The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities

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ABSTRACT

Psychostimulants, including amphetamines and methylphenidate, are first-line pharmacotherapies for individuals with attention-deficit/hyperactivity disorder (ADHD). This review aims to educate physicians regarding differences in pharmacology and mechanisms of action between amphetamine and methylphenidate, thus enhancing physician understanding of psychostimulants and their use in managing individuals with ADHD who may have comorbid psychiatric conditions. A systematic literature review of PubMed was conducted in April 2017, focusing on cellular- and brain system-level effects of amphetamine and methylphenidate. The primary pharmacologic effect of both amphetamine and methylphenidate is to increase central dopamine and norepinephrine activity, which impacts executive and attentional function. Amphetamine actions include dopamine and norepinephrine transporter inhibition, vesicular monoamine transporter 2 (VMAT-2) inhibition, and monoamine oxidase activity inhibition. Methylphenidate actions include dopamine and norepinephrine transporter inhibition, agonist activity at the serotonin type 1A receptor, and redistribution of the VMAT-2. There is also evidence for interactions with glutamate and opioid systems. Clinical implications of these actions in individuals with ADHD with comorbid depression, anxiety, substance use disorder, and sleep disturbances are discussed.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) was initially identified in children (Lahey et al., 1994) but is now understood to persist into adulthood in about two thirds of cases (Barkley et al., 2002; Weiss et al., 1985; Faraone et al., 2006). In a 2007 meta-analysis that included more than 100 studies, the estimated worldwide prevalence of ADHD in individuals < 18 years old was 5.29% (Polanczyk et al., 2007). The estimated prevalence in adults was 4.4% in a national survey in the United States (Kessler et al., 2006), 3.4% in a 10-nation survey (Fayyad et al., 2007), and 2.5% in a meta-regression analysis of 6 studies (Simon et al., 2009).

A large body of evidence suggests that multiple neurotransmitters and brain structures play a role in ADHD (Purper-Ouakil et al., 2011; Cortese, 2012; Faraone et al., 2015). Although a substantial amount of research has focused on dopamine (DA) and norepinephrine (NE), ADHD has also been linked to dysfunction in serotonin (5-hydroxytryptamine [5-HT]), acetylcholine (ACH), opioid, and glutamate (GLU) pathways (Cortese, 2012; Maltezos et al., 2014; Blum et al., 2008; Potter et al., 2014; Elia et al., 2011). The alterations in these neurotransmitter systems affect the function of brain structures that moderate executive function, working memory, emotional regulation, and reward processing (Fig. 1) (Faraone et al., 2015).

Individuals with ADHD are often diagnosed with additional psychiatric comorbidities, including anxiety, mood, substance use, sleep disturbances, and antisocial personality disorders (Mao and Findling, 2014; Kooij et al., 2012; Konofal et al., 2010). Importantly, the neuropsychological substrates that mediate behaviors associated with ADHD share commonalities to some extent with those involved in these comorbid disorders (Farb and Ratner, 2014; Sternat and Katzman, 2016; Schwartz and Kilduff, 2015). Genetic studies have also identified shared genetic risk factors between ADHD and associated comorbid disorders (Sharp et al., 2014; Carey et al., 2016). As such, comorbidities need to be taken into account when considering pharmacotherapy in an individual with ADHD.

Although stimulants (including amphetamine [AMP]-based and...
Attention-decreasing drugs (e.g., methylphenidate, clonidine, and guanfacine) are approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) because of their efficacy in patients with ADHD than in people who do not have the disorder. (f) The alerting network is impaired in ADHD. The frontal and parietal cortical areas and the thalamus intensively interact in the alerting network (indicated by the arrows), which supports attentional functioning and is weaker in individuals with ADHD than in controls. (g) ADHD involves the default-mode network (DMN). The DMN consists of the medial prefrontal cortex and the posterior cingulate cortex (medial view) as well as the lateral parietal cortex and the medial temporal lobe (lateral view). DMN fluctuations are 180° out of phase with fluctuations in networks that become activated during externally oriented tasks, presumably reflecting competition between opposing processes for processing resources. Negative correlations between the DMN and the frontoparietal control network are weaker in patients with ADHD than in people who do not have the disorder.

The objective of this review is to educate physicians about the mechanisms of action of AMP and MPH and the implications of these actions on the management of ADHD and its comorbidities. To achieve this goal, a systematic review of the published literature was conducted to obtain articles describing the cellular- and brain system–level effects of AMP and MPH. The results of relevant studies are described and interpreted in the context of the treatment of ADHD and in light of the comorbidities associated with ADHD.

2. Methods
A systematic literature review of PubMed was conducted on April 24, 2017; no limits were included for publication year or the language of publication. The search consisted of titles and abstracts and used the following search string: (amphetamine [Mesh term] OR methylphenidate [Mesh term]) AND (cellular OR receptor binding OR
neuroimaging OR FMRI OR SPECT OR PET OR positron emission tomography OR magnetic resonance OR tomography OR spectroscopy) AND (dopamine OR serotonin OR norepinephrine OR acetylcholine OR glutamate OR opioid OR opiate) NOT (methamphetamine OR MDMA OR ecstasy OR addiction OR abuse). The literature search included both animal and human studies.

Additional articles of interest were obtained via an assessment of the relevant articles obtained through the literature review and based on author knowledge. A publication was excluded if it did not specifically focus on the mechanism of action or pharmacologic effects of amphetamine or methylphenidate or if the publications were imaging studies in individuals who were not healthy (i.e., studies in those with psychiatric disorders were not included).

3. Results

The literature search yielded 673 articles (Fig. 2). Of these, 137 were considered relevant to the topic of this review. Additional articles (n = 13) were identified based on author knowledge and assessment of the reference sections of relevant citations. The articles included in this review are summarized in Table 1.

3.1. Preclinical studies

3.1.1. Amphetamine

The main mechanism of action of AMP is to increase synaptic extracellular DA and NE levels (Avelar et al., 2013; Covey et al., 2013; Finnema et al., 2015; Floor and Meng, 1996; Jedema et al., 2014; Joyce et al., 2007; Kuczenski and Segal, 1997; May et al., 1988; Mukherjee et al., 1997; Pum et al., 2007; Ren et al., 2009; Schiffer et al., 2006; Xiao and Becker, 1998; Young et al., 2011; Wall et al., 1995). This effect is mediated by inhibition of DA transporters (DAT) and NE transporters (NET) (Avelar et al., 2013; Covey et al., 2013; Easton et al., 2007b), which reduces the reuptake of these molecules from the synapse. In wild-type mice, AMP initially increases surface trafficking of DAT and DA uptake, but continued AMP exposure results in decreased surface expression of the DAT and decreases in DA uptake (Chen et al., 2009).

In a dose-dependent and region-specific manner, AMP also increases vesicular DA release via inhibition of the vesicular monoamine transporter 2 (VMAT-2), which releases DA from vesicular storage, and the concomitant release of cytosolic DA via reverse transport by the DAT (Easton et al., 2007b; Riddle et al., 2007; Sulzer et al., 1995). Furthermore, AMP inhibits monoamine oxidase (MAO) activity (Miller et al., 1980; Robinson, 1985), which decreases cytosolic monoamine breakdown. A wide array of studies using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) have demonstrated that AMP produced reductions in the binding potential of ligands for DA receptors (al-Tikriti et al., 1994; Carson et al., 1997; Castner et al., 2000; Chou et al., 2006; Dewey et al., 1993; Drevets et al., 1999; Gallezot et al., 2014; Ginovart et al., 1999; Howlett and Nahorski, 1979; Laruelle et al., 1997; Le Masurier et al., 2004; Lind et al., 2005; Mukherjee et al., 1997; Pedersen et al., 2007; Saebens et al., 1980; Schiffer et al., 2006; Seneca et al., 2006; Sun et al., 2003; Tomic et al., 1997; Tomic and Joksimovic, 2000; van Berckel et al., 2006) and NE receptors (Finnema et al., 2015; Landau et al., 2012), which is an indirect indicator of increased competition for binding sites resulting from increased extracellular DA or NE. The striatum, which contains most of the DATs in the brain (Volkow et al., 1996b; Fischman et al., 1997), appears to be a principal site of action of AMP (Avelar et al., 2013; Kilbourn and Domino, 2011), but direct effects in the cortex and the ventral tegmental area have also been reported (Pum et al., 2007; Ren et al., 2009; Schwarz et al., 2007b). The effects of AMP extend to and are modulated by other neurotransmitter systems (Choe et al., 2002; Dutarroy et al., 1992; Inderbitzin et al., 1997; Konradi et al., 1996b; Liu et al., 2003; Pum et al., 2007; Quelch et al., 2014; Ritz and Kuhar, 1989; Shaffer et al., 2010; Smith et al., 2005; Yin et al., 2010; Yu et al., 2003), including ACH, 5-HT, opioid, and GLU, either directly through enhanced release from presynaptic terminals or via downstream effects.

