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Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI

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Abstract

The aim of this study was to investigate whether previously observed hypofrontality in adolescents with attention deficit-hyperactivity disorder (ADHD) during executive functioning [Rubia K, Overmeyer S, Taylor E, Brammer M, Williams S, Simmons A, Andrew C, Bullmore ET. Hypofrontality in attention deficit hyperactivity disorder during higher order motor control: a study using fMRI. Am J Psychiatry 1999;156(6):891–896] could be attributed to delayed maturation of frontal cortex. Brain activation of 17 healthy subjects, 9 adolescents and 8 young adults, during performance of a motor response inhibition task and a motor timing task was measured using functional magnetic resonance imaging (fMRI). The effect of age on brain activation was estimated, using the analysis of variance and regression, at both voxel and regional levels. In the delay task, superior performance in adults was paralleled by a significantly increased power of response in a network comprising prefrontal and parietal cortical regions and putamen. In the stop task, alternative neuronal routes – left hemispheric prefrontal regions in adults and right hemispheric opercular frontal cortex and caudate in adolescents – seem to have been recruited by the two groups for achieving comparable performances. A significant age effect was found for the prefrontal activation in both task, confirming the hypothesis of a dysmaturational pathogenesis for the hypofrontality in ADHD.

Keywords: Frontal lobes; Maturation; Brain development; Neurodevelopment; Developmental neuroimaging; Attention deficit-hyperactivity disorder; Motor inhibition; Motor timing

1. Introduction

Attention deficit-hyperactivity disorder (ADHD) is a child psychiatric disorder characterised by inattention, hyperactivity and impulsivity [1]. The pathogenesis is likely to be developmental and the characteristic symptoms are commonly held to reflect deficits of higher order executive functions [2,19]. Using functional magnetic resonance imaging (fMRI) we have recently shown reduced activation of frontal and other brain regions in adolescents with ADHD performing two executive functions: motor timing and motor response inhibition [20]. This finding of hypofrontality was interpreted as indicative of delayed maturation of frontal lobe function in the group of patients with ADHD.

In this study we wanted to investigate further our assumption that functional activation of the human frontal lobes, measured by fMRI, normally tends to increase with age as individuals mature from adolescence to early adulthood. If this were the case, it would support our interpretation of hypofrontality in ADHD as indicative of delayed or deviant brain maturation. The frontal lobes are among the last cortical regions to become anatomically and functionally mature, and this developmental process of frontalisation may not be completed until the mid-twenties or even later [11,26,27]. Dopaminergic projections to prefrontal cortex are thought to play an important role in neurogenesis [14,22], and dysfunction of the mesoneocortical dopaminergic system [8] is one strand of evidence (among others reviewed by Swanson [24]) suggesting a neurodevelopmental model for the pathogenesis of ADHD.

Although it is widely recognised that fMRI offers many potential advantages for developmental neuroimaging in both normal and patient groups, there were no previously published fMRI data either for or against our initial hypothesis that the patterns of frontal activation induced by higher order motor control would show age related changes in normal subjects. We scanned a total of 17 healthy volunteers, nine adolescents and eight adults, under the same two experimental conditions (motor timing and motor response inhibition tasks) as previously reported in our case-control

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study of ADHD [20]. We tested the hypothesis of a group difference in functional brain activation and of a linear effect of age on power of this activation at both voxel and regional levels of analysis.

2. Method

2.1. Subjects

Seventeen healthy right-handed male volunteers participated: age range 12–40 years, mean age = 21.6, standard deviation (SD = 8.45 years). This sample includes 9 normal adolescents previously reported (age range 12–19, mean age = 15.01, SD = 2.3 years) which were compared to 8 adults (age range 22–40; mean age = 28.8, SD = 6.64). No group differences were observed in a non-verbal intelligence measure [17]. For comparative purpose, fMRI data for 7 right-handed, clinically referred and unmedicated adolescents with ADHD (age range 12–18 years; mean age = 15.7, SD = 2.1 years) will also be reviewed here (for further details of this sample see Ref. [20]). All subjects provided for written informed consent; the study was approved by the Bethlem Royal and Maudsley NHS Trust Ethics (Research) Committee.

