Paradoxical Effects of Caffeine in Individuals with ADHD: Arousal, Catecholamines, and Network Control

Michelle Y. Coppes

S3712591

Behavioural and Cognitive Neuroscience

C-Track: Cognitive Neuroscience & Cognitive Modelling

Faculty of Science and Engineering

Supervisor: Prof. dr. R. (Robbert) Havekes

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Abstract

This essay investigates the paradoxical effects of caffeine in individuals with ADHD, noting that it can enhance attention in some cases while inducing overstimulation, impaired control, or subjective calmness in others. These outcomes are best explained by a state-dependent model in which caffeine's antagonism of adenosine receptors alters arousal and indirectly modulates dopamine and norepinephrine signalling. Given that ADHD is characterized by dysregulated catecholaminergic function, altered frontostriatal control circuitry, and unstable interactions between task-positive networks and the default mode network, caffeine may either normalize under-aroused control systems or elevate arousal beyond optimal levels. Evidence from human and animal studies indicates that caffeine's cognitive effects in ADHD are generally modest, inconsistent, and strongly influenced by moderators such as dose, baseline arousal, metabolism, receptor sensitivity, developmental timing, sex, and habitual use. Therefore, caffeine is not a reliable treatment for ADHD, although it may exert conditional and biologically variable effects.

Keywords: ADHD; caffeine; arousal regulation; catecholamines; executive function; default mode network; cognitive control; adenosine receptors

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1. Introduction

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychoactive substance globally and is frequently used to enhance alertness and cognitive performance (Nehlig et al., 1992; Nehlig, 2010). In neurotypical individuals, caffeine intake may improve vigilance, sustained attention, reaction time, and psychomotor speed. However, its effects on working memory and higher-order executive functions are more heterogeneous and dose-dependent (Einöther & Giesbrecht, 2013; Nehlig, 2010; Smith, 2002; Kløve & Petersen, 2025; Fredholm et al., 1999). These cognitive outcomes are primarily attributed to caffeine's antagonism of adenosine A1 and A2A receptors, which modulate arousal systems and indirectly affect catecholaminergic signaling, particularly dopamine and norepinephrine (Fredholm et al., 1999; Ferré, 2008; Ribeiro & Sebastião, 2010). Given that attention and executive control are strongly dependent on catecholamine-regulated frontostriatal and frontoparietal circuits, caffeine's neuromodulatory properties make it a valuable tool for investigating cognitive control mechanisms, especially in clinical populations.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by impairments in sustained attention, inhibitory control, working memory, and broader executive functions (Wilcutt et al., 2005). Neurobiological models consistently implicate dysregulation of frontostriatal control circuitry, including the dorsolateral prefrontal cortex, anterior cingulate cortex, and basal ganglia. These models also identify atypical interactions between large-scale networks that support externally directed task engagement and internally oriented thought (Bush, 2010; Castellanos & Proal, 2012). Reduced suppression of the default mode network (DMN) during task performance has been specifically associated with mind-wandering and attentional lapses in ADHD (Sonuga-Barke & Castellanos, 2007; Castellanos et al., 2008). At

the neurochemical level, both theoretical and empirical studies highlight dysregulated catecholamine transmission, which can disrupt signal-to-noise ratio and the stability of executive control (Arnsten, 2009; Volkow et al., 2009). Collectively, these findings indicate that the cognitive effects of caffeine in individuals with ADHD may differ from those observed in neurotypical populations.

The behavioural literature on caffeine use in individuals with ADHD presents mixed findings. Some studies report that low-to-moderate doses of caffeine yield modest improvements in attention and inhibitory control, while others find no significant effects or even adverse outcomes. In general, the effects of caffeine are smaller and less consistent than those of first-line stimulant medications (Leon, 2000; Ioannidis et al., 2014; Lara, 2010). In addition to objective task performance, subjective responses to caffeine are often counterintuitive; for example, some individuals with ADHD describe caffeine as calming or even sleep-inducing (Lara, 2010). These paradoxical responses raise an important question: how does caffeine's modulation of arousal and catecholamine signaling interact with ADHD-related network dysfunction to produce paradoxical cognitive effects?

This essay examines this question by first outlining the core neurochemical actions of caffeine on adenosine receptors and related arousal-associated neurotransmitter systems. It then summarizes ADHD-related disruptions in catecholamine-regulated control circuitry and network dynamics. Building on these foundations, the essay evaluates evidence from both human and animal studies and examines candidate mechanisms at the circuit and molecular levels. Finally, it considers potential moderators, such as caffeine metabolism, receptor sensitivity, transporter function, developmental timing, sex differences, and habitual use, that may influence whether caffeine produces cognitive benefits or impairments.

2. Caffeine Mechanisms: Arousal and Catecholamines

Caffeine exerts its central stimulant effects primarily by antagonizing adenosine A1 and A2A receptors (Fredholm et al., 1999; Ferré, 2008; Ribeiro & Sebastião, 2010). Adenosine acts as a homeostatic neuromodulator; its concentration increases with extended wakefulness and metabolic activity, thereby elevating sleep pressure and decreasing arousal (Basheer et al., 2004). Activation of adenosine receptors typically reduces neuronal excitability and limits neurotransmitter release, thereby restricting alertness and cognitive effort (Fredholm et al., 1999). By blocking A1 and A2A receptors, caffeine lifts this inhibitory effect and promotes a more wakeful, responsive neural state (Nehlig, 2010).

Adenosine regulates arousal, in part, by enhancing inhibition within the wake–sleep control systems. For instance, adenosine-related mechanisms promote GABAergic inhibition, which decreases neuronal firing in arousal-related regions such as the basal forebrain and hypothalamus (Basheer et al., 2004; Saper et al., 2001). Antagonism of adenosine receptors by caffeine reduces this inhibitory effect, thereby facilitating the activation of arousal networks. This neurobiological action corresponds with caffeine's most robust cognitive outcomes: improved vigilance, sustained attention, and faster reaction times, especially under conditions of reduced baseline alertness (Einöther & Giesbrecht, 2013; Nehlig, 2010; Smith, 2002).

