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Psychostimulants and Cognition: A Continuum of Behavioral and Cognitive Activation

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[1]Although some traditional definitions of the term *psychostimulant* require that the drug increase locomotion in rodents, here we argue that *psychostimulants* should include drugs that may not produce hyperlocomotion (e.g., caffeine and modafinil). We refer to the more narrow class of psychostimulants that also produce significant hyperlocomotion (e.g., cocaine and amphetamine) as *psychomotor stimulants*. Moreover, even psychomotor stimulants only do so for a certain range of doses, usually higher than those that produce cognitive enhancement (see Wood and Anagnostaras, 2009; Wood et al., 2007)

[2]Sparlon is Cephalon's trade name for the failed New Drug Application of their modafinil formulation to be used for the treatment of ADHD. Although it never made it to market, it is included here because much clinical trial information was published using this name, and the drug was effective at treating ADHD.

[3]http://www.drugs-forum.com/forum/showthread.php?t=9078&highlight=Cocaine+Experiences (retrieved on 9/6/2010).

[4]http://www.drugs-forum.com/forum/showthread.php?t=26171&highlight=recreational+amphetamine+dose (retrieved on 9/6/2010). Edited for spelling and grammar. It is common on these forums to use the acronyms "SWIM" (someone who isn't me) to designate yourself, and "SWIY" (someone who isn't you) when giving advice to others. For grammatical clarity, these have been edited to match the intent of the writer. See http://www.urbandictionary.com/define.php?term=SWIM (retrieved on 9/6/2010).

[5]http://www.erowid.org/experiences/exp.php?ID=15261 (retrieved on 9/6/2010).

[6]http://www.dr-bob.org/babble/20080412/msgs/823572.html (retrieved on 7/27/10).

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Abstract——**Psychostimulants such as cocaine have been used as performance enhancers throughout recorded history. Although psychostimulants are commonly prescribed to improve attention and cognition, a great deal of literature has described their ability to induce cognitive deficits, as well as addiction. How can a single drug class be known to produce both cognitive enhancement and impairment? Properties of the particular stimulant drug itself and individual differences between users have both been suggested to dictate the outcome of stimulant use. A more parsimonious alternative, which we endorse, is that dose is the critical determining factor in cognitive effects of stimulant drugs. Herein, we review several popular stimulants (cocaine, amphetamine, methylphenidate, modafinil, and caffeine), outlining their history of use, mechanism of action, and use and abuse today. One common graphic depiction of the cognitive effects of psychostimulants is an inverted U–shaped dose-effect curve. Moderate arousal is beneficial to cognition, whereas too much activation leads to cognitive impairment. In parallel to this schematic, we propose a continuum of psychostimulant activation that covers the transition from one drug effect to another as stimulant intake is increased. Low doses of stimulants effect increased arousal, attention, and cognitive enhancement; moderate doses can lead to feelings of euphoria and power, as well as addiction and cognitive impairment; and very high doses lead to psychosis and circulatory collapse. This continuum helps account for the seemingly disparate effects of stimulant drugs, with the same drug being associated with cognitive enhancement and impairment.**

I. Introduction

Psychostimulants are a broad class of sympathomimetic drugs whose effects can include increased movement, arousal, vigilance, anorexia, vigor, wakefulness, and attention (Westfall and Westfall, 2006). Some psychostimulants, especially at high doses and with a rapid route of administration, produce euphoria, a sense of power and confidence, and addiction, in certain susceptible individuals (Boutrel and Koob, 2004). The present review focuses on the cognitive effects of psychostimulants, with particular attention to low doses associated with cognitive enhancement (Kuczenski and Segal, 2002; Arnsten, 2006; Wood and Anagnostaras, 2009).

A. History of Use. Psychostimulants,[1] broadly construed, include drugs of abuse, such as cocaine and methamphetamine, as well as therapeutic drugs such as mixed amphetamine salts (Benzedrine, Adderall, Vyvanse), methylphenidate (Ritalin, Concerta, Focalin), and modafinil (Provigil, Sparlon[2]). Psychostimulants are also used nonmedically, with caffeine, coca leaves, and khat being examples of stimulants consumed today primarily for quality-of-life purposes. Casual use of stimulants for wakefulness or performance enhancement dates back centuries. For example, evidence for use of khat (which contains cathinone, a moderate amphetamine-like stimulant), popular in parts of the Middle East and Africa, dates back to at least the 11th century (Al-Motarreb et al., 2002). Today, khat is a social mainstay in several countries (e.g., Yemen), and chewing khat leaves remains legal in many nations, including Israel (Siegel-Itzkovich, 2009). Interestingly, and in parallel to mainstream medicine's approach toward improving academic performance in children

ABBREVIATIONS: ACC, anterior cingulate cortex; AD, Alzheimer's disease; ADHD, attention deficit/hyperactivity disorder; DA, dopamine; DAT, dopamine transporters; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; EDS, excessive daytime sleepiness; FA, fractional anisotropy; fMRI, functional MRI; 5-HT, 5-hydroxytryptamine; LSD, D-lysergic acid diethylamide; MRI, magnetic resonance imaging; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; OFC, orbitofrontal cortex; OROS, osmotic-release oral system; PET, positron emission tomography; SRT, simple reaction time; WCST, Wisconsin Card Sorting Task.

with attention deficit/hyperactivity disorder (ADHD), khat is sometimes given to school-age children by parents who believe that it improves academic performance (Al-Motarreb et al., 2002).

In the United States and other Western cultures, amphetamine, methylphenidate, and other closely related drugs are successfully used in the treatment of a variety of disorders, including ADHD. However, psychostimulants are also subject to abuse that can sometimes lead to addiction. Drug addiction is a chronic disease characterized by the compulsion to seek out and consume a drug, even in the face of escalating drug-related emotional and physical problems (O'Brien, 2006; Koob and Volkow, 2010). Addiction involves the loss of control over taking the drug, including a tendency to relapse after detoxification and prolonged periods of abstinence. Mechanistically, addiction is hypothesized to hijack healthy learning, memory, and motivation circuits, altering them to focus on the procurement and consumption of the drug of abuse (Hyman, 2005). The difference between performance enhancement and addiction, with respect to stimulants, prominently depends on two closely related factors: dose and route of administration (Boutrel and Koob, 2004; Volkow et al., 2005; Ferrario et al., 2008; Fowler et al., 2008; Wakabayashi et al., 2010). Specifically, high doses and rapid routes of administration seem integral to the development of addiction.

B. The "Yerkes-Dodson Law" and the "Inverted UShaped Curve". In 1908, Robert Yerkes and John Dodson examined the effect of shock intensity on the acquisition of a visual discrimination task in mice (Yerkes and Dodson, 1908). Mice were trained to enter a white passageway, with entrance into the alternate, black passageway leading to a shock. Differences in brightness of the apparatus were used to vary the difficulty of the task. For "difficult" (dark) discriminations, performance on the habit-learning task varied with shock intensity along an "inverted U"–shaped function. That is, animals did best when a moderate shock was used, compared with a mild or strong shock. Interestingly, for the "easy" (bright) version, animals showed a monotonic improvement in performance as shock intensity increased. Although the original version of this experiment has rarely been replicated, and its interpretation remains problematic, it has generated a basic law in psychology textbooks known as the Yerkes-Dodson law. Descriptions of this law are usually inaccurate with respect to the original experiment. The manipulation of degree of difficulty in the task is usually ignored, as exemplified in this typical textbook description of the law: "performance increases with arousal up to an optimal point and then decreases with increasing arousal" (Gazzaniga et al., 2009). "Optimal arousal theory" and the figure typically attributed as the Yerkes-Dodson law actually seem to originate from a review published by Donald Hebb (see Fig. 1; Hebb, 1955). Hebb himself drew heavily on an earlier review by Harold Schlosberg (Schlosberg, 1954). Schlosberg wrote of a "level of activation continuum" (p.85), in characterizing "the inverted U relationship," with low and high levels of activation ("sleep" and "tension," respectively) associated with poor performance, and moderate activation associated with the

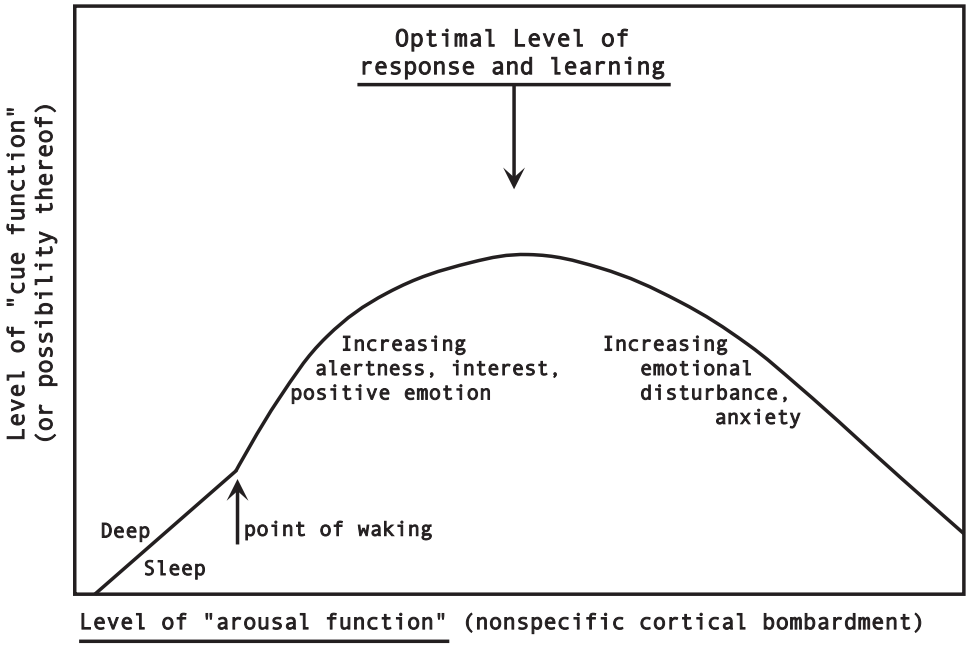


Fig. 1. Donald Hebb's "optimal arousal theory," as depicted in Fig. 2 in Hebb (1955). Redrawn from content in the public domain. Hebb was describing Schlosberg's "level of activation continuum." This theory is often conflated, somewhat incorrectly, with the Yerkes-Dodson law.

best performance. In the simplest terms, our review lays out the rationale for psychostimulant dose as a proxy for the level of activation.

C. A Continuum of Psychoactivation. We begin this review with an overview of several popular psychostimulants: cocaine, amphetamine, methylphenidate, modafinil, and caffeine. We then propose a "continuum of psychostimulant activation," outlining the full range of responses typically seen after psychostimulant administration, with low doses producing beneficial cognitive effects and high doses producing addiction and psychosis. Cognitive and performance enhancement will be closely associated with low doses, less efficacious drugs, and slow (usually oral) administration, whereas addiction will be closely associated with high doses, more efficacious or potent drugs, and rapid routes of administration (insufflation or injection; Bickel et al., 2007).

This continuum complements earlier work by Lyon and Robbins (1975), in which an inverted U–shaped function of amphetamine effects on specific rodent behaviors is described. They theorized that a "single increasing stimulatory effect" can account for both sides of the curve, with amphetamine resulting in the organism exhibiting "increasing response rates within a decreasing number of response categories" (see Fig. 2; Lyon and Robbins, 1975). This accounts for behaviors typically seen at high doses of stimulants, such as stereotypic behaviors and impaired cognitive flexibility. Later, Robbins and Sahakian also emphasized that "dosage is one of the most important determinants of the behavioural response to amphetamine-like drugs. Dose-response curves of the effects of amphetamine on simple behavioural responses…often have the form of an inverted U–shaped function" (Robbins and Sahakian, 1979).

The psychostimulant continuum's emphasis on dose also parallels a current neurobiological model of ADHD, which focuses on catecholamine levels. This ADHD model posits that symptoms are evident in the bottom, left portion of an inverted U–shaped curve of catecholamine level in the prefrontal cortex (Arnsten, 2009). Peak cognitive performance is found with a moderate amount of monoamines present, whereas high levels are evidenced by stress and, again, poor performance. Similarly, a review of trends in cognitive enhancement hypothesized that an intermediate level of prefrontal cortex catecholamine concentration corresponds with optimal cognitive performance (de Jongh et al., 2008).

II. Cocaine

A. History of Use. Cocaine is an alkaloid derived from the coca plant (*Erythroxylum coca*), typically extracted in a paste form and converted into a hydrochloride or sulfate salt because of instability of the free base. This salt can be prepared in a variety of ways to facilitate intake by methods such as i.v. injection or snorting, or converted back to a free base for smoking (i.e., "crack"). However, coca leaves have been used for thousands of years in Central and South America for their more modest stimulant effects (Cartmell et al., 1991; Indriati and Buikstra, 2001). Today, it is claimed that no profound illness is found in studies of modern habitual chewers of coca leaf, perhaps due to the low doses used by chewers, in contrast to the high doses given in laboratory studies or taken by addicts (Hanna, 1974).

