



From neurons to brain networks, pharmacodynamics of stimulant medication for ADHD

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ABSTRACT

Stimulants represent the first line pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD) and are among the most prescribed psychopharmacological treatments. Their mechanism of action at synaptic level has been extensively studied. However, it is less clear how their mechanism of action determines clinically observed benefits. To help bridge this gap, we provide a comprehensive review of stimulant effects, with an emphasis on nuclear medicine and magnetic resonance imaging (MRI) findings. There is evidence that stimulant-induced modulation of dopamine and norepinephrine neurotransmission optimizes engagement of task-related brain networks, increases perceived saliency, and reduces interference from the default mode network. An acute administration of stimulants may reduce brain alterations observed in untreated individuals in fronto-striato-parieto-cerebellar networks during tasks or at rest. Potential effects of prolonged treatment remain controversial. Overall, neuroimaging has fostered understanding on stimulant mechanism of action. However, studies are often limited by small samples, short or no follow-up, and methodological heterogeneity. Future studies should address age-related and longer-term effects, potential differences among stimulants, and predictors of treatment response.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental conditions and is characterized by age-inappropriate inattentive and/or hyperactive-impulsive symptoms (APA, 2022; Priya Ra 2023, WHO, 2019/2021). It is often diagnosed in childhood, with a community prevalence between 2% and 7% (Cortese et al., 2023, Sayal et al., 2018). Impairing symptoms of ADHD persist in up to 75% of adults (Sibley et al., 2016). Individuals with ADHD may

present with neuropsychological deficits, mainly affecting executive functions, such as attention, response inhibition, planning, and working memory (Faraone et al., 2021). Co-occurrent conditions, such as affective, substance use or other neurodevelopmental disorders, are also common (Gnanavel et al., 2019, Katzman et al., 2017). ADHD is associated with educational and occupational failure, teenage pregnancies, legal offences, road accidents, and increased mortality; as well as with high costs related to income/health-related losses and educational support (Faraone et al., 2021). Pharmacological treatment has been

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shown to reduce these risks, while improving outcomes and quality of life (Bellato et al., 2024, Cortese et al., 2018, Faraone et al., 2021). Stimulants represent the first line pharmacological treatment and are generally effective in ameliorating symptoms (Cortese et al., 2018). Stimulants include methylphenidate (MPH) and various forms of amphetamines, such as dexamfetamine and lisdexamfetamine (Cortese et al., 2018, Faraone et al., 2021). Stimulants are among the most prescribed psychopharmacological treatments, and rates are increasing especially in adults, as highlighted by a recent data release of the UK NHS Business Services Authority (NHSBSA) (<https://www.nhsbsa.nhs.uk/statistical-collections/medicines-used-mental-health-england/medicines-used-mental-health-england-201516-202223>). Stimulants act by modulating dopamine and norepinephrine neurotransmission in striato-cortical regions (Faraone, 2018). Although their mechanism of action at synaptic level has been extensively studied, e.g. *in vitro* and in animal models (Zimmer, 2017), it is less clear how these neurochemical changes determine the beneficial clinical and behavioral effects. Neuroimaging studies, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI), represent a powerful tool to address this gap by investigating treatment effects on the brain at a macroscopic level.

Given the lack of recent and comprehensive reviews in this fast-evolving field, here we present a timely overview of brain mechanisms underpinning stimulant mechanism of action, spanning from cellular to brain network levels, with an emphasis on neurotransmission and novel insight provided by neuroimaging research. This comprehensive narrative review builds on evidence from relevant systematic and narrative reviews and meta-analyses and expands their findings by including updated evidence up to the 17th July 2024. We identified the studies via a systematic screening of publications in PubMed using the following search strategy: (ADHD [tiab] OR attention-deficit/hyperactivity disorder [tiab] OR attention-deficit [tiab] OR attention deficit [tiab] OR hyperkinetic syndrome [tiab] OR hyperkinetic disorder [tiab]) AND (separately for molecular mechanisms and each imaging modality) (pathogenesis [tiab] OR pathophysiology [tiab] OR molecular [tiab]); (PET [tiab] OR positron emission [tiab]); (SPECT [tiab] OR photon emission [tiab]); (MRI [tiab] OR magnetic resonance imaging [tiab] OR fMRI [tiab] OR connectivity [tiab] OR diffusion [tiab]). We did not include case reports and studies focusing on new methods development instead of ADHD pathophysiology or treatment.

We will first describe neurotransmission systems involved in ADHD, capitalizing on findings from nuclear medicine imaging techniques. We will then discuss stimulant mechanism of action and review current evidence from structural and functional MRI studies, including anatomical and functional connectivity analyses. Finally, we will discuss limitations of current research and suggest ways forward. Ultimately, this work can provide clinicians and researchers working in the field with a deeper understanding of the biological correlates of the most prescribed pharmacological treatments for ADHD.

2. Catecholaminergic neurotransmission

ADHD research has traditionally focused on catecholaminergic neurotransmission. Dopamine (DA) is predominantly synthesized from the amino acid L-tyrosine within the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) (Blanchard et al., 1994, Dahlstrom and Fuxe, 1964). This catecholamine directly acts as a neurotransmitter or is converted into norepinephrine (NE) by the enzyme dopamine β -hydroxylase (DBH). DA and NE are the main catecholamines in the brain and exert a predominant modulatory action on other neurotransmitters. There are two main DA receptor families, D1 (including D1 and D5) and D2 (including D2, D3, D4), which are differently distributed throughout the brain (Aston-Jones and Cohen, 2005, Beaulieu and Gainetdinov, 2011). DA acts through highly topographically organized projections, such as the nigrostriatal pathway, which connects the SNc to the striatum as part of the fronto-striatal

circuits, and is well known for its role in movement regulation. Further, mesocortical and mesolimbic dopaminergic pathways are involved in executive functions and affect regulation, as they project from the SNc and the VTA directly to cortical regions, such as the mesial frontal and anterior cingulate cortex (ACC), and to limbic structures, such as the amygdala and hippocampus (Moore and Bloom, 1978) (Fig. 1). ADHD has been associated with dysfunction in all these three pathways (Del Campo et al., 2011, Mehta et al., 2019).

The role of fronto-striatal pathways has been the most investigated in ADHD research (da Silva et al., 2023, Del Campo et al., 2011, Mehta et al., 2019, Parlatini et al., 2023b). These are GABA-glutamatergic circuits modulated by dopamine. They contribute to motor, cognitive and affective regulation by connecting different parts of the cortex to the basal ganglia and thalamus, which then projects back to the cortex (Alexander and Crutcher, 1990, Alexander et al., 1986). Although there is no consensus on their exact number, three major loops can be identified according to their main function and the cortical regions they originate from: 1) the sensorimotor loop originates from the sensorimotor cortex; 2) the cognitive circuit from the dorsolateral prefrontal cortex (DLPFC); and 3) the affective (limbic) loop from the ACC and orbitofrontal cortex. Through these fronto-striatal loops, multiple cortical inputs are integrated and conveyed to a specific single cortical area in order to modulate motor planning/initiation or to select and enable cognitive/emotional programs (Alexander et al., 1986, Allen and Tsukahara, 1974, Kemp and Powell, 1971). Overall, these circuits contribute to executive functions and affect regulation, which can be impaired in ADHD.