In other studies, AMP has been shown to produce changes at a more global level. In studies of cerebral blood flow (CBF), AMP increased whole brain CBF in rats and baboons (Chen et al., 2008; Kashiwagi...
Table 1
Studies of the Actions of AMP and MPH.

| Preclinical studies                                                                                   | AMP                                                                                          |
|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Al-Tikriti et al. (1994)                                                                               | • AMP increased the washout rate of [123I]IBF (a D2 receptor antagonist) from the striatum of baboons, as measured using PET |
| Annamalai et al. (2010)                                                                                | • AMP-stimulated downregulation of the NET was linked to the KCN-resistant T258/S259 structural motif and mediated by reduced plasma membrane insertion and enhanced endocytosis |
| Avelar et al. (2013)                                                                                   | • AMP increased electrically evoked DA levels, inhibited DA uptake, and upregulated DA vesicular release in rat striatum |
| Bjorklund et al. (2008)                                                                               | • Adenovirus A9 receptor knockout mice exhibited reduced locomotor responses to AMP, suggesting potential alterations in monoaminergic (DA, 5-HT, or NE) systems |
| Cannon et al. (1997)                                                                                  | • AMP reduced [11C]raclopride (a D2 receptor antagonist) binding in the striatum of rhesus monkeys, as measured by PET |
| Castner et al. (2000)                                                                                 | • AMP reduced [11C]IBZM (a D2 receptor antagonist) binding in the striatum of rhesus monkeys, as measured by PET |
| Chen et al. (2006)                                                                                    | • AMP-induced increases in whole-brain relative cerebral blood volume were attenuated by electrophysiology (electrical paw stimulation) in rats |
| Chen et al. (2009)                                                                                    | • Rapid AMP-induced increases in striatal surface DAT levels and DA release in mice were not observed in PKC-β knockout mice |
| Choe et al. (2002)                                                                                    | • AMP increased phosphorylation of CREB in rats; intrastratal administration of PHCCH (an mGlur type 1 antagonist) and systemic administration of MPFP (an mGlur type 5 antagonist) attenuated this effect |
| Chou et al. (2000)                                                                                    | • AMP reduced [11C]FLB 457 (a D2 receptor antagonist) binding in the thalamus, cortex, and striatum of cynomolgus monkeys, as measured by PET |
| Covey et al. (2013)                                                                                   | • AMP increased DA release in rat striatum when administered with a short-duration electrical stimulus and decreased DA release when administered with a long-duration electrical stimulus |
| Dewey et al. (1993)                                                                                   | • AMP increased DA release in awake and anesthetized rats, with changes correlated to changes in striatal DA and 5-HT concentrations |
| Dixon et al. (2005)                                                                                   | • AMP caused widespread increases in fMRI BOLD signal intensity in subcortical structures containing rich DA innervation, with decreases in BOLD signal observed in the superficial layers of the cortex in rats |
| Duttaroy et al. (1992)                                                                                | • Chronic AMP exposure blocked naxone-mediated supersensitivity of μ- and δ-opioid receptors without altering naloxone-induced upregulation of these receptors in mice |
| Easton et al. (2007a)                                                                                 | • AMP increased DA release (basal and electrically stimulated) in the nucleus accumbens, medial entorhinal cortex, colliculi, hippocampal area CA1, and thalamic nuclei of rats |
| Easton et al. (2007b)                                                                                 | • AMP inhibited accumulation of DA or NE in rat brain synaptosomes and vesicles, which was mitigated by inhibitors of the DAT and NET |
| Finnema et al. (2015)                                                                                 | • AMP reduced binding of [123I]NORM-13070 (an adrenergic α2A receptor antagonist) in the striatum of cynomolgus monkeys, as measured by PET, and increased rat striatal NE and DA concentrations |
| Floor and Meng (1996)                                                                                | • AMP reduced [11C]raclopride (a D2 receptor antagonist) binding in the striatum of baboons, as measured by PET |
| Gallezot et al. (2014)                                                                                | • AMP increased DA release in the caudate, putamen, and ventral striatum of pigs, as measured by PET |
| Ginovart et al. (1999)                                                                               | • AMP caused widespread increases in fMRI BOLD signal intensity in subcortical structures containing rich DA innervation, with decreases in BOLD signal observed in the superficial layers of the cortex in rats |
| Hartvig et al. (1997)                                                                                 | • AMP increased DA release in awake and anesthetized rats, with changes correlated to changes in striatal DA concentration |
| Helme and Seeman (1982)                                                                              | • AMP increased dopamine synthesis in the brain in nonhuman primates, as measured by PET |
| Howlett and Nahorski (1979)                                                                            | • AMP exposure increased [3H]ipiperone (a D2/D3 receptor antagonist) binding affinity and density after 4 days of exposure and decreased binding density after 20 days of exposure in rat striatum |
| Inderbitzin et al. (1997)                                                                             | • AMP increased preproenkephalin mRNA expression and µ-opioid receptor binding in the basal ganglia of rats |
| Jedema et al. (2014)                                                                                 | • AMP increased DA release in the caudate and prefrontal cortex of rhesus macaques, as measured by microdialysis, with DA levels remaining elevated for a longer duration in the prefrontal cortex than in the caudate |
| Joyce et al. (2007)                                                                                  | • AMP inhibited accumulation of mixed amphetamine salts directly into the striatum of rats stimulated DA release |
| Kashiwagi et al. (2015)                                                                               | • AMP increased relative cerebral blood volume in awake and anesthetized rats, with changes correlated to changes in striatal DA concentration |
| Konradi et al. (1996)                                                                                 | • AMP-induced activation of immediate early genes in dissociated rat striatal cultures was blocked by MK-801 (an NMDA receptor antagonist) |
| Kuczynski and Segal (1997)                                                                            | • AMP increased DA and 5-HT efflux in the caudate and NE efflux in the hippocampus of rats following systemic administration |
| Le Maurer et al. (2004)                                                                              | • AMP increased D2 receptor occupancy in the cortex and caudate of rats, as measured by receptor autoradiography |
| Le Maurer et al. (2004)                                                                              | • AMP increased phosphorylation of CREB in rats; intrastriatal administration of PHCCH (an mGlur type 1 antagonist) and systemic administration of MPFP (an mGlur type 5 antagonist) attenuated this effect |
| Lind et al. (2005)                                                                                    | • AMP decreased [11C]raclopride (a D2 receptor antagonist) binding in the striatum of rats, as measured by PET, was attenuated by pretreatment with a tyrosine-free amino acid mixture |
| Liu et al. (2003)                                                                                     | • AMP increased tyrosine-free amino acid mixture |
| May et al. (1988)                                                                                     | • AMP increased the washout rate of [123I]IBF (a D2 receptor antagonist) from the striatum of baboons, as measured using PET |
| Miller et al. (1980)                                                                                 | • AMP inhibited MAO type A activity |
| Mukherjee et al. (1997)                                                                              | • AMP increased [11C]raclopride (a D2 receptor antagonist) binding in the striatum of rhesus monkeys, as measured by PET |
| Patrick et al. (1981)                                                                                | • AMP increased [11C]raclopride (a D2 receptor antagonist) binding in the striatum of rhesus monkeys, as measured by PET |
| Pedersen et al. (2007)                                                                               | • AMP increased BOLD signal intensity in the nucleus accumbens and prefrontal cortex and increased signal intensity in the motor cortex of rats as measured by fMRI; the signal intensity changes in the nucleus accumbens and caudate (but not in the motor cortex) were attenuated by pretreatment with a tyrosine-free amino acid mixture |
| Price et al. (2002)                                                                                  | • After administration of AMP, a general increase in CBF that gradually declined toward baseline values was observed using a bolus injection PET method in baboons |
| Pum et al. (2007)                                                                                     | • AMP dose-dependently increased DA and 5-HT levels in the perihellar, entorhinal, and prefrontal cortices |

