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Overlapping and differential neuropharmacological mechanisms of stimulants and nonstimulants for attention-deficit/hyperactivity disorder: a comparative neuroimaging analysis

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Abstract

Background. Psychostimulants and nonstimulants have partially overlapping pharmacological targets on attention-deficit/hyperactivity disorder (ADHD), but whether their neuroimaging underpinnings differ is elusive. We aimed to identify overlapping and medication-specific brain functional mechanisms of psychostimulants and nonstimulants on ADHD.

Methods. After a systematic literature search and database construction, the imputed maps of separate and pooled neuropharmacological mechanisms were meta-analyzed by Seed-based *d* Mapping toolbox, followed by large-scale network analysis to uncover potential coactivation patterns and meta-regression analysis to examine the modulatory effects of age and sex.

Results. Twenty-eight whole-brain task-based functional MRI studies (396 cases in the medication group and 459 cases in the control group) were included. Possible normalization effects of stimulant and nonstimulant administration converged on increased activation patterns of the left supplementary motor area ($Z = 1.21$, $p < 0.0001$, central executive network). Stimulants, relative to nonstimulants, increased brain activations in the left amygdala ($Z = 1.30$, $p = 0.0006$), middle cingulate gyrus ($Z = 1.22$, $p = 0.0008$), and superior frontal gyrus ($Z = 1.27$, $p = 0.0006$), which are within the ventral attention network. Neurodevelopmental trajectories emerged in activation patterns of the right supplementary motor area and left amygdala, with the left amygdala also presenting a sex-related difference.

Conclusions. Convergence in the left supplementary motor area may delineate novel therapeutic targets for effective interventions, and distinct neural substrates could account for different therapeutic responses to stimulants and nonstimulants.

Introduction

As one of the most common neurodevelopmental disorders, attention-deficit/hyperactivity disorder (ADHD) is characterized by problems of inattention, impulsivity, and hyperactivity (Battle, 2013), which approximately affect 84.7 million individuals worldwide (Collaborators, 2020). Psychostimulants, such as methylphenidate, are widely prescribed to ameliorate ADHD symptoms, at least in improving attention span and reducing distractibility (Janssen et al., 2016). These medications work by increasing levels of specific neurotransmitters in the brain, especially dopamine and norepinephrine. For individuals who respond poorly to stimulants, nonstimulant alternatives may be considered, including norepinephrine modulators like atomoxetine and certain antidepressants such as bupropion. (Mechler, Banaschewski, Hohmann, & Häge, 2022). However, individualized management for ADHD cases in clinical settings is still hard to achieve due to the elusive neuropsychological mechanisms of first-line medications. At the same time, the factors of age and sex also complicate individual medication selection as they influence the effectiveness of medication treatment (Childress, Newcorn, & Cutler, 2019; Dafny & Yang, 2006; Wigal, Kollins, Childress, & Adeyi, 2010).

From a neurobiological perspective, psychostimulants exert their therapeutic effects as indirect catecholamine agonists by blocking the dopamine transporter (DAT) and norepinephrine transporter (NET), and atomoxetine, the most commonly used nonstimulant for ADHD treatment, is a selective NET inhibitor. Through their common neuropsychological actions

and partially overlapping pharmacological targets, both psychostimulants and nonstimulants may mitigate the dysfunctional inhibition and execution processing deficits seen in ADHD (Gilbert et al., 2006). Finding similarities of mechanisms between of stimulants and nonstimulants in clinical application may enhance the understanding of their biochemistry pathways and lead to the development of targeted medications. Functional magnetic resonance imaging (fMRI) studies have found that treatment with methylphenidate and atomoxetine produces clinical improvement for ADHD via both common and divergent neurophysiologic actions in frontoparietal regions. Given that youth with ADHD may have a preferential or atypical response to either stimulants or nonstimulants based on their dissociable therapeutic targets (Elliott et al., 2020; Schulz et al., 2012), it is reasonable that approximately 56% of ADHD cases may achieve clinical improvement with stimulants, while 45% of cases achieve so with non-stimulants (Mechler et al., 2022; Newcorn et al., 2008).

Regarding various treatment responses among individuals, investigation of their neuropharmacological bases that may facilitate the selection of preferential responders becomes indispensable (Newcorn et al., 2008). Neurobiological studies revealed that increased dopamine (DA) concentration in the prefrontal cortex was observed in individuals taking medications, whether stimulants or nonstimulants (Koda et al., 2010). Meanwhile, neuroimaging studies have reported inconsistent neuropsychological mechanisms by which stimulants or nonstimulants act to improve ADHD symptomology. Due to localized effects at DAT sites corresponding to the action of stimulants (Ciliax et al., 1999; Schou et al., 2005), abnormalities of the anterior cingulate cortex (ACC) and supplementary motor area (SMA) regions were normalized along with improved capacity of self-regulatory control (Baldaçara, Borgio, De Lacerda, & Jackowski, 2008; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Posner, Rothbart, Sheese, & Tang, 2007; Rubia et al., 2014; Stray, Ellertsen, & Stray, 2010), and the neuropharmacological effects were associated with increased activation in the brain executive control and attention networks (Farr et al., 2014; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004). In contrast, nonstimulants may improve the top-down guidance of attention, thought and working memory in those with ADHD via direct effects on NET in the prefrontal cortex (Borchert et al., 2019; Bymaster et al., 2002; Lin & Gau, 2015; Mechler et al., 2022; Morón, Brockington, Wise, Rocha, & Hope, 2002). Besides, they also have downstream effects that modulate the activation patterns of frontoparietal regions through extracellular catecholamine and indirect effects that regulate the brain connectivity patterns of the central executive network and default mode network (Borchert et al., 2019; Farr et al., 2014; Lin & Gau, 2015; Schulz et al., 2012; Shafritz et al., 2004). Taken together, both stimulants and nonstimulants may act on brain frontoparietal circuity to ameliorate the dysfunction of cognitive control and attention in ADHD individuals (Cubillo et al., 2014; Fu et al., 2022; Tomasi et al., 2011), and the normalization effects of stimulants could also modulate the frontolimbic abnormalities (Wiguna, Guerrero, Wibisono, & Sastroasmoro, 2014).