Further, ADHD has been linked to noradrenergic dysfunction. In contrast to dopaminergic connections, noradrenergic pathways are highly distributed throughout the brain. These originate from the locus coeruleus (LC), which is in the brainstem and is reciprocally connected with cortical regions, such as the PFC (Gerfen and Clavier, 1979, Morrison et al., 1982, Ramos and Arnsten, 2007) (Fig. 1). Animal studies have demonstrated that these connections modulate neural functions according to arousal state and attention (Aston-Jones and Cohen, 2005). The LC shows a phasic activity when an animal is awake, characterized by low levels of spontaneous firing alternated to bursts when a stimulus of interest is perceived. Conversely, when an animal is stressed or anxious, the LC enters a tonic phase, characterized by enhanced firing and decreased cognitive performance. Once released, NE acts through three receptor families, including the α 1, α 2 and β receptors. NE has the highest affinity for the α 2 receptors, among which the α 2A is the most common in the PFC (Ramos and Arnsten, 2007). In summary, the balance between tonic and phasic NE release in the PFC is pivotal to maintain performance in cognitive functions that are affected in ADHD (da Silva et al., 2023, Del Campo et al., 2011).

DA and NE critically contribute to optimal PFC activity, and this allows 'top-down' regulation of response inhibition, attention, and motivation, through its connections with subcortical nuclei and posterior cortical regions, such as the parietal cortex (Arnsten and Rubia, 2012, Xing et al., 2016). As mentioned, this top-down regulatory PFC function relies on local microcircuits of GABAergic inhibitory interneurons and glutamatergic neurons. Neuronal excitability is dynamically modulated by catecholamines, through cyclic adenosine monophosphate (cAMP) signaling. Whilst DA increases the production of cAMP within the target neurons through D1 receptors, and thus weakens microcircuit inappropriate connections; NE inhibits cAMP production through α 2A receptors, and thus enhances the strength of specific connections. Thus, DA and NE optimize PFC function by respectively reducing 'noise' and enhancing 'signal' within glutamatergic circuits (Arnsten, 2009, Arnsten and Rubia, 2012, da Silva et al., 2023). These microcircuits are very sensitive to their neurochemical environment. Therefore, unbalanced levels of catecholamines may have a detrimental effect on PFC functions. Specifically, an inverted U-shape relationship exists between catecholaminergic signaling in the PFC and cognitive performance, and both excessive and insufficient

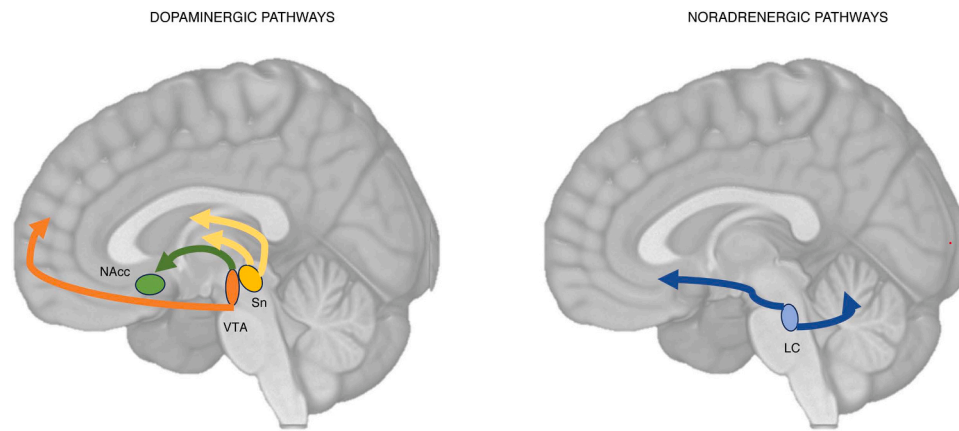


Fig. 1. Catecholaminergic projections. Dopamine acts through highly topographically organised projections, such as the nigrostriatal pathway, which connects the substantia nigra (SN) to the striatum (in yellow). Further, the mesocortical pathway (in green) and the mesolimbic pathway (in orange) are involved in executive functions and affect regulation. They project from the SN and the ventral tegmental area (VTA) to cortical regions, such as the mesial frontal and anterior cingulate cortex, and to limbic structures, such as the nucleus accumbens (NAcc), amygdala, and hippocampus (left panel). Conversely, noradrenergic projections originate from the locus coeruleus (LC) in the brainstem, which directly connects to cortical areas, such as the prefrontal cortex, and the cerebellum (in blue) (right panel).

catecholamine release negatively impact on PFC functions (da Silva et al., 2023, Granon et al., 2000, Robbins and Arnsten, 2009, Zahrt et al., 1997). In sum, DA and NE optimize PFC activity by both activating their respective receptors and favoring signaling integration within local circuitries (Xing et al., 2016).

3. Catecholaminergic dysfunction in ADHD

There is substantial evidence that catecholamine dysregulation plays an important role in ADHD pathophysiology. This is supported by several pieces of evidence, such as candidate gene studies (Faraone et al., 2021); animal models of the disorder (Rahi and Kumar, 2021); and the efficacy of stimulants (Cortese et al., 2018). Evidence of altered dopaminergic transmission, especially in fronto-striatal circuits, also came from studies using nuclear medicine techniques, such as PET and SPECT (Weyandt et al., 2013, Yamamoto and Inada, 2023, Zimmer, 2017). In PET studies, active molecules, such as receptor or transporter ligands, are injected after being labelled with positron-emitting radionuclides. The emitted positron combines with an electron and generates two photons, which are then captured simultaneously by a camera, thus allowing the localization of the original binding site of the tracer (Zimmer, 2009). Similarly, a gamma camera detects gamma rays emitted by the tracers used in SPECT studies (Accorsi, 2008). Of note, transporter and receptor density measured using specific radioligands is considered an indirect measure of neurotransmitter binding and may reflect altered neurotransmission (Weyandt et al., 2013). These techniques have allowed the investigation of catecholaminergic pathways dysfunction in ADHD (Zimmer, 2017), e.g. by measuring DA transporter (DAT) occupancy (Cheon et al., 2004, Spencer et al., 2007), DA synthesis (Forssberg et al., 2006), and receptor density (Ilgin et al., 2001).