(continued on next page)
**Table 1 (continued)**

**Preclinical studies**

- Quelch et al. (2014)
  - AMP reduced [3H]carfentanil (a μ-opioid receptor antagonist) binding in rat total brain homogenate, as measured by Scatchard analysis, and in the superior colliculus, hypothalamus, and amygdala of rats, as measured by in vivo receptor binding
- Ren et al. (2009)
  - AMP increased DA release in the caudate/putamen and cAMP activity in the caudate/putamen, nucleus accumbens, and medial prefrontal cortex in rats
- Riddle et al. (2007)
  - Administration of low-dose AMP altered VMAT-2 distribution within nerve terminals selectively in monoaminergic neurons
- Ritz and Kühn (1989)
  - AMP exhibited high affinity for DA, NE, and 5-HT reuptake sites and for α2 adrenergic receptor sites, as measured using in vivo binding in rats
- Robinson (1985)
  - AMP enantiomers (d and l) inhibited MAO type A and MAO type B activity in rat liver mitochondria
- Saelens et al. (1980)
  - AMP increased [3H]piripiperoide (a D2 receptor antagonist) binding in regions containing DA terminals (e.g., the septum, nucleus accumbens, cortex, caudate-putamen) or dendrites (e.g., ventral tegmental area, substantia nigra), as measured by in vivo receptor binding
- Schiffer et al. (2006)
  - AMP elevated extracellular DA in the striatum but to a greater degree than MPH; reductions in [11C]raclopride (a D2 receptor antagonist) binding were similar with AMP and MPH
- Schwartz et al. (2007a)
  - AMP produced widespread increases in regional CBF in multiple brain region clusters that are involved in primary DA pathways in rats
- Schwendt et al. (2006)
  - AMP decreased RGS4 mRNA in the caudate-putamen and cortex and RGS4 protein levels in the caudate-putamen of rats but did not modify the effects of SCH 23390 or eticlopride (D2 receptor antagonists) on RGS4 mRNA or protein levels in these same brain regions
- Seneca et al. (2006)
  - AMP reduced binding of [3H]MNI and [11C]raclopride (D2 receptor antagonists) in the striatum of cynomolgous monkeys, as measured by PET
- Shaffer et al. (2010)
  - AMP reduced striatal and increased medial prefrontal cortical protein expression of mGluR type 5 in rats
- Smith et al. (2005)
  - AMP-induced decreases in [18F]fallypride (a D2 receptor antagonist) binding were associated with receptor internalization, as assessed using PET in knockout mice lacking the ability to internalize D2 receptors
- Sun et al. (2003)
  - AMP reduced [11C]raclopride binding of [3H]raclopride but not of [3H]spiperone (D2 receptor antagonists) in rat striatum
- Tomić et al. (1997)
  - AMP increased [11C]SCH 23390 (a D1 receptor antagonist) binding in the caudate and nucleus accumbens, increased [11C]SCH 23390 binding in the substantia nigra, and decreased [3H]spiperone (a D2 receptor antagonist) binding in the striatum and nucleus accumbens in rats, as measured using autoradiography
- van Berckel et al. (2007)
  - AMP elevated extracellular DA in the striatum and nucleus accumbens in rats, as measured by autoradiography
- Kuczenski and Segal (1997)
  - AMP-induced decrease in [3H]raclopride (a D2 receptor antagonist) binding in the striatum of baboons was enhanced by LY354740 (an mGluR type 2/3 receptor agonist), as measured by PET
- Young et al. (2011)
  - AMP increased DA concentrations in the striatum, but not in the cortex or ventral tegmental area, in prairie voles
- Yu et al. (2003)
  - AMP enhanced the cellular expression of corticotropin and hippocampal neurons to CHPG (an mGluR type 5 agonist) in rats

**Methylenidate**

- Andrews and Lavin (2006)
  - Intracortical MPH increased cortical cell excitability in rats, an effect that was lost following catecholamine depletion and was mediated via stimulation of α2 adrenergic receptors but not D2 receptors
- Bartl et al. (2010)
  - MPH exerted diverse cellular effects including increased neurotransmitter levels, downregulated synaptic gene expression, and enhanced cell proliferation in pheochromocytoma cells
- Ding et al. (1994)
  - MPH reduced binding of [11C]dl-threo-MPH in the striatum of baboons, as measured by PET
- Ding et al. (1997)
  - MPH reduced binding of [11C]dl-threo-MPH (but not [11C]dl-threo-MPH) in the striatum of baboons, as measured by PET
- Drexl et al. (1999)
  - MPH reduced [3H]trodat-1 (a DAT/SERT ligand) binding to DAT in the striatum, but not to the SERT in the midbrain/hypothalamus in baboons, as measured by PET
- Eaton et al. (2007b)
  - MPH inhibited accumulation of DA or NE in rat brain synaptosomes and vesicles, with greater potency observed for synaptosomal inhibition
- Federici et al. (2005)
  - MPH reduced spontaneous firing of DA neurons, as measured by electrophysiologic recordings in rat brain slices, via blockade of the DAT
- Gamo et al. (2010)
  - MPH decreased DA activity in the striatum and increased medial prefrontal cortical protein expression of mGluR type 5 in rats
- Gatley et al. (1995)
  - MPH increased cortical cell excitability in rats, an effect that was lost following catecholamine depletion and was mediated via stimulation of α2 adrenergic receptors but not D2 receptors
- Gatley et al. (1996)
  - MPH increased cortical cell excitability in rats, an effect that was lost following catecholamine depletion and was mediated via stimulation of α2 adrenergic receptors but not D2 receptors
- Kuczenski and Segal (1997)
  - MPH increased DA efflux in the caudate and NE efflux in the hippocampus of rats following systemic administration
- Markowiak et al. (2009)
  - MPH reduced the pH gradient in rat chromaffin cells, resulting in reduced DA uptake
- Markowiak et al. (2006)
  - MPH reduced DA release in the caudate/putamen and cAMP activity in the caudate/putamen, nucleus accumbens, and medial prefrontal cortex in rats
- Michaelides et al. (2010)
  - MPH reduced the pH gradient in rat chromaffin cells, resulting in reduced DA uptake
- Nikolau et al. (2005)
  - MPH reduced [3H]trodat-1 (a DAT/SERT ligand) binding to DAT in the striatum, as measured by SPEC
- Nikolau et al. (2011)
  - MPH reduced [3H]trodat-1 (a DAT/SERT ligand) binding to DAT in the striatum, as measured by SPEC
- Riddle et al. (2007)
  - MPH reduced [3H]trodat-1 (a DAT/SERT ligand) binding to DAT in the striatum, as measured by SPEC
- Sandovall et al. (2002)
  - MPH increased vesicular DA uptake and binding of VMAT-2 and altered VMAT-2 cellular distribution
- Schiffer et al. (2006)
  - MPH reduced [3H]trodat-1 (a DAT/SERT ligand) binding to DAT in the striatum, as measured by SPEC
- Somkuwar et al. (2013)
  - MPH reduced [11C]raclopride (a D2 receptor antagonist) binding potential but not binding affinity in baboons, as measured by PET
- Wall et al. (1995)
  - MPH increased the pH gradient in rat chromaffin cells, resulting in reduced DA uptake
- Volkow et al. (1999a)
  - MPH increased DA efflux in the caudate and NE efflux in the hippocampus of rats following systemic administration
- Wall et al. (1995)
  - MPH reduced [11C]trodat-1 (a DAT/SERT ligand) binding to DAT in the striatum, as measured by SPEC

