Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder

Grainne M. McAlonan, Vinci Cheung, Siew E. Chua, Jaap Oosterlaan, Se-fong Hung, Chun-pan Tang, Chi-chieh Lee, Shi-leung Kwong, Ting-pong Ho, Charlton Cheung, John Suckling and Patrick W. L. Leung

Background
Children with attention-deficit hyperactivity disorder (ADHD) have difficulties with executive function and impulse control which may improve with age.

Aims
To map the brain correlates of executive function in ADHD and determine age-related changes in reaction times and brain volumes.

Method
Attention-deficit hyperactivity disorder and control groups were compared on the change task measures of response inhibition (stop signal reaction time, SSRT) and shifting (change response reaction time, CRRT). Voxel-wise magnetic resonance imaging (MRI) correlations of reaction times and grey matter volume were determined, along with bivariate correlations of reaction times, brain volumes and age.

Results
Individuals in the ADHD group had longer SSRTs and CRRTs. Anterior cingulate, striatal and medial temporal volumes highly correlated with SSRT. Striatal and cerebellar volumes strongly correlated with CRRT. Older children had faster reaction times and larger regional brain volumes. In controls, orbitofrontal, medial temporal and cerebellar volumes correlated with CRRT but not SSRT. Neither reaction times nor regional brain volumes were strongly age-dependent.

Conclusions
Our evidence supports delayed brain maturation in ADHD and implies that some features of ADHD improve with age.

Declaration of Interest
None. Funding detailed in Acknowledgements.

Cognitive testing
Children taking methylphenidate were asked to stop taking their medication 48 h prior to testing. Participants were tested on an extended version of the stop task – the change task. In the change task, the stop signal prompts both response inhibition and re-engagement which can be measured by two performance indices (i.e. SSRT and CRRT). In brief, 75% of trials in the task were ‘go’ trials; participants had to locate an aircraft presented on the left or right of a computer screen and use their left hand to press the corresponding left or right response button with middle or index fingers respectively. Twenty-five per cent of trials were stop trials presented pseudo-randomly. In response to an auditory signal in stop trials, participants had to inhibit their response and immediately press a third button with their right thumb (the change response). A lengthened SSRT is thought to reflect impaired inhibitory control and is derived from the ‘inhibition function’; generated by plotting the probability of inhibition against the range of stop signal intervals and correcting for non-responses, as previously reported. The rationale behind this correction is that non-responses may occur on stop trials, thereby increasing the probability of inhibition. The CRRT is...
the time taken to shift to a new response using the right
thumb. A lengthened reaction time suggests inefficient response
re-engagement, i.e. difficulty shifting to a new response.

We used independent t-tests in SPSS (version 15.0 for
Windows) to examine group differences in SSRT and CRRT. In
addition, although the groups were balanced for age, we also
examined the relationship of age to reaction time indices for each
group separately in bivariate correlation analyses. Between-group
differences in age-related performance were investigated by
transforming Pearson r’s into Fisher z-scores to test the
significance of the difference between correlations.12

MRI acquisition and analyses

Three millimetre slice thickness, dual-echo fast spin echo data-sets
aligned to the anterior–posterior commissural (AC–PC) line were
acquired across the whole brain on a GE signa 1.5 T system
(General Electric, Milwaukee, Wisconsin, USA). Pre-processing
of the images followed methods previously described in a group
comparison study which included the majority of these children.6
That is, images were segmented by setting voxels representing
extracerebral tissue to zero and probability of each intracerebral
voxel belonging to grey matter, white matter, cerebrospinal fluid
or dura/vasculature tissue classes was calculated. Knowing the
voxel size (2.2 mm³), the volume of any tissue class could be
estimated at each voxel and summed across all intracerebral voxels
to yield global tissue class volumes. The segmented grey matter
images were mapped onto standard space by minimising the
sum of square intensity difference of each proton density image
to a group-specific template and smoothed with a 4.4 mm kernel.
Simple linear regression of reaction time indices with grey matter
volume at each intracerebral voxel was carried out using BAMM
software (Brain Analysis Morphological Mapping version 2.5,
Cambridge University) for each group separately. Regions of
significant correlation were identified in two stages by permuta-
tion test. Initially, a voxel-wise probabilistic threshold was applied
to generate three-dimensional clusters characterised by their mass,
or the sum of suprathreshold voxel statistics it comprised. Clusters
were then subject to a non-parametric analysis by randomly
generating 10 permuted maps to sample the null hypothesis that
significant correlations occur by chance. The statistical thresholds
were corrected for multiple comparisons by controlling the ‘family
wise error rate’ expected such that the number of false positive
tests for each map was less than 1 false positive cluster. We also
examined the bivariate correlations of age with the brain volumes
derived from the voxel-based analysis in each group using SPSS
15.0 for Windows.