The DAT has been the main target of these studies. DAT is considered a specific marker of DA neuronal integrity (Weyandt et al., 2013, Zimmer, 2009), and modulates the magnitude and duration of the dopaminergic signal by reuptaking DA from the synaptic cleft. Radioligands targeting this transporter, such as substituted (nor)phenyltropanes, have been primarily used to quantify DA binding in the striatum, which has the highest DAT density (Piccini, 2003). Studies of DAT binding have yielded inconsistent results - reporting higher or lower binding in ADHD or no group differences (Weyandt et al., 2013). However, a meta-analysis including 9 PET/SPECT studies of striatal DA transporter density highlighted that these inconsistencies may be related to the confounding effect of previous treatment (Fusar-Poli et al., 2012). Although the ADHD group showed 14 % greater striatal DAT binding than controls, a meta-regression analysis on the same sample revealed

that the percentage of individuals receiving stimulant treatment was positively associated with higher DAT levels (Fusar-Poli et al., 2012). Therefore, the studies reporting higher DAT density in ADHD were likely biased by an adaptive response to chronic exposure to stimulants, which induces persistent DAT blockade (Fusar-Poli et al., 2012). Conversely, in line with the dopaminergic dysfunction theory of ADHD, medication naïve individuals were more likely characterized by lower striatal DAT density. A more recent investigation pooling results from 20 studies confirmed increased striatal DAT binding but also highlighted an effect of age, as no regional group differences were observed when the three studies in adolescents were excluded (Nikolaus et al., 2022). Additional evidence of reduced dopaminergic activity in individuals with ADHD came from studies targeting post-synaptic D2/D3 receptors, e.g. by injecting radiolabeled raclopride (Volkow et al., 2007b); or investigating DA synthesis, by using the radiolabeled DA precursor DOPA (Ludolph et al., 2008). A recent investigation observed a significant reduction in D2 binding in the caudate and in DA synthesis in the frontal cortex when pooling the existing studies in adults (5 each) (Nikolaus et al., 2022). Taken together, PET/SPECT studies supported the suggestion that individuals with ADHD have altered striatal dopaminergic transmission (Weyandt et al., 2013).

Initial studies focused on striatal DAT due to lack of radiotracers suitable to investigate cortical DAT and NET (Weyandt et al., 2013). Indeed, DAT density is limited in the PFC (Piccini, 2003), where DA reuptake is likely mainly mediated by NET (Moron et al., 2002). The potential role of NET in ADHD has been supported by candidate gene studies (Faraone et al., 2021); by the involvement of the NE system in cognitive processes affected in ADHD (Arnsten and Rubia, 2012, Brennan and Arnsten, 2008); and by the effect of medications (Cortese et al., 2018). Thus, there have been increasing efforts to develop radiotracers to target NET (Logan et al., 2007, Takano et al., 2008, Vanicek et al., 2014). For example, analogues of the antidepressant reboxetine can be used to target NET but mainly in subcortical regions, such as the LC and thalamus, or in the striatum, where it has the lowest concentration (Logan et al., 2007, Takano et al., 2008). This limitation might explain why an initial study did not identify significant differences between individuals with ADHD and controls in NET regional distribution or availability (Vanicek et al., 2014). However, a subsequent study from the same group identified genotype-dependent differences in the NET binding potential between adults with ADHD and neurotypical controls in the thalamus and cerebellum; as well as genotype-dependent associations between cerebellar NET binding potential and hyperactivity/impulsivity in the ADHD group (Sigurdardottir et al., 2016). Finally, a more recent epigenetic analysis has shown that the promoter

region of the gene encoding for NET was hypermethylated in adults with ADHD as compared to neurotypicals. This resulted in a reduced transcriptional activity and NET binding potential in subcortical regions only in the ADHD group (Sigurdardottir et al., 2021). Taken together, these results point to genetic and epigenetic influences leading to altered NET expression in ADHD.

In summary, PET and SPECT studies support the role of catecholaminergic systems in ADHD pathogenesis.

4. Beyond catecholaminergic neurotransmission

Although ADHD research has primarily focused on catecholamines, there is increasing evidence that other neurotransmitter systems are involved in its pathophysiology. Among these, the role of serotonin (5-HT) has been supported by animal models as well as candidate gene and imaging studies (Banerjee and Nandagopal, 2015, Quintero et al., 2022). 5-HT is known to influence activity levels, impulsivity, aggression, attention, mood, and appetite (Banerjee and Nandagopal, 2015, Quintero et al., 2022). Seminal animal studies showed that the administration of 5-HT precursors, selective serotonin re-uptake inhibitors (SSRI), or an antagonist of the 5-HT_{2A} receptor (excitatory) reduced hyperactivity in DAT knock-out mice. Conversely, stimulation of the pre-synaptic receptor 5-HT_{1B} (inhibitory) increased anxiety and locomotion. These findings suggest that serotonergic stimulation affects hyperactivity by modulating striatal dopaminergic neurotransmission (Banerjee and Nandagopal, 2015, Barr et al., 2004, Gainetdinov et al., 1999). Similarly, genetic studies have suggested associations between specific polymorphisms of the serotonin transporter gene (SERT) and the 5-HT_{1B} and 5-HT_{2A} receptors and ADHD, although associations were not confirmed in all samples (Banerjee and Nandagopal, 2015, Hawi et al., 2002, Kent et al., 2002). Finally, nuclear medicine studies have provided evidence of altered serotonergic neurotransmission in ADHD. A recent work pooling the results of three adult studies reported reduced SERT binding in the striatum and thalamus, irrespective of medication-status, and in the striatum and midbrain of medication-naïve individuals (Nikolaus et al., 2022).

Emerging evidence also highlights an altered balance between excitatory/inhibitory neurotransmission, i.e., between glutamatergic and GABAergic signaling, in individuals with ADHD, although with some inconsistencies. Magnetic resonance spectroscopy (MRS) has been used to quantify metabolites in specific brain areas, which can be interpreted as surrogate markers for cellular mechanisms, from neurotransmission to neuronal integrity (Vidor et al., 2022). Considering GABAergic neurotransmission, an initial meta-analysis including only three MRS studies did not find significant differences between individuals with ADHD and controls in fronto-striatal GABA levels (Schur et al., 2016). However, as recently reviewed by Ferranti et al. (2024), other studies have shown that lower GABA levels in the anterior cingulate cortex were significantly associated with inattention and impulsivity in individuals with ADHD (Ferranti et al., 2024, Mamiya et al., 2022, Silveri et al., 2013). Further, specific single nucleotide polymorphisms (SNPs) in the glutamic acid decarboxylase (*GAD1*) gene, encoding for an enzyme involved in GABA synthesis, were found to increase susceptibility to ADHD (Bruxel et al., 2016). Thus, it has been suggested that inefficient GABAergic transmission may favor neuronal stimulation and contribute to hyperactivity and reduced focus in at least some ADHD subpopulations, although this warrants further investigation (Ferranti et al., 2024, Quintero et al., 2022). Considering glutamate, a meta-analysis of 6 MRS studies revealed increased glutamate/glutamine levels, a marker of excitatory neurotransmission, in the right medial frontal cortex of children with ADHD as compared to neurotypical controls (Vidor et al., 2022). As glutamate/glutamine were measured together, authors suggested that both glutamate neurotoxicity or depletion could underlie these findings and potentially contribute to the cortical thinning observed in ADHD. Extending these results, a more recent work from the same authors indicated lower glutamate levels in the posterior cingulate cortex in 88