In the West, cocaine was widely used toward the latter half of the 19th century in coca wines, cigarettes, and patent medicines, including Coca-Cola (see Fig. 3; Meyer and Quenzer, 2005). The beneficial effects of

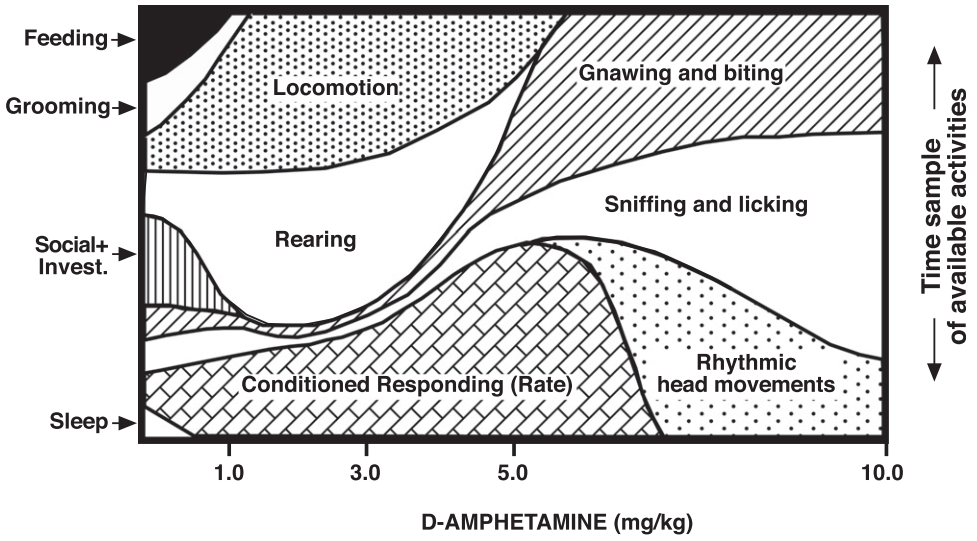
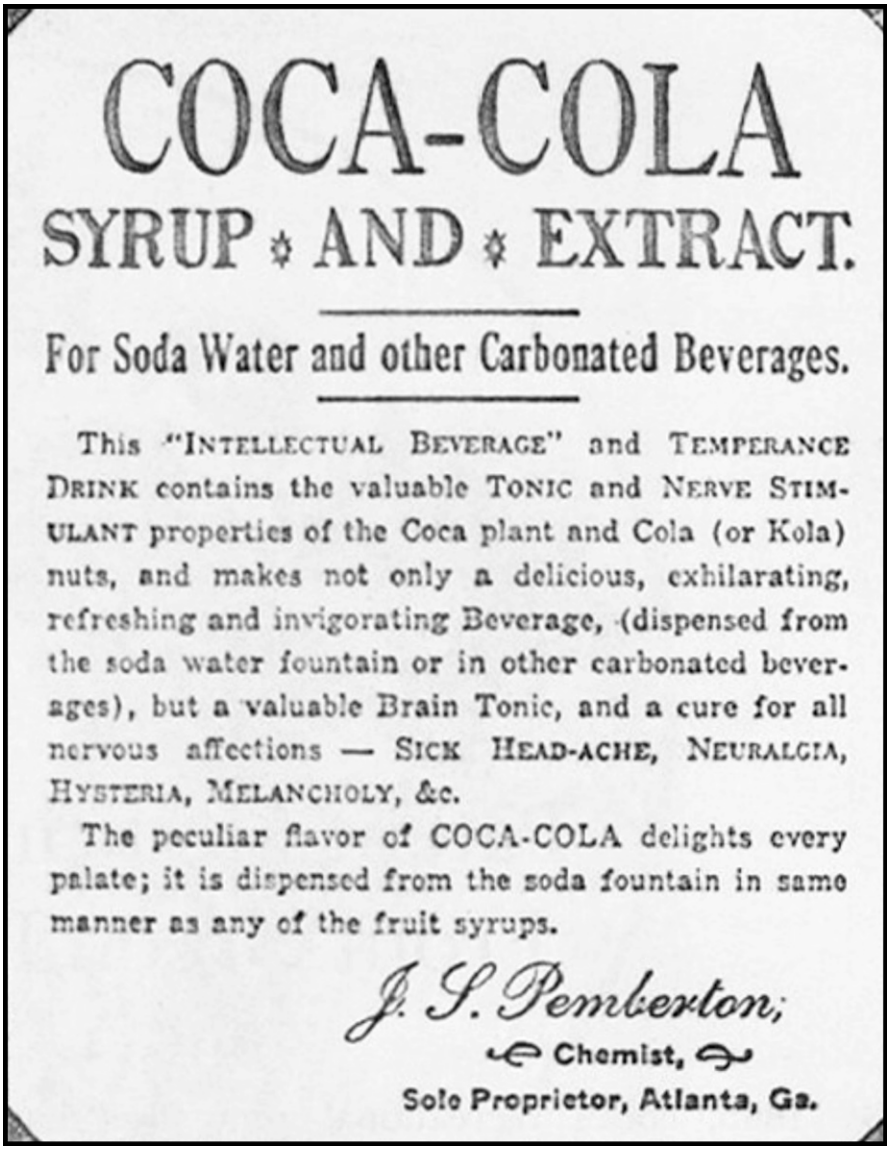


Fig. 2. Behavioral activation continuum as described by Lyon and Robbins (1975). Redrawn from their Fig. 3, with permission. The relative distribution and availability within a given time sample of varying activities in the rat is determined by the increasing dose-response effect of D-amphetamine.

cocaine were famously promoted by Sigmund Freud (who, at that time, used low doses, roughly 25–50 mg, or ~0.35–0.7 mg/kg) in his essay, *Über Coca* (Shaffer, 1984): "exhilaration and lasting euphoria, which in no way differs from the normal euphoria of the healthy person...You perceive an increase of self-control and possess more vitality and capacity for work...Long intensive physical work is performed without any fatigue." Freud himself descended into addiction before eventually conquering it much later (Markel, 2011). Cocaine addiction was a nationally recognized problem by the late 1880s (Mattison, 1887; Candler, 1891), but cocaine distribution was not illicit in most countries, including the United States, until 1914, following the International Opium Convention of 1912 (the first of many international treaties regulating drug use).

B. Mechanism of Action. Cocaine blocks the reuptake of monoamine neurotransmitters, including dopamine (DA), norepinephrine (NE), and serotonin [5-hydroxytryptamine (5-HT)]. Blockade of DA reuptake has been closely associated with the reinforcing and addictive properties of cocaine (O'Brien, 2006). Furthermore, behavioral studies have shown reduced striatal dopaminergic functioning in recreational cocaine users (Colzato et al., 2008), and positron emission tomography (PET) studies have confirmed a reduction in DA D_2 receptor availability in cocaine abusers, even after months of abstinence (Volkow et al., 1993). Cocaine's behavioral activating and dopaminergic effects further depend on glutamate *N*-methyl-D-aspartate (NMDA) receptors, although the exact mechanism is somewhat unclear. NMDA receptors are functionally coupled to


COCA-COLA

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This "INTELLECTUAL BEVERAGE" and TEMPERANCE DRINK contains the valuable TONIC and NERVE STIMULANT properties of the Coca plant and Cola (or Kola) nuts, and makes not only a delicious, exhilarating, refreshing and invigorating Beverage, (dispensed from the soda water fountain or in other carbonated beverages), but a valuable Brain Tonic, and a cure for all nervous affections — SICK HEAD-ACHE, NEURALGIA, HYSTERIA, MELANCHOLY, &c.

The peculiar flavor of COCA-COLA delights every palate; it is dispensed from the soda fountain in same manner as any of the fruit syrups.

J. S. Pemberton,
Chemist,
Sole Proprietor, Atlanta, Ga.

Fig. 3. One of the early labels for Coca-Cola. Note its emphasis on performance-enhancing effects and its description as a psychiatric panacea (Ludlow Santo Domingo Library). The actual amount of coca leaves per glass was described by Coca-Cola in an editorial letter as 0.11 g (Candler, 1891), or enough to produce about 0.5 mg of cocaine, less than 0.01 mg/kg in an adult (Jenkins et al., 1995).

D_2 receptors in the striatum, and this coupling is critical for even the acute behavioral response to cocaine (Liu et al., 2006). Blockade of NMDA receptors reduces the efficacy of cocaine in terms of its ability to increase extracellular dopamine concentrations, and reduces cocaine's locomotor activating effects. Finally, activation of DA triggers second messengers that regulate expression of both NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Svenningsson et al., 2005).

Cocaine also blocks sodium (Na^+) channels, thereby acting as a powerful local anesthetic (Billman, 1990; Rump et al., 1995), its only medically approved use in the United States. This mechanism is not shared with other stimulants, such as amphetamine, and has been traditionally blamed for cocaine's cardiotoxic and convulsigenic effects. However, recent evidence suggests that cocaine's convulsigenic effects may be due to action on NMDA receptors (see Lason, 2001 for a brief review).

Outside of Freud's (Shaffer, 1984) description, there is little formal knowledge regarding the potential performance-enhancing effects of cocaine, which might occur at doses lower than those used by addicts.

C. Therapeutic Use. The Drug Enforcement Administration of the United States considers cocaine a Schedule II drug, determining it to be highly addictive and dangerous to the user's health, but appropriate for restricted medicinal use (Controlled Substances Act (21 USC § 812, 2002)). Both prolonged and acute use of cocaine can lead to a wealth of cardiotoxic (Kloner et al., 1992) and neurovascular (Tamrazi and Almast, 2012) complications, the severity of which is dependent upon the dose used. However, cocaine inhibits Na^+ channels at high concentrations, and historically was widely used as a local anesthetic, especially in dentistry and ophthalmology (Catterall and Mackie, 2006). Today, similar compounds (e.g., lidocaine) are more commonly used for this purpose. Medicinal cocaine use is rare, but is sometimes argued to be optimal for certain eye or ear surgeries because of its vasoconstrictive (sympathomimetic) properties, useful in controlling bleeding and swelling, in addition to its local anesthetic properties (Catterall and Mackie, 2006; Henderer and Rapuano, 2006).

D. Abuse. The effects of different doses of cocaine on human cognition are difficult to pinpoint. Although drugs such as caffeine can be ethically administered within a range of doses to undergraduate volunteers, cocaine can be administered exclusively to those who have recently used or are currently using the drug (an estimated 2.1 million people in 2007, or 0.8% of the U.S. population, according to a recent survey by the Substance Abuse and Mental Health Services Administration, 2008). The consumption of cocaine or any illegal, highly addictive substance is difficult to estimate when bought on the street, as it is probably impure and may be laced with any number of other substances. Researchers have attempted to estimate the amount of cocaine consumed by users via the following measures: the self-reported amount of money spent on the drug per week (Bolla et al., 2003), the amount consumed in a month's time (Colzato et al., 2008), or the amount consumed within a week (Goldstein et al., 2004).

Laboratory studies can control the amount of cocaine administered and record the opinions of experienced users regarding the subjective effects of different doses. In a study investigating the cardiovascular and subjective effects of smoked cocaine over time, participants consumed six 25-mg doses per experimental session (roughly 0.31 mg/kg per dose or 1.86 mg/kg per session in an 80-kg individual). Participants in the study were experienced cocaine users and expressed positive attitudes toward this dose of drug, although tolerance emerged over several days, evidenced by reduced drug ratings on a visual analog scale (Reed et al., 2009). In a larger sample of users, the overall positive ratings of the first study administration of this dose of drug (25 mg) were not influenced by years of experience, suggesting that this dose may be a reasonable estimate of what users typically self-administer (Kalapatapu et al., 2012).

There is a wealth of literature concluding that habitual cocaine use impairs a subset of neurocognitive functions. An effect size analysis concluded that cocaine's largest impact on cognition is evidenced by tests of attention, as well as visual and working memory (Jovanovski et al., 2005). An electrophysiological study of cocaine-dependent participants revealed a reduced amplitude in the P300 component, considered to reflect an impairment in attention and working memory functions, compared with controls (Gooding et al., 2008). Likewise, a study of 42 crack cocaine–addicted individuals demonstrated a general, mild level of cognitive impairment as measured by a battery of 16 different tests (Goldstein et al., 2004).

Disruption of prefrontal cortical activation, measured by PET, has also been found in cocaine abusers. One study showed that cocaine users, defined here as those who self-administer cocaine at least four times per month, performed as well as controls on the Stroop Task (Bolla et al., 2004). Despite no difference in behavior, PET images revealed that the cocaine users showed less activation in the left anterior cingulate cortex (ACC) and right lateral prefrontal cortex compared with controls, while exhibiting higher levels of activation in the right ACC. Moreover, the greater the amount of self-administered cocaine per week leading up to the 23 days of enforced abstinence, the lower the activity in the rostral ACC and the right lateral prefrontal cortex. Similarly, a PET study from the same research group revealed an increased activation in the right orbitofrontal cortex (OFC) and decreased activation in the right dorsolateral prefrontal cortex in cocaine abusers, as compared with controls, while performing the Iowa

Gambling Task. This task requires participants to weigh smaller, long-term losses more heavily than larger, immediate gains to succeed, and lesion studies have shown it to be related to OFC function (Bolla et al., 2003). In this study, as well, the amount of cocaine consumed prior to the enforced abstinence period was negatively correlated with left OFC activation. Metabolism in the dorsolateral prefrontal cortex was also found to predict performance on tasks tapping into visual memory and verbal memory (Goldstein et al., 2004). These studies indicate that frontal areas involved in attention and executive functioning are particularly affected by extended cocaine use, although, with no corresponding behavioral impairments, the functional implications of these findings remain opaque.

Magnetic resonance imaging (MRI) has also provided evidence of cortical disruption in cocaine abusers. In a large sample (n = 60) of cocaine-dependent individuals, reduction in gray matter OFC volume was related to compulsivity measures, whereas enlargement of the caudate was associated with attentional impairments (Ersche et al., 2011). Importantly, these changes in gray matter volume were correlated with the duration of cocaine abuse. A functional MRI (fMRI) study found no significant behavioral differences between treatment-seeking, cocaine-dependent participants and controls on a working memory task (Moeller et al., 2010). However, the data demonstrated a reduction in thalamic activity during performance of the task in the cocaine group compared with controls. This thalamic deactivation was associated with subsequent treatment outcome, with less thalamic activation related to worse outcome. This study, as with many others, was able to show a neural difference but not a cognitive deficit in cocaine-dependent participants. However, it was able to describe a functional outcome related to these brain differences outside the realm of cognitive tests that could help lead the way for future treatment studies.

Other studies have shown a mixture of impairments as well as enhancements on different cognitive tasks in cocaine-dependent individuals. Thirty-eight crack cocaine–dependent men showed a host of deficits compared with controls, including poorer performance in object-naming ability as measured by the Boston Naming Test, executive control as measured by the Booklet Categories Test, spatial memory as measured by the Benton Visual Retention Test, and concentration or speed as measured by Trail Making Test (Trails), Part B. Interestingly, cocaine-dependent participants performed better on the Controlled Oral Word Association Test, a word-list–generation task that measures verbal fluency. They also achieved a higher number of correct categories on the Wisconsin Card Sorting Test (WCST), a standard neuropsychological test used to measure executive functioning, specifically the ability to shift strategies when appropriate. Performance on these cognitive tasks did not show a relationship to years of cocaine abuse or abstinence, making the implications of these results difficult to interpret (Hoff et al., 1996). These findings are supported by other research, however, with 30 polysubstance abusers, 28 of whom used cocaine regularly for an average of more than 7 years, performing as well as controls on the WCST (Grant et al., 2000). In this study, drug abusers showed a marked deficit on performance of the Gambling Task (an earlier name for the Iowa Gambling Task discussed earlier). Finally, in a novel pilot study examining cognitive functioning in older and younger cocaine abusers and controls, the main effect of age appeared to result in a greater number of cognitive impairments than the effect of cocaine (Kalapatapu et al., 2011). The older participants (ages 51–70 years) performed worse on a series of tasks (Mini-Mental State Examination, Digit Span Backward, Trails A, B and B-A) compared with the younger participants (ages 21–39 years), regardless of cocaine abuse status. A main effect of cocaine was found only for Trails A and B-A. In examining the older participants, a deficit was seen in the cocaine abusers only for Trails A performance compared with older controls. As the number of subjects for this study was relatively small (n = 20 per group), more subjects are likely needed to uncover the more nuanced cognitive changes between groups. However, it is notable that the effect of age is already apparent in the data, and is perhaps more powerful than the effect of cocaine abuse.

