Anatomic magnetic resonance imaging studies of attention-deficit/hyperactivity disorder

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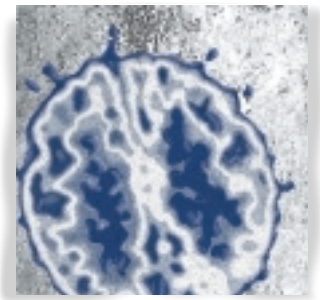

Neuroimaging techniques are increasingly being applied to the study of attention-deficit/hyperactivity disorder (ADHD). This review focuses on magnetic resonance imaging studies of the brain anatomy of ADHD. Such studies were first conducted over a decade ago, and most focus on frontal-striatal regions and tend to find smaller volumes in ADHD children than in controls. Recently published analyses with the largest sample so far of patients and controls found that ADHD is associated with a statistically significant 3% to 4% global reduction in brain volume in both boys and girls, with abnormally small caudate nuclei only being found in younger patients. After adjusting for global brain differences, only cerebellar hemispheric volumes remained significantly smaller in ADHD, and these differences continued throughout childhood and adolescence. Pathophysiological models of ADHD need take into account cerebellar dysfunction, as well as prefrontal-striatal dysregulation.

Dialogues Clin Neurosci. 2002;4:444-448.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by the chronic presence of impairing symptoms of excessive hyperactivity, impulsivity, and/or inattention.[1] The clinical diagnosis of *International Statistical Classification of Disease, 10th Revision (ICD-10)* hyperkinetic disorder (HKD)[2] is a restricted subset of ADHD, with narrower inclusion criteria and more exclusions.[3] Given the high degree of heterogeneity and comorbidity in ADHD,[4] most neurobiological studies of ADHD have focused on combined type ADHD, which requires the presence of at least 6 symptoms of hyperactivity/impulsivity and at least 6 symptoms of inattention, and is closer to HKD. Clinical diagnoses such as ADHD or HKD are necessary for the fundamental decision of whether or not to treat. However, since these, like all psychiatric diagnoses, are based exclusively on symptoms, they can result from a wide range of causes and susceptibilities. Thus, diagnostic categories do not provide an optimal basis for neurobiological investigations, although they are a necessary starting point.[5] In the case of ADHD, they have been the basis for an increasing number of structural as well as functional neuroimaging studies. Functional imaging studies have used a wide variety of approaches, and none of the findings reported to date have been convincingly replicated. For this reason, and due to limitations of space, this brief review will focus on one simple question: what are the anatomic substrates associated with combined type ADHD? (In the text below, ADHD refers to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]*[1] combined type ADHD.)

Keywords: *attention-deficit/hyperactivity disorder; magnetic resonance imaging; prefrontal brain; basal ganglia; cerebellum*

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ADHD as a disorder cannot be considered without taking into account developmental factors, and an examination of the brain anatomy of ADHD must be referenced to healthy brain development. The most influential early work on brain development was based on postmortem specimens from over 200 autopsy brains obtained from midpregnancy through the first year of life, and a large collection of adult brains, but very few specimens (about 12) in the age range extending from childhood through adolescence. Yakovlev and Lecours demonstrated that myelination continued well beyond the first year of life,[6] but they were circumspect about their more speculative findings, which they explicitly acknowledged were based on "a crude method of staining myelin sheath" of undetermined reliability. Nevertheless, they tentatively concluded that myelination proceeds along a caudal-rostral gradient. Because of the lack of postmortem tissue for children and adolescents, this finding has not been directly examined.

In vivo magnetic resonance imaging

The quantitative study of brain development in vivo during childhood and adolescence began in the late 1980s.[7,8] Subsequent cross-sectional[1,9-11] and mixed longitudinal/cross-sectional studies[12] have confirmed that although total brain volume changes negligibly between ages 5 and 18, this masks robust and complex changes in white and gray matter compartments. White matter volume and signal intensity increase linearly during this age range, presumably reflecting increasing myelination,[11,13] and gray matter volume increases until early to mid-adolescence before decreasing during late adolescence,[12] apparently representing synaptic pruning and reduction in neuropil, which has been documented during these developmental periods.[14,15] Though most existing studies begin after age 4, these show that cortical gray matter volumes reach their peak at about age 12 in frontal and parietal lobes, and that the maximum for temporal lobe gray matter occurs about 4 years later.[12,16] In healthy normal volunteers, the white matter intensity of the left (but not the right) arcuate fasciculus increases monotonically with increasing age throughout adolescence,[13] suggesting that continuing development of language-related functions may be reflected in these anatomical changes. The cross-sectional area of anterior regions of the corpus callosum also reaches adult size long before posterior regions.[12,17] Since changes in white matter volumes may reflect more than just myelination, it is not clear if these findings contradict the tentative conclusions formulated by Yakovlev and Lecours,[6] but novel techniques such as diffusion tensor imaging[18] should help clarify this question.