2.2. Experimental design

Each experiment had a blocked periodic design involving a repeated contrast between 33 s epochs of an activation (A) condition and a baseline (B) condition. The cycle of BA alternation was repeated five times in the course of each 5.5 min experiment.

2.2.1. Stop task B:

An airplane appeared on a computer screen, with inter-stimulus-interval (ISI) = 650 ms and duration of stimulus = 1000 ms, followed by 650 ms of a blank screen. Eighteen such sequences were presented in each epoch. On 50% of trials the airplane was followed (250 ms later) by a zeppelin, which replaced the airplane for 300 ms and was then followed by a blank screen for 1100 ms. The subject was required to press a button with his right index finger whenever an airplane appeared, whether or not it was followed by a zeppelin. A: This condition was identical except that a bomb (instead of a zeppelin) appeared 250 ms after the airplane on 50% of trials. The subject was instructed to press the button only if the airplane appeared alone, and not, if the airplane was followed by a bomb [4,19,20].

2.2.2. Delay task

In this experiment two motor synchronization tasks were alternated, which differed exclusively in terms of ISI (short and long event rate condition). B: in the short event rate condition, a visual stimulus appeared on a computer screen with an ISI of 600 ms. The subjects had to produce high-frequency movements (tapping) in order to synchronise their motor response to the visual stimulus. A: in the long event rate (delay) condition a visual stimulus appeared with an ISI of 5 s and the subjects had to synchronise their motor response to the visual stimulus. In both conditions, the subjects were instructed to synchronise their motor response to the appearance of the stimuli by pressing a response button with their right hand at the same time or shortly after seeing the visual stimuli. In order to be able to synchronise, especially in the long event rate condition, subjects were instructed to monitor the time elapsed since presentation of the previous stimulus. Time estimation functions develop during intervals exceeding several seconds; the long event rate condition therefore imposes a higher load on time estimation and motor timing compared to the short event rate condition [20,21].

Both experimental paradigms were visually presented to the subjects in the scanner via a mirror from an LCD projector. Throughout image acquisition, each subject's performance was monitored by right-handed button press and recorded by means of a MR-compatible interface to a PC.

2.3. fMRI data acquisition

Gradient-echo echoplanar MR images were acquired using a 1.5 T GE Signa System (General Electric, Milwaukee W1) fitted with Advanced NMR hardware and software (ANMR, Woburn MA) at the Maudsley Hospital, London, UK. In each of 15 non-contiguous planes parallel to the intercommissural (AC-PC) line, 100 $T2^*$-weighted MR images depicting blood oxygenation level dependent (BOLD) contrast were acquired with $TE = 40$ ms, $TR = 3000$ ms, flip angle = 90°, in-plane resolution = 3.1 mm, slice thickness = 5 mm, slice-skip = 0.5 mm.

2.4. fMRI data analysis

Methods used for fMRI time series analysis have been described elsewhere in detail [3,5]. Following estimation and correction of movement-related effects on each individual fMRI dataset, the standardised power of periodic signal change at the frequency of alternation between baseline and activation conditions (1/66 Hz) was estimated by fitting a sinusoidal regression model to the fMRI time series at each voxel. Maps of standardised power, or the fundamental power quotient (FPQ), estimated at each voxel were registered in the standard space of Talairach and Tournoux [25] and smoothed by a 2D Gaussian filter with full width at half maximum (FWHM) = 7 mm [3]. This procedure was repeated identically after 10 random permutations of the observed fMRI time series, resulting in 10 permuted power maps for each subject in standard space. Voxels demonstrating significant median power of response over all 9 adolescent subjects (age less than 20 years) and over all 8 adult subjects (age greater than 20 years) were identified by a permutation test with one-tailed probability of false

