

Appendix 1 to van der Meer D, Hartman CA, van Rooij D, et al. Effects of dopaminergic genes, prenatal adversities, and their interaction on attention-deficit/hyperactivity disorder and neural correlates of response inhibition. *J Psychiatry Neurosci* 2016.

DOI: 10.1503/jpn.150350

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Supplementary Information

ADHD diagnostic algorithm

To determine psychiatric diagnoses, all participants (children and parents alike) were assessed with a combination of ADHD rating scales and a semi-structured diagnostic interview. In order to determine ADHD diagnoses, a diagnostic algorithm was applied based on the behavioral questionnaires (typically filled in by parents as well as a second observer) and the diagnostic interview, using DSM-IV criteria (American Psychiatric Association, 2000). Inconsistent cases were reviewed by a team of trained experts, in order to derive a consensus diagnosis.

Measures

Children were assessed with a parent rating scale (CPRS-R:L; 1998a), and either a teacher rating scale (CTRS-R:L; 1998b), applied for children < 18 years, or a self-report (CAARS-S:S; 1999), applied for children ≥ 18 years. A semi-structured diagnostic interview (KSADS-PL; Kaufman et al., 1997) was administered to both the children (if ≥ 12 years old) and their parents separately. Initially, all participants were only administered the screening interview. Participants with elevated scores on any of the screen items were administered the full ADHD section.

Parents were assessed similarly with an observer ADHD rating scale (CAARS-O:SV; 1999), typically filled in by their partner. The KSADS-PL was administered to all parents, who were, if possible, interviewed together with their partner.

Of the Conners' ADHD questionnaires the following scales were used:

- DSM Inattentive behavior
- DSM Hyperactive/Impulsive behavior
- DSM Total

For all participants using medication, ratings were done of the participant's functioning off medication.

The diagnostic algorithm

The diagnostic algorithm applied to all participants was based on a combination of symptom counts on the ADHD rating scales and the KSADS-PL, both providing operational definitions of each of the 18 behavioral symptoms of ADHD defined by the DSM-IV. Combined counts for each symptom were determined based on the KSADS-PL scores combined with scores on either the teacher rating scale (for children <18 years), the self-report (for children ≥18), or the observer rating (for parents).

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Based on the algorithm, participants were given either an 'affected' (ADHD diagnosis) status or 'unaffected' status.

The following criteria were used to classify ADHD ('affected' status):

- Combined symptom count of ≥ 6 symptoms of inattentive or hyperactive/impulsive behavior
- T-score ≥ 63 on at least one of the ADHD subscales on at least one of the available Conners' ADHD rating scales
- Age of onset before 12
- Symptoms cause clinical impairment
- Symptoms are not better accounted for by another disorder

For children ≥ 18 years and parents, criteria were slightly adapted, such that a combined symptom count of 5 symptoms and age of onset before 15 years were sufficient for an 'affected' status.

Participants were labelled 'unaffected' if they received a $T < 63$ on each of the scales of the Conners' rating scales, and if they had ≤ 3 symptoms (or ≤ 2 symptoms for children of ≥ 18 years and parents), derived from the combined symptom counts.

For analysis purposes, participants who did not meet criteria for either affected or unaffected status, were labelled 'subthreshold ADHD'.

Comorbid disorders

Participants were diagnosed with ODD if they exhibited four or more of the DSM-IV symptoms derived from the K-SADS. Likewise, conduct disorder (CD) was determined if a participant exhibited three symptoms or more DSM-IV symptoms derived from K-SADS interviews.

For internalizing disorders, we used the anxiety and depression module of the K-SADS, which was administered if the participants had elevated scores on the screening section. Diagnoses were made based on the instructions given therein, in accordance with DSM-IV-TR criteria.

Reading disorder was not diagnosed directly within the NeuroIMAGE project, but pre-existing diagnosis of reading disorder by a recognized medical institution were incorporated in the study design.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*: American Psychiatric Publishing, Inc.

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Conners, C. K., Erhardt, D., & Sparrow, E. P. (1999). *Conner's Adult ADHD Rating Scales: CAARS*: Multi-Health Systems, North Tonawanda, NY.

Conners, C. K., Sitarenios, G., Parker, J. D. A., & Epstein, J. N. (1998a). The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of abnormal child psychology*, 26(4), 257-268.

Conners, C. K., Sitarenios, G., Parker, J. D. A., & Epstein, J. N. (1998b). Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *Journal of abnormal child psychology*, 26(4), 279-291.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., et al. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*, 36(7), 980-988.