While caffeine's primary mechanism involves adenosine receptor blockade, its cognitive effects are largely mediated by downstream modulation of catecholaminergic systems, particularly dopamine and norepinephrine (Nehlig et al., 1992; Nehlig, 2010). A critical pathway includes adenosine–dopamine receptor interactions within the striatum. A2A receptors, which are abundantly expressed in striatal circuits, can form functional complexes with dopamine D2 receptors (D2R). Activation of A2A receptors restricts D2R signaling, whereas A2A antagonism enhances dopaminergic effects (Ferré et al., 1997; Ferré, 2008). Through this mechanism, caffeine can indirectly increase dopaminergic transmission in neural

circuits involved in motivation, effort allocation, and response selection, thereby supporting sustained task engagement (Volkow et al., 2009). Additionally, caffeine is linked to elevated noradrenergic tone, which contributes to increased alertness and attentional stability (Nehlig et al., 1992; Nehlig, 2010).

Caffeine's effects vary according to dose and context. At standard consumption levels, adenosine receptor antagonism predominates. However, at higher doses, caffeine can also inhibit phosphodiesterase (PDE), leading to increased intracellular cyclic AMP (cAMP) and amplification of signaling pathways involved in neurotransmission and synaptic plasticity (Fredholm et al., 1999; Daly, 2007; Ribeiro & Sebastião, 2010). Caffeine may further activate physiological stress responses via the hypothalamic–pituitary–adrenal (HPA) axis, resulting in elevated cortisol and heightened arousal (Lovallo et al., 2005; Nehlig, 2010). These secondary mechanisms may underlie symptoms of overarousal, such as jitteriness and anxiety, which can impair cognitive control despite enhanced alertness (Smith, 2002).

Overall, caffeine modulates arousal primarily by blocking adenosine receptors and indirectly shaping dopamine- and norepinephrine-linked signaling (Fredholm et al., 1999; Ferré, 2008; Nehlig, 2010). These mechanisms are particularly relevant for understanding caffeine's variable cognitive outcomes in ADHD, where baseline arousal regulation and catecholamine-dependent control circuits may differ from neurotypical profiles (Arnsten, 2009; Volkow et al., 2009).

3. ADHD Mechanisms: Networks and Catecholamines

ADHD is characterized by impairments in sustained attention, inhibitory control, working memory, and executive functions (Wilcutt et al., 2005). At the neural systems level, these behavioral deficits are linked to dysregulation in frontostriatal and frontoparietal control circuits, which are essential for top-down regulation of attention and action (Bush, 2010; Castellanos & Proal, 2012). Functional neuroimaging studies often report atypical activation of

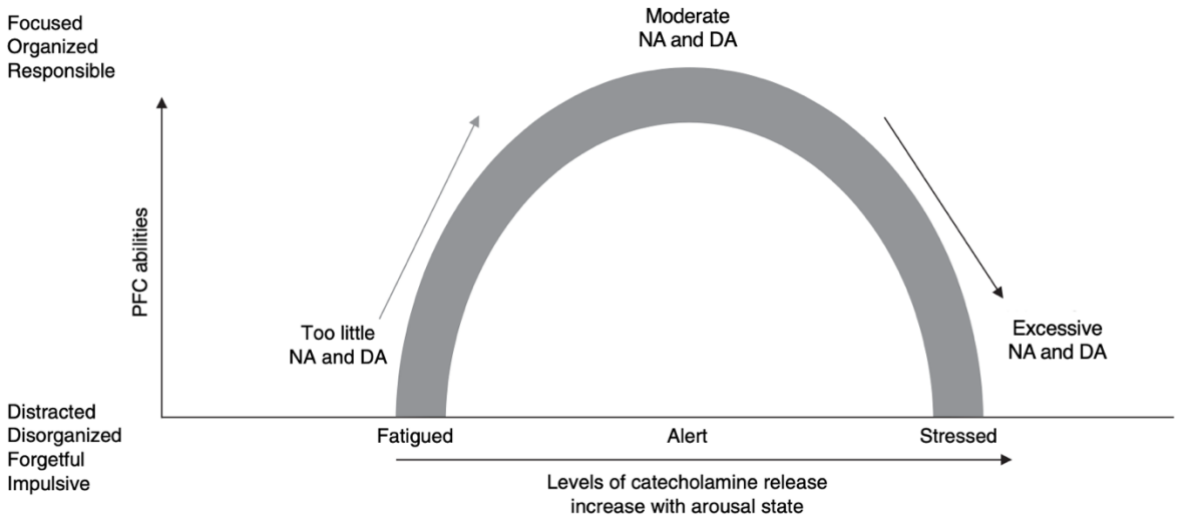
the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), as well as altered basal ganglia function, during tasks involving cognitive control, error monitoring, or response inhibition (Bush, 2010; Konrad & Eickhoff, 2010). These regions rely on neuromodulatory input, particularly dopamine and norepinephrine, for stable, goal-directed signaling. Consequently, ADHD-related circuit differences provide a mechanistic explanation for altered responsiveness to compounds that affect arousal and catecholaminergic tone, such as caffeine (Arnsten, 2009).

In addition to regional abnormalities, ADHD is increasingly understood as a disorder of large-scale network dynamics, particularly involving interactions between task-positive control networks and the default mode network (DMN) (Castellanos & Proal, 2012). The DMN is most active during internally oriented thought and is typically suppressed during externally focused cognitive tasks. In ADHD, reduced or unstable suppression of DMN activity during tasks is associated with mind-wandering and attentional lapses (Sonuga-Barke & Castellanos, 2007; Castellanos et al., 2008). This network perspective helps explain paradoxical responses to stimulants. If attentional difficulties result from competition between internally focused brain activity and control-network engagement, substances that change arousal and neuromodulatory tone might either stabilize task-related network activity or increase variability and distractibility, depending on a person's baseline state and the dose given.

Neurochemical models offer a complementary explanation for these circuit and network-level findings. Prominent theories highlight dysregulated catecholamine transmission, including reduced dopamine signaling in frontostriatal pathways and altered regulation of dopamine and norepinephrine in the prefrontal cortex (Arnsten, 2009; Volkow et al., 2009). Figure 1 illustrates that catecholaminergic influences on prefrontal cortex function exhibit a non-linear pattern. Insufficient catecholaminergic modulation reduces the signal-to-noise ratio and weakens the stability of prefrontal representations, while excessive neuromodulatory input

Figure 1

Non-linear effects of catecholaminergic arousal on prefrontal cortex function



Note. NA = noradrenaline; DA = dopamine. Adapted from Arnsten (2009).

also impairs executive control (Arnsten, 2009). Reductions in dopaminergic tone in ADHD are also associated with differences in motivational control and reward processing, which may contribute to increased performance variability and a tendency to seek stimulation or novelty (Volkow et al., 2009). These findings are directly relevant to caffeine, as caffeine indirectly modulates dopamine and norepinephrine via adenosine receptor antagonism (Fredholm et al., 1999; Ferré, 2008; Nehlig, 2010).