adults with ADHD as compared to 44 controls. Authors concluded that a glutamatergic imbalance in this key region of the default mode network (DMN) may contribute to dysfunctional activation and interaction with task-based networks (Vidor et al., 2024). This finding contradicts an earlier study in a mixed sample of children and adults (Arcos-Burgos et al., 2012), although this inconsistency might be driven by age-related differences. Further evidence for glutamatergic alterations in ADHD has been provided by genetic, animal model, and post-mortem studies (Huang et al., 2019, Kus et al., 2023, Sudre et al., 2023). Glutamate acts through fast ionic receptors, i.e., the N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors; and through slower metabotropic (protein G-coupled) receptors, part of the mGluR family. The NMDA receptors are well known for their role in long term-potential and are involved in learning and memory. As reviewed by Huang et al. (2018), association studies have primarily supported the involvement of ionotropic receptors in ADHD, with kainate receptors potentially more associated with hyperactive-impulsive symptoms (Naaijen et al., 2017) and NMDA receptors with inattention (Huang et al., 2019, Kim et al., 2020). Further, copy number variations in metabotropic receptors have been implicated in ADHD and the often-associated low intelligent quotient or anxiety (Akutagava-Martins et al., 2014, Huang et al., 2019). Human post-mortem studies also highlighted significant downregulation of neurotransmitter gene pathways, particularly glutamatergic, especially in the ACC of individuals with ADHD (Sudre et al., 2023). These findings are in line with the known reciprocal interaction between glutamatergic and dopaminergic systems. For instance, stimulation of D2 and D4 receptors respectively inhibits NMDA and AMPA receptors (Kotecha et al., 2002, Yuen and Yan, 2009, Yuen et al., 2010). Further, animal studies have revealed that the hyperactivity of DAT knock-out mice could be reduced by stimulation of NMDA receptors (Gainetdinov et al., 2001), and that of AMPA GluR1 knock-out mice by an D2 receptor antagonist (Boerner et al., 2017). Taken together, these findings indicate that several neurotransmitter systems may be affected in ADHD. It is important to notice that these systems have also been implicated in other neurodevelopmental and mental health disorders, from autism to schizophrenia and depression, which supports the suggestions that transdiagnostic neurobiological features underlie these conditions (Lawn et al., 2024, Nguyen et al., 2024).

Finally, although in our review we primarily focused on neurotransmitters and related neuroimaging findings, it is important to highlight that there is increasing evidence that ADHD is also associated with alterations in genes encoding for transcription factors, synaptic adhesion molecules, and micro-RNAs (Demontis et al., 2023, Demontis et al., 2019, Ferranti et al., 2024, Parlatini et al., 2024c). It has been noted that there is little/no convergence between candidate gene or linkage studies and Genome-Wide Association Studies (GWAS) findings (Poelmans et al., 2011). Meta-analyses of candidate gene studies yielded significant associations primarily with genes involved in dopaminergic and serotonergic pathways (i.e., DAT, SERT, D4, D5, HTR1B), in addition to SNAP25, encoding for synaptosome associated protein 25 involved in vesicular release during neurotransmission (Gizer et al., 2009, Li et al., 2006, Parlatini et al., 2024c). However, the only identified overlap between these studies and GWAS is represented by the cadherin-13 (*CDH13*) gene, which encodes for a cell adhesion molecule that has been implicated in several conditions, from ADHD to autism and depression. Although the exact mechanism remains unclear, it has been suggested that *CDH13* affects GABAergic neurons and thus excitatory/inhibitory balance (Rivero et al., 2015). Finally, a recent work integrating results from the 5 GWAS in ADHD highlighted that, among the 85 top-ranked ADHD-related genes, 45 encoded for proteins involved in neurite outgrowth especially during neurodevelopment (Poelmans et al., 2011). These findings are in line with previous reports both in ADHD and other neurodevelopmental disorders suggesting an imbalance between synaptic proliferation and pruning (Quintero et al., 2022, Ugarte et al., 2023). For instance, a review highlighted the potential role of neurotrophins in ADHD pathophysiology, especially the

brain-derived neurotrophic factor (BDNF), which is involved in neuroplasticity (Tsai, 2017). Its involvement is supported by animal models but results from human genetic and blood level studies have been inconsistent (El-Saied et al., 2024, Quintero et al., 2022, Tsai, 2017).

Taken together, these findings suggest that several molecular and cellular mechanisms contribute to ADHD pathophysiology, although variably according to clinical profiles, associated cognitive deficits, and comorbidities. Given the substantial heterogeneity of ADHD, future studies are needed to map the underlying alterations according to the specific clinical profile. Clarifying these mechanisms can also provide a more solid base to understand stimulant mechanisms of action, as discussed in the following section.

5. Stimulant mechanisms of action

Stimulants used for the treatment of ADHD include MPH and amphetamines (Cortese et al., 2018, Faraone et al., 2021). MPH exists as two enantiomers (i.e. two compounds with mirrored chemical structure), respectively called d-threo and l-threo-MPH, but its therapeutic effects are primarily due to the d-enantiomer (Kimko et al., 1999). MPH blocks both DA and NE transporters through allosteric binding (i.e. on a different site from that of the endogenous neurotransmitter), inhibiting both catecholamines reuptake and increasing their availability (Arnsten and Pliszka, 2011, Kuczenski and Segal, 2002, Seu et al., 2009) (Fig. 2). Conversely, amphetamines block DAT and NET by binding on the same site of the endogenous neurotransmitter, thus they act as a competitive inhibitor (Fig. 2). At higher than therapeutic doses, such as those taken for abuse, they may also induce the release of DA from intrasynaptic vesicles into the cytoplasm, and then into the synaptic cleft through DAT reversal, a phenomenon which is linked to euphoria and addiction (Calipari and Ferris, 2013). Amphetamines also exist as D- and l-isomers but, although the former is more potent for DAT binding, they are equally potent for NET binding. Notably, lisdexamfetamine is a long-acting d-amphetamine prodrug. It is hydrolyzed into d-amphetamine in the blood and has a different pharmacokinetic profile than short-acting amphetamines, offering the longest therapeutic action among stimulants (up to 13–14 hours)(Ermer et al., 2016).

The ability of stimulants to act as DA and NE reuptake inhibitors has been demonstrated *in vitro* and later in animal models, before being confirmed *in vivo* in humans through nuclear medicine studies (Zimmer, 2017). Considering animal models, it is worth mentioning that early studies in rats used high doses of stimulants, generally administered intraperitoneally, and reported a positive association between the release of striatal DA and activity levels (Segal and Kuczenski, 1987). These findings contributed to the misleading interpretation that the calming effect observed in individuals with ADHD was paradoxical. Later studies reported that lower doses, more comparable to therapeutic doses and administered orally, were associated with reduced locomotor activity in animals (Kuczenski and Segal, 2002) as in neurotypical humans (Rapoport and Inoff-Germain, 2002). Further, lower doses mainly modulate PFC catecholamine levels, and especially those of NE (Berridge et al., 2006). In line with these findings, stimulant beneficial effects have also been observed in DAT knock-out mice, further supporting the role of the NE system in mediating treatment response (Rahi and Kumar, 2021). In sum, animal studies have revealed that stimulants mainly affect DA in the striatum and NE/DA in the PFC, in line with their distinct transporter density (Hannestad et al., 2010, Madras et al., 2005, Rahi and Kumar, 2021).