However, it remains unknown whether dissociable therapeutic responses to medications are mediated by shared or distinct neural underpinnings, and studies that directly compare the neural bases of stimulants and nonstimulants are limited, which poses challenges to statistical power given the concern about the clinical applicability of simultaneously studying ADHD patients taking either stimulants or nonstimulants in real-world scenarios (Chou, Chia, Shang, & Gau, 2015; Schulz et al., 2012, 2017; Smith et al., 2013). The lack of evidence linking pharmacologic actions to neural correlates and therapeutic improvement provides limited opportunity to understand how these medications work in the brain, which is an essential step in developing targeted approaches to treatment. The approach of neuroimaging meta-analysis provides an objective method for producing higher-level evidence-based reliable findings on its neural mechanisms (Cheung & Vijayakumar, 2016). This allows for a judicious selection among conflicting research outcomes and deriving fresh insights from the collective body of evidence on stimulants and nonstimulants in ADHD treatment.

Herein, we hypothesize that differential and overlapping actions for stimulant and nonstimulant treatments of ADHD are derived from alterations in frontoparietal activation patterns. To investigate their normalization effects on neural mechanisms, we performed a comparative meta-analysis on task-based fMRI studies to identify altered brain activation patterns in response to stimulants and nonstimulants. Our neuroimaging findings may help to explain their similar efficacy in treating ADHD, and provide insights for individualized medication strategies and enhance treatment response by improving the precision of therapeutic targets.

Methods and materials

Literature selection and database construction

We pre-registered the research protocol on the Open Scientific Framework (https://osf.io/65vn4, registration DOI: https://doi.org/10.17605/OSF.IO/65VN4) before obtaining datasets. This pre-registered systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The literature search was systematically and comprehensively conducted in the PubMed, Medline and Web of Science databases before May 8, 2022 (literature search strategy in Online Supplementary Appendix 1), and we manually added records based on the reference lists of previous meta-analyses (Rubia et al., 2014). Only studies with task-based fMRI methods were included, and we extracted their coordinate-based whole-brain activation patterns based on reported significant clusters (including nonsignificant results) rather than region of interest (ROI) outcomes. Medication effects were identified in contrasts between (Ma, 2015): (1) pre- and post-treatment sessions in within-subject studies; (2) medication group and placebo/control groups in within- or between-subject studies; and (3) group (with or without medication) × time (pre- or post-treatment) interaction in mixed-design studies. Studies were excluded if they (1) were not original articles; (2) lacked ADHD samples; or (3) lacked clear medication categorizations.

For each study, we recorded each study with sample size, age range, sex ratio, medication and dose, scanner parameters (i.e. Tesla and slice thickness), statistical approach (i.e. kernel smoothing and multiple corrections), and their primary findings. Age and sex across stimulant and nonstimulant samples were compared in SPSS Statistics, version 24. Given that a neural circuit may underlie various task paradigms due to their many-to-one relationship, pooling findings across experiments in the cognitive domain might be an objective approach that facilitates the comprehensive investigation of functional responses of ADHD medications (Janiri et al., 2020; van den Heuvel & Sporns, 2019). The

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task and corresponding Research Domain Criteria (RDoC) construct and domain were labeled for each included fMRI study (Cuthbert, 2014; Janiri et al., 2020; Pan et al., 2022) (approach to coding task experiments in Online Supplementary Appendix 2). We evaluated all included studies with a 12-point Imaging Methodology Quality Assessment Checklist for their quality and limitations to infer the importance of those findings (Shepherd, Matheson, Laurens, Carr, & Green, 2012) (for details, see Online Supplementary Appendix 3).

Voxel-based overlapping and comparative meta-analysis

We analyzed the extracted data using anisotropy effect size signed differential mapping (AES-SDM, currently 'Seed-based d Mapping', https://www.sdmproject.com/old/) software. AES-SDM is a statistical technique and toolbox to identify neural abnormalities on account of voxel-based neuroimaging meta-analysis (Zhao, Yang, Gong, Cao, & Liu, 2022). Files containing both the peak coordinates and the corresponding statistical values of brain functional activation patterns were extracted from the included studies. After creating maps of d values and brain variances, we then combined them to create meta-analytic maps during preprocessing. Effect-size statistical maps were generated utilizing a standard random-effects general linear model with an anisotropic nonnormalized Gaussian kernel. For medication-specific analysis, we employed $p < 0.005$ as the threshold, and only clusters over 10 voxels were counted (Radua et al., 2012; Radua & Mataix-Cols, 2009).

The conjunctive neuroimaging analysis in the multimodal models was performed to localize the common neuropharmacological substrates across two kinds of medications (i.e. psychostimulants and nonstimulants) (Chavanne & Robinson, 2021; Pan et al., 2022), which represents an overlap of the significant clusters in a meta-analytic map based on the between-group contrasts of priori regions of medication-specific analysis (Radua, Romeo, Mataix-Cols, & Fusar-Poli, 2013). The AES-SDM has the capacity to adjust the raw union of probabilities to curb the false positive rate in the worst-case scenario with regards to the presence of noise in the estimation of statistics (Norman et al., 2016; Radua et al., 2013). In addition, we applied SDM linear models between the two medication groups to perform comparative analyses to assess their distinct responding activation patterns (Long et al., 2022; Norman et al., 2016). For the above two-modality analysis, we decreased the voxel-wise threshold to a corrected stringent level of $p < 0.0025$ for four tails (Schulze, Schmahl, & Niedtfeld, 2016).

Large-scale network analysis

To uncover potential coactivation patterns of their shared and distinct neuropharmacological mechanisms at the brain network level, we decoded the meta-analytic results using large-scale network analysis (Li et al., 2020). We dropped those identified clusters to seven brain networks that represent a typical integration and segmentation of the cerebral functional parcellation, including the default mode network (DMN), dorsal attention network (DAN), central executive network (CEN), affective network (AFN), sensorimotor network (SMN), ventral attention network (VAN), and visual network (VN) (Yeo et al., 2011). We calculated the relative distribution that represented the proportion of identified voxels in a given network $v.$ all voxels of the cluster (Li et al., 2020).