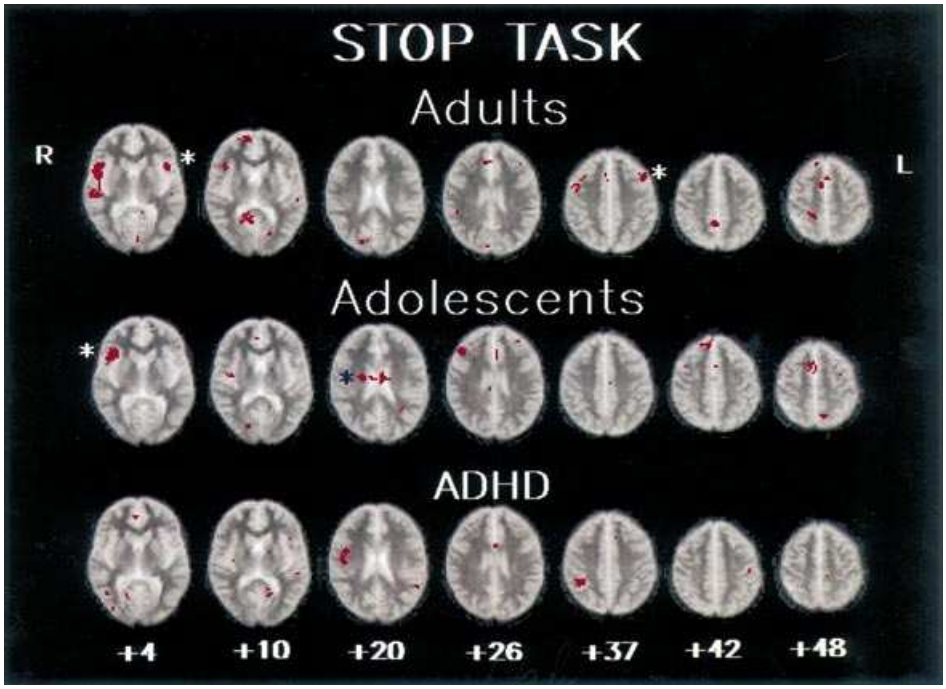

Fig. 1. Generic brain activation maps for adults, adolescents and adolescents with ADHD during performance of the *stop task*. The distance from the anterior/posterior comissure is indicated in mm. The right side of the image corresponds to the left side of the brain. Voxelwise probability of Type I error = 0.003. Stars refer to significant group differences between adults and adolescents (ANOVA, $P < 0.05$).

positive error $P = 0.003$ and represented in a pair of generic brain activation maps (GBAM, Ref. [3]).

Differences in power of functional response between these two subgroups of the sample were estimated by fitting the following analysis of variance model at each intracerebral voxel where we had data from all 17 subjects.

$$\mathrm{FPQ}_{ij} = \mu_I + \beta\mathrm{Group}_j + \varepsilon_{ij} \quad (1)$$

Here FPQ_{ij} is the standardised power of response by the jth subject at the ith voxel; μ_I is overall mean power at the ith voxel; and ε_{ij} is a residual term. The coefficient b was tested by permutation at each generically activated voxel with two-tailed probability of false positive error $P = 0.05$.

To estimate the relationship between age and power of functional response, we fitted a simple linear regression model at each intracerebral voxel where we had data from 16 subjects (excluding the oldest subject, aged 40 years):

$$\mathrm{FPQ}_{ij} = \mu_i + \beta\mathrm{Age}_j + \varepsilon_{ij} \quad (2)$$

The coefficient was tested by permutation [7] at each generically activated voxel, with two-tailed probability of false positive error $P = 0.05$.

To explore the relationship between age and power of functional response in greater detail, locally weighted regression was used to fit potentially nonlinear curves to scatterplots of regional mean FPQ against age. Regional mean FPQ for each subject was defined as the mean FPQ over an index voxel and its eight nearest neighbours in standard space. The strength of linear association between regional mean FPQ and age was evaluated by Pearson's correlation coefficient, r.