E. Summary

> *I snorted the first line and initially didn't feel much…Gradually, I became aware that my mood was significantly elated. I had another line and…I seemed to have much quicker and more incisive analytical abilities. After the next line…I felt like a God. I felt untouchable, invincible.*[3]

Although the studies reviewed demonstrate that prolonged use of high-dose cocaine may lead to altered patterns of brain activation and a specific set of cognitive impairments, virtually no studies have examined the effects of low-dose cocaine. Our laboratory examined the effects of a wide range of doses of cocaine (0.1–15 mg/kg i.p.) on fear conditioning, a prominent model of memory, in mice (Wood et al., 2007). Pavlovian fear conditioning, particularly contextual fear learning, is a leading model of memory (Anagnostaras et al., 2001). We found that a moderately high dose of cocaine (15 mg/kg i.p.), similar to or higher than what addicts might take, led to memory impairments. In contrast, a low dose (0.1 mg/kg i.p.) actually enhanced memory (Fig. 4); cocaine also produced hyperlocomotion at even the lowest doses. Our data indicate that low doses of cocaine may lead to cognitive enhancement, whereas very high doses may lead to cognitive impairments.

III. Amphetamine

A. History of Use. Use of amphetamine and similar compounds has been documented for centuries. Ephedra (also known as ma huang), specifically the *Ephedra sinica* species, is an herb that has been used in Traditional Chinese Medicine for an estimated 5000 years (Abourashed et al., 2003). Although used in Traditional Chinese Medicine primarily for the treatment of asthmatic symptoms, in the United States, modern use of ephedra and its active ingredient, ephedrine, has been associated with weight loss and performance enhancement (Mehendale et al., 2004). After mounting evidence for their involvement in adverse side effects and death, the U.S. Food and Drug Administration banned the sale of dietary supplements containing herbal ephedra in 2004 (Food and Drug Administration, 2004). Ephedrine, however, remains for sale in certain preparations, including antiasthmatics and decongestants (e.g., Bronkaid, Primatene).

The efficacy of ephedra as a bronchodilator encouraged the scientific community to seek out a synthetic, inexpensive version of the herbal remedy in the early 1900s (Meyer and Quenzer, 2005). Amphetamine was marketed as an over-the-counter nasal inhaler under the brand name Benzedrine (mixed D- and L-amphetamine salts). Benzedrine was also administered in pill form and was used to treat maladies, including sea sickness, narcolepsy, and Parkinson's disease (Davies et al., 1939). The United States and other countries have used amphetamine for military purposes (Somerville, 1946). For example, Caldwell (2003) has extensively investigated its use in pilots, primarily for relief from fatigue and prevention of sleep deprivation–related performance decline; in these situations, amphetamine has proven highly effective (Fig. 5).

Evidence for the use of amphetamine for cognitive enhancement dates back decades. Young male inmates (ages 11–17 years) displayed enhancement in physical (strength of grip) and mental performance after amphetamine administration (10, 20, or 30 mg; Molitch and Eccles, 1937). In addition, patients with diagnoses ranging from anxiety to schizophrenia experienced an average 8% improvement on an IQ test with 20 mg of amphetamine (Fig. 6; Sargant and Blackburn, 1936). Prolonged amphetamine administration (5 mg per day for 3 months and then 7.5 mg per day for an additional 3 months) did not improve the IQs of "moron and borderline defective children" (Cutler et al., 1940), and acute amphetamine (10 mg) did not enhance attention (Barmack and Seitz, 1940) or performance on mental ability tests (Barmack, 1940; Hecht and Sargent, 1941) in healthy participants. However, another study found that amphetamine (individually tailored doses, 10–30 mg) led to improved school performance in roughly half of the child participants, who were at a hospital due to a range of behavior disorders (Bradley, 1937).

Interestingly, early articles also report evidence for academic doping (see discussion of academic doping in section IV.D). Severe cardiac collapse occurred after excessive amphetamine had been self-administered by one individual who "said the drug was being used to some extent by individuals studying for examinations" (Davies et al., 1939). Other early reports proclaimed that college students "have great interest in stimulants or 'pep pills' that promise to help them over their academic hurdles" (Flory and Gilbert, 1943), and that "many students have come to cherish this drug as a gift of the Gods, relying upon it to carry them through prolonged periods of cramming for examinations" (Minkowsky, 1939).

Published in 1962, a review of the performance-enhancing effects of amphetamine and caffeine found that, although the findings were mixed, the literature generally showed that both substances improve cognitive and physical performance (Weiss and Laties, 1962). Interestingly, from the studies they reviewed, the authors determined that, at the "dose levels that clearly enhance performance, the amphetamines seem not only more effective than caffeine, but less costly in terms of side-effects." Furthermore, and in stark contrast

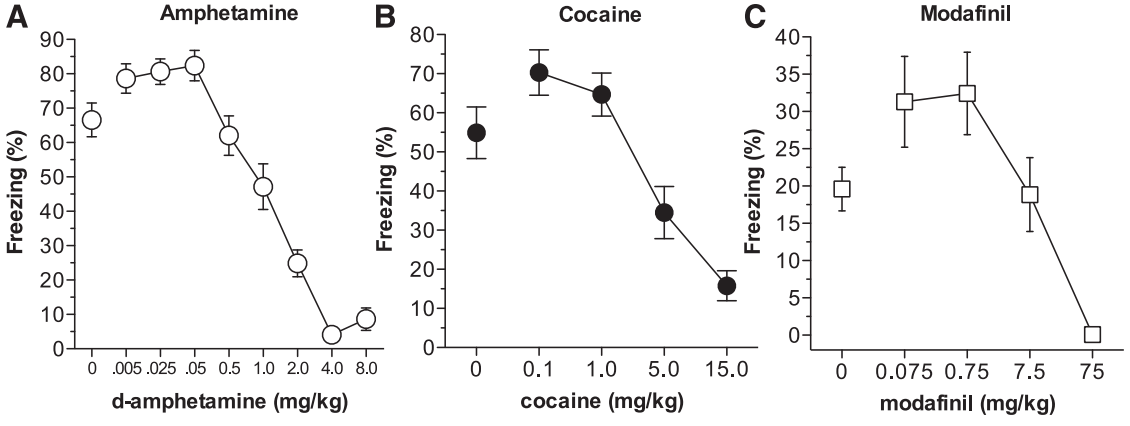

Fig. 4. Fear memory was enhanced at low doses and impaired at high doses of D-amphetamine (A), cocaine (B), or modafinil (C) in mice. Data redrawn with permission from Wood and Anagnostaras (2009), Wood et al. (2007), and Shuman et al. (2009), respectively.

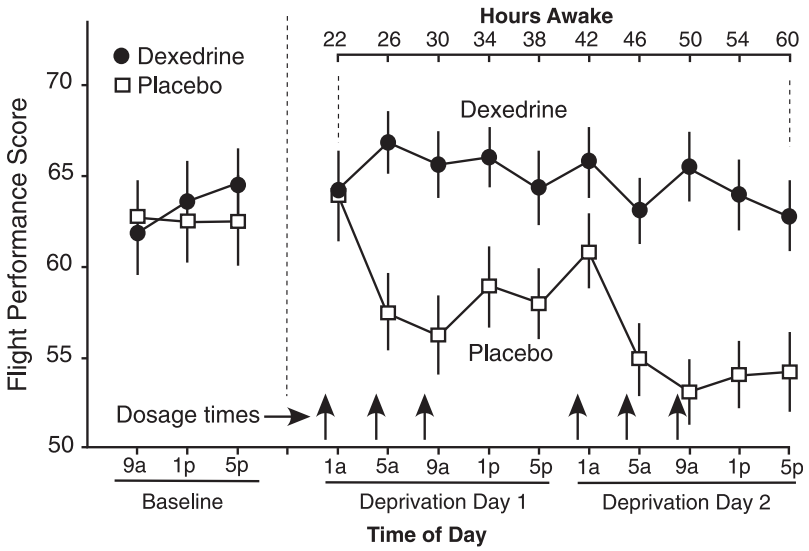

Fig. 5. Prevention of sleep deprivation–related performance decline in flight performance by repeated doses of 10 mg of amphetamine (Dexedrine). Data are from the U.S. Army Aeromedical Research Laboratory. Redrawn with permission from Fig. 7 in Caldwell (2003).

to today's predominant viewpoint, the authors declared "neither [substance] is addicting in the sense that narcotics are," with only "occasional individuals, usually individuals with neurotic or psychotic symptoms, habitually [taking] extremely high doses."

Dexedrine (pure D-amphetamine) was introduced as a more potent version of Benzedrine, and in 1944, methamphetamine (Methedrine) was introduced as the most potent amphetamine, prescribed for hay fever, alcoholism, narcolepsy, and other indications (Food and Drug Administration, 2010). Today, methamphetamine is not widely prescribed and remains approved only for ADHD and obesity (Ovation Pharmaceuticals, 2007), although it has also been found to be effective, off label, for narcolepsy as well as treatment-resistant depression (Morgenthaler et al., 2007; Orr and Taylor, 2007; Candy et al., 2008).

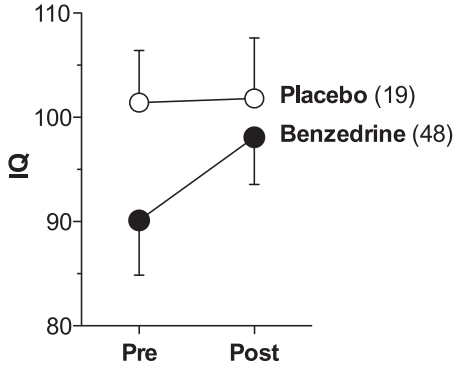

Fig. 6. Cognitive enhancement of IQ by 20 mg of amphetamine (Benzedrine). An early formal study of amphetamine's cognitive-enhancing effects by Sargant and Blackburn (1936). Twenty milligrams of amphetamine improved IQ in mentally ill patients by almost a full standard deviation. Scores here (drawn from their Table 1) have been adjusted to a scale of 100, and the Benzedrine group includes subjects tested 90 or 150 minutes after administration (both groups performed similarly). Drawn from Sargant and Blackburn (1936) with permission from Elsevier.

B. Mechanism of Action. Amphetamine acts to dramatically increase the amount of extracellular monoamines available in the brain, through blockade and/or reversal of the DA, NE, and 5-HT reuptake transporters and regulation of their surface expression levels. Converging evidence suggests that amphetamine enters the cell through various monoamine reuptake transporters, and reverses the vesicular monoamine transporter. This leads to a large release of cytoplasmic and vesicular stores of transmitter (Robertson et al., 2009). In contrast to cocaine, the release of transmitter is Ca^{2+}-independent (Sulzer et al., 2005).

C. Therapeutic Use. Amphetamine is a Schedule II drug, indicating that it has the potential for abuse and addiction, but also has medical use (Controlled Substances Act (21 USC § 812, 2002)). Whereas low doses are typically ingested orally for therapeutic purposes, high doses of amphetamine (especially methamphetamine) tend to be injected or smoked, and have been associated with addiction and cognitive deficits (however, see section IV.D for discussion of the illicit consumption of Adderall for academic doping).

Amphetamine is prescribed for a number of diagnosable conditions, including narcolepsy, shift-work sleep disorder, and, most commonly, ADHD. ADHD consists of a combination of behaviors that fall within the diagnostic criteria of inattention, hyperactivity, and impulsivity (America Psychiatric Association, 2000). A meta-analysis estimated the global prevalence of ADHD to be 5.29%, varying significantly by region (Polanczyk et al., 2007). By 2003, ADHD had been diagnosed in an estimated 11.0% of boys and 4.4% of girls ages 4–17 years in the United States (Visser and Lesesne, 2005). A more recent estimation set the number of ADHD diagnoses at 8.4% of all children in the United States between the ages of 6 and 17 years (Pastor and Reuben, 2008). Of those diagnosed, more than half were

currently taking medication for ADHD. Finally, a recent study made headlines when researchers discovered that the rate of ADHD diagnosis jumped 24% between 2001 and 2010, from 2.5 to 3.1%, in a cohort of southern Californian children between the ages of 5 and 11 years (n = 842,830) (Getahun et al., 2013).

Stimulants are a first-line treatment of ADHD, with various preparations of amphetamine (e.g., Adderall) and methylphenidate (e.g., Concerta, Focalin) providing high levels of efficacy (Faraone and Biederman, 2002; Pietrzak et al., 2006). Stimulant medication use in U.S. youth has been increasing over the decades, with 0.6% of all surveyed youth using in 1987, jumping to 2.4% in 1996 (Olfson et al., 2002). In recent years, the prevalence of prescription stimulant use among children 18 years old and younger has been estimated from 2.2 million children, or 2.9% of the youth population (Zuvekas et al., 2006), to approximately 2.5 million children (Visser and Lesesne, 2005), demonstrating that legal stimulant use in the United States is pervasive. Increases in prescription stimulant use have been reported globally in the last decade, in countries such as The Netherlands (a 6.5-fold increase in 5 years; van den Ban et al., 2010), Australia (an 87% increase in 7 years; Hollingworth et al., 2011), and Sweden (an increase in the number of children receiving their first treatment with stimulants jumping from close to 0 in 1990 to almost 1200 in 2002; Janols et al., 2009).