**Human neuroimaging studies**

**Amphetamine**

- Aalto et al. (2009)
  - AMP did not alter [11C]FLB 457 (a D1/D2 receptor ligand) binding in the cortex of healthy adults, as measured by PET
- Boileau et al. (2007)
  - AMP decreased [11C]raclopride (a D2 receptor antagonist) binding in ventral striatum and putamen of healthy adults in response to conditioned stimuli, as measured by PET
- Buckholz et al. (2010)
  - AMP decreased reductions in [11C]fallypride (a D2 receptor antagonist) binding in the striatum of healthy adults who were associated with increased trait impulsivity

(continued on next page)
| Preclinical studies | Summary of effects |
|---------------------|--------------------|
| Cardenas et al. (2004) | AMP produced decreases in [11C]raclopride (a D2 receptor antagonist) binding that were sustained for up to 6 h in healthy adults, as measured using PET studies |
| Colasaanti et al. (2012) | AMP reduced [11C]carfentanil (a μ-opioid receptor antagonist) binding in the caudate, putamen, frontal cortex, thalamus, insula, and anterior cingulate cortex of healthy adult males, as measured by PET |
| Cropley et al. (2008) | AMP reduced [18F]fallypride (a D2 receptor antagonist) binding in the substantia nigra, medial prefrontal and orbital cortices, and caudate of healthy adults, as measured by PET |
| Devos et al. (2001) | AMP increased regional CBF to the prefrontal cortex, inferior orbital frontal cortex, ventral tegmentum, amygdala, and anterior thalamus, and decreased regional CBF to the motor and visual cortices, fusiform gyrus, and regions of the temporal lobe of healthy adults, as measured by SPECT |
| Drevets et al. (2001) | AMP-induced reductions in [11C]raclopride (a D2 receptor antagonist) binding in the anteroventral striatum of healthy adults, as measured by PET, were negatively correlated with feelings of euphoria |
| Garrett et al. (2015) | AMP increased fMRI-based BOLD signal variability in healthy adults, with the effects being more pronounced in older adults (60–70 years old) than younger adults (20–30 years old) |
| Gutermst et al. (2013) | AMP had no effect on [11C]carfentanil (a μ-opioid receptor antagonist) binding in the striatum, cortex, amygdala, or hippocampus of healthy adult males, as measured by PET |
| Hariri et al. (2002) | AMP potentiated responses of the right amygdala to angry and fearful facial expressions of healthy adults, as measured by fMRI, without producing changes in performance of an emotional recognition task or a somatosensory control task |
| Kegeles et al. (1999) | AMP decreased [11C]IBZM (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by SPECT |
| Knutson et al. (2004) | AMP exerted an equalizing influence on activity in the ventral striatum by enhancing tonic activity over phasic activity during anticipation of positive and negative incentives in healthy adults, as measured by fMRI |
| Laruelle et al. (1995) | AMP decreased [11C]IBZM (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by SPECT |
| Laruelle and Innis (1996) | AMP decreased [11C]IBZM (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by SPECT |
| Leyton et al. (2002) | AMP decreased [11C]raclopride (a D2 receptor antagonist) binding in the ventral striatum of healthy adults, as measured by PET, was correlated with increases in drug wanting and novelty seeking |
| Leyton et al. (2004) | AMP-induced decreases in [11C]raclopride (a D2 receptor antagonist) binding in the ventral striatum of healthy adults, as measured by PET, were attenuated by acute depletion of phenylalanine and tyrosine |
| Martinez et al. (2003) | AMP decreased [11C]raclopride (a D2 receptor antagonist) binding in healthy adults, as measured by PET, with larger reductions observed in the limbic (ventral) and the sensorimotor (postcommissural) striatal regions than associated with caudate and precommissural striatal regions |
| Mick et al. (2014) | AMP increased [11C]carfentanil (a μ-opioid receptor antagonist) binding in the caudate, putamen, frontal lobe, thalamus, nucleus accumbens, insula, amygdala, and anterior cingulate cortex of healthy adults, as measured by PET |
| Narendran et al. (2009) | AMP decreased [11C]FLB 457 (a D2/D3 receptor ligand) and [11C]fallypride (a D2 receptor antagonist) binding in the medial temporal lobe, anterior cingulate cortex, dorsolateral and medial prefrontal cortices, and parietal cortex of healthy adults, as measured by PET |
| Narendran et al. (2010) | AMP decreased [11C]NPA (a D2/D3 receptor agonist) and [11C]raclopride (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by PET, with reductions of [11C]NPA binding being greater than those of [11C]raclopride |
| Oswald et al. (2005) | AMP-induced reductions in [11C]raclopride (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by PET, were correlated with increased cortisol release and positive subjective ratings of AMP |
| Oswald et al. (2015) | AMP decreased [11C]raclopride (a D2 receptor antagonist) binding in the striatum of healthy adults, with lower binding in the right dorsal caudate being associated with lower winnings in the Iowa Gambling Task |
| Riccardi et al. (2006a) | AMP reduced [18F]fallypride (a D2 receptor antagonist) binding in healthy adults, as measured by PET, with the reductions across brain regions differing as a function of gender |
| Riccardi et al. (2006b) | AMP decreased [11C]fallypride (a D2 receptor antagonist) binding in the striatum, substantia nigra, amygdala, temporal cortex, and thalamus of healthy adults, as measured by PET |
| Riccardi et al. (2011) | AMP reduced [18F]fallypride (a D2 receptor antagonist) binding in healthy adults, as measured by PET, with the reductions in selected bar regions being correlated with Stroop test scores, Stroop test interference, and affective state |
| Rose et al. (2006) | AMP increased CBF in the cerebellum, brainstem, temporal lobe, striatum, and prefrontal and parietal cortices of healthy adults, as measured by MRI |
| Schouw et al. (2013) | AMP increased in regional CBF in the striatum, anterior cingulate cortex, thalamus, and cerebellum of healthy adults, as measured by MRI, were not correlated with reductions in [11C]IBZM receptor binding in the striatum, as measured by SPECT |
| Shotbolt et al. (2012) | AMP reduced in [11C]-(-)-PHNO (a D2/D3 receptor agonist) binding in the ventral pallidum, ventral striatum, thalamus, and putamen of healthy adults, as measured by PET, which were greater than the reductions in [11C]raclopride (a D2 receptor antagonist) binding |
| Silverstone et al. (2002) | AMP increased [11C]NPA (a D2/D3 receptor agonist) binding in the substantia nigra, as measured by PET |
| Slietstein et al. (2010) | AMP reduced [18F]fallypride (a D2 receptor antagonist) binding in the striatum, globus pallidus, midbrain, hippocampus, and amygdala of healthy adults, as measured by PET |
| Vollenweider et al. (1998) | AMP increased regional cerebral glucose metabolism in the anterior and posterior cingulate cortex, caudate nucleus, putamen, and thalamus of healthy adults, as measured by PET with [18F]-FDG |
| Wand et al. (2007) | AMP-induced reductions in [11C]raclopride (a D2 receptor antagonist) binding in striatum of healthy adults, as measured by PET, were associated with stress-induced cortisol levels |
| Willeit et al. (2008) | AMP reduced [11C](-)-PHNO (a D2/D3 receptor agonist) binding in the striatum but not in the globus pallidus of healthy adults, as measured by PET |
| Wolk et al. (1987) | AMP decreased regional cerebral glucose metabolism in the frontal cortex, temporal cortex, and striatum of healthy adults, as measured by PET |
| Woodward et al. (2011) | AMP-induced reductions in [18F]fallypride (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by PET, were positively correlated with overall schizotypal traits |