Prefrontal brain

Anatomic hypotheses of the substrates of ADHD have focused on the role of the prefrontal brain. Normally, the right anterior brain is slightly, but consistently, larger than the left.[19] Significant decreases in this asymmetry in ADHD have been observed using computed tomography[20] and magnetic resonance imaging (MRI).[11,21-23] Volumetric measures have also detected smaller right-sided prefrontal brain regions[22,23] in boys with ADHD, which were correlated with neuropsychological performance on tasks that required response inhibition.[24,25] In the only study to date to use voxel-based unbiased analyses, gray matter deficits in ADHD were found in right superior frontal gyrus (Brodmann areas 8 and 9) and right posterior cingulate gyrus (Brodmann area 30).[26] Such voxel-based methods have not yet been applied to the National Institute of Mental Health (NIMH) dataset of MRI images.[27] Algorithmically obtained measures recently applied to these images have shown that total cerebral volume is decreased in subjects with ADHD by 3% to 4% by comparison to age- and sex-matched controls.[27] These differences were roughly equivalent across all four major lobes; laterality measures were not obtained because of limitations of the algorithm used.

Basal ganglia

Along with the prefrontal cortex, the caudate nucleus and its associated circuits have long been suspected to play a pivotal role in ADHD.[28] Abnormalities of caudate nucleus volume[22,23] or asymmetry[22,29,30] have been reported, although the studies differ in whether the normal caudate is asymmetric, and whether this asymmetry normally favors the right[22] or the left caudate.[12,23,29-31] These inconsistencies may reflect differences in methodology and comorbidity. In girls with ADHD, we found no differences in asymmetry relative to controls, but the ADHD girls had smaller left and total caudate volumes, which remained significant after covariance for total cerebral volume and Wechsler Intelligence Scale for Children-Revised (WISC-R) Vocabulary subscale score.[31] Combining boys and girls, we were unable to measure right and left caudate nucleus volumes separately. When caudate volumes were compared

with those of controls, diagnostic differences were only present for subjects between ages 6 and 15 years.[27]

Neither of the anatomic MRI studies that reported putamen volumes detected significant diagnostic group differences.[22,32] However, studies of secondary ADHD suggest that the putamen lesions can contribute to ADHD symptomatology. In a study of 76 children with severe closed head injury, those who developed secondary ADHD were significantly more likely to demonstrate lesions in the right putamen.[33] Likewise, children with focal strokes and ADHD symptoms were significantly more likely to have involvement of right ventral putamen.[34]

The caudate, putamen, and nucleus accumbens receive efferents from the entire cerebral cortex. This impressive convergence of information is then processed and emerges from the output nuclei of the basal ganglia, which, in primates, are the internal segment of the globus pallidus and the substantia nigra pars reticulata. However, the volume of the latter cannot be reliably measured with current MRI parameters, and the size of the globus pallidus can only be measured as a unit (internal and external segments together), and then only with difficulty. Still, this region was found to be significantly reduced in size in boys with ADHD,[22,32] although these two studies differed in side of the larger difference (left or right). Globus pallidus volume differences in girls with ADHD did not survive covariance for total cerebral volume and IQ.[31] A report of two cases of severe iatrogenic ADHD presumed to have been caused by traumatic amniocentesis at 17 weeks' gestation found complete ablation of right caudate, putamen, and globus pallidus in both.[35]

Cerebellum

An early computed tomography study found a trend toward greater cerebellar atrophy in adults with a prior history of hyperkinetic minimal brain dysfunction.[36] In a quantitative MRI study of 112 subjects, the volumes of the cerebellar hemispheres were found to be significantly smaller in ADHD boys.[22] In a follow-up study within the same sample, the cerebellar vermis as a whole, and particularly the posterior-inferior lobules (lobules VIII to X) were found to be significantly smaller in ADHD.[37] Smaller lobules VIII-X were independently replicated in boys with ADHD,[38] and in girls with ADHD[31] where the posterior-inferior cerebellar vermis was the only structure that was rigorously replicated, with a comparable standardized effect size (d=0.66 in boys, d=0.63 in girls). Recently completed automated analyses of brain anatomy in 152 children and adolescents with ADHD and 139 age- and sex-matched controls revealed highly significant global decreases in overall cerebral volume in patients, which were statistically comparable in all four lobes, and which were statistically more prominent only in cerebellum.[27]