A significant overlap between ADHD neurobiology and caffeine pharmacology is found in the interactions between adenosine and dopamine within the striatum. In striatal circuits, adenosine A2A receptors counteract dopamine D2 receptor signaling, and caffeine's blockade of A2A receptors can enhance dopaminergic effects (Ferré et al., 1997; Ferré, 2008). Given that dopaminergic signaling is already altered in ADHD, the cognitive effects of this disinhibition are unlikely to follow a linear pattern. In certain individuals or contexts, caffeine may temporarily optimize catecholamine activity and improve attentional stability, while in others it may offer minimal benefit or contribute to overarousal and diminished executive control.

This variability aligns with evidence that ADHD is heterogeneous at both neurocognitive and neurobiological levels, with considerable differences in symptom expression and neural recruitment among individuals (Castellanos & Proal, 2012).

ADHD is frequently associated with atypical arousal regulation, often characterized by lower or more variable tonic alertness, which may manifest as sluggish attention, mind-wandering, or stimulation-seeking behaviors (Sonuga-Barke & Castellanos, 2007). From a network perspective, fluctuations in arousal can destabilize coupling between control networks and the DMN, increasing the likelihood of attentional lapses (Sonuga-Barke & Castellanos, 2007; Castellanos & Proal, 2012). Since caffeine can alter arousal state and catecholaminergic tone, its cognitive effects in ADHD likely depend on baseline arousal and the extent of control-network engagement at the time of intake (Arnsten, 2009; Smith, 2002). This mechanistic understanding underpins the central question of this essay: caffeine may not produce a uniform stimulant effect in ADHD but may instead interact with network-level dysfunction and catecholamine regulation to produce variable, and sometimes paradoxical, cognitive outcomes.

These circuit, network, and neurochemical characteristics associated with ADHD provide a foundation for a stage-dependent account of the effects of caffeine. Outcomes may depend on whether caffeine stabilizes control-network recruitment and reduces DMN interference, or alternatively, amplifies arousal and performance variability under specific conditions (Castellanos et al., 2008; Arnsten, 2009).

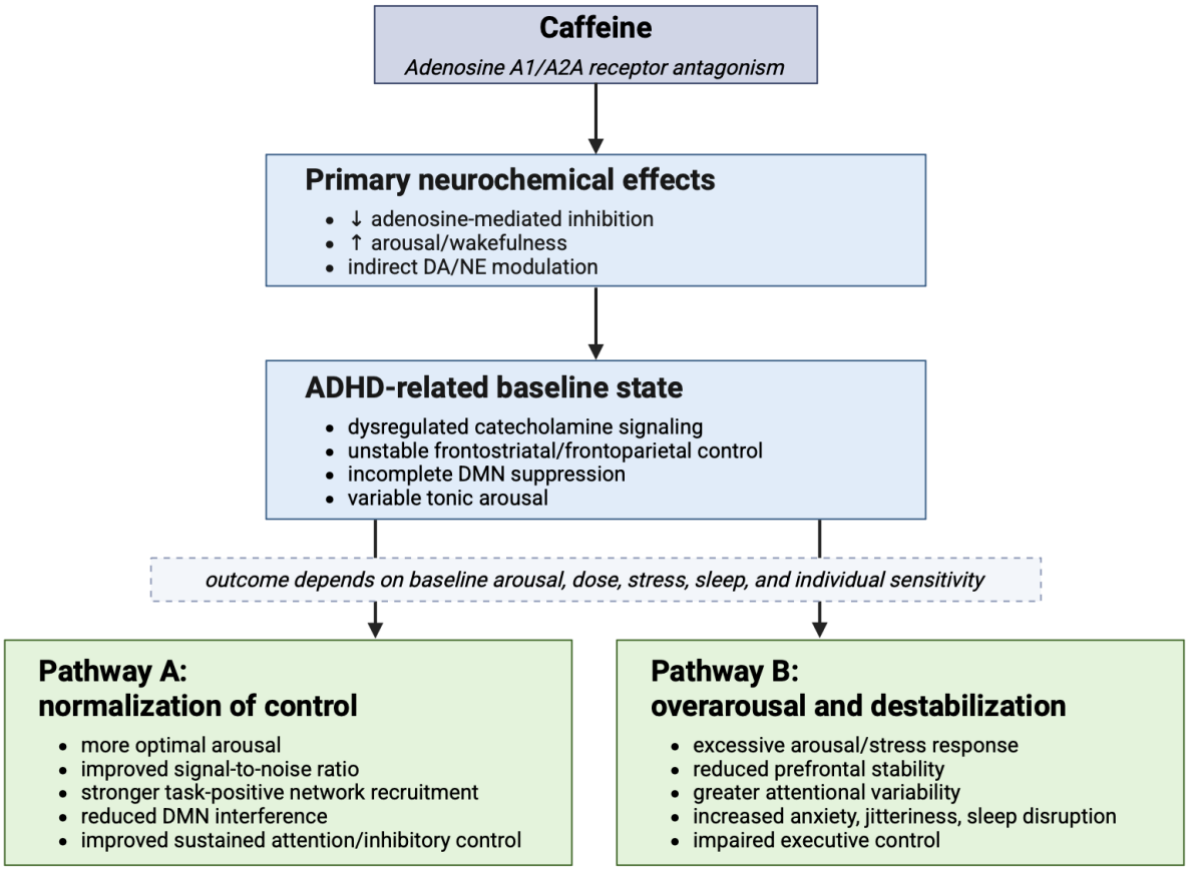
4. A State-Dependent Model of Paradoxical Caffeine Effects

The heterogeneous behavioral literature on caffeine in ADHD, which reports modest benefits in some studies, null effects in others, and occasional adverse outcomes, indicates that caffeine does not exert a uniform cognitive effect in this population (Leon, 2000; Ioannidis et al., 2014; Lara, 2010). One approach to reconciling these inconsistencies is to conceptualize caffeine's effects as state-dependent and non-linear. As illustrated in Figure 2, caffeine's

antagonism of adenosine receptors and the resulting modulation of catecholaminergic tone can shift individuals toward or away from an optimal range of arousal and control-network engagement, contingent upon baseline neurophysiology, contextual factors, and dosage (Smith, 2002; Arnsten, 2009). This perspective is consistent with established models in which catecholamine influences on prefrontal control follow non-linear dynamics, such that both insufficient and excessive neuromodulatory tone can impair executive function (Arnsten, 2009).