**Methylphenidate**

| Bojo et al. (1997) | MPH reduced [11C]IBZM (a D2 receptor antagonist) binding in the striatum of healthy adults, as measured by SPECT |
| Clavoorthy et al. (2009) | MPH reduced [11C]raclopride (a D2 receptor antagonist) binding in the putamen, ventral striatum, and postcommissural caudate of healthy adults, as measured by PET, with reductions in the postcommissural caudate being negatively correlated with reversal learning performance |
| Costa et al. (2013) | MPH increased neuronal activation in the putamen of healthy adults as measured by fMRI, during a go/no-go task when a response inhibition error occurred but not when a response was successfully inhibited |
| Ding et al. (1997) | MPH reduced binding of [11C]d-threo-MPH to a greater degree than [11C]l-threo-MPH in the striatum of healthy adults, as measured by PET |
| Hannestad et al. (2010) | MPH dose-dependently reduced [11C]MRB (a NET ligand) binding across the brain (e.g., locus coeruleus, raphe nucleus, hypothalamus, thalamus) of healthy adults, as measured using PET |
| Kasparbauer et al. (2015) | MPH increased BOLD signal during successful go/no-go trials in healthy adult carriers of the SLC6A3 9R allele of the DAT gene but a decrease in 10/10 allele homozygotes, as measured by fMRI |

(continued on next page)
Methylphenidate

3.1.2. Methylphenidate

The direct effects of MPH include inhibition of the DAT and NET (Dresel et al., 1999; Federici et al., 2005; Gatley et al., 1996; Markowitz et al., 2006; Nikolaus et al., 2007; Wall et al., 1995), an affinity for and agonist activity of the 5-HT_1A receptor (Markowitz et al., 2009; Markowitz et al., 2006), and redistribution of VMAT-2 (Riddle et al., 2007; Sandoval et al., 2002). As a consequence of these interactions, MPH elevates extracellular DA and NE levels (Easton et al., 2007bb; Kuczenski and Segal, 1997; Schiesser et al., 2006; Nikolaus et al., 2007). The enhanced efflux of DA and NE associated with MPH exposure results in increased availability of DA and NE to bind to their respective transporters (i.e., the DAT or NET) or to DA or NE receptors, as evidenced by reductions in ligand binding in PET and SPECT studies (Ding et al., 1999; Dresel et al., 1999; Gatley et al., 1999; Nikolaus et al., 2005, Nikolaus et al., 2007, 2011; Volkow et al., 1999a).

Although increases in extracellular levels of striatal DA in rats measured using microdialysis are less pronounced with MPH than with AMP, both compounds have been shown to exhibit similar magnitude of effects with regard to reductions in DA binding potential as measured et al., 2015; Price et al., 2002; Schwarz et al., 2007aa), with changes in CBF being correlated with striatal DA concentration (Kashiwagi et al., 2015). In a functional magnetic resonance imaging (fMRI) study in rats, AMP caused widespread increases in oxygen-level–dependent (BOLD) signal intensity in subcortical structures with rich DA innervation and with decreases in BOLD signal in the superficial layers of the cortex (Dixon et al., 2005). In another fMRI study in rats, AMP reduced BOLD signal intensity in the nucleus accumbens and prefrontal cortex and increased signal intensity in the motor cortex of rats, with signal intensity changes in the nucleus accumbens and caudate (but not in the motor cortex) being attenuated by pretreatment with a tyrosine-free amino acid mixture (Preece et al., 2007).
by PET in rodents and nonhuman primates (Schiffer et al., 2006). Multiple studies have demonstrated that MPH also directly interacts with adrenergic receptors (Andrews and Lavin, 2006; Gamo et al., 2010; Markowitz et al., 2009, 2006). Through activation of α2 adrenergic receptors, MPH has been demonstrated to stimulate cortical excitability (Andrews and Lavin, 2006). Further evidence for the interaction of MPH with α2 adrenergic receptors comes from data indicating that the procognitive effects of MPH in a working memory task are blocked by the α2 adrenergic antagonist idazoxan (Gamo et al., 2010). The effects of MPH on α2 adrenergic receptors are notable given that two α2 adrenergic receptor agonist drugs (extended-release forms of guanfacine and clonidine) are indicated for the treatment of ADHD (Jain and Katic, 2016).

3.2. Human neuroimaging studies

3.2.1. Amphetamine

Reductions in ligand binding in PET (Boileau et al., 2007; Buckholtz et al., 2010; Cardenas et al., 2004; Crolepy et al., 2008; Drevets et al., 2001; Leyton et al., 2002, 2004; Martinez et al., 2003; Narendran et al., 2009, 2010; Oswald et al., 2005, 2015; Riccardi et al., 2006a,b, 2011; Shotbolt et al., 2012; Slifstein et al., 2010; Wand et al., 2007; Willeit et al., 2008; Woodward et al., 2011) and SPECT (Kegeles et al., 1999; Laruelle et al., 1995; Laruelle and Innis, 1996; Schouw et al., 2013) studies in healthy humans indicate that AMP increases DA release across multiple brain regions, including the dorsal and ventral striatum, substantia nigra, and regions of the cortex. AMP also has been shown to alter regional CBF to areas of the brain with DA innervation, including the striatum, anterior cingulate cortex, prefrontal and parietal cortex, inferior orbital cortex, thalamus, cerebellum, and amygdala (Devous et al., 2001; Rose et al., 2006; Schouw et al., 2013; Vollenweider et al., 1998; Wolkin et al., 1987). The effects of AMP on regional CBF appear to depend on the dose, with lower doses decreasing rates of blood flow in the frontal and temporal cortices and in the striatum (Wolkin et al., 1987) and higher doses increasing blood flow in the anterior cingulate cortex, caudate nucleus, putamen, and thalamus (Vollenweider et al., 1998). In fMRI studies in healthy adults, AMP increased BOLD signal variability (Garrett et al., 2015) and exerted an “equalizing” effect on ventral striatum activity during incentive processing (Knutson et al., 2004). In addition, AMP was shown to strengthen amygdalar responses during the processing of angry and fearful facial expressions (Hariri et al., 2002).

Changes in neuronal activity have been shown to correlate with various behavioral traits (Buckholtz et al., 2010; Drevets et al., 2001; Leyton et al., 2002; Woodward et al., 2011). In PET studies, changes in the binding potential of [11C]raclopride (a D2 receptor antagonist) in regions of the ventral striatum of healthy adults associated with AMP binding have been reported to be negatively correlated with changes in AMP-associated euphoria (Drevets et al., 2001) and with increases in drug wanting and novelty seeking (Leyton et al., 2002).

3.2.2. Methylphenidate

Methylphenidate has also been shown to increase striatal DA availability, as measured by reductions in ligand binding potential in PET studies (Booij et al., 1997; Clatworthy et al., 2009; Montgomery et al., 2007; Spencer et al., 2006, 2010; Udo de Haes et al., 2005; Volkow et al., 1994, 2001, 2004; Wang et al., 1999), with evidence to indicate that this effect is related to binding to the DAT (Volkow et al., 1998, Volkow et al., 1999a,b, 2002a). MPH-induced reductions in striatal [11C]raclopride binding were associated with MPH-induced changes in euphoria and anxiety and were correlated to age (Udo de Haes et al., 2005; Volkow et al., 1994). In addition, NE systems have been implicated as key targets for MPH, with MPH dose-dependently blocking the NET in the thalamus and other NET-rich regions; the estimated occupancy of the NET at therapeutic doses of 0.35–0.55 mg/kg MPH is 70%–80% (Hannestad et al., 2010).