By acting on the catecholamine transporters, stimulants increase the endogenous DA stimulation of D1-receptors, and the NE-dependent activation of post-synaptic α 2A-receptors (Arnsten and Dudley, 2005, Gamo et al., 2010). As discussed above, an optimal stimulation of these receptors enhances PFC function, by respectively reducing ‘noise’ and enhancing ‘signal’ within glutamatergic circuits (Arnsten, 2006, Arnsten, 2009, Arnsten and Rubia, 2012). However, PET studies in humans suggest that the ultimate effect of stimulant treatment is more complex than a simple increase in catecholaminergic transmission (Swanson et al., 1999, Volkow et al., 1999), and likely involve the optimization of the balance between tonic and phasic catecholamine release (Grace, 1995). Catecholaminergic modulation may in turn support the engagement of task-related brain networks, such as the dorsal frontoparietal attentive network, and reduce (i.e., focus) attentional resources that are needed to ensure cognitive performance (Volkow et al., 2008). It might also reduce the activation of the DMN, which connects medial brain

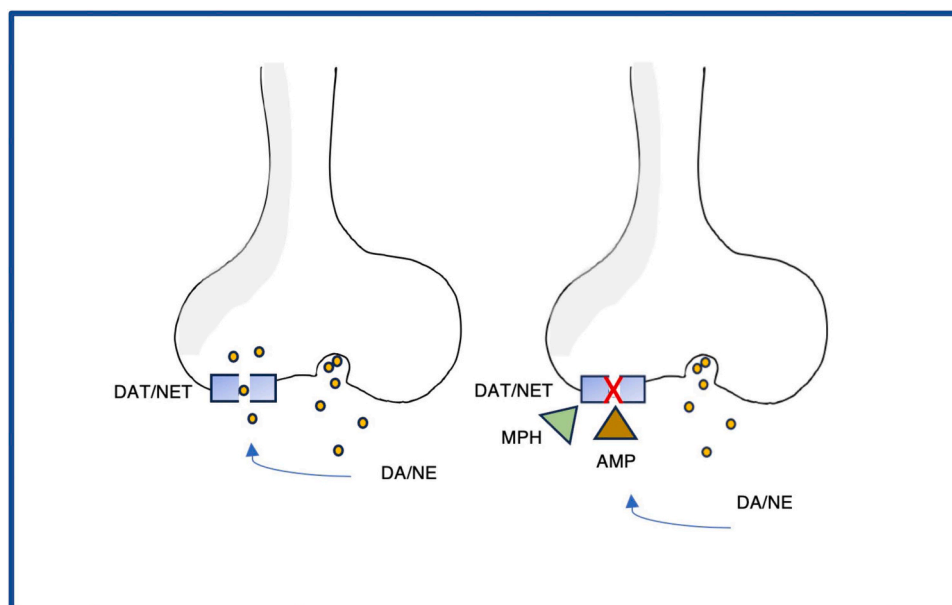


Fig. 2. Mechanism of action of stimulants at synaptic level. The function of dopamine (DA) and norepinephrine (NE) transporters (DAT and NET) is to reuptake DA and NE after they have been released in the synaptic cleft (left panel). Methylphenidate (MPH) acts by blocking both DAT and NET through allosteric binding (i.e. it binds them on a different site from that of the endogenous neurotransmitter). Conversely, amphetamines (AMP) block DAT and NET by binding on the same site of the endogenous neurotransmitter, thus acting as a competitive inhibitor. As a result, they both inhibit catecholamines reuptake and increase their availability in the synaptic cleft. However, at high doses, AMPs also induce more complex changes within catecholaminergic neurons (see main text)(right panel).

areas and is associated with mind wandering, and thus decrease distractibility (Tomasi et al., 2009, Volkow et al., 2008). Finally, catecholamine modulation may increase the perception of events as salient. This in turn improves attention and performance, as revealed by studies using academic tasks and appetitive stimuli (Volkow et al., 2002, Volkow et al., 2004). Stimulant-induced catecholaminergic increases in both cortical regions (e.g., fronto-temporal) and subcortical structures (e.g., ventral striatum) have been associated with long-term symptomatic improvement in adults with ADHD (Volkow et al., 2012). However, MPH induced a comparable increase in striatal DA levels in individuals with/without ADHD and improved attention irrespective of diagnosis (del Campo et al., 2013). Notably, the effect of stimulant treatment appeared to depend on both the degree of transporter blockade and on the baseline rate of DA release (Volkow et al., 2001). This has been noted to be reduced in individuals with ADHD (Forssberg et al., 2006, Volkow et al., 2001, Volkow et al., 2007a), although this was not confirmed by all studies (Cherkasova et al., 2014). Further, higher baseline DAT availability has been associated with increase probability of responding to MPH in adults with ADHD (Krause et al., 2005, la Fougere et al., 2006). Treatment effects appear to be task-dependent, as DA release is higher during a rewarded task than during a neutral one (Volkow et al., 2005) and distinct tasks have different dose–response associations (Arnsten and Rubia, 2012). In sum, as described in a comprehensive systematic review of preclinical and imaging studies in humans (not specifically with ADHD), MPH and amphetamines increase catecholaminergic availability in cortico-striatal regions that are altered in ADHD, and positively affect executive functions, decision making, emotion and reward processing (Faraone, 2018). There is substantial evidence that stimulants increase endogenous catecholaminergic transmission in proportion to transporter blockade and basal DA levels. However, the final effect depends on the task at hand and its saliency. Further, the basal activity of catecholaminergic neurons and the U-shaped relationship between neurotransmission and cognitive performance may account for individual variability in response to treatment (Swanson et al., 2011, Volkow et al., 2005, Zimmer, 2017).

Neuropharmacological studies using PET and SPECT in ADHD have been dependent on the development of radioligands, thus they have primarily focused on dopaminergic transmission (Yamamoto and Inada, 2023). Their use has also been limited due to the risks concerning exposure to ionizing radiations. As a result, most studies included a small sample and were in adults. Nevertheless, there is some recent evidence of similar effects in adolescents. For instance, a recent SPECT study comparing striatal DAT binding on/off MPH reported that treatment was associated with a ~30 % reduction of DAT binding potential, especially in those with higher baseline symptom severity (Aster et al., 2022). Further, another SPECT study showed that decreased DAT availability was observed after two months of MPH treatment in the basal ganglia, especially in adolescents with more robust clinical response (Akay et al., 2018). In sum, PET/SPECT studies have been pivotal to clarify the effects of stimulants on catecholaminergic neurotransmission.