In an early meta-analysis, mixed D,L-amphetamine salts (Adderall) reliably effected a large improvement in ADHD symptoms, compared with placebo. This improvement was consistent over different dosing regimens and scales of measurement (Faraone and Biederman, 2002). In addition, a double-blind, placebo-controlled, crossover study examined the effects of mixed D,L-amphetamine (0.15 and 0.3 mg/kg) in 154 children ranging in age from 5 to 16 years (Ahmann et al., 2001). Mixed D,L-amphetamine was shown to have an efficacy rate of 59%, when examined with the criteria that parents and teachers agreed on during their evaluation of the child's behavior. Mixed D,L-amphetamine had an efficacy rate of 81%, when based on parental feedback alone. Appetite suppression, nausea, insomnia, and headaches were some of the side effects reported by parents of children taking mixed D,L-amphetamine, whereas higher levels of staring/daydreaming and sadness/unhappiness were reported for children on placebo. A randomized, double-blind, crossover study of 35 children ages 6–12 years demonstrated a high level of efficacy for three types of amphetamine medications, including mixed D,L-amphetamine, compared with placebo (James et al., 2001). Another study found similarly effective results with extended-release amphetamine (Adderall XR) in 258 adolescents with ADHD, ages 13–17 years (Spencer et al., 2006). Participants were randomly assigned to one of five groups, one receiving placebo and four receiving extended-release amphetamine (10, 20, 30, or 40 mg/day), with doses in the higher-dose groups being escalated throughout the 4-week experiment. All extended-release amphetamine groups showed improvement in ADHD symptoms as assessed by both the ADHD Rating Scale-IV and the Clinical Global Impressions–Improvements for ADHD, compared with placebo. Side effects, such as insomnia, headaches, abdominal pain, and weight loss, had an increased prevalence in the extended-release amphetamine groups, but were typically mild or moderate in their intensity.

Another school study compared the efficacy of daily, extended-release amphetamine (10 mg/day escalated to 30 mg) with that of atomoxetine (Strattera; 0.5 mg/kg escalated to 1.2 mg/kg), a popular "nonstimulant" treatment of ADHD, in 215 schoolchildren ages 6–12 years (Wigal et al., 2005). Over the course of the 3 weeks of the study, both medications led to improvement on a number of behavioral measures (e.g., academic productivity, attention), but extended-release amphetamine led to greater gains in these measures than atomoxetine.

An early study on D-amphetamine indicated that its behavioral benefits are not seen exclusively in those with ADHD. A group of 15 boys with ADHD as well as a group of 14 healthy boys were each administered placebo and D-amphetamine on different days in a randomized, double-blind fashion. As a testament to the popularity of D-amphetamine at the time, the authors noted that the healthy boys were well aware of "the use of 'speed' among older children and did appear to look forward to the experiment" (Rapoport et al., 1980). In both healthy boys and those with ADHD, D-amphetamine (0.25 mg/kg) decreased motor movement and increased performance on a free recall verbal memory task (Fig. 7, A and B).

Although the benefits of amphetamine seem robust, a study found that ADHD patients on mixed D,L-amphetamine, atomoxetine, or methylphenidate did not perform neurocognitive tasks on par with control participants, despite performing better than untreated ADHD patients (Gualtieri and Johnson, 2008). In addition, there has been speculation regarding mixed D,L-amphetamine's potentially deleterious effects on creativity. This topic warrants further research, although one study found no evidence for stunted creativity (Farah et al., 2009).

Off-label use of stimulants has also revealed therapeutic results. Ten participants with schizophrenia, currently taking antipsychotics, were administered 0.25 mg/kg D-amphetamine before a series of cognitive tasks. D-Amphetamine improved reaction time on spatial working memory and Stroop tasks in both participants with schizophrenia and controls, and increased language production and improved working memory accuracy in those with schizophrenia (Barch and Carter, 2005). By contrast, an earlier study found either no difference or minor impairments on a range of

cognitive tasks (e.g., symbol copy, digit symbol) when those with schizophrenia were administered D-amphetamine (10 or 20 mg; Kornetsky, 1976). L-Amphetamine, administered orally in increasing doses throughout a 29-day period (5 mg for days 1–7, 15 mg for days 8–14, and 30 mg for days 15–29), enhanced verbal and spatial memory in cognitively impaired multiple sclerosis patients (Morrow et al., 2009). D-Amphetamine, compared with placebo in a double-blind study, enhanced recovery from aphasia in stroke patients who were administered 10 mg of drug 30 minutes before speech therapy for 1 week (Walker-Batson et al., 2001).

In addition to studies in patient populations, studies in healthy individuals have also found that low doses of amphetamine can improve measures of cognition. For example, 10 healthy subjects were enlisted to take 0.25 mg/kg D-amphetamine or placebo before performing a working memory task while undergoing fMRI scanning (Mattay et al., 2000). Each subject participated on placebo as well as on drug to establish a baseline score for comparison of the drug effects. Subjects who had low working memory on placebo showed improvement while on D-amphetamine for the most challenging parts of the task; those with high working memory at baseline were impaired by the drug. Imaging revealed that participants who showed a small increase in prefrontal cortex activation after drug, compared with placebo, improved their performance on the task, whereas larger increases in activity were accompanied by impairment.

D. Abuse. The literature is replete with studies outlining problems associated with long-term intake of high doses of amphetamine (e.g., Rogers and Robbins, 2001). One popular meta-analysis found that participants with histories of long-term methamphetamine abuse or dependence had cognitive deficits, with the largest effect sizes in abilities related to learning and memory, as well as executive functioning (Scott et al., 2007). Many studies also point to deficits in social-cognitive functioning, which could compound the difficulties in daily living for those recovering from methamphetamine addiction (Homer et al., 2008). For example, a group of adults with a history of methamphetamine dependence displayed significant impairment on social-cognitive tasks (facial affect recognition, theory of mind) after an average of 6 months of abstinence (Henry et al., 2009).

Converging evidence indicates that frontal brain areas mediate these cognitive deficits. One study demonstrated that methamphetamine-dependent adults, abstinent for an average of 3 weeks, showed dysfunctional decision-making, relying more on an outcome-dependent (win-stay/lose-shift) strategy than controls on a two-choice prediction task (Paulus et al., 2002). The difference between groups decreased with longer periods of sobriety. Functional imaging showed that the methamphetamine-dependent participants had a pattern of hypofrontality, with diminished activation in a host of frontal regions during the task (inferior prefrontal, left prefrontal, bilateral ventromedial prefrontal, and right OFC). Another study gathered resting PET scans on 24 abstinent methamphetamine-dependent males, finding significant hypometabolism in the left inferior frontal white matter, compared with 21 male controls (Kim et al., 2009). Using diffusion tensor imaging, methamphetamine users were found to display lower fractional anisotropy (FA), an indicator of white matter integrity, in frontal areas (Chung et al., 2007). For the male participants of this study, right frontal white matter correlated negatively with the number of errors on the WCST, a test of cognitive flexibility thought to measure frontal lobe function.

The corpus callosum has also been implicated in cognitive deficits in methamphetamine abusers. A structural MRI study found a number of differences within regions of the corpus callosum (e.g., increased curvature of the genu, decreased width of the posterior midbody and isthmus) of abstinent methamphetamine users compared with controls (Oh et al., 2005). A diffusion tensor imaging study examining the corpus callosum in methamphetamine-dependent volunteers found that FA measures of the genu correlated with performance on the Stroop Task in the methamphetamine users, but not in controls (Salo et al., 2009). Although there was no significant group difference in the genu FA between users and nonusers ($P = 0.09$), these results indicate that the more deterioration in the genu of the corpus callosum, the worse the performance on cognitive control tasks, such as the Stroop interference task.

Along with these findings comes a word of caution. Although the sheer volume of studies outlining cognitive deficits in stimulant abusers may seem authoritative, the chapter is not closed on the cognitive effects of prolonged illicit stimulant use. A concern is growing over the methods and conclusions of many of the

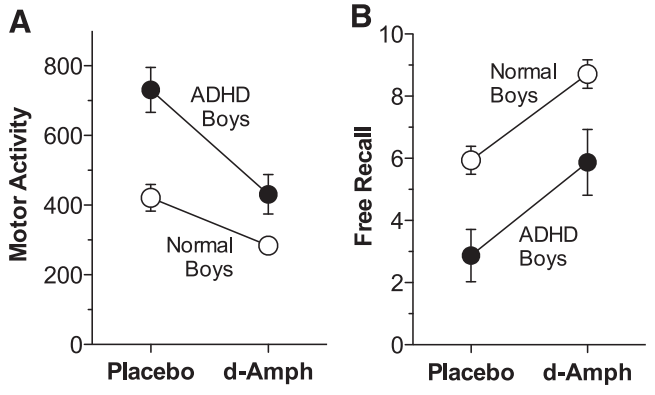

Fig. 7. D-Amphetamine reduces motor activity and increases memory in both ADHD and healthy boys. (A) Reduction of motor activity in normal and ADHD boys after 0.5 mg/kg D-amphetamine sulfate. (B) Improvement in verbal memory in normal and ADHD boys after D-amphetamine administration. Data are drawn with permission from Table 4 (activity) and Table 9 (memory) in Rapoport et al. (1980). Data shown are the mean ± 1 S.E.

aforementioned studies and others similar to them. In particular, Hart et al. (2012) question the appropriateness of the controls used in research examining the cognitive effects of illicit methamphetamine use. Much of the published research has fallen victim to using controls with significant baseline differences from the drug group, such as years of education. In addition, the use of the term "impairment" is ambiguous in many of these studies (Hart et al., 2012). Methamphetamine users are considered as showing impairments if their test performance is lower than that of the control subjects of the study. However, rarely are normative data mentioned. Performance by methamphetamine users may simultaneously fall below that of controls, but may very well lie within normative data for the test being used. While also considering that many of the control groups are not well matched to the members of the drug group, these findings can prove weaker still. Sweeping statements regarding the detrimental effects of long-term stimulant use on cognition should therefore be tempered, and the definition of "impairment" should be clarified.

E. Summary

> *Therapeutic doses are normally given up to about 60 mg. … [I have] never gone over 40 mg, but based on the experiences of others who have, [I recommend] this estimated dosing schedule: (1) Light increase in motivation: 10–15 mg. (2)'Good' club buzz: 20–40 mg (add 1-2 drinks and [you are] set!). (3) Highway speeds: 60–80 mg (might start cleaning the club/party your at, lol). (4) TWEAKED OUT: 100–120 mg (not recommended). **Based on Instant-release pills take orally... as always tolerance and body-type depending…*[4]

While much research has been devoted to studying the effects of low-dose, prescription amphetamine and separate research has investigated the effects of high-dose street amphetamine, little research has examined the effects of both low and high doses in the same study. To examine the boundary between the cognitive impairments and enhancements seen with amphetamine use, we examined the dose-response curve for D-amphetamine (0.005–8 mg/kg) on fear conditioning in rodents (Wood and Anagnostaras, 2009). In line with the effects of amphetamine seen in the literature discussed earlier, we found memory enhancements in mice administered low doses of amphetamine (0.005, 0.025, and 0.05 mg/kg i.p.), whereas memory impairments were evident in those administered moderate to high doses of amphetamine (8 mg/kg i.p.; Fig. 4). Interestingly, D-amphetamine only produced significant locomotor hyperactivity at 4 and 8 mg/kg, well beyond the range at which it produced memory enhancement. These data further support the idea that amphetamine's performance-enhancing effects are dissociable from its effects on locomotor activity. These findings are also in agreement with previous work showing hyperactivity in rats given amphetamine (3 mg/kg s.c.; Searle and Brown, 1938) and cognitive impairment in rats administered 0.5 mg s.c. of amphetamine (1.25 mg/kg in a 400-g rat), as measured by maze errors (Minkowsky, 1939). A reduction in learning has also been found in rats administered 7–8 mg/kg/day D-amphetamine in their drinking water, whereas those receiving 3–4 mg/kg/day were not impaired (Janicke et al., 1990). Finally, our results show the same pattern as those collected in rats trained on a conditioned avoidance response paradigm, in which low doses (0.0625, 0.125, 0.25, and 0.5 mg/kg i.p.) of D,L-amphetamine enhanced performance, whereas a higher dose (5.0 mg/kg) impaired it (Davies et al., 1974).

IV. Methylphenidate

A. History of Use. The Journal of the American Medical Association's Council on Drugs announced the introduction of methylphenidate (Ritalin) in its "New and Nonofficial Drugs" section in 1957 (Kautz, 1957). The report proclaimed methylphenidate to be a "central nervous system stimulant…less potent than amphetamine but more so than caffeine." The report also optimistically proclaimed that the effects of methylphenidate "on the gastrointestinal tract are negligible, and, unlike amphetamine, it does not produce anorexia." Subsequently, doctors used methylphenidate to combat a host of ailments. Intravenous methylphenidate (10–30 mg, three times daily) improved the majority of 164 patients manifesting a variety of symptoms including sleepiness, tremors, drooling, and nasal congestion (Ferguson et al., 1956). Methylphenidate (50 mg i.v.) was also used to increase blood pressure in a comatose woman who had attempted suicide by overdose on the sedative hypnotics ethchlorvynol (Placidyl) and methyprylon (Noludar) mixed with alcohol (Ivey, 1958). Methylphenidate (0.4 mg/kg i.m.) was also injected into newborn infants with "depression," describing poor breathing, resulting in a "marked increase in respiratory activity" and "increased crying and bodily activity" (Gale, 1959).

Today, methylphenidate is most commonly prescribed for treatment of ADHD, and the number of prescriptions has remained high over the decades. Between 1971 and 1987, in Baltimore County, methylphenidate increased from 40 to 93% of the total stimulants prescribed for ADHD (Safer and Krager, 1988). From 1990 to 1993, the number of outpatient visits for ADHD in the United States increased from 1.6 to 4.1 million, whereas the number of prescriptions for methylphenidate as a percentage of total ADHD prescriptions increased from 67 to 71% (Swanson et al., 1995). However, in a survey of more than 2 million participants in the United States with prescription benefit plans during the period of January 2000 through

December 2005, the percentage of youth (ages 0–19 years) prescribed ADHD medication and opting for methylphenidate dropped slightly from 55.8% in 2000 to 46.9% in 2005 (Castle et al., 2007). In the same time period, the number of adults (ages 20 years and older) prescribed ADHD medication and taking methylphenidate dropped more drastically from 54.9 to 34.5%. The introduction of the nonstimulant ADHD treatment atomoxetine in late 2002 can, in part, account for the decrease in methylphenidate's market share, with 16.7% of youth and 13.7% of adults prescribed ADHD medication opting for this new medication in 2005. In addition, the percentage of affected adults taking amphetamine mixtures also increased by roughly three-quarters between 2000 (24.5% of ADHD adults) and 2005 (43.4% of ADHD adults).

