortical areas but apparently reduced glucose metabolism in subcortical regions [57]. When participants were studied in early abstinence (4-7 days) corresponding to the time that many clients would approach a treatment episode, there was clear evidence for corticolimbic dysregulation, with reduced activity in prefrontal and limbic cortex, but elevated activity in ventral striatum and amygdala (Figure 1); hyperactivity in the amygdala was associated with depression and anxiety [58]. Among a variety of cognitive deficits [59], the early-abstinent methamphetamine users had higher error rates than control subjects on a vigilance task and abnormal relationships between task performance and activity in the cingulate cortex and the insula, brain regions important for cognitive control, error-monitoring and decision-making [60]. Over the course of a month of abstinence, cortical activity, especially in parietal cortex, increased [61], consistent with an umasking of reactive gliosis [56]. With protracted abstinence (12-17 months), glucose metabolism in thalamus but not the striatum recovered to control levels [62].

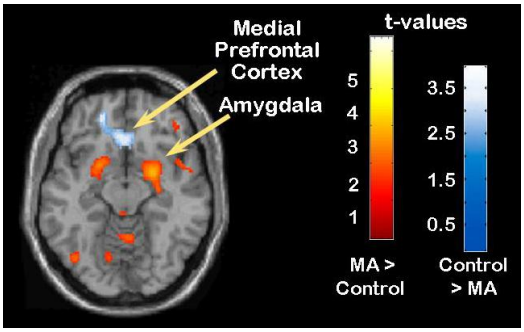

Figure 1. Methamphetamine users (MA) in early abstinence have dysregulated glucose metabolism. Warmer values (reds/yellows) indicate higher activity in MA users than in control subjects especially in the amygdala. Cooler values (blues) indicate lower activity in MA users than in control subjects (from London et al., 2004 [53]).

In addition to PET, functional MRI (fMRI) provides valuable information about brain function. With substantially greater time resolution than available with functional studies that use PET, fMRI allows measurement of brain activation while participants perform tasks that invoke cognitive and/or emotional processing. Such studies have shown that when abstinent, methamphetamine users exhibit less activation in prefrontal cortex than healthy controls during learning, attention, and emotion processing, consistent with deficits in cortical information processing [63-65]. Functional MRI studies also have also indicated that methamphetamine abusers have abnormalities in cortical activation when abstinent methamphetamine users choose between smaller, more immediate monetary rewards (which they favor) over larger, more delayed rewards [66]. While performing a task to test their temporal discounting of rewards, methamphetamine users exhibit as much recruitment in prefrontal and parietal areas of cortex when making an easy choice as when making a hard choice, suggesting an inefficiency of cortical function [66]. Defective prefrontal cortical control may also contribute to heightened aggression, a common feature of methamphetamine abuse [67], by limiting emotional insight. Functional MRI data have suggested that emotional insight relies on activity of the ventral inferior frontal gyrus, but that in methamphetamine-dependent participants exposed to an emotional probe, activity is low bilaterally in this area [68].

Broadly consistent with these findings and the view that a deficit in "top-down" cortical control is an important feature of methamphetamine abuse is the observation that cortical activation during a simple decision-making task can predict relapse risk in methamphetamine-dependent individuals [69]. The regions involved include components of the prefrontal cortex and the insula. These and other studies have shown the usefulness of fMRI for determining which brain regions under specific behavioral conditions are affected by prolonged methamphetamine use. They also point to fMRI as a valuable technique to evaluate the effects

of potential treatments for methamphetamine dependence. For example, medications, such as modafinil, which improve cognition, in part by promoting greater dopamine function, enhance brain function in the prefrontal cortical regions affected by methamphetamine abuse (Figure 2) [63].

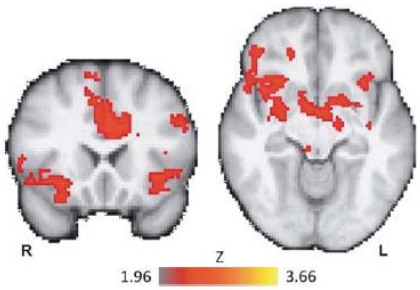

Figure 2. fMRI brain activation maps showing response to Modafinil in prefrontal cortex during learning in methamphetamine users that corresponded with improvements in learning. Prefrontal regions include the anterior cingulate cortex and bilateral anterior insula/ventrolateral prefrontal cortex, orbito-frontal cortex. No difference in activation was observed in healthy individuals (from Ghahremani et al,, 2011 [63]).

Structural Brain Imaging. In keeping with the observations of brain function and biochemistry as related to methamphetamine abuse, abnormalities in components of frontostriatal circuitry have been demonstrated by structural brain imaging as well. Structural MRI studies have generally yielded the unexpected finding that methamphetamine abuse is associated with greater gray-matter volume in the basal ganglia (including the striatum) than in healthy control subjects [70, 71]. Until recently, however, it was unknown whether these differences in gray matter were caused by methamphetamine or if they reflected vulnerability factors that predated substance abuse. One study revealed that stimulant abusers and their unaffected siblings have greater volume in the putamen than healthy control participants, suggesting that the difference reflects familial risk for drug dependence [72]. Animal studies, however, have also shown that monkeys exposed to methamphetamine, using a regimen that simulates human patterns of drug use, have increases in putamen gray matter [73] (Figure 3). The structural change is correlated with impaired performance on a three-choice visual discrimination task that evaluates inhibitory control/cognitive flexibility.