3. Results

3.1. Performance data

3.1.1. Stop task

No differences were observed between adults and adolescents in mean reaction time to airplanes (mean reaction time for adults: 631.6 ms, SD = 118.0 ms; mean reaction time for adolescents: 664.2 ms; SD = 66.4 ms, $t = 0.71$; df = 15, $P = 0.5$) or percentage of correctly inhibited responses following presentation of a bomb (adults: 93.1%, SD = 7.5%; adolescents 93.4% SD = 4.9%, $t = 0.07$, df = 15, $P = 0.95$). There was no significant correlation between percentage of correctly inhibited responses and age ($r = 0.09$, df = 15, $P = 0.74$).

3.1.2. Delay task

Motor timing was more accurate in adults compared to adolescents. The mean absolute discrepancy between stimulus onset and response, or mean synchronization time, was significantly less for adults than adolescents (adult mean synchronization time: 250.5 ms, SD = 25.3 ms; adolescent mean synchronization time: 307.0 ms, SD = 56.8 ms; $t = 2.59$, df = 15, $P = 0.02$). However, the negative correlation between mean synchronization time and age was not statistically significant ($r = -0.37$, df = 15, $P = 0.14$).

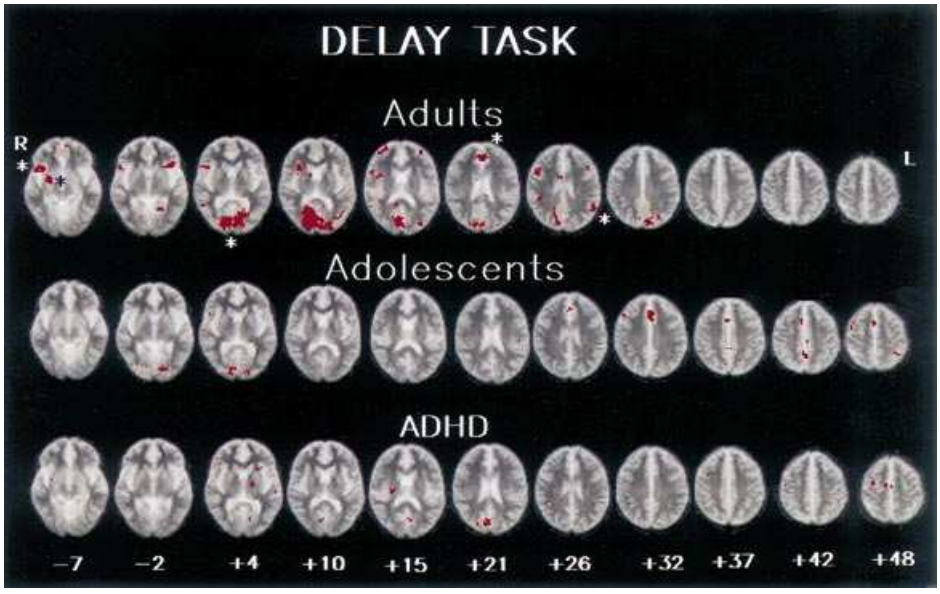

Fig. 2. Generic brain activation maps for adults, adolescents and adolescents with ADHD during performance of the *delay task*. The distance from the anterior/posterior comissure is indicated in mm. The right side of the image corresponds to the left side of the brain. Voxelwise probability of Type 1 error = 0.003. Stars refer to significant group differences between adults and adolescents (ANOVA, $P < 0.05$).