Ancillary analyses

To explore the heterogeneity derived from demographic variables, we complemented the meta-regression analysis to examine the modulatory effects of age and sex on altered neural activations. We also conducted subgroup analyses on studies focused on the cognitive control construct and those only involving child samples to further address the heterogeneity among our included studies. We used funnel plots and Egger's test to detect potential publication biases (Egger, Davey Smith, Schneider, & Minder, 1997; Peters, Sutton, Jones, Abrams, & Rushton, 2008). To assess the robustness of our main findings, we performed a Jackknife analysis, which consists of repeating the statistical analyses by discarding one study each time, thus demonstrating the stability of the results (Müller et al., 2018).

Results

Included studies and sample characteristics

In total, 19 studies specific to stimulants and 9 studies specific to nonstimulants were included after a systematic literature search (procedure of literature search is listed in Fig. 1). These articles incorporated eligible observations from 396 cases in the medication group and 459 cases in the control group (details of the included articles are shown in Table 1). Among 28 samples in the meta-analysis, no significant difference between stimulant and nonstimulant groups was noted in the independent-samples t test in age (15.40 ± 6.52 $v.$ 17.1937 ± 8.46, $t = 0.533$, $p = 0.605$), and the type of medication did not differ by sex (90.27% $v.$ 83.85%, $\chi^2 = 3.202$, $p = 0.074$).

Shared and distinct neuropharmacological effects

Normalization effects of stimulant or nonstimulant administration for ADHD converged on increased activation patterns of

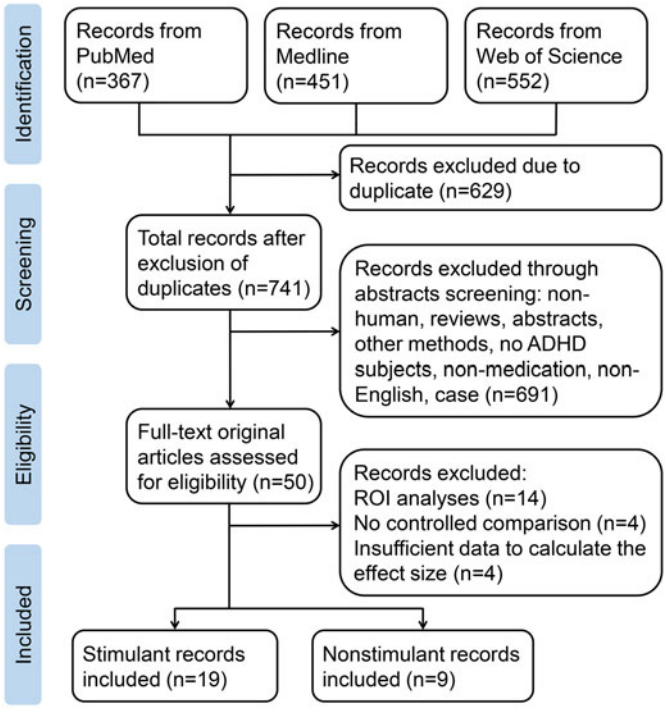

Figure 1. Flowcharts of the literature search and selection criteria. *Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; ROI, region of interest.

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Table 1. Sample characteristics and summary findings of stimulant and nonstimulant studies

	Medication group				Control group									
Study	*N.*	Age	% Male	Medication/dose	*N.*	Age	% Male	Scan./ FWHM (mm)	Slice thick. (mm)	Corr.	Quality score	RDoC construct	Task	Main finding
Studies for stimulants														
Rubia et al., 2009	13	12.5 ± 1.3	100%	MPH: 0.3 mg/kg/h	13	13.1 ± 1.7	100%	1.5T/7.2	7	N	10	Attention	Continuous performance	MPH > CON: PCUN, IPL, OFC MPH < CON: IFG, OFC, STG, putamen, HIP, Cereb
Cubillo et al., 2014a	20	10–17	100%	MPH: 0.3 mg/kg/1.5 h	20	10–17	100%	3T/7.2	3.5	N	9	Working memory	N-back	MPH > CON: SFG
Kowalczyk et al., 2019	14	13.3 ± 1.6	100%	MPH: 0.3 mg/kg/1.5 h	14	13.3 ± 1.6	100%	3T/8	5	N	9.5	Attention	Sustained attention to response	MPH > CON: MTG, PCC
Cubillo et al., 2014b	19	13.1 ± 1.6	100%	MPH: 0.3 mg/kg/1.5 h	29	13.8 ± 2.5	100%	3T/7.2	5.5	Y	11	Cognitive control	Stop signal	MPH > CON: Cereb, MOG, PCUN CON > MPH: MTG
Konrad et al., 2007	9	11.1 ± 1.3	100%	MPH: 30 mg or 0.8 mg/kg/day for 1 year	16	11.3 ± 1.3	100%	1.5T/10	4	N	10.5	Cognitive control	Stroop	MPH < CON: INS, putamen, TPJ, ACC
Rubia et al., 2011a	12	13.0 ± 1.0	100%	MPH: 0.3 mg/kg/1 h	13	13.0 ± 1.0	100%	1.5T/7.2	7	Y	10.5	Cognitive control	Stop signal	MPH > CON: IFG, putamen, caudate, IPL, MOG
Stoy et al., 2011	11	28.5 ± 3.9	100%	MPH: 9.6 mg/day for one year	12	26.2 ± 3.7	100%	1.5T/8	3.3	N	10.5	Reward attainment	Monetary incentive delay	MPH < CON: IFG, IPL, cuneus, MFG
Sheridan et al., 2010	5	14.8 ± 2.4	0%	MPH and atphetamine: individualized	5	14.8 ± 2.4	0%	4T	5.5	N	8	Working memory	Delayed match-to-sample	MPH < CON: MFG, PCUN
Lee et al., 2010	8	10.3 ± 1.3	100%	Concerta: 34.2 ± 7.5 mg/day Metadate CD: 36.7 ± 5.8 mg/day	8	10.3 ± 1.3	100%	3T/8	7	N	8	Cognitive control	Flanker	NS
Mizuno et al., 2013	17	13.3 ± 2.2	100%	MPH: 0.4–0.2 mg/kg/day	17	13.0 ± 1.9	100%	3T/8	3	Y	9.5	Reward attainment	Monetary incentive delay	MPH > CON: THAL
Sweitzer et al., 2018	17	31.2 ± 8.5	100%	MPH: 40 mg/0.5 h	18	29.8 ± 10.2	100%	3T/8	4	Y	11.5	Cognitive control	Go/no-go	MPH > CON: SPL, posG, SFG, OFC, ACC, HIP
Peterson et al., 2009	16	14.1 ± 2.5	81%	MPH: 24.8 mg/day Dextroamphetamine: 21.3 mg or 30 mg/day	20	13.4 ± 3.1	60%	1.5T/6.3	7	N	9	Cognitive control	Stroop	MPH > CON: ACC, PCC
Bush et al., 2008	11	29.5 ± 5.9	64%	MPH: 1.3 mg/kg/day or 36 mg/week	10	34.4 ± 9.2	20%	3T/4	5	Y	11	Cognitive control	Multisource interference	MPH > CON: INS, MCC, MFG, IFG, HIP, posG, SFG, STG, THAL, SPL, caudata, Cereb, LING, SPL