Nevertheless, there is increasing evidence that other neurotransmitter systems are involved in their mechanisms of action. Considering serotonin, as reviewed in Banerjee et al. (2015), preclinical studies have suggested that MPH also acts as an agonist to the 5-HT_{1A} receptor and has low affinity for SERT, thus might balance serotonergic and dopaminergic signaling (Banerjee and Nandagopal, 2015, Gatley et al., 1996, Markowitz et al., 2009). Studies in rats have shown that MPH administration leads to increased SERT density (Daniali et al., 2013), whilst a 5-HT_{1B} agonist potentiates MPH effects on activity levels (Borycz et al., 2008). Further, MPH can reduce hyperactivity levels in DAT knock-out mice without affecting DA levels (thus may act through NET or SERT) (Gainetdinov et al., 1999). However, other studies have suggested that the activity on SERT is more typical of amphetamines (Quintero et al., 2022). Pharmacogenetic studies in humans corroborated serotonergic involvement, by highlighting that variants of the

SERT promoter region were associated with varying degree of response to MPH in children - but not in adults (Banerjee and Nandagopal, 2015, Contini et al., 2012, Thakur et al., 2010). Further, stimulants have been shown to increase GABA levels in animal models; however, a more recent study in humans has shown that MPH effects may be age-dependent (Ferranti et al., 2024). In fact, an MPH challenge increased GABA levels in the medial prefrontal cortex only in adult participants treated since childhood, which had lower levels of GABA compared to those treated in adulthood only (Solleveld et al., 2017). Considering glutamatergic neurotransmission, animal studies have suggested that low and high doses of MPH respectively enhance and reduce NMDA receptor response, possibly through $\alpha 1$ receptor stimulation (Cheng et al., 2014, Zhang et al., 2012). Pharmacogenetic studies in humans have reported that genetic variants of the *GRIN2B* gene, encoding for an NMDA subunit, and the *SNAP-25* gene, linked to NMDA receptor trafficking, were associated with better response to MPH in children (Kim et al., 2017, Song et al., 2014). Overall, these findings indicate that stimulants may affect several neurotransmitter systems, although they may partly differ in their effects (Quintero et al., 2022). For instance, studies *in vitro* have shown that amphetamines may also affect monoaminergic neurotransmission through inhibition of the synaptic vesicular amine transporter (VMAT2) and a weak inhibition of the monoaminoxidase (MAO), rather than 5-HT_{1A} stimulation (Hutson et al., 2014). Further, they can stimulate the trace amine-associated receptor 1 (TAAR1), which is highly expressed in monoaminergic brain regions and may contribute to modulation of activity and motivated behavior (Sotnikova et al., 2009). These differences may contribute to individual variation in the response to MPH and amphetamines, as well as the beneficial effects of medications such as lisdexamfetamine in binge eating disorder (Guerdjikova et al., 2016).

Beyond neurotransmitter systems, stimulants have been shown to modulate neurotrophic factors, such as BDNF (Quintero et al., 2022). For instance, as reviewed in Tsai et al. (2017), MPH increases BDNF expression and alleviates hyperactivity in the spontaneously hypertensive rats, a model of ADHD (Kim et al., 2011b). However, other studies reported that MPH and amphetamines both increased and decreased BDNF brain levels and suggested reduced or opposite findings in adult as compared to juvenile animals (Banerjee et al., 2009, Tsai, 2017). Pharmacogenetic studies in children with ADHD highlighted that *BDNF* and *neurotrophin-3* gene variants were associated with better response to MPH or side effects respectively (Kim et al., 2011a, Park et al., 2014). Further, MPH-related increased blood BDNF levels were associated with improvement in hyperactive-impulsive symptoms in children with ADHD (Amiri et al., 2013, Tsai, 2017). Finally, there is preliminary evidence that stimulants may indirectly affect other cellular processes, such as genetic transcription, apoptosis, and release of proinflammatory cytokines (Quintero et al., 2022). Of note, a recent systematic review of neuroimaging studies reported that two out of the three identified studies found that stimulants increased brain iron levels in children with ADHD. However, the underlying mechanisms remains unclear (Morandini et al., 2024).

In sum, multiple molecular and cellular mechanisms may contribute to stimulant mechanisms of action. However, it is less clear how these changes at microscopic level translate into beneficial clinical effects. MRI represents a powerful tool to address this gap by investigating stimulant effects on the brain at a macroscopic level. Importantly, as they do not involve ionizing radiation, they have become the main instrument to investigate stimulant mechanism of action in children and adults with ADHD in recent years.

6. Stimulant effects on brain regional structure and function

MRI studies have suggested that stimulants may reduce some of the structural and functional brain alterations observed in untreated individuals with ADHD (Albajara Saenz et al., 2019, Firouzabadi et al., 2022, Frodl and Skokauskas, 2012, Nakao et al., 2011, Pereira-Sanchez

et al., 2021, Santos et al., 2019).

Structural MRI studies using a cross-sectional design suggested that stimulant treatment is associated with attenuation or absence of some gray matter volumetric reductions often observed in untreated children with ADHD, e.g. in the ACC (Semrud-Clikeman et al., 2006), middle frontal and precentral gyri (Villemonteix et al., 2015), pulvinar of the thalamus (Ivanov et al., 2010), posterior inferior vermis and executive/non-motor portions of the cerebellum (Bledsoe et al., 2009, Fernandez et al., 2023), splenium of the corpus callosum (Schnoebelen et al., 2010), or whole gray matter volume (Priya 2023). Several studies reported no differences in overall caudate volume (Castellanos et al., 2002, Semrud-Clikeman et al., 2006, Sobel et al., 2010). However, fewer basal ganglia morphological alterations were observed in medicated as compared to unmedicated children (Sobel et al., 2010). Similarly, a positive association was reported between the duration of stimulant treatment and the volume of the left nucleus accumbens (Villemonteix et al., 2015). Volumetric differences between treated and treatment-naïve individuals have also been detected in adults with ADHD (Onnink et al., 2014, Seidman et al., 2011), although not in all studies (Maier et al., 2015). A treatment-related attenuation of gray matter volumetric alterations was further supported by two meta-analyses (Frodl and Skokauskas, 2012, Nakao et al., 2011). The former conducted a meta-regression analysis on a pool of 14 voxel-based morphometry (VBM) studies in children and adults with ADHD and reported that the percentage of individuals on stimulants was associated with larger (thus more similar to controls) volumes of the right caudate (Nakao et al., 2011). Similarly, the latter reported more prominent volumetric reduction in the ACC (children and adults) and in the caudate (children) in studies with more untreated individuals (Frodl and Skokauskas, 2012). Only few longitudinal studies have explored this further. A small longitudinal volumetric study in adults suggested that medication-induced volumetric changes in the ventral striatum might be transient (Hoekzema et al., 2014). However, a small longitudinal study in a pediatric sample reported that 4 years' stimulant treatment was associated with a lower rate of cortical thinning, and thus with cortical thickness more similar to controls in frontal and parieto-occipital regions, compared to untreated individuals (Shaw et al., 2009). Gray matter changes, either transient or persistent, have been suggested to reflect an activity-induced neuronal plasticity, since catecholaminergic transmission may affect neuronal morphology (Robinson and Kolb, 2004, Schweren et al., 2013). Nevertheless, more recent studies do not appear to support this treatment-related effect (Greven et al., 2015). For instance, two large multi-center studies reported no effect of current stimulant treatment on ADHD versus controls differences in total intracranial and subcortical structures volumes, as well as in cortical thickness (Hoogman et al., 2017, Hoogman et al., 2019). However, those on medication had lower surface area in two frontal regions as compared to those not on medication (Hoogman et al., 2019). In sum, the potential long-term effects of stimulant treatment on brain anatomy remain controversial. Moving forward, it would help to account for the potential effect of treatment duration, as well as the pre-treatment differences between responders and non-responders to treatment. In fact, it has been suggested that the proposed 'normalizing' effect of treatment with time may partly depend on a selection bias, as those that respond to (and thus continue) stimulants have less evident pre-treatment brain alterations (Parlatini et al., 2024a).