3.2. fMRI data: generic brain activation maps

3.2.1. Stop task

Generic activation in adults was observed in predominantly left middle frontal lobe (approximate Brodmann areas (BA) 9) and in right and left infero-lateral frontal lobe (BA 45) extending into the insula, right mesial frontal lobe including anterior cingulate (BA 10, 32, 24) and predominantly right posterior cingulate (BA 31), and right supplementary motor area (SMA; BA 6). Generic activation in adolescents was slightly reduced, but in homologous areas of the right hemisphere activation of the adults: in mesial frontal cortex bordering anterior cingulate (BA 8, 32), right medio-inferior and inferior prefrontal lobe (BA 9/45, 45), and right SMA (BA 6). Activation in right and left caudate nuclei was observed only in the adolescents. Adolescents with ADHD activated a different network compared to the other two groups, including right pre- and postcentral gyrus (BA 4/3/2/1), right inferior parietal lobe (BA 40), and right caudate nucleus [20]; see Fig. 1.

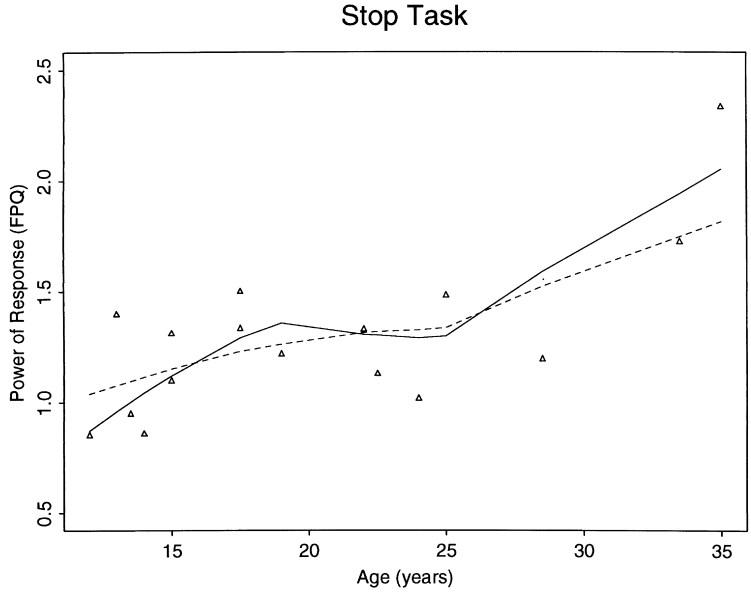

Fig. 3. Regional effects of age (years) on power of functional response (FPQ) to the *stop task*. Locally weighted regression lines are plotted for left frontal opercular (solid line) and left middle frontal (dashed line) regions. The points indicate average power of response over both regions for each subject. The age related trend in power of response was significantly different from zero in both regions at both voxel and regional levels of analysis.

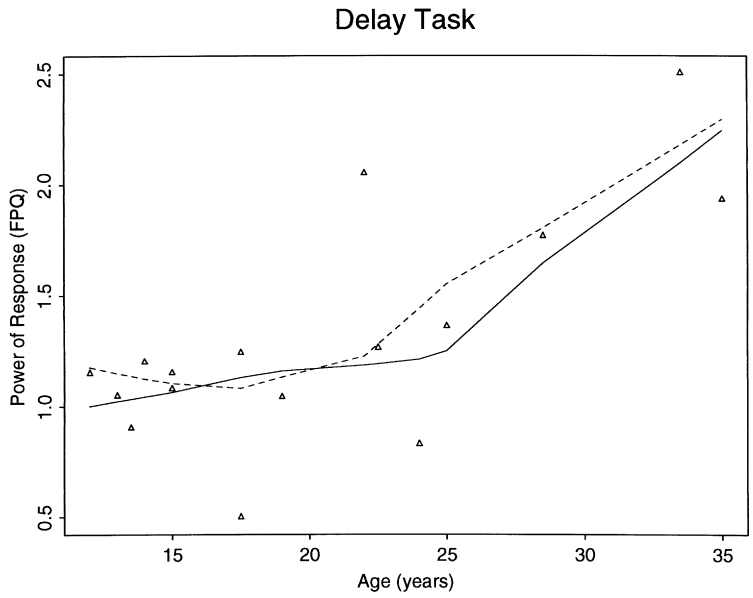

Fig. 4. Regional effects of age (years) on power of functional response (FPQ) to the delay task. Locally weighted regression lines are plotted for right inferior frontal (solid line) and anterior cingulate (dashed line) regions. The points indicate average power of response over both regions for each subject. The age related trend in power of response was significantly different from zero in both regions at both voxel and regional levels of analysis.