Assessments of functional activity using fMRI have provided evidence for the widespread functional effects of MPH (Costa et al., 2013; Moeller et al., 2014; Mueller et al., 2014; Ramaekers et al., 2013; Schlosser et al., 2009; Tomasi et al., 2011). Using fMRI, it has been shown that MPH increases activation of the parietal and prefrontal cortices and increases deactivation of the insula and posterior cingulate cortex during visual attention and working memory tasks (Tomasi et al., 2011). Another fMRI study reported MPH-induced activation in the putamen during a go/no-go task when a response inhibition error occurred but not when a response was successfully inhibited (Costa et al., 2013), suggesting that the effects of MPH are context dependent. Furthermore, MPH exposure altered connectivity strength across various cortical and subcortical networks (Mueller et al., 2014) and shifted brain activation under conditions of uncertainty to higher levels of activation in left and right parahippocampal regions and cingebellar regions (Schlosser et al., 2009). Lastly, MPH-associated decreases in task-related errors on the Stroop color-word task were associated with concurrent decreases in anterior cingulate cortex activity (Moeller et al., 2014). MPH has also been shown to reduce regional CBF in the prefrontal cortex and increase regional CBF in the thalamus and prefrontal gyrus (Schweitzer et al., 2004). In another study that used functional near-infrared spectroscopy, MPH-associated improvements in the performance of a working memory task corresponded with decreased oxy-hemoglobin levels in the right lateral prefrontal cortex, which is a surrogate for decreased neural activation (Ramasubbu et al., 2012).

4. Discussion

Although their mechanisms of action differ, the primary central nervous system effects of AMP and MPH within the brain include increased catecholamine availability in striatal and cortical regions, as evidenced in preclinical (Avelar et al., 2013; Covey et al., 2013; Easton et al., 2007b; Finnema et al., 2015; Floor and Meng, 1996; Jedema et al., 2014; Joyce et al., 2007; Kuczenski and Segal, 1997; May et al., 1988; Muhkerjee et al., 1997; Pum et al., 2007; Ren et al., 2009; Schiffer et al., 2006; Xiao and Becker, 1998; Young et al., 2011; Wall et al., 1995) and human (Boileau et al., 2007; Buckholtz et al., 2010; Cardenas et al., 2004; Crolepy et al., 2008; Drevets et al., 2001; Kegeles et al., 1999; Laruelle et al., 1995; Laruelle and Innis, 1996; Leyton et al., 2002, 2004; Martinez et al., 2003; Narendran et al., 2009, 2010; Oswald et al., 2005, 2015; Riccardi et al., 2006a,b, 2011; Schouw et al., 2013; Shotbolt et al., 2012; Slifstein et al., 2010; Wand et al., 2007; Willeit et al., 2008; Woodward et al., 2011; Booj et al., 1997; Clatworthy et al., 2009; Montgomery et al., 2007; Spencer et al., 2006, 2010; Udo de Haes et al., 2005; Volkow et al., 1994, 2001, 2004; Wang et al., 1999) studies. These increases in DA and NE availability affect corticostriatal systems that subserve behaviors related to cognition and executive function (Moeller et al., 2014; Schlosser et al., 2009; Tomasi et al., 2011), risky decision making (Oswald et al., 2015), emotional responsivity (Hariri et al., 2002), and the regulation of reward processes (Haber, 2016). Importantly, ADHD has been associated with structural and functional alterations in regions of the brain where AMP and MPH have been shown to alter DA and NE activity.

4.1. Structural alterations in ADHD

A meta-analysis of imaging data from individuals with ADHD across all age groups revealed altered white matter integrity in diverse brain areas, including the striatum and the frontal, temporal, and parietal lobes (van Ewijk et al., 2012). In a meta-analysis of imaging data from children and adults (Nakao et al., 2011), global gray matter volume was significantly smaller in those with ADHD, especially in basal ganglia structures integral to executive function. In adults with ADHD, reduced gray matter volume in the caudate and parts of the dorsolateral prefrontal cortex, inferior parietal lobe, anterior cingulate cortex,
putamen, and cerebellum were observed; increased volume was noted in other parts of the dorsolateral prefrontal cortex and inferior parietal lobe (Seidman et al., 2011). A meta-analysis of 1713 persons with ADHD and 1529 controls found volumetric reductions in the accumbens, amygdala, caudate, hippocampus, and putamen (Hoogman et al., 2017).

In a meta-analysis of 9 PET and SPECT studies, which included 169 patients with ADHD and 173 healthy controls, it was reported that striatal DAT density in patients with ADHD was 14% higher than in healthy controls (Fusar-Poli et al., 2012). Meta-regression analysis further revealed that previous exposure to ADHD medication influenced striatal DAT density, with lower DAT density being associated with a lack of medication exposure (Fusar-Poli et al., 2012). As the correlation between medication exposure and striatal DAT density accounted for 48% of the variance across studies (Fusar-Poli et al., 2012), it was suggested that the higher striatal DAT density in individuals with ADHD was a neuroadaptive response to stimulant exposure.

4.2. Functional alterations in ADHD

A meta-analysis of imaging data focusing specifically on timing function, which is important for impulsiveness in ADHD, showed consistent deficits in the left inferior prefrontal, parietal, and cerebellar regions of individuals with ADHD (Hart et al., 2012). A meta-analysis of 24 task-related fMRI studies coupled with functional decoding based on the BrainMap database reported hypoactivation in the left putamen, inferior frontal gyrus, temporal pole, and right caudate of individuals with ADHD (Cortese et al., 2016). When examining these deficits in regard to the BrainMap database, it was suggested that individuals with ADHD may exhibit deficits in the cognitive aspects of music, perception and audition, speech and language, and executive function (Cortese et al., 2016).

In high-functioning, drug-naive young adults with ADHD, resting-state fMRIs revealed altered connectivity in the orbitofrontal-temporal-occipital and frontal-amygda-occipital networks (relating to inattentive and hyperactive/impulsive symptoms, respectively) compared with matched controls; these abnormalities were not related to developmental delays, impaired cognition, or use of pharmacotherapy (Cocchi et al., 2012). Imaging studies have also reported hypoactivity in the prefrontal cortex and weak connections to other brain regions in individuals with ADHD (Arns et al., 2009). A review of progress in neuroimaging indicated that the initial focus on frontostriatal dysfunction has given way to a broader understanding of the complex interactions of various regions of the brain in which alterations may contribute to ADHD symptoms across the life span (Cortese and Castellanos, 2012).

A substantial body of literature has examined the role of DA systems in the neurobiology of ADHD and ADHD-related symptoms and behaviors. Among treatment-naive adolescents with ADHD, DAT density shows a significant inverse relationship with blood flow in the cingulate cortex, the frontal and temporal lobes, and the cerebellum, brain regions which are involved in modulating attention (da Silva et al., 2011). In a PET study of treatment-naive men with ADHD and men without ADHD, more pronounced reductions in AMP-induced reductions in striatal [11C]raclopride binding were associated with worse response inhibition, and those with ADHD had the highest-magnitude reductions and AMP-induced reductions in striatal [11C]raclopride binding (Cherkasova et al., 2014). Two SPECT studies and 1 PET study showed that adults with ADHD had higher DAT concentrations than adults without ADHD (Dresel et al., 2000; Krause et al., 2000; Spencer et al., 2007), with the SPECT studies further reporting that MPH reduced DAT availability in adults with ADHD (Dresel et al., 2000; Krause et al., 2000). Furthermore, studies have shown significant correlations between global clinical improvement in ADHD symptoms following MPH treatment and striatal DAT availability (Krause et al., 2005; La Fougere et al., 2006), and the MPH-induced increases in DA availability in the ventral striatum are associated with improved ADHD symptomology in adults with ADHD (Volkow et al., 2012). In another study, in adults with ADHD, long-term MPH treatment increased striatal DAT availability (Wang et al., 2013). In another PET study in adults with ADHD, decreased DAT and D2/D3 receptor availability in the nucleus accumbens and midbrain compared with individuals without ADHD was reported, and reduced availability of DAT and D2/D3 receptor availability was significantly correlated with lower indices of motivation only in those with ADHD (Volkow et al., 2011). Also, a PET study in young male adults with ADHD has also reported dysfunctional DA metabolism in the putamen, amygdala, and dorsal midbrain relative to healthy controls regardless of treatment status (naive vs previously treated with MPH) and that a history of MPH treatment resulted in a down-regulation of DA turnover (Ludolph et al., 2008). Despite the neuroimaging evidence that supports a role for the DAT in adult ADHD, a systematic literature review examining the pharmacogenetics of adult ADHD found that only 1 of 5 identified studies reported finding a polymorphism at the DAT gene associated with ADHD (Contini et al., 2013).