Figure 2

Proposed state-dependent model of caffeine effects in ADHD



Pathway A: Normalization of arousal and network control

One potential pathway is that caffeine normalizes under-engaged control systems by increasing arousal and indirectly facilitating dopamine and norepinephrine signaling (Fredholm et al., 1999; Ferré, 2008; Nehlig, 2010). In individuals with ADHD who exhibit low baseline

alertness or reduced catecholamine-driven stability in prefrontal control, caffeine may enhance the signal-to-noise ratio and promote more sustained recruitment of task-positive networks (Arnsten, 2009; Volkow et al., 2009). At the neural network level, improved control stability is expected to reduce interference from the DMN during externally oriented tasks, thereby decreasing mind-wandering and attentional lapses (Sonuga-Barke & Castellanos, 2007; Castellanos et al., 2008). Behaviorally, this pathway predicts the most pronounced improvements in sustained attention, reduced lapses, and potentially enhanced inhibitory control, particularly when baseline arousal is low (e.g., Leon, 2000; Smith, 2002).

This pathway may also account for subjective reports that caffeine produces a calming effect in some individuals with ADHD. If caffeine enhances the efficiency of top-down control and reduces internally generated noise, such as intrusive task-unrelated thoughts, the subjective experience may be characterized by increased cognitive quietness rather than stimulation. In certain cases, this reduction in perceived internal restlessness may make underlying fatigue more apparent, leading individuals to report feeling "sleepy" despite increased arousal-related neurotransmission.

Pathway B: Overarousal and destabilization of executive control

A second pathway involves caffeine pushing arousal beyond the optimal window, resulting in jitteriness, anxiety, or heightened distractibility that undermines executive control (Smith, 2002; Arnsten, 2009). Although adenosine antagonism promotes wakefulness at typical doses, higher intake or increased sensitivity can activate secondary mechanisms that elevate physiological stress responses, including activation of the hypothalamic–pituitary–adrenal (HPA) axis (Lovallo et al., 2005; Nehlig, 2010). Overarousal is particularly likely to impair functions that require stable prefrontal regulation, such as working memory maintenance and response inhibition, rather than simpler vigilance tasks (Smith, 2002; Arnsten, 2009). From a network perspective, excessive arousal in individuals with ADHD may increase variability in

attentional allocation and destabilize coordination between task-positive control networks and the DMN, resulting in inconsistent task engagement and greater performance variability (Sonuga-Barke & Castellanos, 2007; Castellanos et al., 2008).

A state-dependent framework suggests that "paradoxical" outcomes occur because caffeine's neuromodulatory effects interact with baseline state and individual neurobiology, rather than reflecting different pharmacology in ADHD. This perspective establishes clear boundary conditions: benefits are most likely at low to moderate doses and under low baseline arousal, whereas impairments are more probable at higher doses, under stress, or in biologically sensitive individuals (Smith, 2002; Arnsten, 2009). It also generates testable neural predictions: beneficial effects should correspond with more stable recruitment of control networks and reduced DMN interference, while counteractive effects should be linked to increased arousal-related variability and diminished executive stability (Castellanos et al., 2008; Castellanos & Proal, 2012). The following sections evaluate these predictions using evidence from human studies and mechanistic findings from animal models, before addressing moderators, such as metabolism and receptor or transporter differences, that may account for divergent responses to the same caffeine dose across individuals with ADHD.

5. Human Evidence: Cognitive and Behavioural Effects

Caffeine is not an approved treatment for ADHD; however, its stimulant-like properties and widespread use have prompted extensive research into its potential to modulate core cognitive domains affected by the disorder, including sustained attention, response inhibition, and executive functioning (Kløve & Petersen, 2025; Lara, 2010; Ioannidis et al., 2014). Across this body of literature, behavioural effects are generally modest and variable. When benefits are observed, they are typically smaller and less reliable than those produced by first-line psychostimulant medications (Leon, 2000; Ioannidis et al., 2014). This pattern aligns with the state-dependent framework described in Section 4, which posits that caffeine may enhance

cognition under specific baseline conditions and doses, but may yield null or adverse effects in other contexts (Smith, 2002; Arnsten, 2009).

Early experimental studies suggest that low-to-moderate doses of caffeine may produce measurable, although limited, improvements in ADHD-relevant behaviors. Leon (2000) found that caffeine could enhance certain aspects of attention and, in some cases, reduce hyperactivity in children with ADHD, with the most pronounced effects observed in sustained attention and response inhibition. However, these effects were inconsistent and generally weaker than those produced by stimulant medications, suggesting that caffeine is unlikely to serve as a replacement for established pharmacological treatments. Consistent with this, Ioannidis et al. (2014) reviewed caffeine-related outcomes in ADHD and reported modest improvements in attention and inhibitory control but emphasized considerable variability across studies and relatively small effect sizes compared to those of psychostimulants.

A significant challenge in interpreting the human literature is methodological heterogeneity, which complicates determining whether inconsistent outcomes reflect true neurobiological variability or differences in study design. Grimes et al. (2015) identified substantial variability in dosing strategies (approximately 3–10 mg/kg), administration formats (capsules versus beverages), participant age, and outcome measures. Many studies employ within-subject crossover designs, but differ in washout periods, baseline caffeine abstinence requirements, and the degree to which expectancy effects are controlled (Grimes et al., 2015; Ioannidis et al., 2014). Outcome assessments also vary considerably, ranging from behavioural observations and informant ratings to laboratory tasks measuring sustained attention, response inhibition, and reaction time. This methodological variability likely obscures state-dependent effects, especially when baseline arousal, habitual caffeine intake, sleep, or comorbid anxiety are not measured or controlled (Smith, 2002; Arnsten, 2009; Ioannidis et al., 2014).

Beyond controlled laboratory studies, real-world patterns of caffeine use further complicate the interpretation of caffeine as a cognitive aid in ADHD. Lara (2010) observed that caffeine's stimulant-like effects are most consistently found in domains related to vigilance and cognitive control, but emphasized that outcomes depend on dose, individual sensitivity, and contextual factors. In adults, large-scale observational studies have not established a clear association between daily caffeine intake and ADHD symptom severity. For instance, Ágoston et al. (2022) found no significant relationship between habitual caffeine consumption and symptom levels in a large adult sample. However, higher ADHD symptom severity was associated with caffeine use disorder, suggesting that caffeine may serve as a form of self-medication for some individuals rather than as a reliable cognitive enhancer.

Recent reviews emphasize that any beneficial effects of caffeine may be counterbalanced by adverse outcomes such as tolerance, withdrawal, sleep disruption, or anxiety, all of which can impair attention and executive functioning (Perrotte et al., 2023; Lara, 2010; Smith, 2002). According to the state-dependent perspective outlined in Section 4, these findings are not contradictory: caffeine may enhance performance by shifting an under-aroused state toward an optimal range but may impair performance if it induces overarousal or disrupts sleep and recovery. This suggests that paradoxical outcomes may arise not only between individuals but also within the same individual across different days, depending on factors such as fatigue, stress, and baseline arousal.

Overall, human research demonstrates that caffeine can produce small and inconsistent improvements in ADHD-relevant cognitive domains, particularly sustained attention and inhibitory control, although outcomes vary considerably across studies and individuals (Leon, 2000; Ioannidis et al., 2014; Grimes et al., 2015). These findings highlight the importance of shifting the focus from whether caffeine is effective in ADHD to identifying the conditions and individuals for whom its effects are beneficial or harmful. The following section expands on

this behavioural evidence by examining neural and network-level correlates that may differentiate normalization from overarousal pathways.

6. Neural Evidence: Network-Level Effects of Caffeine

The state-dependent framework described in Section 4 generates specific predictions at the neural-systems level. If caffeine enhances attention and executive control in ADHD through a normalization pathway, it should correspond with stronger and more sustained recruitment of task-positive control networks, as well as reduced interference from internally oriented activity. This would be reflected in more effective suppression or decoupling of the default mode network (DMN) during task performance (Sonuga-Barke & Castellanos, 2007; Castellanos et al., 2008; Castellanos & Proal, 2012). In contrast, if caffeine induces overarousal, neural signatures are expected to include less efficient network coordination, increased variability in task-related dynamics, and patterns indicative of heightened stress or arousal that compromise prefrontal performance (Smith, 2002; Arnsten, 2009).

While few neuroimaging studies have directly examined caffeine effects in ADHD populations, research in neurotypical samples offers mechanistic support for these predictions. Task-based fMRI studies demonstrate that caffeine can increase activation in frontal control regions under certain conditions. For example, Haller et al. (2013) found that acute caffeine administration was associated with changes in N-back working memory-related brain activation in older adults, including increased BOLD responses in prefrontal and anterior cingulate regions, which are central to cognitive control and error monitoring. These results are consistent with the normalization pathway, where caffeine facilitates more effective engagement of control networks when baseline activation is low or inefficient (Arnsten, 2009; Smith, 2002).

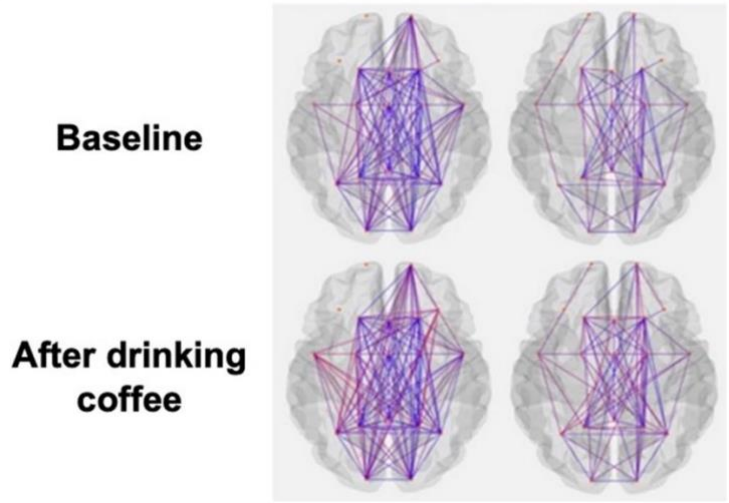
Electrophysiological evidence further indicates that caffeine can enhance cognitive processing speed and attentional allocation. In a simultaneous EEG-fMRI study, Diukova et al. (2012) observed caffeine-related changes in neural measures alongside modest behavioral

effects, including increased frontal BOLD responses during cognitive tasks and reduced P300 latency. These findings are consistent with faster stimulus evaluation and improved attentional processing. Notably, this multimodal approach is valuable because caffeine influences vascular physiology and can affect BOLD signals through both neurovascular and neural mechanisms (Diukova et al., 2012).

In addition to localized activations, caffeine appears to modify large-scale network organization. As illustrated in Figure 3, Kim et al. (2021) found that caffeine reorganized functional brain connectivity, particularly enhancing network efficiency in the delta and theta frequency bands. These changes were associated with improvements in working memory and executive performance. This is significant because theta-band dynamics are closely linked to

Figure 3

Changes in functional brain connectivity before and after coffee consumption



Note. Adapted from Kim et al. (2021).

attentional control and executive engagement, and shifts in network efficiency may contribute to reduced lapses or improved sustained attention and task focus (Kim et al., 2021; Sonuga-Barke & Castellanos, 2007). Further pharmacological evidence indicates that caffeine can modulate interactions between major task-related networks. Becker et al. (2022) demonstrated that caffeine altered functional connectivity between the frontoparietal network (FPN) and the

DMN, along with memory-related effects in healthy adults. These findings suggest that caffeine can influence the balance between task-positive engagement and internally oriented activity, a process often disrupted in ADHD (Castellanos et al., 2008).

Taken together, evidence from neurotypical samples supports the plausibility of both neural pathways: caffeine can facilitate frontal control engagement and accelerate attentional processing (Haller et al., 2013; Diukova et al., 2012), and it can shift large-scale connectivity toward more efficient or task-supportive configurations (Kim et al., 2021; Becker et al., 2022). However, these neuromodulatory actions may also result in overarousal or inefficiency depending on dosage or baseline state (Smith, 2002; Arnsten, 2009). Consequently, individual differences are critical. To account for paradoxical outcomes in ADHD, neural studies must consider moderators that influence whether caffeine stabilizes control-network recruitment and DMN suppression or increases variability and destabilizes executive control. The following section examines molecular and phenotypic moderators, such as metabolism, receptor and transporter function, developmental timing, and sex, which may determine the neural pathway expressed in each individual.

7. Moderators and Individual Differences

The state-dependent model described in Section 4 suggests that the behavioural and neural effects of caffeine in ADHD are influenced not only by dose and context but also by individual differences in pharmacokinetics and pharmacodynamics (Kapellou et al., 2023; Low et al., 2024). These factors may determine whether caffeine shifts neural function toward normalization (Pathway A) or leads to overarousal and instability (Pathway B) in individuals with ADHD. Such outcomes may result from alterations in baseline arousal, catecholaminergic tone, and the sensitivity of adenosine–dopamine interactions (Arnsten, 2009; Smith, 2002; Ferré et al., 2018).