3.2.2. Delay task

Generic activation in adults was located in right mesial frontal cortex (BA 32, 24), right and left inferior frontal lobe (BA, 45, 47) extending into the insula, right rostro-dorsolateral prefrontal cortex (BA 10,46), right putamen, right and left posterior cingulate gyri (BA 23, 31), right and left extrastriate cortex (BA 19) and left supramarginal gyrus (BA 40). Healthy adolescents showed a weaker BOLD response located in homologous regions of right anterior cingulate gyrus (BA 32, 24) bordering SMA (BA 6), middle posterior cingulate gyrus (BA 31), and right and left extrastriate cortex (BA 18, 19). Adolescents with ADHD showed an even weaker response than the healthy adolescents. They did not show the frontal response observed in the other two groups except for a minor focus in right SMA (BA 6) similar to that observed in the healthy adolescents [20]; see Fig. 2.

3.3. fMRI data: group differences

3.3.1. Stop task

Adults compared to adolescents showed increased power of response in two left hemispheric prefrontal regions: in middle frontal gyrus (BA 9; Talairach coordinates in mm (*x*,*y*,*z*): −43, 19, 37); and in the opercular part of the inferior frontal gyrus (BA 45; −40, 6, 4) extending medially into the insula. Adolescents showed increased power of response in right caudate nucleus (26, −6, 20) and in right inferior frontal gyrus (BA 45; 38, 22, 4); see Fig. 1.

3.3.2. Delay task

Adults compared to adolescents showed increased power of response in anterior (BA 32; 0, 36, 20) and posterior (BA 23; 17, −57, 4) cingulate gyri, in right inferior frontal gyrus (BA 45/47; 46, 14, −7), in right putamen (20, −11, −7), and in left supramarginal gyrus (BA 40; −49, −53, 26); see Fig. 2.

3.4. fMRI data: effects of age

3.4.1. Stop task

At a voxel level of analysis, there was a significant linear increase in power of response with age in two left frontal regions: in middle inferior frontal gyrus (BA 9; −40, 11, 31), and the opercular part of the inferior frontal gyrus (BA 44; −43, 6, 4). At a regional level, age was positively and significantly correlated with power of functional response in both left middle-inferior frontal gyrus ($t = 2.58$, df = 14, $p < 0.02$, r = 0.59) and left infero-opercular frontal gyrus ($t = 3.3$, df = 14, $p < 0.0049$, r = 0.66); see Fig. 3. There was no significant relationship between performance and power of response in these regions.

3.4.2. Delay task

At a voxel level of analysis, there was a significant linear increase in power of response with age in anterior (BA 32; 0, 30, 20) and in right posterior cingulate gyri (BA 23/31; 17, −61, 9), and in right inferior frontal gyrus (BA 47; 46, 11, −7). At regional level, age was positively and significantly correlated with power of functional response in anterior cingulate gyrus ($t = 3.35$, df = 14, $p < 0.0048$, $r = 0.66$, inferior frontal gyrus; $t = 3.63$, df = 14, $p < 0.0027$, r = 0.69 and posterior cingulate gyrus ($t = 3.85$, df = 14, $p < 0.0017$, $r = 0.71$); Fig. 4. There was no significant relationship between performance and power of response in these regions.

4. Discussion

The main findings of this study support our hypothetical expectation that power of functional activation of frontal cortex would normally increase over the age-range of adolescence and adulthood.