B. Mechanism of Action. Methylphenidate is a piperidine derivative whose structure and pharmacological properties are similar to those of amphetamine (Westfall and Westfall, 2006). In vivo microdialysis studies in rats have helped clarify the mechanism of action of the drug. Methylphenidate (0.25, 0.5, and 1.0 mg/kg i.p.) was found to dose-dependently increase extracellular levels of DA and NE in the prefrontal cortex (Berridge et al., 2006). The higher doses (0.5 and 1.0 mg/kg) led to an increase in DA in the nucleus accumbens, whereas the lowest dose (0.25 mg/kg) had no effect in the structure. Very high doses (10 and 20 mg/kg i.p.) of methylphenidate have also been found to increase both NE in the prefrontal cortex and DA in the striatum (see Heal et al., 2009 for a review of pharmacological profiles of popular ADHD medications). A range of doses of methylphenidate (1.0, 2.5, and 5.0 mg/kg p.o.) increased NE in the hippocampus in a dose-dependent fashion, whereas only the highest dose, considered to exceed the therapeutic dosage, increased DA in the nucleus accumbens (Kuczenski and Segal, 2002). Another study determined the optimal dose of methylphenidate for each of eight rats, as measured by improvement on the spatial delayed alternation task. For most rats, a lower dose (1.0–2.0 mg/kg p.o.) improved performance, whereas higher doses (2.0–3.0 mg/kg p.o.) often impaired performance (Arnsten and Dudley, 2005). The enhancing effects were reversed with coadministration of either the NE α_2-receptor antagonist idazoxan or the DA D_1 receptor antagonist, (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (SCH23390). These findings suggest that methylphenidate improves performance by increasing the availability of NE and DA, which stimulate α_2 and D_1 receptors, respectively. Similar results were found for low-dose methylphenidate locally administered in the lateral amygdala (Tye et al., 2010). Rats treated with methylphenidate alone displayed increased reward earning and task efficiency during an amygdala-dependent, cue-reward learning task. However, when SCH23390 was coadministered with methylphenidate, those enhancements vanished.

Human PET studies agree with the animal literature in implicating both dopamine and norepinephrine as critical to the mechanism of action of methylphenidate. Oral methylphenidate was shown to block dopamine transporters (DAT) in the human brain, with only approximately 0.25 mg/kg methylphenidate leading to 50% blockage of dopamine transporters (Volkow et al., 1998). Oral methylphenidate, still within the therapeutic range (0.8 mg/kg, on average), dramatically increased extracellular dopamine concentration, with the effect more pronounced in younger participants (Volkow et al., 2001). Clinically relevant doses of oral methylphenidate (roughly 0.14 mg/kg) were also shown to bind to the norepinephrine transporter with high affinity (Hannestad et al., 2010). The authors note that the dose of methylphenidate leading to 70% DAT occupancy also causes more than 80% norepinephrine transporter occupancy, lending support to the importance of norepinephrine in the therapeutic effects of the drug.

C. Therapeutic Use. Methylphenidate has been shown repeatedly to be an effective therapeutic for ADHD. In a review of 40 articles on methylphenidate's effects on ADHD published between 1993 and 2006, 63.5% of the studies identified improvements in cognitive function due to immediate-release methylphenidate (Pietrzak et al., 2006). Measures of planning/cognitive flexibility, attention/vigilance, saccadic eye movement, and inhibitory control showed improvement in roughly 70–83% of the studies. There is some evidence that these benefits may be seen exclusively when neural resources need to be recruited. For example, oral methylphenidate (40 mg) decreased the amount of glucose used to perform a cognitive task, but did not affect glucose utilization under resting conditions that did not require cognitive effort (Volkow et al., 2008).

A pivotal study followed 103 children with ADHD over a 2-year period, comparing three interventions: methylphenidate alone, methylphenidate plus multimodal psychosocial treatment, and methylphenidate plus attention control psychosocial treatment (Abikoff et al., 2004). Improvements in behavior were found across all groups, but, surprisingly, no additional benefit was found in those who had received psychosocial interventions in addition to drug treatment. These data contribute to the rationale for the use of stimulants as a first-line of treatment of ADHD.

A host of studies have also found supporting results. Seventy-five children with ADHD, ages 6–17 years, were administered between 5 and 20 mg/day D-methylphenidate (Focalin) during a 6-week, open-label titration period, followed by a 2-week, double-blind, placebo-controlled withdrawal period (Arnold et al., 2004). The primary measure of efficacy was the difference in Clinical Global Impressions–Improvements scores acquired

during the last week of optimal dose administration compared with those gathered at the end of the withdrawal period. Participants administered placebo in the withdrawal period received ratings well below those of participants continuing with D-methylphenidate treatment. A similar pattern was found with behavioral ratings provided by teachers and parents, as well as with performance on a math test. Another study of 132 children with ADHD, ages 6–17 years, found similar results when comparing the effects of D-methylphenidate (18.25 mg/day, average), D,L-threo-methylphenidate (32 mg/day, average), and placebo for 4 weeks (Wigal et al., 2004). Both teachers and parents rated the participants' behavior as improved while on drug using the Swanson, Nolan, and Pelham Rating Scale. Generally, D-methylphenidate was found to be both safe and effective in the majority of participants.

As taking multiple doses of drug throughout the day can prove a hindrance to children in school, leading to less compliance, more efforts are being made to create extended-release tablets. A study comparing extended-release D-methylphenidate (20 or 30 mg/day) and extended-release racemic methylphenidate hydrochloride (40 or 60 mg/day) with placebo in 84 children with ADHD, ages 6–12 years, also found significant improvement in attention and behavior after intake of either medication (Muniz et al., 2008). Measures of change from predose rating on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale–Combined to ratings collected at different intervals postdose demonstrated that extended-release dexmethylphenidate was faster acting at improving attention and behavior, whereas the extended-release racemic methylphenidate hydrochloride provided less dramatic, but longer-lasting improvement, seen at 10, 11, and 12 hours postdose. Similar findings were also reported for adolescents (n = 177), ages 13–18 years, in a study of the efficacy and safety of osmotic-release oral system (OROS) methylphenidate (Concerta; Wilens et al., 2006). Adolescents completed a titration period, after which they received OROS methylphenidate (18, 36, 54, or 72 mg/day) or placebo. ADHD symptoms improved more with drug treatment than with placebo, as measured by the investigator, parents, and adolescents, using the ADHD Rating Scale. Similarly, a group in Turkey found that OROS methylphenidate improved parent-rated ADHD symptoms in affected children in an open-label study of OROS methylphenidate and atomoxetine (Fig. 8A; Yildiz et al., 2011). OROS methylphenidate also improved performance on the WCST by reducing perseveration errors and increasing correct conceptual responses (Fig. 8B).

An fMRI study of 20 healthy adults examined the effects of 60 mg of methylphenidate on a probabilistic reversal learning task (Dodds et al., 2008). Interestingly, the effects of methylphenidate on the blood-oxygen level–dependent signal varied based on the cognitive requirements of specific parts of the task. Activity in the putamen was modulated by methylphenidate during task switching, but prefrontal cortical areas were modulated during the active maintenance of information. A lower dose of oral methylphenidate (20 mg) in a group of healthy males showed a distinct pattern of activation and deactivation in different brain regions during a working memory task and a visual attention task (Tomasi et al., 2011). Increased activation was found in regions affiliated with the dorsal attention network (e.g., parietal and prefrontal cortex), whereas decreased activation was revealed in the areas involved in the default mode network (e.g., insula and posterior cingulate cortex). In all, these studies indicate that methylphenidate may exert its cognitive-enhancing effects by a complicated interplay of activation and deactivation in different regions throughout the brain.

D. Abuse: Academic Doping. As is true with amphetamine, methylphenidate is a Schedule II drug, considered to be medically useful as well as to have the potential for abuse and dependence (Controlled Substances Act (21 USC § 812, 2002)). The U.S. 2007 National Survey on Drug Use and Health reported that an estimated 6.9 million people had used psychotherapeutic drugs for nonmedical purposes within the previous month, with 1.1 million total users opting for stimulants (Substance Abuse and Mental Health Services Administration, 2008).

Although those addicted to other stimulants may abuse methylphenidate, the more common abuse of the drug today is described as academic doping. Generally speaking, academic doping is the use of stimulants to enhance scholastic performance by increasing focus or decreasing the need for sleep. Evidence for academic doping can be found in early literature discussing the introduction of amphetamine in the United States. In discussing what ailments could benefit from treatment by amphetamine (Benzedrine), one doctor included

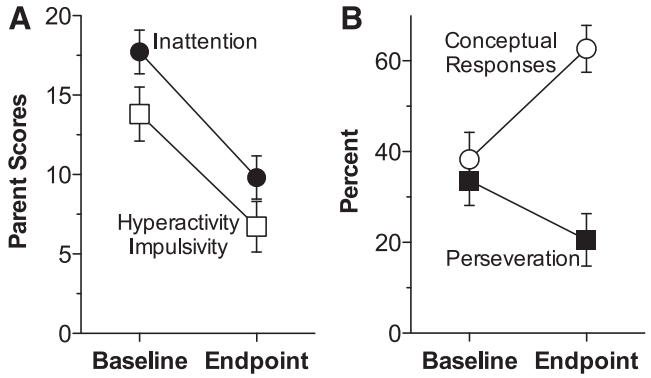

Fig. 8. Methylphenidate is effective in treating ADHD symptoms. (A) Reduction in ADHD symptomatology with methylphenidate (Concerta, 18 mg, roughly 0.5 mg/kg) treatment. (B) Improvement in WCST cognitive scores with Concerta treatment. Drawn from data reported in Tables 1 and 2 from Yildiz et al. (2011). Data shown are the mean ± 1 S.E.

a section on "Application in Normal Individuals" (Nathanson, 1942):

> Various studies indicate that Benzedrine increases intelligence score under test conditions, and that psychomotor skill is increased. It is true that the improper use of the drug for this purpose has led to considerable publicity, and much warning as to possible harmful effects. The wide-spread and indiscriminate use by students in preparation for examinations is an illustration of improper usage.

Students who use prescription stimulants illicitly for studying today seem to feel justified in doing so, separating themselves from those who use what are perceived as harder, or "bad," nonprescription drugs (DeSantis and Hane, 2010).

The prevalence of trivializing the use of prescription drugs illegally is evidenced in the data gathered by researchers in recent years. A nationwide survey of 10,904 randomly selected students from 199 U.S. colleges and universities in 2001 revealed a lifetime prevalence of nonmedical stimulant use of 6.9%, with 4.1% using within the previous month (McCabe et al., 2005). A survey of 3401 first-year students at a large, public university found that an estimated 13.3% had used prescription stimulants nonmedically at least once in their lives (Arria et al., 2008). Another survey at a large, public, southeastern university found that, of the 1811 student participants, 34% had used ADHD medications nonmedically (DeSantis et al., 2008). A sample of 390 college students found that 7.5% had used prescription stimulants for nonmedical purposes within the past 30 days (Weyandt et al., 2009). Questionnaires collected from 381 students at a midwestern university revealed that 13.7% of participants (17% of men, 11% of women) had taken stimulants for nonmedical purposes (Hall et al., 2005). Another study at a large, midwestern university surveyed 4580 undergraduates, revealing that 8.3% had used illicit prescription stimulants in their lifetime, and 5.9% in the past year (Teter et al., 2006). Of the users, 75.8% reported using amphetamine and 24.5% reported using methylphenidate. An informal survey administered by *Nature* found that roughly 20% of its 1400 respondents had used drugs for nonmedical reasons, and 62% of those users had taken methylphenidate (Maher, 2008). In all, a recent review of the literature found a total of 21 studies on the illicit use of prescription stimulants, including 113,145 participants (Wilens et al., 2008). Rates of stimulant misuse within the preceding year ranged from 5 to 9% in school-age children, and 5 to 35% in college-age adults.

Although students may perceive stimulants to provide the boost needed for success, evidence for scholastic improvement is lacking. Illicit users of prescription stimulants repeatedly have been found to achieve lower grade point averages than their nonusing counterparts (McCabe et al., 2005; Arria et al., 2008; Wilens et al., 2008). In fact, there is recent evidence pointing to detrimental effects of infrequent prescription stimulant use on a verbal memory task, with cumulative prescription stimulant use correlating with verbal learning and memory impairment (Reske et al., 2010). Interestingly, by comparison, infrequent users of cocaine showed virtually no deficits compared with controls, although the sample size for the cocaine-only group was admittedly small (n = 13, compared with 48 controls). However, it is important to note that, taken together, the entire group of infrequent stimulant users in this study did not show a correlation between extent of use and decrease in verbal memory performance. The authors interpret these findings to support a view of a pre-existing neuropsychological trait that may lead to stimulant use, suggesting the possibility of pre-existing deficits in learning and memory.

Patients who are prescribed stimulants may abuse those stimulants, as well. A study surveying 545 patients in an ADHD treatment center revealed that 14.3% of respondents had abused prescription stimulants (Bright, 2008). Of those who had abused, 79.8% opted for short-acting agents, whereas 17.2% chose long-acting stimulants; 75% preferred crushing pills and snorting them over injection or other methods. This preference in route of administration should come as no surprise, as faster routes, such as snorting or intravenous injection, lead to stronger drug effects. In fact, when cocaine abusers were administered methylphenidate (0.5 mg/kg i.v. followed by 0.25 mg/kg i.v. 90 minutes later), they reported strong feelings of "high" as well as craving for cocaine (Volkow et al., 1999).

E. Summary

> *I usually snort my Ritalin if I'm doing it for fun… I've found taking it before school to be very beneficial, and it actually makes what I'm learning almost seem interesting. It really does increase my attention span at lower doses. On the flip-side, higher doses (over 20 mg) usually send me into super-deep thought chains. If I'm very high on Ritalin, I'm usually too busy listening to my own thoughts race to listen to my teachers. It may help me pay attention and makes me more creative, but it won't get me into Harvard.*[5]

Methylphenidate is commonly prescribed for a host of medical conditions, typically safely and effectively. Illicit use of this drug tends to involve academic doping, rather than self-administration of high doses and addiction, as seen with cocaine and amphetamine. However, self-administered at high doses, or using rapid routes of administration, methylphenidate can

also lead to the subjective "high" and cognitive deficits found in the stimulants more typically considered to be addictive. In an early study of the effects of methylphenidate on "hyperkinetic" children (Sprague and Sleator, 1977), cognitive improvement was found on a difficult test, but not an easy test of short-term memory after methylphenidate administration at a low dose (0.3 mg/kg p.o.). Importantly, a higher dose (1.0 mg/kg p.o.) of methylphenidate reversed this effect, bringing performance back down to the level of placebo. This is an early example of a drug effecting cognitive enhancement, but exclusively at a low dose.

