

Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study

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Summary A functional magnetic resonance imaging mental rotation paradigm was used to investigate the patterns of activation of fronto-parietal brain areas in male adolescents with attention-deficit hyperactivity disorder, combined type (ADHD-CT) compared with age-, gender-, handedness- and performance IQ-matched healthy controls. The ADHD-CT group had (a) decreased activation of the 'action-attentional' system (including Brodmann's areas (BA) 46, 39, 40) and the superior parietal (BA 7) and middle frontal (BA 10) areas and (b) increased activation of the posterior midline attentional system. These different neuroactivation patterns indicate widespread frontal, striatal and parietal dysfunction in adolescents with ADHD-CT.

Declaration of interest None.

There is functional imaging evidence that the heteromodal association areas, the dorsolateral prefrontal (including Brodmann's areas (BA) 44, 45, 46), lateral temporal (including 38, 21, 20) and posterior parietal regions (including BA 40), form a functional system of neural networks (Mesulam, 1990) that subserve disengaged, reoriented and maintained attentional focus (Peterson *et al*, 1999) and inhibition of contextually irrelevant stimuli (Garavan *et al*, 1999) and that these neural networks are dysfunctional in adolescents with attention-deficit hyperactivity disorder, combined type (ADHD-CT) (Sowell *et al*, 2003). In addition, the core ADHD-CT symptoms are associated with caudate nucleus lesions, decreased caudate volume and decreased left caudate activation (Rubia *et al*, 1999).

To date, the specific patterns of activation of fronto-parietal brain areas in

adolescents with ADHD-CT compared with matched healthy controls have not been reported. Mental rotation tasks are known to activate the superior parietal areas (Parsons, 2003) and the middle frontal areas (Booth *et al*, 2000), in healthy children and adults. In this study we used a functional magnetic resonance imaging (fMRI) mental rotation task paradigm to examine the patterns of activation of these brain areas in adolescents with ADHD-CT.

METHOD

Participants

Seven right-handed male adolescents aged 11–17 years (mean=14.38 (s.d.=1.85) years) were identified with ADHD-CT, defined through a semi-structured clinical interview (Silverman & Albano, 1996) with their parent(s) and by the parent and/or teacher report of the sub-scale scores of the core symptom domains of ADHD-CT (Conners, 1985) being greater than 1.5 standard deviations above the mean for a given child's age and gender (Abbreviated Conners' Rating Scale score mean=22.48 (s.d.=4.49)). The adolescents were all medication-naïve before scanning and met the inclusion criteria of living in a family home and attending normal schools. All had an IQ above 70 (Wechsler, 1991) (mean =109.29 (s.d.=12.30)) and none had overt neurological disease, psychotic symptoms, learning or speech disorder, conduct disorder or major depressive disorder. Seven healthy male control participants, who did not meet criteria for any psychiatric disorder were matched by age (mean=14.56 years (s.d.=1.77); $t(12)=0.92$, $P=0.38$) and performance IQ (Educational Testing Service, 1996) (mean=113.00 (s.d.=8.34); $t(12)=-0.66$, $P=0.52$) to the ADHD-CT group.

Participants were presented 18 baseline and 18 mental rotation trials, each comprising one target stimulus together with four test stimuli, with speed and

accuracy instructions. Participants were required to indicate by button-press which test stimulus matched the target. The stimuli consisted of Shepard-Metzler-type three-dimensional cube objects, with target and matching stimuli differing by between 45° and 180° rotation. The baseline condition required judgement of which spatial Fourier transformed 'noise' patch of four was a best visual match to the target. For each trial, stimuli were presented for 10 s with a 1 s inter-stimulus interval. Groups of three baseline trials alternating with three rotation trials were presented in 12 blocks over a total scan duration of 6 min 36 s.

Data were acquired on a 3.0 Tesla GE Signa Horizon LX magnetic resonance imaging (MRI) scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). Gradient echo planar images were acquired (repetition time 3000 ms, echo time 40 ms, 128 × 128 matrix at 1.875 × 1.875 mm², 22 slices at 4.5+0.5 mm thickness); 136 volumes were acquired per scanning session. High-resolution structural MRI images were also acquired for each participant (repetition time 120 ms, 256 × 256 × 128 matrix, voxel=0.9 × 0.9 mm², slice thickness=1.4 mm). Functional images were realigned, spatially normalised to Talairach space, and spatially smoothed (full width at half maximum=8 mm) using general linear model analysis using SPM2 software for Linux (University College London, UK). For SPM2 analysis, each stimulus was modelled as a discrete event, using the SPM2 canonical haemodynamic response function with temporal and dispersion derivatives. Realignment parameters were also included as regressors in the model to account for residual signal variance related to the individual's head motion. Group analysis was based on random-effects models, using single-sample *t*-tests to examine activation in ADHD-CT and control groups separately, and independent *t*-tests to examine differences between groups.

