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Seed-based resting-state functional connectivity in children and adolescents with attention-deficit/ hyperactivity disorder: an activation likelihood estimation meta-analysis

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ADMINISTRATIVE INFORMATION

Support - This research was supported by the National Social Science Fund of China (21BTY096).

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2024 and was last updated on 8 November 2026.

INTRODUCTION

Review question / Objective To assess whether between-group differences in whole-brain seed-based static resting-state functional connectivity between children and adolescents with ADHD and controls show spatial convergence across published studies.

Rationale Previous resting-state meta-analyses of ADHD have reported inconsistent findings and differed in eligibility criteria, inclusion of adults, comparability of connectivity metrics, handling of sample dependence, and statistical thresholds. A pediatric synthesis restricted to comparable static seed-based contrasts, with explicit handling of sample dependence and corrected inference, is therefore needed.

Condition being studied Attention-deficit/ hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, with a pooled worldwide prevalence of approximately 7.2% in children and adolescents.

METHODS

Search strategy PubMed, Cochrane Library, Web of Science, EBSCO (MEDLINE, APA PsycInfo, ERIC), Embase, Scopus, CNKI and Wanfang were searched from inception to 7 December 2024, and the search was updated to 19 October 2026 using the same strategy. Search terms combined subject headings and free-text terms for ADHD, resting-state fMRI, functional connectivity and children. Reference lists of relevant systematic reviews were also screened.

Participant or population Children and adolescents younger than 18 years diagnosed with ADHD according to DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5 or ICD-10 (including earlier versions).

Intervention Not applicable.

Comparator Typically developing or healthy control children and adolescents.

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Study designs to be included Case–control resting-state fMRI studies reporting whole-brain seed-based (seed-to-seed or seed-to-voxel) static functional connectivity group contrasts.

Eligibility criteria Inclusion criteria: (1) original studies using whole-brain seed-based resting-state functional connectivity to compare ADHD and control groups; (2) the compared measure was static (time-averaged) functional connectivity; (3) ADHD diagnosed according to DSM-III to DSM-5 or ICD-10, including earlier versions; (4) peak coordinates of group differences reported in MNI or Talairach space; (5) between-group contrasts reported; (6) published in peer-reviewed journals; (7) participants younger than 18 years.
Exclusion criteria: (1) neuroimaging techniques other than resting-state fMRI; (2) within-group comparisons only; (3) samples including ADHD in partial remission; (4) studies examining medication effects without baseline or post-washout fMRI data; (5) unobtainable peak coordinates; (6) non-seed-based methods; (7) studies or contrasts reporting only dynamic functional connectivity (e.g., sliding-window variability); (8) studies based on ADHD-200 or other public imaging databases.

Information sources Electronic databases listed under Search strategy and reference lists of relevant systematic reviews. Only studies published in English or Chinese were included.

Main outcome(s) Spatial convergence of reported peak coordinates of between-group functional connectivity differences in two directions (ADHD > controls; controls > ADHD), assessed in pooled ALE meta-analyses.

Additional outcome(s) Exploratory analyses: (1) network-seed analyses grouping studies by the network membership of their seeds; (2) a stimulant-naïve subgroup; (3) a subgroup without psychiatric comorbidity. Robustness of significant clusters was assessed with fail-safe N and leave-one-experiment-out analyses.

Data management Screening and coding were performed by the first author at two time points; disagreements were discussed with the second author and adjudicated by a third reviewer when necessary. Extracted information included demographic and clinical characteristics, ADHD subtype, psychiatric comorbidity, stimulant history and washout, comparison group composition, scan duration, eye status, motion exclusion criteria, motion correction and denoising, seed definition, coordinate space, peak coordinates, contrast direction and group sample sizes. All coordinates entered into the analyses were re-checked by two authors.

Quality assessment / Risk of bias analysis Reporting completeness was assessed with a 10-item checklist adapted from Zhang et al. (2025); scores describe reporting completeness and were not used to weight or exclude studies. Study-level domains relevant to bias (participant selection, motion handling, multiple-comparison correction in primary studies, comparability of connectivity metrics and sample dependence) are reported descriptively.

Strategy of data synthesis Coordinate-based ALE meta-analyses were performed in GingerALE 3.0.2. Talairach coordinates were converted to MNI space using the Lancaster transformation, and the Turkeltaub non-additive algorithm was applied. Significance was determined using cluster-level family-wise error correction at $p < 0.05$ with a cluster-forming threshold of $p < 0.001$ (1,000 permutations). This replaces the originally registered threshold (uncorrected $p < 0.001$ with an extent threshold of 120 mm^3).

Subgroup analysis (1) Network-seed subgroups: studies were grouped according to the network membership of their seeds (visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal and default mode networks), and separate ALE analyses were conducted for networks with at least 9 experiments in both directions; this subgroup analysis and its criterion were added after data extraction. (2) Network assignment of seeds: the network membership of each seed was determined from its reported coordinates using the cortical (Yeo et al., 2011), cerebellar (Buckner et al., 2011) and striatal (Choi et al., 2012) 7-network parcellations in FreeSurfer 7.4.1; target foci were retained regardless of location.(3) Subgroup without psychiatric comorbidity: comorbidity was excluded or reported absent in the ADHD group. English and Chinese.

Sensitivity analysis Leave-one-experiment-out (jackknife) analyses were conducted for every significant cluster, and fail-safe N was calculated. The planned sensitivity analysis removing studies with fewer than 8 participants was not performed because no included experiment had fewer than 8 participants.

Language English and Chinese.

Country(ies) involved China.

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Other relevant information This protocol was originally registered on 28 July 2024, when the review was at the data-extraction stage. It was updated on 8 November 2026 during peer review to document deviations from the original protocol.

Keywords attention-deficit/hyperactivity disorder; resting-state functional magnetic resonance imaging; functional connectivity; activation likelihood estimation; meta-analysis; children and adolescents

Contributions of each author

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(1) Sample dependence: contrasts derived from the same participants or sharing the same control group were combined into a single experiment within each analysis, and articles explicitly using the same dataset were combined; for each experiment, the smaller group size was used to determine the ALE kernel.
(2) Network assignment of seeds: the network membership of each seed was determined from its reported coordinates using the cortical (Yeo et al., 2011), cerebellar (Buckner et al., 2011) and striatal (Choi et al., 2012) 7-network parcellations in FreeSurfer 7.4.1; target foci were retained regardless of location. Network-seed analyses were conducted only for networks with at least 9 experiments in both directions; this criterion was set after data extraction.
(3) Fail-safe N: the lower bound was 30% of the number of experiments in an analysis and the upper bound was (number of contributing experiments / 0.05) – number of experiments; FSN values above the upper bound indicate possible dominance by a few influential experiments rather than greater robustness.
(4) The original main-outcome statement interpreting abnormal regions as dysfunctional nodes of large-scale networks was replaced; network labels are used only to describe the origin of seeds.

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