V. Modafinil

A. History of Use. Modafinil (Provigil, Modiodal, Nuvigil) is a psychostimulant that was developed to treat narcolepsy (Bastuji and Jouvet, 1988), and has emerged as the leading therapeutic used to treat sleep disorders. Modafinil is also approved for use with obstructive sleep apnea/hypopnea disorder and shift-work sleep disorder. Recently, numerous off-label applications have been tested, including the treatment of ADHD, Alzheimer's disease, Parkinson's disease, depression, and cocaine addiction.

B. Mechanism of Action. Modafinil was originally classified as a nonamphetamine psychostimulant because its pattern of activation was shown to be distinct from the more typical psychostimulants (Lin et al., 1996; Engber et al., 1998), although subsequent evidence has indicated that it may rely on similar mechanisms. Modafinil has actions on a host of neurotransmitter systems, including orexin (also called hypocretin), 5-HT, glutamate, GABA, DA, and NE. Although a clear mechanism has not yet emerged, the primary action of modafinil is generally considered to be on DA and/or NE signaling, with secondary changes in other systems (e.g., Minzenberg and Carter, 2008).

Disrupted transmission of the neuropeptide orexin has been strongly implicated in the etiology of narcolepsy. Analysis of human narcoleptic hypothalamic tissue revealed dramatic cell loss specific to orexin neurons (Thannickal et al., 2000). In addition, the cerebrospinal fluid of people with narcolepsy revealed greatly diminished or nondetectable levels of orexin, compared with the levels of healthy controls (Nishino et al., 2000). Interestingly, both orexin and modafinil increase hypothalamic histamine release (Scammell et al., 2000; Huang et al., 2001; Ishizuka et al., 2002). Researchers investigated whether orexin neurons were required for this increase in histamine by modafinil, in an attempt to uncover one of its potential mechanisms. Orexin neuron–deficient mice displayed no change in hypothalamic histamine release in response to modafinil (150 mg/kg), whereas control mice showed a dramatic increase in release. In addition, the orexin neuron–deficient mice displayed no change in c-Fos expression in the tuberomammillary nucleus of the hypothalamus after injection with the same dose of modafinil, whereas control mice showed a striking increase in expression (Ishizuka et al., 2010). Thus, these data suggest modafinil increases histamine release via intact orexin neurons.

However, other studies challenge the idea that orexin plays a role in the direct actions of modafinil. Orexin-null mice (*orexin*$^{-/-}$ mice) showed a strong wakefulness response to modafinil administration. In fact, the null mice showed a greater and longer-lasting response to modafinil than their wild-type littermates (Willie et al., 2005). Additionally, in a study of squirrel monkeys, modafinil significantly increased cerebrospinal fluid levels of the hypothalamic neuropeptide orexin-A (hypocretin-1), only when administered during the nighttime sleep period of the monkeys. Although modafinil administered during the day also increased cerebrospinal fluid orexin-A levels, it did not do so significantly above placebo baseline (Zeitzer et al., 2009). Thus, orexin levels seem to be modulated by the indirect effects of wake and sleep, and not by the direct effects of modafinil.

Modafinil has also been shown to increase levels of 5-HT across several brain regions. An in vivo microdialysis study in rats revealed that dialysate 5-HT levels increased with doses of modafinil as low as 10 mg/kg i.p., administered to areas including the frontal cortex, amygdala, and dorsal raphe nucleus. Doses of 100 mg/kg were needed to increase 5-HT in the medial preoptic area and posterior hypothalamus (Ferraro et al., 2002). A different research group also found modafinil to increase 5-HT levels in the prefrontal cortex at a dose of 128 mg/kg i.p. (de Saint Hilaire et al., 2001).

Interestingly, 5-HT transmission may also mediate modafinil's effects on GABA. Modafinil decreased GABA dialysate levels in the medial preoptic area at doses of 60 mg/kg i.p. and higher. Modafinil also decreased GABA levels in the posterior hypothalamus at a dose of 100 mg/kg (Ferraro et al., 1996a). Modafinil's effect on GABA release was examined during the local perfusion of the 5-HT_3 receptor antagonist 3-tropanyl 3,5-dichlorobenzoate (MDL72222), as well as the less selective 5-HT receptor antagonist methysergide. Before modafinil administration, perfusion of MDL72222, alone or along with methysergide, reduced the decrease in GABA release in both the medial preoptic area and the posterior hypothalamus. Importantly, neither MDL72222 nor methysergide altered GABA levels when administered without modafinil (Ferraro et al., 1996a). These findings suggest that modafinil's reduction in GABA release is, to some extent, mediated by 5-HT.

In parallel, modafinil increases glutamate in areas nonoverlapping with those discussed earlier, in which GABA transmission is primarily affected. GABA transmission in the ventromedial and ventrolateral thalamus is reduced only by a high dose of modafinil (300 mg/kg

i.p.), whereas GABA levels in the hippocampus are not affected by modafinil at any dose, ranging from 30 to 300 mg/kg. In contrast, doses from 60 to 300 mg/kg increase glutamate levels in the ventromedial and ventrolateral thalamus, whereas a 300 mg/kg dose is necessary to increase glutamate in the hippocampus (Ferraro et al., 1997a). A different group found that modafinil (80 mg/kg i.p.) increased speed of performance on a multiple T-maze task and increased glutamatergic receptor complex levels for the GluRa, GluR2, and NMDA receptor subunit 1 subtypes in the hippocampus. This shifting in the balance of inhibitory and excitatory neurotransmitter concentration may also be a mechanism by which modafinil leads to greater arousal.

Evidence has been mixed since the early studies on modafinil as to whether catecholamine transporters or receptors underlie its action. An early study indicated that modafinil had only a weak affinity for the DA transporter, in comparison with reference compounds such as the DA reuptake blocker nomifensine (Mignot et al., 1994), indicating that this was unlikely to be the primary action of the drug. In contrast, DA transporter knockout mice failed to show the wake-promoting effects of modafinil (Wisor et al., 2001). These mice, however, also have reduced levels of D_1 and D_2 receptors, making it impossible to rule out the involvement of DA receptors in the study's results (Fauchey et al., 2000). In addition, nomifensine did not alter modafinil-evoked currents in acutely isolated neurons, indicating the action of modafinil may be distinct from the DA transporter (Korotkova et al., 2007). Furthermore, the wake-promoting effects of modafinil are attenuated in D_2 receptor knockout mice, and are completely abolished in these mice when combined with a D_1 receptor antagonist (Qu et al., 2008). The authors interpret these findings as evidence that D_1 and D_2 receptors are essential for the arousal effect of modafinil; however, this study is also consistent with modafinil as a DA transporter blocker. Blocking the DA transporter would increase extracellular DA, but the DA would be unable to bind to D_1 or D_2 receptors. Thus, although D_1 and D_2 receptors appear to be involved in the actions of modafinil, the direct target remains unclear.

A PET study, however, indicated that modafinil can bind to both DA and NE transporters at clinically relevant doses (2–8 mg/kg), and occupy the DA transporter to an extent comparable to methylphenidate (Madras et al., 2006). This finding indicates that DA and NE transporter inhibition remains a viable mechanism for the action of modafinil. Furthermore, an in vitro binding study indicated that modafinil selectively binds to DA transporters, with no affinity for DA receptors (Zolkowska et al., 2009). The authors also demonstrated that modafinil attenuated methamphetamine-induced locomotor activity and dopamine release. Finally, they established a strong correlation between modafinil-induced extracellular DA release and locomotor activity. Together, these findings indicate that modafinil acts as an inhibitor of the DA transporter. A recent study corroborated this conclusion by reporting that modafinil reduced the spontaneous firing rate of dopaminergic cells in control mice, while leaving unaffected the neurons of mutant mice insensitive to the DAT blocker cocaine (Federici et al., 2013). Thus, although modafinil may have some direct actions on dopamine receptors, current evidence suggests that the primary mechanism of action of modafinil is inhibition of dopamine transporters.

C. Therapeutic Use. Modafinil is currently approved for the treatment of narcolepsy, obstructive sleep apnea/hypopnea disorder, and shift-work sleep disorder (Cephalon, 2004). Multiple randomized, double-blind, placebo-controlled studies have confirmed the efficacy of modafinil in treating excessive daytime sleepiness (EDS) associated with narcolepsy (Bastuji and Jouvet, 1988; Billiard et al., 1994; Broughton et al., 1997; Fry et al., 1998; Gross et al., 2000), ensuring its emergence as the leading pharmacological therapeutic. Clinical trials have also shown modafinil to be effective in the treatment of obstructive sleep apnea/hypopnea disorder (Kingshott et al., 2001; Pack et al., 2001; Black and Hirshkowitz, 2005) and shift-work sleep disorder (Czeisler et al., 2005; Erman et al., 2007).

Armodafinil consists of the longer-lasting *R*-enantiomer of modafinil, a racemic drug. Armodafinil is eliminated at a 3-fold slower rate than D-modafinil (Wong et al., 1999), a property that has led to great interest in its potential therapeutic utilities. A large, 12-week international study of patients with narcolepsy (n = 196) found that armodafinil (150 or 250 mg p.o.) was effective in sustaining wakefulness, as well as boosting attention and memory (Harsh et al., 2006). In healthy volunteers experiencing acute sleep loss, armodafinil (100, 150, 200, and 300 mg p.o.) and modafinil (200 mg p.o.) also significantly improved wakefulness at all doses (Dinges et al., 2006). Mean plasma concentration levels of the 200-mg armodafinil dose were higher than those of the same dose of modafinil, beginning from 5 hours after drug administration through 14 hours after administration, when the final measurements were taken. A multicenter study of night workers with shift-work sleep disorder (n = 254) found that armodafinil (150 mg p.o.) reduced sleepiness during night work shifts, as well as during the commute home (Czeisler et al., 2009). Episodic memory and attention were also improved by armodafinil.

The unknown mechanism of action and minimal side effect profile has made modafinil a prime candidate for a variety of investigational uses. Moreover, modafinil is a Schedule IV drug in the United States, reflecting reported low abuse potential and allowing for easier prescribing. Medical uses have been reviewed recently (Kumar, 2008) and include treating ADHD, depression, bipolar disorder, schizophrenia, cocaine addiction,

general fatigue, as well as EDS in Parkinson's disease, myotonic dystrophy, and traumatic brain injury. A host of clinical trials were completed to test the efficacy of modafinil in treating these disorders; however, many of them suffer from inconsistent findings and small sample size. The most consistent positive results for modafinil were in the treatment of ADHD in children and adolescents. Three large, double-blind, placebo-controlled clinical trials concluded that modafinil (170–425 mg/day) was an effective treatment, significantly decreasing primary and secondary efficacy measures of ADHD more than placebo (Biederman et al., 2005; Greenhill et al., 2006; Swanson et al., 2006). A separate study compared modafinil (200–300 mg/day) to methylphenidate (20–30 mg/day) and found that both drugs effectively reduced ADHD symptoms; no differences were found between the two drug groups (Amiri et al., 2008). Thus, modafinil appeared to be effective at treating ADHD in children and adolescents, and the most serious side of effects of methylphenidate and amphetamine (increased blood pressure and reduced appetite) were greatly reduced. However, due to very rare suspected cases of Stevens-Johnson syndrome during the ADHD clinical trials, the Food and Drug Administration failed to approve modafinil, to be marketed under the trade name Sparlon, for this indication (Cephalon, 2006; Food and Drug Administration, 2007). Modafinil was also effective at treating EDS in myotonic dystrophy (MacDonald et al., 2002; Talbot et al., 2003; Wintzen et al., 2007). All other therapeutic applications that were discussed in the review produced inconsistent findings or were inconclusive because of extremely small sample sizes (Kumar, 2008).

D. Abuse. Modafinil is an attractive therapeutic because it appears to have limited abuse potential (Myrick et al., 2004). There are no reported cases of addiction to modafinil, and several reports have indicated that, at therapeutic doses, the drug does not produce euphoria (Malcolm et al., 2002; Rush et al., 2002). Several factors may contribute to this lack of euphoria, including a relatively slow onset and a long half-life (10–12 hours), compared with stimulants of abuse. It remains possible, however, that high doses of modafinil, especially if given via a rapid route of administration, could be addictive. High doses of modafinil (150–250 mg/kg) were able to substitute for cocaine in rats run on a drug discrimination task (Gold and Balster, 1996). In a parallel study, monkeys trained to self-administer cocaine displayed rates of modafinil self-administration similar to cocaine (Gold and Balster, 1996). Initial rodent studies indicated that modafinil (32, 64, 128, or 256 mg/kg i.p.) was not reinforcing when administered alone (Deroche-Gamonet et al., 2002); however, we have recently found that modafinil (75 mg/kg i.p.) alone can produce a conditioned place preference (Shuman et al., 2012), indicating that modafinil is at least a weak reinforcer. Indeed, administration of modafinil (800 mg, roughly 10 mg/kg p.o.) in polysubstance abusers was reported to increase "liking" and experiences of a "high" similar to methylphenidate (Jasinski, 2000); modafinil (1.75, 3.50, or 7.00 mg/kg p.o.) administered to healthy subjects led to "liking" similar to D-amphetamine (Makris et al., 2007). Consistent with this profile, modafinil modestly increases extracellular dopamine in the nucleus accumbens in both rats and humans (Ferraro et al., 1996b, 1997b; Volkow et al., 2009).

A common abuse of modafinil is academic doping (Garreau, 2006), similar to amphetamine and methylphenidate (see section IV.D). A number of studies have reported increased cognition and attention in humans (Turner et al., 2003; Muller et al., 2004) and rodents (Beracochea et al., 2001, 2002, 2003; Ward et al., 2004; Waters et al., 2005; Morgan et al., 2007; Shuman et al., 2009;).

E. Summary

> *For me, I started with 100 mg and am still at that level after 2 months…Sleep will probably be a problem the first couple of days, even if you only take a dose in the morning, but you'll adjust in a few days. You will probably end up cleaning your whole house those first few days, waxing and detailing your car, etc. Enjoy! I no longer experience that physical energy lift, but mental and emotionally I still get great benefit from Provigil. Try doing some Sudoku puzzles or crossword puzzles and see if you find them easy and enjoyable while on Provigil – I know I do.*[6]

A sharp discord exists between the doses of modafinil studied in humans and in rodents. Human studies have focused on clinically relevant doses (100–400 mg = 1.25–5 mg/kg), whereas rodent studies have used a very large range of doses, focusing on the highest doses (generally 32–128 mg/kg). Indeed, some effects of modafinil do not appear until these high doses, whereas other effects may be overlooked. We recently completed a dose-effect analysis of modafinil and its memory-enhancing effects using multiple doses ranging from below the clinically relevant dose (0.075 mg/kg) to the highest dose we could give without noticeable side effects in mice (75 mg/kg). We found that the dose closest to the clinically prescribed dose (0.75 mg/kg) was able to enhance memory, whereas the highest dose (75 mg/kg) disrupted memory (Fig. 4; Shuman et al., 2009). Thus, there were clear dose-dependent effects of modafinil. In addition, the lowest dose of modafinil (0.075 mg/kg) was able to significantly reduce locomotor activity, despite being 1/1000th of the dose that is typically tested in rodents. In our hands, even the highest dose of modafinil (75 mg/kg) failed to produce

locomotor activity. However, others have shown modafinil to produce some hyperactivity at high doses, particularly when the subjects have been habituated to the training context (Simon et al., 1994, 1996; van Vliet et al., 2006; Zolkowska et al., 2009).