A primary pharmacokinetic moderator is caffeine metabolism, which is largely governed by the CYP1A2 gene. CYP1A2 encodes the liver enzyme responsible for metabolizing most caffeine, and common genetic variants can classify individuals as relatively fast or slow metabolizers (Low et al., 2024). Slow metabolizers experience prolonged caffeine exposure, increasing the likelihood of sustained arousal and sleep disruption, particularly when caffeine is consumed later in the day (Nehlig, 2010; Kapellou et al., 2023; Low et al., 2024). In individuals with ADHD, where arousal regulation is often unstable, prolonged stimulation may heighten susceptibility to anxiety, irritability, or executive destabilization, whereas fast metabolizers may experience weaker or shorter-lived cognitive effects.

Pharmacodynamic moderators include adenosine receptor sensitivity and expression, particularly involving the A2A receptor (A2AR). A2ARs are densely expressed in striatal circuits and are functionally coupled to dopamine D2 receptors (D2R), making them a key node through which caffeine can alter dopaminergic signaling (Ferré et al., 2018). Given that ADHD involves differences in dopamine signaling and receptor regulation, blocking A2ARs with caffeine may produce variable effects across individuals. In some cases, A2AR antagonism may enhance motivational drive and attentional stability, while in others it may have minimal effects or increase variability in cognitive control (Ferré et al., 2018; Arnsten, 2009). Consistent with this, Kapellou et al. (2025) found that genetic variation linked to caffeine sensitivity, including adenosine-related pathways, moderated whether caffeine improved or impaired executive function.

Another significant moderator is dopamine transporter (DAT) function, which determines synaptic dopamine clearance and is a central target of stimulant medication. Genetic variation in the DAT gene (SLC6A3) has been associated with ADHD and with individual differences in dopaminergic signaling and treatment response (Roman et al., 2004; Faraone et al., 2013). Although caffeine does not directly block DAT, its modulation of adenosine-

dopamine interactions may produce different downstream effects depending on baseline transporter activity and dopamine availability. This mechanism may explain why caffeine enhances attention in some individuals but fails to improve, or even worsens, executive stability in others (Faraone et al., 2013; Ferré et al., 2018).

Sex and neuroplasticity-related factors may also moderate caffeine response. Evidence from a rat study using the spontaneously hypertensive rat (SHR) ADHD model demonstrated that chronic caffeine administration produced sex-dependent cognitive and behavioural effects (Nunes et al., 2018). These differences were associated with changes in BDNF and its receptor TrkB, both of which are critical for synaptic plasticity. While caution is warranted when translating these findings to humans, the results suggest a plausible pathway by which caffeine could influence cognition through neuroplasticity mechanisms, with outcomes that may vary by sex and developmental stage.

Several non-genetic, experiential factors are also likely to influence the cognitive effects of caffeine. Regular caffeine use, tolerance, withdrawal symptoms, and caffeine-related sleep disruption can independently affect attention and executive control, apart from any acute cognitive benefits caffeine may provide (Nehlig, 2010; Perrotte et al., 2023). Additionally, transient state factors such as fatigue, stress, and anxiety may modulate caffeine's effects over time, leading the same individual to experience beneficial effects in some contexts and overstimulation in others, thereby contributing to within-person variability in response (Smith, 2002; Arnsten, 2009).

Taken together, these factors support the central argument of this essay: the apparently contradictory effects of caffeine in ADHD are neither unusual nor surprising. Rather, they likely reflect interacting individual differences in caffeine metabolism, receptor-level sensitivity, and state-dependent arousal regulation (Ferré et al., 2018; Low et al., 2024). The following section examines evidence from animal models, which provide tighter experimental control over dose,

developmental timing, and neurobiological phenotype, and can help clarify the causal mechanisms underlying caffeine's effects in ADHD.

8. Animal Evidence: Mechanisms and Boundary Conditions

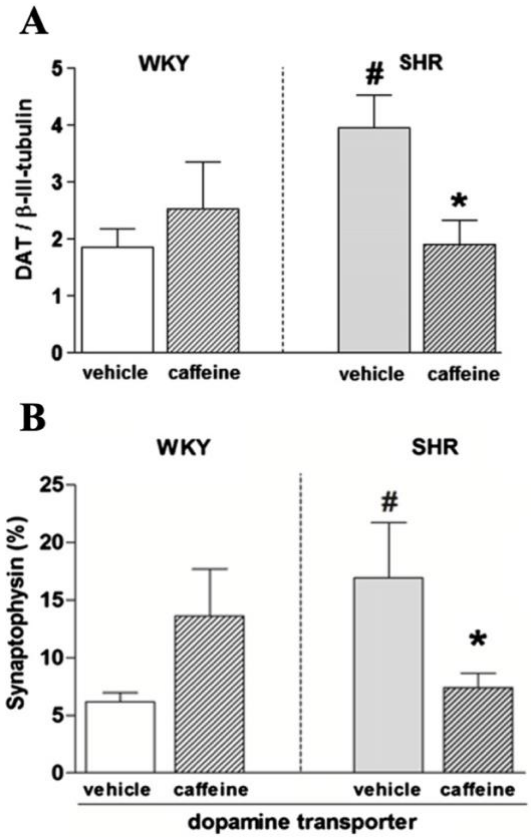
Animal models provide experimental control over variables such as dose, timing, and developmental stage, and enable direct measurement of neurochemical and molecular outcomes that are challenging to assess in humans. In ADHD research, the spontaneously hypertensive rat (SHR) is commonly employed due to its exhibition of ADHD-relevant phenotypes, including hyperactivity, impulsivity, attentional deficits, and altered dopaminergic function (Prediger et al., 2005; Vendruscolo et al., 2009; Wultz et al., 1990).

Dopaminergic and corticostriatal mechanisms represent a key area of evidence. As shown in Figure 4, Pandolfo et al. (2013) found chronic caffeine administration in adolescent SHRs reduced the elevated DAT density in the striatum and frontal cortex, which aligns with normalization of dopaminergic function. Since DAT regulates synaptic dopamine clearance, these findings suggest that caffeine modulates dopamine-related function in ADHD-like phenotypes and may enhance cognitive control. Additionally, França et al. (2018) found that adolescent caffeine treatment reduced hyperactivity and enhanced working memory in SHRs, further supporting the conclusion that caffeine can influence ADHD-like behavioral outcomes under specific neurodevelopmental conditions.