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MRI data acquisition and preprocessing

Data were acquired at two sites on similar 1.5 Tesla Siemens scanners (Siemens Sonata at VU UMC in Amsterdam; Siemens Avanto at Donders Centre for Cognitive Neuroimaging in Nijmegen) using identical protocols. The data was collected in four fMRI runs of 60 trials using a T2*-weighted echo planar imaging sequence (TR=2340 ms, TE=40 ms, FOV=224x224 mm, 37 slices, voxel size=3.5x3.5x3.5 mm, 94 volumes per run). For spatial localization and normalization, we included each participant's high resolution MPAGE T1 scan (TR=2730ms, TE=2.95ms, TI=1000ms, voxel size=1x1x1mm, FOV=256mm, 176 slices).

The data was processed using FSL FEAT (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl); fMRI Expert Analysis Tool, version 6.0). Preprocessing included removal of the first four volumes of each run, within run motion correction to the middle volume, slice-timing correction, spatial smoothing using a 6mm Gaussian kernel, and highpass temporal filtering (0.01 Hz). For all runs we calculated transformation to the participant's T1 anatomical image using linear, boundary-based registration implemented in FSL-FLIRT.

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Sensitivity Analyses

We conducted sensitivity analyses to investigate whether the significant findings were driven by specific groups of participants. We reran the analyses within diagnostic groups (ADHD, controls), testing locations (Amsterdam, Nijmegen), parental education levels (above or below median)*, and age groups (adults, children) to check whether the direction of effects was the same between groups. The results of these analyses are summarized in Table S1.

As can be seen in Table S1, the direction of effects were the same across the two locations, for those with and without an ADHD diagnosis, and for those with low and high parental education levels, for all clusters found to be significant in the main analysis.

* The highest, successfully completed education level of the parents was recoded into a measure reflecting years of education. This scale contained nine levels, ranging from 0 (no formal education) to 17 (university) years of education (25). The average of both parents was used, which, in this sample, ranged from 5 to 17 with an average of 12.1. The median in this sample was 11.

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Table S1. Direction of effects within the subsamples for the mean value of clusters found to be significant in the main analysis. The regression coefficients refer to that of the risk factor for each subset, the numbers next to these (in brackets) are the associated standard errors.

Predictor	Brain region	Amsterdam	Nijmegen	ADHD	Control	Low SES	High SES	Child	Adult
<i>Successful response inhibition</i>									
Prenatal smoke exposure	Superior frontal, anterior cingulate gyrus	-9.56 (2.14)	-9.26 (2.26)	-10.60 (2.43)	-7.06 (2.02)	-9.96 (2.09)	-6.22 (2.30)	-9.76 (2.22)	-7.75 (2.12)
<i>DRD4</i> genotype	Superior frontal, middle frontal gyrus	-8.64 (1.57)	-6.04 (1.97)	-5.89 (2.18)	-8.10 (1.55)	-7.34 (1.67)	-7.36 (1.81)	-8.29 (1.60)	-6.06 (2.06)
<i>Failed response inhibition</i>									
Prenatal smoke exposure	Superior parietal lobule, postcentral, supramarginal gyrus	9.20 (2.69)	9.18 (2.70)	6.05 (2.41)	11.87 (2.75)	6.87 (2.14)	12.31 (3.29)	7.22 (2.92)	11.10 (2.24)
Prenatal alcohol exposure	Orbitofrontal cortex	11.03 (2.29)	7.15 (1.72)	5.55 (2.58)	11.11 (1.66)	7.77 (2.27)	9.29 (1.81)	10.05 (1.85)	6.41 (2.21)
<i>DRD4</i> genotype	Superior parietal lobule, supramarginal gyrus	-5.09 (2.58)	-9.53 (2.51)	-2.91 (2.94)	-8.96 (2.26)	-4.85 (2.51)	-9.27 (2.52)	-5.62 (2.43)	-10.87 (2.73)
<i>Failed – successful inhibition</i>									
Prenatal smoke exposure	Supramarginal, superior temporal, postcentral gyrus	13.82 (3.01)	11.36 (2.49)	11.01 (2.92)	13.10 (2.60)	12.49 (2.49)	11.61 (3.05)	8.80 (2.55)	15.85 (2.81)
Prenatal smoke exposure	Supramarginal, postcentral gyrus	10.82 (2.75)	10.73 (2.10)	10.34 (2.60)	11.31 (2.34)	10.70 (2.20)	10.08 (2.74)	9.03 (2.08)	12.40 (2.59)

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<i>DAT1</i> genotype	Cerebellar Crus II	-6.94 (2.74)	-8.41 (2.33)	-9.47 (3.20)	-6.92 (2.13)	-9.89 (2.42)	-3.89 (2.47)	-7.21 (2.22)	-7.55 (3.05)
<i>DRD4</i> genotype	Lateral occipital cortex	14.82 (3.30)	12.63 (3.18)	14.35 (3.87)	14.46 (2.95)	14.48 (3.09)	13.97 (3.33)	7.02 (3.13)	18.26 (3.17)
<i>DRD4</i> genotype	Frontal pole, frontal medial cortex	8.07 (2.60)	13.50 (2.64)	11.87 (3.30)	9.99 (2.29)	11.50 (2.69)	10.47 (2.50)	10.13 (2.43)	11.37 (2.90)