VI. Caffeine

A. History of Use. Caffeine is found naturally in more than 60 plants, and is popularly used in the production of coffee, tea, and cocoa. Although the details surrounding the discovery of coffee are still debated, it is certain that coffee consumption was present thousands of years ago in both Africa and the Arabian Peninsula (see Smith et al., 2007 for a detailed history of coffee, as well as other caffeinated consumables such as tea, chocolate, and soft drinks).

B. Mechanism of Action. Caffeine is a legal stimulant used widely around the world, typically not considered a drug of abuse (Graham, 2001). Unlike many of the other stimulants discussed earlier, caffeine does not exert its primary actions on the dopamine receptor, but rather on subtypes of the adenosine receptor. Specifically, caffeine is a nonselective antagonist, acting on the A_1 and A_{2A} receptor subtypes (Takahashi et al., 2008). Caffeine inhibits phosphodiesterase, thereby preventing the breakdown of the intracellular second messenger cAMP (Butcher and Sutherland, 1962; Ribeiro and Sebastiao, 2010).

C. Use Today. Caffeine is typically consumed in drinks such as coffee, tea, and soda, although today its presence is ubiquitous, with caffeine found in products such as breath mints, lip balm, and shampoo (Bramstedt, 2007). The per capita daily intake of caffeine in the U.S. population has been estimated to be 3 mg/kg or roughly 240 mg of caffeine for an 80-kg individual, with the heaviest consumers ranging from 5 to 7 mg/kg, or approximately 400 to 560 mg of caffeine (Barone and Roberts, 1996). It also has been estimated that a 5-oz (~150-ml) cup of coffee contains between 60 and 85 mg of caffeine, although the same amount of coffee has been reported to contain anywhere between 21 and 176 mg, depending on the preparation of the beans and the type of drink (Barone and Roberts, 1996). It is worth noting that a "small" coffee sold today in the United States is typically between 8 and 12 oz (230–350 ml), indicating that a single serving of caffeine might be more accurately estimated at twice the previously reported amounts (roughly 120–170 mg).

With such heavy consumption throughout society, it is relevant to determine the health effects of caffeine at regularly consumed doses. Unlike most of the other stimulants discussed herein, a review of the literature on caffeine found its habitual consumption to be quite safe, revealing no adverse effects on a number of health measures, including cardiovascular health, cancer incidence, and calcium balance (Nawrot et al., 2003). Although the literature is mixed, women who are pregnant or attempting to become pregnant seem to be at higher risk, with female fertility and fetal growth possibly adversely affected by moderate caffeine consumption at doses up to 400 mg per day, or roughly 5 mg/kg in an 80-kg individual. The authors also discovered that caffeine is unlikely to have teratogenic effects in the human fetus, although some animal literature is apparently in contradiction to these findings, demonstrating fetal malformations after caffeine intake.

The incongruous results found in the realms of animal and human research are a common problem throughout the research performed on stimulants, in general, and are worth discussing here. In this example, a review article noted that animal studies have shown caffeine to have teratogenic effects at doses ≥80 mg/kg (Nawrot et al., 2003). In humans, 1 g (12.5 mg/kg in an 80-kg individual) of caffeine is able to induce hallucinations, whereas 5 g (62.5 mg/kg) can be fatal (Bramstedt, 2007). With this in mind, it should come as no surprise that a dose of caffeine that is potentially lethal in humans produces teratogenic effects in the rat fetus. In comparing human and animal research on drugs, it is important to keep in mind the different doses being administered, and the possible effects on the results and conclusions drawn from the studies.

Along the same lines, another issue worth noting in the caffeine literature that is relevant to all stimulant research is the variability in methods used to determine dose. In many studies, a single amount of caffeine is administered to all participants, regardless of weight. As Graham (2001) pointed out, this could lead to females in a study receiving a dose roughly 20% higher than what men receive, due to their overall smaller bodyweight. It is less common for doses to be administered to humans in milligram per kilogram doses, whereas that is the norm in animals.

Finally, another common problem that may selectively taint caffeine data is that of withdrawal effects. The "withdrawal reversal hypothesis" (Rogers and Dernoncourt, 1998) states that caffeine does not enhance cognition or attention, but it reverses the negative effects of caffeine withdrawal in those who typically consume caffeine daily. Many studies ask their participants to not ingest any caffeine for a set time before the study, typically around 24 hours, leaving the participants in a withdrawal state if they habitually ingest caffeine. Evidence for this hypothesis can be found scattered throughout the literature. A 200-mg dose of caffeine was found to improve performance on a difficult multiplication task compared with 400 mg or placebo, although habitual caffeine use (low, moderate, or high: less than about 55 mg/day, between approximately 56 and 132 mg/day, or above roughly 133 mg/day, respectively) was a more important factor on word recall, with high to moderate caffeine users

remembering more words (Loke, 1988). A relationship was found between typical level of caffeine consumption and performance on Rapid Visual Information Processing, a test of sustained attention, after caffeine consumption (Smit and Rogers, 2000). Participants who were lower consumers of caffeine (<100 mg/day) did not show any benefit from consuming any dose of caffeine (12.5, 25, 50, or 100 mg) compared with the higher consumers (>200 mg/day), who uniformly demonstrated enhanced performance compared with controls after administration of any dose tested. In another study by the same group, participants were divided in two groups, one which consumed virtually no caffeine, the "nonconsumers," and the other whose daily intake of caffeine averaged more than 200 mg, the "consumers" (Rogers et al., 2003). After administration of 100 mg of caffeine or placebo, caffeine improved the performance of the simple reaction time (SRT) task in consumers, but not in nonconsumers. The authors also pointed out that the three nonconsumers whose SRT performance declined substantially after caffeine administration also reported large increases in jitteriness and tension. This study demonstrates that even a small to moderate amount of caffeine can affect fine motor tasks in those who do not typically consume caffeine.

Despite these potential confounds, much research has been conducted using different doses of caffeine on a variety of cognitive tasks. For example, compared with placebo, 250 mg (~3 mg/kg) of caffeine improved performance on the digit symbol substitution task, a test of perceptual speed and memory, more so than a 500-mg (~6 mg/kg) dose (Kaplan et al., 1997). A different study found that the relatively low doses of 12.5, 50, or 100 mg of caffeine all enhanced SRT performance, compared with controls (Smit and Rogers, 2000). A low dose of caffeine (150 mg) was also found to improve the speed of digit vigilance reaction time, as well as the accuracy of Rapid Visual Information Processing (Haskell et al., 2008). This study was the only one reviewed, herein, that took saliva samples from its participants to confirm abstinence from caffeine preceding the test days; however, no records were taken on habitual caffeine use.

Caffeine has also been found to affect declarative memory, with more varied results. For example, 2 and 4 mg/kg caffeine impaired recall of a word list read one word every 3 seconds, but not one word every second, compared with placebo in female, but not male, participants (Erikson et al., 1985). In a study designed to replicate and expand upon these results, the opposite effect was found in females, with 2 and 4 mg/kg caffeine enhancing word list recall after practice (Arnold et al., 1987). In the same study, caffeine impaired word recall for males at 2 mg/kg at certain amounts of practice, whereas 4 mg/kg had no effect. Disruption of free-recall of word lists (Auditory Verbal Learning Task) has also been reported after a 100-mg dose of caffeine, although participants were allowed to have any caffeinated beverage just 3 hours before testing, resulting in an unknown amount of caffeine actually consumed and processed during testing (Terry and Phifer, 1986). No difference was found between placebo and 200 mg of caffeine for word recognition and recall after a 7-hour delay period (Mednick et al., 2008). Participants who chewed gum containing 20 mg of caffeine during encoding and recall of word and name lists performed better on short-term (minutes after learning) and long-term (24 hours after learning) memory tests, compared with regular bubble gum chewers and those who did not chew gum (Davidson, 2011). Figure 9 depicts the averages of short- and long-term memory tests, representing data from the test of words as well as names. Caveats for the study should be noted, however; in particular, the gum-chewing groups were not blinded, so participants were told if they received caffeine. Expectation effects could have affected the data. In addition, this single-author article was written by the founder of the company that produces the gum tested.

Animal studies have been conducted to avoid a number of the potential confounds in the human literature. Several studies have used the passive avoidance task in rodents to examine the effects of caffeine and adenosine receptor agonists and antagonists on learning. For example, the A_1 adenosine receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) infused (1, 25, or 50 nM) directly into the posterior cingulate cortex in rats, post-training, significantly enhanced both short- and long-term passive avoidance retention at the 50 nM concentration (Pereira et al., 2002). However, when administered i.p. (0.1, 0.3, 1.0, and 3.0 mg/kg) in mice, post-training, DPCPX had no effect on learning at any dose (Kopf et al., 1999). The discrepancy in results may lie in the different routes of administration used, with the direct infusion of DPCPX allowing the drug to bind more selectively than an intraperitoneal injection.

When caffeine (0.1, 0.3, 1.0, and 3.0 mg/kg i.p.) was used on the passive avoidance task in mice, the 0.3 mg/kg dose administered immediately, but not 180 minutes, following training produced a better performance on the test 24 hours later (Kopf et al., 1999). Interestingly, another study in mice found that doses of 10, 30, and 100 mg/kg administered 30 minutes before training impaired learning, whereas doses of 1, 3, 10, and 30 mg/kg i.p., administered immediately following training enhanced learning (Angelucci et al., 1999). It is worth noting that the study by Kopf et al. (1999) found no increase in learning with a 3.0 mg/kg dose of caffeine administered immediately after training, whereas Angelucci et al. (1999) (who used weaker training) did find a significant enhancement in learning with this dose. These findings demonstrate that, although rodent studies are able avoid confounds such as caffeine

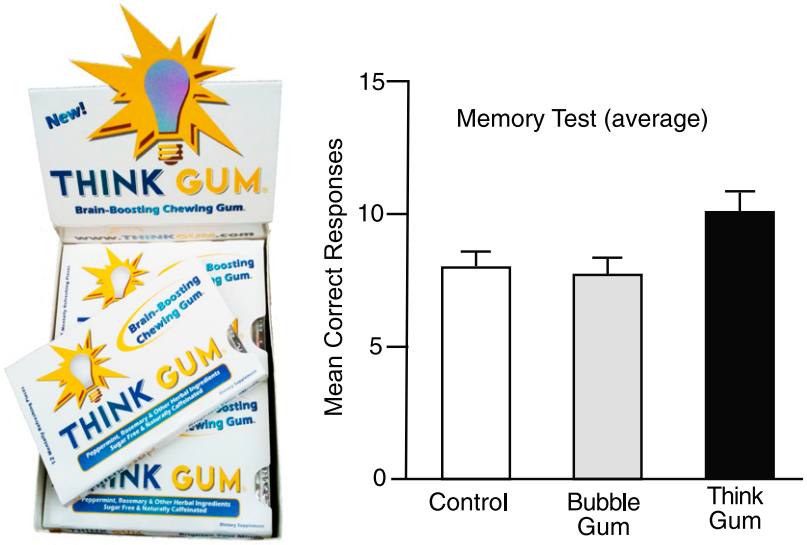

Fig. 9. Cognitive-enhancing properties of caffeine. It is not unusual for caffeinated products (and those containing guarana, which contains considerable caffeine) to claim cognitive enhancement. "Think" gum produced memory enhancement in word list learning (Davidson, 2011; adapted from their Fig. 2B). Davidson is also the founder of the company, raising some caution about the impressive results. Redrawn from Davidson (2011) with permission from Elsevier.

pre-exposure, attention to the details of the experimental design is still necessary when comparing results.

The conditioned response to shock in humans (Galvanic skin response latency) was found to be potentiated in those administered roughly 325 mg (5 grains) of caffeine before five separate training sessions (Switzer, 1935b). The same dose of caffeine also inhibited the extinction of conditioned shock (Switzer, 1935a). On the other hand, in animals, the A_1 adenosine receptor agonist N^6-cyclopentyladenosine was effective at disrupting memory for Pavlovian fear conditioning (Corodimas and Tomita, 2001). Rats administered 1.0 or 1.5 mg/kg i.p. N^6-cyclopentyladenosine 30 minutes before fear conditioning training showed significant impairment in fear memory when tested for contextual fear 24 hours after training. Cued fear was intact, however, indicating selective disruption of the acquisition of hippocampus-dependent learning. Caffeine (20 and 30 mg/kg, but not 10 mg/kg i.p.) administered 15 minutes before training also disrupted contextual fear conditioning, with no significant effect on tone conditioning (Corodimas et al., 2000). Interestingly, no deleterious effects on contextual or cued learning were found with long-term administration of caffeine (5-, 10-, or 25-mg s.c. pellets of caffeine) over the course of 7 days. The authors hypothesize that this could be due to a change in the number of adenosine receptors in areas such as the hippocampus and lateral nucleus of the amygdala, two areas critical for the acquisition and performance of fear conditioning.

Caffeine has also repeatedly been shown to lead to a high level of locomotor activity in rats (e.g., Swerdlow et al., 1985; Pulvirenti et al., 1989). However, a strikingly rapid tolerance develops to this locomotor activation when caffeine is administered long-term in the drinking water, in contrast to when it is delivered short term (Holtzman, 1983; Finn and Holtzman, 1986). These findings can be considered evidence, perhaps, for why caffeine has not proven to be a particularly effective therapeutic, as well as why the vast majority of users do not show compulsive use, hoarding, or other standard addictive behaviors (G. Koob, personal communication, October 30, 2010). If the locomotor effects undergo robust, rapid tolerance in animal models, it is not a far stretch to consider that caffeine-related effects may undergo similarly rapid tolerance in humans. Evidence for this idea can be found scattered throughout the literature, although the findings are not always consistent. For example, one recent study found no difference in performance on a choice reaction time task among regular caffeine consumers when administered either caffeine (250 mg) or placebo 45 minutes before the task (Addicott and Laurienti, 2009). This pattern did not hold up in a selective attention task in the same subjects, however, with caffeine leading to decreased reaction time, even in those with regular caffeine intake.