Developmental timing and phenotype serve as critical boundary conditions. Pires et al. (2010) found that chronic caffeine exposure during the prepubertal period led to lasting improvements in object recognition memory in adult SHRs, whereas the same treatment impaired memory performance in neurotypical Wistar rats. This contrast supports the hypothesis that caffeine's effects depend on the underlying neurodevelopmental state. In subjects with ADHD-like traits, caffeine may optimize brain function, while in neurotypical individuals, it may disrupt optimal functioning.

Figure 4

Effects of chronic caffeine administration on dopamine transporter measures in the striatum and frontal cortex of SHR rats



Note. Adapted from Pandolfo et al. (2013). (A) DAT protein in the striatum was quantified by Western blot and expressed relative to β-III-tubulin, which served as a reference protein. (B) In the frontal cortex, DAT was assessed by co-localization with synaptophysin, a presynaptic marker.

In addition to dopaminergic mechanisms, animal studies implicate inhibitory neurotransmission. Kubrusly et al. (2021) found that moderate caffeine exposure enhanced GABA transporter function in the striatum of SHRs, a region essential for inhibitory control and motor regulation. This effect depended on A1 receptor–cAMP–PKA signaling, which is functionally altered in SHRs, and pharmacological blockade of this pathway abolished caffeine's effect. In contrast, caffeine did not significantly alter GABA transport in Wistar rats.

These findings indicate that caffeine may normalize brain function in specific phenotypes rather than providing a general enhancement across all cases.

Overall, evidence from animal models supports the hypothesis that caffeine can improve ADHD-like behaviors through dopaminergic and inhibitory mechanisms, with clear boundary conditions related to phenotype and developmental timing (Pandolfo et al., 2013; Pires et al., 2010; Kubrusly et al., 2021). These findings reinforce the state-dependent hypothesis and underscore the importance of careful translation to heterogeneous human ADHD populations.

9. Caffeine and ADHD Stimulant Medication

The concurrent use of caffeine and ADHD medication presents clinically significant questions regarding whether their combined effects are additive, collaborative, or potentially adverse. This issue is particularly relevant given the widespread consumption of caffeine and its possible use alongside prescribed stimulants. Mechanistically, overlap is plausible: stimulant medications such as methylphenidate (MPH) increase synaptic dopamine and norepinephrine primarily by blocking their transporters, whereas caffeine antagonizes adenosine A1 and A2A receptors and indirectly modulates catecholaminergic signaling and arousal (Arnsten, 2009; Fredholm et al., 1999; Ferré, 2008). As both substances influence catecholamine-dependent control circuits, their combined use may shift individuals along the state-dependent axis toward normalization or, conversely, toward overarousal and executive instability if stimulation becomes excessive (Smith, 2002; Arnsten, 2009).

Preclinical evidence indicates that interaction effects are strongly influenced by baseline neurobiology. For example, as mentioned in Section 8, Pandolfo et al. (2013) demonstrated in spontaneously hypertensive rats (SHRs) that chronic caffeine administration improved attention and reduced hyperactivity, while also shifting DAT density in frontostriatal regions toward control levels. Co-administration with methylphenidate (MPH) resulted in greater behavioural improvement, suggesting potentially additive or synergistic effects in an ADHD-

like phenotype. This pattern supports a normalization model in which caffeine facilitates dopaminergic signaling through adenosine mechanisms, while MPH directly increases synaptic catecholamines via transporter blockade.

However, evidence also indicates that combined stimulation may be detrimental under certain conditions. In adult zebrafish, Freddo et al. (2022) found that low doses of caffeine or MPH alone produced modest cognitive benefits, whereas co-administration impaired cognition and increased oxidative stress markers. While cross-species generalization is limited, these findings highlight an important boundary: increased catecholaminergic stimulation does not always yield better outcomes and may induce neurochemical strain, consistent with overarousal dynamics (Smith, 2002; Arnsten, 2009).

Research on the combined use of caffeine and stimulant medications in humans remains limited, with most studies conducted in healthy individuals rather than those with ADHD. Brain imaging studies indicate that caffeine and stimulants may influence similar brain networks involved in attention. For instance, Becker et al. (2022) demonstrated that caffeine modulated functional connectivity between major cognitive networks, including the frontoparietal network (FPN) and default mode network (DMN), as well as memory-related effects in healthy adults. Given that ADHD is associated with differences in the engagement of attention-control networks and reduced suppression of the DMN during tasks (Castellanos et al., 2008; Castellanos & Proal, 2012), these findings imply that caffeine and stimulant medications may affect overlapping brain systems. However, this overlap does not necessarily translate to combined clinical efficacy or enhanced treatment benefits.

Pharmacokinetic factors further complicate the combined use of caffeine and stimulant medication. Some studies have identified potential pharmacokinetic interactions arising from interindividual differences in metabolism, such as variation in caffeine clearance due to CYP1A2 activity, which may prolong caffeine exposure. This can elevate the risk of side

effects, including insomnia, anxiety, or restlessness, when caffeine is used with stimulants (Low et al., 2024; Nehlig, 2010). Additionally, observational studies suggest that individuals with higher levels of ADHD symptoms may use caffeine for self-regulation, potentially increasing the risk of overuse and sleep disturbances (Ágoston et al., 2022; Perrotte et al., 2023).

In summary, current evidence indicates that interactions between caffeine and ADHD medication are influenced by individual characteristics and contextual factors. In certain ADHD-like conditions, caffeine may enhance the therapeutic effects of stimulant medication (Pandolfo et al., 2013). Conversely, concurrent use may increase physical stress or exacerbate sleep disturbances, thereby impairing attention (Freddo et al., 2022; Nehlig, 2010).

10. Discussion and Conclusions

Main interpretation

This essay analyzed how caffeine's modulation of arousal and catecholamine signaling interacts with ADHD-related network dysfunction, resulting in paradoxical cognitive effects. The evidence indicates that these outcomes are best conceptualized as state-dependent and non-linear. Caffeine may enhance attentional control when baseline arousal and catecholaminergic tone are low, but may also exceed the optimal arousal window, thereby increasing variability and impairing executive function when arousal is high or biological sensitivity is elevated (Smith, 2002; Arnsten, 2009). Therefore, individual differences are essential considerations for any mechanistic explanation of caffeine's cognitive effects in ADHD.