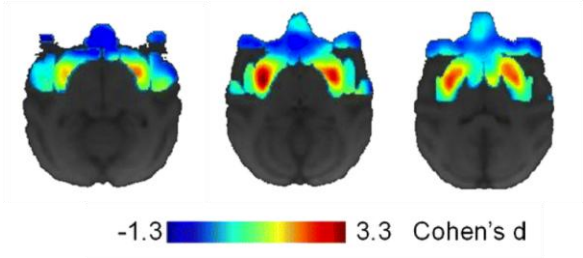

Figure 3. Exposure to methamphetamine is associated with structural differences in the brain. Warmer values (reds) indicate increases in gray matter in the putamen. Cooler values (blues) indicate trends toward losses of gray matter in the prefrontal cortex (from Groman et al., 2013 [73]).

With respect to the cerebral cortex, it was unexpectedly found that in addition to larger striatal volumes, research participants who had used methamphetamine but had maintained abstinence for an average of three months, exhibited larger volumes of the parietal cortex [70]. This effect was not seen in a study of participants who had used methamphetamine for most of the 30 days before enrolling in a brain imaging study and then maintaining abstinence for about 1-2 weeks [74]. Cortical maps of the MRI data revealed severe gray-matter deficits in medial aspects of the brain, including the cingulate, limbic, and paralimbic cortices as compared to control values, deficits in hippocampal volumes, which were related to verbal memory

performance, and an unexpected observation of white-matter hypertrophy. The findings suggested that chronic methamphetamine abuse causes a selective pattern of deterioration that contributes to impaired cognitive performance, and white-matter hypertrophy that may reflect adaptive glial changes, including gliosis secondary to neuronal damage. Although not as dramatic, the same study found a gray-matter deficit in lateral prefrontal cortex [74], including a region (right inferior frontal gyrus) that is important for several forms of self-control [75].

Given the prominence of self-control deficiencies in methamphetamine addiction as well as other substance use disorders, it is important to understand the etiology of this structural abnormality and the extent to which it may be reversed with abstinence from drug of abuse. Therefore, methamphetamine-dependent subjects underwent structural MRI before and after approximately 3 weeks of abstinence from the drug [76]. Gray matter volume increased over time in the prefrontal cortex and other brain regions in methamphetamine-dependent participants, but not in members of a healthy control group that were scanned at a similar time interval (Figure 4, from Morales et al., 2012 [76]). Lack of full recovery may indicate the need for prolonged abstinence, some permanent damage, or the influence of a factor other than methamphetamine use. For example, approximately 87-92% of individuals who abuse methamphetamine also smoke cigarettes [77], and research suggests that some of the of the gray matter deficits in prefrontal cortex detected in MA-dependent individuals may be attributable to cigarette smoking or premorbid factors that promote it [76]. More research is necessary to determine how smoking and other factors may interact to influence gray matter in stimulant abusers as these interactions may have important implications for treatment.

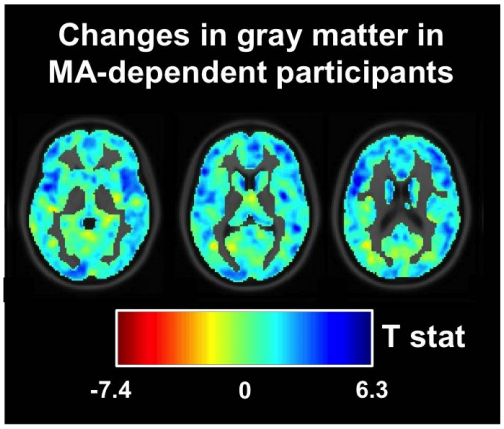

Figure 4. Abstinence from methamphetamine increases gray matter in the brain. Cooler values (blues) indicate increases in gray matter in over the course of the first month of abstinence from methamphetamine, while warmer values (yellows and reds) indicate losses of gray matter (from Morales et al., 2012 [76]).

4. What Promising Treatments have been Developed as a Result of Basic Science Research?

At this time, behavioral treatments are the most effective ones for methamphetamine dependence [78-81]. These include cognitive behavioral therapy and contingency management, but both are associated with high dropout rates early in treatment [82] and more than 50% relapse in the first 6-19 months after treatment ends [83, 84]. After more than two decades of concerted effort to develop a broadly effective medication for MA dependence, clinical trials have yielded no such agent [85 review]. One potentially very important consideration is the heterogeneity among methamphetamine users and the need to personalize treatment. In this

regard, promising findings have been observed with a handful of agents that reduce stimulant use in subgroups of patients. The approaches include opiate receptor antagonism, augmentation of dopamine action with medications that have relatively low abuse potential, antagonism of dopamine D3 receptors, and reducing glial cell activation.

Naltrexone, an opiate receptor antagonist drug has been considered as a medication for stimulant abuse, in part, because of its potential to antagonize stimulant-induced augmentation of dopaminergic neurotransmission indirectly [86]. To date, clinical trials with naltrexone for treatment of amphetamine dependence have shown stronger effects than those of placebo on drug abstinence [86, 87] and retention in treatment [87]. These findings suggest that naltrexone may be useful for the treatment of methamphetamine dependence.

The "agonist medication" approach, used successfully for treatment of opiate and nicotine use disorders, involves using a medication that mimics some of the actions of the abused drug without the same high addiction potential. In this regard, methylphenidate reduced amphetamine-positive urines in intravenous amphetamine users [88]. A phase II clinical trial involving methamphetamine users is now underway at UCLA, directed by Walter Ling.

