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Genetic and environmental substrates of white matter changes in ADHD: a combined VBM/DTI study

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Introduction

Anatomical studies have indicated structural abnormalities of both gray and white matter in several brain areas of ADHD subjects (Makris et al., 2008; Seidman et al., 2005). In this study we evaluated the extent to which ADHD related white matter changes are mediated by genetic and/or external environmental influences. 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. 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

Participants: Attention problem (AP) T-scores (defined separately for boys and girls) were available for 4877 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 (7 pairs; 15.0 ± 2.4 yrs) : both twins high on AP
2: unaffected concordant (15 pairs; 15.1 ± 1.1 yrs) : both twins low on AP
3: discordant (8 pairs; 14.2 ± 1.8 yrs): one twin high, and co-twin low

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.

MRI acquisition and preprocessing: Of each twin, whole brain structural T1 weighted MR scans and diffusion tensor imaging (DTI) scans were collected (1.5 T Siemens Sonata scanner). Local changes of white matter (WM) were assessed using Voxel Based Morphometry (VBM) and voxel by voxel comparison of Fractional Anisotropy (FA) and Apparant Diffusion Coefficient (ADC) scalars computed from the diffusion scans.

Statistical analysis: Data were compared between *affected* and *unaffected concordant* twin pairs by one-way ANOVA and between AP *discordant* twins by paired T-test.

Results

Local white matter decrements (fig. 1): Relatively decreased white matter in AP high compared to AP low scoring twins was mainly restricted to the posterior cortex and cerebellum.

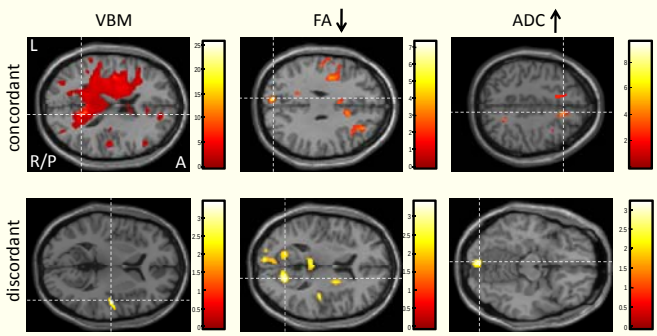

Figure 1: Clusters of local white matter decrements associated with attention problems from VBM (left), DTI-FA (middle) and DTI-ADC (right) in the concordant AP high versus low twin pair ANOVA comparison (top) and discordant AP high-low twin paired t-test comparison (bottom). Color bars indicate statistical t-value coding. Cross hairs indicate cluster with maximal statistical significance (global maximum).

Local white matter increments (fig. 2): Evidence for local white matter enhancement in AP high scoring twins was more abundant. Both VBM and DTI techniques indicated clusters of locally increased white matter for concordant as well as discordant AP high scoring twins, in particular within the frontal lobes.

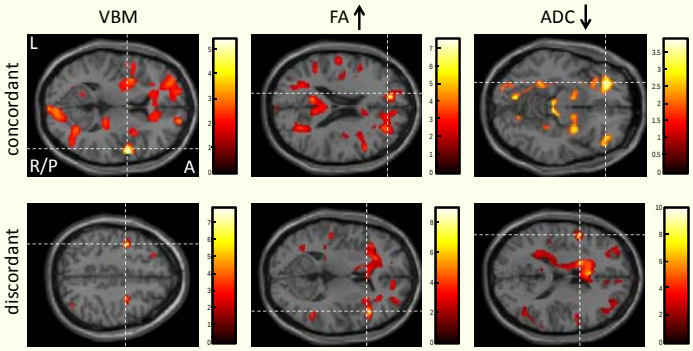

Figure 2: Clusters of local white matter increments associated with attention problems from VBM (left), DTI-FA (middle) and DTI-ADC (right) in the concordant AP high versus low twin pair ANOVA comparison (top) and discordant AP high-low twin paired t-test comparison (bottom). Color bars indicate statistical t-value coding. Cross hairs indicate cluster with maximal statistical significance (global maximum).

Conclusions

The most prominent result of our study is the finding of AP related white matter increments in both AP concordant and AP discordant twin-pairs, in particular for anterior regions of the brain.

White tissue enhancement in adolescents with attention problems is in line with a previous report on structural brain changes in adult ADHD patients (Seidman et al., 2006) and may exist for many reasons. It may reflect an abnormal gray-white matter balance due to excessive growth of white matter or a regional lack of synaptic pruning during brain development (Huttenlocher, 1979). Alternatively, local white matter volume increments may indicate a plastic adjustment to compensate for neural loss and consequently reduced processing capability of adjacent brain regions.

Our finding that frontal white matter enhancement was present in both concordant and discordant twin comparisons suggests that aberrant white matter development in ADHD is driven by genetic as well as environmental risk factors.

References:

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