Results

Change task performance

Children with ADHD made more errors than children in the
control group. Despite having similar reaction times to controls
on go trials, their reaction times were more variable, as indicated
by their significantly greater reaction time standard deviations. We
also confirmed a significantly slower SSRT and CRRT in this
sample of children with ADHD compared with typically develop-
ing controls (Table 1). Older children with ADHD had faster
reaction times than younger children (SSRT: age \( r = -0.45,\)
\( P=0.04;\) CRRT: age \( r = -0.56,\) \( P=0.007).\) As shown in Fig. 1,
children with ADHD had similar reaction times to controls at a
later age, and tended to ‘catch-up’ with controls by 12 years.
Age did not strongly correlate with SSRT in the control group
(\( r = 0.33,\) \( P=0.11); the correlation of age with CRRT in the
control group just failed to reach significance (\( r = 0.39,\)
\( P=0.054).\) However, the group difference between the correlation

Table 1  Group statistics

<table>
<thead>
<tr>
<th>Parametera</th>
<th>Mean (s.d)</th>
<th>t-test</th>
<th>Significance (2-tailed)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>112.34 (10.98)</td>
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<td>0.672</td>
</tr>
<tr>
<td>ADHD</td>
<td>114.09 (18.14)</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.01 (1.65)</td>
<td>0.293</td>
<td>0.771</td>
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<td>ADHD</td>
<td>8.87 (1.78)</td>
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<tr>
<td>Stop signal reaction time</td>
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<tr>
<td>Control</td>
<td>355.65 (134.85)</td>
<td>-2.232</td>
<td>0.030</td>
</tr>
<tr>
<td>ADHD</td>
<td>451.22 (171.11)</td>
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<tr>
<td>Change response reaction time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>592.23 (133.95)</td>
<td>-3.157</td>
<td>0.003</td>
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<tr>
<td>ADHD</td>
<td>731.89 (182.23)</td>
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<td>Change response reaction time standard deviations</td>
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<tr>
<td>Control</td>
<td>188.45 (89.07)</td>
<td>-2.53</td>
<td>0.015</td>
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<tr>
<td>ADHD</td>
<td>263.16 (121.98)</td>
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<tr>
<td>Total errors</td>
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<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>8.79 (13.07)</td>
<td>-2.07</td>
<td>0.044</td>
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<tr>
<td>ADHD</td>
<td>19.27 (22.78)</td>
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<tr>
<td>Mean reaction times²</td>
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<tr>
<td>Control</td>
<td>543.23 (108.12)</td>
<td>-1.41</td>
<td>0.16</td>
</tr>
<tr>
<td>ADHD</td>
<td>589.13 (108.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time standard deviations</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>139.38 (32.49)</td>
<td>-4.44</td>
<td>0.000</td>
</tr>
<tr>
<td>ADHD</td>
<td>195.10 (56.54)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD, attention-deficit hyperactivity disorder.
a. Control, \( n=29;\) ADHD, \( n=22.\)
b. Significant group differences are shown in bold.
c. Mean reaction times, reaction times on go trials.
coefficients for SSRT or CRRT was not significant (z_0.45 and z_0.80 respectively).