Some positive findings were obtained with modafinil, a non-amphetamine stimulant that has cognitive enhancing properties, and augments synaptic dopamine and norepinephrine [89, 90]. In a randomised, double-blind, placebo-controlled trial with methamphetamine users, the medication was no more effective than placebo in improving retention in the trial or in reducing methamphetamine use in the full sample, but there was an indication of reduced stimulant use among participants who were compliant with their medication [91]. Negative findings were obtained in subsequent trials [92, 93], but compliance in one of these trials was cited as a problem [93]. Nonetheless, preliminary findings from the human laboratory indicate that modafinil reduces the rewarding effects of intravenous methamphetamine [94], and further studies are warranted, especially with the active enantiomer, R-modafinil [95].

Another medication that augments dopamine transmission is bupropion, which inhibits the dopamine transporter [96] and shows promise as a medication in subgroups of methamphetamine abusers. One placebo-controlled double-blind trial indicated that sustained-release bupropion did not outperform placebo in enhancing retention in the trail or in increasing methamphetamine-free urine samples, but participants who used methamphetamine 18 or fewer days in the month before randomisation exhibited a positive response to bupropion [97]. This finding was supported in a subsequent trial [98]. Finally, a small, randomised, placebo-controlled trial with high-risk men who have sex with men lacked the statistical power to detect differences in treatment outcome, but the findings were in the direction of efficacy of bupropion [99].

Another promising pharmacotherapy is buspirone, which has antagonist properties at the dopamine D_3 and D_4 receptor subtypes [100 review]. Buspirone (Buspar®) is approved by the US Food and Drug Administration for treating anxiety, and its anxiolytic effect is thought to be mediated by a partial agonist action at a serotonin receptor ($5HT_{1A)}$ subtype [101-103]. Buspirone also exhibits antagonist properties at dopamine D_3 and D_4 receptors [100, 104-106]. The affinities of buspirone for D_3 and D_4 receptors are an order of magnitude higher than for D_2 receptors, but are similar to the affinity for $5HT_{1A}$ receptors [100]. Thus, any behavioral effects of buspirone are attributable to activity at D3, D4 or $5HT_{1A}$ receptors.

D_3 receptor antagonists reduce the reinforcing and reward-facilitating properties of methamphetamine in rats. For example, administration of the D_3 receptor antagonist SB-277011A [107] or PG01097 [108, 109] attenuate methamphetamine self-administration under a progressive ratio schedule of reinforcement, suggesting that the reinforcing efficacy or the incentive motivational properties of methamphetamine are counteracted. Notably, D_3 receptor blockade appears to diminish reinstatement of extinguished MA-seeking behavior [107, 108, 110]. Combined with the demonstration of D_3 receptor upregulation in methamphetamine users [52], these findings from animal studies identify buspirone as a potential medication for methamphetamine use disorders.

Finally, given substantial evidence from studies of animal models of methamphetamine toxicity [53-55] and PET studies of human methamphetamine users [56], it is reasonable to believe that reactive gliosis and inflammation may contribute to the neuropathology of methamphetamine dependence. For this reason, there is interest in the potential for medications that reduce microglial activation as medications for methamphetamine use disorders. One candidate is ibudilast, which is approved for treatment of bronchial asthma, post-stroke dizziness and ocular allergies in Asia. Ibudilast reduced methamphetamine self-administration in the rat [111] as well as methamphetamine prime-induced reinstatement of methamphetamine-seeking behavior in rats [112]. A phase Ib clinical trial of ibudilast for the treatment of methamphetamine dependence is now being conducted by Steven Shoptaw at UCLA.

5. How Can the Scientific Disciplines Complement Ongoing Research Efforts in Methamphetamine Addiction?

An interdisciplinary approach is needed for basic science to facilitate rapid progress in treatment for methamphetamine addiction. We have made great progress in understanding how methamphetamine alters brain function and behavior through the use of noninvasive brain imaging. This effort has required the collaborative effort of physicists and mathematicians to develop and improve the instrumentation for data collection as well as the algorithms for data analysis. Moreover, this research was linked to the efforts of cognitive neuroscientists to develop appropriate behavioral probes and clinicians to integrate this work in a way that targeted the problems of the addict.

Certainly, the field would be advanced with the development of new probes and more sensitive instruments. For example, there is still a substantive need for new radiotracers that can be used in molecular imaging to assess the complexities of brain chemistry, how it changes with the progression of addiction and how it responds to treatment. However, the greatest advances require a strong collaboration involving a multi-disciplinary team.

Such collaboration has been undertaken using cutting-edge neurotechnology in other areas of mental health, and can be used as models of success for addiction. For example, deep brain stimulation of neurocircuitry for the treatment of depressive illness has proven to be effective in mitigating relapse [113]. The work leading to this development comprised the confluence of several fields, including bioengineering, electrical engineering, materials science, neurosurgery, MRI physics, psychology, and neuroscience, to determine the optimal methods

and procedures for successful outcomes. Discussions of applying this technology to addiction have begun [114], yet much more interdisciplinary effort is required to adapt the technology to the context of addiction and to verify its efficacy.

References

1. R Gonzales, L Mooney, and RA Rawson (2010): The methamphetamine problem in the United States. Annu. Rev. Public Health, 31:385-98.
2. RA Rawson and TP Condon (2007): Why do we need an Addiction supplement focused on methamphetamine? Addiction, 102 Suppl 1:1-4.
3. Substance Abuse and Mental Health Services Administration (SAMHSA) (2011): Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings (Vol. NSDUH Ser. H-41): Substance Abuse and Mental Health Services Administration.
4. United Nations Office on Drugs and Crime (UNODC) (2012). 2012 World Drug Report (ISBN 978-92-1-148222-5 ed.): United Nations Office on Drugs and Crime.
5. N Nicosia, RL Pacula, B Kilmer, R Lundberg, and J Chiesa (2009): The Economic Cost of Methamphetamine Use in the United States, 2005. RAND Corporation http://www.rand.org/pubs/monographs/MG829.
6. CW Meredith, C Jaffe, K Ang-Lee, and AJ Saxon (2005): Implications of chronic methamphetamine use: a literature review. Harv. Rev. Psychiatry, 13(3):141-54.
7. J Pasic, JE Russo, RK Ries, and PP Roy-Byrne (2007): Methamphetamine users in the psychiatric emergency services: a case-control study. Am. J. Drug Alcohol Abuse, 33(5):675-86.
8. S Shoptaw, RE Weiss, B Munjas, C Hucks-Ortiz, SD Young, S Larkins, GD Victorianne, and PM Gorbach (2009): Homonegativity, substance use, sexual risk behaviors, and HIV status in poor and ethnic men who have sex with men in Los Angeles. J. Urban Health, 86 Suppl 1:77-92.
9. Substance Abuse and Mental Health Sciences Administration (2013): Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD.
10. Substance Abuse and Mental Health Services Administration (2011): Treatment Episode Data Set (TEDS): 1999-2009. State Admissions to Substance Abuse Treatment Services, DASIS Series S-58, HHS Publication No. (SMA) 11-4663. Rockville, MD.
11. Substance Abuse and Mental Health Services Administration (2012): Treatment Episode Data Set (TEDS): 2000-2010. State Admissions to Substance Abuse Treatment Services, DASIS Series: S-63, HHS Publication No. (SMA) 12-4729. Rockville, MD.
12. C E Cook, A R Jeffcoat, J M Hill, D E Pugh, P K Patetta, B M Sadler, W R White, and M Perez-Reyes (1993). Pharmacokinetics of methamphetamine self-administered to human subjects by smoking S-(+)-methamphetamine hydrochloride. Drug Metab. Disposition, 21(4): 717-23.
13. P Wilkinson, C Van Dyke, P Jatlow, P Barash, and R Byck (1980): Intranasal and oral cocaine kinetics. Clinical Pharmacol. Ther. 27: 386–94.

14. LJ Schep, RJ Slaughter, and Beasley DM (2010): The clinical toxicology of metamfetamine. Clin. Toxicol., 48: 675–94.

15. N Lee, L Johns, R Jenkinson, J Johnson, K Connolly, K Hall, and R Cash (2007): Clinical Treatment Guidelines for Alcohol and Drug Clinicians, No. 14: Methamphetamine dependence and treatment. Fitzroy, Victoria: Turning Point Alcohol and Drug Centre Inc.

16. C Lopez-Quintero, J Pérez de los Cobos, DS Hasin, M Okuda, S Wang, BF Grant, and C Blanco (2011): Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 115:120-30.

17. CY Chen and JC Anthony (2004): Epidemiological estimates of risk in the process of becoming dependent upon cocaine: cocaine hydrochloride powder versus crack cocaine. Psychopharmacology, 172:78-86.

18. V Shetty, L Mooney, CM Zigler, TR Belin, D Murphy, and R Rawson (2010): Methamphetamine use is associated with increased dental disease. J. Am. Dental Assoc., 141:307-18.

19. S Glasner-Edwards, LJ Mooney, P Marinelli-Casey, M Hillhouse, A Ang, R Rawson, and the Methamphetamine Treatment Project corporate authors (2008): Clinical course and outcomes of methamphetamine-dependent adults with psychosis. J. Subst. Abuse Treat., 35:445–50.

20. H Ujike and M Sato M (2004). Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis Ann. NY Acad. Sci., 1025:279-87.

21. S Glasner-Edwards, LJ Mooney, P Marinelli-Casey, M Hillhouse, A Ang, R Rawson, and the Methamphetamine Treatment Project corporate authors (2008): Risk factors for suicide attempts in methamphetamine-dependent patients. Am. J. Addictions, 17: 24–7.

22. F Molitor, SR Truax, JD Ruiz, and RK Sun (1998): Association of methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. Western J. Med., 168:93-7.

23. PN Halkitis, KA Green, and P Mourgues (2005): Longitudinal investigation of methamphetamine use among gay and bisexual men in New York City: findings from Project BUMPS. J. Urban Health, 82 (Suppl.): pp. i18–i25.

24. L Chang, T Ernst, O Speck, and CS Grob (2005): Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. Am. J. Psychiatry, 162:361-9.

25. K Baicy, ED London (2007): Corticolimbic dysregulation and chronic methamphetamine abuse. Addiction, 102s1: 5–15.

26. BK Yamamoto, A Moszczynska, and GA Gudelsky (2010): Amphetamine toxicities: classical and emerging mechanisms. Ann. NY Acad. Sci., 1187:101-21.

27. N Krasnova and J-L Cadet (2009): Methamphetamine toxicity and messengers of death. Brain Res Rev., 60(2):379-407.

28. Y Sekine, Y Ouchi, N Takei, E Yoshikawa, K Nakamura, M Futatsubashi, H Okada, Y Minabe, K Suzuki, Y Iwata, KJ Tsuchiya, H Tsukada, M Iyo, N Mori (2006): Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. Arch. Gen. Psychiatry, 63:90-100.

29. DE Payer and ED London (2009): Methamphetamine and the brain: findings from brain imaging studies, In: Methamphetamine: A Guide for Practitioners. J. Roll, R. Rawson, W. Ling, and S. Sh*o*ptaw (eds.), Guilford Press NY, pp. 61-91.