Kobel et al., 2009	14	10.4 ± 1.3	100%	MPH: 0.3 mg/kg/1.5 h	12	10.9 ± 1.6	100%	3T/8	3	Y	10.5	Working memory	N-back	NS
Chou et al., 2015	20	10.5 ± 2.3	85%	MPH: 18 mg/day	20	12.1 ± 2.7	80%	3T/10	3	N	9.5	Cognitive control	Stroop	MPH > CON: IFG
Prehn-Kristensen et al., 2011	12	13.0 ± 1.8	100%	MPH: 0.6 mg/kg/day	12	13.6 ± 2.0	100%	3T/8	2.7	N	10	Working memory	Delayed match-to-sample	MPH > CON: INS CON > MPH: MOG, Caudate
Rubia et al., 2011b	12	13.0 ± 1.0	100%	MPH: 0.3 mg/kg/1.5 h	13	13.0 ± 1.0	100%	1.5T/7.2	7	N	10	Cognitive control	Simon	MPH > CON: Cereb, IFG MPH < CON: ACC, MTG, STG
Congdon et al., 2014	10	29.9 ± 9.5	50%	MPH, amphetamine, lisdexamfetamine: individualized	25	31.2 ± 10.4	56%	3T/5	4	N	10	Cognitive control	Stop signal	Stimulants < CON: SMG, IFG, Cereb, preG
Posner et al., 2011	15	13.5 ± 1.2	87%	Stimulant: individualized	15	13.4 ± 1.2	87%	3T/6	3.8	Y	11.5	Cognitive control	Stroop	Stimulants < CON: MFG
Studies for nonstimulants														
Fan et al., 2017	12	28.9 ± 7.8	42%	ATX: 0.5 or 1.2 mg/kg/day	12	32.5 ± 9.8	42%	3T/10	3	Y	11.5	Cognitive control	Stroop	ATX < CON: IFG, ACC ATX > CON: PCUN
												Working memory	Delayed match-to-sample	
Bedard et al., 2015	12	11.1 ± 2.2	72%	Guanfacine: 1 or 4 mg/day	13	11.1 ± 2.2	72%	3T/8	4	Y	10.5	Cognitive control	Go/no-go	Guanfacine < CON: SMA, PCC
Bush et al., 2013	11	29.5 ± 5.9	64%	ATX: 0.5 or 1.0 mg/kg/day	10	34.4 ± 9.2	20%	3T/4	5	Y	9	Cognitive control	Multisource interference	ATX > CON: MFG, SMA, INS, IPL, posG, Cereb, FUS
Suzuki et al., 2019	14	32.4 ± 5.1	57%	ATX: 40 mg/1.5 h	14	32.4 ± 5.1	57%	1.5T/8	1.2	N	9	Reward attainment	Monetary incentive delay	ATX < CON: putamen, caudate, AMYG
Cubillo et al., 2014a	20	10–17	100%	ATX: 1 mg/kg/1.5 h	20	10–17	100%	3T/7.2	3.5	N	9	Working memory	N-back	ATX > CON: INS ATX < CON: SFG
Kowalczyk et al., 2019	14	13.3 ± 1.6	100%	ATX: 1 mg/kg/1.5 h	27	14.6 ± 2.3	100%	3T/8	5	N	9.5	Attention	Sustained attention to response	ATX > CON: PCC
Cubillo et al., 2014b	19	13.1 ± 1.6	100%	ATX: 1 mg/kg/1.5 h	29	13.8 ± 2.5	100%	3T/7.2	5.5	Y	11	Cognitive control	Stop signal	ATX < CON: MTG
Chou et al., 2015	22	10.6 ± 2.2	77%	ATX: 0.5 mg/kg/day	20	12.1 ± 2.7	80%	3T/10	3	N	9.5	Cognitive control	Stroop	ATX < CON: ACC, SFG
Chantiluke et al., 2015	17	14.7 ± 1.9	100%	Fluoxetine: 8–15 mg	22	14.0 ± 2.6	100%	3T/7.2	3.5	Y	10.5	Working memory	N-back	Fluoxetine < CON: PCC

Abbreviations: MPH, methylphenidate; ATX, atomoxetine; FWHM, full wave at half maximum; %Male, proportion of males in the whole sample; % Medication, proportion of medicated patients; T, Tesla; RDoC, Research Domain Criteria; CON, control; PCUN, precuneus; IPL, inferior parietal lobule; OFC, orbitofrontal cortex; STG, superior temporal gyrus; IFG, inferior frontal gyrus; HIP, hippocampus; Cereb, cerebellum; SFG, superior frontal gyrus; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; MOG, middle occipital gyrus; INS, insula; TPJ, temporoparietal junction; ACC, anterior cingulate cortex; MFG, middle frontal gyrus; NS, no significance; THAL, thalamus; SPL, superior parietal lobule; posG, postcentral gyrus; MCC, median cingulate gyrus; LING, lingual gyrus; SMG, supramarginal gyrus; preG, precentral gyrus; SMA, supplementary motor area; FUS, fusiform gyrus; AMYG, amygdala.

the left SMA (peak coordinates: 0, 20, 44; $Z = 1.206$; cluster size = 44), and the cluster mainly overlaid the CEN (%relative distribution, %RD: 43.18%) (Table 2 and Fig. 2).