**MRI reaction time correlates**

In the ADHD group, two scans with movement artifact were excluded. In the control group, four children refused a scan; one scan with movement artifact was excluded. Therefore, scans from 20 children with ADHD and 24 controls entered analyses.

**Grey matter correlates of SSRT**

Attention-deficit hyperactivity disorder

There was a significant negative correlation between SSRT and the volume of grey matter clusters in the anterior cingulate, right lentiform nucleus and the left medial temporal lobe (involving amygdala, hippocampus and parahippocampal regions) in children with ADHD (false positive clusters < 1, cluster test significance P=0.001; Fig. 1 and Table 2). Thus, better/faster inhibition was associated with greater grey matter volumes in these regions in those with ADHD. Grey matter regions correlated with SSRT showed significant positive intercorrelations (Table 2). Eighty-nine per cent of the variance in SSRT was jointly explained by these volumes (r= –0.94, P < 0.001, R^2=0.887). Age was significantly positively correlated with regional grey matter volumes, but not total grey matter volumes. Thus older children, who had larger regional brain volumes in temporal–pallidal–anterior cingulate, had faster SSRT (Fig. 2).

Controls

No regional volumes were correlated with SSRT in the control group. Age was not correlated with SSRT in the control group (r= –0.33, P=0.11).

**Grey matter correlates of CRRT**

Attention-deficit hyperactivity disorder

Negative correlations between regional brain volumes and CRRT in the ADHD group involved the right lentiform nucleus and left cerebellum (false positive clusters < 1, cluster test significance P=0.001; Fig. 2 and Table 3). Again, larger regional volumes were linked with faster reaction times (Table 2). The volume of the cerebellar cluster and basal ganglia clusters correlated with CRRT also showed a significant positive intercorrelation (Table 3). Approximately 75% of the variance in CRRT was jointly explained by these volumes (r= –0.87, P < 0.001, R^2=0.75). Age was significantly correlated with these volumes, but not total grey matter volume as shown in Table 2. Thus, older children with larger regional brain volumes in basal ganglia and cerebellum had faster CRRT (Fig. 2).

Controls

The volume of grey matter clusters in ventral prefrontal cortex, right medial temporal lobe and cerebellum (midline and left hemisphere) was negatively correlated with CRRT (false positive clusters < 1, cluster test significance P=0.001; Fig. 2 and Table 4). Thus, larger regional volumes were linked with faster reaction times. These grey matter volumes showed significant positive intercorrelations (Table 4). Seventy-seven per cent of the variance in CRRT in controls was jointly explained by these volumes (r= –0.88, P < 0.001, R^2=0.77). Age did not correlate with regional brain volumes.

**Supplementary analysis**

To control for the confounding effect of age on regional brain volume we ran a partial correlation analysis on regional volumes and reaction times with age controlled. For all children, controls and those with ADHD, the highly significant correlation between
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Consistent with previous reports, the ADHD group performed more poorly than age and IQ-matched typically developing controls in the change task. They had difficulty inhibiting a prepotent response (longer SSRTs) and took longer to shift to a new response (CRRT). These reaction times were very highly correlated with fronto-striatal-temporal volumes. The volumes increased with age, and older children with ADHD had faster reaction times than younger children. Specifically, more efficient inhibitory control was linked to larger regional grey matter volumes in bilateral anterior cingulate, right basal ganglia and left temporal circuitry in ADHD. Faster response re-engagement was linked to larger regional grey matter volumes in striatum and medial temporal lobe. The choice of the change task rather than the stop signal task, meant that additional demands upon executive function, in terms of regional brain volume and reaction time was preserved. The minimum Pearson \( r = 0.53, P < 0.01 \).