30. JD Salamone and M Correa (2012): The mysterious motivational functions of mesolimbic dopamine. Neuron, 76(3):470-85.

31. M Kohno, DG Ghahremani, and AM Morales (2013): Risk-taking behavior: dopamine D2/D3 receptors, feedback, and frontolimbic activity. Cerebral Cortex, in press.

32. ND Volkow, L Chang, G-J Wang, JS Fowler, Y-S Ding, M Sedler, J Logan, D Franceschi, J Gatley, R Hitzemann, A Gifford, C Wong, and N Pappas (2001): Low level of brain dopamine d_2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex Am. J. Psychiatry, 158:2015-21.

33. B Lee, ED London, RA Poldrack, J Farahi, A Nacca, JR Monterosso, JA Mumford, AV Bokarius, M Dahlbom, J Mukherjee, RM Bilder, AL Brody, and MA Mandelkern (2009): Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J. Neurosci., 29:14734-40.

34. GJ Wang, L Smith, ND Volkow, F Telang, J Logan, D Tomasi, CT Wong, W Hoffman, M Jayne, N Alia-Klein, P Thanos, JS Fowler (2012): Decreased dopamine activity predicts relapse in methamphetamine abusers. Mol. Psychiatry, 17(9): 918-25.

35. T Zorick, B Lee, MA Mandelkern, T Fong, C Robertson, DG Ghahremani, AK Brown, B Sumerel, and ED London (2012): Low striatal dopamine receptor availability linked to caloric intake during abstinence from chronic methamphetamine abuse. Mol. Psychiatry, 17:569-71.

36. UD McCann, DF Wong, F Yokoi, V Villemagne, RF Dannals, and GA Ricaurte (1998): Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. J. Neurosci., 18(20): 8417-22.

37. Y Sekine, M Ivo, Y Ouchi, T Matsunaga, H Tsukada, H Okada, E Yoshikawa, M Futatsubashi, N Takei, and N Mori (2001): Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. Am. J. Psychiatry, 158(8):1206-14.

38. ND Volkow , L Chang, GJ Wang, JS Fowler, M Leonido-Yee, D Franceschi, MJ Sedler, SJ Gatley, R Hitzemann, YS Ding, J Logan, C Wong, and EN Miller (2001): Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am. J. Psychiatry, 158(3):377-82

39. ND Volkow, L Chang, GJ Wang, JS Fowler, D Franceschi, M Sedler, SJ Gatley, E Miller, R Hitzemann, YS Ding, and J Logan (2001): Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J. Neurosci., 21:9414-18.

40. CE Johanson, KA Frey, LH Lundahl, P Keenan, N Lockhart, J Roll, GP Galloway, RA Koeppe, MR Kilbourn, T Robbins, and CR Schuster (2006): Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers. Psychopharmacology (Berl), 185:327-38.

41. JM Wilson, KS Kalasinsky, AI Levey, C Bergeron, G Reiber, RM Anthony, GA Schmunk , K Shannak, JW Haycock, and SJ Kish SJ (1996): Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat. Med, 2:699-703.

42. Boileau, P Rusjan, S Houle, D Wilkins, J Tong, P Selby, M Guttman, JA Saint-Cyr, AA Wilson, and SJ Kish (2008): Increased vesicular monoamine transporter binding during early abstinence in human methamphetamine users: Is VMAT2 a stable dopamine neuron biomarker? J. Neurosci., 28:9850-6.

43. ND Volkow, JS Fowler, AP Wolf, D Schlyer, CY Shiue, R Alpert, SL Dewey, J Logan, B ND Volkow, JS Fowler, AP Wolf, D Schlyer, CY Shiue, R Alpert, SL Dewey, J Logan, B Bendriem, D Christman, R Hitzemann and F Henn (1990): Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am. J. Psychiatry, 147:719-24.

44. ND Volkow, G-J Wang, JS Fowler, J Logan, R Hitzemann, Y-S Ding, N Pappas, C Shea, and K Piscani (1996): Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcohol Clin. Exp. Res., 20:1594-8.

45. G-J Wang, ND Volkow, JS Fowler, J Logan, NN Abumrad, RJ Hitzemann, NS Pappas, and K Pascani (1997): Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. Neuropsychopharmacology, 16:174-82.

46. C Fehr, I Yakushev, N Hohmann, HG Buchholz, C Landvogt, H Deckers, A Eberhardt, M. Klager, MN Smolka, A Scheurich, T Dielentheis, LG Schmidt, F Rosch, P Bartenstein, G Grunder, and M Schreckenberger (2008): Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. Am. J. Psychiatry, 165:507-14

47. AK Brown, MA Mandelkern, J Farahi, C Robertson, DG Ghahremani, B Sumerel, N Moallem, and ED London (2012): Sex differences in striatal dopamine D2/D3 receptor availability in smokers and non-smokers. Int. J. Neuropsychopharmacol. 15(7):1-6

48. SM Groman, B Lee, E Seu, AS James, K Feiler, MA Mandelkern, ED London, and JD Jentsch (2012): Dysregulation of d2-mediated dopamine transmission in monkeys after chronic escalating methamphetamine exposure. J. Neurosci., 32:5843-52.

49. AA Wilson, P McCormick, S Kapur, M Willeit, A Garcia, D Hussey, S Houle, P Seeman, and N Ginovart N (2005): Radiosynthesis and evaluation of [11C]-(+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9 -ol as a potential radiotracer for in vivo imaging of the dopamine D2 high-affinity state with positron emission tomography. J. Med. Chem., 48:4153–60.