Comparative analysis showed that taking stimulants, relative to nonstimulants, increased brain activations in the left amygdala (peak coordinates: −32, 0, −22; $Z = 1.295$; cluster size = 199), middle cingulate gyrus (MCC, peak coordinates: 0, −6, 34 and −12, −34, 44; $Z = 1.222$ and 1.271; cluster size = 174 and 63, respectively), and superior frontal gyrus (SFG, peak coordinates: −22, 44, 38; $Z = 1.243$; cluster size = 68). These regions are distributed within the VAN (%RD: 15.08%, Table 2 and Fig. 2).

Stimulant- and nonstimulant-specific brain effects

In the medication-specific analysis compared to control groups, the treatment response of stimulants in individuals with ADHD was associated with increased brain activation patterns in the left cerebellum (peak coordinates: −10, −54, −10; $Z = 1.449$; cluster size = 537), right SMA (peak coordinates: 18, −6, 68; $Z = 1.226$; cluster size = 152), ACC (peak coordinates: 12, 40, −4; $Z = 1.560$; cluster size = 125), right postcentral gyrus (posG, peak coordinates: 30, −42, 62; $Z = 1.132$; cluster size = 99), and left middle frontal gyrus (MFG, peak coordinates: −42, 32, 28; $Z = 1.100$; cluster size = 32, Table 2 and Fig. 3). Meanwhile, psychostimulant treatment reduced neural responses in the left SMA (peak coordinates: −2, 20, 50; $Z = -1.307$; cluster size = 356) relative to control conditions.

Nonstimulant treatment in ADHD youth changed neural bases by reducing activations in the left MCC (extending to bilateral SMA, peak coordinates: 6, 26, −10; $Z = -1.808$; cluster size = 2557), left amygdala (extending to left temporal pole, peak coordinates: −32, 2, −18; $Z = -1.345$; cluster size = 475), left SFG (peak coordinates: −22, 46, 32; $Z = -1.819$; cluster size = 447), and right caudate nucleus (CAU, peak coordinates: 12, 18, 14; $Z = -1.540$; cluster size = 151, Table 2 and Fig. 3).

Ancillary findings

Meta-regression analyses revealed that younger age was associated with stimulant-induced reduced activation patterns in the right SMA (peak coordinates: 16, −6, 70). In terms of neuropharmacological effects of nonstimulants, male patients with greater age modulated the reduced activation of the left amygdala (peak coordinates: −32, 2, −18 and −34, 4, −18, Online Supplementary Table S1). Egger's tests revealed no potential publication bias ($p > 0.10$) identified in the separate analysis of the stimulant group, and funnel plots were found to be symmetric across all clusters (Online Supplementary Table S2). Jackknife sensitivity analyses substantiated the reliability and robustness of our findings (Online Supplementary Table S3). Subgroup analyses results for studies focused on cognitive control and child samples are presented in the Online Supplementary Tables S4 and S5. In studies examining cognitive control, significant clusters of increased activation following stimulant medication were primarily located in the left lingual gyrus (peak coordinates: −12, −50, −8; $Z = 1.660$; cluster size = 773), while decreased activation was found in the right SMA (peak coordinates: 2, 14, 54; $Z = -1.346$; cluster size = 454). For nonstimulant medication, the main cluster of increased activation was identified in the right SMA (peak coordinates: 2, −12, 58; $Z = 1.893$; cluster size = 1801), with decreased activation in the left SFG (peak coordinates: −20, 48, 34; $Z = -2.172$; cluster size = 654). In the subgroup analyses of children with ADHD, stimulant medication was mainly associated with increased activation in the left cerebellum (peak coordinates: −10, −54, −6; $Z = 1.627$; cluster size = 984) and decreased activation in the right MCC (peak coordinates: 2, 24, 30; $Z = -1.368$; cluster size = 841). Nonstimulant medication was primarily associated with increased activation in the right putamen (peak coordinates: 34, −12, −8; $Z = 1.094$; cluster size = 194) and decreased activation in the left SFG (peak coordinates: −22, 48, 38; $Z = -1.825$; cluster size = 623).

Discussion

Our comparative meta-analytic analysis showed that stimulants and nonstimulants have overlapping actions on brain activation patterns of the left SMA in individuals diagnosed with ADHD. In contrast, increased activation patterns in the left amygdala, MCC and SFG were more pronounced in individuals who received stimulants compared to those who received nonstimulants, demonstrating their distinct neuropharmacological mechanisms. These shared and distinct substrates may delineate a novel therapeutic target for effective interventions and could account for different therapeutic responses to stimulants and nonstimulants among individuals with ADHD (Newcorn et al., 2008; Schulz et al., 2012).

Common neuropharmacological effects

In line with previous studies (Schulz et al., 2012), the overlapping mechanism between the neuropharmacological effects of stimulants and nonstimulants was mapped in the inhibited activation patterns of the left SMA that coactivated with the CEN. As part of the premotor area, SMA sends its output to the primary motor cortex to produce motor sequences (Côté, Elgbeili, Quessy, & Dancause, 2020; Dum & Strick, 2002). When accounting for the psychological processing of behavioral inhibition, SMA acts as a top-down hub that integrates information from the parietal and frontal lobes (Bari & Robbins, 2013), corresponding to task selection and behavior control of CEN functioning. Functional hypoactivation and volumetric reduction of the SMA constitute the psychopathological model of ADHD underlying excessively impulsive actions (Cortese et al., 2012; Jarczok, Haase, Bluschke, Thiemann, & Bender, 2019). Both stimulant and nonstimulant medications used for ADHD have been shown to decrease cortical inhibition and increase cortical facilitation in the SMA (Gilbert et al., 2006). The normalization of SMA activation patterns may correspond directly to drug action given the massive presence in DAT and NET expression in the motor cortex, while also being associated with indirect and downstream effects modulated by responses of the prefrontal cortex (Lewis et al., 2001; Peterson et al., 2009; Schulz et al., 2012; Seneca et al., 2006; Tomasi et al., 2011). These findings documented similarities in the neural pharmacological effects of stimulants and nonstimulants, which refined the understanding of brain alterations from medication effects that lead to the shared efficacy of both classes of ADHD medications.