Studies of NET availability have not consistently reported altered NET availability in individuals with ADHD (Sigurdardottir et al., 2016; Vanicek et al., 2014), but one study reported genotype-dependent increases in NET binding in the thalamus and cerebellum of adults with ADHD compared with controls; this effect was largely due to the effect of NET gene polymorphisms on NET binding potential (Sigurdardottir et al., 2016). Another study reported no NET differences across multiple brain regions, including the hippocampus, thalamus, and midbrain, in individuals with ADHD compared with controls (Vanicek et al., 2014). Beyond the changes observed in DA and NE systems in individuals with ADHD, there is evidence that GLU, 5-HT, ACH, and opioid systems play a role in ADHD. Studies examining neurometabolism using proton MRIs have reported glutamatergic deficits in the frontal cortical and striatal regions in individuals with ADHD that may be related to cognitive control and symptom severity (Maltezos et al., 2014; Dramsdahl et al., 2011; Arcos-Burgos et al., 2012). Regarding the 5-HT systems, it has been reported that increased methylation of the 5-HT transporter is associated with worse clinical presentation and reduced cortical thickness in children with ADHD (Park et al., 2015). In adults, significant differences in 5-HT transporter interregional correlations between the precuneus and hippocampus have been reported in adults with ADHD compared with controls without ADHD (Vanicek et al., 2017). Functionally, it has been reported that decreased levels of activation are observed in the precuneus of adolescents with ADHD compared with individuals without ADHD; however, there is a significantly greater increase in the activation of the precuneus following the administration of fluoxetine in adolescents with ADHD compared with controls (Chantiluke et al., 2015). At present, there are no published neuroimaging studies of endogenous opioid or ACH systems in individuals with ADHD. However, altered function in both systems has been implicated in ADHD (Blum et al., 2008; Potter et al., 2014).

4.3. Co-occurring psychiatric conditions and ADHD

Attention-deficit/hyperactivity disorder is often associated with comorbid psychiatric disorders (Mao and Findling, 2014; Kooij et al., 2012; Konofal et al., 2010), such as anxiety and mood disorders. Importantly, the same brain regions and neurotransmitter systems that underlie ADHD are also implicated in the psychiatric disorders that are frequently comorbid with ADHD (Farb and Ratner, 2014; Sernat and Katzman, 2016; Schwartz and Kilduff, 2015). Thus, it is important to understand how ADHD therapies might influence psychiatric comorbidities.

4.3.1. Anxiety disorders

In healthy human volunteers, AMP has been reported to potentiate amygdalar activity in response to the processing of angry and fearful facial expressions (Hariri et al., 2002). These data provide a potential
neurobiologic basis for the anxiogenic effects of AMP (Hariri et al., 2002). However, it has been theorized that stimulant-associated augmentation of serotonergic drive could ameliorate the comorbid anxiety associated with ADHD (Heal et al., 2013). In practice, the effects of stimulants on anxiety can be complex, with acute administration of MPH reducing anxiety in adults and chronic treatment during early life increasing anxiety during adulthood (Sanchez-Perez et al., 2012).

4.3.2. Depressive disorders

Psychostimulants have been used in the treatment of major depressive disorder (MDD) since the early 1950s, when the use of MPH was first examined for MDD (Robin and Wisberg, 1958). The rationale for examining the potential utility of psychostimulants in depressive disorders is based on preclinical and clinical evidence implicating DA in depressive symptomatology (Treadway and Zald, 2011). However, the rapid onset of action of psychostimulants suggests the mechanisms by which they may influence depressive symptoms is likely to differ from that of antidepressants (Malhi et al., 2016).

Based on the published literature, the effects of psychostimulants on depressive symptoms appear equivocal. Although one meta-analysis published in 2008 based on 3 short-term trials reported statistically significant improvements favoring monotherapy with psychostimulants compared with placebo for depressive symptoms (Candy et al., 2008), a systematic review of augmentation therapy for MDD published in 2009 based on MPH (2 studies) and modafinil (2 studies) reported that neither augmentation strategy was clinically superior to antidepressant monotherapy in reducing depressive symptoms (Fleurence et al., 2009). In addition, 2 large phase 3 studies and a phase 2 study of lisdexamfetamine dimesylate augmentation in adults with MDE and inadequate response to antidepressant therapy failed to meet their primary efficacy endpoint versus placebo (Richards et al., 2016; Richards et al., 2017). The lack of treatment effect in these recently published studies, taken together with inconsistent findings based on meta-analyses and systematic reviews, suggests that psychostimulants are ineffective in treating the undifferentiated symptoms of depression. Psychostimulants have also been examined in other mood disorders, including treatment-resistant depression, bipolar depression, and depression associated with specific medical conditions (Dell’Osso and Ketter, 2013). For bipolar depression, there is some evidence supporting the efficacy of psychostimulant augmentation, but the quality and quantity of studies does not allow for a strong evidence-based recommendation for their use to be put forth (Dell’Osso and Ketter, 2013).

Despite inconclusive evidence regarding the efficacy of psychostimulants in treating depressive symptoms, the continued publication of review articles on this topic (Malhi et al., 2016; McIntyre et al., 2017; Hegerl and Hensch, 2017) demonstrates continued interest in this area of research. These review articles hypothesize that the lack of consistent clinical efficacy of psychostimulant augmentation could be due to poorly defined psychopathology and that psychostimulant effects may be more pronounced in selected symptom domains (McIntyre et al., 2017; Hegerl and Hensch, 2017) or that the effects of psychostimulants are short-lasting (Malhi et al., 2016). It has also been speculated that the use of clinician-rated scales (rather than patient-rated scales) in some studies (Richards et al., 2016, 2017) may not have adequately captured the effects of psychostimulant treatment.

It should also be noted that the use of stimulants as augmentation agents in combination with tricyclic antidepressants and MAO inhibitors is controversial, with issues concerning the possible development of an adrenergic crisis, the emergence of serotonin syndrome, or a hypertensive crisis being raised (Stotz et al., 1999). In fact, both MPH-based agents and AMP-based agents are contraindicated in individuals taking an MAO inhibitor (currently or within the preceding 2 weeks) because a hypertensive crisis may result (Thomas et al., 2015).

4.3.3. Substance use disorders

The neurobiology of reward and addiction and the key role of mesolimbic DA systems have been described in great detail (Volkow and Morales, 2015; Koob, 2006). Although associations have been made between ADHD and substance abuse, their relationship is complex. Several reviews have emphasized that substance use disorders can be comorbid with ADHD (Mao and Findling, 2014; Kooij et al., 2012). For example, in a study of 208 adults diagnosed with ADHD and treated with psychostimulants as youths, the relative risk of having a diagnosis of substance use disorder or alcohol abuse, respectively, compared with the general population was 7.7 or 5.2 (Dalsgaard et al., 2014). Furthermore, a 2012 review noted that there was evidence for increased rates of substance abuse in individuals with ADHD treated with psychostimulants (Nelson and Galon, 2012). Given the known abuse liability of psychostimulants and data indicating that psychostimulant medications are associated with misuse and diversion (Rabiner et al., 2009; Garnier et al., 2010), it is not surprising that psychostimulant medications approved for use in ADHD are schedule II medications with black box warnings for potential drug dependence (Panagiotou et al., 2011). Some treatment guidelines suggest that nonstimulant alternatives be considered as therapies for ADHD when issues related to abuse and dependence are a concern (Atkinson and Hollis, 2010; Bolea-Alamanac et al., 2014; Pliszka and AACAP Work Group on Quality Issues, 2007).