In the delay task, which adults performed better than adolescents, there was an increase in power of activation in adults compared to adolescents in a fronto-striato-parietal network. Most of the brain regions showing a significant group difference in mean power of response also demonstrated a significant increase in power of response with age. These regions include right inferior frontal gyrus extending medially to insula, and anterior and right posterior cingulate gyri. In the stop task, which adults and adolescents performed equally well, adults showed more power of response in left hemispheric middle and inferior prefrontal brain regions, while adolescents showed an increase of response in right inferior frontal cortex and in right caudatc. It thus seems that the between-group differences in activation patterns have an interesting relationship to between-group differences in task performance. In the delay task, superior performance by the adults was paralleled by increased power of response throughout a similarly distributed system including areas of prefrontal cortex and posterior cingulate; whereas comparable performance on the stop task was mediated by activation of two slightly differing systems – a right hemispheric middle and inferior fronto-insular-striatal system in the adolescents compared to a bilateral middle and inferior frontal system in the adults. These data suggest that maturation of frontal cortex may be achieved either by a continuous enhancement of physiological and cognitive function or by a relatively discontinuous transition from a functionally adequate but immature prototype system to the more definitive adult network. These findings are clearly relevant to the debate concerning effects of differential performance on case-control psychiatric imaging studies. Impaired performance has been implicated as an important cause of hypofrontality in patients [10,15]. We show here that hypofrontality may coexist with impaired task performance in some experiments (delay task), but in other experimental conditions hypoactivation in specific frontal regions can be observed without performance discrepancies (stop task) and may reflect "qualitative" differences in neurocognitive strategies for task performance.

It remains an interesting question how these maturational changes in physiological activation might be determined neurodevelopmentally. Over the age range of our sample, axonal projections to and from frontal cortex are becoming myelinated, and this likely accounts for well-documented increases in white matter volume [6,12,13,16,18]. It is arguable that myelination of axonal tracts interconnecting frontal cortex with other cortical and subcortical regions may considerably enhance integrated physiological activation of distributed neurocognitive systems by "higher order" cognitive motor tasks.

The caudate and opercular frontal/insula activation in adolescents, compared to the adult bilateral prefrontal activation during the stop task, may be taken as evidence for a developmental process of encephalisation by which function is transferred from subcortical to cortical representations as a function of increasing age. This could be the functional index of above mentioned physiological changes in myelination and synaptogenesis during frontal lobe maturation in our age range and of reduction in the size of caudate with age [9,12,13,16,23]. The linear increase in left hemispheric functioning with age is an interesting and, to our knowledge, new finding; if replicated in larger samples, it may add an interesting new focus on lateralisation in brain development. Clearly further studies would be of considerable value, perhaps combining functional MRI with structural MRI studies of normal subjects in a mixed longitudinal design, to clarify the relationship between maturational effects on brain structure and function.

Our observation that power of frontal response to both higher order motor tasks is relatively attenuated in younger normal subjects is compatible with our previous dysmaturational interpretation of hypofrontality in a group of adolescents with ADHD scanned under identical experimental conditions [20]. More direct proof of the dysmaturational model will require study of a larger sample designed explicitly to test the hypothesis of an interactive effect of age and diagnosis on frontal lobe activation.

In summary, we have reported first fMRI data to provide direct evidence for functional frontalisation in the course of normal maturation from adolescence to adulthood during executive functions. This work represents a preliminary attempt to measure human neurodevelopmental trajectories using fMRI and an incremental step towards functional neurodevelopmental models of child psychopathology.