Distinct neural responses in ADHD

The treatment responses to stimulants and nonstimulants showed inverse activation patterns in the amygdala, MCC and SFG for ADHD individuals, and the distinct patterns mainly overlaid brain networks of the VAN and AFN. The AFN (also called the

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Table 2. Neuropharmacological effects of stimulants and nonstimulants on neuroimaging phenotypes

Contrast/brain region	Brodmann area	MNI coordinates (*x*, *y*, *z*)	SDM-Z	*p* Value	Cluster size	Cluster breakdown (number of voxels)
Stimulant and nonstimulant (overlapping findings)						
L supplementary motor area	32	0, 20, 44	1.206	<0.0001	44	L supplementary motor area (24) L superior frontal gyrus, medial (12)
Stimulant vs. nonstimulant (comparative findings)						
L amygdala (extending to L temporal pole)	34/38	−32, 0, −22	1.295	0.0006	199	L amygdala (40) L temporal pole, superior temporal gyrus (40)
L middle cingulate gyrus	23	0, −6, 34	1.222	0.0008	174	L middle cingulate gyrus (62) R middle cingulate gyrus (62) R anterior cingulate gyrus (13)
		−12, −34, 44	1.271	0.0006	63	L middle cingulate gyrus (53)
L superior frontal gyrus	9	−22, 44, 38	1.243	0.0007	68	L superior frontal gyrus, dorsolateral (47) L middle frontal gyrus (21)
Stimulant vs. control						
L supplementary motor area	6/8	−2, 20, 50	−1.307	0.0013	356	L supplementary motor area (281) R supplementary motor area (105) L superior frontal gyrus (16)
L cerebellum	18	−10, −54, −10	1.449	0.0001	537	L cerebellum, hemispheric lobule IV/V (331) L lingual gyrus (140) L cerebellum, hemispheric lobule VI (45)
R supplementary motor area	6	18, −6, 68	1.266	0.0007	152	R superior frontal gyrus, dorsolateral (109) R supplementary motor area (43)
R anterior cingulate gyrus	10/11	12, 40, −4	1.560	<0.0001	125	R superior frontal gyrus, medial orbital (54) R anterior cingulate gyrus (41) R superior frontal gyrus, medial (11)
R postcentral gyrus	2	30, −42, 62	1.132	0.0016	99	R postcentral gyrus (95)
L middle frontal gyrus	45	−42, 32, 28	1.100	0.0020	32	L inferior frontal gyrus, triangular part (18) L middle frontal gyrus (12)
Nonstimulant vs. control						
L anterior/middle cingulate gyrus (extending to bilateral supplementary motor area)	23/24/32	6, 26, 16	−1.808	<0.0001	2557	L middle cingulate gyrus (730) R middle cingulate gyrus (673) L anterior cingulate gyrus (287) R anterior cingulate gyrus (208) L paracentral lobule (126) R supplementary motor area (120)

(*Continued*)

Table 2. (*Continued.*)

Contrast/brain region	Brodmann area	MNI coordinates (*x*, *y*, *z*)	SDM-Z	*p* Value	Cluster size	Cluster breakdown (number of voxels)
						L supplementary motor area (112) L superior frontal gyrus, medial (61)
L amygdala (extending to L temporal pole)	34/48	−32, 2, −18	−1.345	0.0010	475	L temporal pole, superior temporal gyrus (143) L amygdala (93) L insula (43)
L superior frontal gyrus	9	−22, 46, 32	−1.819	<0.0001	447	L superior frontal gyrus, dorsolateral (204) L middle frontal gyrus (200) L superior frontal gyrus, dorsolateral (11)
R caudate nucleus	25	12, 18, 14	−1.540	0.0002	151	R caudate nucleus (105)

Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute.
Note: Suprathreshold clusters were identified at $p < 0.005$ and cluster size >20 voxels. The number of cluster breakdowns (>10 voxels) was calculated by adding subclusters reported by SDM software.

limbic system) has long been regarded as having an integral role in emotion-based decision-making, reward and motivation (LeDoux, 2000; Phelps, 2006). As part of the AFN, aberrant activation patterns of the amygdala in ADHD individuals suggest related deficits in emotional processing, control of impulsivity and reward sensitivity (Gallagher & Chiba, 1996; van Hulst et al., 2017). In treatment, stimulants act on the amygdala, which is distributed with monoamine transporters (i.e. DAT and NET inhabitation) and strengthen the current of cortico-amygdala synapses, which enhance emotional memory retention and learning performance (Smith & Porrino, 2008; Tye et al., 2010). Both stimulants and nonstimulants are posited to be less effective on dysfunction in the bottom-up circuits encompassing the amygdala and ventral striatum (Lenzi, Cortese, Harris, & Masi, 2018), and this may reduce the scope of presumed medication action. As it is embedded in the VAN, the MCC is considered a key area of emotion and cognition processing and subserves bottom-up attention diversion. Underactivated MCC in ADHD individuals may be construed as connected with the core symptom of inattention (Emond, Joyal, & Poissant, 2009; Rolls, 2019; Vossel, Geng, & Fink, 2014). For ADHD treatment responses, the normalization effects of stimulants aligning with the underactivity of MCC echoes previous evidence that stimulants may improve cingulate dysfunction through bidirectional remediation by dopaminergic modulation, and the DA system controlled by cholinergic receptors in the MCC is a likely target (Murray et al., 2019; Vogt, 2019). Regarding the differential findings in the SFG, which has been suggested to be associated with inattention and hyperactivity (Briggs et al., 2020; King, Floren, Kharas, Thomas, & Dafny, 2019), stimulants and nonstimulants act to alter the abnormal neural responses in ADHD patients through α2-adrenergic and dopamine D1 receptors to improve cognitive functions through the reactivity of the prefrontal cortex based on its high sensitivity to catecholamines (Gamo, Wang, & Arnsten, 2010; Schulz et al., 2012). However, different neural responses toward the two medications have observed, and we argue that these responses might be induced by both normalization and side effects. As per previous evidence, we speculate that reduced activation patterns in the above regions may be therapeutic effects that inhibit excessive neuropsychological functioning, while the hyperactivated responses of these regions may indicate side effects, which could be a consequence of different dopaminergic receptors corresponding to different medication actions.

