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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No code was used to collect the data used in this study
Data analysis	Freesurfer: FreeSurfer v5.3.0 software (http://surfer.nmr.mgh.harvard.edu/) was used to derive tessellated models of the cortical surface for each T1-weighted image. Vertex-wise statistical analyses of each cortical feature were conducted using the SurfStat toolbox (www.math.mcgill.ca/keith/surfstat/) for MATLAB (R2014a, The Mathworks, Massachusetts). Statistics: We used SPSS (v28, IBM) to run the statistical analyses. Decoding: Following a previously published approach (Pretzsch et al 2023, Pretzsch et al 2022), we leveraged the Allen Human Brain Atlas (AHBA) of gene expression (Hawrylycz et al 2012) and Neurovault (https://neurovault.org), a python code embedded within Neurovault and Neurosynth (https://neurosynth.org). Enrichment: The gene list overlap was computed using a specific R (v4.3) code written by MV Lombardo, as previously described (github.com/mvlombardo/utils/blob/master/genelistOverlap.R)(Pretzsch et al 2023).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Methods:
Decoding:
We used the Allen Human Brain Atlas (AHBA) of gene expression (Hawrylycz et al 2012), currently the most comprehensive publicly available atlas of gene-expression in the brain (http://www.brain-map.org).

Enrichment:
The tested genes were based on gene-set annotations listed in the human gene ontology database (http://www.gsea-msigdb.org/) (The Gene Ontology 2019).

Imaging:
Imaging files are publicly available on OSF (http://osf.io/mw4y3/).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Methods: We only recruited males, because ADHD is more commonly diagnosed in males (Young et al., 2020) and there is preliminary evidence of sex differences in brain morphometry and biological response to stimulants (Carucci et al 2023, Duffy & Epperson 2022, Manza et al., 2022), thus we included only males to enhance sample homogeneity (see Discussion for potential limitations).
Population characteristics	Sample characteristics are detailed in suppl. material (page 2) as follows: Sample characteristics 60 male adults with ADHD completed the study. They mostly identified as White British (71%), had a mean (± SD) age of 28 (±7) years and a full-scale IQ of 109 (±12); most of them was right-handed (78%) and medication-naïve (77%). Controls were matched for age, sex and IQ, and were predominantly right-handed (90%). Concerta XL was titrated up to 54 mg in most ADHD individuals but, due to side effects, the dose was reduced to 36 mgs in 24% of cases and to 18 mgs in 7% of cases. Only two individuals increased the dose. We included dose among covariates in our analyses (see Methods). Most participants (72%) were not assessed for ADHD before taking part into this study. None had a clinically diagnosed co-occurrent condition; however, one of them was diagnosed with Oppositional Defiant Disorder (ODD) and 8 with Dyslexia as children. Most of them were ADHD medication-naïve (77%); and none was on any psychotropic medication at the time of the study. Only 14 individuals were previously treated with ADHD medication. Among these, only three were classified as responders during this study. Abstinence from illicit drugs was tested using urine drug screening at the time of the scan. Out of the 56 completed urine drug screenings, 46 were negative (82%). Treatment adherence was tested by carrying out MPH assays at follow-up. Out of the 55 completed MPH assays, 49 were positive (89%). All 60 ADHD participants were analyzed according to an intention to treat approach. At follow-up, 42 participants were classified as responders and 18 as non-responders based on their total BAARS-IV score (reduction above or below 30% as compared to baseline). Average improvement of symptoms was 19.9 (± 7.85) in responders and 4.17 (± 4.17) in non-responders. The two groups did not significantly differ in ethnicity, age, total IQ, handedness, clinical presentation, baseline severity, and MPH dose at follow-up. Full details are reported in [3].
Recruitment	Details on recruitment and inclusion criteria are provided in Methods ('Sample and research protocol') and potential limitations in the Discussion.
Ethics oversight	Methods: Ethical approval by Camden and Islington Research Ethics Committee (12/LO/0630).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Methods: the sample size was determined based on a power calculation (supplementary material).
Data exclusions	No participant was excluded. See also note in suppl. material (page 2): all 60 participants were analyzed according to an intention to treat approach.
Replication	Conclusion: These results need to be replicated and extended in independent samples and, preferably, confirmed by meta-analyses (Fusar-Poli et al 2018).
Randomization	Methods: This study is part of a single-blind placebo-controlled cross-over study, followed by a longitudinal open-label phase (NCT 03709940). This was not a randomized controlled trial. We divided the ADHD sample in responders and non-responders as descrived in Methods: According to previously published criteria, we used a categorical definition of treatment response based on a symptomatic improvement of at least 30%, as measured by the BAARS-IV total score at follow-up as compared to baseline (Biederman et al 2006, Rosler et al 2009).
Blinding	Methods: This study is part of a single-blind placebo-controlled cross-over study, followed by a longitudinal open-label phase (NCT 03709940). This was not a randomized controlled trial.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Magnetic resonance imaging

Experimental design

Design type	Methods: This study is part of a single-blind placebo-controlled cross-over study, followed by a longitudinal open-label phase (NCT 03709940).
Design specifications	Methods: In this report, we focused on the structural MRI data. We included 60 adults with ADHD [...]. They completed MRI scanning before starting routine treatment with the same long-acting formulation of MPH.
Behavioral performance measures	No fMRI task.

Acquisition

Imaging type(s)	T1 weighted
Field strength	3T
Sequence & imaging parameters	parameters: 196 slices, 1.2 mm thickness with 1.2 mm gap, TR= 7.312 ms, TE= 3.016 ms, and flip angle= 11°.
Area of acquisition	Whole brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	FreeSurfer v5.3.0 software (http://surfer.nmr.mgh.harvard.edu/) was used to derive tessellated models of the cortical

Preprocessing software	surface for each T1-weighted image.
Normalization	Individual freesurfer data was normalized into standard fsaverage space using mris_preproc.
Normalization template	fsaverage (full resolution)
Noise and artifact removal	no additional beyond standard freesurfer recon-all pipeline
Volume censoring	not applied

Statistical modeling & inference

Model type and settings	general linear model (Yi = β0 + β1 Group + β2 Age) and (Yi = β0 + β1 Group + β2 Age + β3 IQ + β4 BAARS-IV + β5 Dose + β6 Weight + β7Handedness + εi). Default settings for the surfstat package were used to estimate models.
Effect(s) tested	group (i.e., ADHD v control), treatment response (i.e., responders v non-responders)

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)	'random field theory' (RFT)-based cluster analysis for non-isotropic images at a cluster-threshold of p<0.05 (two-tailed) (Worsley et al 1999)
Correction	corrections for multiple comparisons were performed using a 'random field theory' (RFT)-based cluster analysis

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis