Autistic traits in children with ADHD index clinical problems
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Which conditions are being investigated?
Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)
Common, highly heritable childhood onset neurodevelopmental disorders with established clinical and genetic overlap1

Background to ASD traits in ADHD
The significance of autistic traits in ADHD is not fully understood
Studies investigating ASD traits in ADHD have found increasing autistic levels of autistic symptoms index
- Increased likelihood of having ADHD combined subtype2
- Greater frequency of hyperactive-impulsive symptoms1
- Increased comorbidity with oppositional defiant disorder (ODD) and conduct disorder (CD)1
- But only tentative conclusions can be made as there have been few studies, with conflicting results and methodological limitations

Aims
To address whether ASD traits in ADHD index a more severe clinical profile
To determine whether any ASD sub-domain is independently associated with outcome measures found to have association in the main analysis

Sample
Clinical sample (SAGE – Study of ADHD Genes and Environment) of 711 young people age 5-18 with any subtype of ADHD, 84% male, IQ 43-124
Exclusions: ASD, Tourette’s, epilepsy, bipolar, >10% missing data on ASD trait measure (total score or any sub-domain score)

Measures
ADHD, ODD, CD, anxiety, depression: Child & Adolescent Psychiatric Assessment
ASD traits: Social Communication Questionnaire (SCQ) (>15/40 = cut-off threshold for suspected ASD)
SCQ subscales: Social deficits, communication deficits and restrictive and repetitive behaviours (RRBs)
Full scale IQ: WISC-IV

Total SCQ score (predictor variable)
Associations measured using linear & logistic regression

Clinical characteristics (outcome variables)

Outcome variable | Unadjusted (max n=711) | Adjusted (max n=599) | Adjusted (max n=599)
<table>
<thead>
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<tr>
<td></td>
<td>p-value</td>
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<tr>
<td>DSM-IV combined ADHD diagnosis</td>
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<td>ADHD symptoms: inattentive</td>
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<td>DSM-IV ODD diagnosis</td>
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<td>DSM-IV CD diagnosis</td>
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<td>ODD symptoms</td>
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<td>2.6E-08</td>
<td>6.4E-06</td>
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<td>CD symptoms</td>
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<tr>
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<td>Depression symptoms</td>
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Primary analyses
Significant associations between increasing levels of autistic traits and
a) ADHD severity
b) ODD, CD and anxiety symptoms

Secondary analyses
Aggressive conduct symptoms showed independent association with SCQ scores
Sub-domain scores (social deficits, communication deficits and RRBs) did not show unique contributions to most outcomes except...
Social deficits were independently associated with oppositional symptoms
RRBs independently predicted hyperactive-impulsive and anxiety symptoms

Strengths
Large sample size, correction for multiple testing
Rigorous phenotyping, putative confounders addressed
Inclusion of those with intellectual disability (ID) (pattern of results the same as those with ID excluded)
Continuous analysis of ASD trait scores (pattern of results the same when analysed according to above / below SCQ screening threshold cut-off score)

Limitations
Unclear whether SCQ has validity for autistic traits in ADHD in the same way it does in the general population / in ASD
Possible that some of those who score highly on the SCQ may go on to receive a diagnosis of ASD
A small proportion of parents did not withhold stimulant medication for 24 hours prior to cognitive testing
Research is cross-sectional

Clinical implications
Rather than considering mutually distinct categorical diagnostic classes, it would be worthwhile acknowledging the strong presence of ASD traits in young people with ADHD
Levels autistic traits should be considered in those with ADHD who do not meet full diagnostic criteria for ASD, as such traits index higher levels of phenotypic complexity and adversity
Undiagnosed deficits in socio-communicative abilities may impact on the effectiveness of behavioural interventions for ADHD. If strategies aimed at addressing ASD symptoms could also be implemented, these might improve the effect of ADHD interventions, reduce comorbidities and distress, and facilitate learning

Conclusions
In children with ADHD, increasing levels of ASD symptomatology index a more severe clinical phenotype
Associations unlikely to be driven simply by ADHD severity as this was accounted for in the adjusted analyses
Results confirm and expand findings from previous research
White matter microstructure predicts autistic traits in ADHD
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To be published as ‘White matter microstructure predicts autistic traits in attention-deficit/hyperactivity disorder’, Journal of Autism and Developmental Disorders, in press