Medication-specific neural mechanisms

Our study reveals that stimulants may upregulate neuroimaging activation patterns in the left cerebellum compared to controls given their indirect phosphorylation of the glutamate receptor through modulating the release of norepinephrine (Arnsten & Dudley, 2005; Cutando et al., 2021). In addition, the altered activation of the cerebellum incident to stimulant use may ameliorate problems of dysfunctional control and reward processes based on cerebro-cerebellar interactions (Abdallah, Farrugia, Chirokoff, & Chanraud, 2020). In the ADHD group with nonstimulants, activation in the right caudate was inhibited, unlike stimulant action in the same region (Rubia et al., 2014). The disparity in their responses indicates the presence of distinct pathways in the brain for stimulants and nonstimulants. Nonstimulants act on glutaminergic signaling, which affects the dopaminergic neurons in the caudate nucleus (Easton, Marshall, Fone, & Marsden,

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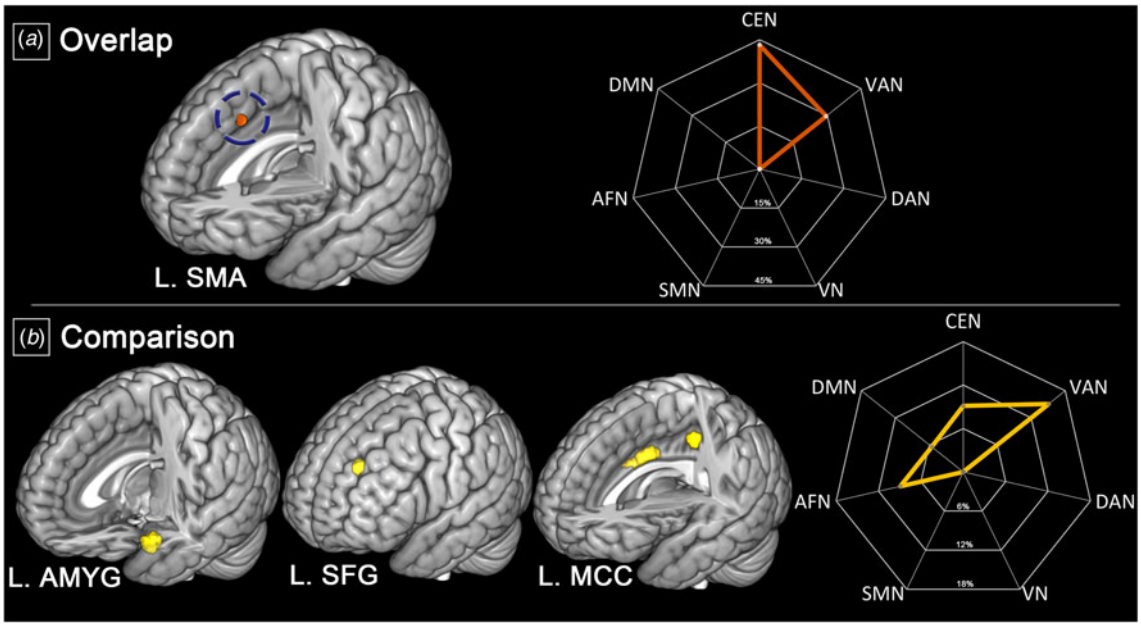

Figure 2. Comparative findings of stimulant and nonstimulant effects for ADHD and their corresponding distribution in brain networks. Orange, the same brain region that was affected by both medications. Yellow, more increased activity by stimulants. The radar charts show the effects of the medication on the brain network. *Abbreviations:* L, left; R, right; SMA, supplementary motor area; AMYG, amygdala; SFG, superior frontal gyrus; MCC, middle cingulate gyrus.

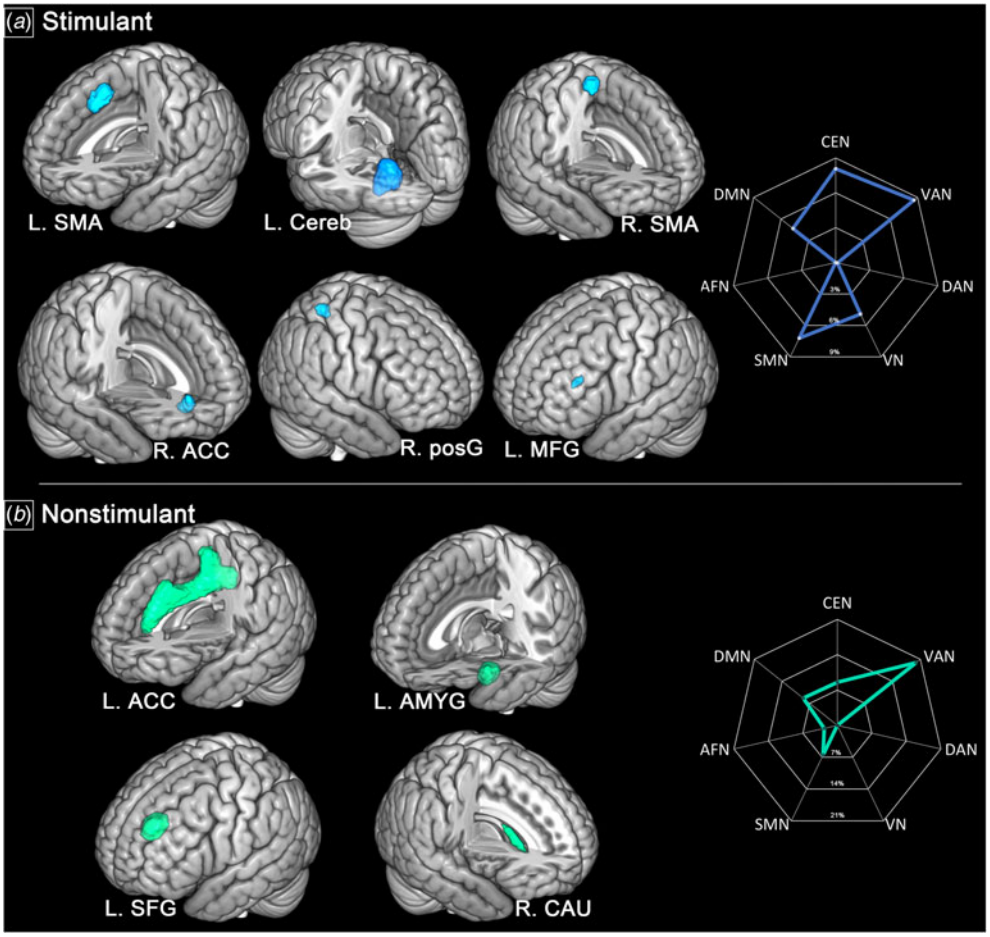

Figure 3. Medication-specific effects of stimulants or nonstimulants and corresponding distribution in brain networks. Blue, brain regions affected by stimulants. Green, brain regions affected by nonstimulants. The radar charts show the effects of the medication on the brain network. Abbreviations: L, left; R, right; SMA, supplementary motor area; Cereb, cerebellum; ACC, anterior cingulate cortex; posG, postcentral gyrus; MFG, middle frontal gyrus; AMYG, amygdala; SFG, superior frontal gyrus; CAU, caudate nucleus.

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2007; King et al., 2019), and may in turn, improve deficits in response inhibition and tendencies for impulsive choices in ADHD individuals (Szekely, Sudre, Sharp, Leibenluft, & Shaw, 2017). The neuropharmacological processes behind them can help choose medications based on the key symptoms that different individuals experience, providing guidance for individualized treatment and ultimately improving outcomes. Additionally, examining the pharmacological mechanisms of stimulants and non-stimulants may reveal new treatment targets that could lead to the development of state-of-the-art ADHD medications.

Modulatory effects of age and sex

Age-related modulatory effects on neuropharmacological alterations were delineated, as youth seen with stimulants showed more reduced neural responses in the right SMA relative to adults, implying they may have a higher sensitivity to stimulants to improve excessive involuntary movements (Carucci et al., 2021; Karl et al., 2006). Longitudinal studies on ADHD patients reported age-dependent amelioration of symptoms of hyperactivity, and those adults may develop hypo-responsiveness or resistance to psychostimulants induced by specified developmental trajectories (Biederman, Mick, & Faraone, 2000; Rubia et al., 2000; Santosh & Taylor, 2000), suggesting that reduced activations of the right SMA play a role in compensatory mechanisms in ADHD adults and that they may not need the intervention of stimulants to improve hyperactivity deficits (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013).

A negative correlation between age and activation alterations was found in the left amygdala in nonstimulant cases, indicating that nonstimulants may have better inhibitory effects on abnormal affective processes in ADHD adults relative to youth (Aggleton, 1993; Phelps & LeDoux, 2005; Winstanley, Theobald, Cardinal, & Robbins, 2004). Emotional dysregulation is more prevalent in ADHD adults relative to adolescents (Shaw, Stringaris, Nigg, & Leibenluft, 2014), and they may have better treatment responses to nonstimulants in refining affective stability as informed by our neuroimaging findings in the amygdala (Wang, Zuo, Xu, Hao, & Zhang, 2021). Similarly, the brain mechanisms of nonstimulants also presented a sex-related difference in the left amygdala wherein there were greater reductions in activation patterns in males than females, which may suggest better therapeutic effects on emotion regulation in ADHD males with nonstimulant use.

Subgroup analyses of cognitive control construct and child samples

To compare findings of subgroup analysis on experiments in cognitive control and pooling findings, we revealed consistent patterns of inhibited neural responses in the right SMA triggered by stimulants and these in the left SFG affected by nonstimulants, even when pooling findings incorporating attention, working memory and reward constructs. Notably, stimulant-induced neuropharmacological effects in the left lingual gyrus were observed exclusively in response to the experiments of cognitive control. The lingual gyrus, a component of the visual cortex underlying word identification and recognition, has also been implicated in irritability and impulsive aggression in subclinical samples (Besteher et al., 2017; Mechelli, Humphreys, Mayall, Olson, & Price, 2000). Thus, medication responses in the lingual gyrus may reflect symptom amelioration of disruptive behavior within the domain of cognitive control. Subgroup analysis on children with ADHD yielded consistent findings in the increased activation in the left cerebellum induced by stimulants and the reduced activation in the left SFG induced by nonstimulant compared to our pooling findings. This consistency indicates that these neuropharmacological bases may be inherent, regardless of their developmental trajectories. However, medication response mechanisms in the reward system, particularly in the right MCC and putamen, only emerged in child samples, suggesting that underdeveloped corticostriatal circuits in children might serve as a potential target for medication treatment (Buckholtz & Meyer-Lindenberg, 2012).

Limitations

Even though the results of the sensitivity analysis substantiated the reliability of our meta-analytical findings, our study still has limitations that need to be considered. First, the source of heterogeneity was still noticeable, as most included studies evaluated cognitive control function, while others measured working memory and attention problems. Further investigations may subclassify medication effects on homogenous psychological constructs when more studies emerge. Considering the inclusion of both child and adult samples in our study, it is inevitable to confront the considerable heterogeneity in age within study population when interpreting our findings. Second, various protocol designs of the included studies with both randomized controlled and cross-sectional trials may also contribute to the heterogeneity (Ma, 2015). Third, we failed to differentiate the short- and long-term effects of psychostimulants and nonstimulants on brain activity due to the limited number of corresponding studies. Fourth, the neuropharmacological pathways of nonstimulants are notably diverse, yet they all converge on targeting the norepinephrine transporter in some capacity for the treatment of ADHD (Newcorn, Krone, & Dittmann, 2022). Lastly, we were unable to obtain clinical ratings to speculate treatment responses of ADHD medications based on reanalyzed neuroimaging datasets, and whether these neuropharmacological effects in ADHD have disorder or diagnostic specificity remains unclear.

Conclusion

This study, to the best of our knowledge, is the first to focus on the overlapping and comparative neuropharmacological mechanisms of stimulants and nonstimulants for ADHD in a meta-analytical approach. The convergence of psychostimulant and nonstimulant effects on the left SMA may delineate a novel therapeutic target for effective interventions for ADHD, and these distinct neural substrates could account for individual differences in therapeutic responses. Our neuroimaging findings may have implications for individualized medication strategies and enhance treatment response by precisely matching therapeutic targets.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172400285X

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Author contributions. NP and YC designed the study. TM and YL collected the data from previous studies. NP, TM, and YL performed the data analysis

and wrote the paper. SZ helped with data processing. SH, AS, HC, YC, and QG revised the paper. All authors contributed to the results' interpretation and discussion and approved the final manuscript.

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Data availability statement. The atlas files of the overlapping and distinct mechanisms of psychostimulants and nonstimulants are available at https://osf.io/2wghs/files/, and other data that support the findings of the present study are available from the corresponding author through reasonable request.

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