### Discussion

Associations between right-sided frontostralial volumes and response inhibition have previously been reported in a region-of-interest study of ADHD. In their study, Casey et al investigated three different response inhibition tasks. However, only one component of the range of attention tasks examined is in some way comparable to the SSRT measure of inhibition examined here, namely the reaction time in go/no-go ‘response execution’ inhibitory trials. Interestingly, Casey’s group found a significant positive correlation between left globus pallidus volume and mean reaction time in control boys, but not boys with ADHD. In contrast, in our whole brain grey matter voxel-wise analyses we found the SSRT was very strongly correlated with a prefrontal-temporal-right pallidal circuit in boys with ADHD and not controls. Thus task differences, as well as very different approaches to analysis, may contribute to the discrepancy between the studies.

Our findings of bilateral frontal correlations of impaired inhibitory control in ADHD deviate from those of an elegant series of studies comparing inhibitory dysfunction after right frontal lesions to dysfunction in ADHD. These authors emphasised right lateralised frontal involvement in this function. However, both studies implicated the right striatum. Disentangling the direct effects of a lesion from the indirect or compensatory actions of intact brain structures is a challenge which can complicate interpretation of lesion studies. The voxel-based approach adopted here has the advantage of exploring potential whole brain grey matter correlates of inhibitory control in ADHD directly, and may explain why our results do not completely coincide with lesion studies.

The choice of the change task rather than the stop signal task, meant that additional demands upon executive function, in terms...
of response re-engagement, could be addressed. We found the volume of the right basal ganglia linked to both inhibition and response shifting ability in ADHD. The demands of response re-engagement were also correlated with left cerebellar volume in ADHD. In the control group, this reaction time index was strongly correlated with cerebellar volumes. The implication, that the cerebellum is important for response shifting, fits growing recognition of its interaction with the prefrontal lobe to affect higher order cognitive processing.27,28 Indeed CRRT in the control group was also correlated with volumes in the ventral prefrontal cortex.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Correlates of change response reaction times in controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control and CRRT (n=24)</td>
<td>Vermis</td>
</tr>
<tr>
<td></td>
<td>-9.2 – 57.3 – 34.8</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>0.896**</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.805**</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.930**</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>0.889**</td>
</tr>
<tr>
<td>Total grey</td>
<td>0.428*</td>
</tr>
<tr>
<td>CRRT</td>
<td>-0.836**</td>
</tr>
<tr>
<td>Age</td>
<td>0.253</td>
</tr>
</tbody>
</table>

BA, Brodmann area; CRRT, change response reaction time.

*P<0.05, **P<0.01 (2-tailed).

Fig. 2 Regional brain volume correlates of reaction time indices.
(a) Stop signal reaction time correlates in attention-deficit hyperactivity disorder (ADHD), (b) change response reaction time (CRRT) correlates in ADHD, (c) CRRT correlates in controls. Blue clusters: negative correlation (false positive clusters < 1, P=0.001). Left side of brain is on the right of the panel (z-coordinates shown).
We expected to find prefrontal cortex volumes correlated with CRRT in the ADHD group. Therefore, since the variance in CRRT accounted for jointly by the volumes of clusters in the right basal ganglia and left cerebellum was modest at 75%, we relaxed the statistical thresholding to allow <2 false positive clusters at P < 0.002. In this analysis we found significant clusters in anterior cingulate and right medial temporal lobe were also associated with time taken to shift response. When subsequently added, these volumes together explained approximately 83% of the variance in CRRT (r = −0.91, P < 0.001, R² = 0.83). Thus, the correlates of inhibition and choice reaction times appear to involve a similar neural system in ADHD. Interestingly, studies of other populations with neurodevelopmental difficulties agree that a selective network incorporating the cerebellum, right basal ganglia, and cingulate appears important for inhibitory processes.