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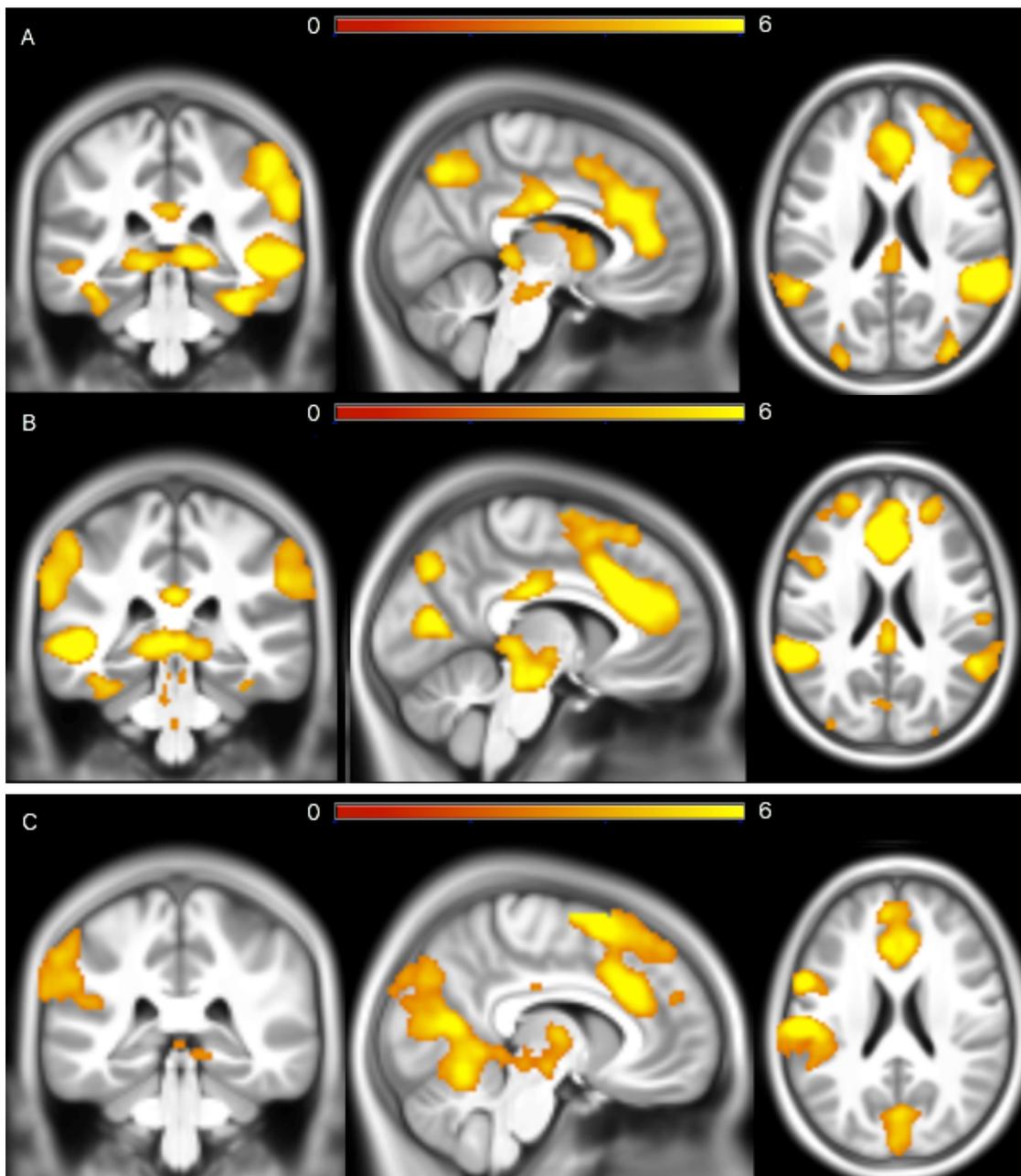
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Task activity

Figure S1. Task activity maps identified for the successful inhibition - go contrast (A), failed inhibition - go contrast (B), and failed - successful inhibition (C).



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Note: the color-coding of these maps reflects Z-values, with yellow hues representing stronger effects. The maps are thresholded at $Z=2.3$ and overlaid on the study sample's average anatomical image at MNI-coordinates $X=-8$, $Y=-32$, $Z=24$