Genetic and environmental substrates of structural brain abnormalities in ADHD

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Introduction

Anatomical studies have indicated volume reductions in several brain areas of ADHD subjects. We evaluated the extent to which these are mediated by genetic and/or external environmental influences.

A: the contribution of genetic factors was studied by comparing monozygotic (MZ) twin pairs who were ADHD concordant with pairs in which both twins were unaffected. ADHD is highly heritable, thus differences in brain volumes between these groups are likely of genetic origin.

B: environmental influences were assessed by comparing brains of MZ pairs discordant for ADHD in which one twin was affected and the other unaffected. MZ twins are genetically identical, ADHD within pair discordance is likely to arise from different environmental exposure.

Methods

Attention problem (AP) T-scores (defined separately for boys and girls) were available for 6150 MZ twin pairs, from The Netherlands Twin Register. At least two AP ratings from the Child Behaviour Checklist (CBCL4/18) had to be available at age 7, 10, and/or 12. Three groups were selected and successfully completed an MRI session:

1: affected concordant (3 pairs; 15.0 ± 2.4 yrs) : both twins high on AP
2: unaffected concordant (17 pairs; 15.1 ± 1.1 yrs): both twins low on AP
3: discordant (5 pairs; 14.2 ± 1.8 yrs): one twin low, and co-twin high

AP high: a T-score above 60 at all times, with at least one above 65.
AP low : a T-score below 55 at all times.

Of each twin, 3 whole brain MR scans (1.5 T) were collected. Local changes in gray matter (GM) volume were assessed using Voxel Based Morphometry (VBM). Data were compared between *affected* and *unaffected concordants* by one-way ANOVA and between AP *discordants* by paired T-test. Individual voxel p-value threshold was p < 0.0005, with minimal cluster size of 2000 voxels.

Results

A: Genetic contrast: *affected* versus *unaffected* concordants

Global GM volume: no difference

Regional GM volume (VBM results):

reduced GM (fig1: top)	increased GM (fig 1: bottom)
1: midline parietal	1: left motor
2: right temporoparietal	2: left ventral PFC
3: right orbitofrontal	3: right ventral PFC.

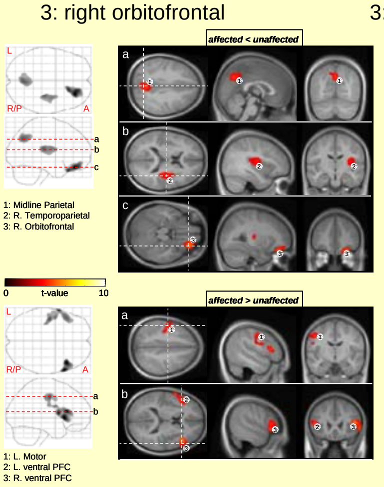

Fig. 1: Parametric *t* maps, projected on MR sections, showing regional gray matter volume decreases (top) and increases (bottom) in the affected relative to the unaffected concordant twins.

B: Environmental contrast: *affected* versus *unaffected* discordants

Global GM volume: reduced in the affected child in 4 of the 5 twin pairs

Regional GM volume (VBM):

reduced GM (fig2: top)	increased GM (fig 2: bottom)
1: right parietal	1: right frontal
2: right occipitotemporal	2: left frontal
3: midline occipital	3: right dorsal PFC
4: left anterior temporal	4: left anterior cingulate
5. left ventral PFC	5: right anterior cingulate

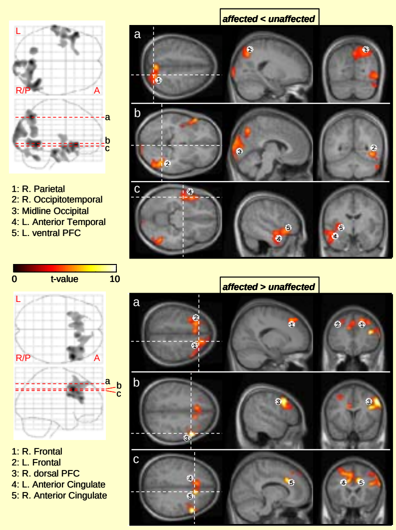

Fig. 2: Regional gray matter decreases (top) and increases (bottom) in the affected versus unaffected discordants.

Conclusions

ADHD related GM abnormalities between *affected* and *unaffected concordants* and between MZ *discordants*:
This indicates that ADHD related brain changes are not necessarily genetically driven. Different brain regions emerged in the comparison of affected and unaffected pairs relative to the comparison of affected and unaffected subjects in discordant pairs. This suggests that the cognitive problems in ADHD with a genetic origin reflect a different anatomical substrate compared to ADHD with an environmental origin.

In ADHD likely of genetic origin, GM volume reductions were observed in midline parietal and right temporoparietal areas associated with attention and motor processing, respectively. A reduction in orbitofrontal cortex may relate to emotional instability and impulsivity symptoms in ADHD.

In ADHD through external environmental influences, GM reductions in midline occipital, right parietal and right occipitotemporal areas point to involvement of the visual processing and attention system. Reductions of left ventral prefrontal and anterior temporal cortices indicate possible impairments of the action-attentional network subserving attentional focus and behavioural inhibition.

Our finding of *frontal GM increases* with ADHD in both concordant and discordant comparisons appears to contrast with earlier studies. However, earlier results predominantly relied on measures of global frontal cortex volume. Our study compared regional ADHD related brain changes on a voxel by voxel basis.