However, multiple studies have provided evidence that psychostimulant treatment in individuals with substance use disorders and ADHD is not associated with a significant worsening of substance abuse (Konofal et al., 2016; Levin et al., 2015). In a study that examined the efficacy of extended-release mixed AMP salts in the treatment of ADHD symptoms and cocaine abuse in 126 cocaine-dependent adults with ADHD (Levin et al., 2015), significantly greater reductions in ADHD symptoms and higher abstinence from cocaine use were observed with extended-release mixed AMP salts than placebo. In another study, osmotic-controlled release oral delivery system (OROS) MPH did not produce significantly greater reductions in ADHD symptoms than placebo in 24 AMP-dependent adults with newly diagnosed ADHD. However, OROS MPH treatment also was not associated with evidence of increased AMP abuse, as measured by self-reported days of AMP use or craving for AMP, time to relapse, or cumulative abstinence duration (Konofal et al., 2010).

4.3.4. Sleep disturbances

The neurobiologic substrates of sleep are diverse and distributed throughout the brain, with monoaminergic systems playing an important role in wakefulness (Schwartz and Kilduff, 2015). Substantial literature exists regarding the sleep disturbances associated with ADHD, which include insomnia, disordered sleep, difficulty falling asleep, sleep apnea, daytime somnolence, and increased nocturnal motor activity (see Konofal et al., 2010; Cohen-Zion and Ancoli-Israel, 2004; Lecendreux and Cortese, 2007; Snitselaar et al., 2017 for reviews). Evidence suggests that impaired and/or disordered sleep is present in individuals not being treated with psychostimulants (Konofal et al., 2010). For example, in a study of the effects of MPH on sleep in children with ADHD, parents reported that approximately 10% of study participants had sleep problems before starting their medication (Becker et al., 2016). However, in regard to the reported effects of psychostimulants on sleep in individuals with ADHD, there are some discrepancies. In a meta-analysis of 9 articles, the use of psychostimulant medication was associated with longer sleep latency, worse sleep efficiency, and shorter sleep duration (Kidwell et al., 2015). A review of the safety and tolerability of ADHD medications noted that insomnia was one of the most commonly reported adverse events associated with psychostimulant treatment (Duong et al., 2012). In contrast, some studies have shown that psychostimulants have no significant negative impact on sleep (Becker et al., 2016; Owens et al., 2016; Surman and Roth, 2011). A post hoc analysis of the effects of lisdexamfetamine or
SHP465 mixed amphetamine salts in adults with ADHD demonstrated that the proportions of participants exhibiting a worsening of sleep during treatment, as measured by the Pittsburgh Sleep Quality Index, did not differ from that of placebo (Surman and Roth, 2011). Discrepancies in the effects of stimulants on sleep in individuals with ADHD might be attributable to various factors, including sleep quality prior to treatment, the stimulant formulation, the length of treatment, and the method of sleep assessment (Cohen-Zion and Ancoli-Israel, 2004; Becker et al., 2016; Kidwell et al., 2015). For example, in a study of MPH in children with ADHD, 23% of participants without preexisting sleep problems developed sleep problems while taking MPH, whereas 68.5% of those with preexisting sleep problems no longer experienced sleep problems after taking MPH (Becker et al., 2016).

### 4.4. Other safety concerns

In addition to considering the potential effect of AMP and MPH in individuals with other comorbid psychiatric disorders, the peripheral effects of AMP and MPH related to their pharmacology need to be considered, particularly in regard to their effects on cardiovascular function. Increased heart rate and blood pressure are among the most frequent treatment-emergent adverse events reported with psychostimulant treatment (Duong et al., 2012; Vaughan and Kratchovil, 2012); increases in pulse and blood pressure are also frequently reported (Duong et al., 2012; Vaughan and Kratchovil, 2012; Santosh et al., 2011). There is also a safety concern related to the potential for adverse cardiovascular outcomes, including ischemic attacks, myocardial infarction, and stroke (Westover and Halm, 2012). In a self-controlled case series analysis, treatment with MPH was associated with an increased overall risk of arrhythmia and with an increased risk of myocardial infarction from 1 week to 2 months after treatment initiation in children and adolescents with ADHD (Shin et al., 2016). Another study reported that the risk for an emergency department visit for cardiarelated reasons among youths did not differ between those being treated with AMP versus MPH (Winterstein et al., 2009). However, these findings should be considered in light of data from 2 large studies that reported no significant increase in risk for cardiovascular events in current users of ADHD medications compared with nonusers (Cooper et al., 2011; Habel et al., 2011).

The neurotransmitter systems responsible for stimulant-associated adverse events and safety concerns are in large part related to stimulation of peripheral NE activity (Duong et al., 2012; Westover and Halm, 2012). Based on these concerns, package inserts for stimulants include black box warnings regarding the potential for serious adverse cardiovascular events (Panagiotou et al., 2011). Assessments of the risks and benefits of stimulant therapy for ADHD should be made on an individual basis, and individuals on psychostimulant treatment should be monitored.

Another issue of potential concern is the possible neuroinflammatory effects of psychostimulants. In rats, MPH administration has been reported to produce neuroinflammation and oxidative stress in the hippocampus and cerebral cortex, as measured by the inflammatory markers tumor necrosis factor α and interleukin 1β (Motaghinejad et al., 2017, 2016). In a systematic review of 14 studies (Anand et al., 2017), no study assessed the relationship between psychostimulant treatment and neuroinflammation so the relevance of preclinical models of neuroinflammation to psychostimulant treatment in individuals with ADHD is unknown. The same review did find evidence suggesting a role for inflammation in the pathogenesis of ADHD (Anand et al., 2017), which is consistent with a meta-analysis finding elevated levels of oxidative stress in patients diagnosed with ADHD (Joseph et al., 2015). Oxidative stress has also been implicated in the lower brain volumes seen in ADHD patients (Hess et al., 2017).

### 5. Conclusions

Based on the published literature, the primary pharmacologic effects of both AMP and MPH are related to increased central DA and NE activity in brain regions that include the cortex and striatum. These regions are involved in the regulation of executive and attentional function (Faraone et al., 2015). In ADHD, dysfunction in the DA and NE systems, which are critical to proper cortical and striatal function, likely account for some of the pathophysiology of ADHD (Cortese, 2012; Faraone et al., 2015; Arntsen, 2009). Although it is a limitation of the review that the only database searched was PubMed, it is unlikely that important studies were not captured.

It has been speculated that the moderately greater efficacy of AMP-based agents compared with MPH-based agents in ADHD may be related to differences in their molecular actions (Faraone and Buitelaar, 2010), but to date there is no conclusive clinical evidence to support this speculation. Furthermore, there is no conclusive clinical evidence supporting a prospective choice for an AMP-based agent over an MPH-based agent (or vice versa) based on the mechanisms of action of these drug classes. As such, the current understanding of differences in the mechanisms of action of AMP and MPH has not led to clinical guidelines regarding their use in specific patient populations. Furthermore, it is possible that differences in the pharmacologic profile between AMP and MPH, in combination with the complexities associated with the etiology of ADHD (Faraone et al., 2015), contribute to individual differences in treatment response to AMP-based agents or MPH-based agents in individuals with ADHD. Interactions among these factors might explain why some patients have a differential response to these drugs.

When contemplating pharmacotherapy for ADHD, in addition to taking into account the potential for adverse cardiovascular outcomes (Westover and Halm, 2012), the presence of comorbid psychiatric disorders should be considered. Multiple psychiatric comorbidities, including depression and anxiety (Mao and Findling, 2014; Kooij et al., 2012), are thought to be mediated in part by shared neurobiological pathways that are also implicated in the pathophysiology of ADHD (Farb and Ratner, 2014; Sernat and Katzman, 2016). As such, the effect of psychostimulant treatment on the symptoms of these disorders and the potential interactions with medications used to treat these disorders need to be considered.

### Author contribution

Dr. Faraone designed the systematic literature review, is responsible for the content of the manuscript, and approved the final draft.

### Disclosures

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