The present study implicates the medial temporal lobe in inhibitory control in ADHD. Disinhibition may theoretically arise from disruption to a motivational limbic-based system.32,33 In this conceptualisation, motivational anomalies in children with ADHD result in inappropriate behaviour. Animal models support a key role for hippocampal areas in a ‘behavioural inhibition system’ which normally interrupts ongoing activity when an expected reward is not evident, or when a signal for punishment is detected.34 This model has been applied to children with ADHD35 who appear to have an altered sensitivity to reward contingencies.36,37 Thus, our finding that inhibitory control in children with ADHD is associated with the volume of both frontal (anterior cingulate) grey matter and the amygdala/hippocampal complex is exciting. It fits with recent evidence that the anterior cingulate in humans is essential for integrating information about reward and directing decision-making.38,39 Of note, unlike for the striatum and cingulate, age did not strongly correlate with temporal volumes in the ADHD group. This may point to some rather more fixed impact of temporal lobe structure. It will be interesting to manipulate reward contingencies in future studies to explore how motivational variables might have contributed to the present result.

Age-related changes in grey matter in ADHD were not global and only regional, not total, grey matter volumes showed significant age-related increase. Thus, there appeared to be a dissociation of global grey matter volumes and the striatal network implicated here in ADHD. We speculate that this may have something to do with an altered pattern of maturation in ADHD. Indeed, the regional brain volumes implicated in reaction timing in ADHD did not correlate with total grey matter volumes. In contrast, regional grey matter volumes associated with CRRT in the control group did generally correlate with total grey matter volume. We postulate that a delay in grey matter maturation in a restricted striatal network in ADHD might render this circuit ‘out-of-step’ with overall whole brain development. We identified strong positive volumetric correlations between prefrontal cortex, basal ganglia and medial temporal lobe linked to reaction time indices in ADHD. Such intercorrelations are thought to reflect connectivity as interconnecting systems share common developmental and maturation influences. The present anatomical pattern is consistent with known direct projections between the anterior cingulate and amygdala/hippocampus and indirect connections via the basal ganglia.41 Moreover, a genetic ‘dopamine-deficit’ in this mesolimbic-cortical network, especially the D2-rich frontal lobes, has been postulated in ADHD.42 Taken together, the evidence suggests that executive dysfunction in ADHD depends upon maturation of a restricted dopaminergic frontostriatal network.

Limitations

Our study has a number of limitations. We documented the relationship between functional indices, brain volume and age in children less than 12 years old, i.e. likely to be prepubertal. Cortical grey matter volumes begin to decrease from the age of 12 years, with prefrontal lobe volume reduction happening last in sequence.43 Thus, it will be important to establish how neuro-psychological function and brain morphology are affected by ADHD in an older age group. Our study was cross-sectional, therefore we can only comment on age-related findings. Clearly further longitudinal studies are needed to properly address the issue of brain maturation delay in ADHD. This would be particularly important in those few individuals with ADHD in whom regional brain volumes were markedly lower and reaction times longer than children of a similar age. It is possible that deviations from the age-dependent pattern observed here have implications for prognosis.

With the exception of three newly diagnosed children, the participants in our study were considered to be responsive to stimulant medication. Therefore we cannot say whether the results apply to children with ADHD who do not respond to medication. Moreover, we did not have detailed information about the treatment protocol followed by these boys, so we cannot be certain what effect drug treatment had on the results. Although medication does not appear to grossly alter brain structure in ADHD,44 evidence from a recent positron emission tomography study suggests that the degree of inattention and impulsivity in adolescents with ADHD is linked with dopamine receptor sensitivity to medication.45 The interaction of brain, behaviour and medication needs closer examination and will be a focus of further studies. Lastly, our work focused solely on male children with ADHD and we do not know to what extent our observations generalise to females and adults with ADHD. Future work is planned to address these issues.

Our study illustrates the use of voxel-based methods to explore the brain morphology underlying complex behavioural indices affected by ADHD and should encourage its wider application. The results link grey matter volume of a discrete prefrontal-pallidal-temporal circuit to executive performance in ADHD. In older children with ADHD the volume of this circuitry is greater and their reaction times are faster. This has the welcome implication that some features of ADHD may improve with age.

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References


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