50. P Sokoloff, B Giros, MP Martres, ML Bouthenet, and JC Schwartz (1990): Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature, 347:146–51.

51. AM Murray AM, HL Ryoo, E Gurevich, and Joyce JN (1994): Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. Proc. Natl. Acad. Sci. USA, 91:11271–5.

52. I Boileau, D Payer, S Houle, A Behzadi, PM Rusjan, J Tong, D Wilkins, P Selby, TP George, M Zack, Y Furukawa, T McCluskey, AA Wilson, and SJ Kish (2012): Higher binding of the dopamine D_3 receptor-preferring ligand [^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin in methamphetamine polydrug users: a positron emission tomography study. J. Neurosci., 32: 1353-9.

53. B Ladenheim, IN Krasnova, X Deng, JM Oyler, A Polettini, TH Moran, MA Huestis, and J-L Cadet (2000): Methamphetamine-induced neurotoxicity is attenuated in transgenic mice with a null mutation for interleukin-6. Mol. Pharmacol., 58:1247–56.

54. MJ LaVoie, JP Card, and TG Hastings (2004): Microglial activation precedes dopamine terminal pathology in methamphetamine-induced neurotoxicity. Exp Neurol.,187:47–57.

55. DM Thomas, PD Walker, JA Benjamins, TJ Geddes, and DM Kuhn (2004): Methamphetamine neurotoxicity in dopamine nerve endings of the striatum is associated with microglial activation. J. Pharmacol. Exp. Ther., 311:1–7.

56. Y Sekine, Y Ouchi, G Sugihara, N Takei, E Yoshikawa, K Nakamura, Y Iwata, KJ Tsuchiya, S Suda, K Suzuki, M Kawai, K Takebayashi, S Yamamoto, H Matsuzaki, T Ueki, N Mori, MS Gold, and J-L Cadet (2008): Methamphetamine causes microglial activation in the brains of human abusers. J. Neurosci., 22:5756-61.

57. N Volkow, L Chang, G Wang, J Fowler, D Franceschi, M Sedler, S Gatley, R Hitzemann , Y Ding, C Wong, and J Logan (2001): Higher cortical and lower subcortical metabolism in detoxified methamphetamine abusers. Am. J. Psychiatry, 158:383-9.

58. ED London, SL Simon, SM Berman, MA Mandelkern, AM Lichtman, J Bramen, AK Shinn, K Miotto, J Learn, Y Dong, JA Matochik, V Kurian, T Newton, R Woods, R Rawson, and W Ling (2004): Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. Arch. Gen. Psychiatry, 61:73-84.

59. SL Simon, AC Dean, X Cordova, JR Monterosso, ED London (2010): Methamphetamine dependence and neuropsychological functioning: Evaluating change during early abstinence. J. Stud. Alcohol Drugs 71(3):335-44.

60. ED London, SM Berman, BT Voytek, SL Simon, J Monterosso, JA Geaga, MS Hong, KM Hayashi, P Thompson, M Mandelkern, A Brody, R Rawson, and W Ling (2005): Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. Biol. Psychiatry, 58: 770-8.

61. M Berman, B Voytek, MA Mandelkern, BD Hassid, A Isaacson, JR Monterosso, K Miotto, W Ling, and ED London (2008): Changes in cerebral glucose metabolism during early abstinence from chronic methamphetamine abuse. Mol. Psychiatry, 13:897-908.

62. G-Jack Wang, ND Volkow, L Chang, E Miller, M Sedler, R Hitzemann, W Zhu, J Logan, Y Ma, and JS Fowler (2004): Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. Am. J. Psychiatry 161(2):242-8.

63. DG Ghahremani, G Tabibnia, J Monterosso, G Hellemann, RA Poldrack, and ED London (2011): Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. Neuropsychopharmacology, 36:950-9.

64. LJ Nestor, DG Ghahremani, J Monterosso, ED London (2011): Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. Psychiat. Res.- Neuroim., 194:287-95.

65. DE Payer, MD Lieberman, JR Monterosso, J Xu, TW Fong, ED London (2008): Differences in cortical activity between methamphetamine-dependent and healthy individuals performing a facial affect matching task. Drug Alcohol Depend., 93(1-2):93-102.

66. JR Monterosso, G Ainslie, J Xu, X Cordova, CP Domier, ED London (2007): Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. Hum. Brain Mapp. 28(5):383-93.

67. J Cartier, D Farabee, and ML Prendergast (2006): Methamphetamine use, self-reported violent crime, and recidivism among offenders in California who abuse substances. J. Interpers. Violence, 21(4) 435- 45.

68. DE Payer, MD Lieberman, and ED London (2011): Neural correlates of affect processing and aggression in methamphetamine dependence. Arch. Gen. Psychiatry, 68:271-82.

69. MP Paulus, SF Tapert, and MA Schuckit (2005): Neural activation patterns of meth-amphetamine-dependent subjects during decision making predict relapse. Arch. Gen. Psychiatry, 62(7):761-8.

70. TL Jernigan, AC Gamst, SL Archibald, C Fennema-Notestine, MR Mindt, TD Marcotte, RK Heaton, RJ Ellis, and I Grant I (2005): Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am. J. Psychiatry, 162:1461–72.

71. L Chang, C Cloak, K Patterson, C Grob, EN Miller, and T Ernst (2005): Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. Biol. Psychiatry, 57:967–74

72. KD Ersche, PS Jones, GB Williams, AJ Turton, TW Robbins, and ET Bullmore (2012): Abnormal brain structure implicated in stimulant drug addiction. Science, 335:601–4.