RESULTS

The ADHD-CT and control groups significantly differed in their accuracy (ADHD-CT, mean=27% (s.d.=15%); control, mean=56%, (s.d.=11%); Mann-Whitney test, $P<0.05$), but response time between the groups did not differ significantly (ADHD-CT, mean=4.8 s (s.d.=1.8); control, mean=6.4 s (s.d.=0.6)),

probably secondary to decreased power owing to our small sample size.

During mental rotation compared with the baseline task (see figure published as a data supplement to the online version of this paper), the ADHD-CT group showed significant activation (cluster level $P_{\text{corr}} < 0.05$, voxel level $P_{\text{uncorr}} < 0.001$) in the right premotor cortex (BA 6; coordinates 27, 9, 54), as well as pre- and post-central gyri (BA 6/3), and the right frontal cortex including the insula (BA 13; 36, 9, 18) and dorsal regions of inferior and middle frontal gyri (9/46; 45, 18, 21). Activation was also found occipitally in the left cuneus (BA 19; -15, 90, 24) and in the cerebellum. The control group similarly showed significant activation in the right premotor cortex (BA 6; 21, -6, 51) as well as the occipital cortex (right precuneus BA 7; 15, -75, 42 and BA 18; 30, -84, 3) and the right inferior parietal cortex (BA 40; 48, -39, 3). Significant activation for controls was also found in the anterior cingulate (BA 32/8; 3, 27, 39), which was not apparent for the ADHD-CT group, as well as bilateral activation in dorsal regions of the inferior/middle frontal gyri (-51, 3, 24 and 39, 12, 80) and in a ventral region of the right inferior frontal gyrus (BA 11; 24, 27, -18).

Random effects group analysis showed significantly greater activation (cluster level $P_{\text{uncorr}} < 0.05$, voxel level $P_{\text{uncorr}} < 0.01$) for the control compared with ADHD-CT participants in the left caudate head and left prefrontal cortex, including superior and inferior frontal gyri (BA 10/46), as well as the right inferior frontal gyrus (BA 47), also extending into the right caudate head, the bilateral visual association cortex (BA 19), extending rostrally to the right superior temporal gyrus (BA 39) and in the right superior and inferior parietal lobules (BA 7/40). In contrast, the ADHD-CT group showed significantly more activation in the left middle and superior temporal gyri (BA 13/39/41), medial areas including the posterior cingulate (BA 31) and the medial superior prefrontal cortex (BA 8/10).

DISCUSSION

Two interconnected neural networks were activated less in those with ADHD-CT: (a) the 'action-attentional' (Mesulam, 1990) system (including BA 46, 39, 40) that subserves disengaged, reoriented and maintained attentional focus and inhibition of contextually irrelevant stimuli and (b) the superior parietal (BA 7) and middle

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frontal (BA 10) areas that are involved in visuospatial manipulation (Booth *et al*, 2000). In contrast, superior and middle temporal regions were preferentially activated in the ADHD-CT group. These lateral temporal areas are involved with the ventral visual stream for object recognition, particularly for manipulable objects (Beauchamp *et al*, 2002), and may suggest a more object-based approach to the mental rotation task used by the ADHD-CT group. Posterior cingulate and medial superior prefrontal areas also showed greater activation in the ADHD-CT group. These areas are functionally linked in the motivational shifting of attentional focus (Small *et al*, 2003). The posterior cingulate is more active in children than adults (Booth *et al*, 2003), similar to the difference found between our ADHD-CT and control adolescents. The area of increased activation in the medial superior frontal region also corresponds with the area that has a larger structural extent in ADHD-CT, correlating with levels of hyperactivity (Sowell *et al*, 2003).

In conclusion, these findings suggest a widespread maturational lag affecting fronto-parietal functional neural systems associated with more diffuse, inefficient activation of the midline attentional cortical networks. This is consistent with emerging theoretical models of immature, inefficient neural networks being replaced by mature, efficient neural networks that then attempt to maintain themselves across the entire lifespan (Rakic, 2004).

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