What is the background to autistic traits in ADHD?
Autistic traits in ADHD are common¹ and are a marker of clinical severity² However their biological significance is unclear

1) Romanek et al (2010); 2) Cooper, Martin et al (2014)

What is diffusion MRI?
Diffusion MRI is a type of magnetic resonance imaging (MRI) scanning which examines white matter (WM) pathways - networks of nerve fibres which connect different brain areas
Diffusion parameters derived from diffusion MRI scans, such as the fractional anisotropy (FA) and mean, axial and radial diffusivities (MD, AD and RD) provide measures of the microstructure of white matter (WM) pathways. WM microstructure includes axonal density, diameter, branching and myelination
In this way, alterations in diffusion parameters allow us to infer alterations in WM microstructure from the typical

What has diffusion MRI found in ADHD and ASD to date?
Alterations in WM microstructure have been found throughout the brain in both ADHD³ and ASD⁴ Correlations have also been found between symptom severity and microstructure in both disorders, but with no clear patterns of findings to date
However no study to date has investigated associations between diffusion parameters and autistic traits in ADHD

Aims
To establish whether there is a microstructural correlate of autistic traits in ADHD, i.e. are there any associations between diffusion parameters and the level of autistic traits in ADHD?
To examine whether there are associations between WM microstructure and current ADHD severity
To examine whether there are case-control differences in the WM microstructural network

Sample
40 young people age 14-18, all right handed males with IQ >70 19 with combined type ADHD (from SAGE), 21 controls
Exclusions: ASD, ID, Tourette’s, psychosis, extreme prematurity or low birth weight, contraindications to MRI scanning

MRI scanning and data processing
Mock scanner prior to scan
3T MRI, 60 direction diffusion scan, cardiac gating
Not required to stop medication as no functional scans
Motion/distortion correction
Outliers/residual plots inspected, significant artefact/exclusion Tensor estimated by RESTORE
17 ADHD and 17 control participants in final analyses

Analysis by tract-based spatial statistics (TBSS)⁵
TBSS carries out voxelwise analysis of diffusion data across the white matter of the whole brain Reduces the WM to a skeleton, which reduces the number of independent comparisons made 500 permutations, threshold-free cluster enhancement, correction for multiple testing
5) Smith et al 2006

Measures
ADHD severity: DuPaul rating scale
ASD traits: Social Communication Questionnaire (SCQ)
Full scale IQ: WISC-IV

Strengths
Relative sample homogeneity (lifetime diagnoses of combined type ADHD in patient group) Narrow age range
All right handed males (reduces influence of potential confounding variables) 600 diffusion imaging with cardiac gating Medication > decrease motion

Limitations
Small sample size Variable medication histories of ADHD group Limitations of TBSS approach – cannot delineate complex WM fibre architecture Research is cross-sectional

Interpretation
Not in areas where there are extensive reports of ASD case-control differences, though some reports of ADHD case-controls differences in the PLIC/CST Implies autistic traits may relate to microstructure differently in the context of a primary diagnosis of ADHD

Conclusions
This is the first report of a microstructural signature of autistic traits in ADHD Adds to the growing evidence on the nature of links between these conditions Highlights the potential impact of even sub-threshold socio-communicative difficulties in ADHD

Many thanks to all the families who gave their time and effort to take part in this research

Summary
Autistic traits in ADHD were predicted by a particular pattern of WM microstructure
Positive correlations between SCQ score and FA, predominantly in the right inferior posterior limb of the internal capsule / corticospinal tract, and negative correlation between SCQ score and RD in the midbrain

Areas of correlation between WM microstructure and autistic traits in the ADHD group
Associations driven predominantly by socio-communicative component of SCQ scores
No associations between microstructure and current ADHD severity
No case-control differences
No effect of age as a covariate
No correlation between diffusion parameters and age across the total sample
No age x group interactions
Results same when two ‘remitted’ subjects excluded

Areas of significant (p<0.05, corrected) positive correlation between FA and SCQ score (red)
Areas of significant (p<0.05, corrected) negative correlation between RD and SCQ score (blue)