fMRI studies reported that an acute administration of stimulants upregulate the under-activation observed at baseline in key regions involved in cognitive functions implicated in ADHD, such as in fronto-parietal, subcortical, and cerebellar regions during attentive tasks (Kowalczyk et al., 2019, Rubia et al., 2009, Shafritz et al., 2004, Shang et al., 2016); in fronto-striatal areas during inhibition (Chou et al., 2015, Cubillo et al., 2014b, Epstein et al., 2007, Rubia et al., 2014, Rubia et al., 2011, Schulz et al., 2017, Shang et al., 2022, Vaidya et al., 1998); and in frontal and subcortical (caudate, putamen) areas involved in reward processing (Newcorn et al., 2024). More conflicting results, however,

have been reported for working memory - with some studies reporting no effect of medication on the brain regions involved in this function (Cubillo et al., 2014a, Kobel et al., 2009, Rubia et al., 2014). Notably, stimulants also improve suppression of regions belonging to the DMN, such as the ACC, during working memory tasks (Cubillo et al., 2014a) and interference inhibition (Peterson et al., 2009). Beyond executive functions, treatment effects on brain activation have been observed during reward processing, with an attenuation of the baseline increased orbitofrontal activation (Rubia et al., 2009); and during time estimation tasks, with the upregulation of the underlying fronto-striato-cerebellar network (Noreika et al., 2013, Smith et al., 2013). A meta-analysis including 14 whole brain fMRI studies reported that treatment-enhanced activation of the right inferior frontal cortex and insula was the most consistent finding across a range of cognitive functions. In addition, a 'normalization' of putamen activity was observed (although at a less restrictive significance threshold) (Rubia et al., 2014). Taken together, these studies suggest that stimulants modulate brain activity levels in individuals with ADHD towards those of their neurotypical peers (Schweren et al., 2013, Spencer et al., 2013). Importantly, there is preliminary evidence that early rather than late treatment may be associated with more evident beneficial effects on brain activity in youths with ADHD (Schweren et al., 2017).

Conversely, the few studies that investigated the effect of chronic treatment with MPH reported scarce, inconclusive, or no evidence of improvement on brain function after wash-out (Kobel et al., 2009, Konrad et al., 2007, Pliszka et al., 2006). Thus, stimulant treatment might not translate into long-lasting changes of brain activity (Schweren et al., 2013). However, two studies have shown that adults with ADHD treated with MPH during childhood did not show the pattern of altered activation observed in treatment-naïve individuals compared to neurotypical controls during reward and emotional processing (Schlochtermeyer et al., 2011, Stoy et al., 2011). This finding was in line with that of two meta-regressions conducted in a mixed pediatric-adult sample, which showed that prolonged stimulant treatment was significantly associated with a pattern of activation similar to controls in the right DLPFC during timing tasks (Hart et al., 2012) and in the right caudate during attention tasks (Hart et al., 2013). The effect on striatal activation was remarkably similar to that observed for striatal volumes in two meta-analyses of structural MRI studies (Frodl and Skokauskas, 2012, Nakao et al., 2011). Taken together, fMRI studies suggest that an acute stimulant administration may improve the function of brain areas affected in individuals with ADHD. However, potential longer-term effects need further investigation. Further, as reviewed in the following section, brain regions do not operate in isolation, but are part of circuits whose 'connectivity' is crucial to cognitive functions.

7. Stimulant effects on brain structural and functional connectivity

MRI studies have revealed that the effects of stimulants extend to brain anatomical and functional connections, especially in fronto-striato-parieto-cerebellar circuits (Bouziane et al., 2019, de Luis-Garcia et al., 2015, Kowalczyk et al., 2022, Pereira-Sanchez et al., 2021). An early structural MRI study showed that total white matter volume was reduced in unmedicated ADHD children compared to both medicated and neurotypical individuals (Castellanos et al., 2002). Since then, the study of anatomical (white matter) connectivity in ADHD has grown, thanks to the increasing use of diffusion-weighted imaging (DWI). The most recent systematic review of DWI studies in ADHD included 129 studies, however, they mostly focused on ADHD versus controls comparisons (Parlatini et al., 2023a). Among the included studies, only two investigated the potential effect of treatment in children with ADHD. The first, a tractography study, found no differences in fractional anisotropy (FA), a measure of white matter microstructural organization, between treated and untreated children with ADHD. However, the former had a reduced mean diffusivity (MD) in the inferior

longitudinal fasciculus, uncinate fasciculus, and posterior corpus callosum (de Luis-Garcia et al., 2015). The second study reported no significant differences in asymmetry of brain networks between treated and medication-naïve children but greater interhemispheric asymmetry of the uncinate fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and cortico-spinal tract in those treated compared to controls (Douglas et al., 2018). Of note, the meta-regression analysis testing the effect of previous exposure to stimulant medication, did not yield significant results (Parlatini et al., 2023a). Another study including 172 children and young adults (mean age: 17 years), showed that higher cumulative stimulant intake was associated with lower MD, but no differences in FA, in orbitofrontal-striatal white matter (Schworen et al., 2016). Further, a study suggested an age-dependent effect, since an increase in FA was observed after 16 weeks of MPH treatment in several association tracts of the left hemisphere and lateral aspect of the body of the corpus callosum in boys (but not men) with ADHD (Bouziane et al., 2019). Although preliminary, these findings suggest that protracted stimulant use might be associated with microscopic changes in white matter brain connections, although longitudinal studies controlling for treatment parameters are needed.

A few studies have investigated stimulant effects on functional connectivity in ADHD youths. A recent systematic review identified 8 task-based studies investigating the impact of stimulants in ADHD (among which only two were in adults) (Kowalczyk et al., 2022). These studies showed that stimulants significantly improved fronto-striatal and fronto-cerebellar connectivity in children with ADHD during vigilant and sustained attention (Rubia et al., 2009), as well as fronto-parietal and fronto-striatal connectivity during working memory (Abi-Dargham and Horga, 2016, Wong and Stevens, 2012, Wu et al., 2017). The observed changes in brain functional connectivity might represent the mechanisms underlying the beneficial effects of stimulants on task performance. Beyond 'cold' executive functions, stimulants might also affect emotion processing, as they have been reported to reduce the increased functional connectivity between the amygdala and the lateral PFC observed in ADHD adolescents during the subliminal presentation of fearful faces (Posner et al., 2011). A later study showed that lisdexamfetamine increased the activation of the right amygdala and reduced its connectivity with the orbitofrontal cortex in response to sad faces in adults with ADHD. Changes in amygdala activation were associated with symptom improvement (Schulz et al., 2018). MPH may also reduce functional fronto-striatal connectivity during reward processing in adults with ADHD (Furukawa et al., 2020). Further, treatment has been shown to optimize suppression of the DMN network during cognitive tasks, such as the Stroop and the flanker test, and to decrease the associated response time variability typical of individuals with ADHD (Peterson et al., 2009, Querne et al., 2014). These findings are in line with those of a recent systematic review of 12 studies investigating treatment-related changes on the DMN using different techniques in children or adults with ADHD. The most consistent result was an increased deactivation of the DMN during tasks (Santos et al., 2019). However, this was not confirmed by all studies. For instance, a study including 20 adults with ADHD on and off MPH and 27 controls showed that MPH shifted within-network connectivity of the DMN, but not between-network connectivity, during a reward based decision-making task (Mowinckel et al., 2017). Taken together, these findings suggest that acute treatment may produce functional changes within task-related brain networks and/or reduce DMN-mediated interference, perhaps especially during 'cool' executive function tasks.