73. SM Groman, AM Morales, B Lee, ED London, JD Jentsch (2013): Methamphetamine-induced increases in putamen gray matter associate with inhibitory control. Psychopharmacology (Berl)., in press.

74. P Thompson, KM Hayashi, SL Simon, JA Geaga, MS Hong, Y Sui, JY Lee, AW Toga, W Ling, and ED London (2004): Structural abnormalities in the brains of human subjects who use methamphetamine. J. Neurosci., 24:6028-6036.

75. G Tabibnia, JR Monterosso, K Baicy, S Chakrapani, B Lee, AR Aron, RA Poldrack, and ED London (2011): Different forms of self-control share a neurocognitive substrate. J. Neurosci., 31:4805-10.

76. Morales AM, Lee B, Hellemann G, O'Neill J, London ED (2012) Gray-matter volume in methamphetamine dependence: cigarette smoking and changes with abstinence from methamphetamine. Drug Alcohol Depend., 125:230–8.

77. AH Weinberger and M Sofuoglu (2009): The impact of cigarette smoking on stimulant addiction. Am. J. Drug Alcohol Abuse, 35:12–7.

78. JM Roll (2007). Contingency management: an evidence-based component of methamphetamine use disorder treatments. Addiction, 102:114-20.

79. JM Roll, NM Petry, ML Stitzer, ML Brecht, JM Peirce, MJ McCann, J Blaine, M MacDonald, J DiMaria, L Lucero, and S Kellogg (2006): Contingency management for the treatment of methamphetamine use disorders. Am. J. Psychiatry, 163(11):1993-9.

80. NK Lee and RA Rawson (2008): A systematic review of cognitive and behavioural therapies for methamphetamine dependence. Drug Alcohol Rev., 27(3):309-17

81. MF Smout, M Longo, S Harrison, R Minniti, W Wickes, and JM White JM (2010): Psychosocial treatment for methamphetamine use disorders: a preliminary randomized controlled trial of cognitive behavior therapy and acceptance and commitment therapy. Subst. Abuse, 31(2):98-107.

82. RA Rawson, P Marinelli-Casey, MD Anglin, A Dickow, Y Frazier, C Gallagher, GP Galloway, J Herrell, A Huber, MJ McCann, J Obert, S Pennell, C Reiber, D Vandersloot, and J Zweben (2004): A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. Addiction, 99(6):708-17.

83. ML Brecht, C von Mayrhauser, and MD Anglin (2000): Predictors of relapse after treatment for methamphetamine use. J. Psychoactive Drugs, 32(2):211-20.

84. MF Smout, M Longo, S Harrison, R Minniti, W Wickes, and JM White (2010): Psychosocial treatment for methamphetamine use disorders: a preliminary randomized controlled trial of cognitive behavior therapy and acceptance and commitment therapy. Subst. Abuse, 31(2):98-107.

85. M Brensilver, KG Heinzerling, S Shoptaw (2013): Pharmacotherapy of amphetamine-type stimulant dependence: an update. Drug Alcohol Depend., in press.

86. N Jayaram-Lindstrom, A Hammarberg, O Beck, and J Franck (2008): Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. Am. J. Psychiatry 165(11):1442-8.

87. J Tiihonen, E Krupitsky, E Verbitskaya, E Blokhina, O Mamontova, J Föhr , P Tuomola, K Kuoppasalmi, V Kiviniemi, and E Zwartau (2012): Naltrexone implant for the treatment of polydrug dependence: A randomized controlled trial. Am. J. Psychiatry 169(5):531-6.

88. J Tiihonen, K Kuoppasalmi K, J Fohr, P Tuomola, O Kuikanmaki, H Vorma, P Sokero, J Haukka, and E Meririnne (2007): A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am. J. Psychiatry, 164(1):160-2.

89. RE Bernardi, JR Lewis, KM Lattal, and SP Berger (2009): Modafinil reinstates a cocaine conditioned place preference following extinction in rats. Behav. Brain Res., 204(1):250-3.

90. ND Volkow, JS Fowler, J Logan, D Alexoff, W Zhu, F Telang, et al (20090:. Effects of modafinil on dopamine and dopamine transporters in the male human brain: Clinical implications. JAMA-J. Am. Med. Assoc. 301(11):1148-54.

91. J Shearer, S Darke, C Rodgers, T Slade, I van Beek, J Lewis , D Brady, R McKetin, RP Mattick, and A Wodak (2009): A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. Addiction, 104(2):224-33.

92. KG Heinzerling, AN Swanson, S Kim, L Cederblom, A Moe, W Ling, and S Shoptaw (2010): Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. Drug Alcohol Depend.,109(1-3):20-9.

93. AL Anderson, S-H Li, K Biswas, F McSherry, T Holmes, Iturriaga E, eR Kahn, N Chiang, T Beresford, J Campbell, W Haning, J Mawhinney, M McCann, R Rawson, C Stock, D Weis, E Yu, and AM Elkashef (2012): Modafinil for the treatment of methamphetamine dependence. Drug Alcohol Depend., 120(1–3):135-41.

94. R De La Garza, II, T Zorick, ED London, TF Newton (2010): Evaluation of modafinil effects on cardiovascular, subjective, and reinforcing effects of methamphetamine in methamphetamine-dependent volunteers. Drug Alcohol Depend., 106 (2-3):173-80.

95. CJ Loland, M Mereu, OM Okunola, J Cao, TE Prisinzano, S Mazier S,T Kopajtic, L Shi, JL Katz, G Tanda, and AH Newman (2012): R-Modafinil (Armodafinil): A unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. Biol. Psychiatry, 72(5):405-13.