D. Potential Therapeutic Use. The greatest benefits of caffeine on cognition may lie in the realm of disease, with caffeine lending neuroprotective support against a host of conditions, ranging from the general effects of aging (Hameleers et al., 2000) to ADHD (Prediger et al., 2005). One community-based, observational study of older (age 50 years or older) adults found that lifetime coffee consumption in women was positively correlated with performance on measures of long-term memory, short-term memory, verbal fluency, and attention (Johnson-Kozlow et al., 2002). A study

conducted in The Netherlands with a large number of participants (1875) stratified for age (24–81 years) found a positive correlation between habitual caffeine consumption and measures of simple response speed and verbal long-term memory (Hameleers et al., 2000). The study, however, did not find an association between caffeine intake and short-term memory, planning capacity, information processing, or attention. Data from a 6-year follow-up with the same cohort revealed that caffeine intake was not predictive of enhanced performance on the verbal long-term memory task, and that the benefits on a motor task were small (van Boxtel et al., 2003).

Epidemiological evidence also indicates that caffeine consumption may be linked to a lower chance of developing Parkinson's disease in older women who never used postmenopausal hormones and in older men (Ascherio and Chen, 2003). Neurophysiological and behavioral research supports the validity of this trend, with A_{2A} adenosine receptor antagonists implicated in the prevention of excitotoxicity in models of stroke and Huntington's disease through the suppression of excessive glutamate release throughout the cortex (Schwarzschild et al., 2003). In addition, A_{2A} adenosine receptors densely populate the striatum. Converging evidence suggests blockade of these receptors may help protect the dopaminergic nigrostriatal neurons, whose destruction is the main cause of symptoms of Parkinson's disease (Schwarzschild et al., 2003).

Long-term caffeine consumption was also shown to have neuroprotective effects in a mouse model of Alzheimer's disease (AD), the amyloid precursor protein in Swedish mutation transgenic mice (Arendash et al., 2006). Caffeine was administered in the drinking water of the mice starting from 4 months of age throughout behavioral testing until sacrifice at 9 1/2 months of age, at a rate of roughly 1.5 mg consumed daily (estimated by the authors to equate to 500-mg intake by humans, roughly 6 mg/kg, or 5 cups of coffee). Caffeine consumption provided cognitive protection in the Morris water maze, the platform recognition task, a hippocampus-dependent reference memory task (circular platform task), and a working memory task (radial arm water maze). Moreover, caffeine seemed to reduce the production of hippocampal β-amyloid, a protein that is found in higher levels in those with AD. Although the density of A_1 or A_{2A} receptors throughout the cortex or hippocampus was not altered by caffeine, adenosine levels in the transgenic mouse brain were restored to those found in the wild-type mouse brain. Caffeine (3 mg/day) also exhibited protective effects against the disruption of the blood-brain barrier in a rabbit model of AD (Chen et al., 2008). These effects are likely not mediated by an increase in neuron production, as a recent study found effects of caffeine on cell proliferation in the dentate gyrus, at very high doses, but no effects on survival or differentiation at any dose (Wentz and Magavi, 2009).

E. Summary. Some potential confounds discussed earlier are seen throughout the stimulant literature (e.g., use of very high doses with rapid routes of administration in animal studies and comparatively low doses and slow routes of administration in human studies), whereas others are specific to the caffeine literature (e.g., the "withdrawal reversal hypothesis"). Despite these issues, a general pattern emerges from the human and animal studies on caffeine. As found with the other stimulants reviewed herein, dose seems to be the primary determinant of caffeine's effects. In general, lower doses of caffeine lead to positive effects, whereas higher doses produce disruptive effects.

VII. Pharmacokinetics

Pharmacokinetics is the study of the factors that determine the bioavailability of a drug upon its entrance into the body, addressing issues such as route of administration, absorption and distribution of the drug, as well as its metabolism and excretion. There is evidence that different aspects of pharmacokinetics vary between species, such as clearance rates (Boxenbaum, 1980) and overall metabolism in relation to body surface area and weight. Estimates of "metabolic body size" are popularly determined among adults of a species by calculating the subject's body weight in kilograms raised to the 3/4 power (Kleiber, 1947). It is important to note, however, that this conversion can be substantially more or less conservative depending on the efficiency of the respective metabolites and elimination process, although some maintain it is a more conservative estimate than a direct milligram per kilogram measure between species (O'Flaherty, 1989).

The accuracy of dose conversion also varies with the type of drug being administered. In a study of the effects of over a dozen compounds in only mice, the majority, but not all, demonstrated a linear relationship of toxicity (LD_{50}, lethal dose in 50% of subjects) to body weight (Lamanna and Hart, 1968). The fact that most substances followed a linear trend indicates that using a direct milligram per kilogram conversion might be a good starting point for many drugs; however, the few substances that did not follow the linear trend show that, as expected, this conversion will not be applicable every time (see Riviere et al., 1997 for an allometric analysis of 44 veterinary drugs across species showing similar findings).

More variability is naturally found between species, as opposed to within species. As a notable example, researchers in the 1960s were studying musth, an aggressive period in male elephants that can last for multiple weeks, and deemed a "periodic madness" that provided "an interesting opportunity for psychiatric research" (West et al., 1962). In an attempt to mimic musth, the researchers administered D-lysergic acid diethylamide (LSD) to a captive elephant, named

Tusko, in Oklahoma City. To determine the appropriate dose, effective doses for humans, capable of producing hours of hallucinations and thought disturbances (0.1–0.2 mg, or 0.00125–0.0025 mg/kg in an 80-kg individual), were compared with those administered to macaques to produce temporary blindness (0.5–1.0 mg/kg), and with those administered to cats to produce a rage reaction (0.15 mg/kg) or death (6.5 mg/kg). The dose settled on for experimentation was 0.1 mg/kg, or 297 mg, via intramuscular injection, representing an overdose in humans, but a marginally effective dose in the aforementioned animals. Soon after injection, Tusko had a dramatic seizure and died within 2 hours, leading the authors to conclude that elephants are particularly sensitive to LSD.

Although we may never know the true effective dose of LSD to administer an elephant, this study demonstrates the difficulty in determining dose across species in relatively novel compounds. The metabolism of some of the more frequently prescribed and self-administered drugs has been systematically analyzed across species. The metabolic profile of cocaine was found to be similar in humans and in rats, as shown in a study utilizing ion cluster technique and gas chromatography–mass spectrometry (Jindal and Lutz, 1989). The metabolic profile of different doses of radiolabeled amphetamine, as measured by metabolites in urine and feces, was found to be similar among monkeys (0.66 mg/kg p.o.), greyhounds (5 mg/kg i.p.), and humans (5 mg or ~0.07 mg/kg p.o.). Interestingly, however, it differed among rats (10 mg/kg p.o.), rabbits (10 mg/kg p.o.), guinea pigs (5 mg/kg i.p.), and even mice (10 mg/kg p.o.; Dring et al., 1970). This amphetamine study, unfortunately, used two different methods of drug administration, did not use a standard dose of drug, and did not use measures to help determine if the variable doses used led to any notable behavioral differences between species.

Route of administration of drugs in animal (typically intraperitoneal injection) in comparison with human (typically oral) pharmacology research tends to vary greatly (see Kuczenski and Segal, 2005 for an in-depth discussion of these issues as they relate to ADHD pharmacotherapy research). Relatively slower methods, such as oral administration, lead to slower, smaller behavioral effects compared with faster methods, such as intraperitoneal injection. Although the studies using these different methods can surely help to inform future pharmacology work, care must be taken when choosing the proper dose if utilizing different routes of administration. In general, previous work should be referenced as much as possible to help address concerns related to toxicology, metabolism, kinetics, etc. (see Davidson et al., 1986 for a table of "Components in Extrapolation Assessment").

Although the difference in drug dosage from animal to human use varies by drug, the larger concern for pharmacokinetic differences, overall, is between small and large animals, as well as between children and adults. Small mammals have proportionally faster metabolisms than larger mammals (von Bertalanffy, 1957), thus indicating that mice would need higher doses of drug for the same effect in larger species, such as humans. Similarly, pediatric populations have a range of pharmacokinetic differences relating to absorption, distribution, metabolism, and excretion of drugs, compared with adults, generally leading to the need for a higher milligram per kilogram dose (see Benedetti and Baltes, 2003 for review). One way to try to address these issues is to take blood samples throughout the time the drug is active. However, even plasma levels do not provide information about the potency of the drug at the level of the synapse, a concern that is addressed in the study of pharmacodynamics.

VIII. Pharmacodynamics

Pharmacodynamics is the study of the interaction of drug molecules with their physiological targets. Dopamine receptors are typically examined when investigating psychostimulant pharmacodynamics. Many studies have shown that dopamine receptors are distributed differently throughout the brain when comparing multiple species of animals (e.g., Richfield et al., 1987), or comparing animals with humans (for discussion of D2-like receptor distribution differences between rats and humans, see Khan et al., 1998). These studies bring up an important factor that contributes to differences in drug effects between species, in addition to the pharmacokinetic concerns mentioned earlier. Plasma levels or other less-invasive, on-line measurements cannot indicate where and how successfully drugs are binding. This concern can only be addressed by comparative physiological studies to outline the different locations of receptors, as well as behavioral studies to characterize species differences in drug effects. To address differences in pharmacodynamics, previous literature is the best resource for determining what effects these differences might have on the study of interest.

Despite the pharmacokinetic and pharmacodynamic concerns presented earlier, we believe that the field of pharmacology could take a simple step to improve the ability to generalize results across species. Specifically, we believe it would be useful to administer doses of drugs to animals that are within the same order of magnitude of dose used for humans.

IX. A Continuum of Psychostimulant Activation

In summarizing these studies, we have emphasized the role of dose in determining psychostimulant action. In borrowing from the conception of describing the action of sedative-hypnotics (e.g., Meyer and Quenzer, 2005), we propose that psychostimulant action is best

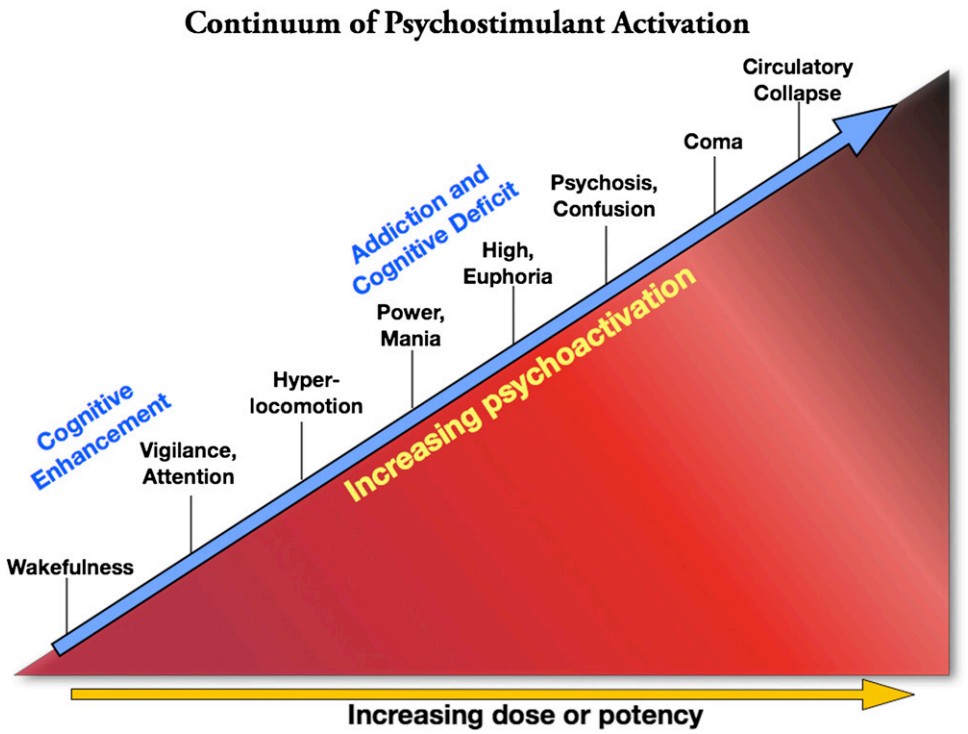

Fig. 10. Continuum of psychostimulant activation. Increasing cognitive activation as stimulant dose increases initially produces increased wakefulness and cognitive enhancement. These are the desired therapeutic effects. As dose increases, a sense of power and euphoria can ensue; these are the effects addicts seek and are accompanied by cognitive deficits. Higher doses can result in overdose, psychosis, coma, and eventual circulatory collapse.

considered on a continuum (Fig. 10). At low doses, stimulants produce an increase in wakefulness, attention, and confidence and vigor. Drugs with low potency or maximum effect, such as caffeine or modafinil, act much like low doses of amphetamine or methylphenidate. As dose or potency increases, hyperlocomotion is seen, with an increased sense of power, perhaps accompanied by mania. This is closely followed by euphoria, or a drug-induced high. This is the domain of the addict, who is likely to use high-potency drugs such as cocaine or methamphetamine, and administer them rapidly to achieve this effect. These effects are well outside of the range of cognitive enhancement; in fact, deficits in cognition and disturbed thinking are usually observed. As overdose begins, agitation, confusion, and psychosis are seen. At very high doses, stimulants produce typical toxic effects, including coma, circulatory collapse, and, ultimately, death.

Lyon and Robbins (1975) proposed a general theory to account for the effects of amphetamine, modeled with rat behavior, with increasing dose leading to a greater repetition of a smaller number of brief behaviors (see Fig. 2). This theory helps account for the physical and cognitive behaviors seen after high-dose amphetamine administration, marked with stereotypical behaviors and cognitive deficits. Our continuum builds upon this theory, maintaining a focus on the importance of dose, and expands upon it to reflect the current literature, as well as to emphasize human research and the effects of low doses.

Therefore, the continuum of psychostimulant activation draws critical attention to dose, rather than particular drug, in terms of determining psychiatric efficacy of stimulants versus their liability for abuse and addiction. Low doses of even the most potent stimulants (e.g., methamphetamine) have been used clinically for more than 50 years with much success, but at the same time, reckless use of these drugs at high doses continues to be a social epidemic.

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Wrote or contributed to the writing of the transcript: Wood, Sage, Shuman, Anagnostaras.

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