In recent years, there has been a greater emphasis on functional connectivity at rest. Resting-state functional connectivity (rs-fc) is based on the observation that brain networks functionally activated at rest correspond to those activated during cognitive and motor tasks (Smith et al., 2009). Thus, rs-fc MRI offers the opportunity to investigate functional networks in a task-independent manner and at a whole brain level. A recent systematic-review identified only 9 studies (5 in children and 4 in adults) investigating effects of ADHD medications on rs-fc, and

they were mostly in small samples and greatly differed in study design and analytic approach (Pereira-Sanchez et al., 2021). For instance, most included individuals already on medication, after a short wash-out period, and only two investigated the effects of an acute challenge of MPH on rs-fc in children/adolescents. The former reported that a single dose of MPH 'normalized' case-control differences in fronto-cerebellar-parietal regional homogeneity (a measure of local functional connectivity), and that the treatment-induced change in parietal areas was associated with symptom improvement at two months in the 7 followed-up participants (An et al., 2013). The latter only included 16 adolescents and reported that a single dose of MPH 'normalized' rs-fc in several brain networks (Silk et al., 2017). Two more recent studies showed that MPH enhanced rs-fc in the reward network, including the nucleus accumbens, both in children and adults with ADHD (Mizuno et al., 2023, Rode et al., 2023). Increased rs-fc within the DMN has also been reported in both adolescents (Kim et al., 2021) and adults with ADHD (Picon et al., 2020). A more recent study showed that MPH-induced changes in latent brain dynamics and functional connectivity between the salience and DMN networks at rest were associated with behavioural improvement (Cai et al., 2023). Considering longer-term effects, a graph theory study reported that treated children with ADHD had increased connectivity between sensory and higher order brain regions subserving executive functions and attention as compared to untreated individuals (Carmona et al., 2015). This suggests that stimulants may support a more effective balance between internal and external sources of information. Studies in adults have been more limited. A recent study in 53 medication-naïve adults and 50 controls showed that 6-week MPH treatment increased functional connectivity between the precentral gyrus (salience network) and the precuneus towards that of neurotypical controls (Ulrich et al., 2022). Further, there is some preliminary evidence that the beneficial effects of amphetamines and MPH on symptom improvement are related to changes in fronto-limbic or fronto-cerebellar rs-fc (Yang et al., 2016) (Pretzsch, Parlatini et al., under review). Taken together, these findings suggest that stimulants may exert their effects through shifting functional connectivity within the affected networks in both children and adults with ADHD.

8. Conclusion

Nuclear medicine approaches have primarily documented the catecholaminergic dysregulation that underlies ADHD pathophysiology, and helped clarify the molecular targets of stimulants, their pharmacokinetics, and their effects on brain networks. They elucidated how stimulants fine tune catecholaminergic transmission, which in turn optimizes attention and executive control by engaging task-related brain networks and deactivating the DMN. However, their use has been limited by the available radioligands and concerns related to ionizing radiations, especially in children. MRI studies have been more widely used in recent years, especially in pediatric samples. They showed that an acute administration of stimulants may reduce or abolish brain regional or functional connectivity alterations observed in untreated individuals during tasks or at rest. However, potential longer-term effects of stimulant treatment remain unclear.

Overall, nuclear medicine and MRI studies have shed light on stimulant neuropharmacology. However, they are often limited by small and heterogeneous samples. This unfortunately does not allow them to robustly account for the effects of clinicodemographic characteristics, such as ADHD presentation, age, sex, and comorbidities, on treatment-related brain effects. Most anatomical studies have adopted a cross-sectional design, thus limiting our understanding of longer-term treatment effects. Longitudinal studies or meta-regression analyses often controlled for present versus absent previous exposure to stimulants, but did not have more fine grained available data on treatment characteristics (Hoogman et al., 2017, Hoogman et al., 2019, Parlatini et al., 2023a). Thus, although subtle differences have been reported in both

gray and white matter between treated and untreated individuals, follow-up studies are needed to disentangle potential effects of age, stimulant dose/duration, and variable response to treatment. Several functional studies investigated brain differences on/off medication after a variable period of treatment, thus may be confounded by previous exposure to stimulants and adaptive brain responses (Pereira-Sanchez et al., 2021). Another limitation is represented by the heterogeneity among analytic approaches, which limits comparisons among studies. For instance, a recent systematic review could not quantitatively combine the results of the 9 identified rs-fc studies investigating ADHD medication effects, due to their heterogeneity in study design, analytic approach, and parameters reported. Use of regions of interest and non-randomized designs were also identified as limitations. Therefore, it was not possible to conclude on a coherent mechanistic hypothesis of treatment effects (Pereira-Sanchez et al., 2021). Finally, most MRI studies focused on the effects of MPH or combined stimulants. However, MPH and amphetamines partly differ in their mechanism of action, and this may influence brain effects and treatment response (Faraone, 2018).

Moving forward, the development of ligands targeting cortical NET and the combination of PET-MRI techniques may enable a more comprehensive tracking of stimulant effects on neurotransmission and brain function. Similarly, the combination of imaging and gene expression analyses may help bridge the gap between macroscopic alterations and underlying molecular mechanisms. For instance, recent studies have shown that regions of altered rs-fc in children or cortical morphology in adults were respectively enriched for genes associated with GABAergic/serotonergic or noradrenergic neurotransmission (Chen et al., 2024, Parlatini et al., 2024a).

It would also be beneficial for MRI studies to clarify differences among stimulants and between these and other ADHD medications. For instance, there is preliminary evidence of shared and specific effects of MPH and atomoxetine (Fu et al., 2022, Kowalczyk et al., 2023, Schulz et al., 2017). Ultimately, this knowledge may help guide their use in specific ADHD subgroups (Faraone, 2018). Similarly, it would help to clarify dose and treatment duration effects, as well as age-related differences in brain mechanisms. Finally, we encourage future studies to investigate brain features associated with treatment response (Cao et al., 2023, Parlatini et al., 2024b, Parlatini et al., 2023c). To date, there is preliminary evidence of pre-treatment anatomical and functional brain characteristics associated with varying treatment response, including the anatomy of the basal ganglia and fronto-temporo-parieto-occipital regions (Chang et al., 2021, Moreno et al., 2014, Parlatini et al., 2024a); frontoparietal and cerebellar anatomical connectivity (Parkkinen et al., 2024, Parlatini et al., 2023c); and fronto-striatal, parietal and fronto-cerebellar rs-fc (An et al., 2013, Hong et al., 2015) (Pretzsch, Parlatini et al., under review). Ultimately, this knowledge may help clarify the biological basis of treatment resistance and potentially assess the probability of good treatment response ahead of starting treatment.

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Data Availability

No data was used for the research described in the article.

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