The mechanistic rationale for this claim is grounded in the overlap between the neurobiology of caffeine and ADHD. Caffeine's antagonism of A1 and A2A receptors reduces inhibitory constraints on arousal systems and indirectly modulates dopamine- and norepinephrine-mediated signaling (Fredholm et al., 1999; Ferré, 2008; Nehlig, 2010). ADHD involves altered catecholaminergic regulation of frontostriatal and frontoparietal control circuits, as well as atypical large-scale brain network dynamics, including reduced or unstable

suppression of the DMN during task performance (Arnsten, 2009; Castellanos et al., 2008; Castellanos & Proal, 2012). The critical interaction is not simply caffeine versus ADHD, but rather caffeine acting upon neural systems already dysregulated in ADHD. The same neuromodulatory shift may normalize control-network engagement in one context or baseline state (Pathway A) but destabilize performance and control in another (Pathway B).

Empirical evidence

Empirical findings from human behavior support this state-dependent account precisely because they are inconsistent. Controlled studies and reviews report small and variable effects of caffeine on ADHD-related functions such as sustained attention and inhibitory control, typically smaller than those of stimulant medication (Leon, 2000; Ioannidis et al., 2014). Methodological heterogeneity in dose, age, baseline caffeine use, outcome measures, and abstinence requirements likely masks conditional effects that depend on baseline arousal and individual susceptibility (Grimes et al., 2015). Neurotypical neuroimaging and electrophysiological studies provide mechanistic plausibility for the model's network predictions, including caffeine-related shifts in frontal engagement and connectivity patterns involving task-positive networks and the DMN (Haller et al., 2013; Diukova et al., 2012; Kim et al., 2021; Becker et al., 2022). Animal studies strengthen the causal interpretation: in SHRs, caffeine can improve ADHD-like behavior and alter dopamine- and inhibition-related mechanisms, while developmental timing and phenotype produce divergent outcomes (Pandolfo et al., 2013; Pires et al., 2010; Kubrusly et al., 2021). Taken together, these lines of evidence support the central argument that caffeine's "paradoxical" effects arise from interactions between its neuromodulatory actions and the brain's baseline state.

A broader perspective

These findings can be interpreted within the context of an emerging precision psychiatry framework. Rather than focusing solely on whether caffeine is generally beneficial or harmful

in ADHD, this approach emphasizes integrating symptomatic, biological, and behavioural information. Such integration seeks to move beyond symptom-based categories toward mechanism-informed, biologically grounded treatment models (Fernandes et al., 2017; Kas et al., 2025; Miller et al., 2025). Within this framework, the central question shifts from whether caffeine is effective in ADHD to identifying for which individuals, under what biological and contextual conditions, and through which mechanisms caffeine may improve or impair cognition.

From this perspective, the mixed findings reviewed may not solely reflect methodological variability but may also indicate meaningful inter-individual differences. Inconsistent caffeine effects are expected if ADHD is not a unitary neurobiological condition but rather a clinically shared phenotype arising from partially distinct underlying mechanisms (Fernandes et al., 2017; Kas et al., 2025). A precision psychiatry approach aligns with the state-dependent model proposed here, as caffeine response may depend on identifiable moderators such as baseline arousal, habitual caffeine use, sleep quality, stress, metabolic variation, receptor sensitivity, or broader neurocognitive profile.

A precision psychiatry approach shifts the focus away from average effects within broad diagnostic groups and toward stratification based on biologically relevant differences that may better predict response (Kas et al., 2025; Miller et al., 2025). Applied to ADHD, this framework raises an important question: could paradoxical responses to caffeine help identify subgroups defined by differences in arousal regulation, network control, or catecholaminergic sensitivity? Although current evidence remains limited, the proposed model suggests that this may be a productive direction for future ADHD research, particularly if subsequent studies combine behavioural data with biomarkers, sleep measures, and other indicators of biological state.

Limitations

However, this broader perspective does not negate the fact that the current evidence base remains limited. Several significant limitations restrict the strength of the conclusions presented. Direct neuroimaging studies investigating caffeine's effects in ADHD remain limited, so many claims regarding large-scale network mechanisms are inferential rather than empirically established in clinical populations. Human studies are also vulnerable to confounding factors such as tolerance, withdrawal, expectancy, sleep disruption, and comorbid anxiety, all of which can alter baseline arousal and influence the observed direction of caffeine's effects (Nehlig, 2010; Perrotte et al., 2023). Additionally, caffeine's impact on cerebral blood flow complicates the interpretation of BOLD signals, underscoring the importance of multimodal neuroimaging approaches (Diukova et al., 2012). Finally, while findings from spontaneously hypertensive rat (SHR) models offer mechanistic insight, their applicability to the heterogeneous presentation of human ADHD requires caution, particularly regarding developmental timing and long-term exposure (Pires et al., 2010).

Future research directions

Future research should more directly evaluate the state-dependent model by grouping participants based on baseline arousal and biological differences, rather than conceptualizing ADHD as a homogeneous condition. Effective study designs may include within-person comparisons that assess varying caffeine doses and systematically measure arousal-related factors such as sleep and stress alongside behavioral outcomes. Additionally, these studies could integrate brain-based measures, such as EEG or fMRI, with genetic data or indirect markers of caffeine metabolism and receptor sensitivity (Low et al., 2024; Kapellou et al., 2023).

Another priority is to determine whether variability in caffeine response can be used to identify more meaningful subgroups within ADHD. Accordingly, future studies should not only examine average symptom changes following caffeine administration but also assess whether

distinct response profiles are associated with differences in arousal regulation, sleep, network engagement, or other biologically relevant factors. This approach aligns with recent precision psychiatry frameworks that emphasize stratification, multimodal data integration, and mechanism-based treatment development (Kas et al., 2025; Miller et al., 2025).

Conclusion

In summary, caffeine's cognitive effects in ADHD are best understood as conditional and state-dependent, arising from interactions between arousal, catecholamine modulation, and underlying brain network dysfunction. In some contexts, caffeine may improve performance by stabilizing control processes, whereas in others it may worsen symptoms by increasing overarousal and performance variability (Arnsten, 2009; Smith, 2002). Clinically, current evidence does not support caffeine as a stand-alone treatment for ADHD. At most, caffeine may function as a mild adjunct under specific conditions, but it may also carry risks, particularly when combined with stimulant medication or when it disrupts sleep (Pandolfo et al., 2013; Freddo et al., 2022; Nehlig, 2010). The mixed findings reviewed in this essay therefore suggest that the caffeine response in ADHD is unlikely to be explained by a single, uniform mechanism and may instead reflect biologically meaningful heterogeneity between individuals.

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