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References

[1] American Psychiatric Association. Diagnostic and statistical manual

of mental disorders, 4. Washington: American Psychiatric Association, 1994.
[2] Barkley RA. Behavioural inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121(1):65–94.
[3] Brammer MJ, Bullmore ET, Simmons A, Williams SCR, Grasby PM, Howard RJ, Woodruff PWR, Rabe-Hesketh SR. Generic brain activation mapping in functional magnetic resonance imaging: a non-parametric approach. Magn Reson Imaging 1997;15(7):763–70.
[4] Brandeis D, van Leewen TH, Rubia K, Vitacco D, Steger J, Pascual-Marqui RD, Steinhausen H-CH. Neuroelectric mapping reveals precursor of stop failures in children with attention deficits. Behav Brain Res 1998;94(1):25–32.
[5] Bullmore ET, Brammer MJ, Williams SCR, Rabe-Herketh S, Janot N, David AS, Mellers JDC, Howard R, Sham P. Statistical methods of estimation and inference for functional MR image analysis. Magn Reson Medicine 1996;35:261–77.
[6] Caviness Jr CS, Kennedy DN, Richelme C, Rademacher J. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cerebral Cortex 1996;6(5):726–36.
[7] Edgington ES. Randomization tests, New York: Marcel Dekker, 1980.
[8] Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen R. DOPA decarboxylase ativity in attention deficit hyperactivity disorder adults. A [Fluorine-18] Fluorodopa positron emission tomographic study. J Neurosci 1988;18(15):5901–7.
[9] Giedd JN, Snell JW, Lange N, Rajapakse B, Casey BJ, Kozuch PL, Vaituzis C, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cerebral Cortex 1996;6:551–60.
[10] Gur RC, Gur RE. Hypofrontality in schizophrenia: R.I.P. Lancet 1995;345:1383–4.
[11] Huttenlocher PR. Morphometric studies of human cerebral cortex development. Neuropsychologia 1990;28(6):517–27.
[12] Iwasaki N, Hamano K, Okada Y, Horigome Y, Nakayama J, Takeya T, Takita H, Nose T. Volumetric quantification of brain development using fMRI. Neuroradiology 1997;39(12):841–6.
[13] Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. Brain 1991;114:2037–49.
[14] Levitt P, Harvey JA, Friedman E, Simansky K, Murphy EH. New evidence for neurotransmitter influences on brain development. Trend Neurosci 1997;20:269–74.
[15] Liddle PF. Brain imaging. In: Hirsch SR, Weinberger DR, editors. Schizophrenia. London: Blackwell, 1995. p. 425–39.
[16] Pfefferbaum A, Mathalon D, Sullivan EV, Rawls JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurology 1994;51:874–87.
[17] Raven JC. Guide to the standard progressive matrices, London: HK Lewis, 1960.
[18] Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB. Brain development, gender and IQ in children. A volumteric imaging study. Brain 1996;119(5):1763–4.
[19] Rubia K, Oosterlaan J, Sergeant JA, Brandeis DV, Leeuwen T. Inhibitory dysfunction in hyperactive boys. Behav Brain Res 1998;94(1):25–32.
[20] Rubia K, Overmeyer S, Taylor E, Brammer M, Williams S, Simmons A, Andrew C, Bullmore ET. Hypofrontality in Attention Deficit Hyperactivity Disorder during higher order motor control: a study using fMRI. Am J Psychiatry 1999;156(6):891–6.
[21] Rubia K, Overmeyer S, Taylor E, Brammer M, Williams S, Simmons A, Andrew C, Bullmore ET. Prefrontal involvement in temporal bridging and timing movement. Neuropsychologia 1998;12(36):1283–93.
[22] Schmidt U, Beyer C, Oestreicher AB, Reister I, Schilling K, Pilgrim C. Activation of dopaminergic D1 receptors promotes morphogenesis of developing striatal neurons. Neuroscience 1996;74:453–60.
[23] Steen RG, Ogg RJ, Reddick WE, Kingsley PB. Age-related changes in the pediatric brain: quantitative MR evidence of maturational changes during adolescence. Am J Neuroradiol 1997;18(5):819–28.
[24] Swanson JM, Sergeant J, Taylor E, Sonuga-Barke E, Cantwell D. Attention deficit hyperactivity disorder and hyperkinetic disorder. Lancet 1998;351:429–33.
[25] Talairach J, Tournoux P. A co-planar stereotactic atlas of the human brain, New York: Thieme Medical Publishers, 1988.
[26] Yakovlev PI, Lecours AR. The myelogenic cycles of regional maturation of the brain. In: Minkowski, editor. Regional development in early life, Oxford: Blackwell, 1967. p. 3–23.
[27] Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiat 1987;44:660–9.