Conclusions

Although most studies have used small samples and quantitative methodology is still evolving, anatomic MRI studies support the notion that a distributed circuit underlies some of the manifestations of ADHD. At least in boys, this circuit appears to include right prefrontal brain regions, the caudate nucleus, globus pallidus, cerebellar hemispheres, and a subregion of the cerebellar vermis. With one exception,[30] all groups have reported reduced volumes (or areas), which is consistent with the broad notion that the relevant brain regions are hypofunctioning. It is generally accepted, to a first approximation, that cortico-striatal-thalamo-cortical (CSTC) circuits[39] select, initiate, and execute complex motor and cognitive responses,[40] and that cerebellar circuits provide on-line guidance of these functions.[41] The remarkable selectivity of the result within the cerebellar vermis, ie, that the region involved is limited to the posterior-inferior lobules, together with the finding that this is the only region in the cerebellum that receives a dense dopaminergic innervation,[42] support the speculation that the vermis exerts important regulatory influences on prefrontal-striatal circuitry via the ventral tegmental area and locus ceruleus. Such effects may go beyond known cerebellar vermal influencing of cardiovascular physiology[43] and heart rate conditioning,[44] which have been implicated in the state dysregulation hypothesis of ADHD. More specifically, it is possible that findings such as smaller anticipatory cardiac deceleration[45] and greater low frequency heart rate variability,[46] which are associated with poor motor activation state and greater difficulty in allocating effort, respectively, may be anatomically linked to dysfunction in the vermis outputs to midbrain monoaminergic nuclei. Also worth considering is the hypothesis that the remarkable trial-to-trial variability in responding on speeded reaction time tasks[27] by patients with ADHD may reflect deficiencies in temporal computations performed within cerebellum.[47] While there remain many questions yet to be addressed using anatomic neuroimaging, testing these specific hypotheses will require interdisciplinary efforts[5] that are just now beginning. ❑

Estudios anatómicos de imágenes de resonancia magnética del trastorno por déficit atencional con hiperactividad

Las técnicas de neuroimágenes están siendo aplicadas cada vez más al estudio del trastorno por déficit atencional con hiperactividad (TDAH). Esta revisión se enfoca en los estudios de imágenes de resonancia magnética de la anatomía cerebral del TDAH. Dichos estudios se realizaron inicialmente hace una década y se orientaron de preferencia a las regiones fronto-estriatales observando volúmenes más pequeños en niños con TDAH que en controles. Los análisis publicados recientemente, con la mayor muestra de pacientes y controles hasta la fecha, encontraron que el TDAH se asociaba con una reducción global, estadísticamente significativa, de 3% a 4% en el volumen cerebral tanto de niños como de niñas, con núcleos caudados encontrados anormalmente menores sólo en los pacientes más jóvenes. Después de ajustar las diferencias cerebrales globales, solamente los volúmenes hemisféricos cerebelosos se mantuvieron significativamente menores en el TDAH, y estas diferencias continuaron a través de la niñez y la adolescencia. Los modelos fisiopatológicos del TDAH requieren tener en consideración la disfunción del cerebelo, como también la disregulación prefrontal-estriatal.

Études anatomiques par résonance magnétique nucléaire du trouble déficit de l'attention/hyperactivité

Les techniques d'imagerie neurologique sont de plus en plus utilisées pour l'étude du trouble déficit de l'attention/hyperactivité (TDAH). Cette analyse met l'accent sur les études d'imagerie par résonance magnétique nucléaire de l'anatomie cérébrale du TDAH. De telles études ont été effectuées à l'origine il y a une dizaine d'années ; la plupart s'intéressaient aux régions frontostriatales et avaient tendance à trouver des volumes inférieurs chez les enfants atteints de TDAH que chez les sujets témoins. Des analyses récemment publiées concernant le plus grand échantillon à l'heure actuelle de patients et de témoins ont montré que le TDAH est associé à une diminution globale statistiquement significative de 3 % à 4 % du volume du cerveau aussi bien chez les garçons que chez les filles, avec un noyau caudé anormalement petit trouvé seulement chez les plus jeunes patients. Après ajustement pour les différences du cerveau entier, seuls les volumes des hémisphères cérébelleux restaient significativement plus petits en cas de TDAH, et ces différences persistaient pendant l'enfance et l'adolescence. Les modèles physiopathologiques de TDAH doivent prendre en compte les dysfonctionnements cérébelleux, ainsi que la dysrégulation pré-fronto-striatale.

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