96. KS Rau, E Birdsall, JE Hanson, KL Johnson-Davis, FI Carroll, DG Wilkins, JW Gibb,GR Hanson, and AE Fleckenstein (2005): Bupropion increases striatal vesicular monoamine transport. Neuropharmacology, 49(6):820-30.

97. AM Elkashef, RA Rawson, AL Anderson, SH Li, T Holmes, EV Smith, N Chiang, R Kahn, F Vocci, W Ling, VJ Pearce, M McCann, J Campbell, C Gorodetzky, W Haning, B Carlton, J Mawhinney, and D. Weis (2008): Bupropion for the treatment of methamphetamine dependence. Neuropsychopharmacology, 33(5):1162-70.

98. S Shoptaw, KG Heinzerling, E Rotheram-Fuller, T Steward, J Wang, AN Swanson, R De La Garza, T Newton, and W Ling (2008): Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. Drug Alcohol Depend., 96(3):222-32.

99. M Das, D Santos, T Matheson, GM Santos, P Chu, E Vittinghoff E, S Shoptaw, and GN Colfax (2019): Feasibility and acceptability of a phase II randomized pharmacologic intervention for methamphetamine dependence in high-risk men who have sex with men. AIDS, 24(7):991-1000.

100. AH Newman, BL Blaylock, MA Nader, J Bergman, DR Sibley, and P Skolnick (2012): Medication discovery for addiction: translating the dopamine D3 receptor hypothesis. Biochem. Pharmacol. 84(7):882-90.

101. AS Eison, MS Eison, M Stanley, LA Riblet (1986): Serotonergic mechanisms in the behavioral effects of buspirone and gepirone. Pharmacol. Biochem. Behav. 24(3):701-7.

102. R Schreiber, J De Vry (1993): Neuronal circuits involved in the anxiolytic effects of the 5-HT1A receptor agonists 8-OH-DPAT ipsapirone and buspirone in the rat. Eur. J. Pharmacol., 249(3):341-51.

103. H Wong, RC Dockens, Pajor L, Yeola S, Grace JE Jr, Stark AD, Taub RA, Yocca FD, Zaczek RC, Li YW. 6-Hydroxybuspirone is a major active metabolite of buspirone: assessment of pharmacokinetics and 5-hydroxytryptamine1A receptor occupancy in rats. Drug Metab. Dispos., 2007; 35(8):1387-92.
104. NS Kula, RJ Baldessarini, JW Kebabian, and JL Neumeyer (1994): S-(+)-aporphines are not selective for human D3 dopamine receptors. Cell Mol. Neurobiol., 14(2):185-91.
105. JF Tallman, RJ Primus, R Brodbeck, L Cornfield, R Meade, K Woodruff, P Ross, A Thurkauf, and DW Gallager (1997):. I. NGD 94-1: identification of a novel, high-affinity antagonist at the human dopamine D4 receptor. J. Pharmacol. Exp. Ther., 282(2):1011-9.
106. AK Banala, BA Levy, SS Khatri, CA Furman, RA Roof, Y Mishra, SA Griffin, DR Sibley, RR Luedtke, and AH Newman (2011): N-(3-fluoro-4-(4-(2-methoxy or 2,3-dichlorophenyl)piperazine-1-yl)butyl)arylcarboxamides as selective dopamine D3 receptor ligands: critical role of the carboxamide linker for D3 receptor selectivity. J. Med. Chem., 54(10):3581-94.
107. AE Higley, SW Kiefer, X Li, J Gaál, ZX Xi, and EL Gardner (2011): Dopamine D(3) receptor antagonist SB-277011A inhibits methamphetamine self-administration and methamphetamine-induced reinstatement of drug-seeking in rats. Eur. J. Pharmacol. 659(2-3):187-92.
108. AE Higley, K Spiller, P Grundt, AH Newman, SW Kiefer, ZX Xi, and EL Gardner (2011): PG01037, a novel dopamine D3 receptor antagonist, inhibits the effects of methamphetamine in rats. J. Psychopharmacol. 25(2):263-73.
109. L Orio, S Wee, AH Newman, L Pulvirenti, and GF Koob (2010): The dopamine D3 receptor partial agonist CJB090 and antagonist PG01037 decrease progressive ratio responding for methamphetamine in rats with extended-access. Addict. Biol., 15(3):312-23.
110. KL Shelton, ES Hendrick, and PM Beardsley (2013): Efficacy of buspirone for attenuating cocaine and methamphetamine reinstatement in rats. Drug Alcohol Depend., 129(3):210-6.
111. SE Snider, ED Hendrick, and PM Beardsley (2013): Glial cell modulators attenuate methamphetamine self-administration in the rat. Eur. J. Pharmacol.701(1-3):124-30.
112. Beardsley PM, Shelton KL, Hendrick E, Johnson KW (2010): The glial cell modulator and phosphodiesterase inhibitor, AV411 (ibudilast), attenuates prime- and stress-induced methamphetamine relapse Eur. J. Pharmacol., 637(1-3):102-8.
113. HS Mayberg, AM Lozano, V Voon, HE McNeely, D Seminowicz, C Hamani, JM Schwalb, and SH Kennedy (2005): Deep brain stimulation for treatment-resistant depression. Neuron, 45(5), 651–60.
114. J Luigjes, W van den Brink, M Feenstra, P van den Munckhof, PR Schuurman, R Schippers, A Mazaheri, TJ De Vries, and D Denys (2012): Deep brain stimulation in addiction: a review of potential brain targets. Mol. Psychiatry, 17(6): 572–83.